Staphylococcus Infection Mimicking Clinical Anaphylaxis.

Summary and Lessons Learned:
A 2-year-old previously healthy boy was brought to the Emergency Department with history of sudden onset of worsening generalized rash associated with swelling of eyelids and lips of 3 hours duration. The rash was described as erythematous with intense itchiness. His past medical history was significant for inguino-scrotal orchidopexy surgery done 5 days prior to this presentation. He did not have any past history of allergies, nor any new exposures to food, medications, etc. On presentation, his vital signs were within normal parameters and he was afebrile. On physical exam, he was not in distress but appeared fussy. He did have a generalized urticarial rash covering his trunk and extremities. Also, significant edema of his eyelids and lips were noted. Wheezing was appreciated bilaterally. Site of surgery was mildly indurated and seems tender to palpation, no erythema, no discharges, rest of abdominal exam is unremarkable. The rest of his physical examination was unremarkable. In the ED he was managed with subcutaneous epinephrine, IV methylprednisolone, IV diphenhydramine for clinical anaphylaxis. His facial angioedema quickly improved; his rash significantly improved but persisted.

Results: His initial complete blood count and basic metabolic panel were within normal limits with C-reactive protein of 19.86 (normal <5). Chest X-ray was unremarkable. He was admitted to the pediatric floor for observation. Within 4 hours of admission he had fever of 39°C. Wound culture grew Staphylococcus aureus, surgical intervention done, and the patient was started on IV clindamycin. Within 4-5 hours the rash and fever completely resolved and he improved clinically.

Lessons Learned: In this case we found that localized staphylococcus aureus infection was masquerading as an anaphylactic reaction. Identifying the cause of anaphylactic reaction at times can be challenging. We hypothesize that Staphylococcus infection may mimic anaphylaxis by causing mediator release from mast cells via its δ-toxin. In vitro studies have identified δ-toxin as a potent inducer of mast cell degranulation and suggest a mechanistic link between S. aureus colonization and allergic skin disease. Providers should suspect an infectious when the cause of clinical anaphylaxis is suspected.

Patient Presentation and Testing:
Previous research has shown that Staphylococcus aureus toxin, specifically δ toxin can help mediate release of mast cells. The patient was a 2-year old boy who developed anaphylactic like reaction to a unsuspected staphylococcus aureus infection. We present a case of suspected anaphylaxis that was found to be due to underlying Staph infection resulting from a previous orchidopexy.

Diagnosis, Treatment and Patient Outcomes:
After the allergy team was consulted a thorough physical examination revealed draining pus after manipulating the surgical site. Wound culture grew Staphylococcus aureus, surgical intervention done, and the patient was started on IV clindamycin. Within 4-5 hours the rash and fever completely resolved and he improved clinically. The patient did well and was discharged accordingly.
Use of prophylactic C1 inhibitor in a patient with hereditary angioedema to prevent an attack during plasmapheresis.

Summary and Lessons Learned:
A 25 year-old female with a history of Type II hereditary angioedema (HAE) and dual kidney-pancreas transplant presented with antibody mediated rejection of her transplanted kidney requiring plasmapheresis. Several previous HAE attacks had been successfully treated with prompt administration of C1 inhibitor concentrate, although one late administration of C1 inhibitor resulted in intubation for laryngeal swelling. Her mother has a history of hereditary angioedema. Physical examination revealed normal vital signs and no significant swelling. Laboratory evaluation revealed a C4 level of 4 mg/dL and C1 inhibitor level of 20 ng/ml. Kidney biopsy showed diffuse glomerular and peritubular capillaritis consistent with acute antibody-mediated rejection. The patient received 1000 units of C1 inhibitor concentrate immediately after each of five episodes of plasmapheresis without precipitation of HAE attack.

Discussion:
Plasmapheresis is a known precipitant of HAE attacks. Use of prophylactic medication in patients with HAE requiring plasmapheresis has not been previously reported. After careful review of the literature and discussion with the patient, we concluded that our team had two options: 1) to perform plasmapheresis and closely observe the patient, treating with C1 inhibitor concentrate at the first sign of swelling, or 2) to treat prophylactically with C1 inhibitor after each round of plasmapheresis. In the end, we opted to treat the patient prophylactically with C1 inhibitor concentrate because historically, the severity of her attacks had been life-threatening.

For patients with HAE, a rare disease, much remains unknown regarding care recommendations in specific complex medical situations. As advances in medical care continue, the appropriate care of patients with HAE will continue to evolve. For the first time, we report successful administration of prophylactic C1 inhibitor concentrate in a patient with HAE requiring plasmapheresis for antibody mediated organ rejection.

Patient Presentation and Testing:
The patient is a 25 year-old woman with a history of HAE and kidney/pancreas transplant who was hospitalized for antibody mediated graft rejection. Treatment of antibody mediated graft rejection involves immunoglobulin administration and plasmapheresis. The treating transplant team was concerned that plasmapheresis would dramatically lower the patient’s C1 inhibitor level, precipitating an angioedema attack.

The patient, originally from Mexico, has a history of type 1 diabetes causing end stage renal disease. She has lived in the United States for the past 5 years. She received kidney/pancreas transplant in August, 2016.

The patient was diagnosed with Type II HAE in 2014. The initial episode that suggested HAE involved lip and mucosa swelling. Diagnosis was suggested by a family history of HAE in her mother. Laboratory evaluation revealed the following: C4, 8; C1 inhibitor level 30, C1 inhibitor function, 3%. Since the time of her diagnosis, she continues to have approximately 3 episodes of angioedema per year. Typical episodes involve swelling of her lip and tongue. Triggers of HAE attacks include both trauma and stress. The patient was placed on C1 inhibitor concentrate as needed for attacks, which was stored at the local emergency department initially and later administered at home. Treatment of attacks with C1 inhibitor concentrate, when administered promptly, almost uniformly resulted in swift resolution of symptoms.
One attack, however, involved late administration of C1 inhibitor concentrate, and the patient developed life-threatening airway swelling requiring airway intubation.

Recent laboratory evaluation revealed renal failure and positive donor specific antibodies. Kidney biopsy showed diffuse glomerular and peritubular capillaritis consistent with acute antibody-mediated rejection.

In determining a treatment plan, we reviewed the medical literature and discussed with the patient the following options: 1) perform plasmapheresis and closely monitor the patient, administering C1 inhibitor concentrate in the event of an attack, or 2) prophylactically treat the patient with C1 inhibitor concentrate following each round of plasmapheresis. Since the patient’s history included a life-threatening episode of angioedema, we opted to treat prophylactically with C1 inhibitor concentrate.

**Diagnosis, Treatment and Patient Outcomes:**
The patient tolerated five rounds of plasmapheresis well, receiving C1 inhibitor concentrate immediately after each episode of plasmapheresis. She remained asymptomatic, with no swelling or tingling or her lips or oropharynx. Upon discharge, she continues to have C1 inhibitor concentrate ready for administration as needed at home. We remain hopeful that her renal graft remains free from rejection.
A case report: Red pepper allergy accompanied with mugwort–mustard syndrome

Summary and Lessons Learned:
Red pepper allergy is an infrequent event, but it may trigger anaphylaxis. We report a case of red pepper anaphylaxis with mugwort-mustard syndrome which might be caused by cross-reactivity between mugwort and red pepper is discussed. A 58-year-old female with a medical history of pollinosis (birch, timothy, orchard grass, and mugwort), mugwort–mustard syndrome, and chronic urticaria visited our hospital and complained about her allergic symptoms. She has suffered from nasal obstruction for years due to the smell of red pepper. She reported some histories of allergic symptoms and anaphylaxis every time she consumed mustard and red pepper. She was brought to the emergency department every time she ate red pepper owing to nasal obstruction, abdominal pain, diarrhea, vomiting, and general itchy rash. These symptoms developed starting within 15–120 min from the ingestion of red pepper. She has never experienced allergic symptoms with other foods and after eliminating red pepper and mustard by herself. We performed serum allergen-specific IgE, skin prick, and basophil activation tests as well as oral food challenge with red pepper. The results revealed that the anaphylaxis was caused by red pepper allergy accompanied with mugwort–mustard syndrome. We suggested that the anaphylaxis in this case was caused by cross-reactivity between Artemisia vulgaris (mugwort) and Solanaceae family (Capsicum annuum: hot pepper). More investigations on the cross-reactivity between mugwort and other foods are necessary.

Patient Presentation and Testing:
The patient was a 58-year-old female who owns a store for Japanese-style pickles called Tsukemono. She had a medical history of pollinosis (birch, timothy, orchard grass, and mugwort), mugwort–mustard syndrome, and chronic urticaria. She visited our hospital and complained of her allergic symptoms. She has suffered from nasal obstruction for years due to the smell of red pepper. She reported some histories of allergic symptoms and anaphylaxis every time she consumed mustard, lotus with mustard, Japanese-style pickles with red pepper, and jellyfish with red pepper. She has never experienced allergic symptoms with other foods and after eliminating red pepper and mustard by herself. Hence, we performed serum allergen-specific IgE test including pollen and food sensitization, skin prick, and basophil activation tests and the oral food challenge with red pepper.

Diagnosis, Treatment and Patient Outcomes:
Her serum allergen-specific IgE test was elevated in birch, timothy, orchard grass, and mugwort. The results of the skin prick and basophil activation tests were positive for mustard, but were negative for red pepper. We performed the oral food challenge with red pepper to determine the red pepper allergy. After ingesting 0.2 g of red pepper, she complained of abdominal pain and was immediately administered H1 antihistamine. The results revealed that anaphylaxis was caused by red pepper allergy with mugwort–mustard syndrome. We suggested that the anaphylaxis in this case was caused by the cross-reactivity between Artemisia vulgaris (mugwort) and Solanaceae family (Capsicum annuum: hot pepper). We instructed her to avoid Artemisia vulgaris and other foods and prescribed self-injectable epinephrine for anaphylaxis. After our visit, she has not experienced allergic symptoms.
Seminal Fluid Hypersensitivity

A 37-year-old woman presented with vaginal irritation, burning, and itching following unprotected sexual intercourse with her husband. Condom use or coitus interruptus prevented symptoms. Cutaneous skin prick testing using her husband’s semen produced a 7mm wheal, confirming IgE-mediated seminal fluid hypersensitivity. Allergen avoidance through abstinence, coitus interruptus, or condom use was unfeasible, as she wanted to conceive. Prophylactic oral antihistamine provided no perceivable benefit. Five milliliters of 6% cromolyn applied intravaginally prior to sexual intercourse successfully prevented symptoms, allowing the patient to engage in asymptomatic unprotected coitus.

Symptoms of seminal fluid hypersensitivity caused by IgE-mediated sensitization to seminal plasma proteins range from post-coital vaginal pruritus to anaphylaxis. This condition makes conception challenging and causes significant psychological stress. Allergen avoidance through abstinence or condom use is the mainstay of treatment. In this case, we demonstrate that in patients with localized vaginal symptoms for whom abstinence or condom use is impractical, prophylactic topical cromolyn preparations can prevent vaginal edema and pruritus.

Patient Presentation and Testing:
A 37-year-old G0P0 woman with sickle cell anemia, allergic rhinoconjunctivitis, and mild, persistent asthma presented to UNC Allergy/Immunology clinic reporting recurrent vaginal itching, irritation, and burning after unprotected sexual intercourse with her husband. Symptoms started 30 seconds after ejaculation. She denied systemic cutaneous rash, hives, nausea, vomiting, diarrhea, or dizziness. On two occasions, she developed cough post-coitus relieved with inhaled albuterol. Condom use or coitus interruptus prevented symptoms. Vaginal irritation improved with unprotected sexual intercourse daily or every-other-day, but rebounded with abstinence of one week or longer. She denied food, medication, or latex allergies. She and her husband had no histories of STIs. As the couple desired a pregnancy, condom use and coitus interruptus during sexual intercourse was undesirable.

Her husband provided a fresh semen sample that was allowed to liquefy for at least 30 minutes at room temperature. The upper layer of sample, containing the seminal plasma proteins, was used for skin prick testing, producing a 7mm wheal. Histamine and saline controls produced 8mm and 3mm wheals, respectively.

Diagnosis, Treatment and Patient Outcomes:
Skin prick testing confirmed IgE-mediated seminal fluid hypersensitivity. Given the patient’s desire to conceive, allergen avoidance was impractical. Oral cetirizine 10mg, 45 minutes prior to intercourse did not prevent local symptoms. Pretreatment with 5mL of 6% cromolyn in VersaBase®, a proprietary compounding base by Professional Compounding Centers of America (Houston, TX), applied intravaginally 15 minutes before intercourse successfully prevented symptoms with unprotected coitus. She and her husband are actively pursuing pregnancy.
Case Title:
Acquired Angioedema Secondary To Myeloma With Exacerbations Due To Fresh Frozen Plasma

Summary and Lessons Learned:
We present a case of acquired angioedema that emphasizes the importance of increased clinical suspicion and a broad diagnostic workup beyond C1 esterase inhibitor (C1INH) studies, and the potential for paradoxical exacerbations with fresh frozen plasma (FFP). This case will open discussion for diagnosing acquired angioedema as well as management of this disease process and other associated pathologies.

Patient Presentation and Testing:
Patient is a 53-year-old man with obesity, mitral valve prolapse, and acquired angioedema. He had been experiencing worsening recurrent abdominal pain with nausea and vomiting since age 49 and was tentatively diagnosed with angioedema at an outside institution. At that time, his complement studies were reduced or at the lower limit of normal: C4 was 16 mg/dl (ref: 16-47), C1INH protein was 21 mg/dl (ref: 21-39), C1INH function was 78% (ref: >68%), and C1Q was <3.6 mg/dl (ref 5-8.6), with normal levels of C2, C3, and a normal CH50. He had no family history of angioedema or autoimmune disease. He was initially tried on recombinant human C1INH but was changed to C1INH concentrate from human plasma due to poor response to the former. He subsequently began developing episodes of hand and foot angioedema. A workup for fatigue revealed severe mitral regurgitation, and mitral valve surgery was attempted with C1INH concentrate and FFP prophylaxis, but during induction the patient developed severe laryngeal edema that was refractory to additional C1INH concentrate and FFP; he remained intubated for four days and developed a pulmonary embolus. Three weeks later he experienced hematochezia on anticoagulation, and after isolated administration of prophylactic C1INH concentrate and FFP prior to endoscopy he again suddenly developed severe refractory laryngeal edema and remained intubated for four days. He was advised complete avoidance of FFP in the future and instead receive human prothrombin complex concentrate if needed for coagulation.

Diagnosis, Treatment and Patient Outcomes:
Due to difficulty controlling his angioedema and an association with malignancy, further work up was pursued in our clinic. Kappa and lambda free light chains were found to be elevated and serum protein electrophoresis showed an M-spike. A bone marrow biopsy demonstrated plasma cell population of 20%. Patient was started on dexamethasone by hematology. Patient was pretreated with human C1INH concentrate and icatibant before and after surgery. He successfully received surgery for mitral valve replacement and was extubated without event. He continues to be managed on C1INH concentrate from human plasma and icatibant for rescue therapy.
Summary and Lessons Learned:
Anaphylaxis to drumstick plant (moringa oleifera) has not been documented in the literature. Here, we report a case of a young man who presented with anaphylaxis to this vegetable.
A 35 year old man presented to the emergency department with diffuse hives after eating drumstick vegetable. He had generalized hives, angioedema, shortness of breath and was hypotensive. He was given epinephrine injection and oral antihistamine and referred to allergy clinic. There, skin testing to drumstick vegetable was negative. A food challenge was then done in clinic, during which he developed anaphylaxis to drumstick vegetable.

Drumstick vegetable is commonly ingested in Southeast Asian countries, including India, from which this patient originates. This plant is thought to have anti-inflammatory and anti-oxidant benefits, hence its high intake in this region. It is normally eaten after being sautéed or boiled, and is generally not ingested raw. Despite its common place in Southeast Asian diets, this is the first reported case of anaphylaxis to drumstick vegetable. Whilst true allergy to the drumstick vegetable may not be common, it is important to note that anaphylaxis in some individuals to this vegetable may be possible and should remain in the differential. Other plants in the same genus as drumstick vegetable are not ingested in typical diets, though plants in the same order (brassicales) include papaya, capers, which have been documented as causing anaphylaxis in certain patients. Perhaps a similar protein in all these related plants is the causative agent. Further investigation is necessary to know which protein from the drumstick vegetable caused anaphylaxis in our patient, and if that protein is present in these related plants.

Patient Presentation and Testing:
A 35 year old male was referred to the allergy clinic for further work up after presenting to ED with anaphylaxis. Two weeks prior, patient presented to ED with diffuse hives and shortness of breath. He had just eaten lunch at his home, drumstick vegetable stew - which included sautéed drumstick vegetable mixed in various Indian herbs and spices. Within the next half hour, he developed generalized hives, lip and tongue swelling, nausea, throat tightness, shortness of breath, and lightheadedness, prompting him to go to the ED. At presentation to ED, he was hypotensive to 88/33, HR 114. Vitals and urticaria improved after epinephrine injection 0.3mg and antihistamines.
He recalls he had drumstick vegetable once prior to this episode, roughly one year ago, after which he developed mild hives on his body that self resolved. Interestingly, drumstick vegetable is only sold for one month of every year in the region where this patient resides, thus, his intake is infrequent.
His PMH includes vitiligo and hyperlipidemia. No hx of eczema, rhinitis, asthma. No family hx of allergic conditions. He is on no medications.
A complete physical exam was unremarkable. No eczema or hives noted.
To assess if the patient had an allergy to and developed anaphylaxis to drumstick vegetable, the decision was made to pursue skin testing.

Diagnosis, Treatment and Patient Outcomes:
Our patient underwent epicutaneous testing via prick technique for raw and cooked drumstick vegetable, both were negative (0mm), histamine was 4mm. Because his history was heavily suggestive of anaphylaxis, the decision was made to pursue an oral challenge in clinic. He was slowly given progressively increasing increments of drumstick vegetable and closely observed. He tolerated up to the last and largest dose of his food challenge, which was 6gm drumstick vegetable, after which he quickly developed diffuse hives, mild angioedema and nausea. His blood pressure dropped 20 systolic
Epinephrine injection 0.3mg, cetirizine and prednisone 30mg po were given promptly. His hives resolved and his blood pressure improved. His response to the food challenge was suggestive of anaphylaxis to drumstick vegetable. Because the patient developed anaphylaxis to drumstick vegetable in clinic during the oral challenge, he will have to be very careful to avoid exposure to drumstick vegetable going forward. His treatment plan will also include carrying an epipen for accidental ingestion. The patient had plans to follow up to get protein testing done to further assess is reaction to drumstick vegetable, though he never followed up to have this lab work done.
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Case Title:
Exercise-induced anaphylaxis with hyperleukotrieneuria in the challenge tests

Summary and Lessons Learned:
We experienced a case of exercise-induced anaphylaxis which was diagnosed by the exercise challenge test. The production of leukotrienes (LTs) is known to be involved in the pathogenesis of exercise-induced anaphylaxis. In our case, even in asymptomatic phase after cold stimulation test, urinary LTE4 was already elevated. The measurement of urinary LTE4 during day-by-day challenge test was important for accurate diagnosis of exercise-induced anaphylaxis.

Patient Presentation and Testing:
A 12-year-old girl presented symptoms of acute flushing, cyanosis, eye lids swelling and dyspnea after an endurance run, swimming and an intake of cold drink. She did not have any history of food allergy. And also, specific IgE and skin prick test were also negative for any suspected causal food. Based on her symptomatic episode, we performed two-day challenge tests. On the first day, cold water intake test did not induce any symptom. After the test, plasma histamine level did not show significant change, but urinary LTE4 was clearly elevated (pre 295, post 400pg/mg · cr.). On the second day, exercise challenge test (strongest load 80watt by ergometer) induced acute flushing, cyanosis, eye lid swelling, dyspnea and hypotension. After challenge test, plasma histamine (pre 0.7, post 81ng/mL) and urinary LTE4 were elevated (pre 579, post 846 pg/mg · cr). Her serum tryptase level was measured once during the asymptomatic period, and was within normal range.

Diagnosis, Treatment and Patient Outcomes:
We diagnosed her as exercise-induced anaphylaxis. We restricted her strong range exercise and prescribed adrenaline autoinjector. Twelve years have passed safely, and now she is working as a teacher for handicapped children.
Case Title:
Anaphylaxis caused by omega-5-gliadin initially diagnosed as idiopathic anaphylaxis.

Summary and Lessons Learned:
We herein report the case of a 59-year-old man who experienced two episodes of wheat dependent exercise induced anaphylaxis, initially diagnosed as idiopathic anaphylaxis.

The first episode took place in July 2016. The patient woke up in the morning and drove for an hour to his resort. While driving, he ate a piece of cheese and ham pie. Upon his arrival, he walked some meters to the garden and started feeling generalized pruritus and dizziness. He lost consciousness for five minutes and recovered by himself. He was carried to hospital where his vital signs were normal.

A month after the first episode he visited an allergist. His physical exam was non contributory. Skin prick tests to aeroallergens and prick to prick tests to the ingredients of the pie were negative. Tryptase levels were within normal limits and skin biopsy was negative for mastocytosis. An endocrinology workup to rule out pheochromocytoma and carcinoid tumours was also carried out and was negative. The patient was diagnosed with idiopathic anaphylaxis and was prescribed an epinephrine auto-injector. He was asymptomatic for eight months.

The second episode took place in March 2017 at his resort. That morning he had a cup of milk and two slices of toast for breakfast and started working in the garden. Two hours later he experienced generalized pruritus and urticaria and fell unconscious. His wife had to administer two epinephrine auto-injectors before he regained consciousness.

After the second episode of anaphylaxis it was decided to start treatment with omalizumab. Two months later he experienced an episode of generalized urticaria while working in the garden. He could not recall what he had eaten before.

The patient visited our department in June 2017. We performed skin prick tests to a panel of common aeroallergens and food allergens. The test to gliadin was positive. Specific IgE in serum (Immunocap Phadia) to omega-5-gliadin was also positive. The patient was advised to avoid wheat and has been asymptomatic ever since.

Cases diagnosed with idiopathic anaphylaxis may actually be cases in which the culprit allergen has not been identified. Detailed history and extensive workup may contribute to the successful management of these patients.

Patient Presentation and Testing:
The patient's physical exam at his first visit to our department was unyielding. His personal and family history of atopy was negative. He had a history of atrial fibrillation and had been on flecainide 100 mg BID and aspirin 100 mg at noon for four years. He was really worried about his condition, as he had experienced two near death reactions and he did not know what had caused them. He had stopped treatment with omalizumab a month ago.

We tried to identify any possible factor that could have been the cause of anaphylaxis or might have contributed to its occurrence. The patient denied having taken any other drug except from flecainide the mornings he experienced the anaphylactic reactions. He also denied having been stung by an insect. He had eaten cheese and ham pie bought from the same bakery, as well as toast and milk, several times after the reactions, without any problem. He had been in good health before the reactions at all times.

The only common factor we identified in all occasions was mild to moderate exercise while walking or working in the garden. So, we concluded that exercise could be a co-factor for the occurrence of anaphylaxis. In this case, food dependent exercise induced anaphylaxis (FDEIA) could be the diagnosis. Gliadin and LTP are allergens associated with FDEIA in our region. The skin prick test to gliadin was positive (8mm), while the test to peach (LTP) was negative. We
also performed skin prick tests to common aeroallergens and food allergens, including wheat, which were negative as well. Specific IgE in serum (Immunocap Phadia) to omega-5-gliadin was positive (14.00 kUA/l), while specific IgEs to all LTPs tested (wheat, peach, hazelnut, peanut) were negative. Specific IgEs to soya's allergen components were also performed and were negative. Total IgE was 510.8 kU/l.

**Diagnosis, Treatment and Patient Outcomes:**
Our diagnosis was wheat dependent exercise induced anaphylaxis (WDEIA).
Taking into consideration the severity of the anaphylactic reactions the patient had experienced, he was advised to avoid wheat. He also restarted treatment with omalizumab. He was prescribed an epinephrine auto-injector and given an action plan for the management of anaphylaxis. The patient has been asymptomatic ever since and his quality of life has significantly improved, as now he is fully informed about his condition.
Case Title:
Idiopathic Anaphylaxis and Solar Urticaria Respond to a Lower Dose of Omalizumab

Summary and Lessons Learned:
Omalizumab has been used successfully for the treatment of idiopathic anaphylaxis and mast cell disorders.[1,2] We present a 48-year-old male with solar urticaria and idiopathic anaphylaxis whom we have successfully treated with low-dose omalizumab. Since our patient was not responsive to traditional treatment regimens of first-generation antihistamines, second-generation antihistamines, and leukotriene inhibitors, a decision was made to try anti-IgE therapy with omalizumab. What makes this patient unique is his exquisite sensitivity to omalizumab. While on omalizumab several years prior for the treatment of difficult-to-control severe-persistent asthma, he developed severe arthralgias, joint swelling, and tendonitis, after each omalizumab injection. Understanding his hypersensitivity, and being out of treatment options for his idiopathic anaphylaxis, we titrated the dosage of omalizumab to the highest dose tolerated without the manifestation of side effects. A lower-than-standard dose of omalizumab 75mg (6cc) subcutaneous injection every 2 weeks, has proved adequate to control both his idiopathic anaphylaxis and solar urticaria.


Patient Presentation and Testing:
Our patient is a 48-year-old Caucasian male, with a long history of solar urticaria, moderate-persistent asthma (without aspirin sensitivity), allergic rhinitis, and chronic rhinosinusitis with nasal polyps. He presented for an urgent visit because of acute hives, tongue tingling, facial flushing, and lip edema. This initial episode occurred while eating lunch, which included chicken kebabs, hummus, rice with spices, and mint tea -- items which he had consumed without problems in the past. Our initial thought was that a hidden food ingredient caused the reaction. With daily fexofenadine and a 5-day burst of prednisone, the symptoms resolved. Food allergy testing (including chicken, hummus, rice, and mint) did not reveal any specific food sensitivity. He stayed symptom free for the next four months until the sudden onset of symptoms: itchy palms and feet, progressing within several hours to whole body itching, facial flushing, facial edema, throat swelling, and vomiting. There was no exposure to any specific food, environmental, or chemical around the time of this reaction. Symptoms waxed and waned over the next few days, despite self-management with multiple doses of diphenhydramine and fexofenadine. His tryptase level was found to be 20.8 ng/mL. Over the next several weeks, this patient’s symptoms proved difficult to control. Even with high-dose oral steroids, he developed severe respiratory difficulty, requiring 2-days of inpatient hospital care without intubation. After hospitalization with IV solumedrol and IV famotidine, his outpatient anaphylactic symptoms were controlled with a daily regimen of fexofenadine 180mg 4x/day, ranitidine 150mg BID, montelukast 10mg, and prednisone 60mg daily. Oral prednisone required a 1-month long taper. Baseline tryptase levels were normal, ranging from 2.3 to 7.0 ng/mL. Additional labs were obtained, including peripheral blood for cKIT D816V mutation analysis (negative), and 24-hour urine for 5-HIAA, metanephrines, and catecholamines (all negative). The patient continued to have recurrent episodes of symptoms including facial flushing and lip edema, requiring short courses of oral prednisone.

Diagnosis, Treatment and Patient Outcomes:
After ruling out chronic idiopathic urticaria, mastocytosis, pheochromocytoma, and carcinoid syndrome, the diagnosis of idiopathic anaphylaxis vs. idiopathic mast cell activation syndrome was made. Despite maximal treatment with first
generation antihistamines, second generation antihistamines, and leukotriene inhibitors, the patient still had partial flares of anaphylactic symptoms including facial flushing and lip edema requiring multiple courses of oral prednisone. Thus, we decided to treat his condition with anti-IgE therapy. In view of his prior history of side effects associated with omalizumab treatment for moderate-persistent asthma (severe arthralgias, joint swelling, and tendonitis in his finger joints), we started a graded challenge with omalizumab, monitoring both for side-effects and for control of his idiopathic anaphylaxis symptoms. The schedule included a starting dose of omalizumab 75mg (6cc, or one-half the lowest recommended dose for asthma or chronic idiopathic urticaria) subcutaneous injection, and subsequent increase of the dose every 2-weeks to 112.5mg, 150mg, 187.5mg, 225mg, etc. The patient was unable to tolerate the 112.5mg dose, but did not have any significant side-effects with the 75mg dose. Fortunately, we were able to obtain good control of his anaphylactic episodes and solar urticaria with omalizumab at 75mg subcutaneously every 2 weeks. For patients who have intolerable side-effects from omalizumab, this medication should not be abandoned in the treatment of idiopathic anaphylaxis or solar urticaria. As demonstrated in our patient by effective treatment with a 75mg dose of omalizumab, a graded challenge (increasing the dose every 2-weeks) should be attempted.
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Case Title:  
Immediate Hypersensitivity Reaction to Human Serum Albumin in a Patient Undergoing Plasmapheresis

Summary and Lessons Learned:  
We describe the first reported pediatric case of immediate hypersensitivity reaction during infusion of 5% human serum albumin (HSA) for plasmapheresis in a boy with suspected chronic inflammatory demyelinating polyneuropathy. The patient had already received IVIG and failed to have longstanding neurologic improvement. As a result, his medical team, which included Hematology and Neurology, determined that the ideal therapy for his disease process would be plasmapheresis, using 5% HSA, a commonly used colloid. He developed respiratory, gastrointestinal, and cutaneous symptoms within 30 minutes of initiation of his first plasmapheresis with 5% HSA infusion. The reaction was effectively treated with antihistamines and epinephrine, though he did require subsequent transfer and monitoring in the intensive care unit. No other triggers were identified for the reaction. He was skin tested to several formulations of HSA, with negative skin prick but positive intradermal tests and had objective symptoms consistent with a systemic immediate hypersensitivity reaction to intradermally placed HSA. He was also skin tested to fresh frozen plasma (FFP), another possible replacement fluid, with positive intradermal skin test results. Given the clinical presentation and results of skin testing, administration of HSA or FFP through desensitization was considered too high risk in this patient with low reserve, poor sensory perception and poor motor capacity; he therefore received IVIG and steroids as the alternative, but not preferred treatment. HSA is a commonly used colloid and reactions are extremely rare. However, this case demonstrates that colloids should be considered in the differential list of possible triggers in hypersensitivity reactions. Furthermore, there may be utility in skin testing to determine safety of future administration.

Patient Presentation and Testing:  
A 10-year-old male who presented with extremity weakness was diagnosed with Guillain-Barré Syndrome and treated with two courses of IVIG with initial improvement. However, his symptoms were ultimately refractory and there was concern for chronic inflammatory demyelinating polyneuropathy. His past medical history is notable for wheezing and allergic rhinitis, but he had no known drug or food allergies. Given his comorbid conditions including obesity and hypertension, steroids were deferred and the decision was made to proceed with 5 days of plasmapheresis with albumin as the replacement fluid.  
After receiving the first bottle of albumin (250 mL), 10% of the full infusion dose, and less than 30 minutes after initiation of plasmapheresis, he developed throat clearing and nasal congestion followed by acute vomiting, difficulty breathing, and diffuse rash. He was also noted to be hypoxic (pulse oximeter 86%) and wheezing with poor air movement. He was given diphenhydramine and placed on 4L supplemental oxygen without improvement in hypoxia. Though rash improved, he continued to have respiratory distress and albuterol and epinephrine were administered. Blood pressures remained stable. He was transferred to the ICU for further care, where his symptoms quickly resolved following epinephrine administration. Detailed review of history for other possible triggers, including food, latex, and drugs, was unrevealing. This was his first time receiving albumin infusion.  
There are limited cases reporting hypersensitivity reactions to albumin, with ahaptoglobinemia and IgA deficiency thought to be underlying in several cases. Haptoglobin and IgA level were normal in our patient. It is also thought that caprylate, which is added during commercial production of human serum albumin to prevent protein aggregates, which can be immunogenic, can elicit reactions. The albumin administered to this patient contained sodium caprylate. Tryptase was drawn 50 minutes after onset of reaction and was normal (7.5 ug/L). Immune mechanism was not confirmed by in vitro IgE testing.
Though skin testing is not validated for albumin, we proceeded to skin test to determine the safety of future administration given the severity of his reaction and the limited treatment options. We skin tested to three undiluted formulations of 5% HSA: the lot number to which the patient reacted, a different lot number from the same manufacturer, and a different manufacturer. All formulations contained caprylate; a caprylate free formulation was not available despite attempts from our institution’s pharmacy to obtain it. Skin prick testing was negative, but intradermal testing was positive for all 5% HSA formulations. Furthermore, 20 minutes after placement of intradermal testing, the patient developed throat clearing, cough, and nasal congestion that was a clear change from his baseline and concerning for a systemic reaction. Lungs were clear with some transmitted upper airway sounds. Benadryl was administered and symptoms improved within a few minutes. The family reported that these symptoms were similar to those he had at onset of his reaction to plasmapheresis.

FFP was suggested as an alternative replacement fluid, with some promising features: the manufacturing steps used to make HSA preparations that leads to protein aggregates are not done in the production of FFP preparations. In addition, FFP does not contain caprylate. Skin prick and intradermal testing to undiluted FFP from one donor was also performed and was positive at the intradermal level.

**Diagnosis, Treatment and Patient Outcomes:**

In this case, the trigger for the patient’s reaction was suspected to be HSA based on timing of the reaction. HSA is not considered highly immunogenic, but protein aggregates and addition of caprylate can increase its immunogenicity. Though in vitro testing for specific IgE to albumin was not performed, positive skin test and objective symptoms to skin testing suggested that the mechanism was mast cell mediated, and we favor anaphylaxis given that HSA is not known to be an indirect mast cell degranulator. Given the immediate onset of objective symptoms after intradermal skin test, it was decided that attempting to desensitize to albumin would be remarkably high risk and the recommendation was made to strictly avoid any future administration of albumin. We also considered this patient sensitized to FFP and offered desensitization, but recognized that this was extremely high risk given his neurologic status and poor reserve and concern that any potential reactions may be catastrophic. After discussion with the Neurology team about the risks and benefits of desensitization, they elected to proceed with another course of IVIG and initiating steroids, with some improvement in symptoms. He is currently undergoing a prednisone taper while receiving inpatient rehabilitation services. Should the need for plasmapheresis be pressing in the future, we will reconsider desensitization to FFP.
Case Title:
Anaphylaxis with corn pollen aeroallergen exposure

Summary and Lessons Learned:
Anaphylaxis to aeroallergens is exceedingly rare. In 1984, Spitalny et al. described a phenomenon termed “Alpine Slide anaphylaxis”, where five patients developed grass aeroallergen anaphylaxis presumably due to skin abrasions sustained during sledding. Since then, six other cases of systemic symptoms due to aeroallergen exposure have been described, with grass pollen (Ramón et al. 2017, Haluk Akar et al. 2015, Tsunoda et al. 2003, Miesen et al. 2001), the ornamental indoor green plant Tradescantia (Albifloxia) (Wuthrich & Johansson, 1997), and horse allergen (Cavkaytar et al. 2014) as suspected sensitizations.

We present the case of a 29-year-old agricultural sales consultant who developed anaphylaxis after exposure to the aeroallergen corn pollen. The patient was walking through a cornfield in July while pollen-containing tassels were in bloom. He was not physically exerting himself on this walk, and he had no recent ingestion of alcohol or nonsteroidal anti-inflammatory drugs. Within minutes of his walk, he developed diffuse urticaria and facial angioedema with associated respiratory distress. No cardiovascular or gastrointestinal symptoms were noted. The patient drove himself to his nearest emergency department, where he received two doses of epinephrine and oral diphenhydramine. His symptoms completely recovered.

Based on his clinical history, we performed epicutaneous testing with environmental aeroallergens, including corn pollen. Our patient had skin prick IgE-reactivity to corn and grass pollen. His anaphylactic episode in the cornfield is thought to have been due to exposure to a high concentration of corn pollen. Unlike the individuals described in the “Alpine Slide Anaphylaxis” case report, our patient had no known cutaneous injuries; however, he may have had minor abrasions while walking in a cornfield in a short-sleeved shirt, which acted as portals of entry for the aeroallergen. Our case demonstrates a rare case of anaphylaxis to an aeroallergen and highlights the importance of considering aeroallergens as triggers for anaphylaxis. To our knowledge, this is the first reported case of anaphylaxis triggered by corn pollen exposure.

Patient Presentation and Testing:
A 29-year-old agricultural sales consultant with a history of hypothyroidism on thyroid replacement therapy was referred to us for assessment of allergies. He reported rhinoconjunctivitis symptoms between spring and fall seasons, and two episodes of systemic reactions. The first episode occurred when patient was walking through a cornfield in July 2016, with development of diffuse urticaria and facial angioedema with associated respiratory distress within minutes of his walk. There were no features on clinical history to suspect exercise or non-steroidal anti-inflammatory drug associated reactions. Additionally, he is able to consume sweet corn. The patient was treated with epinephrine at his local emergency department, with resolution of his symptoms.

The patient reported one other episode of urticaria, facial and extremity angioedema, and respiratory distress due to the sensation of upper airway obstruction one and a half years earlier. This episode also required emergency department treatment with epinephrine. Possible triggers included ibuprofen (two 400 mg liquid gels taken within an hour of the reaction), or Belgian chocolate or alcohol, both of which were consumed the night before. Our patient’s clinical history was suggestive of anaphylaxis given cutaneous and respiratory organ involvement; we therefore performed epicutaneous testing for aeroallergens including corn. Skin prick testing indicated positive responses for corn pollen (wheal 10 mm, erythema 40 mm) and grass (two preparations used: ALK, wheal 8 mm,
erythema 20 mm; Medic savoure, wheal 9 mm, erythema 25 mm). Serum specific IgE testing indicated elevated IgE for ragweed (0.73 kU/L; normal <0.35). Ragweed was tested, despite negative skin tests, due to the symptoms in fall. Testing for corn pollen was not available at our institution. Serum specific IgE for hazelnut, commonly found in Belgian chocolates, was weakly positive (0.38 kU/L; normal <0.35). Based on the recurrent episodes of anaphylaxis, we also evaluated for potential mast cell dysfunction. Our patient’s serum tryptase was normal at 5.3 ug/L.

As the patient’s second reaction was suspicious for ibuprofen allergy, we performed a graded oral challenge with ibuprofen. The initial dose was 40 mg, this was followed by 360 mg. Within 1 hour of the final dose, the patient developed diffuse urticaria. He was treated with 20 mg of cetirizine with resolution of the urticaria within two and a half hours. No epinephrine was administered.

**Diagnosis, Treatment and Patient Outcomes:**

Based on his clinical history and investigations, the patient was diagnosed with allergy to corn, grass and ragweed pollens. The episode of anaphylaxis in the cornfield is thought to have been due to exposure to a high concentration of corn pollen, an aeroallergen. The exact mechanism of aeroallergen entrance is unclear since the patient was not aware of any cutaneous injuries. However, he may have inadvertently sustained abrasions that acted as portals of entry. He was prescribed epinephrine autoinjectors.

For his seasonal rhinoconjunctivitis with grass and ragweed sensitization, he was started on grass and ragweed subcutaneous immunotherapy. We hope to see some cross-reactivity with corn pollen since the two are related. We were not able to find reports of corn pollen subcutaneous immunotherapy.

Our patient’s second episode of systemic reaction was likely due to ibuprofen, based on the positive oral challenge. As well, the delay in symptom onset and weakly positive serum specific IgE for hazelnut makes this an unlikely culprit. He was advised to carry an epinephrine autoinjector and avoid ibuprofen, other NSAIDs, and hazelnuts (pending an oral challenge).
Case Title:
First case of anaphylaxis to Lepista Nuda mushroom

Summary and Lessons Learned:
Rationale: Although fungi are a well-known cause of respiratory allergy, IgE-mediated food allergy to mushroom is rare. We report the case of a 32-year-old man with seasonal allergic rhinitis and mild asthma who experienced weakness, diffuse pruritic rash, abdominal pain and vomiting immediately after the ingestion of wood blewit mushrooms (Lepista nuda).

Methods: Allergy skin prick tests (SPTs) were performed with 8 common molds and a commercial mushroom extract derived from Agaricus Campestris (Alk, Abello Pharm, Mississauga, Canada). SPTs were also performed to 7 different fresh mushroom species (including Lepista nuda) in both cooked and raw forms. Agaricus bisporus specific IgE (sIgE) were determined by UniCAP (f212, Phadia, Uppsala, Sweden). Commercial sIgE to other mushroom species were not available.

Results: Among molds tested, SPTs were slightly positive to Cladosporium, Aspergillus fumigatus and to mixed Aspergillus species. A negative SPT was obtained with the commercial mushroom extract. The SPTs to both raw and cooked Lepista nuda produced respectively a strongly positive 20 mm and 15 mm wheal, while all other species tested were negative. Four controls had negative SPTs to Lepista Nuda. The patient tolerated other mushrooms including White Button (Agaricus bisporus) and Shiitake (Lentinula edodes) mushrooms, and had a negative open food challenge to King Trumpet (Pleurotes Eryngii) mushroom. Agaricus bisporus sIgE were negative.

Conclusions: We believe that this is the first reported case of anaphylaxis to wood blewit mushroom (Lepista nuda). The patient was able to tolerate other mushrooms, suggesting no clinical cross-reactivity with other species.

Patient Presentation and Testing:
The patient is a 32 year-old Caucasian man referred to the allergy clinic of Notre-Dame Hospital for a suspected mushroom allergy. He was known for mild intermittent asthma and allergic rhinitis with positive skin tests to birch, ragweed, timothy, dust mites, cats, dogs, and horses. The patient had no other health problems other than a childhood penicillin allergy.

In June 2015, a few minutes after eating salmon with eggs and mushrooms at a restaurant (the patient could not recall the exact species), he developed abdominal pain and weakness, followed by multiple episodes of vomiting which lasted all night. He consulted a few days later with persistent abdominal pain and was treated with a proton pump inhibitor. Six months later, while eating pasta with wood blewit mushrooms (Lepista nuda), he immediately experienced weakness, abdominal pain, pharyngeal itching, diffuse pruritic rash as well as hand and feet edema. An hour later, he started vomiting. He was admitted at Sacré-Coeur hospital and was treated with prednisone and benadryl. He subsequently underwent upper GI endoscopy, and abdominal ultrasound, which were normal. Unfortunately tryptase was not dosed during this presentation.
SPTs were performed to a commercial extract of mushroom derived from Agaricus Campestris (Alk, Abello Pharm, Mississauga, Canada) as well as 7 different species of fresh mushrooms in both cooked and raw forms: Lepista nuda, Pleurotus eryngii, Cantharellus cibarius, Boletus edulis, Hydnum repandum, Grifola frondosa, Armillaria mellea. Agaricus bisporus specific IgE (sIgE) were determined by UniCAP (f212, Phadia, Uppsala, Sweden). Commercial sIgE to other mushroom species were not available.

Since cross-reaction between molds and mushrooms were previously reported, skin prick tests (SPTs) were also performed to extracts of Alternaria, Aspergillus fumigatus, Cladosporium, Panicillium, a mix of Aspergillus species, Candida, Mucor racemosus and Fusarium (Alk, Abello Pharm, Mississauga, Canada)

**Diagnosis, Treatment and Patient Outcomes:**

Among molds tested, skin prick tests (SPTs) were slightly positive to Cladosporium, Aspergillus fumigatus and to mixed Aspergillus species. A negative SPT was obtained with the commercial mushroom extract. The SPTs to both raw and cooked Lepista nuda produced respectively a strongly positive 20 mm and 15 mm wheal, while all other species tested were negative. Four controls had negative SPTs to raw Lepista Nuda. The patient tolerated other mushrooms including White Button (Agaricus bisporus) and Shiitake (Lentinula edodes) mushrooms, and had a negative open food challenge to King Trumpet (Pleurotus Eryngii) mushroom. Agaricus bisporus sIgE were negative. Basal tryptase level was normal. We believe that this is the first reported case of anaphylaxis to wood blewit mushroom (Lepista nuda). The patient was able to tolerate other mushrooms, suggesting no clinical cross-reactivity with other species. The patient was told to avoid Lepista nuda mushroom and provided with a portable epinephrine auto-injector.
Case Title:
Anaphylaxis due to Polyether Compounds in Medications and Oral Hygiene Products

Summary and Lessons Learned:
A 33-year-old female with a history of allergic rhinitis presented for evaluation of anaphylactic reactions to multiple medications and mouthwash. After an extensive workup to determine the specific cause of these seemingly unrelated anaphylactic reactions, it was hypothesized that the patient was reacting to one or more of the components common to methylprednisolone acetate (Depo-Medrol®), polyethylene glycol 3350 and the mouthwash (Crest® 3D White™). Sequential and incremental intradermal skin testing demonstrated immediate hypersensitivity to polyether compounds (polyethylene glycol 3350, polysorbate 80, and poloxamer 407). She was advised to assiduously read product labels in order to avoid further inadvertent exposure to these compounds and has not needed to use her epinephrine autoinjector since.

Polyether compounds are common ingredients used in a wide variety of oral hygiene products, cosmetics, and as solvents in liquid and capsule formulations of medications. As they are frequently present in multiple items, caution may be necessary as these may be an underrecognized precipitating factor in allergic reactions. Polyether compounds are often listed as either excipients or inactive ingredients making it very difficult for investigators to decipher the specific cause of a reaction, and for patients to avoid these substances once identified. This case exhibits the importance of obtaining a thorough history when approaching a patient with multiple episodes of anaphylaxis without a clear etiology, and specifically highlights the importance of considering additives and excipients as possible causes of severe, life-threatening allergic reactions.

Patient Presentation and Testing:
The patient is a 33-year-old female with a history of allergic rhinitis who presented for evaluation of multiple medication allergies. Five years prior she was treated for foot pain with an injection of bupivacaine and methylprednisolone. She developed immediate onset of swelling, nausea, emesis, hypotension, and blurry vision. She was treated for anaphylaxis at an outside hospital and was instructed to avoid both medications in the future.

One year prior, after taking polyethylene glycol 3350 in preparation for a colonoscopy, she developed immediate-onset hives, facial swelling, sneezing and difficulty swallowing. One week later she took a dose of bisacodyl and developed an urticarial rash and facial swelling.

The patient was advised to avoid laxatives. While waiting for confirmatory testing, she contacted the office with complaints of a similar reaction following use of a mouthwash.

Initial work up consisted of testing for bupivacaine, and methylprednisolone while strategies were developed to test for polyethylene glycol, bisacodyl and mouth wash components. Allergy skin testing to various anesthetics, including bupivacaine, was negative. Allergy skin testing to various corticosteroids including triamcinolone, dexamethasone, methylprednisolone sodium succinate solution, and methylprednisolone acetate were carried out and findings were significant for a strongly positive result only to methylprednisolone acetate. Due to the strong positivity to methylprednisolone acetate skin testing but negative testing to methylprednisolone sodium succinate solution, it was concluded that patient was likely reacting to one or more of the excipient components in methylprednisolone acetate. These consisted of polyethylene glycol 3350, polysorbate 80, and benzyl alcohol. Reviews of the ingredients of the mouthwash she reacted to indicated that it contained poloxamer 407. The latter compound is composed of two
polyethylene glycol blocks. Polyethylene glycol 3350 and bisacodyl both contain the ingredient polyethylene glycol. An intradermal test was performed with polyethylene glycol 3350, polysorbate 80, poloxamer 407, and benzyl alcohol. Maximum non-irritant concentrations were obtained for polyethylene glycol 3350, polysorbate 80, poloxamer 407, and benzyl alcohol from the literature and validated on healthy controls. After obtaining informed consent, we performed sequential and incremental intradermal skin testing with these compounds. A positive reaction was defined as a wheal measuring greater than 5 mm in diameter. Testing showed the following results (expressed as wheal/flare in millimeters): Polyethylene glycol -7/21, polysorbate 80 -7/11, poloxamer 407-13/37, benzyl alcohol -0/0. The histamine and saline controls were 11/50 and 0/0, respectively.

Diagnosis, Treatment and Patient Outcomes:
The patient was diagnosed with anaphylaxis to polyether compounds, which was confirmed with positive intradermal testing to polyethylene glycol 3350, polysorbate 80, and poloxamer 407. Although previous studies have shown IgE-mediated hypersensitivity to occur with polyethylene glycol, hypersensitivity to a broad range of polyether compounds has not been previously reported. Further research, using the testing protocols identified herein, is needed to determine the extent of cross reactivity between polyether compounds. These results emphasize the importance of physician awareness of the potential for polyether compounds to cause immediate hypersensitivity reactions, including severe reactions such as anaphylaxis. This is especially important because these compounds are frequently listed as inactive ingredients and are, therefore, more difficult to identify as constituents of medications and hygiene products. Patients with this diagnosis need to be counseled on the importance of carrying an epinephrine autoinjector at all times and to practice meticulous label reading.
Submission Number: 189
Poster Number: 14
Keyword: Anaphylaxis

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Case Title:
Protracted Anaphylaxis – an Occupational Hazard?

Summary and Lessons Learned:
Laboratory animal allergy (LAA) is an occupational hazard for individuals working in research settings. Up to 44% of workers have reported a LAA; typically, workers become sensitized to rodent allergens and experience occupational rhinoconjunctivitis, asthma and/or contact urticaria. Here, we describe a case of protracted anaphylaxis to murine blood after an accidental needle stick. The patient did not receive epinephrine until almost 30 minutes after the incident, ultimately requiring multiple doses of epinephrine injection for protracted anaphylaxis.

This case emphasizes two important lessons in anaphylaxis. First, it is important to recognize occupational risk scenarios for anaphylaxis. Secondly, in such scenarios, it is essential to be prepared to treat accidental anaphylaxis expeditiously with epinephrine. A recent survey of animal care laboratories found that 8% of facilities reported at least one episode of anaphylaxis to a rodent bite, suggesting these reactions are not uncommon. (Stave et. al.) Given the high rate of allergic sensitization to mammalian proteins in animal workers, it is imperative that these workers recognize the potential risk of anaphylaxis from systemic exposure to animal allergens via a bite or needle stick. Laboratory animal workers should be counseled on potential risks of developing LAA, advised on proper needle handling, and educated on recognition of symptoms of anaphylaxis. An epinephrine autoinjector should be prescribed to animal handlers with LAA symptoms. Although anaphylaxis to lab animal allergens is a rare event, research institutions should consider implementing action plans for treating such reactions with epinephrine within the first 10 minutes after onset.


Patient Presentation and Testing:
A 31-year-old female worked in a laboratory with mice for 10 years. Initially, she developed pruritus and swelling with direct skin contact as well as dyspnea when cleaning cages. Symptoms resolved after she was moved to other duties. On the day of the incident, she was drawing mouse blood when her hand was accidentally pierced by an uncapped needle of syringe containing mouse blood; the needle went through her hand. Immediately, her fingers swelled followed by diffuse pruritus, periorbital edema and dyspnea. An initial dose of epinephrine was given more than 25 minutes after the needle stick. She was transferred to the emergency room where she presented with a blood pressure of 81/51 and wheezing. She was given intravenous fluids (IVF), albuterol and diphenhydramine with improvement in BP to 101/45 and resolution of wheezing. Three hours later, she developed dyspnea, emesis, fatigue and hives on the back so was given a second dose of epinephrine as well as famotidine, promethazine, prednisone and IVF with amelioration of all symptoms except hives. During the night, she had persistent hives and wheezing and received a third dose of Epinephrine 0.3mg intramuscularly and diphenhydramine. She was admitted and observed for 24 hours without further symptoms and discharged home. At follow-up, mouse epithelium serum specific IgE was 23.20 kU/L (normal < 0.10 kU/L).

Diagnosis, Treatment and Patient Outcomes:
Patient recovered from the anaphylaxis episode after 3 doses of epinephrine were given. We suspect the course was protracted due to delayed administration of the initial epinephrine dose. Shortly after discharge, she followed up with the Allergy/Immunology clinic where mice avoidance was further discussed. However, changing employment was not a feasible option, therefore, it was recommended that she work in different capacity without handling murine blood. She was given an epinephrine autoinjector with instructions on carrying the epinephrine injector at work and educated on recognizing anaphylaxis.
Submission Number: 197  
Poster Number: 15  
Keyword: Anaphylaxis

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Case Title:  
Anaphylaxis following recurring exposure to cold water

Summary and Lessons Learned:  
Known history of cold induced urticaria. Recurring exposure for 30 minutes to cold water while swimming in a lake, whenever the urticaria sets in, the patient would come out of the lake and warm up. Eventually, he collapsed and had systemic reaction following recurring cold exposures. 
Patients with cold urticaria need to be cautioned about recurring exposure to cold within close temporal intervals as this could precipitate anaphylactic symptoms.

Patient Presentation and Testing:  
24 year old male who lives in Ontario Canada has history of recurrent hives when he goes outside in the cold during the winter months for the past few winters. 
However, on Canada day, July 1st, he was at a lake swimming and the water was cold and he kept going in and out because he was breaking out with hives within 1-2 minutes of exposure to the cold water so he would come out to warm up, when he feels better in 5 minutes he will jump back into the cold water. After 30 minutes of recurring exposure to cold water and recurring hives, he felt dizzy and nauseous and he lost consciousness for a brief period of time. He was hypotensive and that he needed oxygen treatment. He regained consciousness without epinephrine and was treated with oral diphenhydramine.

Diagnosis, Treatment and Patient Outcomes:  
In the allergy clinic he had a positive ice cube test. He was counseled about cold induced urticaria and the risk of anaphylaxis. He was prescribed an Epinephrine autoinjector and underwent teaching of when and how to use it.
Case Title:
Early Use of Omalizumab in Idiopathic Anaphylaxis

Summary and Lessons Learned:
Our patient is a 49 year old woman with a past medical history of asthma who was referred for evaluation of multiple anaphylactic episodes, of unknown etiology. She initially described developing urticaria and angioedema with no identifiable trigger, which responded to diphenhydramine. In the year prior to evaluation her symptoms progressed, and she developed episodes of hypotension, syncope and respiratory distress, requiring multiple doses of subcutaneous epinephrine. Given the severity of her reactions, she was started immediately on omalizumab, and had no further reactions. Idiopathic anaphylaxis can lead to severe, sometimes fatal reactions, and early recognition is imperative to treatment. We describe a case of severe recurrent idiopathic anaphylaxis that responded to omalizumab, and should be considered as initial therapy, especially in severe reactions or as a steroid sparing agent.

Patient Presentation and Testing:
We describe a 49 year old female, with mild persistent asthma and no history of venom hypersensitivity, who presented for initial evaluation of recurrent anaphylaxis. Her family history was unremarkable with no reported angioedema or anaphylaxis. She described approximately 12 episodes over the past two years; initially she developed urticaria and angioedema which responded to diphenhydramine. In the year prior to our evaluation, her reactions became more severe including one episode in which she developed laryngoedema and hypotension requiring intramuscular (I.M.) epinephrine. In her most recent episode she had a syncopal event, was hypotensive, and had respiratory distress. She was evaluated and treated in an emergency room, requiring 3 doses of I.M. epinephrine. A serum tryptase was measured, and found to be elevated at 22.6 ug/L (normal 2.2-13.2 ug/L). At the time of our evaluation, patient was quite distressed and anxious. She reported that her quality of life was negatively impacted by her fear of having another reaction. A thorough history didn’t reveal any identifiable triggers to her reactions, such as foods or medications. A baseline serum tryptase was obtained, and was found to be normal (3.7 ug/L).

Diagnosis, Treatment and Patient Outcomes:
The finding of elevated tryptase during an episode, with normalization during asymptomatic periods was highly suggestive of an anaphylactic episode. She was initially started on high doses of antihistamines, including cetirizine 10mg and ranitidine 150 mg both twice a day. Given the severity of her reactions we discussed the risks and benefits of prednisone, a potential treatment option for idiopathic anaphylaxis; however, she did not want to initiate therapy with prednisone due to long term side effects. Although, no randomized control trials have been done with omalizumab as treatment for idiopathic anaphylaxis, case reports have demonstrated resolution of symptoms in severe or refractory cases. Treatment with omalizumab was discussed with the patient, and she was initiated on monthly injections. She has had no further anaphylactic episodes, since starting omalizumab eleven months ago. Furthermore, she has noted significant improvement in her quality of life. Omalizumab is usually reserved for refractory cases but our case report suggests that earlier initiation leads to rapid symptom resolution and quality of life. Furthermore, it can be used as a steroid sparing agent in those with risk factors.
Submission Number: 211
Poster Number: 17
Keyword: Anaphylaxis

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Case Title:
Anaphylaxis to Fresh Coconut

Summary and Lessons Learned:
Allergy to coconut (Coccus Nuefiera) is rare and not well understood. Here we present a case of an allergic reaction to coconut milk and subsequent anaphylactic reaction during the oral food challenge to fresh coconut but not sweetened coconut flakes. Physicians should be aware that tolerance of sweetened coconut flakes, a common ingredient in desserts, does not imply global coconut tolerance.

Patient Presentation and Testing:
This is an 18-year-old woman with a history of multiple tree nut allergies, asthma, and contact dermatitis who was believed to be coconut tolerant based on tolerance of sweetened coconut flakes but developed anaphylaxis with coconut milk and fresh coconut.

She presented for evaluation of an allergic reaction (immediate onset oral pruritus and bronchospasm) to “bubble tea” which amongst other ingredients contained coconut milk. She was believed to be coconut tolerant based on her ability to eat sweetened coconut flakes. She does not have pollen allergies. Serum coconut specific IgE was 1.14 KU/L. She underwent serial oral food challenges with fresh coconut meat, desiccated coconut, sweetened coconut flakes. During the oral challenge to fresh coconut she developed mild oropharyngeal pruritus with 5 g of coconut. At a cumulative dose of 10g she developed abdominal discomfort, nausea and bronchospasm with peak flow decreasing from 350 L/min pre-challenge to 250 L/min. Symptoms resolved with Epinephrine.

Subsequently, a challenge was performed using sweetened coconut flakes, which she tolerated without symptoms (cumulative dose 2 servings, 30g). Similar appearing unsweetened desiccated coconut (pure desiccated coconut) also caused symptoms upon challenge.

Diagnosis, Treatment and Patient Outcomes:
Here we report an IgE mediated anaphylaxis to fresh coconut but tolerance to sweetened coconut flakes. Sweetened coconut flakes contain desiccated coconut processed with sugar, propylene glycol and preservatives. Antigens responsible for anaphylaxis in this patient appear to be susceptible to processing. Given tolerance and negative oral food challenge to sweetened coconut flakes, this patient was advised to continue to eat sweetened coconut flakes but to avoid fresh and desiccated coconut with a prescription for an EpiPen.
Case Title: A Case Report of Anaphylaxis in a Patient Being Evaluated for a Corneal Abrasion.

Summary and Lessons Learned:
Anaphylaxis as defined by the World Health Organization is a severe life threatening generalized or systemic hypersensitivity reaction with sudden onset. The prevalence of anaphylaxis is best estimated at about 2%. Urticaria and angioedema are the most common presenting symptom but lack of cutaneous symptoms has been noted in a series of fatal reactions.

The patient presented to our clinic for eye redness after getting hit with a soft ball to the face. He had no loss of consciousness, vomiting or changes in mental status. He denied changes in vision or eye pain initially. He was not given medications prior to arrival. His eye then became red with pain and photophobia. On presentation he was noted to have left eye conjunctivitis with a subconjunctival hemorrhage. His vital signs were stable. His neurological exam was unremarkable as was the rest of the exam. He was administered two tetracaine and two fluorescein eye drops in order to examine for a corneal abrasion. No corneal abrasion was noted and discharge paperwork was being reviewed. Within fifteen minutes the child vomited twice and became pale. No noted headache, shortness of breath, wheezing, oral swelling, or rash. His heart rate remained stable, but his blood pressure had decreased. He also stated he felt anxious. The rest of his vital signs remained stable. He was promptly administered epinephrine. His color returned, anxiousness resolved, and vital signs returned to normal within ten minutes. He was then given prednisone, diphenhydramine, and ondansetron. He was monitored after injection of epinephrine. No further complications were noted. He was discharged from our care. No further issues noted on follow up call the next day. His parents were told to avoid fluorescein and tetracaine eye drops for the child.

Our patient experienced anaphylaxis to either tetracaine or fluorescein eye drops under our care. A patient having anaphylaxis to fluorescein eye drops has been reported. Severe allergic reactions to local anesthetics are also rare. Prompt recognition allowed for safe resolution of symptoms without further intervention. In any medical setting, early diagnosis of anaphylaxis is critical. If there is concern for anaphylaxis, even if in doubt, it is generally safe to administer a dose of epinephrine.

Patient Presentation and Testing:
This is a case report of a 10-year-old child seen for an eye injury in the urgent care clinic to a university-affiliated children’s hospital.

Presentation: The patient presented to our clinic for eye redness after getting hit with a soft ball to the face. He had no loss of consciousness, vomiting or changes in mental status. He denied changes in vision or eye pain initially. He was not given medications prior to arrival. His eye then became red with some irritation and photophobia. On presentation he was noted to have left eye conjunctivitis with a subconjunctival hemorrhage. His vital signs were stable. His neurological exam was unremarkable as was the rest of the exam. He was administered two tetracaine and two fluorescein eye drops in order to examine for a corneal abrasion or foreign body in the eye given the photophobia and pain. This would have changed management of the patient. No corneal abrasion or foreign body was noted and discharge paperwork was being reviewed. Within fifteen minutes the child vomited twice and became pale. He denied a headache or trouble breathing. On exam there was no shortness of breath, wheezing, oral swelling, or rash. His heart rate remained stable at about 80 bpm, but his systolic and diastolic blood pressure decreased by 20 mm Hg on recheck. He also stated he felt anxious. The rest of his vital signs remained stable, including respiratory rate, and oxygen saturation. He was moved to an observation room via bed, put on cardiopulmonary monitoring, and had an IV placed.
**Diagnosis, Treatment and Patient Outcomes:**

He was promptly administered epinephrine 0.3 mg intramuscularly. Having suffered an acute head injury, an intracranial bleed was on the differential but was less likely at this time given the lack of neurological findings such as a headache. Given the lack of cutaneous symptoms, other diagnosis were considered, but the risk of withholding epinephrine was greater than administering it while other diagnosis were entertained. In anaphylaxis earlier symptom presentation is thought to correlate with more severe reactions. His color returned, anxiousness resolved, and vital signs returned to normal within ten minutes. He was then given prednisone, diphenhydramine, and ondansetron. He was monitored after injection of epinephrine for a period of about 8 hours. No further complications were noted. He was discharged from our care. No further issues noted on follow up call the next day. His parents were told to avoid fluorescein and tetracaine eye drops for the child.
Summary and Lessons Learned:
Introduction: Soy Allergies are typically found during childhood and are often transient. Newly diagnosed cases of soy allergies in adulthood are rare and are occasionally misdiagnosed. We present a case of anaphylaxis to soy milk in a patient not allergic to soy.
Methods: Case report
Results: A 65 year-old female with a history of seasonal allergic rhinitis developed generalized hives, severe itching, wheezing, dry cough and difficulty breathing several minutes after consuming her breakfast, which included coffee, pancakes, chocolate pudding and soy milk. The anaphylactic reaction resulted in hospitalization, and she was referred for allergy evaluation. Our evaluation revealed positive skin testing to pollen, dust mite, roach, mouse, rat, peanut, and hazelnut but not to soy or wheat. Laboratory evaluation found low allergen-specific Immunoglobulin E (ssIgE) to a number of food allergens such as peanut, sesame seed and hazelnut but not to soy, coffee or wheat. However, fresh food testing on the patient with Silk Vanilla soy milk was highly positive but was negative when performed on a non-allergic control subject. Fresh food testing on the patient with boiled soybeans was negative. We performed open oral challenges with both fresh soybeans and the soy milk. She experienced no adverse events consuming the fresh soybeans however, within minutes after ingesting one drop of the soy milk, she developed urticaria, sneezing, itchy nose and oral pruritus. To further determine the responsible allergen, the list of ingredients was review, which included: vitamins and minerals, sea salt, natural flavor, soybean, vanilla extract and gellan gum. Since the patient consumes soybeans and vanilla without any reaction we evaluated her for gellan gum allergy: both fresh food testing and an open oral challenge with gellan gum were negative. The patient experienced a true anaphylaxis after ingesting the soy milk documented with a subsequent open oral challenge but did not experience similar reactions to fresh soybeans or the other ingredients. The allergens responsible for her reaction can possibly include the unknown flavors or contamination of the soy milk during processing.
Conclusion: Anaphylaxis to soy milk in some cases can be attributed to hidden ingredients or methods of processing packaged foods. Thorough allergy evaluation is necessary in cases of anaphylaxis to processed foods in order to determine the responsible allergen, avoid mislabeling an allergy and to provide proper clinical care.

Patient Presentation and Testing:
A 65 year-old female with a history of seasonal allergic rhinitis developed generalized hives, severe itching, wheezing, dry cough and difficulty breathing several minutes after consuming her breakfast, which included coffee, pancakes, chocolate pudding and soy milk. The anaphylactic reaction resulted in hospitalization, and she was referred for allergy evaluation. Our evaluation revealed positive skin testing to pollen, dust mite, roach, mouse, rat, peanut, and hazelnut but not to soy or wheat. Laboratory evaluation found low allergen-specific Immunoglobulin E (ssIgE) to a number of food allergens such as peanut, sesame seed and hazelnut but not to soy, coffee or wheat. However, fresh food testing on the patient with Silk Vanilla soy milk was highly positive but was negative when performed on a non-allergic control subject. Fresh food testing on the patient with boiled soybeans was negative. We performed open oral challenges with both fresh soybeans and the soy milk. She experienced no adverse events consuming the fresh soybeans however, within minutes after ingesting one drop of the soy milk, she developed urticaria, sneezing, itchy nose and oral pruritus. To further determine the responsible allergen, the list of ingredients was review, which included: vitamins and minerals, sea salt, natural flavor, soybean, vanilla extract and gellan gum. Since the patient consumes soybeans and vanilla
without any reaction we evaluated her for gellan gum allergy: both fresh food testing and an open oral challenge with gellan gum were negative.

**Diagnosis, Treatment and Patient Outcomes:**
The patient experienced a true anaphylaxis after ingesting the soy milk documented with a subsequent open oral challenge but did not experience similar reactions to fresh soybeans or the other ingredients. The allergens responsible for her reaction can possibly include the unknown flavors or contamination of the soy milk during processing.
Summary and Lessons Learned:
A 29 year old female with a past medical history of asthma, allergic rhinitis, oral allergy syndrome, and prior aeroallergen immunotherapy presented to the allergy clinic after an episode of anaphylaxis. Immediately prior to the reaction she had consumed prepackaged beignet mix as well as coffee with chicory root, items she had brought home after a trip to New Orleans, LA. Due to her history of oral allergy syndrome, anaphylaxis to chicory was considered due to its cross-reactivity with birch, but testing to birch pollen and the chicory coffee were negative. She had tolerated the individual components of the beignet mix such as wheat and milk since the episode without a reaction, so a contaminant such as dust mite or cockroach was suspected. Skin testing was positive to the beignet mix and to dust mites. Microscopy was then performed and confirmed the presence of large quantities of dust mites in the prepackaged beignet mix. Her anaphylaxis was attributed to ingestion of dust mites in contaminated, prepackaged baked goods. She was counseled to avoid prepackaged baking products and her case was reported to the FDA for a food safety investigation. It is important to consider contaminants in prepackaged foods as a cause of anaphylaxis in patients with a history of environmental allergies, particularly when the patient is tolerating the listed ingredients individually. Cases of food contamination should be reported to the FDA to protect other patients from similar reactions.

Patient Presentation and Testing:
The patient was a 29 year old female with a past medical history of mild persistent asthma, allergic rhinitis, oral allergy syndrome, and prior aeroallergen immunotherapy with incomplete resolution of symptoms who presented to the allergy clinic after an episode of anaphylaxis.
The patient reported that she had recently traveled to New Orleans, LA, and brought home containers of coffee with chicory root and instant beignet mix, a type of pastry that contains wheat, barley, milk, and yeast. Twenty minutes after consuming these at home for the first time, she developed nausea and vomiting, followed by wheezing, hives, angioedema, and sore throat. She went to the emergency room where she was treated for anaphylaxis successfully with epinephrine and diphenhydramine.
At the time of the allergy evaluation, the patient reported that she had eaten wheat, milk, barley, yeast, and coffee in other forms since the reaction without incident, but had avoided chicory, which was not a usual part of her diet. Due to her history of oral allergy syndrome with cherries and apples, I was suspicious for a severe oral allergy syndrome reaction to chicory, which has reported cross-reactivity with birch pollen. I also considered that she could have been reacting to a contaminant in the mix, such as dust mite or cockroach allergen, rather than the mix itself. Skin prick testing was performed to food cross-reactive pollens, dust mites, cockroach, mouse, directly to the coffee with chicory and directly to the beignet mix.

Diagnosis, Treatment and Patient Outcomes:
Despite having symptoms consistent with oral allergy syndrome, the patient had negative birch skin testing, likely due to her prior history of allergy shots. She also had negative testing to the coffee with chicory, ruling this out as the trigger.
She had a large wheal and flare reaction to D. pteronyssinus and D. farinae, and was also positive to the beignet mix with a wheat and flare noted to be about half the size of the recorded dust mite reactions. The cockroach and mouse tests were mildly positive but notably smaller than the wheat and flare triggered by the beignet mix. These results were felt to be consistent with an anaphylactic reaction to dust mite contamination in the beignet mix. I then examined the beignet mix under 10x light microscopy and found copious evidence of dust mite contamination including live mites, dead mites in various stages of degradation, and fecal matter (photos and video obtained).
Due to the severity of the patient’s reaction and the risk such a contamination would pose to others with this allergy, her case was reported to the FDA with her permission and the boxed goods are currently under investigation. The
patient was advised that this is rare but possible risk when consuming prepackaged products. Because it is difficult to predict which of these products is contaminated, and it has been reported in a wide range of baking mixes, she was advised to avoid prepackaged baked goods and recommended to carry an epinephrine autoinjector. She has not had additional episodes since this incident.
Case Title:
ATOPIC DERMATITIS WITH ANAPHYLAXIS CAUSED BY CORN

Summary and Lessons Learned:
Food allergies may trigger atopic dermatitis in 30% of cases, but this occurs infrequently for corn allergies. The aim of this case report was to describe the clinical and diagnostic features of a patient admitted to the outpatient clinic in Brazil with atopic dermatitis who developed anaphylaxis.

Patient Presentation and Testing:
A 2-year-old girl born in Ribeirão Preto, Brazil, was referred to the allergy outpatient clinic for cutaneous xerosis and erythematous and pruriginous micropapules in the flexural regions that began 1 year earlier. She had concurrent nasal itching and improvement of the atopic dermatitis. A skin-prick test performed for inhalant allergens was positive for dust mites.

Diagnosis, Treatment and Patient Outcomes:
She was diagnosed with atopic dermatitis and allergic rhinitis. Treatment with topical corticosteroids, antihistamines, and skin hydration resulted in a partial response and relapses with secondary infections. At 3 years of age, she presented with anaphylaxis after inhaling steam from cooking corn but improved after appropriate treatment. Subsequently, it was discovered that her grandmother frequently fed her industrialized corn-based salted snacks. Exclusion of corn and its derivatives was recommended. Reevaluation 2 months later showed gradual. The patient is currently 10 years old and remains in complete remission of atopic dermatitis, presenting only symptoms of allergic rhinitis. Treatment with nasal topical corticosteroids was reinstated and corn exclusion was continued.

Conclusion: To manage atopic dermatitis, in addition to the usual treatment, it would be ideal to identify and exclude the causal factor. This may change the history of the disease and avoid serious clinical presentations such as anaphylaxis.
Summary and Lessons Learned:
Introduction: Exercise-induced bronchoconstriction (EIB) is manifested by the acute onset of bronchoconstriction during or shortly after exercise. The term is often confused with exercise-induced asthma, as poorly controlled asthma can be triggered by exercise. The underlying mechanism of exercise-induced bronchoconstriction is different from asthma in that air surface liquid osmolarity changes due to cold air and hyperventilation cause mediators to be released from the airway epithelial cells which subsequently act as the primary stimulus for airway bronchoconstriction.

Case: 33 year-old female Veteran presented with shortness of breath, chest tightness and cough triggered by cardiovascular exercise such as running, particularly in the setting of physical training. Her spirometry showed normal airflow with moderate restriction and normal diffusion capacity. ImmunoCap testing was positive for grasses (Timothy, Johnson, Bermuda and Bahia). She was previously instructed to use Fluticasone/Salmeterol 500/50 1 puff twice daily and to use albuterol as needed. Since she had significant history of bronchoconstriction with exercise, she was recommended to warm up and use albuterol 15-20 minutes before exercise. Since her spirometry was normal, methacholine challenge test was performed. Her PD(20)MCH was >32 mg/ml which indicates normal airway reactivity to methacholine. Exercise challenge testing was performed to assess for exercise-induced bronchoconstriction. There was an 18% drop in FEV1 during the first five minutes of the exercise challenge, ie, positive exercise challenge.

Conclusion: EIB can occur in both presence or absence of asthma. It is more prevalent in athletes. Management includes short-acting beta-2 agonists and warming-up 15-30 minutes before exercise. For patients who are not responsive to SABA, long-acting beta agonists with inhaled corticosteroids can be used for inflammation. Combination therapy that includes a LABA should not be used in normal or near-normal baseline lung function (ie, FEV1 >80% of predicted value) because regular use of SABA and LABAs can cause tolerance, reduce bronchoprotection and bronchodilation. We recommended that our patient stop taking Fluticasone/Salmeterol and use SABA and warming-up techniques before exercise. A diagnosis of EIB should be confirmed by demonstration of airways obstruction and reversibility with standardized exercise challenge testing in association with a history consistent with EIB. Self-reported symptoms are not adequate and it could lead to underdiagnosis.

Diagnosis, Treatment and Patient Outcomes:
At the time of initial encounter, patient presented with chief complaint of shortness of breath, tightness of chest and cough which were triggered by cardiovascular exercise such as running especially in physical training. She is a Veteran female who has to do physical training four to five times a week.Her history sounded like bronchoconstriction induced by exercise.She was using Fluticasone/Salmeterol 500/50 1 puff twice daily and albuterol puffs as needed. Spirometry was performed to check her lung function which showed normal airflow with moderate restriction and normal diffusion capacity. Methacholine challenge test was performed to exclude a diagnosis of asthma which indicates normal airway reactivity to methacholine. As the next step, exercise challenge testing was performed to assess for exercise-induced bronchoconstriction. There was an 18% drop in FEV1 during the first five minutes of the exercise challenge, ie, positive exercise challenge.
Exercised-induced bronchoconstriction was diagnosed. Management includes short-acting beta-2 agonists and warming-up 15-30 minutes before exercise. For patients who are not responsive to SABA, long-acting beta agonists with inhaled corticosteroids can be used for inflammation. However, regular use of SABA and LABA can cause tolerance, reduce bronchoprotection and bronchodilation. LABA should not be used in normal or near-normal lung function. We recommended that our patient stop taking Fluticasone/Salmeterol and use short-acting beta-2 agonists and warming up 15-20 minutes before exercise. A diagnosis of EIB should be confirmed by demonstration of airways obstruction and reversibility with standardized exercise challenge testing in association with a history consistent with EIB. Self-reported symptoms are not adequate and it could lead to underdiagnosis.
Case Title:
Development of polymyalgia rheumatic during omalizumab treatment in a patient with severe asthma

Summary and Lessons Learned:
Asthma is a common chronic respiratory disorder characterized by allergic airway inflammation, which is primarily a Th2-weighted process. Omalizumab is a recombinant humanized anti-IgE monoclonal antibody which blocks the binding of IgE to its high affinity receptors, known to strongly suppress Th2-related inflammation. Omalizumab also significantly improves disease control, with a pronounced reduction in the rate of asthma-related emergency medical consultations, an important benefit for patients with moderate-to-severe uncontrolled allergic asthma. However, the potential side effects of this medication have not been well described to date.

From March 2009—when omalizumab was introduced in Japan—to December 2016, a total of 241 patients with severe asthma have been treated with this medication in the Allergy and Respiratory Department of Sagamihara National Hospital (Kanagawa, Japan). The median duration of the treatment was 13 months (interquartile range, 5–37 months). During this period, we observed the development of a Th1-related disease, polymyalgia rheumatica (PMR), in a patient with severe asthma.

Asthma co-morbid PMR cases, which are characterized by a predominant Th1 immune response, are rare. Our case suggests the possibility that omalizumab might suppress Th2-related immune response and promote Th1-related immune response. However, the development of the disease after omalizumab administration might have also been a temporal coincidence.

Although omalizumab is an important medication in the treatment of severe asthma, physicians should pay attention to the development of Th1-related diseases in patients treated with this drug.

Patient Presentation and Testing:
A 51-year-old Japanese woman, with asthma onset when she was 4 years old, received fluticasone/formoterol, montelukast and theophylline with salbutamol, as needed. Her medical history included asthma, chronic rhinosinusitis, and appendicitis. Her mother and two siblings had allergic rhinitis, but no family members had Th1-related diseases. Although she was fully adherent to the treatment, her symptoms remained uncontrolled. Omalizumab was initiated in February 2012 (IgE level of 92.2 IU/mL [normal range 0–173 IU/mL]). In March 2016, she described a morning stiffness in the shoulders, hip and neck girdle over a period of an hour. We suspected musculoskeletal diseases. The X-ray imaging was normal, leukocytes count was 10,330/μL (reference range: 3,500–8,500), erythrocyte sedimentation rate was 57 mm/h (reference range: 3–15), and serum C-reactive protein was 2.78 mg/dL (reference range: 0–0.4). Conversely, anticitrullinated protein antibody (0.5 U/mL, reference range: 0–4.4) and rheumatoid factor (8 IU/mL, reference range: 0–14) levels were within normal range.

Diagnosis, Treatment and Patient Outcomes:
According to the classification criteria of the European League Against Rheumatism (EULAR)/ American College of Rheumatology (ACR), the woman was diagnosed with PMR. In May 2016, omalizumab was stopped because of potential drug-induced adverse effects, and symptoms were rapidly controlled after two days of treatment with
prednisolone (15 mg/day). Twelve months later, as the inflammatory symptoms improved, prednisolone was gradually tapered.
Case Title:
A Conservative Home Aspirin Desensitization Protocol for patients with refractory nasal polyposis and AERD

Summary and Lessons Learned:
Aspirin exacerbated respiratory disease (AERD) is a clinical phenotype that affects 7% of asthmatics and up to twice that number in severe asthmatics. Included in this phenotype are patients with pansinusitis with recurrent nasal polyposis. Since it was first introduced in 1980 desensitizing with aspirin is an effective treatment for either nasal polyposis or asthma. Historically, these have been performed in intensive care units and/or outpatient clinics pending on an individual’s risk. Here, we present a home desensitization protocol on a patient who previously failed desensitization in a medical short-stay unit.

Patient Presentation and Testing:
43 year old Nepalese man who was referred by his otolaryngologist in 2014 for management of recurrent nasal polyposis and poorly controlled asthma. He had undergone functional endoscopic sinus surgery (FESS) in 2010, 2012 and 2014 for his nasal disease. He required frequent ER visits for his asthma. Reproducibly, aspirin led to severe rhinorrhea, congestion and shortness of breath. His maintenance treatment was intranasal fluticasone, inhaled budesonide/fortmoterol, and oral montelukast. He was scheduled for a 1-day aspirin desensitization protocol in a medical short stay setting. He developed congestion, sneezing and a decrease in peak flow after consuming 81mg and the desensitization was stopped. He returned 1 month later to complete a 2–day desensitization protocol successfully. Subsequently, the patient did very well on Aspirin 325 mg twice daily for over 1.5 years. Unexpectedly, he was unable to refill his medications and did not take aspirin for 3 days, and subsequently developed significant upper and lower respiratory symptoms which included congestion, rhinorrhea, cough and wheeze. At this point given his successful prior desensitization we recommended a home protocol, which included: restarting all his maintenance medications and commencement of a 2-week course of prednisone 20mg; after 2 days of prednisone he was to start a 7-day aspirin desensitization protocol. On day 1: 40 mg, day 2: 81 mg, day 3: 162 mg, day 4: 243 mg, day 5: 325mg, day 6: 325mg, day 7: 325 mg twice daily. He successfully completed reintroduction of aspirin and has remained symptom free.

Diagnosis, Treatment and Patient Outcomes:
Here we present a case of a patient with classic AERD with refractory nasal polyposis and poorly controlled asthma, who completed a 7-day home aspirin desensitization protocol. This conservative approach may be considered for patients who have previously completed a monitored aspirin desensitization protocol with more severe symptoms and need reintroduction of aspirin due to missed dosages.
Case Title:
Key Barriers for Asthma Care in School Aged Children

Summary and Lessons Learned:
St Louis Children’s Hospital provides a mobile health unit, Healthy Kids Express Asthma (HKEA), to ensure underserved children in the surrounding area receive free specialty care. The program is delivered in surrounding schools based on healthcare usage and socioeconomic need. For the school year 2015-16 HKE partnered with 14 schools in the St Louis Metropolitan area. Children are examined while at school without care givers present on the mobile health unit by a Pediatric Nurse Practitioner with expertise in asthma management. The PNPs collaborated with Washington University Pulmonary/Allergy physicians to develop the program and meets regularly to evaluate outcomes. An IRB approved database is utilized to collect data for evaluation purposes.

A wide range of children are cared for by HKEA. Social and economic barriers are not easily measured with current methods. A further review of data on a group of 2-3 children randomly selected from each school was completed. Charts were reviewed for 29 children with 140 visits included 45% male, 97% Black, and with 86% Medicaid, 10% private, and 3% other insurance. Ages ranged from 6 to 14 years old with 17% Intermittent, 27% Mild Persistent, and 24% Severe Persistent. Based on recent history 34% were considered lower risk and 65% considered high risk. Obesity was noted in 21% and allergies were reported in 46% of the children. The average number of visits in this group was 4.83 during the school year. This included visits on the van and phone calls with care givers . 20% of the visits with HKEA children had active symptoms requiring albuterol and 6% requiring oral steroids.

Patient Presentation and Testing:
School aged children with the diagnoses of asthma were enrolled in the Healthy Kids Express Asthma program. Each child is seen without parents in order to decrease the barriers to the care givers. Spirometry is preformed as able while on the mobile unit. Investigation into each child’s medication history is done with the state database or calls to pharmacies. Phone calls to the Primary Care Provider is done to help coordinate the care. A treatment plan is developed by including the care givers input. This is done to increase the likelihood of adherence. Children are given extensive education as they are often responsible for their own care at home.

Diagnosis, Treatment and Patient Outcomes:
Socioeconomic disparities need to be considered when caring for school aged children with asthma. HKEA found at 43% of visits the children where adherent to the plan, partial adherence was noted in 50% and non-adherence noted in 39% of visits. Poor refill history was found in 44%, while 9% never picked up the prescribed medications. Interactions with the child while on the van without their care givers gave a unique opportunity to assess the reasons behind this. Medicine confusion was apparent in 24% of the visits and 24% had no medicine at home even after a visit on the van. While 41% noted no barriers, 28% were noted to have none or poor parental supervision with taking their medicine correctly. Encouraging increased supervision by care givers could be beneficial with possible improved asthma control.
Case Title: Cough and Wheeze Masquerading as Asthma

Summary and Lessons Learned:
Our patient came to us with a common diagnosis—asthma, but her failure to respond to standard asthma therapy, as well as parts of her history that were not consistent with asthma, prompted us to reconsider this diagnosis and perform further evaluation that ultimately led to the diagnosis of subglottic stenosis. Prior to this patient, we had another patient who had presented similarly but had different objective findings. However, in both cases, they had a suboptimal response to maximal inhaler therapy. Further evaluation of their spirometry revealed a truncated inspiratory and expiratory flow volume loop in one patient while in the other patient the flow volume loop was relatively preserved. Laryngoscopy and CT neck revealed a diagnosis of subglottic stenosis in both cases. Both cases had symptom improvement after balloon dilation, and they were able to discontinue their inhaler therapies. We retrospectively examined the flow volume loops over several years and found some subtle changes. In one case, the classic pattern of marked truncation of the inspiratory and expiratory loops was noted, but not in the other. These cases not only highlight the relative differences in solely using the flow volume loop for diagnosis but also point out the heterogeneity seen even in the presence of having subglottic stenosis. The two cases emphasize the importance of being aware of asthma mimickers and of interpreting the flow volume loops in context of therapy unresponsive asthma. In addition, the cases highlight some subtle changes in flow volume loops associated with subglottic stenosis that we do not routinely look for, which can be helpful in making this diagnosis.

Patient Presentation and Testing:
Our patient is a 64-year-old female with past medical history significant for seasonal allergies, asthma, and endometrial carcinoma status post total hysterectomy who presented for evaluation of non-productive cough with intermittent associated wheezing and dyspnea. Cough had been present for the past 9-10 years and occurred throughout the day, though not at night. Steam relieved the cough; the patient could not identify any exacerbating factors. She had previously been evaluated by pulmonology, cardiology, and gastroenterology. About two years ago, the pulmonologist diagnosed her with asthma, and she was prescribed an ICS/LABA and a SABA inhaler. She did not feel these were very helpful so only used them a few times monthly. She had never smoked. She was living in a trailer with two dogs. Her physical exam was unremarkable. On auscultation, lungs were clear without wheezing. Her spirometry was normal without airflow obstruction. She brought with her a report from a CT chest performed the prior year that showed a stable benign appearing pulmonary nodule and stable bibasilar atelectasis. We first decided to reexamine her diagnosis of asthma, given that her symptoms did not improve with inhalers and her spirometry was normal. We had a suspicion for vocal cord dysfunction given that steam was helpful in alleviating her symptoms. Thus, we ordered a methacholine challenge with laryngoscopy. She was unable to complete the methacholine challenge test due to wheezing and cough. On laryngoscopy, visualization of her vocal cords was suboptimal due to obscuration from the epiglottis, though it was felt she had vocal cord dysfunction. Additionally, she was noted to have possible subglottic stenosis with a narrow posterior pharynx seen below the vocal cords.

Diagnosis, Treatment and Patient Outcomes:
Based on the laryngoscopy findings, we ordered a CT neck to better evaluate possible subglottic stenosis. We also ordered lab work, including an autoimmune screen and inflammatory markers, to assess for an underlying autoimmune disorder. The CT scan confirmed the diagnosis of subglottic stenosis; she had circumferential narrowing at the level of the inferior cricoid ring. Inflammatory markers, ANA, C-ANCA, P-ANCA, and anti-dsDNA were all within normal limits.
Since we could not find any underlying etiology for the stenosis, we classified hers as idiopathic. She was referred for bronchoscopy, during which balloon dilation was performed. Steroids were injected locally during the bronchoscopy to reduce fibrosis. The patient reported her symptoms improved within a few days of the procedure. She continued to have some cough, though decreased, but no longer had associated shortness of breath. She reported very occasional wheeze. She discontinued her inhalers completely. Interestingly, although she technically had normal spirometry at her initial visit, there were some subtle changes seen in her spirometry after bronchoscopy with dilation. After dilation, her peak expiratory flow was increased, and the expiratory flow loop was peaked, rather than rounded as it had been previously. This prompted us to compare a prior flow volume loops from two years before her initial visit with us. The flow volume loops from two years prior also demonstrated an increased peak expiratory flow with a well-defined peak as opposed to a more rounded plateau, which she had demonstrated on spirometry at her first visit to our clinic.
Case Title:
Considerations in an Adult Male-to-Female Transgender Patient with Asthma

Summary and Lessons Learned:
Asthma is a condition that affects 25.7 million individuals in the United States including transgender patients. However, the natural history of asthma in transgender patients has not been well documented. Despite legal and physical changes in transgender patients, medical issues including appropriate assessments may arise related to their biological sex. The natural history of asthma in transgender patients may also be different from other male and female cis-gender patients due to a combination of factors including the use of hormonal therapy. A male-to-female transgender patient presented to our clinic for assessment and management of asthma. PFTs analyzed in context of male gender designation were found to better represent the patient’s true pulmonary function. As such, we concluded that it is prudent to consider factors that may affect assessments such as PFT, to best classify asthma severity. A greater understanding of the progression of asthma, best assessments, and effects of hormonal therapy in transgender patients is deserved and will ultimately improve asthma management in this population.

Patient Presentation and Testing:
A 70-year-old male-to-female transgender patient receiving hormonal therapy since the 1990’s presented to Allergy Clinic for evaluation of asthma. She is an ex-smoker who also has a past medical history of allergic rhinitis and gastroesophageal reflux disease (GERD). Her asthma was diagnosed 6 years prior based on symptoms of chest-tightness, shortness of breath, and cough with exercise. Albuterol was utilized daily prior to exercise and there was no reported nocturnal awakening. She was using fluticasone propionate/salmeterol combined inhaler as a daily controller medication and daily loratidine for allergic rhinitis. Initial pulmonary function test (PFT) analyzed in the context of female gender designation revealed FEV1/FVC 71% and FEV1 2.99L (114%). Upon confirmation of gender reassignment and estradiol hormone therapy, PFT was repeated and analyzed in the context of male gender designation. The FEV1/FVC was 67% and FEV1 2.90 L (98%), which better reflected the patient’s true pulmonary function. Spirometry also demonstrated increased curvilinearity of expiratory flow volume loop with evidence of moderate baseline obstruction and no significant post-bronchodilator change.

Diagnosis, Treatment and Patient Outcomes:
Based on the findings from PFT and the patient’s history, she was started on daily fluticasone propionate nasal spray for allergic rhinitis in addition to pantoprazole for GERD. Daily tiotropium bromide was also added as a controller medication due to the patient’s history of smoking and lack of response to bronchodilator therapy on spirometry. At follow up visit in 3 months, she reported resolution of chronic post-nasal drip associated with allergic rhinitis as well as all reflux symptoms. She also noted major improvement in her asthma symptoms. PFTs were obtained and analyzed in the context of male gender designation. FEV1 and FEV1/FVC were stable compared to the previous visit but there was improvement of previously noted obstruction based on the expiratory flow volume loop.
Case Title:
Secondary Adrenal Insufficiency in Siblings Associated with Inhaled Fluticasone

Summary and Lessons Learned:
Adrenal insufficiency due to inhaled corticosteroids, although rare in children taking low to medium doses for asthma, can be a difficult to anticipate adverse drug event. Fluticasone is primarily metabolized through CYP3A4, can inactivate CYP3A5, and is not well metabolized via CYP3A5 or CYP3A7 unlike most other inhaled corticosteroids. Although the incidence of adrenal suppression due to inhaled corticosteroids is very low, heritable traits in CYP3A enzymes can contribute significantly to clinical risk. Low-cost testing assessing for genetic variants associated with xenobiotic metabolism phenotypes is now widely commercially available and may have clinical application in personalized selection of inhaled corticosteroid for best efficacy and least risk of metabolic interaction in isolation and with other medications. This single family case series reinforces recommendations to assess growth velocity in all pediatric patients taking even low to moderate dose inhaled corticosteroids.

Patient Presentation and Testing:
The academic allergy clinic had been longitudinally following a 5 year old female (patient A) with mild-moderate persistent asthma and allergic rhinitis and her 8 year old sibling (patient B) with high risk moderate persistent asthma and non-allergic rhinitis. Both siblings were started on fluticasone MDI 110mcg 2 puffs twice daily for 3 years prior to events. Patient A presented with altered mental status, and was admitted to PICU for vomiting with dehydration, severe hypoglycemia, and metabolic acidosis ultimately diagnosed as due to acute viral gastroenteritis. Following a prodrome consistent with a URI, she was readmitted 9 months later with repetitive vomiting, diagnosed with metabolic acidosis and ketogenic hypoglycemia. She had negative screening testing for cyclical vomiting syndrome, maple syrup urine disease, celiac disease and Cornelia De Lange syndrome. Patient B developed a lobar pneumonia with an unexpectedly protracted course. Mother noted her children did not outgrow their clothing for the past 2 years, prompting inspection of the growth curve which demonstrated marked growth velocity reduction of both siblings. Both siblings were ultimately diagnosed via ACTH stimulation tests to demonstrate adrenal insufficiency secondary to exogenous corticosteroid.

Diagnosis, Treatment and Patient Outcomes:
Treatment plans were co-developed with endocrinology consultants given medical indications to continue inhaled corticosteroids. Resumption of normal growth velocity, objective resolution of adrenal insufficiency, and stable asthma control were maintained for 4 years after initiation of equipotent doses of ciclesonide, inferring the etiologic agent was fluticasone. Genotypic evaluation of multiple CYP enzymes is underway.
Boletus edulis induced occupational respiratory allergy

Summary and Lessons Learned:
Boletus edulis is an infrequent cause of occupational respiratory allergy (OA). We present 3 food-processing factory workers who developed rhinitis and asthma symptoms preparing dried vegetable-based dishes. Patients were male, aged between 36 and 50 years, and referred symptoms after B. edulis manipulation (sieving machine and “cut in julienne” vegetables mixers use). Protective measures prior to diagnosis included jumpsuits and a full mask with 3M FFP, without filter. One patient had been previously diagnosed of OA due to B. edulis and advised to use a full mask (3M 6800 model including a 6000-series 3M filter), but did not comply.

Patient Presentation and Testing:
Allergy work-up included skin prick tests (common inhalants and foods, prick-prick with all the vegetables used (samples of 51 dehydrated vegetables, seeds, mushroom [boletus, champignon]) and specific IgE determinations, if available. Respiratory assessment, performed within work period, included rhinomanometry (all the patients), methacoline tests (2 patients), NIOX, and forced spirometry determinations.

Diagnosis, Treatment and Patient Outcomes:
All patients had positive skin tests with dehydrated B. edulis (mushroom and powder). Two tested positive to A. fumigatus and 1 to A. alternata and to champignon. Skin tests with the other vegetables were negative. Specific IgE to Alternaria was positive in a patient.
Two patients had nose obstruction confirmed by rhinomanometry and a positive methacholine test. A patient had an obstructive pattern in the spirometry.
After the diagnosis of occupational rhinitis and asthma due to B. edulis, patients were told to avoid its exposure, changing their position in the same workplace. As an alternative, filter containing protective masks were recommended. First choice was a full mask 3M 6800 model including a 6000-series 3M filter. Despite clinical efficacy, patients did not use it continuously due to heat and communication impairment with the other co-workers. Further avoidance included another mask (3M Versaflo TR-300MR with positive pressure and full helmet). Besides, patients have been advised to continue treatment with inhaled corticosteroids and long-acting bronchodilators.
Patients who use the mask continuously and comply with inhaled treatment have been are asymptomatic, with normal lung function and reduced NIOX levels. However, the patient who used the mask and inhaled treatment just with the direct manipulation of Boletus has weekly symptoms and an impaired lung function.
As relevant points, we present 3 workers affected by an uncommon food allergen and the complexities of occupational allergy management. Recommendations should go beyond avoidance since for many workers finding another different job may not be feasible.
Case Title: Swollen lips, gut and glands - Acquired angioedema secondary to Non-Hodgkin lymphoma

Summary and Lessons Learned:
Introduction:
C1 esterase inhibitor (C1-INH) deficiency with acquired angioedema (AAE) is a rare disorder (1 in 500,000), which is clinically difficult to differentiate from hereditary angioedema (HE). This differentiation is however critical as the former is commonly associated with underlying lymphoproliferative disorders (malignancy of B-lymphocytes or plasma cells).

Case Description:
62-year-old male with recent history of Clostridium difficile (C. diff) colitis presented to the emergency department with recurrent periumbilical abdominal pain with lip swelling, this being his third presentation in the past month. He reported having self-resolving abdominal pain along with ankle and feet swelling infrequently since the past 1 year. He denied any skin rash, pruritus, shortness of breath or choking sensation. He had no prior history of allergy to any food or medications and family history was unremarkable for similar symptoms. CT scan of abdomen showed worsening edema along bowel loops with moderately enlarged mesenteric, pelvic and inguinal lymph nodes and edematous walls of sigmoid colon and rectum compared to prior CT. This finding was thought to be related to colitis previously. Right inguinal lymph node biopsy was performed. He was discharged on amoxicillin-clavulanate and oral vancomycin for possible diverticulitis and refractory C. diff colitis. His biopsy revealed CD-5 positive B-cell lymphoma consistent with small/chronic lymphocytic lymphoma(CLL). C1 esterase inhibitor, C4 and C1q levels were low at 4, <3 and <50 respectively. Patient was diagnosed with acquired angioedema and started on C1 esterase inhibitor every 3-4 days and icatibant for breakthrough anaphylaxis attacks. Bone marrow biopsy was consistent with CLL. He has received 5 cycles of R-CVP (rituximab with cyclophosphamide, vincristine and prednisone) and is on Ibrutinib at present with no recurrence of symptoms.

Discussion:
AAE with C1-INH deficiency should be considered in patients with late onset of angioedema without urticaria in absence of family history of angioedema. A C1-INH deficiency with a negative family history and low C1q is diagnostic of this condition. All patients with acquired C1 inhibitor deficiency should be evaluated for underlying B cell lymphoproliferative disorder and perhaps evaluated annually if no disorder identified. Management includes therapies targeting bradykinin activity, such as C1 inhibitor concentrate, tranexamic acid, androgens and icatibant. Treatment of underlying malignancy may result in complete resolution.

Patient Presentation and Testing:
Patient was seen at Allergy clinic for a post hospital follow up (admission for swelling of lips with abdominal pain and recent diagnosis of CLL). Result of C1 esterase inhibitor, C4 and C1q levels sent during hospital stay were all low suggestive of Hereditary vs. Acquired angioedema. Patient also had been started on R-CVP regimen for CLL. The result of the test was critical in his diagnosis since he did not have any significant family history of angioedema, which did not correlate to the diagnosis of hereditary angioedema.

Diagnosis, Treatment and Patient Outcomes:
On my next follow up with the patient, it was 11 months since he was started on C1 esterase inhibitor for acquired angioedema secondary to underlying Non Hodgkin lymphoma. Patient was doing very well with the treatment and did not have recurrence of swelling of lips and hands since being started on this therapy. He did report cold induced pruritus with angioedema in his last visit (2 months back) which resolved with warming up. He was being continued on chemotherapy for Lymphoma. He had been compliant on C1 esterase inhibitor 1000 units IV every monday and
Thursday, and was on Icatibant 30 mg/3 ml for treatment for attack of angioedema. He was being considered on discontinuing the treatment if cancer was to be in remission (after discussion with Hematology-oncology) as this diagnosis was secondary to his malignancy and would resolve with the resolution of cancer.
Case Title:
Case of Schnitzler Syndrome That Responded to Tocilizumab

Summary and Lessons Learned:
Schnitzler syndrome is a rare, underdiagnosed, chronic auto-inflammatory disease characterized by an urticarial skin rash and monoclonal IgM component and at least two of the following signs: fever, joint or bone pain, lymphadenopathy, hepatosplennomegaly and elevated acute phase reactants. Twenty percent of patients develop lymphoproliferative disorders including Waldenstrom disease and lymphoma. IL-1 is usually elevated and anakinra (IL-1 antagonist) is often a successful treatment. Tocilizumab (an IL-6 antagonist) has been described as successful therapy in 3 patients in Belgium who failed anakinra therapy. We present a patient with Schnitzler syndrome and isolated elevated IL-6 who responded to tocilizumab. Our case suggests that tocilizumab may be efficacious therapy in patients with isolated elevated IL-6 in Schnitzler syndrome.

Patient Presentation and Testing:
We describe a 69 year old female who experienced monthly episodes of facial swelling and a non-pruritic, erythematous rash, accompanied by high fever, nausea, headache and joint pain over 1 year. The predominantly right-sided facial swelling was sometimes accompanied by mild swelling of the upper airway, visualized on laryngoscopy. During episodes, the patient was found to have an elevated white cell count, neutrophils, monocytes, eosinophils and sedimentation rate that would resolve after episodes. The facial swelling was initially attributed to facial cellulitis for which she completed several courses of antibiotics and numerous sinus surgeries without resolution of symptoms. Odontogenic and neurologic causes of infection were also ruled out. A daily antihistamine did not alleviate symptoms. The patient noted some temporary improvement in symptoms with prednisone. Previous medical history was significant for breast cancer and uterine cancer in remission and Hashimoto’s thyroiditis. Rheumatoid factor was elevated (20 IU/ml). C1-esterase inhibitor, complement C1-Q levels and tryptase levels were normal, arguing against mast cell activation syndrome or hereditary angioedema. Complement C2 (less than 1.3 mg/dL) and C4 (10mg/dL) levels were slightly low. The patient had normal immunoglobulin levels and normal IL-2 (less than 38 pg/ml), TNF-α of 2 pg/ml, IL-1β of 3.9 pg/ml but an isolated elevated IL-6 of 30.08 pg/ml which remained elevated (60.45pg/ml) on repeat testing (reference range: 0.31- 5 pg/ml). Considering eosinophilic causes, IL-5 level checked during an attack was found to be normal. The patient also had a monoclonal IgM component. Sjogren-SSA and SSB, Smith, dsDNA, mitochondrial and actin antibodies were negative.

Diagnosis, Treatment and Patient Outcomes:
The patient was diagnosed with Schnitzler syndrome, per Strasbourg diagnostic criteria. Isolated elevated IL-6 made tocilizumab an appropriate choice of therapy and resulted in resolution of symptoms.
Case Title:
Recurrent disseminated MAC in patient with antibodies targeting interferon gamma (IFN-g)

Summary and Lessons Learned:
Mycobacterium avium complex (MAC) is a disease that is caused by nontuberculous mycobacterial organisms such as M. avium and M. intracellulare and transmission is via inhalation and ingestion. Historically, it has been associated with immunocompromised individuals (i.e. CD4+ T cells <50) and presents as disseminated disease. Infections among immunocompetent patients with MAC is more localized such as pneumonia or lymphadenopathy. Diagnosis is made by clinical and microbiologic criteria. Treatment usually consists of multi-agent antimicrobials tailored by susceptibility testing. The IL-12/23 and IFN-g axis activates T and innate cells for clearance of mycobacteria. Mendelian Susceptibility to Mycobacterial Diseases includes inherited immunodeficiencies that are linked to defects in this pathway, however most of these patients present with mycobacterial disease early in life. Late onset recurrent mycobacterial disease may indicate an acquired form of immunodeficiency, especially in a susceptible population of East Asian females. In our case, the patient developed neutralizing anti-IFN-g antibodies that impaired the IL-12/23 and IFN-g axis and clearance of mycobacterium. Elimination of B cell generating pathogenic antibodies resulted in clearing the IL-12/23 and IFN-g pathway and resolution of severe mycobacterial infection. This may eventually alter a patient’s treatment options to include anti-CD20 therapy such as Rituximab.

Patient Presentation and Testing:
We present a unique case of a patient who had recurrent disseminated MAC secondary to immune dysregulation. Patient is 43-year-old Thai female with history of biopsy confirmed Kikuchi Fujimoto disease who initially presented with dyspnea. She was found to have a pericardial tamponade and pulmonary right hilar mass. She underwent pericardial window with fluid positive for MAC. Lung biopsy and bronchoalveolar lavage (BAL) for bronchopneumonia also grew MAC. Patient was started on a multi-antimicrobial regimen narrowed upon sensitivities and eventually discharged. Her clinical course was complicated by septic shock, fever, lymphadenopathy, worsening right hilar granuloma and recurrent disseminated MAC few months after an asymptomatic stage with negative cultures and completion of first course of therapy.

Diagnosis, Treatment and Patient Outcomes:
Given patient’s Thai ethnicity and recurrence of disseminated MAC against appropriate antibiotic regimen, a concern was raised for acquired immunodeficiency in the form of anti-interferon-gamma (IFN-g) antibodies. Testing of patient’s serum revealed high titer anti-IFN-g antibodies (17520 MFI (normal <405)) which were also found to block IFN-g-induced STAT1 phosphorylation in normal monocytes. To remove the source of pathogenic anti-cytokine antibodies, patient received B cell depletion with anti-CD20 therapy which greatly improved her symptoms and she has remained in remission for the past 8 months.
**Case Title:**
Very Early Onset Inflammatory Bowel Disease in a 6 Year Old Girl With LRBA Deficiency

**Summary and Lessons Learned:**
The incidence of pediatric inflammatory bowel disease (IBD), specifically in young children, is rising. Very early onset IBD (VEOIBD), occurring before age 6, occurs in approximately 15% of pediatric IBD patients. While conventional IBD is due to polygenic disorders, there are increasing reports showing monogenic diseases, such as primary immunodeficiencies (PID), to be causative of VEOIBD. These conditions can be difficult to identify and treat. Since IBD is often the first clinical manifestation of the associated PID, prompt recognition is essential to initiate appropriate therapy. We illustrate this with a case of VEOIBD in a patient with LPS-responsive beige-like anchor protein (LRBA) deficiency.

A 6 yo girl with nonallergic rhinitis, asthma and PID due to LRBA deficiency diagnosed by genetic analysis and flow cytometry was admitted with abdominal pain, diarrhea and hematochezia with 20 stools per day. She reported similar intermittent, self-resolving episodes for the past 2 years. EGD and colonoscopy histopathology was consistent with severe colitis, and she was diagnosed with ulcerative colitis. Initial therapies including oral corticosteroids, mesalamine and infliximab were ineffective. With collaboration from her immunologist, she transitioned to abatacept and hydroxychloroquine and achieved improved clinical response with decreased diarrhea and resolution of hematochezia.

LRBA deficiency is an autosomal recessive condition characterized by a CVID-like phenotype, immune dysregulation and autoimmunity such as IBD, autoimmune endocrinopathies and cytopenias. LRBA regulates intracellular trafficking of anti-inflammatory CTLA4 and its paucity results in decreased CTLA4 levels and dysregulated follicular helper T cell responses. With knowledge of this molecular cascade, CTLA4-Ig (abatacept) and chloroquine have emerged as effective treatments for the immune dysregulation associated with LRBA deficiency. Additionally, early HSCT in patients with severe presentations of LRBA deficiency demonstrates curative potential.

Children with VEOIBD are at high risk for underlying PID. Recognition of predictors such as early-onset disease, severe IBD, extra-intestinal complications, and parental consanguinity are important as these conditions have high morbidity and mortality and may not respond to traditional immunosuppressive or immunomodulatory therapies. Timely diagnosis of these monogenic diseases can identify unconventional biological treatment options to target specific pathogenic pathways and potentially offer cure through HSCT.

**Patient Presentation and Testing:**
A 6 yo girl with nonallergic rhinitis, asthma and PID due to LRBA deficiency diagnosed by genetic analysis and flow cytometry was admitted with abdominal pain, diarrhea and hematochezia with 20 stools per day. She reported similar intermittent, self-resolving episodes for the past 2 years. Being aware that LRBA deficiency is characterized by a CVID-like phenotype, immune dysregulation and autoimmunity, there was suspicion for IBD. EGD and colonoscopy histopathology was consistent with severe colitis, and she was diagnosed with ulcerative colitis.

**Diagnosis, Treatment and Patient Outcomes:**
The patient was diagnosed with VEOIBD, specifically ulcerative colitis, based on EGD and colonoscopy histopathology consistent with severe colitis. Initial therapies from her gastroenterologist including oral corticosteroids, mesalamine and infliximab were ineffective. Children with VEOIBD may not respond to traditional immunosuppressive or immunomodulatory therapies. With collaboration from her immunologist, she transitioned to abatacept and
hydroxychloroquine based on knowledge of the LRBA molecular cascade. LRBA regulates intracellular trafficking of anti-inflammatory CTLA4 and its paucity results in decreased CTLA4 levels and dysregulated follicular helper T cell responses. CTLA4-Ig (abatacept) and chloroquine have emerged as effective treatments for the immune dysregulation associated with LRBA deficiency. Since initiation of abatacept and hydroxychloroquine, the patient has achieved improved clinical response with decreased diarrhea and resolution of hematochezia.
Case Title:
Resolution of chronic urticaria in a patient with Hashimoto's thyroiditis after thyroidectomy

Summary and Lessons Learned:
The etiology of chronic urticaria is not identified in most patients and in many severe cases, potent medications with significant side effects are required to control outbreaks. In a significant number of cases, autoimmunity has been associated with the development of urticaria and angioedema. In our case, autoimmune thyroid disease, Hashimoto's thyroiditis, appears to have played a major role in this patient’s disease, given resolution of hives associated with improvement in serology following thyroidectomy for multinodular goiter.

Patient Presentation and Testing:
The patient, a 32-year-old woman with a history of Hashimoto’s thyroiditis on replacement therapy presented to our clinic with recurrent urticaria for the past several months. Her symptoms started five days after starting antibiotics for an episode of colitis. Initially considered a drug allergy, she was treated with diphenhydramine with improvement in her symptoms. A few days later, she developed angioedema of her lips and was given prednisone and diphenhydramine with improvement. She then again developed lip angioedema and diffuse urticaria after stopping the prednisone. Her urticaria would wax and wane over 24 hours. She saw an outside Allergist and was started on fexofenadine 180 mg three times daily, ranitidine 150 mg three times daily, loratadine 10 mg twice a day and hydroxyzine 50 mg at night. Despite this aggressive antihistamine regimen, her urticaria recurred, and she was initiated on daily prednisone at high doses. At doses below 15 mg of prednisone, however, she experienced recurrence of urticaria. She was tried on hydroxychloroquine 200 mg twice day with no improvement. She developed significant and intolerable side effects of prednisone with a 20-pound weight gain and severe mood swings, despite incomplete control of her urticaria. She was then referred to the University of Colorado Allergy/Immunology clinic for further management. The patient’s initial laboratory data showed normal blood count and comprehensive metabolic panel. Her thyroid stimulating hormone (TSH) was 0.77 mIU/L (0.50-5.00 mIU/L), thyroid peroxidase antibodies 194 U/mL (Normal < 60 U/mL) and thyroglobulin antibodies 3 IU/mL (normal <4 IU/mL) on her daily maintenance levothyroxine of 175 mcg.

Diagnosis, Treatment and Patient Outcomes:
To control her chronic urticaria, she was started on cyclosporine 150 mg twice day. Her urticaria improved, but she experienced intolerable side effects of peripheral neuropathy and hair loss and, in addition, a few months into her course, her hives recurred. Given her history of Hashimoto's thyroiditis and hypothyroidism, we increased her levothyroxine to a suppressive dose of up to 300 mcg. Her TSH dropped to 0.02 mIU/L (0.34-5.60 mIU/L). She experienced some mild tremors but otherwise tolerated the increased dose well, with remission of her urticaria. Omalizumab 300 mg every 28 days was added in an attempt to lower the levothyroxine dose and hives were well controlled on the combination of omalizumab and suppressive levothyroxine for about two years Her goiter gradually enlarged, and her thyroid peroxidase and thyroglobulin antibodies reached a peak of 4690 U/mL and 6 IU/mL, respectively. She developed a flare of her hives along with complaints of thyroid enlargement and tenderness. She was found to have a multinodular thyroid gland on ultrasound and underwent total thyroidectomy. Since her thyroidectomy, her TSH is 0.43 mIU/L and thyroid peroxidase antibody level has dropped precipitously to 300 U/mL along with resolution of her hives. Omalizumab has been stopped and she is now on only replacement doses of levothyroxine with no recurrence of her urticaria or angioedema 9 months post thyroidectomy. The course of this patient strongly suggests that Hashimoto's thyroiditis was a significant causal factor of her chronic urticaria and angioedema.
Oral Lichen Planus and Comorbid Oropharyngeal Candidiasis

Summary and Lessons Learned:
Oral lichen planus is a chronic immune-mediated oral mucosal disease frequently involving buccal mucosa, tongue, and gingiva. The etiology is not fully understood, but the mechanism is believed that inflammatory cytokines of keratinocytes play a major role in T lymphocyte-associated immune responses. Oral candidiasis is the most common opportunistic fungal infection in the oral cavity, mainly caused by Candida albicans. Candida albicans is present in around half of the population as one of the normal oral microbiota. However, it often causes opportunistic infections in the oral and pharyngeal areas and even systemically in immunocompromised patients. We report an unusual case of the patient with both oral lichen planus and acute oropharyngeal candidal infection, which may be challenging for clinicians to diagnose and treat. Although the clinical features were complex at the initial visit, the diagnosis of oral lichen planus, one of immune-mediated mucosal diseases, could be predicted based on the histopathologic exam using IHC staining and it was further supported by the treatment results to the corticosteroid therapy.

Patient Presentation and Testing:
A 66-year-old woman visited our clinic complaining of thrush and pain in the whole mouth and throat which had begun 1-2 weeks ago. She had hypertension that had been managed from a private hospital with medication for 10 years. Chronic gastritis was diagnosed one month ago and had been treated with medication thereafter. Clinical examination revealed many shallow ulcers in various sizes and irregular forms with sloughing whitish pseudomembrane in their boundaries on the lower lip, buccal mucosa, lateral borders of the tongue, soft palate and uvula. Fungal infection of oral and throat mucosa or an immune-mediated mucosal disease such as pemphigus was suspected, therefore, fungal culture specifically for candidal species, cytopathology, biopsy and histopathologic exam with immunohistochemistry (IHC) staining on complements and immunoglobulins were used for differential diagnosis. Fungus was not detected in cytopathology, however, fungal organisms were identified in histopathologic exam with Hematoxylin and Eosin staining and they were confirmed with both Periodic Acid-Schiff staining and methenamine silver staining. Furthermore, Candidal albicans was identified with the fungal culture test. Besides, IHC staining demonstrated deposits of IgG, IgA, C3, C1q and fibrinogen in oral epithelium of the specimen.

Diagnosis, Treatment and Patient Outcomes:
Diagnosis was acute oral candidiasis and a comorbid immune-mediated mucosal disease such as lichen planus or pemphigus vulgaris. Antifungal therapy using topical nystatin initially and systemic fluconazole subsequently was very effective in healing multiple oral ulcerous lesions. Interestingly, three weeks after the initiation of the antifungal therapy, whitish patterns suggesting oral lichen planus were noted on the sites where ulcerous lesions had been present and healing. The newly found lesions were managed with topical and systemic corticosteroids with great improvement in signs and symptoms.
Periodic inflammation without fever associated with pathogenic familial NLRP3 variant R262W

Summary and Lessons Learned:
The protein NLRP3 plays a key role in regulation of the inflammatory process. Gain of function mutations of NLRP3 lead to cryoporin-associated periodic fever syndromes (CAPS), including Muckle-Wells Syndrome, Familial Cold Autoinflammatory Syndrome and Neonatal Onset Multisystem Inflammatory Disease. The patient described in this case exhibited painful neutrophilic dermatosis that occurred with regular chronicity and progressive corneal dystrophy without loss of visual acuity. Whole exome sequencing revealed a pathogenic mutation in the NLRP3 gene. Two of the patient’s three children exhibited a similar rash starting at two years of age. Whole exome sequencing of family members revealed the NLRP3 variant in all affected but no unaffected family members. This case highlights the need to consider inflammasome mutations in cases of periodic inflammation without fever leading to the selection of appropriate therapeutic interventions.

Patient Presentation and Testing:
A 26 year-old Caucasian female presented with the chief complaint of a periodic, urticarial rash. She reported that the rash began when she was 15 years old and started occurring almost every day. It was not pruritic but instead very painful, rated at 6 out of 10 in intensity. The patient stated that the rash was raised, or flat, slightly red in appearance with irregular borders. It would almost always appear in the afternoon, first on her legs then progressively spreading in an ascending fashion to involve her abdomen and upper extremities by the time she went to bed, but typically sparing her face and lasting less than twelve hours. The rash was not triggered by cold. A punch biopsy from the rash that had been collected several years prior to her presentation showed neutrophilic infiltration of the dermis. Her CRP values had been mildly elevated on previous occasions. The frequency of her rash had decreased slightly since starting on montelukast several months before presentation. Other than the dermatosis, her medical history was significant only for corneal dystrophy diagnosed several years after the onset of her rash. She reported that her sons aged two and five also had started to exhibit a similar periodic rash. The rest of her immediate family members: father, mother, daughter and husband did not have any similar symptoms. Physical exam was significant for corneal surface irregularity. The patient had no skin lesions during her initial visit but a photo of her rash portrayed a mildly erythematous, macular rash on her abdomen. Labs were notable for a CRP of 1.2 (NL <0.3) and ESR of 23 (NL<20), as well as a normal CBC with differential, CMP and AH50. She had previously tested negative for HAV, HBV, HCV, SS-A Ab, SS-B Ab, and Anti-FcER Ab. Prior workup also included normal levels of C1 esterase inhibitor, C3, C4, and CH50.

Diagnosis, Treatment and Patient Outcomes:
The patient’s symptoms failed to respond to high dose antihistamines, glucocorticoids, or colchicine. Monteleukast reduced the frequency but not the severity of her rash to three to four times per week from daily. Zileuton did not further reduce either the frequency or severity of the dermatosis. Examination of one of the patient’s affected sons demonstrated a similar blanching, erythematous, macular rash on bilateral upper and lower extremities. Due to high suspicion for an inflammasome perturbation rooted in an autosomal dominant mutation, whole exome sequencing of the patient, one of her affected sons and her husband was obtained. This revealed the presence of a NLRP3 R262W mutation in the patient and her affected son, which has previously been linked to cases of Muckle-Wells Syndrome. An ophthalmology exam performed on the patient’s affected children revealed mild corneal dystrophy. With this diagnosis, the patient and her two sons are now seeking treatment with an IL-1 neutralizing therapy which we expect to greatly improve the patient’s and her sons’ cutaneous and corneal symptoms.
Case Title:
A Hot Mess: The Mysterious Case of a Persistent Fever in a Young Man

Summary and Lessons Learned:
A previously healthy 21-year-old man presented with fevers, rash, lymphadenopathy, and anterior uveitis. Autoimmune, infectious, and malignancy evaluations were undiagnostic. Lymph node pathology showed Langerhans cell histiocytosis (LCH), a clonal expansion of Langerhans cells. LCH cells are immunophenotypically and genetically similar to myeloid dendritic cells and distinct from epidermal Langerhans cells. It remains controversial whether LCH develops from malignant transformation or an inflammatory reaction. There is an association between viral illnesses and LCH; we wonder whether recent Coxsackie virus infection contributed. LCH occurs more frequently in patients younger than 10 years old. Adults often present with pulmonary lesions. This patient had multi-organ involvement and significant inflammatory component; LCH should be considered in addition to autoinflammatory syndromes and HLH despite its rarity.

Patient Presentation and Testing:
A previously healthy 21-year-old man presented with 2 weeks of daily fevers responsive to antipyretics, lymphadenopathy, rash, and anterior uveitis. His fevers typically returned 4-6 hours after antipyretic administration without periodicity. He had no infectious exposures, travel abroad, tick bites, or contributory family history. Initial labs showed leukocytosis with neutrophilia, lymphopenia, and eosinophilia, and transaminitis. Chest CT showed right hilar and mediastinal lymphadenopathy and pulmonary nodules. Infectious evaluation revealed only low-titer Coxsackie virus antibodies to serotypes B2-6 suggesting recent infection. Rheumatologic evaluation was non-specific, the exceptions being elevated CRP and positive ANA. Peripheral blood flow cytometry showed no aberrant lymphocyte immunophenotype; IgG, IgA, and IgM levels were normal. Imaging did not reveal additional lesions. Differential diagnosis included autoinflammatory condition, HLH, lymphoproliferative disorder, and malignancy. Per Eurofever Classification Criteria, he warranted testing for TRAPS although we had low suspicion for this; TNFRSF1A analysis revealed no mutation. Normal ferritin and the absence of peripheral blood cytopenias and splenomegaly made HLH less likely.

Diagnosis, Treatment and Patient Outcomes:
Lymph node tissue showed proliferation of mononuclear cells consistent with Langerhans cells. This with his clinical history was consistent with Langerhans cell histiocytosis. PET CT body scan showed FDG-avid mediastinal, hilar, axillary, and inguinal lymphadenopathy. He completed vinblastine and prednisolone induction therapy due to multi-organ involvement and is currently doing well. Next, he will undergo reassessment of his disease to determine whether further or alternative treatment is necessary.
Summary and Lessons Learned:
Brief summary of cases and outcome: Systemic Lupus Erythematosus (SLE) is a multi-systemic autoimmune disease characterized by the development of autoantibodies to self-antigens. Acquired angioedema secondary to autoantibodies against C1-esterase inhibitor (C1-INH) is a known complication of SLE. However, the causes of angioedema in SLE are multifactorial, including concomitant complement deficiency and/or medication exposure. The clinical course and treatment of angioedema in SLE has rarely been reported, particularly in children. Here we describe the clinical presentation, laboratory studies and treatment of angioedema in 3 pediatric and 1 adult SLE patients.

Of these four patients, three were female and all were Caucasian. One patient was diagnosed with hereditary angioedema (HAE) type I at 4 years of age; she later developed other systemic manifestations including urticaria and was diagnosed with SLE at 9 years of age. One patient developed angioedema at the time of SLE diagnosis at 17 years of age. The other two patients had their first episode of angioedema during SLE flares at 13 and 18 years of age. They were also exposed to medications that could potentially trigger angioedema. All patients had elevated autoantibodies to C1-INH and/or C1q during their angioedema episodes. Two patients had life-threatening airway edema requiring emergent intubation. In two of three patients with isolated acquired angioedema, given their clinical deterioration while receiving intravenous steroids, ecallantide was administered with symptomatic improvement.

Lessons learned and its relevance: Angioedema in SLE can occur either at diagnosis or during the disease course. In addition to acquired angioedema from autoantibodies to C1-INH, other etiologies of angioedema should be considered. Ecallantide is a potential treatment option of acute angioedema in steroid-refractory patients. To our knowledge, there is limited literature regarding the use of ecallantide in acquired angioedema and no prior case reports in the pediatric population.

Patient Presentation and Testing:
Patient 1: A 13-year-old Caucasian female with SLE and Graves’ disease who was recently restarted on prednisone 20 mg/day and azathioprine for SLE flares presented with a periorbital/malar rash and eyelid, lip, and tongue swelling shortly after receiving intravenous acyclovir for possible herpes stomatitis. Laboratory evaluation included an undetectable serum tryptase, low complement C3 and C4 levels, positive anti-dsDNA antibody, and normal C1q with negative anti-C1q antibody. She had a normal serum C1-INH antigen and activity level with an elevated anti-C1INH antibody 43.7% (reference range 0.89-36.1%).

Patient 2: A 18-year-old Caucasian female who was admitted for a SLE flare, central line infection, and septic shock. After resolution of the infection, she was treated with pulse intravenous methylprednisolone and rituximab. One week later, she developed acute facial, tongue, neck, and throat swelling requiring emergent intubation. She had no rashes. She had been on chronic treatment with lisinopril and received gadolinium the day prior to the onset of symptoms. Laboratory evaluation included serum tryptase 13.8 ng/ml (reference range < 11.5), low C3 and C4 levels, positive anti-dsDNA antibody, low C1q with negative anti-C1q antibody. She had an elevated serum C1-INH antigen with a normal activity level and positive anti-C1INH antibody 190.6%.

Patient 3: A 18-year-old Caucasian male with newly-diagnosed SLE and lupus nephritis who developed lip, tongue, and throat swelling requiring intubation one day after admission. His only medication prior to the onset was prednisone 1 mg/kg/day. Laboratory evaluation included normal serum tryptase, low C3 and C4 levels, positive anti-dsDNA antibody,
normal C1q with positive anti-C1q antibody 8.1% (reference range 0.0-7.0%). He had a normal serum C1-INH antigen and activity level with an elevated and anti-C1INH antibody 84.2%.

Patient 4: A 13-year-old Caucasian female diagnosed with hereditary angioedema (HAE) type I at 4 years of age, developed photosensitivity, arthritis, leukopenia with positive anti-nuclear antibody and anti-Smith antibody at 9 years of age. She was treated with C1-INH or ecallantide as needed for angioedema and hydroxychloroquine for SLE. Since September 2016, she had increased episodes of angioedema occurring every 1-3 months despite receiving prophylactic C1-INH. In November 2016, she developed chronic urticaria with no evidence of vasculitis on biopsy. Further workup demonstrated a negative chronic urticaria index and anti-IgE receptor antibodies. In February 2017, she was started on azathioprine for serositis and elevated inflammatory markers. Her C4 and C1q levels were persistently low and she had an elevated anti-C1q antibody 26.2%. Anti-C1INH results are pending.

Diagnosis, Treatment and Patient Outcomes:
Patient 1: Her symptoms and laboratory studies supported evidence of a SLE flare with hypocomplementemia and positive autoantibodies including anti-C1INH antibody. However, her history of immediate swelling following intravenous acyclovir administration raised concern for a drug-induced reaction. Acyclovir was discontinued and a desensitization procedure was recommended if acyclovir was required. Due to progressive airway swelling despite 2 doses of 0.3 mg intramuscular epinephrine and 40 mg of intravenous methylprednisolone, one dose of ecallantide 30 mg was given subcutaneously with resolution of swelling in 24 hours. Her steroid dose was increased and she was given one dose of rituximab for treatment of her SLE. She continued to follow with outside rheumatologists.

Patient 2: The etiology is likely multifactorial in this patient, as she had a SLE flare with positive anti-C1INH antibody and history of ACEI and gadolinium exposure. Lisinopril was immediately discontinued. Her SLE was aggressively treated with high dose steroids, mycophenolate mofetil, and intravenous immunoglobulin. She received gadolinium again 2 weeks later for brain imaging with no recurrence of the swelling. She was extubated after 3 days and discharged home on prednisone, hydroxychloroquine, and mycophenolate mofetil. She had no recurrence of angioedema at her 6-month followup.

Patient 3: He most likely had an isolated acquired angioedema episode from anti-C1INH antibodies. He had no history of exposure to common culprit drugs, infection, and a negative HAE workup. Given his low C4 level, he was treated with one dose of C1INH while awaiting C1INH activity level results with no response. Due to persistent swelling while receiving intravenous methylprednisolone, he was given 30 mg SC ecallantide 2 doses with improvement and he was extubated 2 days later. He continues on prednisone, hydroxychloroquine, and monthly intravenous cyclophosphamide for treatment of SLE with nephritis. He had no recurrence of angioedema at his 4-month followup.

Patient 4: There are reports of autoimmunity in patients with HAE. However, this patient may also have C1q deficiency that increased her risk for developing SLE given her persistently low C1q despite normal C3 level. For SLE management, she continues on azathioprine 200 mg once daily and hydroxychloroquine. If she continues to have frequent episodes of angioedema and has an elevated anti-C1INH antibody (results pending), rituximab may be considered as an option in her treatment.
Case Title:
Long-term Anakinra Therapy in a Schnitzler Syndrome Patient

Summary and Lessons Learned:

Background:
Schnitzler syndrome is a rare disorder characterized by hallmark features of urticaria, IgM or IgG monoclonal gammopathy, bone pain, and fevers. It is a late-onset acquired autoinflammatory syndrome seen in adults only, with about 300 cases reported worldwide. The successful use of anakinra for refractory symptoms was first described in 2005. We describe the clinical course of a Schnitzler syndrome patient on high-dose anakinra for 11 years.

Case Presentation:
In 2002, a 50-year-old man presented with an eight-year history of severe urticaria and lymphadenopathy. Extensive prior evaluation revealed an IgM monoclonal gammopathy of unknown significance. Previous workup also included numerous bone marrow and lymph node biopsies, lymph node resections, and PET scans without evidence of lymphoma. The patient saw multiple allergists with complaints of daily diffuse, pruritic, face-sparing urticaria with each lesion lasting 12-16 hours. He also had chronic bone pain, lymphadenopathy, and intermittent fevers. Multiple anti-histamines, aspirin, and montelukast failed to provide relief, and only prednisone 30mg daily was effective. Labs were significant for IgM of 783 mg/dL and anemia of 7-8 g/dL.

The patient was diagnosed with Schnitzler Syndrome based on his constellation of symptoms. He was tried on etanercept, cyclosporine, rituximab, thalidomide, alpha-interferon, and hydroxychloroquine without success. In 2006, he was started on anakinra with dramatic improvement in his urticaria and bone pain. Currently, the patient’s symptoms have remained in remission for 11 years with high-dose anakinra. However, symptoms recur if medication is stopped for 48 hours. Anemia has improved to 12-13 g/dL in the intervening years. During his initial 6 years of anakinra therapy, his IgM level plateaued; however, since then it has steadily increased to 2030 mg/dL. IgG has slowly downtrended to 369.

Discussion:
The remarkable long-term effectiveness of anakinra in Schnitzler Syndrome indicates that IL-1 plays an important role in this autoinflammatory disease. However, our patient’s rising IgM points toward a progressing lymphoproliferative disorder. In 2015, somatic mosaicism of NLRP3 mutation was noted in the myeloid lineage of two IgG variant Schnitzler syndrome patients; however a germline NLRP3 mutation has not been found in Schnitzler syndrome, and the two cases were considered variants of cryopyrin-associated periodic syndrome (CAPS). Despite a well-described phenotype, a unifying genetic cause and pathogenesis linking the monoclonal gammopathy with the autoinflammatory component has yet to be described. Perhaps with better understanding of the underlying mechanism, a curative therapy can be identified that addresses all aspects of Schnitzler’s syndrome.

Patient Presentation and Testing:

No lab tests were necessary for diagnosis at time of initial presentation, as the patient’s history was classic for Schnitzler syndrome. However we followed the trend of his anemia, IgM, and IgG during long-term therapy with anakinra. CBC with differential and complete chemistry panel were also followed, which did not show negative effects on long-term anakinra.

Diagnosis, Treatment and Patient Outcomes:
The patient presented with severe urticaria refractory to anti-histamines, along with a history of IgM monoclonal gammopathy, bone pain, and intermittent fevers. These symptoms are hallmark features of Schnitzler syndrome; thus, he was diagnosed based on clinical history. Anakinra was selected as he had failed a number of anti-histamines and
immunosuppressants, and one case report in 2005 detailed a Schnitzler syndrome patient successfully treated with anakinra. His long-term response to anakinra confirms the diagnosis.
Elevated IgE as a manifestation of underlying Lymphoma

Summary and Lessons Learned:
Elevated Immunoglobulin E (IgE) levels are commonly associated with atopic conditions (eczema, asthma), parasitic infections, immunodeficiency disorders (Hyper IgE syndrome, Omenn’s syndrome), HIV infection and T cell lymphoma. Patients with elevated IgE levels are often referred to Allergy and Immunology clinic for evaluation of either underlying allergy or immunodeficiency. Significant IgE elevations are reported to be rarely associated with Hodgkin’s lymphoma. But there have been no reported associations with non-Hodgkin’s lymphoma (NHL). We present to you a patient who had skin rash and elevated IgE levels eventually diagnosed with mantle cell lymphoma. Mantle cell lymphoma is an aggressive form of NHL. These patients often require hematopoietic stem cell transplantation and maintenance chemotherapy to improve the chances of remission. Hence earlier diagnosis is crucial in evaluating such patients. Patient initially presented to our clinic with persistent pruritic rash. He had no history of atopic dermatitis, asthma, allergic rhinitis, recurrent infections or periodontal disease. There was no history of foreign travel or symptoms suggestive of parasitic infections. Skin prick test to environmental allergies was negative. His IgE levels were markedly elevated. HIV testing and immunodeficiency workup was negative. He failed to respond to steroid therapy for rash. Punch biopsy of the rash was consistent with non-Hodgkin’s lymphoma (mantle cell lymphoma) which was again confirmed by lymph node biopsy. He had two cycles of chemotherapy followed by autologous stem cell transplantation. His IgE levels normalized post treatment.

Patient Presentation and Testing:
Patient is a 49 year old Caucasian male presented to the Allergy clinic for evaluation of Chronic Urticaria, which initially started about a year ago. It was a pruritic rash involving arms, legs and back. He was evaluated by an allergist at that time and found to have negative skin prick testing to environmental allergens. He was prescribed oral antihistamines and topical steroids which helped initially but recurred few months later, with much worse symptoms. He did not have an adequate response to oral or topical steroids and antihistamines. His primary care doctor noted elevated IgE levels and referred to our clinic for further management. His past medical history was significant for thyroid cancer with subsequent thyroidectomy and radioactive ablation, 20 years prior. Family history was significant for ovarian cancer in sister, colon cancer in mother and brain tumor in maternal aunt. At the time of presentation he also had a violaceous rash on hip which was present for 2 months along with pink raised blanchable rash on back, and numerous flesh papules on torso and extremities. Rest of his physical examination was normal. Skin prick test to environmental aeroallergens was negative. CBC and comprehensive metabolic panel were within normal limits. IgE level was more than 50,000 IU (Reference range 0-250 IU). Rests of Immunoglobulins (IgG, IgA, IgM and IgE) were within normal limits.

Diagnosis, Treatment and Patient Outcomes:
Due to atypical presentation of rash and non-responsiveness to steroids we referred the patient to a Dermatologist for skin biopsy. Punch biopsy revealed over expression of cyclin D1 diagnostic of mantle cell lymphoma. CT chest and abdomen revealed generalized lymphadenopathy. Lymph node and bone marrow biopsy were again consistent with mantle cell lymphoma. He was evaluated by an oncologist and underwent 2 cycles of chemotherapy with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) followed by autologous stem cell transplantation which is the standard therapy for mantle cell lymphoma. Patient is currently on Rituximab maintenance therapy to improve the remission rates. Repeat IgE levels one year after the treatment were 250 IU/L (Reference range 0-250 IU).
Underlying malignancy should be considered in patients with otherwise unexplained marked elevations of Immunoglobulin E.
Case Title: A Presentation of NEMO Deleted exon5 auto inflammatory Syndrome (NDAS) in a Young Male

Summary and Lessons Learned:
JM is a now 7 year old male with NEMO Deleted exon5 auto inflammatory Syndrome (NDAS) and now hypogammaglobulinemia. This auto-inflammatory disease is a de-novo mutation of the IKBKG gene. The IKBKG gene encodes the NF-kappa-B essential modulator (NEMO) which is a master regulatory protein of NF-kB (nuclear factor kappa light-chain enhancer of activated B-cells). NF-kB is a protein complex that has been long considered a pro-inflammatory signaling pathway, larger based on the activation of NF-kB by pro-inflammatory cytokines such as interleukin 1 (IL-1) and tumor necrosis factor alpha (TNF-alpha). He is one of only 3 people in the world thought to have this specific gene mutation. Clinically he presented with recurrent, granulomatous panniculitis, periodic fevers, joint swelling, and uveitis. This case is relevant to the practice of allergy/immunology as it sheds light on a new, more rare genetic mutation that may cause pro-inflammatory disease. The case’s relation to NF-kB signaling and its associated cytokines may be useful in therapeutic application, especially as his symptoms have been well-controlled now on an anti-TNF-alpha biologic agent.

Patient Presentation and Testing:
The patient initially presented to an outside institution with recurrent, granulomatous panniculitis starting around one month of age. Since then, he has developed other symptoms such as periodic fevers, rashes, joint swelling and uveitis. Of note, a brain MRI was obtained due to large head circumference which showed some cortical atrophy. Subsequent MRIs have been stable. His initial workup was significant for mildly elevated inflammatory markers only. Rheumatological panel has always been negative. He underwent genetic testing for periodic fever syndrome which was all negative. In September of 2014, he was seen at the NIH and underwent various genetic testing for CANDLE, PFS, and whole exam sequencing. He was initially placed on steroids with moderate improvement of symptoms. Methotrexate was eventually added with great response. Various biologics were tried including anakinra, tocilizumab, entanercept, infliximab. He was referred to our institution in May of 2016 after his previous rheumatologist/immunologist had moved away. He was on steroids, methotrexate, and infliximab at the time. His exact diagnosis of NEMO Deleted exon5 auto inflammatory Syndrome (NDAS) was made during a subsequent visit to the NIH while he receiving care at our institution. He was switched over to adalimumab with optimal control of symptoms. Of note, while he was at his previous institution, he was found to have protection of only 1/14 pneumococcal serotypes despite pneumovax. He was diagnosed with specific antibody deficiency. While at our institution, he eventually began to have low levels of IgG, IgA, IgM and was diagnosed with hypogammaglobulinemia. He will be starting IVIG.

Diagnosis, Treatment and Patient Outcomes:
He was eventually diagnosed with NEMO Deleted exon5 auto inflammatory Syndrome (NDAS) through whole genome sequencing obtained at the NIH. Prior to this formal diagnosis, he had been treated as a systemic JIA patient with steroids, methotrexate, and infliximab with good control of his symptoms. He was started on this regimen largely due to his symptoms of joint swelling, uveitis, and periodic fevers. His infliximab was later switched to adalimumab. Given what we understand about NF-kb -related disease and its pro-inflammatory affect, an anti-TNF-alpha agent is especially useful. He is currently followed by ophthalmology with no current signs or symptoms of uveitis. At his most recent visit, he had sustained low IgG, IgM, and IgA. Clinically however, he had not recently had recurrent infections. We prescribed IVIG in order to replace his immunoglobulins and avoid recurrent infections in the future.
Summary and Lessons Learned:
Microscopic polyangiitis (MPA) is a rare disease that mostly associated with antineutrophil cytoplasmic antibodies (ANCA), and kidney and lung are the most common involved organs. We report a case of a 9-year-old girl with ANCA-negative MPA who initially presents respiratory symptom. At first, she was diagnosed with atypical pneumonia based on her clinical symptoms and finding in chest x-ray, and interstitial lung disease was additionally suspected in chest computed tomography. Dyspnea was relapsed after initial improvement from oral corticosteroid therapy. From lung biopsy under the video assisted thoracoscopic surgery, she was finally diagnosed as MPA. Interestingly, ANCA was negative in the repeated blood tests. Oral cyclophosphamide with prednisolone administered as the initial treatment led her to remission and low dose prednisolone and azathioprine were administered as the maintenance treatment. The treatment response is good, so her clinical symptoms, pulmonary functions, and radiologic findings have been much improved.

Patient Presentation and Testing:
A 9-year-old girl had cough, rhinorrhea, sputum, and dyspnea for 16 days and was given initial diagnosis of upper respiratory infection. However the symptoms did not improve after cold medications, even dyspnea was aggravated from 6 days ago. Chest X-ray showed peribronchial hazy infiltration in both lung, and she felt dyspnea and fatigue from activity. Chest CT scan done after admission revealed diffuse bronchocentric ground glass opacity and consolidations in bilateral lungs that was suspected of atypical pneumonia probably. Initial Percutaneous pulse oxymeter indicated 92% at the time of admission, and 88% at the 3rd admission day without oxygen supplement. BAL was done at 4th hospital day, that showed 42% of macrophage, 49% of segmental neutrophils, and 9% of lymphocytes. PCR and culture studies for viruse, fungi, and bacteria were all negative. There was no effect of antibiotics. Initial improvement after oral corticosteroid, her symptoms aggravated again. So lung biopsy was performed, and microscopic polyangiitis was confirmed.

Diagnosis, Treatment and Patient Outcomes:
Patients with microscopic polyangiitis often showed relapse after corticosteroid only treatment. For remission and continuous symptom control, cyclophosphamide with prednisolone as an initial treatment and long-term low dose prednisolone and azathioprine are necessary. The treatment response for our patient was good. Respiratory symptoms, pulmonary functions, and radiologic findings have been much improved.
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Case Title:
Acute Generalized Exanthematous Pustulosis Caused by Praziquantel

Summary and Lessons Learned:
Praziquantel is the drug of choice for treatment of parasitic infections by trematodes or cestodes. In particular, it is widely used in endemic countries for Schistosomiasis to decrease the number of people infected and, consequently, the spread of the disease. Although Praziquantel has some known adverse effects, it is regarded as safe generally for global use. Therefore, Praziquantel is on the World Health Organization's List of Essential Medicines. It is estimated that about one hundred million people take Praziquantel throughout the world every year, but a search of the literature showed that only five cases of anaphylactic reaction have been attributed to Praziquantel. Acute generalized exanthematous pustulosis (AGEP) characterized by acute onset of numerous sterile, non-follicular pinhead sized pustules, is a rare and severe cutaneous reaction usually triggered by drugs. Patients who develop AGEP occasionally require treatment in an intensive care unit because it can progress to multiple organ dysfunction. We present the first case of AGEP due to Praziquantel as the literature is concerned. A 30-year-old previously healthy Japanese man was admitted to the hospital complaining of a high fever and pruritic generalized maculopapular erythematous eruption affecting the face, neck, trunk and upper arm. The day before admission, he took Praziquantel to for the treatment of Diphyllobothriasis. Over the next three days, he developed pinhead sized, non-follicular pustules mainly in the intertriginous area on a diffuse erythematous background. Laboratory tests showed leukocytosis. Skin biopsy showed spongiform subcorneal pustules with perivascular inflammatory infiltrate consisting of neutrophils, eosinophils and lymphocytes. The non-follicular pustules spontaneously resolved without a systemic corticosteroid and proceeded to desquamate. Based on the clinical course, laboratory findings and histopathological features, he was diagnosed with AGEP due to Praziquantel. He was discharged from the hospital on day 12 after he took Praziquantel, because all cutaneous lesions completely resolved and he became afebrile. In conclusion, Praziquantel causes not only mild adverse reactions but also severe ones such as an anaphylactic reaction or AGEP. It is so rare that doctors and field workers may overlook them especially in developing countries, but they should be aware of these reactions.

Patient Presentation and Testing:
A 30-year-old previously healthy Japanese man, who works as a chef on a luxury cruise ship, presented to the hospital in order to be prescribed anthelmintics. He was asymptomatic but eggs of Diphyllobothrium nihonkaiense were found in his stool when he was examined by an annual detection survey for parasitic infection by his company. He habitually had ingested fish such as salmon cooked by Sous-vide. He had no previous drug allergy and no personal or family history of skin disease. He was prescribed Praziquantel (Biltricide®) 600 mg per day for one day. On the day after he took Praziquantel, he took Acetaminophen 2,400 mg per day, Fexofenadine Hydrochloride 120 mg per day and Loxoprofen sodium 60 mg per day. Laboratory exams on the day of admission showed the following results : C-reactive protein 109.6 mg/l, white blood cells 10,800 /μl with 8,964 /μl polymorphonuclear neutrophils. Serologic evaluation for viruses (Cytomegalovirus, Epstein-Barr virus, Human Herpesvirus-6, Hepatitis B virus, Hepatitis C virus) and for autoimmune diseases (Systemic lupus erythematosus, Dermatomyositis, ANCA-associated vasculitis) were negative. Over the next three days, he developed pinhead sized, non-follicular pustules mainly in the intertriginous area on a diffusely erythematous background. Results of blood and pustules cultures were negative. Histopathological examination from the pustular lesion showed spongiform subcorneal pustules with perivascular inflammatory infiltrate...
consisting of neutrophils, eosinophils and lymphocytes. There were no eggs and segments of the Diphyllobothrium in stool samples which were collected before and after taking Praziquantel. Capsule endoscopy was also negative.

**Diagnosis, Treatment and Patient Outcomes:**
Approximately 8 days after he took Praziquantel, the non-follicular pustules spontaneously resolved without additional treatment e.g. a systemic corticosteroid and were followed by desquamation. He was discharged from the hospital on day 12 after he took Praziquantel, because all cutaneous lesions completely resolved and he became afebrile. He satisfied all the following five criteria which have been suggested for the definition of AGEP: 1) several dozens of small, mostly non follicular pustules arising on a widespread edematous erythema; 2) Typical histopathological changes; 3) fever > 38°C; 4) blood neutrophil counts above 7×109/L; and 5) acute evolution with spontaneous resolution of pustules in less than 15 days. In addition, according to an AGEP validation score which was developed to confirm the diagnosis by the EuroSCAR group, he scored 12, which indicated a definitive diagnosis of AGEP. There has been no recurrence of the eruption for 6 months.
A Successful Case Of Pomalidomide Administration In Patient With Alleged Lenalidomide Stevens–Johnson Syndrome

Summary and Lessons Learned:
It was hypothesized that he would be at high risk for recurrence of SJS since lenalidomide and pomalidomide are closely related. Therefore, the protocol was designed to minimize this chance. Success was achieved and the patient is now on treatment. There is no evidence in the literature to indicate that cross-reactivity exists between these two medications; however, since they share similar molecular structure, it made sense to treat him as indicated to minimize any chance of recurrence of SJS. SJS is perceived not to be amenable to desensitization; however, in this case, the possibility exists that the protocol utilized successfully desensitized him enabling him to receive pomalidomide. The protocol may be useful in future situations in which a medication is absolutely necessary for the welfare of the patient in spite of the fact that a related medication allegedly caused SJS. Use of this protocol may have desensitized him against recurrence of SJS.

Patient Presentation and Testing:
A 32 yr male with multiple myeloma developed biopsy proven Stevens-Johnson syndrome (SJS) attributed to lenalidomide, an immunomodulatory thalidomide derivative. Subsequently, other treatments were unsuccessful. The oncologist indicated that the only treatment alternative was pomalidomide, also immunomodulatory thalidomide derivative. Both pomalidomide and lenalidomide are derived by adding an amino group to the fourth carbon of the phthaloyl ring of thalidomide. Pomalidomide differs from lenalidomide in that it has an additional carbonyl group in the phthaloyl ring. There is no documented allergenic cross-reactivity between lenalidomide and pomalidomide.

Diagnosis, Treatment and Patient Outcomes:
The etiology of this patient’s SJS is unknown. However, it was attributed to lenalidomide. SJS developed 10 days following its administration and resolved following discontinuation. The patient, family, consultants, and oncologists met and discussed the risk/benefit of prescribing pomalidomide via a “desensitization” protocol (Table 1). Pomalidomide was given orally as an outpatient; he was observed for one hour thereafter. On first week, he received 3 doses (Monday 0.00025mg, Wednesday 0.00125mg, Friday 0.0025mg). The second week, 2 doses (Tuesday 0.0125mg, Friday 0.025mg). The third week, 3 doses (Monday 0.125mg, Wednesday 0.25mg, Friday 0.5mg). The fourth week, 2 doses (Tuesday 0.75mg, Friday 1mg). The fifth week, 3 doses (Monday, Wednesday and Friday, 1mg each). By week six, he tolerated 1mg daily. No changes in laboratory data were noted. He took prednisone 15 mg TID daily and diphenhydramine 50 mg PO as needed throughout the escalation doses. Prednisone was discontinued after completing the protocol.
Cardiac transplantation and reaction to heparin

Summary and Lessons Learned:
A 70-year-old male with cardiomyopathy underwent desensitization to heparin prior to cardiac transplant.

Patient Presentation and Testing:
A 70-year-old male with cardiomyopathy was referred for desensitization to porcine heparin. Twenty minutes after a heparin drip for atrial fibrillation, he developed an intolerable sensation of “pins and needles” on his head, torso, and upper extremities, became flushed, and experienced generalized erythema. Diphenhydramine, 12.5mg, IV, was administered. The systemic allergic reaction (SAR) lasted 30 minutes. He was removed from the cardiac transplant list due to the heparin reaction. Alternatives to heparin (ancrod, nafamostat, and bivalirudin) were not acceptable to the transplant team.

Diagnosis, Treatment and Patient Outcomes:
The consultants diagnosed the patient with a SAR to heparin. However, there are no absolute criteria, in this case, to differentiate a SAR from an idiosyncratic reaction. He underwent heparin administration using a modified desensitization protocol in the intensive care unit over four days (hours 0–12, 0.5 units/h; hours 12–24, 1.5 units/h; hours 24–36, 4.5 units/h; hours 36–48, 13.6 units/h; hours 48–60, 40.8 units/h; hours 60–72, 122.5 units/h; hours 72–84, 367.4 units/h; hours 84–96, 1008 units/h). One hour prior to discontinuation of the heparin drip, heparin 5000 units was administered subcutaneously (subQ). Nausea, dizziness, and flushing occurred two hours later. The heparin was reduced to 1000 units, followed by 3000 units 6 hours later, and 5000 units the following morning, all subQ. He was maintained on heparin 5000 units subQ every 12 hours. His cardiac transplant status was upgraded and he successfully underwent cardiac transplantation.

Case Title:
A protocol for skin testing and graded dose challenge in a case of a suspected hypersensitivity reaction to isoniazid

Summary and Lessons Learned:
A 59 year-old Nepalese woman with a recent diagnosis of latent tuberculosis (TB) was referred to Allergy Clinic for evaluation of urticaria and angioedema after starting treatment for latent TB. Approximately 2-3 weeks after starting isoniazid, she developed hyperglycemia. Her PCP added insulin degludec to her DM2 regimen and within 2-3 days, she developed urticaria and facial angioedema. Isoniazid and insulin degludec were stopped, and she received steroids and oral antihistamines with resolution of symptoms.

The allergy work up included skin testing with isoniazid in the patient and a healthy subject. Skin testing was negative in both the patient and control subject. We then performed a graded dose challenge with isoniazid. Patient tolerated the procedure with no adverse reactions. She was instructed to resume a 300 mg daily dose of isoniazid and is currently doing well.

Of note, no standardized non-irritating concentrations are reported for isoniazid. Here, we present a protocol for skin testing and graded dose challenge to isoniazid. This is relevant to the practice of allergy since the number of anti-tuberculosis drugs are limited, and there is often a need to reintroduce anti-TB drugs after an adverse drug reaction.

Patient Presentation and Testing:
A 59-year-old Nepalese woman with diabetes mellitus, type 2 (DM2) and recent diagnosis of latent tuberculosis (TB) was referred to Allergy Clinic for evaluation of urticaria and angioedema after starting treatment for latent TB. The patient was diagnosed by Interferon-γ release assay (IGRA) testing and started on isoniazid. Approximately 2-3 weeks after starting isoniazid, she developed hyperglycemia. Her PCP added insulin degludec to her DM2 regimen. Within 2-3 days, she developed urticaria and facial angioedema. She presented to the ED where isoniazid was stopped, and she was treated with steroids and loratidine. In addition, insulin degludec was switched to insulin glargine, which she is now tolerating well. Her Infectious Disease provider started rifampin as an alternative treatment for latent TB at 11 days from the initial reaction. Within 3 days, the patient had recurrence of her facial angioedema without urticaria. Rifampin was stopped and she received a 7 day course of prednisone and loratidine with resolution of her symptoms.

The allergy work up was performed within two months of the onset of symptoms and included skin testing (prick testing and intradermal testing, all concentrations in duplicate) with isoniazid in the patient and a healthy control subject. A 300 mg tablet of isoniazid was diluted in sterile water. Skin prick testing was performed with 1:10 dilution (30 mg/ml) and full dose, while intradermal testing was performed at 1:100 dilution (3mg/ml). Skin testing was negative in the patient and the control subject. Both patient and control reported mild irritation to the intradermal test.

We then performed a graded dose challenge with isoniazid at doses of 3 mg, 30 mg, and 150 mg at 30 minute intervals, followed by another 150 mg dose and observation for 2 additional hours. Patient tolerated the procedure without adverse reactions. She was instructed to resume a 300 mg daily dose of isoniazid and is currently doing well.

Since no standardized skin testing exist for isoniazid, we performed skin testing at different dilutions (prick testing, 1:10 and full dose and intradermal testing, 1:100 dilution in duplicates) to rule out false positives due to drug irritation. We confirmed these results in a healthy subject who has never received isoniazid. Because of the unavailability of optimal negative predictive values, we also performed a graded dose challenge to confirm tolerance.

Diagnosis, Treatment and Patient Outcomes:
The pathogenesis of angioedema and urticaria is not clear. It is possible that the patient had an IgE mediated reaction, but we do not think it was caused by isoniazid as she was able to tolerate isoniazid upon recurrent exposure through
incremental challenge. Hypersensitivity reactions to insulin digludec, including angioedema and urticaria, were reported in 0.9% in the initial clinical trials, and it is possible that the patient had an IgE mediated reaction to insulin digludec. We did not perform skin testing to confirm this suspicion as the patient was already tolerating an alternative long acting insulin. Further, the patient developed angioedema after being switched to rifampin. There are a few case reports of rifampin induced angioedema, although the pathogenesis is still unclear. Finally, the etiology of the urticaria and angioedema may be idiopathic. However, patient has no prior history of urticaria and angioedema, but this does not rule it out completely. Of note, a serum tryptase drawn at around 2 months from initial reaction was negative and makes a mast cell disorder unlikely.

The recommended regimen by WHO for latent TB consists of isoniazid, rifapentine plus isoniazid or rifampin. Since the number of anti-tuberculosis drugs are limited, there is often a need to reintroduce anti-TB drugs after an adverse drug reaction. In addition, our patient has concomitant diabetes; a diagnosis that is currently the number one opportunistic condition associated with reactivation TB nowadays. Here, we were able to reintroduce isoniazid in a patient with latent TB after demonstrating tolerance. The patient was directed to resume her daily dose of isoniazid 300 mg daily per recommendations by the Infectious Disease provider. She is tolerating isoniazid at a phone call follow up 4 weeks later.
A 54 year old male with a history of chronic obstructive pulmonary disease (COPD) and steroid hypersensitivity presented with an acute COPD exacerbation. He previously experienced immediate and delayed reactions to prednisone and methylprednisone, but tolerated inhaled mometasone and budesonide. He was unable to undergo diagnostic testing due poor lung function and acute dyspnea. Using Coopman’s classification of corticosteroids, he was successfully challenged to a different corticosteroid class: intramuscular triamcinolone acetonide. He tolerated this medication with improvement in symptoms. This case demonstrates that using the classification of corticosteroids can be a helpful tool in considering alternate options for those with corticosteroid allergies.

**Patient Presentation and Testing:**
The patient was a 54 year old Caucasian male with a history of COPD requiring oxygen therapy and multiple drug allergies including corticosteroid hypersensitivity who presented with an acute COPD exacerbation. His maintenance COPD regimen included mometasone/formoterol 200/5 mcg 2 puffs twice daily, tiotropium 1 inhalation daily, and albuterol as needed. He tolerated inhaled budesonide 1mg/ml twice daily without adverse effect. However, he had immediate and delayed reactions to multiple systemic corticosteroids making treatment of acute exacerbations challenging. Oral methylprednisolone resulted in immediate diffuse erythroderma. Intravenous methylprednisolone caused immediate onset of pruritus, blisters, and throat swelling. Oral prednisone caused delayed joint swelling and pain. Oral hydrocortisone resulted in diffuse pruritus and delayed lip blisters, which were directly observed in clinic. Despite the adverse reactions, he remarked on significant improvement in lung symptoms with corticosteroids. His lung function was deemed too poor (forced expiratory volume in one second of 33%) to undergo skin testing to corticosteroids. Patch testing had been planned for the future, however when he presented with acute dyspnea and hypoxia, a more immediate plan was required.

**Diagnosis, Treatment and Patient Outcomes:**
This patient presented with a therapeutic dilemma as he tolerated inhaled corticosteroids but developed reactions to oral and intravenous corticosteroids. He was admitted to the hospital for further evaluation. According to the Coopman’s classification for corticosteroids, the patient reacted to multiple agents in Class A, but had tolerated budesonide and mometasone from Classes B and D1, respectively. Therefore, the decision was made to challenge him to intramuscular triamcinolone acetonide (Class B). He was challenged to 20mg daily but developed isolated lip blisters. He noted significant improvement in his dyspnea so his dose was decreased to 10mg daily which he tolerated for a 5 day course. Triamcinolone acetonide was tolerated via self-administration at home for future exacerbations.
Case Title:
DESENSITIZATION TO ANTITUBERCULOSIS DRUGS IN A STEVENS JOHNSON SYNDROME

Summary and Lessons Learned:
Desensitization is contraindicated in severe adverse drug reactions, but there are cases where there is no treatment alternative. We describe a case of desensitization to anti-tuberculosis drugs in a patient with Stevens Johnson syndrome using a specifically designed premedication, comedication and desensitization protocol.

Patient Presentation and Testing:
A 6-year-old male patient presented with the following history: His 9-year-old sister died due to Steven Johnson syndrome secondary to antituberculosis drugs used to treat military tuberculosis. The patient had a diagnosis of lymph node tuberculosis determined in October 2015 by lymph node biopsy. He began treatment with isoniazid and rifampicin and presented 15 days later with an adverse reaction consisting of erythematous dermal lesions that evolved to blistered lesions affecting 30% of the skin surface, including oral mucosa and a positive Nickolsky sign. He required hospitalization in the intensive care unit and received systemic corticosteroids, intensive fluid therapy, and assessment and management by our Clinical Immunology and Allergy service.

Diagnosis, Treatment and Patient Outcomes:
Demonstrating the absence of associated immunodeficiency (negative or normal ELISA test for HIV, immunoglobulins, blood count, cultures and PCR for Cytomegalovirus) and with the need to treat lymph node tuberculosis and the lack of acceptable alternatives, it was decided to initiate desensitization to isoniazid and rifampin with a slow oral desensitization scheme accompanied by premedication and co-medication. This protocol was begun 4 weeks after hospital discharge, which was 6 weeks after the onset of symptoms. He had no reactions during the desensitization period.

Subsequent to the desensitization, monthly monitoring with history and physical examination was continued for the first 3 months and then bimonthly until maintenance treatment was completed for one year. He manifested no clinical adverse reactions during this year of treatment. Hepatic Function Tests, urianalysis, blood chemistry (Glucose, urea, creatinine, uric acid, cholesterol and triglycerides) were evaluated at 3, 6 and 12 months of treatment and were normal. Desensitization has been considered to be absolutely contraindicated in Stevens Johnson Syndrome and Toxic Epidermal Necrolysis. However given the need for antituberculosis treatment and the absence of first-line treatment alternatives in this patient, it was necessary to propose a new desensitization scheme for rifampicin and isoniazid. Selection of the specific desensitization protocol will depend on the conditions of the patient, the comorbidities present and the type of adverse reaction presented.

There is no consensus on the value of premedication or co-medication during desensitization. Considering that the adverse reactions associated with antituberculosis drugs are mainly delayed, we chose systemic steroids, antihistamines (H1 and H2) and antileukotrienes for pre-medication and co-medication.
In conclusion, the slow desensitization scheme for antituberculosis drugs in a patient who had presented with Stevens Johnson Syndrome after receiving those drugs was effective, using the described protocol and with continuous hospital monitoring for the first 10 days. Such an approach should still be used very cautiously and only when a viable treatment alternative is not available, after a careful assessment of the risk and benefit of the treatment, and after thorough discussion with the patient (and parent if a child) and informed consent obtained.
Summary and Lessons Learned:
Gonadotropin-releasing hormones (GnRH) analogues are the mainstay of treatment for precocious puberty. Hypersensitivity reactions to GnRH analogues are extremely rare. A 6 year old girl developed an immediate-type hypersensitivity reaction to intramuscular Triptorelin Acetate (Decapeptyl) prescribed for central precocious puberty. As no viable alternatives were available, a novel 5-step desensitization protocol was designed which allowed her to continue receiving treatment safely.

Skin prick and intradermal tests performed at the 6th dose of Triptorelin Acetate after starting desensitization showed equivocal findings. The undiluted drug form was also found to be non-irritating in healthy controls. A basophil activation test (BAT) performed at the 12th dose of Triptorelin Acetate after starting desensitization showed failure of normal upregulation of basophil activation markers CD63 and CD203c under Triptorelin and anti-IgE stimulation, but normal responses to anti-IgE in the control – evidence of basophil anergy induced by desensitization. Limitations include the lack of pre-desensitization skin prick, intradermal tests and basophil activation tests due to logistical limitations and the family’s personal preferences.

We thus demonstrate here that desensitization to Triptorelin Acetate can be safely performed with this standardized protocol under appropriate allergy specialist supervision and monitoring, allowing the patient to continue receiving first-line optimal therapy. We also demonstrate the utility of BAT in monitoring response to desensitization. To our knowledge, this is the first report of induction of basophil anergy in drug desensitization, shedding further light on one of the mechanisms involved in successful immunotherapy.

Patient Presentation and Testing:
The patient first presented at age 5 years and 4 months with bilateral breast buds and, after evaluation, was diagnosed with central precocious puberty. She was started on monthly depot injections of Triptorelin, a GnRH analogue, to arrest further progression into advanced puberty.

She received intramuscular (IM) Triptorelin Embonate (Diphereline) as her first dose but was switched to IM Triptorelin Acetate (Decapeptyl) in the second month as she experienced excessive injection site pain after the IM Triptorelin Embonate dose, which is a known side effect. After her third dose of IM Triptorelin Acetate, the patient developed generalized urticaria an hour after the injection, which resolved with one dose of an oral anti-histamine. There was otherwise no angioedema or systemic involvement and vital signs were stable throughout. The clinical history and temporal relation of reaction to the Triptorelin Acetate injection was suggestive of an immediate-type hypersensitivity reaction to Triptorelin Acetate. A subsequent open drug challenge to IM Triptorelin Acetate was also positive.

Diagnosis, Treatment and Patient Outcomes:
As there are no alternative GnRH analogues available in Singapore, where this patient lives, a referral was made to an allergy specialist and a 5-step desensitization regimen to Triptorelin Acetate was designed to allow her to continue receiving optimal medical therapy safely. The patient received half her usual dose of IM Triptorelin Acetate with oral Prednisolone and oral Cetirizine the night before and 30 minutes before her Decapeptyl dose at the first visit. She was
monitored uneventfully for 4 hours in the outpatient Day Therapy Centre located within our tertiary hospital. She was discharged well, with an Epipen Junior, anaphylaxis action plan and oral Cetirizine as standby medications as a precautionary measure.

The second step was performed a month later at the next planned dose, with the same pre-medications, but with the full dose of IM Decapeptyl. Subsequent monthly injections of Triptorelin Acetate were administered with tapering pre-medications (until only oral Cetirizine given 30 minutes before the planned injection remained) without any immediate reactions. She reported episodes of mild, intermittent urticaria without systemic involvement occurring 2 – 3 weeks after each injection, consistent with interval reactions which are attributable to the delayed release of the depot, which were easily managed with antihistamines. The intensity and frequency of urticaria decreased with each step of the desensitization protocol and resolved completely from her 8th Triptorelin Acetate injection onwards. She now continues to receive monthly IM Triptorelin Acetate doses with oral Cetirizine as the single pre-medication, 30 minutes before each injection without reactions.

Skin prick (SPT) and intradermal tests (IDT) were performed on the day of the 6th Triptorelin Acetate injection after starting desensitization. The family’s preferences and logistical constraints did not allow us to perform skin tests between Triptorelin Acetate doses or before desensitization. Undiluted Decapeptyl solution was used for SPT and IDT with appropriate positive and negative controls. Constant agitation of the reconstituted solution was performed to prevent crystallization. The undiluted drug concentration was found to be non-irritating on two healthy control subjects. The patient’s SPT and IDT was equivocal [0 min: Erythema 4x4mm, Wheal 15x5mm; 15min: Erythema 15x15mm, Wheal 4x4mm], which was likely a result of waning IgE response to Triptorelin Acetate with progressive desensitization. A Basophil Activation Test (BAT) was performed prior to the 12th Triptorelin Acetate injection after initiation of her desensitization protocol, with Triptorelin peptide [(D-Trp6), Merck, USA] as well as anti-human IgE antibody (G7-18; BD Biosciences, San Jose, California) as a positive control. The basophil activation markers CD63 and CD203c both remained at baseline levels in both the patient and healthy control. The patient’s basophils failed to upregulate CD63 and CD203c in the presence of anti-human IgE, whereas this normal response was maintained in the healthy control. This suggested a state of basophil anergy in the patient which correlated with the clinical picture of successful desensitization.

This is the first reported desensitization regime for a patient with hypersensitivity to a GnRH analogue – Triptorelin Acetate. Hypersensitivity reactions to GnRH analogues, though rare, can nevertheless be potentially life-threatening. Switching to an alternative GnRH analogue still carries a small risk of cross-reactivity. This novel desensitization protocol allowed for the continued safe use of Triptorelin Acetate, an essential medical therapy for idiopathic central precocious puberty, in a setting where no alternative therapeutic options were available.

There are currently no validated SPT and IDT protocols for Triptorelin Acetate. We demonstrated that undiluted Triptorelin Acetate was non-irritating for the diagnostic evaluation of Triptorelin hypersensitivity reactions. BAT analysis also demonstrated that basophil anergy was induced by the successful desensitization process. Thyagarajan et al. had previously demonstrated that peanut oral immunotherapy was able to induce basophil anergy, a state of basophil suppression which is pathway-specific but not antigen specific. The proposed mechanism for the effector cell anergy likely involves repeated allergen stimulation suppressing signalling pathways downstream of the IgE receptor FceRI, resulting in downregulation of basophil responses.

The slow sustained release of Triptorelin Acetate, through its depot form administered intramuscularly, also likely augmented the efficacy and safety of the desensitization process compared to drugs administered orally or intravenously which are quickly absorbed and attain high blood concentrations soon after administration.

Limitations include the lack of pre-desensitization skin prick, intradermal tests and basophil activation tests due to logistic limitations and the family’s personal preferences.

We demonstrate here that desensitization to Triptorelin can be safely performed with this standardized protocol under appropriate allergy specialist supervision and monitoring; the utility of BAT in monitoring response to desensitization and to our knowledge, the first report of induction of basophil anergy in drug desensitization, shedding light on one of the mechanisms involved in successful immunotherapy.
Successful Vaccination with Tdap after Adverse Reaction to DTaP in a Pediatric Patient

Summary and Lessons Learned:
DTaP vaccine, a critical part of the pediatric immunization schedule, is administered to patients at 2, 4, 6, 15 months and between 4-6 years of age. Contraindications to receiving DTaP include encephalopathy within 7 days of administration or anaphylaxis after a previous dose or to a vaccine component. We describe a patient who initially developed symptoms of urticaria with severe abdominal pain that responded well to epinephrine, and was skin tested years later to both DTaP and Tdap. His skin test to Tdap was negative but positive to DTaP. These findings raise suspicion that this patient may have reacted to a specific component that is found in the DTaP but not Tdap vaccine. Because Diphtheria/tetanus vaccines are prepared in a medium derived from cow’s milk, some experts proposed that intolerance to the vaccines may be due to the presence of residual casein. In accordance with the 2012 Adverse Reaction to Vaccines Practice Parameter, we attempted to identify the culprit antigen. Our patient had a history of bloody stools after ingestion of milk during infancy with positive prick skin testing and immunocap to milk, but outgrew his milk allergy over time. We attempted to determine the culprit antigen in the DTaP administered for his fourth dose on the date of reaction, but were unable to obtain the lot number and specific manufacturer brand. At present, there is limited information and guidance regarding the best approach to challenge for our patients with adverse events following immunization. To the best of our knowledge, this is the first case report of a patient who underwent skin testing to DTaP and Tdap and successful vaccination. This case highlights the fact that by following 2012 Practice Parameter protocol, patients who have previously not tolerated vaccination to DTaP can be skin tested to and safely receive Tdap vaccine.

Patient Presentation and Testing:
We evaluated an 11-year-old male for an adverse reaction following simultaneous vaccination with DTaP and MMR. His mother reported a history of urticaria, emesis, respiratory distress and lethargy within one hour after his vaccinations. Medical records from the primary care provider and the emergency department documented urticaria, nausea and abdominal pain without emesis and no respiratory symptoms, which resolved after administration of epinephrine. The patient had already received 4 doses of DTaP vaccine in the first 2 years of life without incident. After his adverse reaction, he was skin tested to MMR and latex which were both negative. He has also received the influenza vaccine without reaction since the skin testing was done and negative. We performed skin testing to DTaP and Tdap in accordance with the 2012 Practice Parameter guidelines. We planned a cautious challenge to Tdap if the skin testing was negative or desensitization if the skin test to Tdap was positive.

Diagnosis, Treatment and Patient Outcomes:
Prick skin testing was negative to DTaP and Tdap first using a 1:10 dilution and then full-strength with appropriate positive and negative controls. Intradermal testing was performed to both vaccines diluted 1:100 with a positive result to DTaP 8 mm wheal and negative result to Tdap. Tdap was administered as a cautious challenge without difficulty. We recommended that this child receive Tdap for future doses of diphtheria, tetanus, and pertussis vaccination. Following the Practice Parameter protocol we were able to safely skin test and administer Tdap vaccine for a patient who had not tolerated vaccination with DTaP. Due to anxiety following his reaction the family was hesitant to proceed with the recommendation schedule, we were able to provide the subsequent vaccines.
Case Title:
Drug-induced liver injury in the setting of previously undiagnosed primary biliary cirrhosis.

Summary and Lessons Learned:
Primary biliary cirrhosis (PBC) and drug-induced liver injury (DILI) have distinct hepatic pathologies but can have similar clinical presentations. Supporting laboratory studies, patient presentation, history, and histology may delineate these two distinct entities. However, there is great overlap including patient presentation and histologic staining of liver biopsies, which may present a diagnostic quandary to the etiology of liver injury. We present a 69-year-old woman with multiple co-morbidities, including rheumatoid arthritis, hypothyroidism, prior splenectomy secondary to idiopathic thrombocytopenic purpura, and prior history of breast and renal cancer, who came to the emergency room with acute onset fever, nausea, and malaise. Prior to admission, she had a history of recurrent streptococcal pneumonia infections, for which she was started on prophylactic oral penicillin and followed closely in an outpatient setting. On presentation, her initial labs revealed elevated transaminases and accompanying leukocytosis meeting SIRS criteria. She was initially treated with broad-spectrum antibiotics (meropenem and piperacillin-tazobactam) for a presumed pneumonia v. ESBL UTI, but despite the addition of these antibiotics, there was no improvement in labs or symptomatology. Her inpatient stay was also notable for new onset eosinophilia, which coincided with piperacillin-tazobactam administration and worsened in the setting of antibiotic transitions to ceftriaxone and, later, levofloxacin. With other infectious etiologies ruled out, all antibiotics withheld, and an MRCP and liver ultrasound showing no gross evidence of bile outflow obstruction in the face of a stagnantly elevated alkaline phosphatase, she underwent a liver biopsy. The biopsy showed evidence of inflammatory infiltrates concerning for either PBC or DILI. With autoantibodies consistent with PBC, this patient was eventually started on ursodeoxycholate and her alkaline phosphatase returned toward normal. This coupled with the cessation of antibiotics seemed to hasten the improvement of her liver injury. Diagnostic testing including liver enzymes and biopsy may provide insight to the underlying etiology, but in this case the stains would look similar with eosinophilic infiltrates. It becomes a diagnostic quandary to evaluate a patient for drug-induced injury when underlying liver pathology is present. Great care and effort must be shown to separate the two pathologies for eventual symptom remission. This case serves as a reminder that Occam’s razor does not always apply.

Patient Presentation and Testing:
The patient is a 69-year-old woman with multiple co-morbidities who presented to the Tulane University emergency room with fever, tachycardia, and a one-day history of malaise and significant nausea. The patient’s history is notable for multiple co-morbidities including COPD, CHF, Diabetes Mellitus Type 2, Atrial Fibrillation, hypothyroidism, Rheumatoid Arthritis with lung involvement, a history of breast and kidney cancer, ITP s/p splenectomy, and a history of multiple admissions due to pneumococcal sepsis. She is followed by multiple subspecialist in the outpatient setting, including an infectious disease physician who started her on Penicillin VK prophylaxis after a recent hospitalization for community acquired pneumonia, she had been faithfully taking this antibiotic daily for one month prior to presentation. Additionally, she had chronically been on multiple medications associated with DILI including aspirin, atorvastatin, and diltiazem.

Upon initial assessment by our consult service the patient had been hospitalized for 6 days, during which she was under the care of the primary Internal Medicine service, as well as additional consulting services including gastroenterology
and infectious disease. We were initially consulted due to the patient’s increasing peripheral eosinophilia and a possible drug rash concerning for Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). Her absolute eosinophil count (AEC) had increased to 1000 from an admit value of 0. Notably, she has had multiple previously documented episodes of eosinophilia, all in the setting of antibiotics that were given on her many admissions for varying infectious sources varying from ESBL+ Proteus UTI to a streptococcal pneumonia resulting in sepsis and an intensive care stay. At the time of our initial consultation the patient was notable to be itchy with no visible rash; her workup for PBC had already been started by our GI colleagues. While the patient’s RegiSCAR score was only 2, making DRESS unlikely, her overall clinical picture however was not entirely consistent with PBC.

The patient’s family history, social history, and environmental history were noncontributory. Her initial physical evaluation was also not notable for any rash consistent with DRESS. The lab values at the time of evaluation were notable for AST-118 U/L, ALT of 108 U/L, AlkPhos-585 U/L; with a continued leukocytosis of 18.8; comparatively, these labs on admission were: AST 719 U/L, ALT 601 U/L, AlkPhos 413 U/L, GGT 488, and WBC 15.6. The patient’s IgAM were within normal limits, as were her bilirubin levels. Her creatinine and anemia were stable prior lab studies. At the time of initial consult her anti-mitochondrial Abs had resulted positive at a value of 1 : 111.9 U (ref <1:40) had resulted and were positive. Her LFTs on admission were as follows: So we encountered a patient with improving LFTs being treated for a presumptive PBC in the setting of worsening eosinophilia.

The picture of elevated liver function tests in the setting of fever, malaise, and pruritus as well as improvement on ursodeoxycholate point toward a diagnosis of PBC, particularly in the setting of positive anti-mitochondrial antibodies. However, worsening eosinophilia as well as a patient reported rash with antibiotic administration demonstrates that DILI could not be ruled out. At the time of initial assessment, we advised to avoid Penicillin containing agents and to follow the liver biopsy in order to identify the etiology of her liver injury.

**Diagnosis, Treatment and Patient Outcomes:**

Throughout her admission, the patient had a broad differential for the etiology of her liver injury; the primary teams leading diagnoses included infection, autoimmune hepatitis, and DILI. However, in the setting of five days of antibiotics including piperacillin-tazobactam, Meropenem, Ceftriaxone, and Levofoxacin with persistent leukocytosis with no identifiable source of infection and continued lab evidence of liver injury, the focus shifted to primarily an autoimmune process v. DILI. To help clarify her diagnosis, she underwent a liver biopsy that demonstrated a pattern consistent with drug induced liver injury - moderate-severe portal and mild lobular infiltration of lymphocytes, neutrophils, and eosinophils. A diagnosis of DILI seemed most likely, but our GI colleagues and pathologist also believed that an early onset, underlying PBC was also present, which was reinforced by her profoundly elevated AMA.

While PBC may cause an eosinophilia, the sudden increase in her AEC after administration of piperacillin-tazobactam and continued elevation when transitioned to ceftriaxone when combined with the pathology findings of scattered portal and lobular mixed inflammation with focal cholangitis and minimal fibrosis were most consistent with DILI. This case demonstrates two overlapping pathologies, DILI in the setting of undiagnosed PBC. With eventual resolution of symptoms and continued improvement of LFTs and eosinophilia the patient was discharged to follow with us in clinic, where she was found to be in good health and at her functional and clinical baseline. Her labs were noted to be resolving toward normal with AST 27 U/L, ALT 24 U/L, AlkPhos 181 U/L, and GGT 87 U/L. We continue to support her diagnosis of PBC with a elevated AMA titer of 1:320 a month after admission. While the patient had improved, it was advised that utilization of unrelated cephalosporins may be appropriate for antibiotic use, but they should be done in a controlled environment and not in the setting of current liver pathology. She continued to take her ursodeoxycholate and was later seen by GI who advised she should take it indefinitely, or until her AMA sero-converts to negative. She has since had a humoral immune evaluation that showed pneumococcal antibody protection to 8/23 tested serotypes and has undergone a liver biopsy with pathology report pending. The patient’s clinical improvement highlights the importance of discovering this diagnosis prior to irreversible damage and liver failure due to hepatonecrosis.
Clindamycin Desensitization in a Pediatric Patient

Summary and Lessons Learned:
Clindamycin is a lincosamide antibiotic with broad spectrum antimicrobial coverage and is commonly used as an alternative to penicillins and cephalosporins. Hypersensitivity to clindamycin is rare and published guidance about management of clindamycin hypersensitivity is limited. We present an 8-year-old girl with recurrent distal humeral osteomyelitis due to methicillin-sensitive Staphylococcus aureus (MSSA). Patient’s clinical history was suggestive of hypersensitivity to clindamycin and was referred for allergy evaluation. Work up revealed positive intradermal skin testing to clindamycin at a concentration of 15 mg/ml (7 mm wheal, 20 mm flare) and clinical symptoms of hypersensitivity during a graded oral challenge, consistent with a diagnosis of clindamycin hypersensitivity. Despite this, oral clindamycin was determined to be the optimal antibiotic for her incompletely treated MSSA osteomyelitis, and the decision was made to pursue clindamycin desensitization. Patient underwent a 9-step rapid oral desensitization protocol to clindamycin. She successfully completed the desensitization. Following her rapid oral desensitization, she tolerated a full therapeutic course of clindamycin with oral pre-medications. Our experience provides a platform for future rapid oral desensitization of pediatric and adult patients.

Patient Presentation and Testing:
An 8-year-old girl presented with recurrent distal humeral osteomyelitis. She was empirically treated with intravenous (IV) ceftriaxone and vancomycin. After bone cultures grew methicillin-sensitive Staphylococcus aureus (MSSA), her antimicrobial therapy was changed to IV cefazolin. Eight days later, the patient developed a diffuse urticarial rash, vaginal itching, labial swelling, and hand and foot swelling. Cefazolin was discontinued; her symptoms improved but did not resolve completely. The following day, the patient was started on oral clindamycin. One hour after the first dose, she developed subjective throat tightness and worsening urticarial rash. Clindamycin was discontinued immediately. Over the next 48 hours, she developed waxing and waning lip swelling, urticarial rash, joint pain, and extremity swelling. Seventy-two hours after clindamycin was discontinued, her symptoms improved. Antimicrobial therapy with doxycycline was then started. Four days later, she developed nausea, emesis, and maculopapular rash. Doxycycline was discontinued, and the patient was referred for urgent allergy evaluation.

Due to treatment with antihistamines for the rash and pruritus, skin testing could not be performed immediately. Clindamycin was the preferred oral agent, but clinical history alone was insufficient to establish hypersensitivity versus persistent symptoms unrelated to clindamycin treatment. Thus, the patient underwent a three-step graded, oral challenge to clindamycin. She tolerated the first dose (1/100th of the full therapeutic dose [FTD]), but, after the second dose (1/10th FTD), she developed diffuse urticaria consistent with clindamycin hypersensitivity. She was treated with cetirizine and her urticaria resolved. After completing the treatment course of clindamycin, the patient later underwent clindamycin skin testing. Skin prick testing was negative, but intradermal testing was positive at a concentration of 15 mg/ml (7 mm wheal, 20 mm flare), consistent with clindamycin hypersensitivity.

Diagnosis, Treatment and Patient Outcomes:
The patient was determined to have clindamycin hypersensitivity. Alternative oral antibiotic therapies were considered; however, given past hypersensitivity reactions to cefazolin and Bactrim, oral clindamycin was determined to be the optimal antibiotic. Due to the urgent need to restart therapy, the decision was made to pursue rapid clindamycin desensitization. We performed a 9-step rapid oral desensitization to clindamycin. The goal dose was 30 mg/kg/day.
divided every 8 hours (300 mg/dose). Cetirizine 10 mg was given orally one hour prior to desensitization. The patient tolerated the desensitization and received multiple doses of clindamycin under inpatient observation. Following discharge, the patient developed intermittent urticarial rash and throat tightness after taking a dose of clindamycin. She was readmitted for adjustments to her premedication regimen and subsequently tolerated clindamycin without symptoms with the following premedication regimen: cetirizine 10 mg every 8 hours (1 hour before each dose), montelukast 5 mg daily (1 hour before the evening dose), and ranitidine 60 mg every 12 hours (4 hours before the afternoon dose, and 1 hour before the evening dose). She was discharged home and completed four weeks of oral clindamycin without further symptoms after adjustment of her premedication regimen. Her treatment course of clindamycin led to resolution of her MSSA osteomyelitis.
Case Title:
Autoimmune Progesterone Dermatitis Cessation After Menopause

Summary and Lessons Learned:
Case Description: A 50-year-old female presented with pruritic diffuse erythematous papules since 37 years of age, with a cyclical worsening from 5 days before menstruation until 2 days after its ending. She also reported concomitant diffuse arthralgia and some episodes of periorbital edema. First, she was submitted to an intradermal test with medroxyprogesterone acetate, which was positive at the concentration of 0.5 mg/mL after 6 hours of its application. Then, a cutaneous biopsy was performed, whose histopathology showed perivascular lymphohistiocytic infiltration with melanophages and mild collagen hyalinization, with negative direct immunofluorescence. A single-blinded oral challenge test with desogestrel 75 mcg was positive after 6.5 hours, with the appearance of pruritic diffuse erythematous thick papules and plaques. The patient was instructed to avoid progestogen-based contraceptives and underwent remission of the disease after menopause, at age 50. Discussion: Autoimmune Progesterone Dermatitis (APD) is a hypersensitivity reaction to endogenous or exogenous progesterone characterized by the appearance of cutaneous lesions at times of increased serum progesterone levels, usually in the luteal phase of the menstrual cycle. The clinical picture is variable and the histopathology is usually non-specific, although the most commonly described finding in the literature is a perivascular inflammatory infiltrate present in 72% of the cases. Other histologic findings are: a non-specific or interstitial inflammatory infiltrate in 31% of cases; an eosinophilic component in 41% of patients; and a neutrophilic component associated with a predominantly lymphocytic infiltrate in 21% of cases. Final Comments: Although histopathology in APD is usually nonspecific, some patterns have already been identified. There may be an association between the histological pattern and the clinical vignette. Thus, cutaneous biopsy is an important tool for a better understanding of the pathophysiology of APD, besides an intradermal test with medroxyprogesterone acetate or an oral challenge test with desogestrel may help confirm the diagnosis.

Patient Presentation and Testing:
A 50-year-old married female presented with pruritic diffuse non-scaly erythematous papules since 37 years of age, with a cyclical worsening from 5 days before menstruation until 2 days after its ending. She also reported concomitant metacarpophalangeal and interphalangeal arthralgia and some episodes of periorbital edema. She thought loratadine and prednisone improved her symptoms. She denied other complaints. She had no history of drug addiction and her mother had rheumatoid arthritis. It was hypothesized that the increase of progesterone levels, during the luteal phase of the menstrual cycle, could induce urticarial lesions in this patient. Complementary evaluation showed no new findings initially. Assessment of C reactive protein, erythrocyte sedimentation rate, complete blood count, thyroid-stimulating hormone levels, rheumatoid factor, anti-cyclic citrullinated peptides, anti-thyroperoxidase and antinuclear antibodies did not show abnormalities. Then, during an asymptomatic period, she was submitted to an intradermal test with medroxyprogesterone acetate, cutaneous biopsy and an oral challenge with desogestrel to assess the hypothesis of hormonal urticaria.

Diagnosis, Treatment and Patient Outcomes:
The patient was diagnosed with Autoimmune Progesterone Dermatitis, as her intradermal test with medroxyprogesterone acetate was positive at the concentration of 0.5 mg/mL after 6 hours of its application. Twenty healthy volunteers tested negative. Then, a cutaneous biopsy was performed, whose histopathology showed
perivascular lymphohistiocytic infiltration with melanophages and mild collagen hyalinization, with negative direct immunofluorescence. A single-blinded oral challenge test with desogestrel 75 mcg was positive after 6.5 hours, with the appearance of pruritic diffuse erythematous thick papules and plaques. Autoimmune Progesterone Dermatitis (APD) is a hypersensitivity reaction to endogenous or exogenous progesterone characterized by the appearance of cutaneous lesions at times of increased serum progesterone levels, usually in the luteal phase of the menstrual cycle. The clinical picture is variable and the histopathology is usually non-specific, although the most commonly described finding in the literature is a perivascular inflammatory infiltrate present in 72% of the cases. Other histologic findings are: a non-specific or interstitial inflammatory infiltrate in 31% of cases; an eosinophilic component in 41% of patients; and a neutrophilic component associated with a predominantly lymphocytic infiltrate in 21% of cases (1). The diagnosis of APD is based on the association of cyclical or progesterone-induced symptoms, a progesterone hypersensitivity test and response to inhibiting ovulation (2). The patient was instructed to avoid progestogen-based contraceptives and take an anti-histamine (loratadine) when symptomatic. She underwent remission of the disease after menopause, at age 50. Although histopathology in APD is usually nonspecific, some patterns have already been identified. There may be an association between the histological pattern and the clinical vignette. Thus, cutaneous biopsy is an important tool for a better understanding of the pathophysiology of APD, besides an intradermal test with medroxyprogesterone acetate or an oral challenge test with desogestrel may help confirm the diagnosis.

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Case Title:
Insulin Induced Angioedema in a Type I Diabetic: Allergy vs Adverse Effect

Summary and Lessons Learned:
In rare instances, patients on insulin therapy have been reported to develop peripheral or generalized edema. Few cases have been reported in the literature, with many affected patients being children and newly diagnosed with diabetes. Additional risk factors include underweight patients, insulin naïve patients, and patients receiving intensification of insulin therapy. The mechanism for insulin-induced edema is unknown, but is thought to be a consequence of altered sodium handling in the kidney related to alterations in renin and aldosterone physiology. Symptoms of insulin induced edema have been effectively managed with diuresis. IgE mediated reactions to insulin are less common with the introduction of human insulin products, however few cases continue to be reported. Since the presentation of insulin-induced edema may in rare instances be related to IgE mediated reactions, we present a case discussing the utility of IgE mediated allergy testing in an adult with suspected insulin-induced edema.

Patient Presentation and Testing:
We present a 37 year old female with known type 1 diabetes, who had recurrent angioedema involving her face and extremities, within 24-48 hours after bolus doses of insulin lasting for 5-7 days. The swelling was reproducible with exposure and resolved with diuretics. Percutaneous testing with QuinTip and intradermal testing was performed using non-diluted 100 units/mL insulin lispro, insulin human recombinant, insulin aspart, insulin glargine and insulin detemir with negative (saline) and positive (histamine) controls. Testing with these agents was thought to be an effective strategy to rule out IgE mediated reaction to the above insulin products, and would provide evidence to re-introduce insulin for the management of her condition. Skin testing was negative to all the above products with adequate controls.

Diagnosis, Treatment and Patient Outcomes:
Skin testing was negative, which was consistent with a non-IgE mediated drug reaction. Her reaction was similar to the insulin induced edema described in the literature, making this diagnosis more likely. Due to the delayed nature of her reactions, an in-office challenge was not completed. She was agreeable to resuming her insulin pump at a very low dose with consideration of increasing her dose over time, along with low dose thiazide diuretic to minimize edema. This case emphasizes the utility of IgE mediated allergy testing to rule out true hypersensitivity prior to resuming insulin in patients with suspected insulin-induced edema and highlights this important differential diagnosis in patients with insulin reactions.
A 71-year-old female developed a generalized pustular eruption on an erythematous background within three days of initiating metoprolol tartrate; it progressed rapidly to involve the face, torso and limbs with sparing of her palms, soles, oral mucosa and conjunctiva. Based on clinical findings, and supported by a punch biopsy, a diagnosis of Acute Generalised Exanthematous Pustulosis (AGEP) was made, secondary to metoprolol tartrate.

The rash rapidly desquamated upon discontinuation of metoprolol tartrate; after a thorough infectious work up and review of her medication exposures, we concluded that metoprolol tartrate was likely the offending agent. All other medications had been administered for more than five weeks before the development of AGEP.

AGEP is a rare, acute cutaneous reaction characterized by the development of numerous non-follicular sterile pustules with edematous erythema. Over 90% of cases are provoked by antibiotics, antifungals, antimalarials or diltiazem; symptom onset is a few hours to days after administration of the offending agent. Unlike Steven-Johnson syndrome, mucosal involvement is rare and if present, is restricted to lip erosions. Other symptoms include fever and peripheral blood neutrophilia. It is thought to be mediated by drug-specific CD4+ T cells, cytotoxic CD8+ T cells, and inflammatory cytokines and chemokines.

As these patients present with a generalized rash in the setting of fever and leukocytosis AGEP can easily be confused with a systemic infection. This can delay diagnosis and appropriate management. AGEP is readily treatable, by simply discontinuing the offending agent and supporting patient, with topical steroids sometimes offered for symptomatic relief. Although AGEP it has been described as an adverse reaction to numerous drugs, AGEP secondary to beta blockers has not been widely reported. We describe a case of biopsy proven AGEP likely secondary to metoprolol tartrate.

A 71-year-old female with a history of deafness due to Paget’s disease of the bone who was admitted to the ICU for pneumococcal meningitis secondary to a left ear infection. She completed a one month course of intravenous vancomycin, ceftriaxone and ampicillin, with vancomycin and ampicillin discontinued more than 1 month prior to the development of AGEP. She was also initially treated with ciprofloxacin ear-drops, which were discontinued four weeks prior to the onset of AGEP, topical miconazole to the groin and levetiracetam which she continued to receive throughout her hospital stay. On day fifty-five of her hospitalization she developed generalized erythema on her face, chest, back, abdomen, arms and legs, many areas with pinpoint papules without blistering; there were multiple tiny pustules on her face and shoulders. Her palms and soles, as well as her mucosa and conjunctiva were spared. She had mild xerosis and scaling on her bilateral lower extremities. She was febrile to 103.2F with laboratory tests significant for leukocytosis to 24.3 k/UL (neutrophil predominant), bandemia of 28% and lactic acidosis to 4.9mmol/L. The blood cultures, urine culture and chest x-ray were all repeated and returned normal. Metoprolol tartrate was started three days prior to the development of the rash and was her only new medication. Dermatology was consulted and the patient received a punch biopsy; the pathology was notable for scattered neutrophils with subcorneal pustules within the epidermis and interstitial neutrophilic infiltrates with rare eosinophils within the dermis. These findings were consistent with a diagnosis of AGEP.
The patient was ultimately diagnosed with AGEP based on the morphology of the rash as well as the results of the pathology specimen. The causative agent was likely metoprolol tartrate, based on the time course of the rash in relation to the new administration of this agent in the preceding days. Although the patient was also on ceftriaxone and levetiracetam when the rash developed, she had continuously tolerated these medications for over seven weeks. However, given the association of AGEP to antibiotic exposure both ceftriaxone and metoprolol tartrate were discontinued and she was started on IV hydration and topical hydrocortisone ointment with complete resolution within ten days.
Sebelipase Desensitization: A Case Report

Summary and Lessons Learned:
28 years old female with a past medical history of lysosomal lipase deficiency, intermittent asthma, allergic rhinitis and depression presenting with history of systemic adverse reactions to the Sebelipase infusions (enzyme replacement therapy).

Sebelipase alfa is a recombinant form of lysosomal acid lipase enzyme that normally in body catalyzes the lysosomal hydrolysis of cholesteryl esters and triglycerides to free cholesterol, glycerol and free fatty acids.

Anaphylaxis/hypersensitivity reactions have been reported with sebelipase. Depending on the type and severity of allergic reactions, it is usually treated with slower infusion rate, premedication with antihistamine or corticosteroids, temporary interruption in infusions to discontinuing the infusions if the reactions are severe.

The patient’s drug reaction was confirmed as an IgE mediated hypersensitivity reaction with a positive intradermal test (1:100 dilution). She underwent successful rapid drug desensitization in the ICU after pre-medication with H1 and H2 receptor antihistamine. She will be transitioned to the infusion clinic for the sebelipase infusions using the same protocol. If patient continues to have systemic reactions to the infusions, then we will consider adding corticosteroids to the pretreatment. Another option is to start her on omalizumab prior to her infusions.

Desensitization to Sebelipase alfa has never been reported. Because of the high incidence of hypersensitivity reactions (20%), treatment by drug desensitization utilizing our protocol can be considered for patients with history of anaphylactic reaction to Sebelipase or other enzyme replacement therapies.

Patient Presentation and Testing:
28 years old female with history of lysosomal lipase deficiency diagnosed with liver biopsy in November 2013 after persistently elevated ALT. She was started on sebelipase infusions (100 mg over 1 hour) in November of 2016. Treatment was delayed due to pregnancy. Patient was getting the infusions every 2 weeks and was tolerating them till May 2017.

In May 2017, 3 mins after starting her infusion she developed bilateral palm itching followed immediately with hives and throat swelling. Infusion was stopped and she was treated with diphenhydramine and steroids. She continued the infusions after getting pre-medicated with diphenhydramine and any symptoms of itching during the infusions were treated by stopping the infusion and giving patient steroid and diphenhydramine. She would then continue and finish her infusion.

On July 13th, 2017 she got pre medicated with steroids the night before the infusion and diphenhydramine 30 mins before the infusion. She still developed hives with lip swelling and chest tightness. Infusion was stopped and she was treated with more steroids and diphenhydramine.

Patient had skin prick testing and intradermal testing for sebelipase on Aug 9th, 2017. She was positive on intradermal testing (1:100) with appropriate controls.

Diagnosis, Treatment and Patient Outcomes:
Patient showed sensitization to Sebelipase on intradermal (1:100) testing.

She was admitted for rapid drug desensitization in Aug 9th, 2017 over 8 hours. She was pre-medicated 20 mins before the infusion with 25 mg IV diphenhydramine and 50 mg IV Ranitidine and following protocol was followed for desensitization and infusion with a target dose of 100 mg.

Bag 1: (1:10,000 dilution) 0.01% of final dose = 0.01 mg in NS 100 ml over 1 hour.
Bag 2: (1: 1,000 dilution) 0.1% of final dose = 0.1 mg in NS 100 ml over 1 hour.
Bag 3: (1:100 dilution) 1% of final dose = 1 mg in NS 100 ml over 1 hour.
Bag 4: (1:10 dilution) 10% of final dose = 10 mg in NS 100 ml over 1 hour.
Bag 5: 90% of final dose = 88 mg in NS 500 ml over 4 hours.

She developed itching around her ears bilaterally and facial flushing which was treated with diphenhydramine and she tolerated and finished the infusion on a slower rate.

She was again admitted and treated with Zyrtec 20 mg PO once and famotidine 20 mg IV once 30 mins before the desensitization and infusion. Same protocol was used as of 8-9-2017 and patient tolerated the infusion with no problems.

Patient is now planned to follow the protocol every two weeks for her infusions. If she continues to have allergic reactions, then we will consider adding corticosteroids to the pretreatment. Another option is to start her on omalizumab prior to her infusions.
Eosinophilia with delayed rash without DRESS, induced by brentuximab, in cutaneous T cell lymphoma, successfully treated with desensitization.

Summary and Lessons Learned:
A 58-year-old female patient with a 35-year history of cutaneous T cell lymphoma and delayed non-urticarial rash with eosinophilia in response to brentuximab treatment presented to the BWH/DFCI Drug Hypersensitivity and Desensitization Center. She had been treated with nitrogen mustard, photochemotherapy (PUVA), and methotrexate with good control. In 2012 the patient was switched to brentuximab due to liver toxicity. Three weeks after her first lifetime infusion of brentuximab, she presented with facial burning and eye swelling. On the second infusion, the patient developed facial swelling, and rash without mucosal involvement or blistering one week post treatment, which resolved with steroids. Her third infusion of brentuximab was reduced to 40% of the target dose and steroids given as pretreatment. Despite these modifications, the patient developed severe delayed rash with hand and foot peeling, without mucosal or oral involvement. Her symptoms resolved after several weeks with H1 blockade and steroids. Brentuximab was discontinued.

She was evaluated 2 years later due to disease progression and had negative skin testing to brentuximab. Desensitization was recommended given the unknown predictive value of brentuximab skin testing and the patient had no other available treatment options. The patient received a standard 3 bag 12 step desensitization protocol at 50% of target dose and developed a delayed fever and rash with eosinophilia (1940 total) and lower extremity swelling which resolved with steroids. The allergy and oncology teams agreed with desensitization at 25% of the target dose with 3 bag 12 step protocol. During the protocol, the patient developed a single hive and a delayed mild pruritic rash on her legs, without eosinophilia, or mucosal involvement. Symptoms resolved with steroids. With each additional desensitization, her dose was gradually increased until the full target dose was reached (12th desensitization).
To date the patient continues to receive brentuximab desensitization at full dose every 8 weeks, using a down-graded 2 bag 8 step desensitization protocol. Cetirizine and famotidine are given prior to each infusion, without the need of post steroid usage, and has not developed eosinophilia or delayed rash. A total of 27 protocols have been administered since 2014 and her CT scan continues to show no disease progression with her ability to remain on first line therapy.

Patient Presentation and Testing:
When I initially meet the patient, she had received her first brentuximab desensitization. Unfortunately, a severe rash had appeared several days after her treatment, along with lab results showing the patient had a significant elevated eosinophilia count to almost 2000. This made the desensitization team pause and question how we could continue using this medication. When speaking with the patient she expressed worry and sadness and requested that we do not give up on her since no one else would provide this treatment. She basically had no alternative therapies for her underlying lymphoma. We continued treatment with extreme caution with the patient's understanding of our limitations if her symptoms worsen for fear of causing DRESS.

Diagnosis, Treatment and Patient Outcomes:
The diagnosis was shown with lab results and the presence of a significant rash associated to brentuximab. To understand the need to treat the patient with baseline skin lesions in the setting of having cutaneous T cell lymphoma, presenting with a delayed type 4 reaction, without a true understanding of the mechanism that was responsible for the rash was difficult moving forward and continuing treatment with this medication. We monitored her rash and eosinophils closely when re-initiating brentuximab. Providing the offending medication at a lowered dose via a 12 step
desensitization protocol proved to be a success. Every 8 weeks the patient flies to our center for treatment. She is extremely grateful that we did not give up on her and voices this often. This was a difficult case going against the standard of avoidance of this medication for fear of DRESS. This patient received first line therapy, actually with this case the only therapy option that keeps her alive.
Case Title:
Cutaneous vasculitis and exanthema: A late hypersensitivity reaction to dimenhydrinate

Summary and Lessons Learned:
Case Description: A 27-year-old female used oral dimenhydrinate and, after 14 days, developed a maculopapular rash that was slightly painful with areas of palpable purpura, affecting almost the entire abdomen and limbs. She also reported headache, nausea and fever. The complementary evaluation revealed a high C-reactive protein of 7 mg/dL, without other laboratory abnormalities (complete blood count; renal function; liver enzymes; C3; C4; serology for HIV, HBV, HCV and syphilis; cryoglobulin levels and antinuclear antibody screening). Histopathology of cutaneous biopsies revealed vacuolar interface dermatitis, leukocytoclastic purpura, pigment effusion and positive IgG immunofluorescence in keratinocyte nuclei of the epidermis. The patient was treated with prednisone 1 mg/kg/day for one month. She was weaned gradually from prednisone after 2 months with complete regression of symptoms. An intradermal test was performed with 0.03 mL of 0.1 mg/mL dimenhydrinate, which was negative after 20 minutes and after 6 hours, but positive only after 48 hours. Ten healthy volunteers tested negative. Discussion: Dimenhydrinate is an H1 antihistamine ethanolamine, whose allergic reactions are rare. The reported delayed hypersensitivity reaction was shown to be of mixed mechanism according to Gell and Coombs’s classification, as the initial condition was characterized by exanthema and late intradermal test was positive only after 48h (type IV reaction) and skin biopsy was compatible with cutaneous vasculitis and immune complex deposition (type III reaction). There are no similar citations or standardization of cutaneous tests with dimenhydrinate in the literature. Final Comments: The evaluation of allergic reactions to drugs is of great importance for etiological diagnosis. We describe a case of exanthema and cutaneous vasculitis as an adverse reaction to dimenhydrinate. Thus, intradermal testing may be a form of etiological confirmation in type III or IV hypersensitivity reactions to this drug.

Patient Presentation and Testing:
A 27-year-old single female patient was previously healthy, except for motion sickness and the use of 50 mg of oral dimenhydrinate 2 weeks before. She presented with a disseminated maculopapular rash, evolving with purpuric lesions on the trunk and limbs. She also reported headache, nausea and fever at admission. She denied addictions and had no previous history of drug reactions. Family history was not relevant to the case. The skin lesions did not improve with the administration of intravenous diphenhydramine. The diagnostic hypothesis of a delayed hypersensitivity reaction to dimenhydrinate was raised. Thus, the patient was submitted to skin biopsy and laboratory tests and was administered oral corticosteroids. The patient was monitored daily by telephone and in weekly visits until total improvement of the clinical symptoms and total resolution in about one month. After the end of symptoms, an intradermal test was performed with dimenhydrinate.

Diagnosis, Treatment and Patient Outcomes:
The patient was diagnosed with a delayed hypersensitivity reaction to dimenhydrinate, namely exanthema and vasculitis. Diagnostic skin tests were performed 3 months after the onset of the disease, after using prednisone 1 mg/kg/day for a month, gradually weaned over 2 months. An intradermal test was performed with 0.03 mL of 0.1 mg/mL dimenhydrinate, which was negative after 20 minutes and 6 hours, but positive after 48 hours. The complementary evaluation revealed a high C-reactive protein of 7 mg/dL, without other laboratory abnormalities (complete blood count; renal function; liver enzymes; C3; C4; serology for HIV, HBV, HCV and syphilis; cryoglobulin levels and antinuclear antibody screening). Histopathology of cutaneous biopsies revealed vacuolar interface dermatitis,
leukocytoclastic purpura, pigment effusion and positive IgG immunofluorescence in keratinocyte nuclei of the epidermis. The patient was treated with prednisone 1 mg/kg/day for one month. Ten healthy volunteers tested negative. It was possible to establish an initial standardization for skin tests with dimenhydrinate in order to evaluate late hypersensitivity reactions. The patient evolved without sequelae and her condition hasn’t recurred. She was oriented to exclude dimenhydrinate and to use other antiemetics. Dimenhydrinate is an H1 antihistamine ethanolamine, whose allergic reactions are rare. The reported delayed hypersensitivity reaction was shown to be of mixed mechanism, according to Gell and Coombs’s classification, as the initial condition was characterized by exanthema and late intradermal test was positive only after 48h (type IV reaction) and skin biopsy was compatible with cutaneous vasculitis and immune complex deposition (type III reaction). Therefore, intradermal testing may be a form of etiological confirmation in type III or IV hypersensitivity reactions to dimenhydrinate.
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**Case Title:**  
Early recognition of drug-induced immune hemolytic anemia in immunosuppressed patients to prevent life-threatening hemolysis

**Summary and Lessons Learned:**  
Drug-induced immune hemolytic anemia (DIIHA) is a rare adverse effect of Piperacillin-Tazobactam. This is a commonly prescribed antibiotic in the immunosuppressed pediatric population. We describe the case of a 11-year old boy with cystic fibrosis who developed hemolysis on the 10th day of Piperacillin-Tazobactam during an admission for a pulmonary exacerbation. His hemoglobin dropped to 41 g/L and eventually improved after discontinuation of Piperacillin-Tazobactam and administration of several red blood cell transfusions. The report serves to emphasize the importance of recognizing DIIHA early in the course of hemolysis to avoid potential red blood transfusions in the immunosuppressed population. Physicians should be familiar with the most common medications associated with DIIHA as cessation of the medication may prevent life-threatening hemolysis.

**Patient Presentation and Testing:**  
We present a 11-year old boy with cystic fibrosis and pancreatic insufficiency who was admitted with symptoms characteristic of a pulmonary exacerbation. In hospital, he received Piperacillin-Tazobactam IV, Ciprofloxacin IV and Colistin. On Day 10 of admission, his hemoglobin dropped significantly, reaching a nadir of 41g/L later that day. He was treated with packed red blood cell transfusions on Day 10, 13, and 15. He was started on a 4-day course of Prednisone (2mg/kg/day) on Day 13, followed by subsequent weaning. He continued to have fluctuating hemolysis during this time, hemoglobin reaching a high of 78 g/L and 83 g/L on Day 10 and 13, post-transfusion. He did not have systemic symptoms in keeping with an anaphylactic reaction. Piperacillin-Tazobactam was discontinued on Day 15 of admission. He was switched over to Meropenem and continued with Ciprofloxacin and Colistin. Following discontinuation of Piperacillin-Tazobactam, his hemoglobin increased to normal levels and he had no further hemolytic episodes during admission. Drug dependent antibodies studies were sent to a specialized reference laboratory in Wisconsin on Day 18 which were reported positive to Zosyn (Piperacillin-Tazobactam dependent red cell antibodies in serum) and negative to Colistimethate dependent antibodies.

Clinical suspicion of DIIHA and immediate cessation of the medication can be lifesaving. DIIHA typically presents as a hemolytic anemia occurring 6 days after initial drug exposure. The severity of hemolysis can range from mild anemia to fatal hemolysis. The diagnosis requires a high index of suspicion and should be considered in any patient with unexplained hemolysis after drug administration. Once a drug has induced a hemolytic episode, future administration of the agent is generally contraindicated. Our patient developed hemolysis on Day 10 after starting Piperacillin-Tazobactam. The direct Coombs test was positive and Piperacillin-Tazobactam dependent red cell antibodies were present in serum. There was resolution following discontinuation of Piperacillin-Tazobactam on Day 15, five days from onset of hemolysis.

**Diagnosis, Treatment and Patient Outcomes:**  
Diagnosis of DIIHA to Piperacillin-Tazobactam was made following positive results to drug dependent antibodies to Piperacillin-Tazobactam and a positive direct Coombs test. Our patient was advised to wear a Medic-Alert bracelet bearing "DIIHA to Pip-Tazo" and avoidance of Piperacillin-Tazobactam.
The mechanisms and risk factors for the development of DIIHA are not well understood. It has not been proven as to why some patients develop antibodies against certain medications, thus making hemolytic reactions difficult to predict. Furthermore, it is not clear why only a subset of patients with drug-induced red blood cell antibodies experience severe hemolytic reactions. There may also be a concern with other medications known to be cross-reactive with the drug in question. Recognition of DIIHA requires clinical vigilance and close communication with blood banks experienced with the appropriate testing procedures, specifically drug dependent antibody studies. Further, many of the tests needed for an accurate diagnosis are performed only at specialized immuno-hematology reference laboratories thus requiring coordination between institutions to perform a complete work-up.
This case report illustrates the importance of recognizing clinical signs of DIIHA and serologic testing for diagnostic confirmation and prevention of possible life-threatening hemolysis. Physicians should have a high index of suspicion for DIIHA in patients with unexplained hemolytic anemia who are taking medications, even those on long-term medications with no previous history.
Summary and Lessons Learned:
Enoxaparin is one of the most commonly used low molecular weight heparin (LMWH) products for the treatment and prophylaxis of deep venous thrombosis (DVT). Immune mediated reactions are some of the rarest side effects of LMWH, among which, both immediate and delayed-type reactions were reported using the subcutaneous injections. Delayed type hypersensitivity included circumscribed eczematous plaques, maculopapular exanthema, and acute generalized exanthema pustulosis. Few cases of immediate type systemic reactions including anaphylaxis and angioedema have been reported with heparins and heparinoids including enoxaparin, where an IgE mediated mechanism has been proposed to be underlying cause proven by skin testing. Enoxaparin induced immediate type hypersensitivity has been rarely reported and the exact incidence is unclear.

We present a case of a sixty nine year old male with type two Diabetes on hemodialysis who developed angioedema of the periorbital area, face, tongue, oral mucosa and larynx in less than twelve hours of receiving the first dose of subcutaneous enoxaparin requiring emergent intubation and mechanical ventilation. Patient did not develop any skin rash, urticaria or hypotension. Patient had no previous history of angioedema and had no known drug allergies. Patient had a right upper extremity DVT from complication of a line placement for which he received therapeutic dose of enoxaparin, 1mg/kg scheduled to be given every twelve hours. Once intubated, patient was treated with intravenous antihistamines including diphenhydramine 25 mg every eight hours, famotidine 40 mg every twelve hours and prednisone 60 mg every day for the angioedema. Patient improved gradually but remained ventilator dependent after four days, at the time his discharge to a long term acute care facility (LTAC).

Patient Presentation and Testing:
Presentation: A sixty nine year old African American male presented to the hospital from a nursing home after found to have profound hypoglycemia and altered mental status. Pt had history of Insulin dependent type 2 Diabetes Mellitus, End Stage Renal Disease (ESRD) on hemodialysis, Cerebrovascular Accident with permanent lower extremity contracture and seizure disorder. Pt required a central venous access one day two of admission which was attempted on his right arm but due to complications from the line placement, patient was found to have a deep venous thrombosis in this arm. Pt was subsequently scheduled to be given therapeutic dose of Enoxaparin 1 mg/kg subcutaneously every twelve hours. Pt developed angioedema involving his face, lips, tongue, oral mucosa, and larynx in less than twelve hours after receiving the first dose of Enoxaparin requiring emergent intubation and mechanical ventilation. Pt had no sign of anaphylaxis or other systemic reactions. Patient had no previous history of angioedema and had no known allergies to any medications. He also had no known family history of angioedema. All other possible medication administration,
duration and onset of symptom as the cause of this angioedema were ruled out. Pt was also receiving Levetiracetam, which was continued as a prior to admission medication. He was not being given any antibiotics.

Testing: Patient had a negative tryptase level and workup for hereditary or acquired causes of angioedema were ruled out including C4, C1-INH and C1-INH function, and C1q were within normal limits. Interestingly, patient had an elevated CRP level of 13.7 mg/dL and an ESR of 130 mm/hr, with concern for possible hospital acquired pneumonia. His complete blood count showed minimal leukocytosis without eosinophilia.

**Diagnosis, Treatment and Patient Outcomes:**

Patient appeared to have severe swelling of the periorbital area, face, lips, tongue, and larynx. He had no urticaria, flushing, or hypotension. Pt was not on any angiotensin-converting enzyme (ACE) inhibitor which ruled out the bradykinin-induced angioedema. After the initial airway management of acute angioedema related respiratory failure, patient was being given scheduled intravenous antihistamines including diphenhydramine 25 mg every eight hours, famitidine 40 mg every twelve hours and prednisone 60 mg every day. Patient's periorbital and facial swelling improved significantly but he required continuous mechanical for the next four days until getting transferred to a long term acute care (LTAC) facility. Enoxaparin was immediately stopped after the first dose and Dilantin 100 mg every eight hours was substituted for Levetiracetam to rule out a potential culprit causing the angioedema. He was also started on empiric antibiotic coverage for possible hospital acquired pneumonia on day two of intubation. Pt continued to recover from his angioedema at the time of discharge, four days after initiating mechanical ventilation. A concern was raised regarding the appropriate use and dosing of the Enoxaparin due to patient having ESRD on hemodialysis, potentially augmenting the onset and severity of the angioedema. A follow up appointment with an allergist was recommended but unfortunately patient was not seen in follow up at our clinic. We believe this patient would have been benefited by conducting a skin test to confirm the most suspected diagnosis of Enoxaparin induced angioedema but due to the patient’s condition, this could not have been completed, posing a potential limitation in confirming the diagnosis.
Case Title:
Delayed Hypersensitivity Reaction To Subcutaneous Sodium Enoxaparin

Summary and Lessons Learned:
Skin adverse reactions have been reported after subcutaneous low molecular weight heparin (enoxaparin) recommended for prevention and treatment of venous thromboembolism. Enoxaparin induced skin lesions may vary from allergic reactions such as local erythema or eczema to urticaria or bullous hemorrhagic dermatosis[1,2]. We present a case of delayed hypersensitivity reaction due to subcutaneous sodium enoxaparin in a 65 year-old female patient, who presented, in the fifth day of treatment, well delineated eczematous plaques at the injection sites. It is important to diagnose hypersensitivity reaction induced by enoxaparin and to avoid using it in such cases.

Patient Presentation and Testing:
A 65-year-old female patient, presented in the Dermatology Department searching for a diagnose. She was previous hospitalised for a hip fracture and treated with subcutaneous sodium enoxaparin for five days. Her medical history revealed that the patient is diagnosed with osteoporosis, but refuses undergoing medication treatment and has a 20 years history of arterial hypertension under medication with Indapamidum. At the time of initial encounter, no history of allergies. Laboratory examination: analysis within normal limits. A bone density study showed osteoporosis. Physical examination revealed well delineated eczematous plaques at the injection sites [Pictures A; B]. Skin prick tests were positive to enoxaparin undiluted and using series of dilutions (1:100, 1:1.000, 1:10.000); dilutions were obtained using enoxaparin and aqua without further additives. Lower concentrations with positive results proved a true allergic reaction, excluding false positive results [3].

Diagnosis, Treatment and Patient Outcomes:
The patient was included in a clinical follow-up registry and is going under regular 6 months surveillance program. One very important lesson is learned from this case, relevant not only to the practice of allergy/immunology: strict avoidance of all heparins is mandatory in such cases as presented.

*Written informed consent for the publication of potentially identifiable personal details of patient (gender, age, illness, location) was obtained.

**In relation to this presentation, I declare that there are no conflicts of interest.

References:
Case Title: IgE-mediated anaphylaxis to Gadobenate Dimeglumine (Multihance®)

Summary and Lessons Learned:
A 26-year-old male with an anaplastic astrocytoma, status post gross total resection and chemoradiation and undergoing maintenance chemotherapy developed pruritus, urticaria, and dysphagia immediately following intravenous gadolinium-based contrast agent (GBCA) administration during routine surveillance brain MRI despite premedication with corticosteroids and antihistamines. He tolerated gadobenate dimeglumine (Multihance®) during seven previous MRIs. Positive skin prick testing with gadobenate confirmed IgE-mediated hypersensitivity. GBCA avoidance was impractical as there were no alternative non-gadolinium contrast agent and desensitization to GBCAs was unfeasible. Skin prick tests to two macrocyclic contrast agents, gadoterate meglumine (Dotarem®) and gadobutrol (Gadavist®), were negative. The patient subsequently tolerated MRI brain with intravenous gadoterate. Immediate hypersensitivity reactions to GBCAs are rare. Linear ionic GBCAs, especially gadobenate, are more frequently associated with anaphylaxis than macrocyclic GBCAs. In patients with recurrent hypersensitivity reactions to GBCAs who cannot avoid them, there may be negative predictive value in immediate hypersensitivity skin testing, improving chances of selecting safe alternative GBCAs for future imaging.

Patient Presentation and Testing:
A 26-year-old male with a left frontal lobe anaplastic astrocytoma, status post resection followed by chemoradiation, and undergoing maintenance chemotherapy presented with diffuse urticaria and oropharyngeal pruritus and throat tightness 30 seconds after intravenous gadobenate infusion during his ninth routine surveillance brain MRI, despite oral diphenhydramine and prednisone pretreatment. He required surveillance brain MRIs every 2 months and had tolerated seven previous MRIs with gadobenate. During his eighth MRI, he developed facial urticaria 20 minutes after contrast administration that resolved with oral diphenhydramine. His reaction during the ninth MRI was treated with intravenous steroids and antihistamines. He was discharged after symptoms resolved completely within 20 minutes. 12-18 hours after initial symptom resolution, he developed a biphasic protracted reaction with neck and arm erythema and diffuse pruritus requiring oral diphenhydramine every 6 hours until symptoms resolved 24 hours later. Latex-IgE was negative. Immediate hypersensitivity skin prick testing to linear gadobenate produced an 8mm wheal. Skin prick and intradermal tests with sterile water control and macrocyclic compounds gadoterate and gadobutrol were negative.

Diagnosis, Treatment and Patient Outcomes:
Skin-prick testing confirmed IgE-mediated hypersensitivity to gadobenate. Desensitization to gadobenate was unfeasible, but surveillance MRIs were still required. For subsequent brain MRIs, the patient was premedicated with corticosteroids and antihistamines and tolerated intravenous gadoterate.
Case Title:
Is there anything else than omalizumab allergy?

Summary and Lessons Learned:
We present the security results in the use of omalizumab in our hospital between October’04 to August’16, in which 86 patients were treated and 6054 doses of omalizumab were administered.
In our study, we not only analyze the anaphylactic reactions produced by omalizumab but also those produced by its excipients, particularly by polysorbate.
Omalizumab was well tolerated in our hospital until July’16, when a patient with severe bronchial asthma, was administered the first dose of omalizumab. After 30 minutes, the patient started with dry mouth feeling, dizziness, nausea and an episode of vomiting, followed by dyspnea and coughing spells. Also, he presented a cutaneous V-neck erythema and edema of pharyngeal pillars was observed.
Therefore, treatment for anaphylaxis was administered. After 4 hours, significant clinical improvement and hemodynamic stability was observed. Consequently, omalizumab was removed and the allergy study was performed.
The aim of this study is to highlight the security in the use of omalizumab by comparing the data obtained in our study with the one published by the Omalizumab Joint Task Force(OJTF).
For the allergy evaluation, skin prick test(SPT) and intradermal test(IDT) with omalizumab in its commercial form and polysorbate were performed. IDT was positive for both.
The patient started a new biological therapy with reslizumab as it does not have polysorbate within its excipients, being well tolerated and her asthma improved.
Conclusions:
-In our hospital, the incidence of omalizumab-induced anaphylaxis is 0.016%.
-We report a probable anaphylactic reaction caused by polysorbate, an excipient in omalizumab.
-Polysorbate is a very ubiquitous excipient, particularly used for injection preparations, which would explain this reaction with the first dose of omalizumab.
-Reslizumab is a good choice, among the biological treatments, for asthmatic patients allergic to polysorbate.

Patient Presentation and Testing:
Our patient is a 49-year-old woman with a severe persistent allergic asthma. She had had a prior reaction with an influenza vaccine without any atopic family history.
The allergy study was performed taking into account the publications registered until now, SPT and IDT were performed with omalizumab and polysorbate: SPT was negative for both, but IDT was positive for omalizumab at a concentration of 1/1000 and for polysorbate at 1/100.

Diagnosis, Treatment and Patient Outcomes:
According to the medical history, the prior reaction with an influenza vaccine and the skin test results, we suggest a probable anaphylactic reaction caused by polysorbate.
As Reslizumab doesn’t have polysorbate on its excipients, we started this therapy and our patient’s asthma significantly improved.
Case Title:
Acneiform drug eruption following iodinated contrast exposure and a successful strategy for readministration

Summary and Lessons Learned:
Introduction: Adverse reactions to intravenous contrast media are often immediate and non-immunologic in mechanism. In rare cases, however, contrast reactions can present with delayed, immune-mediated symptoms. We present a young woman who developed a delayed acneiform drug eruption following diagnostic cerebral angiography with iodinated contrast. With a successful readministration strategy, she underwent subsequent interventional angiography to repair her intracranial aneurysms.

Case presentation: A 23-year-old woman with chronic migraines presented for evaluation of acute headache of different character from her usual migraines. She underwent diagnostic imaging with noncontrast CT head, then contrast-enhanced cerebral angiography which revealed multiple intracranial aneurysms. She received iohexol contrast without premedications, despite having a history of diffuse erythema and red pruritic pinpoint papules following iodinated contrast on two prior occasions. Five hours later, she developed diffuse pruritic erythema then hundreds of pinpoint red pustules on her face, chest and back. Skin biopsies revealed perifollicular pustules with a mixed inflammatory cell infiltrate of neutrophils, lymphocytes and eosinophils, which suggested an acneiform drug eruption. Her clinical presentation and histologic findings were consistent with iododerma, a rare drug eruption due to iodine itself. She required subsequent repair of her intracranial aneurysms and re-exposure to iohexol contrast. This was achieved with a readministration strategy using premedication with diphenhydramine, cetirizine, famotidine, montelukast, and prednisone.

Discussion: Iododerma is rare in present times owing to the decline in popularity of topical iodine-containing antiseptics. It is now reported to occur with exposure to iodinated contrast media. Its proposed mechanisms include a T cell-mediated process, with risk factors including repeated iodine exposure and delayed clearance of iodine.

Patient Presentation and Testing:
A 23-year-old woman with chronic migraines presented for evaluation of acute headache of different character from her usual migraines. She underwent diagnostic imaging with noncontrast CT head, then contrast-enhanced cerebral angiography which revealed multiple intracranial aneurysms. She received iohexol contrast without premedications, despite having a history of diffuse erythema and red pruritic pinpoint papules following iodinated contrast on two prior occasions. Five hours later, she developed diffuse pruritic erythema then hundreds of pinpoint red pustules on her face, chest and back. Skin biopsies revealed perifollicular pustules with a mixed inflammatory cell infiltrate of neutrophils, lymphocytes and eosinophils, which suggested an acneiform drug eruption.

Diagnosis, Treatment and Patient Outcomes:
Although a diagnosis of acute generalized exanthematous pustulosis was considered, her histologic findings did not support this. The perifollicular distribution of pustules revealed on histology favored an acneiform drug eruption, and clinical history suggested a diagnosis of iododerma. The mixed inflammatory infiltrate of neutrophils, lymphocytes and eosinophils is also consistent with iododerma. Her cutaneous involvement responded remarkably well with treatment using a regimen of triamcinolone wet wraps, doxycycline, and topical clindamycin. The clearance of her rash was maintained despite re-exposure to iohexol contrast for repair of her intracranial aneurysms. This was achieved using a readministration strategy using premedication with diphenhydramine, cetirizine, famotidine, montelukast, and prednisone. Further follow up is planned in the future, including investigation into predisposing factors which may be associated with her multiple vascular aneurysms.
Treatment of Eosinophilic Gastroenteritis: A multiphasic approach

Summary and Lessons Learned:
Treatment of eosinophilic gastroenteritis in pediatrics is limited. Options include dietary restriction which is helpful in about twenty five percent of cases or systemic steroids which cannot be used long term due to side effects. Over time, we ultimately utilized a combination of milk avoidance along with a novel approach to topical steroids targeting our patient’s stomach and upper duodenum. This regimen and targeted therapy significantly reduced her clinical symptoms and objective findings.

Patient Presentation and Testing:
We describe a six year old female with a history of mild atopic dermatitis and IgE mediated food allergy to egg (ingested baked eggs) who presented to our Gastroenterology division in November 2014 at four years of age with intermittent vomiting, thought to be related to constipation which initially improved with polyethylene glycol. In December 2014, following influenza, she was seen in our emergency department with altered consciousness prompting laboratory studies which revealed marked iron deficiency anemia (8 g/dL), low total protein (4.3 g/dL), hypoalbuminemia (2.2 g/dL) and hypereosinophilia (3850). She underwent an endoscopy/sigmoidoscopy in March 2015 while on a proton pump inhibitor (PPI), revealing > 50 eosinophils/hpf in esophagus and dense eosinophilic infiltrate of her stomach. A video capsule endoscopy revealed multiple aphthous lesions and small ulcerations throughout the jejunum and proximal ileum. In March 2015, she was seen in our Allergy division while still having mild intermittent symptoms. The decision made to remove milk from her diet. A repeat EGD in June 2015 revealed normalization of esophageal biopsy (8 eos/hpf), but both biopsies of the antrum and duodenum had markedly increased eosinophils. Laboratory studies remained abnormal. Her AEC at that time remained high at 2800 with an albumin of 3.0 g/dL and a total protein of 4.6 g/dL. She self-restricted peanut and was trialed on montelukast. Her symptoms improved and her family wished to monitor her clinically, but growth became concern. A repeat EGD in September 2016 showed persistently elevated eosinophils in the antrum and her AEC rose to 4740. Elemental diet and systemic steroids were not acceptable options to the family.

Diagnosis, Treatment and Patient Outcomes:
Despite therapy with a PPI, targeted food elimination and montelukast, our patient continued to have intermittent vomiting, new growth concerns and abnormal laboratory studies. Due to the extent of her underlying disease and desire to avoid elemental diet as well as systemic steroids, a unique use of multi-phasic swallowed steroid administration was trialed. As such the patient was instructed to take three capsules of budesonide (Entocort ®) 3mg daily alternating between ingestion of one capsule opened/two capsules crushed and two capsules opened/one capsule crushed (as the patient could not swallow the whole capsule). With this approach, it was thought that the delivery of different Entocort® forms would vary and their effects would target different mucosal areas. The crushed capsule would target the stomach earlier and more directly by bypassing the time and pH dependent release of the medication. The opened capsule would release medication more immediately into the upper intestine. A repeat EGD in January 2017 showed resolution of
eosinophilia in the stomach and duodenum. Her AEC decreased to 1030 and her albumin increased to 4.0 g/dL. By creating a regimen that maximized steroid effect on the mucosa involved, not only was improvement on tissue infiltrate and peripheral eosinophilia seen but clinically the patient experienced cessation of vomiting, abdominal pain and she exhibited improved weight gain.
Case Title:
Hypereosinophilia as an Initial Presentation for Very Early Onset Inflammatory Bowel Disease

Summary and Lessons Learned:
A 5 week old female presented with daily hematochezia and diarrhea for 2 weeks. Her CBC had an absolute eosinophil count of 11,500, and she was ultimately diagnosed with very early onset inflammatory bowel disease (VEOIBD). As opposed to traditional inflammatory bowel disease (IBD), patients who present with symptoms before 6 years of age are more likely to possess monogenic defects. Peripheral blood eosinophilia in association with VEOIBD has been described in children older than 4.5 years, and local eosinophilic inflammatory infiltrates are known to occur in conditions such as chronic granulomatous disease. Additionally, eosinophilia is well described in certain immune disorders. However, reports of peripheral eosinophilia in infants with IBD are scarce. Herein we describe a patient with peripheral eosinophilia and VEOIBD possessing a heterozygous c.442G>C (p.E148Q) variant in the MEFV. No additional variants were found in MEFV or 206 other genes associated with immunodeficiency. Homozygous and compound heterozygous variants in MEFV have been associated with VEOIBD associated with familial Mediterranean fever (including an individual with eosinophilic colitis). However, this variant is found in many asymptomatic individuals and is considered very low penetrance. In the case presented, the variant may be disease-modifying rather than causative. Ultimately, this case highlights that peripheral eosinophilia may be associated with infantile VEOIBD and that certain genetic variants may result in atypical presentations.

Patient Presentation and Testing:
A 5 week old female presented with daily hematochezia for 2 weeks. Her history was significant for a prenatal ultrasound showing an intraabdominal mass. Exploratory laparotomy on day 2 of life revealed an area of intestinal ischemia at the ileocecal junction, thought to be due to volvulus. Seventy-two centimeters of small bowel were resected, and an end-to-end anastomosis was created. She slowly returned to breast milk supplemented with soy-based formula. A CBC with differential at that time was normal. Ten days after discharge, she began to have about 10 loose stools per day streaked with bright red blood. She was placed on an amino acid-based formula by her gastroenterologist due to concern for milk protein allergy. She continued to have multiple loose, bloody stools each day. A repeat CBC from gastroenterology clinic showed a total WBC count of 35.3 x 10e9/L and an absolute eosinophil count (AEC) of 11,500, and she was admitted for further evaluation. Bone marrow biopsy and flow cytometry showed no signs of malignant disease. An elevated CD4 count of 6,572 cells/mm3 was noted, and T-cell clonality testing revealed a monoclonal population of T-cells with a prominent peak in the T beta 1 region. Fluorescence in situ hybridization (FISH) assays for translocation associated with myeloid hypereosinophilic syndrome were negative, as was evaluation for parasites. IgE level was normal, and C-reactive protein was undetectable. She underwent esophagogastroduodenoscopy and colonoscopy that demonstrated areas of erythematous, friable mucosa in the rectum and sigmoid colon macroscopically consistent with inflammatory bowel disease. There were no signs indicating loss of anastomotic integrity. Biopsies revealed focal aggregates of eosinophils in the duodenum with preserved villous architecture. In the colon, dense eosinophilic infiltration of the lamina propria was noted along with reactive crypt epithelium. Esophageal biopsies were normal. Stool studies demonstrated an elevated fecal calprotectin. Given her age and clinical findings, she was diagnosed with VEOIBD. A focused sequencing panel targeting 207 genes associated with immunodeficiency revealed a heterozygous variant in MEFV (C.442G>C; p.E148Q).

Diagnosis, Treatment and Patient Outcomes:
Our patient was worked up for hypereosinophilia and hematochezia which led to the diagnosis of very early onset inflammatory bowel disease with an inflammatory gene panel demonstrating a mutation of the MEFV gene. Multi-
system evaluation for end organ damage in the setting of peripheral eosinophilia was negative apart from gastrointestinal involvement (and sparing the esophagus). Once malignancy was ruled out, the patient was started on IV methylprednisolone. Her dose was 1mg/kg/day initially, but was increased to 2mg/kg/day when her AEC plateaued around 6,000. At this dose, her AEC decreased further, though she continued to have frequent bloody stools ultimately requiring a transfusion. The patient was transitioned to total parenteral nutrition (TPN) for 2 weeks while continuing on corticosteroids, and sulfasalazine and omeprazole were started. Hematochezia gradually resolved while on TPN. After 14 days, she restarted oral feeds with an amino acid-based formula. No significant recurrence of her hematochezia was noted. She was discharged on an oral prednisolone taper with daily sulfasalazine and omeprazole and close outpatient follow-up.
Summary and Lessons Learned:
SUMMARY: A 19-year old female, with a 7 and 3-year history of idiopathic asymptomatic hypereosinophilia and bronchial asthma, respectively, treated for the latter with inhaled budesonide/formoterol (160/4.5 μg twice daily), montelucast (10mg daily) and oral prednisolone (10mg daily) was referred to the Allergy Department of Sotiria Athens General Hospital for further evaluation and potential treatment modification. The patient had been recently diagnosed with osteoporosis and psychosis, which were both presumed to be steroid-induced and were treated with calcium/cholecalciferol and olanzapine (10mg daily), respectively. Furthermore, she had poor compliance with asthma treatment, due to her altered mental status, resulting in acute asthma exacerbations. Following a thorough clinical, imaging and laboratory diagnostic testing, for the exclusion of secondary and clonal causes of peripheral blood hypereosinophilia and the confirmation of bronchial asthma diagnosis, prednisolone administration was discontinued, by gradual reduction of dosage over a period of 6 weeks, and mepolizumab treatment (100mg by subcutaneous injection every 4 weeks) was initiated. A marked reduction (with normalization) of eosinophils blood count was observed (272/μL as compared to 1833/μL) within two weeks after the first mepolizumab injection, and remained within the normal range during a treatment period of 3 months. Asthma symptoms remained well-controlled as well -with no acute exacerbations- throughout the same time period. No mepolizumab-associated side effects were noted.
LESSONS LEARNED: Mepolizumab was both effective and well-tolerated as a second-line corticosteroid-sparing agent in our patient, leading to adequate control of asthma symptoms and resolution of idiopathic hypereosinophilia. Patients with steroid-refractory asthma (or steroid-induced complications, as in our reported case) and other eosinophilic-related comorbidities may represent excellent candidates for mepolizumab treatment.

Patient Presentation and Testing:
PATIENT PRESENTATION: At the time of her initial presentation to our department, the patient had acute exacerbations of asthma, and steroid-induced psychosis and osteoporosis, resulting from chronic corticosteroid treatment for idiopathic hypereosinophilia.
TESTING: Clinical history and physical examination and thorough diagnostic testing (i.e. detailed imaging and laboratory studies, including, but not limited to, the following: serological studies and serum tryptase levels, chest x-ray, thoracic and abdominal CT, electrocardiogram and echocardiogram, pulmonary function tests, bone marrow biopsy and cytogenetic studies, in vitro and in vivo allergy testing) for the exclusion of secondary and clonal causes of peripheral blood hypereosinophilia and evaluation of pulmonary function/asthma status were performed.

Diagnosis, Treatment and Patient Outcomes:
Following detailed diagnostic evaluation/testing of our patient, the diagnosis of idiopathic hypereosinophilia was confirmed. Prednisolone administration was discontinued, by gradual reduction of dosage over a period of 6 weeks, and mepolizumab treatment (100mg by subcutaneous injection every 4 weeks) was initiated. A marked reduction (with normalization) of eosinophils blood count was observed (272/μL as compared to 1833/μL) within two weeks after the first mepolizumab injection, and remained within the normal range during a treatment and
follow-up period of 3 months. Throughout the same time period, asthma symptoms remained well-controlled and no mepolizumab-associated side effects were noted.
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Case Title:  
eosinophilic granulomatosis with polyangiitis presenting with acute polyneuropathy resembling Guillain–Barré syndrome

Summary and Lessons Learned:  
Eosinophilic granulomatosis with polyangiitis (EGPA) is a rare systemic vasculitis that commonly affects the peripheral nervous system. EGPA rarely presents with acute polyneuropathy resembling Guillain-Barré syndrome (GBS). A 51-year-old female patient with a history of asthma, was diagnosed as GBS subtype according to neurologic symptoms and the results of nerve conduction study. Although treatment of GBS, painful motor weakness persisted. Her blood test had marked eosinophilia, positive response to anti-neutrophil cytoplasmic antibodies. Considering the history of asthma, sinusitis and blood test results, we suspected EGPA-associated polyneuropathy and started steroid treatment. Her symptoms and eosinophilia improved rapidly. We identified a case of EGPA with acute polyneuropathy mimic GBS. These should be differentiated because of different treatment strategies. Early diagnosis and prompt treatment help to achieve a good outcome.

Patient Presentation and Testing:  
A 51-year-old female patient with a history of asthma, suddenly developed bilateral lower extremity paresthesia that progressed to asymmetric ascending paralysis within 10 days of onset. Nerve conduction study results were compatible with acute motor sensory axonal neuropathy, consistent with a GBS subtype.

Diagnosis, Treatment and Patient Outcomes:  
A clinical and a neurophysiological diagnosis of GBS was made, and high-dose intravenous immunoglobulins were administered. However, the patient’s painful motor weakness persisted. Furthermore, she had newly developed skin lesions on her back, face, and arms. Her blood test revealed marked eosinophilia (>60%). In addition, anti-neutrophil cytoplasmic antibodies (ANCAs) were reported positive. A Water’s view radiographic image showed bilateral maxillary sinusitis. Considering the history of asthma, we suspected EGPA-associated polyneuropathy and started steroid treatment. The patient’s strength and eosinophilia improved rapidly and dramatically.
Summary and Lessons Learned:
This case describes a 22yo Caucasian female with a history of mild asthma transferred to our facility for concern for worsening rash with peripheral eosinophilia. Our allergy service was consulted for concern for a possible drug reaction. She was previously treated with Vancomycin and ceftriazone and several weeks into course developed peripheral eosinophilia and rash concerning for hypersensitivity reaction. She was transitioned to alternative antibiotic with continued progression of rash and edema to face, trunk, and extremities as well as mild increase in creatinine. Transaminases remained normal. The clinical diagnosis of DRESS (drug reaction with eosinophilia and systemic symptoms) was confirmed using European Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) scoring system with a score of 7(>6 is defined as definite DRESS). She continued to have progression of non-painful, pruritic rash and an extensive evaluation for sepsis was performed. Bronchoscopy with bronchial alveolar lavage revealed eosinophils without other abnormalities. She developed respiratory failure and was subsequently intubated. A repeat bronchoscopy with biopsy showed histopathologic findings consistent with Langerhans cell histiocytosis. This patient's history demonstrates the necessity of an extraordinarily large differential diagnosis in patients with eosinophilia and clinical symptoms. On the basis of our experience with this patient and a single other report with similar findings, we suggest that patients with pulmonary symptoms associated with DRESS may have a pulmonary vasculitic syndrome induced by eosinophil activation from the drug hypersensitivity reaction associated with DRESS.

Patient Presentation and Testing:
On initial presentation, patient had recently been treated with multiple courses of different antibiotics and developed diffuse erythematous rash and edema with eosinophilia and elevated creatinine above baseline. We obtained previous outside hospital records for detailed medication administration history to determine temporal relation of symptoms starting 2-3 weeks after change in antibiotic. We monitored eosinophil count as well as hepatic panel for systemic symptoms which is standard of care for DRESS. Pulmonology made the decision to repeat bronchoscopy for tissue biopsy following respiratory failure which identified pathologic diagnosis.

Diagnosis, Treatment and Patient Outcomes:
The clinical course was consistent with DRESS but her respiratory failure appears related to a second condition, Langerhans cell histiocytosis, the diagnosis of which would have been missed without lung biopsy. Treatment with systemic corticosteroids resulted in rapid improvement in eosinophilia, rash and respiratory status. Repeat imaging demonstrated resolution of previous consolidation. She was discharged on a long steroid taper and upon follow-up three months later, continued to show improvement with no further rash or other systemic symptoms.
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Case Title:  
Eosinophilic Esophagitis after Oral Immunotherapy: have all patients improved?  

Summary and Lessons Learned:  
WCL, male, 9 yo, presented confirmed cow milk allergy (CMA) since 7 months old with classical IgE mediated features including anaphylaxis. At six years old the patient persisted with allergic symptoms and a desensitization protocol was proposed. Before beginning the process, an esophagastroduodenoscopy (EGD) was performed with normal results. After three months of protocol, recurrent vomiting and nausea occurred which demanded reduction of daily milk intake. As patient did not improve, a new EGD was performed and clear signals of EoE were observed (macroscopically and microscopically). Desensitization was stopped and proper clinical treatment was initiated (corticosteroids and proton pump inhibitors - PPI). Despite an initial improvement (new EGD without eosinophils at microscopy), after other 3 months patient presented signs of EoE. Other food exclusions were proposed - soy and egg -, a new EGD was performed at 8 weeks showing rare eosinophils in the proximal esophagus and 25 eosinophils/hpf in the distal esophagus. We performed impedance and pH testing with normal results. Although EoE is a referred complication in IOT protocols, the majority of patients presented reversible disease. It is important to be alert to a more persistent disease and consider if it there is a causal relation between IOT and EoE or if severe food allergies consist a risk factor for this disease.  

Patient Presentation and Testing:  
Patient referred to our service at the age of 2 and presented confirmed CMA, with history of hives and vomiting at 7 months old after contact with infant formula. His parents avoided cow milk protein from the diet but accidental exposures occurred occasionally reproducing symptoms. IgE to casein was 56 KU/L, beta-lactoglobulin 20 KU/L and alpha-lactalbumin 17 KU/L. His past medical history was significant for allergic rhinitis and asthma. At 6 years old he persisted with CMA, therefore we proposed oral immunotherapy (IOT). Before beginning the process, an EGD was performed with normal results. After 3 months, the patient started vomiting once a day everyday, demanding reduction of daily milk intake. We conducted an EGD since evidence suggested gastric complications due to IOT. New EGD showed linear furrows and strictures, with 20 eosinophil/hpf, suggestive of eosinophilic esophagitis.  

Diagnosis, Treatment and Patient Outcomes:  
Patient was diagnosed with eosinophilic esophagitis and was advised to completely discontinue his OIT, we prescribed PPI and swallowed glucocorticoid (Budesonide 1000 mcg / day) for 12 weeks. Repeated EGD appeared normal macroscopically and microscopically with non-specific esophagitis without eosinophils. We suspended drug treatment and maintained dairy-free diet. After 3 months, EGD was repeated, again showing esophagus with longitudinal strains, thickened mucosa, with 38 eosinophils/hpf in proximal mucosa and 25 eosinophils/hpf in distal mucosa. Due to relapse of EoE we reintroduced swallowed glucocorticoid for another 6 months. Patient was asymptomatic in this period and we gradually reduced swallowed glucocorticoid, 200mcg per week, until complete suspension. After 3 months without the use of swallowed glucocorticoid, a new EGD showed linear furrows and fibrin specks throughout the esophagus, with 8
eosinophils/hpf in the proximal esophagus and 50 eosinophils/hpf in the distal. The patient was advised to continued avoiding cow milk and started a trial of a soy and egg-free diet. New EGD was repeated 8 weeks later and showed rare eosinophils in the proximal esophagus and 25 eosinophils/hpf in the distal esophagus. We conducted an impedance and a pH testing with normal results.
Summary and Lessons Learned:
A 61-year-old gentleman with history of headaches and emphysema presented with scalp pruritus following botulinum toxin injections for headaches and was found to have eosinophilia (13%; normal (N): 0-5%) and an elevated immunoglobulin E (IgE) level (15,513 kU/L; N: 0-115 kU/L). Infectious disease evaluation for eosinophilia, including stool ova and parasites, hepatitis B and C (HBV and HCV), HIV, TB, and strongyloides, were all negative. Allergy testing by ImmunoCAP showed no significant amount of IgE against individual environmental allergens. Screening for autoimmune conditions, such as eosinophilic granulomatosis with polyangiitis with ANCA and complement levels, was normal. FIP1L1-PDGFRA mutation testing was negative. C-kit was normal, suggesting no intrinsic issues with mast cells. Peripheral blood flow cytometry demonstrated a monoclonal B cell lymphoproliferative disease. Imaging at the time of presentation was only notable for a non-enlarged spleen with small ill-defined hypodensities. His clinical presentation was thought to be consistent with monoclonal B-cell lymphocytosis. Therapy was not initiated. After one year of observation, he developed night sweats, fatigue, and cervical lymphadenopathy. A PET scan demonstrated new hypermetabolic bilateral cervical and supraclavicular lymphadenopathy, and lymph node and bone marrow biopsies were consistent with chronic lymphocytic leukemia (CLL). He was started on ibrutinib for CLL. His constitutional symptoms resolved, and eosinophilia and elevated IgE have declined significantly since starting therapy.

When evaluating a new patient, it is important to maintain a broad differential diagnosis based upon a patient’s history and physical exam. Flow cytometry is an important part of the work-up for eosinophilia. A clonal B-cell population and CLL are rare causes of elevated eosinophil and IgE levels that must be considered when evaluating patients with a severe eosinophilia of unknown etiology. The resolution of his eosinophilia and elevated IgE after starting therapy with ibrutinib suggests that they were part of a B-cell-induced Th2 response.

Patient Presentation and Testing:
The patient was a 61-year-old male with history of emphysema and headaches who presented for evaluation of elevated IgE (15,513 kU/L; N: 0-115 kU/L) and eosinophil levels (13%; N: 0-5%; absolute eosinophil count 975; N: 15-500 cells/microliter). The patient began to receive botulinum toxin injections in his scalp every 3 months in the year preceding his evaluation for his eosinophilia for severe chronic migraine headaches. While receiving botulinum toxin therapy, he developed pruritic papules on his scalp at the injection sites. His injections were stopped, but his symptoms persisted. He was evaluated by dermatology and treated with antihistamines and topical clindamycin, which failed to control his symptoms. Initial testing identified eosinophilia and elevated IgE level, and he was referred to an allergy and immunology clinic. He did not have any symptoms apart from scalp pruritus at his first clinic visit.

His laboratory evaluation included rechecking his IgE and CBC, which confirmed persistently elevated levels. As the underlying etiology remained unclear from his history and physical exam, a broad laboratory work-up was undertaken to identify the cause of his eosinophilia. In order to determine if there was an infectious etiology behind his condition, HIV, HBV, HCV, stool for ova and parasites, stool culture, clostridium difficile, and strongyloides IgG were checked, and all tests returned negative. ImmunoCAP testing was performed and was unrevealing for any allergic disease. His immune system was evaluated by IgG subclasses, IgM, IgA, FIP1L1-PDGFRA mutation, and C-kit mutation testing, which were all normal. An ANA, ANCA, C3, and C4 levels were checked to determine the presence of an autoimmune condition, such as eosinophilic granulomatosis with polyangiitis. However, all his studies returned normal. A peripheral blood flow cytometry was performed and identified a monoclonal B cell population. T-cell gene rearrangement studies were performed and did not identify any monoclonal T-cell populations.
**Diagnosis, Treatment and Patient Outcomes:**
The patient underwent a thorough evaluation of his immune system, as well as investigation for fungal and parasitic causes of his symptoms and laboratory abnormalities. No atopic disease was identified. The only abnormality identified was a monoclonal B cell population on flow cytometry.
The patient was referred to hematology for evaluation of his B-cell lymphoproliferative disorder. As the patient had no significant symptoms, he was initially observed. However, he developed night sweats, fatigue, and cervical lymphadenopathy over the following year. A PET scan was performed and demonstrated new hypermetabolic bilateral cervical and supraclavicular lymphadenopathy, and lymph node and bone marrow biopsies were consistent with CLL. Ibrutinib therapy was initiated for treatment of his CLL.
The patient’s constitutional symptoms and eosinophilia resolved with ibrutinib therapy, while his IgE level significantly decreased. He continues to be followed by hematology and receives ibrutinib 420 mg daily. The patient’s response to therapy suggests that his B cell CLL was the source of Th2 cytokines that caused his eosinophilia and massive production of non-specific IgE. Lymphoproliferative disorders must be included in the differential diagnosis of eosinophilia of unknown etiology.
Case Title:
Successful use of mepolizumab in a patient with chronic eosinophilic pneumonia

Summary and Lessons Learned:
Chronic eosinophilic pneumonia (CEP) often poses a diagnostic challenge due to its overlapping presentations with other eosinophilic lung diseases. Patients with CEP typically present with gradual onset of cough and progressive shortness of breath over several months. Our patient presented with a 4-month history of cough and respiratory symptoms and had peripheral blood and bronchoalveolar lavage (BAL) eosinophilia. Chest radiographs revealed extensive infiltrations. Her CEP diagnosis was made after other causes of eosinophilic lung disease were excluded. She had a relapse when oral steroids were discontinued. Mepolizumab treatment led to excellent clinical response.
We learned several lessons: Firstly, it is important to broaden differential diagnoses to include common and uncommon conditions.
Secondly, CEP should be considered in the differential diagnosis of patients presenting with thick cast sputum production.
Thirdly, we learned about challenges in the treatment of CEP.
Lastly, mepolizumab can be considered an adjunct therapy in CEP patients who have frequent relapses or are steroid-dependent

Patient Presentation and Testing:
A 20-year-old female with history of asthma, environmental allergies, and eosinophilic esophagitis presented with productive cough and progressive shortness of breath for 4 months. Expectorated sputum often contained whitish-yellowish casts. Inhaled corticosteroids and bronchodilator failed to improve symptoms or FEV1. White blood cell count (25,000/mm3), absolute eosinophil count (10,750/mm3 [43%]), and IgE level (1,122 IU/mL) were elevated. On chest CT, there were bilateral multifocal opacities, predominantly in the upper lobes. Pathologic examination of the casts retrieved during bronchoscopy revealed dense eosinophils and numerous Charcot-Leyden crystals. Blood, sputum, BAL, and stool specimens were negative for microorganisms. Extensive evaluation, including bone marrow examination, was used to determine the cause of eosinophilia. The diagnosis of CEP was made following negative evaluation for environmental or drug allergies, infections, parasitic infestations, hypereosinophilic syndrome, allergic bronchopulmonary aspergillosis, and eosinophilic granulomatosis with polyangiitis.

Diagnosis, Treatment and Patient Outcomes:
Initiation of empiric treatment with antibiotic, anthelminthic agent, and inhaled and systemic corticosteroids markedly improved respiratory symptoms. Relapse occurred when prednisone was stopped. Prednisone was restarted and continued for 6 months; her lowest AEC was 1,224/mm3. Ten months after the initial presentation, chest CT identified a new area of impaction in the bronchus with distal bronchiectasis. Mucinous plugs made of eosinophilic materials persisted in the bronchi. Within one month of starting mepolizumab injections, her spirometry parameters improved and she no longer experienced cough or expectorated thick casts. Over the next year of mepolizumab treatment, her respiratory symptoms remained stable, with no exacerbation or prednisone use.
Summary and Lessons Learned:
Hypereosinophilic Syndrome (HES) is characterized by prolonged eosinophilia leading to damage of various organs. The two variants of HES are myeloproliferative and lymphocytic hypereosinophilic syndrome (L-HES). L-HES is identified by detection of a T-cell clone typically associated with increased expression of IL-5 responsible for production eosinophilia and the toxic effects of their products. The standard of therapy is corticosteroids but studies suggest that the L-HES is inherently less susceptible to respond to steroids which raises the need for emphasis on targeted therapy such as IL-5 inhibitors. We present a case of successful treatment of L-HES with Mepolizumab. Treatment of the L-HES with mepolizumab should be strongly considered to provide an effective targeted, steroid-sparing treatment that aims at reducing the morbidity from long-term steroid use in HES.

Patient Presentation and Testing:
An otherwise healthy 65 year old male, with a past medical history of childhood asthma, presented to the ER with episodes of shortness of breath and cough. He was treated for asthma exacerbation and was discharged. Patient subsequently presented to the hospital with shortness of breath, chest pain, and fever, found to have a SpO2 of 90. Work up revealed an absolute eosinophil count of 15,000, and bilateral consolidation on chest x-ray. He was treated for bacterial pneumonia and asthma exacerbation. Further work up of eosinophilia was negative for ANCA, elevated tryptase, stool for ova/parasites, and Strongyloides. Patient was found to have a T cell clone and a negative FIP1L1-PDGFR alpha by FISH leading to the diagnosis of lymphocytic variant of HES.

Diagnosis, Treatment and Patient Outcomes:
Patient had ongoing symptoms of shortness of breath and cough for which he required maintenance doses of prednisone. He was then trialed on mepolizumab with which he showed marked clinical improvement. The patient was able to be tapered off of steroids in three months time.
Summary and Lessons Learned:
Eosinophilic esophagitis (EoE) has emerged over the last two decades with increasing prevalence and incidence. It presents with a constellation of upper gastrointestinal symptoms and is diagnosed with demonstration of > 15 eosinophils/high powered field (hpf) on esophageal biopsy. Resolution of EoE presents a larger challenge for clinicians given the lack of standardization of pathology reporting. We present a case of EoE in which despite presence of > 20 eosinophils/hpf the patient reported marked improvements and standardization of pathology reporting would have beneficial for tracking the patient’s clinical condition.

Patient Presentation and Testing:
47 year old man from Colombia who presented initially to the allergy clinic for evaluation of food allergies following an upper gastrointestinal endoscopy revealed white plaques in the upper and middle third of esophagus; and tissue biopsy from both sites showed > 25 eosinophils/hpf with eosinophilic micro-abscesses. Allergy skin testing and immunocaps were negative. He was started on omeprazole twice daily and due to patient preference, only a 3-food elimination diet of dairy, soy and nuts. After 7 weeks of elimination diet, repeat endoscopy showed endoscopic improvement, but ongoing tissue infiltration of eosinophils with > 25 eosinophils/hpf. Given the persistence of tissue eosinophil infiltration, oral viscous budesonide (OVB) was added to his 3-food elimination diet. This resulted in significant improvement of patient symptoms. Repeat endoscopy again revealed normal appearing esophagus, but the tissue infiltration with > 20 Eosinophils/hpf persisted. Eosinophil micro abscesses were now rare. At this point we reviewed the pathology from the three endoscopies. We found that biopsies from the first endoscopy had 180 eosinophils/hpf, the second 78 eosinophils/hpf and the third 22 eosinophils/hpf. We inferred that the 3-food elimination diet had 56% reduction in tissue eosinophil infiltration, and OVB resulted in a further 31% reduction.

Diagnosis, Treatment and Patient Outcomes:
This case brings to light the need for standardization of reporting eosinophils in initial and subsequent endoscopic reports. Our patient despite having persistence of eosinophils had clinical improvement and resolution of plaques on the gross appearance of the esophagus. We propose all pathology reports for patients with EoE include an absolute number of eosinophils/hpf versus the currently reporting cutoff of > 15. This method of reporting would help better define the pathologic improvement along with the clinical as therapies are being adjusted and added.
**Case Title:**
Pomegranate anaphylaxis in a Canadian adolescent

**Summary and Lessons Learned:**

**RATIONALE:**
Pomegranate comes from the tree Punica granatum. IgE-mediated allergy to pomegranate is very rare, though has been reported in Mediterranean countries. To the best of our knowledge, we present the first case of pomegranate allergy in North America. Additionally, it is the first case to date of pomegranate allergy in the absence of allergy to other fruits, peanuts and/or tree nuts.

**METHODS:**
Skin prick testing to inhalant aeroallergens and prick-by-prick testing to fresh pomegranate was performed.

**RESULTS:**
A 15-year-old Canadian girl was referred to our allergy clinic following an anaphylactic reaction to pomegranate. She had eaten pomegranate several times in the past with no reaction. However, on that particular morning, she ate a whole pomegranate on its own. Twenty minutes later, she reported an itchy throat. Within minutes, her symptoms escalated to include diffuse urticaria, difficulty breathing, wheezing and significant abdominal discomfort.

Since that incident, the patient avoided pomegranate; however, she continued to eat nuts and other fresh fruits with no concerns, including peaches. She denied any history of oral allergy syndrome. Her physical examination was unremarkable. Skin prick testing was positive for fresh pomegranate at 7x7mm and to Alternaria, trees, grass, weed mix, ragweed and cat.

The patient was diagnosed with a pomegranate allergy. Strict avoidance was recommended and she was prescribed an epinephrine autoinjector.

**CONCLUSIONS:**

There are approximately fifteen cases of pomegranate allergy in the medical literature, and all occurred in Mediterranean countries, including Spain, Italy and Turkey. The reason for this geographic pattern is unclear, though it may be because pomegranate is widely cultivated in the Mediterranean. Like our patient, many of these patients had a history of pollen allergy. However, unlike our patient, each of these patients had additional food allergy or oral allergy syndrome with other fruits, most notably peaches, peanuts and/or tree nuts. Based on immunoblotting studies in which pomegranate extract is incubated with patient sera, several protein allergens have been identified. This includes: one of 29 kDa, two lipid transfer proteins (LTP), and pathogenesis-related protein 4 (PR-4). In most cases, the LTP was implicated for the cross-reactivity between pomegranate and other fruits, nuts and pollens. Unfortunately, we did not have the means to perform immunoblotting on our patient, but should further cases arise in North America, this would be worthwhile to pursue.

In conclusion, pomegranate allergy can occur outside of the Mediterranean and can occur in the absence of other food allergies.

**Patient Presentation and Testing:**
A 15-year-old Canadian girl was referred to our allergy clinic in Burlington, Ontario, following an anaphylactic reaction to pomegranate. This patient was previously healthy, except for a history of seasonal allergies in the spring and summer. She had eaten pomegranate several times in the past with no reaction. However, on that particular morning, she ate a whole pomegranate on its own. Twenty minutes later, she reported an itchy throat. Within minutes, her symptoms escalated to include diffuse urticaria, difficulty breathing, wheezing and significant abdominal discomfort. She took an antihistamine, which helped to improve her symptoms, and was then seen in the emergency department but epinephrine was not administered.
Since that incident, the patient avoided pomegranate; however, she continued to eat peanuts, tree nuts and other fresh fruits with no concerns, including peaches. She denied any history of oral allergy syndrome. Her physical examination was unremarkable. We performed prick-by-prick testing to fresh pomegranate, which was positive at 7x7mm. Given her history of seasonal allergies and known cross-reactivity between pomegranate and pollens, we also performed skin prick testing for inhalant aeroallergens, which were positive for alternaria, trees, grass, weed mix, ragweed and cat. Unfortunately, there is no specific IgE test available for pomegranate and therefore, this could not be ordered. We purposely did not perform skin prick testing to other fruits, peanuts or tree nuts, because she was eating these foods regularly with no symptoms. We felt that performing additional skin prick testing to those foods could result in false positive results, perhaps leading to inappropriate avoidance of foods that she was clinically tolerating. As this patient was seen in a community clinic, unfortunately, we did not have the means to perform immunoblotting studies to determine which specific protein allergen she had reacted to within the pomegranate.

**Diagnosis, Treatment and Patient Outcomes:**
The patient was diagnosed with a pomegranate allergy based on a clear history of anaphylaxis to pomegranate in the absence of confounding factors, given that she had not eaten any other foods that day. The diagnosis was confirmed via positive prick-by-prick testing to fresh pomegranate, as described above. She was also diagnosed with perennial and seasonal allergic rhinitis to alternaria, trees, grass, ragweed and cat.

For the pomegranate allergy, we advised strict avoidance of pomegranate. We also prescribed an epinephrine autoinjector and counselled the patient regarding indications and proper use. For her allergic rhinitis, allergen immunotherapy was offered but the patient declined. Instead, we discussed allergen avoidance measures and prescribed an intranasal steroid spray, antihistamine eye drops and an oral antihistamine.

The patient continues to avoid pomegranate and has been clinically well since our last clinic visit.
Case Title:
Food-dependent exercise-induced urticaria with panallergen sensitization (LTP) and alcohol cofactors.

Summary and Lessons Learned:
Exercise induced anaphylaxis is a potentially fatal clinical syndrome in which anaphylaxis is triggered by mild to vigorous exercise. When food is involved as a cofactor, the condition is called food-dependent exercise-induced anaphylaxis (FDEIA). Mild physical activity can trigger severe systemic reactions and some patients experience mild-moderate systemic allergic reactions with exercise, dependent on food ingestion. These milder reactions have been recently reported as food dependent exercise-induced urticaria, both associated with lipid transfer protein (LTP) and with wheat. Diagnosis is highly dependent on a thorough clinical history including a detailed description of all food ingested before and after the physical activity that triggered the anaphylactic reaction and the use a combination of skin prick tests, prick to prick tests to allergens chosen according to the clinical history and in vitro tests. Challenge tests are needed to provide a definite diagnosis but false-negative results can occur and food-exercise challenges fail to confirm diagnosis in up to 30% of patients. False negative can be explained by the unpredictability of FDEIA, as it can occur during exercise of different intensities and other cofactors include stress, drugs (anti-inflammatory), menstruation and weather.

To report the case of a 32-year-old female with a previous diagnosis of oral allergy syndrome with nut, hazelnut, peanut, kiwi and pineapple. Palpebral bilateral and lips angioedema with unpeeled apple. She didn't have rhinitis or asthma. The first episode was 3 months ago, urticaria symptoms develop mostly within 10 minutes from the onset of physical activity. The patient noticed pruritus in ears, on the scalp, she developed generalized urticaria, and experienced palpebral bilateral angioedema and flushing face. No respiratory nor gastrointestinal symptoms. She didn’t require medical attention. The symptoms resolved 2 hours later.

She had eaten 4 hours beforehand bread with meat, beer and nachos with guacamole. She had menstruation in that moment. No infections. No co-administration of drugs. No stress. Then, she ate these foods without exercise and she didn't have symptoms.

2 days later, during physical activity (running) she had the same symptoms. She had eaten 2 hours beforehand milk with toast with butter and strawberry jam. She didn’t require medical attention. Then, she ate these foods without exercise and she didn’t have symptoms.

And she had practiced exercise without problems without food intake.
The outcome of this case is food-dependent exercise-induced urticaria with panallergen sensitization (LTP) and alcohol cofactors at the first episode but not in the second.

Patient Presentation and Testing:
To report the case of a 32-year-old female with a previous diagnosis of oral allergy syndrome with nut, hazelnut, peanut, kiwi and pineapple. Palpebral bilateral and lips angioedema with unpeeled apple. She didn’t have rhinitis or asthma.
She didn’t have other medical or surgical history.
She doesn’t take any usual treatment.
She has had two episodes of exercise-induced urticaria with concomitant food and alcohol intake: The first episode was 3 months ago, 4 hours after had eaten bread with meat, one beer and nachos with guacamole. She had menstruation in that moment.
The second time she ate 2 hours beforehand milk with toast with butter and strawberry jam. She didn’t drink alcohol in this episode.

Tests performed in that time:
- Skin prick tests were positive against house dust mite, pollen (plane and cynodon) and Lipid Transfer Protein (LTP).
- Skin prick test were positive against mix of nuts, chestnut, peanut, hazelnut, almond, peach, apple, kiwi, lentil, rice, prick by prick of strawberry jam and prick by prick of guacamole.
- Skin prick testing were negative for fungus, cat and dog dander, other pollen, profilin, polcalcin.
- Skin prick testing was negative for other commercial food extracts.
- Routine blood test without alterations. Total IgE: 51 KU/l. Tryptase 1,96 KU/l.
- Specific- IgE (sIgE) were positive for nut, kiwi, strawberry, peanut, rice, almond, hazelnut, Cor a8, Ara h9, Jug r3 and pru p3 and were negative for Tri a19, Tri a14.
- Exercise test was negative without eating any food.

We have performed all these tests because it is necessary to know foods to which she have allergy and to know if the patient had exercise- induced anaphylaxis.

We didn’t do an oral challenge with the suspected food followed by physical exercise because the patient didn’t consent the test and false- negative results can occur.

**Diagnosis, Treatment and Patient Outcomes:**
The diagnosis is exercise- induced urticaria with lipid transfer protein (LTP) and alcohol cofactors.

The patient had food- dependent exercise- induced urticaria because she didn’t suffer all the symptoms of anaphylaxis and she didn’t have cholinergic urticaria because there are involved LTP and alcohol cofactors with skin tests positive and in the first time alcohol such a cofactor.

She usually exercises and she didn’t have any symptoms.

On the other hand, when she ate strawberry, guacamole, beer, bread with meat, nachos and milk she didn’t have symptoms.

The treatment that we recommended was:
- Take rosaceae fruits peeled (peech, apple, pear, plum, grape,etc). To avoid packaged juices and jams.
- Continue taking foods that hasn’t produced problems so far.
- Forbidden ingestion of peanut, hazelnut, nut, kiwi, pineapple. Continue taking pineapple in syrup as before.
- Approximately 2 hours prior to exercise avoid cofactors which can precipitate urticaria or anaphylaxis such as: alcohol, NSAIDs and foods containing LTP like rosaceae fruits.
- In case of pruritus, hives, difficult to breath, difficult to swallow, etc Adrenalin autoinjector 300 mcg will be given (according to indications explained by the doctor), and then go to emergency department or hospital emergency.
- Prednisone 30 mg in case of pruritus or eyelid edema or palpebral angioedema after accidental ingestion of nuts or fruits containing LTP.

The patient didn’t have any problem following these recomendations and she didn’t have a new episode by now. It is important to avoid cofactors such as NSAIDs, alcohol consumption, foods containing LTP and infectious disease when she exercise.
Summary and Lessons Learned:
Food protein-induced enterocolitis syndrome (FPIES), a non-IgE-mediated food allergy, presents with prolonged vomiting 1-4 hours after ingestion of the offending food(s), lethargy, pallor, and diarrhea. Identification of offending foods can be difficult when an infant is exposed to multiple foods during complementary feeding introduction. This can impact growth, development, and quality of life. Here we present a 5 month old who developed chronic FPIES, potentially to multiple foods. We describe difficulties in identifying potential food triggers, discuss strategies for further food introduction to optimize nutrition during this critical time of growth and development, and focus on feasibility.

Patient Presentation and Testing:
We present an 8-month-old previously healthy fraternal twin term female with history of gastroesophageal reflux that developed chronic FPIES, potentially to multiple foods, and failure to thrive. Symptoms included vomiting, lethargy, floppiness, grey skin, dry heaving, and diarrhea for 12 hours after ingesting peaches at 5 months, peas at 5 months, and chicken broth/avocado/multi-vitamin at 7 months. After each episode, they resumed exclusive breast feeding. The mother had reintroduced milk intermittently into her diet, which had previously been held to assist with infant reflux management.

Her weight decreased from the 65th percentile at 4 months to the 18th percentile at 8 months. Skin testing was positive to egg and negative to milk, wheat, corn, soy, peanut, cod, shrimp, oat, walnut, cashew, and almond. Total IgE was 7.8 kU/L and specific IgE was negative to beef, casein, chicken, egg, milk, oat, pea, pork, soy, peach, and rice. Extensive infectious and gastrointestinal evaluations were unrevealing.

Diagnosis, Treatment and Patient Outcomes:
The mother was extremely concerned about the potential of multiple food triggers and was reluctant to proceed with further complementary solid food introduction. The child remained exclusively breastfed.

We performed in-office single oral food challenges (OFC) to various solid foods, recommending avoidance of other solid foods until the infant passed an OFC. We prioritized OFCs to foods that would provide appropriate nutrition to a growing infant. She now tolerates many foods withholding the possible offending foods only. Fortunately we identified many safe foods, allowing recovery from her failure to thrive and potentially preventing associated neurodevelopmental delays. We must consider nutritional value of foods when considering selection for OFCs, especially with failure to thrive. The decision to exclusively breast feed with maternal avoidance of soy and dairy allowed us to slowly reintroduce foods individually in order to improve nutritional status rapidly.
**Case Title:**
Food Aversion in a Young Child Following a Positive DBPCFC to Peanut

**Summary and Lessons Learned:**
This is a case report of a 3y11mo old male who experienced grade 2 anaphylaxis during a double-blind placebo-controlled food challenge (DBPCFC) to peanut and subsequently developed a significant food aversion with accompanying weight loss requiring interventional therapy.

The DBPCFC occurred after 2.5 years of daily dosing with peanut/placebo oral immunotherapy (OIT) as a part of a clinical trial. A cumulative dose of 200mg peanut protein elicited the following symptoms: change in affect, generalized pruritus, and one episode of vomiting. He required one dose of epinephrine 0.15mg IM and one dose of oral antihistamine to treat his symptoms. He was safely discharged several hours later after a return to baseline.

Three weeks after the DBPCFC, the research team was notified by the child’s parents that he had developed a food aversion. According to his parents, the child would only eat yogurt, and he reported that he was “scared to eat.” Prior to initiating the DBPCFC, the subject weighed 17.2kg, was 103cm tall (BMI 16.2, 72.6 percentile weight for age). Four months after the DBPCFC, he had a total weight loss of 2kg from his pre-challenge weight, weighing 15.2 kg (24.2 percentile weight for age). He lost 11.6% of his body weight and had BMI of 14.3 kg/m2, down from a BMI of 16.2 kg/m2. The child started weekly occupational therapy (OT) for his food aversion. Seven months after the DBPCFC, the parents reported some improvement with the OT, as the child had successfully reintroduced certain foods into his diet but continued to refuse to eat at school, camp, or other situations where his parents were not with him.

The child was randomized to peanut/placebo OIT at 16 months of age, weighing in the 64th percentile for age at that time. His OIT treatment course was unremarkable, including the positive entry DBPCFC. There were no signs of anxiety or psychological concerns prior to conducting the DBPCFC 2.5 years into the study. Therefore, in this case it would have been difficult to determine any risk factors in this child for developing feeding aversion after the 2.5 year DBPCFC. This case demonstrates the importance of assessing and closely following the psychological well-being of children after an oral food challenge. This is especially important in younger children, who have difficulty rationalizing the outcomes of food challenges, and who may transfer the negative experience of a positive food challenge to all eating situations.

**Patient Presentation and Testing:**
The child in this case had no previous medical history aside from peanut allergy. He lived in a single family home with his parents, and no siblings. He first ingested peanut on at 13 months old, resulting in generalized urticaria. He practiced avoidance of peanut prior to entering the clinical trial at the age of 16 months. At the entry food challenge for this study, a cumulative peanut protein dose of 75mg resulted in angioedema and rhinorrhea, requiring treatment of 0.15mg epinephrine and one dose of an oral antihistamine. At randomization for this trial, he weighed 11.9kg (64.8 percentile weight for age).

It is unknown whether he was randomized the active treatment arm or to the placebo arm in the duration of the trial. The 2.5 years of his study participation were unremarkable, as he had minimal adverse events, no instances of accidental peanut ingestion, and no subjective or objective reactions to the daily-dosed study product. Throughout the study, peanut-specific IgE remains blinded; at the exit food challenge, he had a positive skin prick test to peanut with a mean wheal diameter of 24.5mm. After the 2.5 years of daily study drug, each participant is to undergo a DBPCFC to peanut, and to undergo a third DBPCFC to peanut after a period of avoidance.
As previously described, this child underwent the post-treatment DBPCFC at the age of 3 years 11 months, and developed a feeding aversion thereafter. He did have a 2kg (11.6%) decrease in body weight over 4 months due to this poor oral intake due to fear of eating. When the study center was made aware of this case, the child had already been evaluated by his pediatrician, and referrals had been made. He was active in feeding aversion therapy. The family initially opted out of counseling to see if the feeding therapy was sufficient to improve his feeding anxieties. This child was closely monitored by the food allergy research team. An initial plan was created to have routine phone calls with the family to monitor the child’s progress. The food allergy research team ensured that the child was receiving appropriate psychological and physical care. No tests were necessary for this subject; the history alone was adequate to determine a diagnosis and treatment plan.

**Diagnosis, Treatment and Patient Outcomes:**
The child was diagnosed by his pediatrician with non-organic oral aversion. This diagnosis was likely related to the oral food challenge.
Due to complex nature of this problem, multidisciplinary management was necessary. The intervention from the perspective of a food allergy center was the decision to withdraw this subject from the trial, and abstaining from further food challenges or oral immunotherapy. Continuing OIT in this child could risk impeding his recovery from the oral aversion.
Post-traumatic stress disorders (PTSD) has not been well-studied in patients with food allergies, but this case represents a child with possible PTSD after a food challenge. This child experienced a threat to his well-being, and a characteristic of individuals with PTSD is avoidance of the situations that trigger memories of the event (Kelsay, 2003). In this case, the avoidance of the stressful stimuli resulted in food aversion, weight loss, and a drop of two curves on the growth chart. Despite the child’s progress in OT for feeding, performing a post-avoidance food challenge in this child may either provoke the previous anxieties surrounding food, or create additional stressors that could result in increased avoidance of the catalyst stimuli, food.
This child remains in weekly feeding therapies, and continues to improve. His most recently reported weight (4 year 5 months old) was 17.6kg and his height was 105.8cm (BMI 15.7; 60.6 percentile weight for age). This improvement further reaffirms the decision not to administer a third DBPCFC or continue OIT therapy with this child. The food allergy team has used this case as a cautionary tale and prompted the pursuit of resources to share with other children who may have similar experiences.

**References**
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A Heart Gone Bananas: Allergy-induced coronary vasospasm due to banana (Kounis Syndrome).

Summary and Lessons Learned:
Kounis Syndrome encompasses a variety of cardiovascular signs and symptoms associated with mast cell activation in the setting of allergic or hypersensitivity and anaphylactic or anaphylactoid insults. It can manifest as coronary vasospasm, coronary or in-stent thrombosis, and acute myocardial infarction with plaque rupture. Various medications as well as foods such as fish, shellfish, mushroom, and rice pudding have been implicated as causal agents. We present the case of what we believe to be the first documented case of Kounis Syndrome manifesting as coronary vasospasm as the result of an allergy to banana. This case highlights the importance of considering allergic causes of angina in a patient with known atopy and an otherwise normal cardiovascular workup.

Patient Presentation and Testing:
The 56 year-old woman initially presented with daily, intermittent, substernal angina exacerbated by exertion and cool temperatures. Her angina was only relieved with sublingual nitroglycerin, which she was using up to 10 times daily. The patient has a past medical history of asthma, contrast allergy as well as multiple medication allergies, as well as a distant history of Hodgkin’s Lymphoma treated successfully with radiation therapy. She has a family history significant for atopy, asthma, and coronary artery disease. Initial cardiac workup included negative troponin levels and normal electrocardiograms. Coronary catheterization revealed normal coronaries. She was diagnosed as having variant angina with vasospasm, and was started on a trial of calcium-channel blockers, without relief. Given her history of atopy, tryptase levels were checked which were found to be persistently elevated over the next year while her anginal symptoms persisted. She was referred to an allergist, and allergy-specific IgE testing for banana and latex were found to be significantly elevated after the patient reported perioral itching and tingling with banana ingestion. She had been eating multiple bananas daily as part of a heart-healthy diet. Upon discontinuing bananas from her diet, her chest pain improved dramatically both in severity and frequency. Several tryptase levels taken after the discontinuation of bananas have been within normal range.

Diagnosis, Treatment and Patient Outcomes:
This was found to be a case of Kounis Syndrome Type I with allergy-induced coronary vasospasm due to banana. Her symptoms and quality of life have improved significantly since withholding the offending agent, and at her last visit she was not requiring any regular use of nitroglycerin. She is to undergo formal skin testing as part of her full allergic workup.
Peanut specific IgE testing leading to unnecessary peanut elimination following early introduction in 2 children.

Summary and Lessons Learned:
The early introduction of peanut in high-risk patients who are not allergic to peanut can significantly reduce development of peanut allergy. Here we describe two cases in which peanut was initially tolerated and subsequently avoided after serum IgE testing was performed, likely leading to the development of a peanut allergy.

OW presented at 5 months of age for food allergy evaluation. He had eczema and a family history of peanut allergy in his brother and mother. He had never ingested peanut and had a negative skin prick test (SPT) to peanut. At 7 months, he passed an oral food challenge (OFC) to peanut and incorporated it in his diet at least 2-3 times per week. Four months later, the family revealed they had cut peanut from OW’s diet for the previous 2 months after his pediatrician sent a panel of IgE testing as part of a work-up for eczema. He instructed them to avoid peanut after noting a sIgE of 75 kUA/L. Our repeat peanut sIgE level was 62.3 kUA/L.

MB presented at 17 months of age with a history of egg allergy, mild eczema, and no prior peanut ingestions. Her initial SPT was 6 mm and peanut sIgE 5.47 kUA/L. Component testing revealed sensitization to only Ara h 3 (0.17 kUA/L) and 9 (1.87 kUA/L). Six months later, she passed an OFC to peanut. After a month of regular consumption, her pediatrician sent “routine lab testing”, including a panel of food allergens, which demonstrated a peanut sIgE of 52.4 kUA/L. Her mother asked if it was safe to continue peanut ingestion, and we recommended continuing regular consumption. Six months later, her mother reported she had cut peanut from the diet due to fear of a reaction. Our repeat peanut sIgE was 54.6 kUA/L with a sIgE to Ara h 2 of 24.6 kUA/L.

Given the markedly elevated peanut sIgE levels and extended periods of avoidance, we felt that it was not safe to reintroduce peanut to either patient. These cases represent the danger in performing panels of IgE testing in patients who are tolerating peanut and the potential misinterpretation of results. As noted in the LEAP study, patients consuming peanut may develop increased sIgE levels to peanut despite tolerating this food. Healthcare professionals should not obtain peanut sIgE levels in patients tolerating peanut, as this can lead to unnecessary avoidance, and the possibility of developing a peanut allergy.

Patient Presentation and Testing:
Patient OW had a history of eczema and had never ingested peanut due to concern for food allergy. His mother and brother both had an allergy to peanut and were avoiding it. To determine if he had sensitization, he was initially skin tested to peanut and found to be negative. Given that he never ingested peanut and had a negative skin prick test (SPT), and that the family was nervous about home introduction, we proceeded with a physician supervised oral food challenge (OFC) to peanut which he passed. He stopped incorporating peanut in his diet after the peanut sIgE was noted to be elevated on a serum allergy panel sent by his pediatrician. Similarly, patient MB had a history of eczema, along with egg allergy, and was avoiding peanut. Based on favorable SPT and peanut sIgE, she underwent an OFC to peanut and passed, and began tolerating peanut her diet. Similarly to OW, MB had a serum food allergy panel sent by her pediatrician. Her family cut this food from the diet after seeing the elevated sIgE level to peanut, despite guidance to continue regular peanut consumption. In both patients, follow up testing confirmed markedly elevated sIgE levels to peanut, well above the 95% predictive values for reactivity to peanut, and given the periods of avoidance we were not comfortable attempting reintroduction of this food.

Diagnosis, Treatment and Patient Outcomes:
In both cases, we encounter patients who passed physician supervised oral food challenges to peanut and were tolerating peanut products in the diet at home. However, peanut sIgE levels were obtained by their primary doctors and
were noted to be elevated. After testing, peanut was cut from the diet (one due to the recommendations of the pediatrician, the other due to parental fear of an allergic reaction after seeing the peanut sIgE level) even though the patients were tolerating peanut without any allergic symptoms. As months passed without exposure to peanut and a persistently elevated peanut sIgE, the likelihood of clinical reactivity to peanut became increasingly high. We now classify these patients as peanut allergic. Though we did not challenge the patients to confirm this, the risk of a reaction is extremely high, with elevated peanut sIgE levels > 50 kUA/L in both cases. They now must strictly avoid peanut, and are at risk for potentially severe allergic reactions if this food is accidentally ingested.
Case Title:
A Case of Anaphylaxis after Vaccination in a Pediatric Patient with Alpha-Gal Allergy

Summary and Lessons Learned:
Introduction
It is well known that immunoglobulin (Ig) E antibodies to galactose-α-1,3-galactose (alpha-gal) are associated with delayed anaphylaxis to mammalian meat and gelatin-based products. Recently, it has been reported that vaccines containing both bovine calf serum and gelatin in their ingredient list are capable of inducing immediate hypersensitivity and anaphylaxis in alpha-gal allergic adult patients, due to their parenteral route of administration. Binding and depletion of alpha-gal specific IgE antibodies was demonstrated in these vaccines, though such reactions may hypothetically be due to coexisting gelatin specific IgE. Importantly, multiple vaccines utilized during the routine series of pediatric immunizations potentially contain alpha-gal due to the presence of bovine calf serum or gelatin. Here, we report a case of vaccine-induced anaphylaxis associated with alpha-gal allergy in a child.

Case description
The patient is a 5 year old male with a history of alpha-gal allergy who presented one week after an allergic reaction upon receipt of MMR (Merck), Varicella (Merck), and TDAP/IPV(GSK) vaccines. Five minutes after receiving the vaccines, he developed shortness of breath, wheezing, disseminated urticaria, and angioedema of the face and oropharynx, warranting a visit to the emergency room where he received epinephrine, diphenhydramine, prednisone and famotidine with relief of symptoms within ten minutes. He was diagnosed with alpha-gal allergy 8 months prior to presentation (alpha-gal sIgE of 8.19 kU/L) after several episodes of hives and facial angioedema on exposure to mammalian meat, following a tick bite, and was avoiding mammalian meat at the time of his vaccine reaction. He had no history of egg, latex, dairy, or gelatin allergy. We repeated his sIgE titers, demonstrating an increase in the galactose-α-1,3-galactose sIgE level to 26.9 kU/L, a beef sIgE level of 14 kU/L, a lamb/mutton sIgE level of 5.54 kU/L, and a pork sIgE level of 11.2 kU/L (Reference range for all being <0.35 kU/L).
Conclusion
Of the administered vaccines, MMR has already been demonstrated to bind and deplete sIgE to alpha-gal. All three vaccines contain bovine calf serum, which has not been ruled out as a potential source of alpha-gal contamination, and two (MMR and Varicella) contain gelatin. Although porcine and bovine gelatin sensitivity has been described in children with red meat allergy in vitro, this is the first case of vaccine-induced anaphylaxis in a pediatric patient that implicates alpha-gal allergy as a possible mechanism. Importantly, this is a single case and most patients with alpha-gal tolerate vaccination uneventfully.

Patient Presentation and Testing:
A five year old with a history of alpha-gal allergy diagnosed 8 months prior to presentation came to our office after having an allergic reaction upon receiving his routine 4-6 year vaccines of MMR (Merck), Varicella (Merck), and TDAP/IPV(GSK). Five minutes after administration of the above vaccines he had shortness of breath, wheezing, disseminated urticaria and angioedema of the face and oropharynx after which he went to the Emergency Department. In the Emergency Department he received 1 dose of epinephrine, diphenhydramine and famotidine with relief of symptoms within an hour. At the time of administration of the vaccines, he was avoiding all red meat but had no food restrictions otherwise and was tolerating egg, latex and gelatin containing products. The diagnosis of alpha-gal allergy was made 8 months prior to this clinic visit after he was having recurrent hives and facial angioedema following a tick bite. His alpha-gal sIgE at the time of diagnosis was 8.19 kU/L. Since then he had been strictly avoiding mammalian meat, with uneventful consumption of dairy and gelatin, and had not had any recurrence of symptoms until he was exposed to the vaccine. His repeat titres in our office showed galactose-α-1,3-galactose sIgE level to 26.9 kU/L, a beef sIgE level of 14 kU/L, a lamb/mutton sIgE level of 5.54 kU/L, and a pork sIgE level of 11.2 kU/L (Reference range for all being <0.35 kU/L). As mentioned above, there was an increase in his alpha gal sIgE titres post vaccination despite avoiding red meat and tick bites.

On review of the vaccine ingredients, both MMR (Merk) and Varicella (Merk) contain high amounts of gelatin (14,500 μg per 0.5 ml dose and 12,500 μg per 0.5ml dose respectively). MMR, Varicella, and TDaP/IPV combination vaccine also contain bovine calf serum. While patients with alpha-gal allergy may also be sensitized to gelatin, our patient was tolerating gelatin containing foods with no symptoms. There is literature on safe administration of high gelatin containing vaccines in an adult with alpha-gal allergy. A recent study also demonstrated that pre-incubation of patient sera with MMR depleted alpha-gal sIgE greater than did gelatin alone. This raised the possibility of these bovine or porcine derived products being a potential source of antigen in this patient with preexisting alpha-gal allergy.

Diagnosis, Treatment and Patient Outcomes:
We gave our patient a provisional diagnosis of vaccine-induced anaphylaxis due to his preexisting alpha-gal allergy, based on his clinical history, changes in specific IgE to alpha-gal despite complete avoidance, and review of the recent literature. It is unclear to what degree the patient will need to receive a modified immunization schedule going forward, but we advised continued avoidance of tick bites and mammalian meat. We will be monitoring the patient’s alpha-gal sIgE concentrations yearly and would do pre-testing with graded challenge to any vaccines containing mammalian products, prior to administration.

In follow up of the patient’s original reaction, we plan to perform vaccine skin testing in this patient using the vaccines he received, at both full strength skin prick and diluted intradermal concentrations. We plan to measure specific IgE to bovine and porcine gelatin from the patient’s plasma, to confirm whether or not he is gelatin sensitized, despite not having any reported reactions. We further plan to utilize ex vivo studies to interrogate the patient’s sIgE to alpha-gal’s ability to bind the vaccines he received, and others which contain either bovine calf serum, gelatin, both, or neither. We intend to review publicly available reports of vaccine anaphylaxis to identify any other cases which might fit criteria for preexisting alpha-gal allergy.
Case Title:
Red Meat Allergy with Late Symptoms: IgE mediated allergy for Alpha-Gal

Summary and Lessons Learned:
A 37-year-old male patient was referred to our service presenting recurrent episodes of generalized urticaria and tongue angioedema after 4 hours intake of red meat. In 2015, he referred approximately 200 lone star tick bites with local symptoms. This case is compatible with a pattern of a specific IgE against Alpha-Gal oligosaccharide (Galactose-Alpha-1,3-Galactose). These antibodies are associated with urticaria and angioedema or anaphylaxis beginning 3 to 5 hours after the intake of red meat or non-primate mammalian food products and they are produced after lone star tick bite sensitization. In Brazil was demonstrated the presence of the Alpha-Gal Epitope in the saliva of the Amblyomma Scultum ticks. The tick bite could lead to the production of antibodies against Alpha-Gal and the presences of late symptoms after the ingestion of non-primate mammalian food products. The late reaction differs from the classic pattern of IgE mediated symptoms which generally has an early presentation (up to 2 hours), being important to considered this hypothesis in late reaction cases, however with a clinical pattern of type 1 hypersensitivity.

Patient Presentation and Testing:
A 37-year-old male patient was referred to our service presenting recurrent episodes of generalized urticaria and tongue angioedema after 4 hours intake of red meat. He also has allergic rhinitis, he denies other diseases or use of frequent medications. The patient works in a farm where he has contact with equine, caprine and swine animals. In 2015, he referred approximately 200 lone star tick bites with local symptoms. In June 2016, five hours after ingestion of bovine meat developed generalized urticaria. In August 2016, four hours after ingestion of red meat in barbeque shown urticaria. In April 2017, 4 hours after ingestion of bovine meat developed urticaria, tongue and feet angioedema. Swine and bovine meat specific IgE were positive (3.7 and 5.6 kU/L respectively) and Alpha-Gal specific IgE was 3.65 kU/L. A prick to prick test was performed with raw bovine meat, and the result was 9x6 mm with a histamine of 5x6mm and a negative control of 0 mm.

Diagnosis, Treatment and Patient Outcomes:
This case is compatible with a pattern of a specific IgE against Alpha-Gal oligosaccharide (Galactose-Alpha-1,3-Galactose). These antibodies are associated with urticaria and angioedema or anaphylaxis beginning 3 to 5 hours after the intake of red meat or non-primate mammalian food products and they are produced after lone star tick bite sensitization.
It’s important to know that between the episodes, the patient referred to consume read meat without any reactions, nevertheless the patient realized that the quantity and the steak doneness were associated with better food tolerance. (Smaller quantities and well-done meat were better tolerated).
We suggest to the patient to follow an action plan to prevent fatal reactions, that include medications, doses and the suggestion of eating lean meat in small quantity.
Meat Reintroduction in a Patient with Alpha-Gal Allergy

Summary and Lessons Learned:
We present a case of successful red meat reintroduction in a patient with alpha-gal allergy. Alpha-gal, or galactose-α-1,3-galactose, is an oligosaccharide found to cause IgE-mediated delayed-onset hypersensitivity reactions. It is introduced into humans via tick bites, where some develop sensitivity to these shared sugar epitopes on red meat. Some food allergies can be “outgrown.” This appears to be the case in this patient. A lack of booster effect from repeated tick bites as well as red meat avoidance may have played a role in diminishing alpha-gal IgE and possibility of allergic reactions to red meat exposure. There are food-specific IgE levels for predicting symptomatic food allergy to some foods. Such levels have not been established for red meat allergy but they likely exist.

Patient Presentation and Testing:
A 56-year-old woman presented to a drug allergy clinic for evaluation of a possible allergic reaction to acetaminophen. On two occasions after taking acetaminophen, patient developed pruritic hives after four hours. During the second episode, she also experienced vomiting, pruritic mouth, and sensation of throat closure. Her past medical history is non-contributory. Since her reactions were non-immediate, patient was questioned regarding food ingestion. She recalled that on both occasions she had consumed red meat. Patient also mentioned a tick bite in New York state prior to these episodes with a long-lasting local reaction. Therefore, serum alpha-gal IgE was checked and found to be elevated to 46 kU/L. Total serum IgE was 264.1 IU/mL. Graded oral challenge to 850mg acetaminophen in the clinic was negative.

Diagnosis, Treatment and Patient Outcomes:
Patient was diagnosed with alpha-gal allergy. On three-year follow-up, she had been avoiding red meat and had not experienced any additional reactions. However, the patient wished to reintroduce meat into her diet. Alpha-gal was 3.5 kU/L and total IgE 60.8 IU/mL. She underwent graded oral challenge to red meat; she remained asymptomatic throughout the challenge and was observed for a total of five hours. The patient began ingesting modest amounts of meat, without any reaction. Alpha-gal measured 1.6 kU/L on eight-month follow-up. One year later, she presented after one episode of burning sensation of palms and feet after eating a large amount of beef. This reaction occurred after a week of increased exercise activity and sun exposure. She denied additional tick bites. Alpha-gal measured 3.14 kU/L at this time with total IgE 57 IU/mL. Patient resumed red meat consumption after this episode and has not had any additional allergic reactions to date.
Case Title:
Peanut-triggered food protein-induced enterocolitis syndrome presenting in late childhood.

Summary and Lessons Learned:
Food protein-induced enterocolitis syndrome (FPIES) is a non-IgE mediated food allergy characterized by delayed severe, repetitive vomiting and diarrhea. FPIES can be triggered by a variety of foods and typically presents during infancy. We report a rare case of a 4 year-old female who was referred for possible IgE-mediated food allergy, but instead was found to have peanut-induced FPIES. This case supports prior observations that FPIES can present later in childhood, even to previously tolerated foods. Furthermore, we demonstrate the importance for clinical staff to be trained in the recognition and management of both IgE- and non-IgE-mediated reactions during an oral food challenge.

Patient Presentation and Testing:
The patient is a healthy child with no atopic history. Several weeks prior to presentation, she had eaten peanut butter on two occasions, followed by the development of severe vomiting 2 hours afterwards without cutaneous, respiratory or cardiovascular symptoms. During one of the episodes the child had a concurrent viral illness. Prior to these episodes, the child had eaten peanuts without any symptoms. She had negative peanut skin prick testing and in vitro IgE testing. Given negative testing and the low likelihood of new-onset peanut allergy at this age, her symptoms were attributed to a viral syndrome. Given the suspicious history, the patient underwent a graded oral food challenge to peanut, with a two hour monitoring period after conclusion of the challenge. The child consumed a full serving of peanut over a 60-minute period without incident. Ninety minutes after challenge, the child developed emesis. The emesis recurred, prompting administration of intramuscular epinephrine. The patient continued to vomit and subsequently developed watery diarrhea and drooling. Administration of a second dose of epinephrine was ineffective. The child was then given ondansetron 4 mg sublingually, and the vomiting resolved. Vital signs revealed no hypotension, and the patient was able to tolerate oral rehydration. She was observed for another 150 minutes after return to baseline.

Diagnosis, Treatment and Patient Outcomes:
Evidence supporting a diagnosis of peanut-induced FPIES includes the sudden onset of repetitive vomiting and diarrhea two hours after food ingestion; lack of response to antihistamines and epinephrine; improvement with ondansetron; and reproducibility of reaction after peanut ingestion. The family was educated on peanut avoidance, natural history, and clinical symptoms of FPIES. Given the low level of awareness that emergency clinicians have regarding acute treatment of FPIES, the family was provided with an emergency action letter for management of future episodes.
Case Title:
A Case of Adult-Onset Food Protein Induced Enterocolitis Syndrome (FPIES) to Cashew

Summary and Lessons Learned:
FPIES is a non-IgE mediated gastrointestinal food hypersensitivity reaction that is traditionally considered to be a pediatric disease. Symptoms can lead to shock and require hospitalization. FPIES is considered to be rare in adults, especially new-onset to a previously tolerated food. There is one published case report of a 53-year-old man with reproducible gastrointestinal symptoms to shellfish and another retrospective report of thirty-one adults with reproducible food-specific gastrointestinal reactions. In both publications, the patients had negative food-specific IgE testing. We present a case of FPIES in an adult confirmed by graded food challenge to cashew, which the patient had previously tolerated. This case demonstrates that an FPIES-like syndrome can develop in adulthood and should be a diagnostic consideration in patients with severe gastrointestinal symptoms after ingestion of a specific food, including one previously tolerated.

Patient Presentation and Testing:
A 68 year-old otherwise healthy man presented to the University of Washington Allergy and Immunology clinic for evaluation of possible reactions to cashews. Over an 18 month period, he had had 4 episodes of sudden-onset severe diarrhea, abdominal cramps, nausea/vomiting, and hypotension. The most severe episode had led to syncope and acute kidney injury requiring hospitalization and treatment with epinephrine and IV fluids. The patient had associated each episode with the consumption of cashews approximately 40-60 minutes earlier. He had previously consumed cashews on a regular basis but was now avoiding them. Workup included skin prick testing and serum IgE to tree nuts, which were both negative, random tryptase level of 5.3 ng/ml, and total IgE level of 40 kU/L. At the patient’s request and after informed consent, he underwent a graded food challenge to cashews in clinic. At 3 hours, after consuming 6.5 cashews, he developed abdominal pain, emesis, and hypotension to 70/40. He was treated with 2 rounds of IM epinephrine, IV odansetron, IV fluids and glucocorticoids. At 8 hours he developed grossly bloody diarrhea. He did not have any skin manifestations of pruritis, hives, rash, nor did he have respiratory involvement, such as difficulty breathing or swelling, stridor, wheezing, or swelling of lips or tongue. Labs were notable for leukocytosis (WBC = 21.4 x103/mm3) with eosinophilia (AEC = 1.5 x103/mm3), and normal tryptase (3.4 ng/ml). Our diagnosis was FPIES related to cashew consumption and our recommendation was that he strictly avoid all foods containing cashews.

Diagnosis, Treatment and Patient Outcomes:
We believe this to be the oldest patient reported with a new-onset, non-IgE mediated gastrointestinal food hypersensitivity reaction consistent with FPIES and the first report of cashew causing this in an adult. This case demonstrates that an FPIES-like syndrome can develop in adulthood and should be a diagnostic consideration in patients with severe gastrointestinal symptoms after ingestion of a specific food, including one previously tolerated.
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Case Title:  
Hypogammaglobulinemia Secondary to Multiple Myeloma with Amyloidosis  

Summary and Lessons Learned:  
We report a case of hypogammaglobulinemia secondary to multiple myeloma with light-chain (AL) amyloidosis. A 58-year-old white male non-smoker presented with a 5-year history of shortness of breath and lower extremity myalgias, but no history of recurrent sinopulmonary infections. Initial PFT evaluation showed an obstructive pattern (FEV1 2.62 L, 67% of predicted). He demonstrated historical reversibility but his dyspnea failed to symptomatically improve with anti-asthmatic therapy and prednisone. Chest CT revealed mild diffuse cardiomegaly and a small pericardial effusion. BNP was elevated. Marginally elevated D-dimer was noted, but V/Q scan was normal. Echo revealed significant cardiomyopathy and left ventricular diastolic dysfunction. He failed to respond to diuretics and ionotropic agents. Reduced globulin level (1.4 g/dL) was noted after developing community-acquired pneumonia, atrial fibrillation, and recurrent constipation. Evaluation of immunoglobulins and light chain analysis revealed pan-hypogammaglobulinemia and Bence-Jones proteinuria. Further cardiac and hematologic testing was done. Cardiac catheterization showed no evidence of significant coronary artery disease. Bone marrow biopsy showed lambda-restricted plasma cell dyscrasia, and fibroadipose tissue Congo red stain was positive for amyloidosis. Skeletal survey was negative. He began chemotherapy for multiple myeloma, but his dyspnea persisted. He was subsequently separately hospitalized for pneumonia and thoracentesis for a large transudative pleural effusion.  

Upon review of this case report, practicing allergists and immunologists should:  
1. recognize that dyspnea not responsive to anti-asthmatic therapy, despite improvement in FEV1, should prompt further cardiac and pulmonary evaluation.  
2. recognize that reduced serum globulin levels should prompt further B and T cell evaluation for immunodeficiency.  
3. recognize hypogammaglobulinemia as an uncommon but significant complication of multiple myeloma and AL amyloidosis.  
4. appreciate the multitude of clinical findings, immunologic abnormalities, and complications associated with multiple myeloma and AL amyloidosis.  
5. understand the appropriate tests used for the diagnoses of multiple myeloma and AL amyloidosis.  
6. understand the role of immunoglobulin replacement in the treatment of secondary hypogammaglobulinemia from multiple myeloma and AL amyloidosis.  

Patient Presentation and Testing:  
At the time of the initial encounter, a 58-year-old male non-smoker patient presented with a 5-year history of shortness of breath and lower extremity myalgias. The patient had no prior history of recurrent sinusitis, pneumonia, bronchitis, COPD, or asthma. He had undiagnosed chronic bilateral calf pain for the prior 15 years with negative muscle biopsies. Prior catheterization revealed no significant coronary disease. Methacholine challenge was done to evaluate his dyspnea and obstructive PFT. Initial spirometry showed FEV1 of 2.62 L, 67% of predicted. Methacholine challenge was negative. His PFT improved after prednisone therapy (FEV1 3.31 L, 26% reversibility), but his dyspnea did not. Further pulmonary and cardiac testing was done to evaluate his dyspnea. Chest CT showed mild diffuse cardiomegaly, a small pericardial effusion, and a small left pleural effusion. V/Q scan was negative, despite a marginally elevated D-dimer level. A sleep study demonstrated obstructive sleep apnea, and CPAP therapy was initiated. Cardiac symptoms were investigated using EKG, echo, and cardiac catheterization. EKG was initially normal, but months later showed atrial fibrillation. Echo
showed significant cardiomyopathy, EF 38%, and left ventricular diastolic dysfunction. Catheterization ruled out significant coronary artery disease and showed mild elevation of right ventricular, pulmonary artery, and pulmonary capillary wedge pressures, minimally elevated left and right sided filling pressures, and normal pulmonary artery pressure. A reduced serum globulin prompted a B and T cell evaluation for immunodeficiency. Normal albumin, IgG 384 mg/dL, IgA 51 mg/dL, and IgM 41 mg/dL were noted. ANA and ANCA were negative. CD19+ lymphocytes were normal at 45/uL (4.1%), CD3+ lymphocytes were elevated at 990/uL (90%), CD4+ lymphocytes were elevated at 64.6/uL (58.7%), and CD8+ lymphocytes were normal at 355/uL (32.3%). Before receiving the Pneumovax vaccination, 23/23 pneumococcal antibodies were low (less than 1.3 mcg/mL). After the Pneumovax vaccination, 7/14 pneumococcal antibodies were low. Urinalysis showed normal protein levels (39.5 mg/dL), which ruled out nephrotic syndrome. However, monoclonal lambda light chain Bence-Jones proteinuria was present on spot urine electrophoresis. Free kappa and lambda light chains were elevated at 28.1 mg/L and 680.0 mg/L, respectively, on spot urine electrophoresis. Serum IEP and SPEP were normal. It was initially thought that the patient had non-ischemic cardiomyopathy, but in the context of his hypogammaglobulinemia and development of chronic constipation, atrial fibrillation, and Bence-Jones proteinuria, multiple myeloma and AL amyloidosis with amyloid cardiomyopathy were considered diagnostically. Consequently, bone marrow biopsy and fibroadipose tissue Congo red stain were performed, which were diagnostic for lambda-restricted plasma cell dyscrasia and AL amyloidosis.

**Diagnosis, Treatment and Patient Outcomes:**

This patient, presenting with dyspnea and history of obstructive lung disease, was ultimately diagnosed with presumptive amyloid cardiomyopathy associated with multiple myeloma. Laboratory workup demonstrated Bence Jones proteinuria, with biopsy-confirmed multiple myeloma and AL amyloidosis, along with hypogammaglobulinemia. His hypogammaglobulinemia was thought to be secondary to multiple myeloma and AL amyloidosis. His dyspnea was thought to be due to a combination of underlying obstructive lung disease and, more significantly, non-ischemic amyloid cardiomyopathy. His multiple myeloma was treated with chemotherapy including cyclophosphamide, bortezomib, and dexamethasone. Immunoglobulin replacement will start after completion of chemotherapy and autologous bone marrow stem cell transplant. In most cases, treatment for AL amyloidosis follows treatment of the underlying primary disease to suppress new amyloid formation and to induce regression of current deposits. Specifically, treatment for cardiac amyloidosis includes diuretics, salt restriction, and non-digoxin inotropic agents. Effectiveness of beta-blockers, calcium channel blockers, and digoxin are limited. His amyloid cardiomyopathy did not respond to diuretics and inotropic agents and has yet to respond to chemotherapy. If his cardiomyopathy fails to respond to the complete course of chemotherapy and/or autologous bone marrow stem cell transplant, he may be a candidate for cardiac transplantation.
Case Title:
Immunodeficiency in a patient with post-Fontan associated protein losing enteropathy

Summary and Lessons Learned:
A 3-year-old male with a history of hypoplastic left heart syndrome (HLHS) one year from fenestrated Fontan surgery and protein losing enteropathy (PLE) presented with significant infection triggering a PLE flare. Immunologic evaluation demonstrated severe CD4 (34 cells/µL), CD8 (38 cells/µL), and NK cell (55 cell/µL) lymphopenia, low IgG (56 mg/dL) and poor anti-diptheria, anti-pneumococcal, and anti-tetanus titers. He was started on 20% subcutaneous immunoglobulin replacement and trimethoprim-sulfamethoxazole prophylaxis due to his presentation with severe infection and experienced overall clinical improvement. This case emphasizes the questions regarding best evaluation and management of immunodeficiency in post-Fontan PLE patients. The pathophysiology behind development of PLE and associated immune deficiencies is incompletely understood. It is likely that CD4 and immunoglobulins are lost through the GI tract in these patients due to loss of chyle. Previous studies have shown selective severe CD4 lymphopenia as well as humoral and cell mediated immune abnormalities without increased evidence of opportunistic or severe infections, but other studies have reported significant infections in patients who are not supported with antibiotic prophylaxis or prophylaxis. We propose that the decision to start immunoglobulin replacement and/or antibiotic prophylaxis in post-Fontan patients should be made on a case by case basis rather than simply based on the use of lymphocyte counts or immunoglobulin levels. Further study is needed to determine if there are biomarkers that can identify a subset of patients with low lymphocytes and/or immunoglobulins who are at risk for severe infections and would most benefit from additional intervention.

Patient Presentation and Testing:
The patient presented with symptoms of cough, congestion, fever, and diarrhea and was diagnosed with rhinovirus infection and S. pneumoniae bacteremia associated with flare of his PLE. He also had history of chylos effusions that improved following embolization of his lymphatic duct, but he subsequently developed PLE. His initial labs were pertinent for a WBC of 11.1 K/µL with an ALC of 490 /µL, and an albumin of 1.9. In the setting of a patient with significant lymphopenia and bacteremia, the immunology team recommended a broad screen of the immune system as described above. His ALC prior to embolization of his lymphatic duct was consistently within normal limits.

Diagnosis, Treatment and Patient Outcomes:
He was diagnosed with immunodeficiency secondary to PLE after Fontan procedure and was started on trimethoprim-sulfamethoxazole prophylaxis and subcutaneous immunoglobulin replacement therapy. Since starting these treatments, he has been doing very well with no further infections or hospitalizations and improvement in his PLE.
Case Title:
Disseminated Nontuberculous Mycobacterial Infections in a Child with Mendelian Susceptibility to Mycobacterial Diseases (MSMD)

Summary and Lessons Learned:
IL-12/IFN-γ-mediated activation of mononuclear phagocytes is necessary to control infections with nontuberculous mycobacteria (NTM) and intracellular pathogens, including salmonella. Disseminated NTM infection should raise concern for defects in the IL-12/IFN-γ signaling pathway, resulting in the diagnosis of Mendelian Susceptibility to Mycobacterial Diseases (MSMD). We present a 6-year old boy with recurrent NTM infections, including recurrent preseptal cellulitis, cervical lymphadenitis and chronic osteomyelitis due to NTM. This case illustrates that, although uncommon, MSMD is a recognizable immunodeficiency that should prompt appropriate diagnostics, genetic confirmation, and targeted therapies to ensure best patient outcomes.

Patient Presentation and Testing:
At 2 years of age, an otherwise healthy boy developed left periorbital swelling. Symptoms seemingly resolved with antibiotic therapy. At 3-years, the preseptal cellulitis returned; PET scan showed multifocal sclerotic lesions of the skull, vertebrae, arms, and legs. Bone marrow biopsy was unremarkable. Femur biopsy showed crushed and devitalized bone while orbital biopsy showed acute on chronic osteomyelitis. Cultures were unrevealing and a diagnosis of Chronic Recurrent Multifocal Osteomyelitis was suspected. At 4 years, he developed a lytic parietal lesion; however, the family declined a biopsy and at 5 years, the preseptal cellulitis recurred. Cultures were obtained and were positive for Mycobacterium avium complex (MAC). Despite continuous treatment with antitycobacterial therapy, he developed left cervical lymphadenitis that cultured positive for Mycobacterium fortuitum and MAC. Antimicrobial coverage for NTM was broadened, but the lymphadenitis worsened, necessitating parotidectomy and cervical lymph node dissection. Cultures from the dissection were negative.

Due to significant concern for MSMD, IFN-γ induced STAT1 phosphorylation in monocytes was assessed as a marker of susceptibility to intracellular bacterial pathogens; this was decreased at a fluorescence ratio of 1 (normal > 4). Cell surface expression of IFN-γ receptor (IFNGR) was measured using CD119 as a marker; this was increased with a mean IFNGR expression of 2,788 (normal 200-400), suggesting an autosomal dominant defect in the IFN-γ receptor. Mutations in the IFNGR are known to prevent degradation of the receptor, thus the greatly increased expression seen in this patient.

Diagnosis, Treatment and Patient Outcomes:
Genetic testing subsequently confirmed MSMD due to an autosomal dominant frameshift mutation in IFNGR 1 (c.819_822delTAAT), located on chromosome 6q23-q24. While continuing his NTM antimicrobials, the patient was promptly started on adjuvant therapy with IFN-γ (actimmune 50 mcg/m2, 3 times/week). He will continue on this regimen for 1-year from the first negative culture and then transition to lifelong prophylaxis with azithromycin. He
continues to experience post-surgical left facial weakness. Delayed diagnosis of autosomal dominant IFNGR 1 defect postponed targeted treatment contributing to surgical morbidity; thus, highlighting the need for prompt recognition of this condition.
B Cell Lymphocytosis and Immunodeficiency: A Gain-Of-Function Mutation in CARD 11 Results in BENTA Disease

Summary and Lessons Learned:
Caspase recruitment domain family member 11 (CARD11) is an important signal transducer in nuclear factor-κB (NF-κB) activation. Germline gain-of-function (GOF) mutations in CARD11 have been identified and referred to as B cell expansion with NF-κB and T cell anergy (BENTA) disease. This case highlights the functional dichotomy of CARD11 signaling in T and B cells, with a known GOF CARD11 mutation promoting both B cell lymphocytosis and T cell anergy.

Patient Presentation and Testing:
A 16-year-old Caucasian female was referred to the immunology clinic for persistent cervical lymphadenopathy and splenomegaly noted since infancy. There was no associated fever, weight loss, or organ-specific symptoms. Other history included recurrent sinopulmonary and ear infections in early childhood that required two tympanostomy tube placements. She denied serious viral and fungal infections. Both her maternal grandfather and mother also had recurrent ear infections and lymphadenopathy, and her maternal grandfather died of lymphoma at age 26. There was no known history of consanguinity.

Diagnosis, Treatment and Patient Outcomes:
She had significant cervical lymphadenopathy (largest lymph node measuring 3.5 x 2.3 x 4.5 cm) but no palpable splenomegaly. Ultrasound of the abdomen indicated spleen size at the upper limit of normal range. Immunophenotyping showed increased transitional CD10+ B cells and double negative αβ-T cells, but reduced memory and isotype-switched B cells. Polyclonal IgH rearrangements were detected in peripheral blood. Serum antibody titers showed IgG (1115 mg/dL), IgA (159 mg/dL), and IgM (232 mg/dL). Her antibody titers to measles, rubella, tetanus, diphtheria and pneumococcus were protective whereas those to varicella-zoster virus and meningococcus were negative. Lymphocyte proliferation assays demonstrated normal proliferation to mitogens and antigens, except for a low stimulation index to Candida albicans (< 3). Histological evaluation of patient’s tonsillar tissue revealed significant follicular hyperplasia and expanded mantle zones comprised of IgD+ naïve B cells. Next-generation sequencing revealed a heterozygous CARD11 mutation (c.146G>A, p.C49Y), which was present in both patient and mother and previously reported in three other cases of mild BENTA disease. A positive long-term prognosis of waning B cell burden over time is expected for this disease. Nevertheless, our patient continues to be carefully monitored in case she develops monoclonal B cell proliferation or increased infections with waning humoral immunity.
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**Case Title:**  
Is TAF7L a Tumor Suppressor Gene? An XLA Contiguous Gene Syndrome with Metachronous Co-Primary Testicular Cancers

**Summary and Lessons Learned:**  
This report describes an association between the X-linked agammaglobulinemia (XLA) contiguous BTK, TIMM8A, TAF7L gene deletion syndrome and repeated testicular cancers. The pathogenic roles of BTK and TIMM8A deletions are known causes of XLA and Mohr-Tranebjaerg syndrome (MTS); however, the consequence of TAF7L mutations in humans is unknown. TAF7L (TATA-box binding protein associated factor 7-like) is located primarily in the human testis, appears to play a role in spermatogenesis, and is a paralogue of a negative cell cycle regulatory protein. While mutations in the TAF7L gene have not been reported with testicular cancers, the gene may play a role in colorectal cancers through its role as a core component for transcription by RNA polymerase II. We investigated the testicular germ cell tumor (TGCT) data set (inclusive of 157 tumors) but found no association with TAF7L. We then evaluated DNA methylation of the TAF7L gene in a sample of 90 pairs of patient matched specimens of primary breast tumor and adjacent normal breast tissue. Among three island CpGs, methylation of TAF7L was significantly higher in tumors when compared to normal breast tissue. This finding of enhanced CpG methylation may be supportive of a TAF7L role in tumor suppression. This is the first report of a primary testicular cancer and subsequent metachronous contralateral testicular cancer occurring with an XLA contiguous gene syndrome. The association questions what role TAF7L may play as a tumor suppressor gene in the testis, and possibly other tissues. While most BTK mutations are missense, nonsense, splice site, and small deletional events, large deletions still account for around 3.5% of XLA cases. This report highlights the need to suspect the MTS/XLA contiguous gene syndrome in patients who present with XLA and sensorineural hearing loss, as well as the possible role for careful and prolonged testicular cancer surveillance in patients with TAF7L mutations.

**Patient Presentation and Testing:**  
The patient is a 28 year old man first diagnosed at 11 months of age when he presented with bilateral flaccid paralysis subsequent to a varicella vaccination and was found to have profound hypogammaglobulinemia (IgG <7 mg/dL; IgA <7 mg/dL; IgM 21 mg/dL) and absent B cells. Around 2 years of age hearing concerns arose and evaluation revealed severe bilateral hearing loss. At 20 years of age he was diagnosed with a metastatic right testicular seminoma, completing four cycles of chemotherapy after right orchiectomy with no residual disease. Because of concerns of decreased visual acuity, further genetic evaluation at 24 years of age led to the diagnosis of MTS when microarray identified a 111-kb deletion of genetic material from chromosome region Xq22.1 resulting in the absence of the BTK, TIMM8A, and TAF7L genes. Seven years after initial diagnosis of his first testicular cancer, the patient presented with swelling of the remaining testicle. Evaluation revealed pulmonary and hepatic metastases of a new primary embryonal testicular cancer.

**Diagnosis, Treatment and Patient Outcomes:**  
Our patient has the XLA- MTS contiguous gene syndrome with metachronous bilateral testicular cancers. The population risk of contralateral testicular cancer is low, on the order of 0.5-2%, so his presentation is unusual. Our patient was treated with left orchiectomy, four cycles of chemotherapy, partial hepatectomy, and periarotic mass removal. He has completed treatment without evidence of residual metastatic disease, continues to receive regular intravenous immune
globulin infusions and has begun testosterone supplementation while receiving multi-disciplinary follow-up with immunology, endocrinology, oncology, and neurology.
Case Title:
Evaluation of the Effects of a STIM1 Variant of Uncertain Significance on Calcium Influx

Summary and Lessons Learned:
Stromal Interaction Molecule 1 (STIM1) is a transmembrane protein in the endoplasmic reticulum (ER) which activates Ca2+ influx through plasma membrane Calcium release-activated channels (CRAC). STIM1 is activated after its N terminus domain senses decreased ER Ca2+ concentrations ([Ca2+]ER), resulting in STIM1-mediated activation of CRAC and increased intracellular Ca2+ concentrations [Ca2+]i. Loss-of-function (LOF) mutations in the STIM1 gene are associated with combined immunodeficiency (CID), whereas gain-of-function (GOF) mutations result in Stormorken syndrome. We present the case of a 3-year-old male with recurrent infections, myalgias, and muscle spasms who was heterozygous for a novel variant in STIM1 (c.1601 C>T; p.A534V).

Patient Presentation and Testing:
A 3-year-old male presented for immunologic workup because of recurrent infections consisting of cellulitis, abscesses, and acute otitis media. For 2 years, he had intermittent myalgias and spasticity. Muscle biopsy revealed mitochondrial proliferation and electron transport chain analysis demonstrated increased mitochondrial activity. Live PBMCs were analyzed for [Ca2+]i directly or after they were taken into cell culture (stimulated with irradiated Buffy coat cells, B cells, PHA and IL-2 for 10-14 days). PBMC or T cells were loaded with Ca2+ indicators (Fura-2 or Fluo-4) and analyzed for [Ca2+]i levels using a Flexstation 3 plate reader or LSR2 flow cytometer, respectively. To measure [Ca2+]i, cells of the patient and a healthy donor were kept in Ca2+-free Ringer solution (0 mM Ca2+) followed by perfusion with Ringer solution containing 2 mM Ca2+. Cells were either left unstimulated or stimulated with 1 mM thapsigargin to deplete ER Ca2+ stores, activate STIM1, and induce store-operated Ca2+ entry (SOCE).

Diagnosis, Treatment and Patient Outcomes:
The patient’s heterozygous STIM1 c.1601 C>T, p.A534V missense mutation occurred in a STIM1 domain not previously associated with human STIM1 mutations. His phenotype was not typical of that observed in patients with known LOF or GOF mutations, but did have some features of both. We sought to characterize the effects of this mutation knowing that LOF and GOF mutations in STIM1 either abolish or enhance SOCE, respectively. Under non-stimulated conditions, switching from 0 mM to 2 mM extracellular Ca2+ did not result in increased [Ca2+]i as would have been expected for a GOF mutation. Stimulation of the patient’s PBMCs or T cells with thapsigargin to induce SOCE resulted in [Ca2+]i increases similar to those found in healthy donor control T cells when averaged over a series of several experiments. Likewise, no consistent decrease or increase in [Ca2+]i was observed in the patient’s T cells after CD3 crosslinking to induce TCR-mediated Ca2+ influx. Similar results were obtained with T cells from the patient’s father, who is heterozygous for the same mutation. In summary, the heterozygous STIM1 c.1601C>T, p.A534V missense mutation does not appear to affect SOCE or cytokine production of the patient’s T cells and remains a variant of uncertain significance.
A 11-month old with MIRAGE Syndrome and SAMD9 gene mutation found to have B and NK cell deficiency with hypogammaglobulinemia

MIRAGE syndrome is a rare multisystem disorder associated with myelodysplasia, infection, restriction of growth, adrenal hypoplasia, genital phenotypes, and enteropathy. Prior literature reveals no shared immune defect however these patients often present with severe invasive infections including sepsis and meningitis. Fatal infections have arisen from bacterial, fungal, and viral infections.

We describe an 11-month old male with multiple upper respiratory infections since birth. He was born preterm at 26 weeks with a four month stay in the MICU. His initial hospitalization was complicated by necrotizing enterocolitis requiring colostomy and G tube placement. He was also found to have adrenal hypoplasia and hypospadias. Whole genome sequencing revealed SAMD9 mutation and diagnosis of MIRAGE syndrome was made. On the most recent admission for viral URI with parainfluenza, immunology was consulted to work up possible immune deficiency. Initial work up revealed total IgG of 162 with low subclasses 1,2, and 4. IgM and IgA levels were normal. Flow cytometry revealed low CD4 and CD8 T cells, low B cells, and NK cells. He had absent functional responses to HIB, pneumococcal, and tetanus vaccines. Based on these findings he was started on IVIG at dose of 5gm monthly with the goal to keep total IgG > 800. Prophylaxis for viral and fungal infections was started with acyclovir and fluconazole. Follow up flow cytometry showed normal T cells but persistently low B and NK cells. He has been offered a bone marrow transplant and is awaiting a donor.

MIRAGE syndrome has no known shared immunologic defect. Given that there is no guidance regarding therapy for immune deficiency in the literature, this case highlights possible treatment with IVIG and prophylaxis with antivirals and antifungals as a bridge to bone marrow transplant.

An 11 m.o. male with MIRAGE syndrome admitted to the PICU with respiratory distress. He was intubated and a diagnosis of parainfluenza was made. Upon improvement of his respiratory status following nebulizer and steroid treatments, he was extubated. He has a history of frequent RSV infections and had two prior hospitalizations for bronchiolitis. His surgical history includes a pericardiocentesis and gastrostomy tube placement following necrotizing enterocolitis. Immunology was consulted to evaluate for possible immune deficiency. His family history is positive for hypertension and diabetes however no immune deficiencies. He was evaluated for immune deficiency with flow cytometry, immunoglobulin levels, and functional titers for vaccines including tetanus, HIB, and pneumonia. His total IgG was low at 162 and he had low IgG subclasses 1, 2, and 4. He did not show appropriate response to tetanus, HIB, and pneumococcal vaccines. His flow cytometry initially showed low CD4 count of 349, low CD8 count of 371, low B cell count of 158, and low NK cells of 39. Based on the findings of low immunoglobulins with absent functional responses to vaccines and lymphopenia, we recommended to start the patient on IVIG supplementation and fungal/viral prophylaxis with fluconazole and acyclovir.

The patient was diagnosed with hypogammaglobulinemia with lymphopenia and started on IVIG. He is doing well with infusions and his total IgG has improved to 884. He tolerates prophylaxis with fluconazole and acyclovir without any adverse effects. He has not had any infections since his discharge. Per his mother’s report, he is more alert and active
after starting IVIG. His repeat flow one month later showed his CD4+ and CD8+ T cells counts had normalized however he still has persistent depression of his B and NK cells. He is being followed by hematology/oncology for a possible bone marrow transplant. He will continue treatment with IVIG and prophylaxis as a bridge to bone marrow transplant.
Case Title:
Hennekam Lymphangiectasia-Lymphedema Syndrome: A Rare Cause of Secondary Immunodeficiency

Summary and Lessons Learned:
INTRODUCTION
Hennekam Syndrome is a rare autosomal recessive disorder. The prevalence is unknown but less than 50 cases have been reported in the literature. It is characterized by lymphedema, lymphangiectasia and developmental delay. Patient’s have variable facial features that are often characterized by flat facies, flat and broad nasal bridge and hypertelorism. 25% of patients are known to have mutations of collagen and calcium binding EGF domain (CCBE1) which plays a vital role in lymphangiogenesis during embryonic development. The lymphangiectasias are commonly found in the intestines, and often lead to a protein losing enteropathy. Patients often present with secondary immunodeficiencies resulting from PLE with lab abnormalities such as hypogammaglobulinemia and decreased CD4 T cell. We present a 9 year old female with Hennekam Syndrome who was referred to us for a finding of hypogammaglobulinemia

Patient Presentation and Testing:
CASE PRESENTATION
We present a 9 year old female born to non consanguineous parents of Puerto Rican descent. Family history was significant for an older brother who passed away at 17 months old from pneumonia. The patient was initially diagnosed with with intestinal lymphangiectasia at 4 months old in the setting of FTT, and diarrhea and was subsequently diagnosed with Hennekam Syndrome. Her history is also notable for developmental delay, hypoalbuminemia, Vitamin D and E deficiency, FTT, recurrent pneumonias, bronchiectasis, congenital optic nerve anomaly, hearing loss and asthma. Physical exam is significant for microcephaly, flattened facies, hypertrichosis, low set and malformed ears, epicanthal folds, overcrowding teeth and coarse crackles bilaterally on respiratory exam. Her infectious history includes nine lifetime episodes of pneumonia, one episode of acute otitis media and one episode of influenza B. She has no history of sinusitis, abscesses, viral or fungal infections, septicemia, or meningitis. Prior lab evaluations were notable for significant hypogammaglobulinemia and lymphopenia. Our inpatient evaluation showed decreased CD4, and CD8 counts, and a mild hypogammaglobulinemia. Specific antibody titers showed good responses to mumps, rubella, diphtheria and tetanus, with a mildly decreased response to measles. Initial titers to Prevnar were near absent but following immunization she had greater than 70% protective antibodies to PCV. It was unclear if she had previously received the vaccine. We continue to follow this patient monthly to trend lymphocyte subsets and immunoglobulins, she has remained infection free since our initial evaluation.

Diagnosis, Treatment and Patient Outcomes:
CONCLUSIONS
We describe a rare cause of secondary immunodeficiency. Hennekam Syndrome has been reported in the literature roughly 50 times, but never with a focus on immunodeficiency. Hennekam Syndrome should be considered in any patient with secondary immunodeficiency caused by a PLE with dysmorphic facial features and developmental delay.
Summary and Lessons Learned:
X-linked agammaglobulinemia (XLA) is a hereditary primary immunodeficiency that results from Bruton's tyrosine kinase (BTK) gene mutations. Mutation in the BTK gene interferes with development and function of B-cell. To date, more than 1000 BTK mutations have been identified to be associated with XLA.

The patient described is a 55 year old gentleman who was referred to our Allergy and Immunology clinic with previous diagnosis of common variable immunodeficiency (CVID) since age 4. However over the time he was followed in the clinic he was noted to have more complications and infections than expected with a CVID patient on prophylactic antibiotic and IVIG with adequate IgG levels. As well his blood work revealed no mature B-cells and therefore the suspicion of X-linked agammaglobulinemia was raised. Hence he underwent a BTK gene analysis and was found to have a novel T354I missense mutation of BTK gene. Other missense mutations in close proximity to T354I (A347P, I355N, L358F, and Y361D/C) have been reported in association with agammaglobulinemia. Additionally, in silico algorithms (PolyPhen, SIFT) predict T354I to be damaging. Therefore we consider T354I a novel mutation and its presence consistent with a diagnosis of X-linked agammaglobulinemia. Since the XLA diagnosis his IVIG therapy has been adjusted to 35g q3weeks and he is on prophylactic azithromycin 250mg every other day and is doing quite well with less frequent infections. This case emphasizes that suspicion for XLA and gene-study is essential for patients presenting with clinically overlapping disorders that would include XLA as a differential diagnosis. This is especially crucial when a patient fails to respond appropriately to adequate therapy for their presumed diagnosis.

Patient Presentation and Testing:
A 55 year old gentleman presented to respiratory ambulatory unit in 2007 with one month history of greenish-yellow productive cough not responsive to antibiotics, including two courses of cefuroxime, one course of amoxicillin-clavulanate followed by a course of moxifloxacin. At age 4 he was found to have hypogammaglobulinemia and was diagnosed with common variable immunodeficiency (CVID) and was started on intramuscular immunoglobulin and then later switched to IVIG in the 1980s; despite this he continued to have recurrent sinopulmonary infection. He underwent a left lower lobectomy in 1986 for bronchiectasis. His other history included paroxysmal atrial fibrillation and a TIA. His investigations included a CT chest, which revealed volume loss in the left with some focal bronchiectatic changes and linear densities with some traction bronchiectasis in residual left lung. As well there was some airway thickening diffusely and some mucous plugging on the left. His pulmonary function test was consistent with airflow obstruction, largely reversible post-bronchodilator (consistent with inflammatory airway disease). Sputum cultures had grown Moraxella catarrhalis, streptococcus pneumonia and haemophilus influenza. Testing for cystic fibrosis and Alpha-1 Antitrypsin were negative.

He was then referred to our clinic for further assessment and over the 3 years he was followed at the clinic he was noted to have more complications and infections than expected with a CVID patient on prophylactic antibiotic (clavulin 500mg bid) and IVIG 25 g monthly, with adequate IgG levels (average of ~11 g/L). Blood work from 2009 had revealed no mature B-cells and therefore the suspicion of X-linked agammaglobulinemia was raised. In 2010 he underwent a BTK gene analysis (by Gene Dx DNA Diagnostic Experts), which revealed a novel T354I missense mutation in the BTK gene, reported as highly likely to be associated with XLA. To our knowledge it has not been published as a mutation, nor has it been reported as a benign polymorphism.
Diagnosis, Treatment and Patient Outcomes:
The diagnosis that we arrived at was X-linked agammaglobulinemia (XLA) and since the diagnosis the patient's IVIG therapy has been adjusted to 35g q3weeks and he is on prophylactic azithromycin 250mg every other day and is doing quite well with less frequent infections.
Since it was first described in 1952, XLA has been treated with immunoglobulin (IgG) replacement therapy. IgG replacement reduces infections, need for antibiotics, end-organ damage and mortality. Dosing of IgG replacement therapy was previously based on specific IgG trough levels however recent consensus recommends that IgG replacement therapy should be based on the individual clinical response. Our patient’s most recent trough level was 12.1 g/L on 35 g IVIG (every 3 weeks) and he has had less frequent sinopulmonary infections.
Summary and Lessons Learned:
Hereditary angioedema (HAE) is a rare disorder characterized by potentially life-threatening episodes of angioedema without urticaria persisting for several days. HAE types I and II present with low C4 and low C1 esterase level/function while type III estrogen-dependent presents with normal labs coupled with a family history of swelling or a Factor XII mutation. However, allergists will often encounter patients with history highly suggestive for HAE but normal labs, no family history of angioedema, and no Factor XII mutation, making encounters, as in the case of the following patient, very difficult to treat.

The patient, a 37-year-old female with a past medical history significant only for allergic rhinitis, presented with a 7-year history of episodes of idiopathic recurrent laryngeal edema refractory to corticosteroids, epinephrine, and antihistamines but responsive to icatibant and C1 esterase inhibitor concentrate. She reported numerous ED admissions for “tongue and throat swelling” without urticaria that was refractory to corticosteroids, epinephrine, and antihistamines; “cleaning chemicals” seemed to provoke these exacerbations. She had been thoroughly evaluated by two academic institutions with no satisfactory treatment, and episodes were debilitating to the point of the patient seeking disability approval. Testing for environmental, food, and chemical triggers was unrevealing. C1 esterase inhibitor level/function and C4 were checked on multiple occasions and found normal; Factor XII mutation was negative. The patient was seen in clinic with confirmed uvula/throat swelling and resulting “hot potato” voice after exposure to cleaners. She was treated with an icatibant sample with some improvement and reported a slow return to baseline. During a subsequent attack two months later, a trial of recombinant C1 esterase inhibitor was administered, and symptoms resolved within two hours. At her follow-up appointment two months later, she reported two further exacerbations that she treated at home with C1 esterase inhibitor concentrate with full symptomatic resolution within hours.

Non-histaminergic angioedema is a scenario that allergists commonly encounter, and HAE should always be included in the differential. However, when patients do not conform to the guidelines for one of the HAE categories, treatment can be difficult and patients can end up going to numerous specialists and academic institutions, often without relief. This case highlights the potential for traditional HAE treatments in patients with a history suggestive of HAE but without classic lab findings or family history.

Patient Presentation and Testing:
A 37-year-old female with a past medical history significant only for allergic rhinitis and no positive family history presented with a 7-year history of episodes of laryngeal edema and glossitis lasting for several days without urticaria. She reported numerous ED admissions for “tongue and throat swelling” refractory to corticosteroids, epinephrine, and antihistamines. She had previously been evaluated by two academic institutions with no satisfactory treatment, and episodes were debilitating to the point that at the time of the initial encounter, the patient was seeking disability approval. There seemed to be no specific triggers for her condition, as chemical patch testing and environmental/food prick testing were obtained and found unrevealing. Due to the patient’s description of her symptoms, and her lack of symptomatic resolution with corticosteroid, epinephrine, and antihistamine medical management, hereditary angioedema was included in the differential. C1 esterase inhibitor level and function and C4 were thus repeatedly measured but found to be within normal limits, and she also tested negative for Factor XII mutation. The patient was seen in clinic with confirmed uvula/throat swelling and resulting “hot potato” voice on one occasion after exposure to cleaners. She was treated with an icatibant sample with some improvement and reported a slow return to baseline. During a subsequent attack two months later, a trial of recombinant C1 esterase inhibitor was administered and symptoms resolved within two hours. At her follow-up appointment two months after this incident, she reported two
further exacerbations that she treated at home with C1 esterase inhibitor concentrate with full symptomatic resolution
within hours.

**Diagnosis, Treatment and Patient Outcomes:**
The patient's chief symptoms, laryngeal edema and glossitis, did not resolve with corticosteroids, epinephrine, and
antihistamines, making anaphylaxis an unlikely diagnosis. Environmental and food prick testing were unremarkable, as
was chemical patch testing. While hereditary angioedema was considered a viable diagnosis, the patient lacked any
significant family history, and C1 esterase inhibitor level and function and C4 were repeatedly measured and found to be
within normal limits. Factor XII mutation testing was also negative. However, symptoms were highly consistent with
HAE. After being exposed to cleaning agents at work on one occasion, the patient presented to clinic during an episode
of uvula/throat swelling and resulting "hot potato" voice. There, recombinant C1 esterase inhibitor was administrated
on a trial basis, and she achieved full symptomatic resolution within two hours. The patient successfully treated two
exacerbations afterward with C1 esterase inhibitor concentration administered at home and was highly satisfied with
the results. At her most recent follow-up appointment one month ago, the patient reported immense improvement in
her quality of life after establishing the diagnosis and treatment of her condition.
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Case Title:  
CTLA-4 Haploinsufficiency Presenting in a Child with Very Early-Onset Colitis  

Summary and Lessons Learned:  
This is a 2-year-old boy of African American heritage with multiple congenital malformations who was diagnosed with very early-onset inflammatory bowel disease, which proved to be resistant to treatment. Subsequent testing revealed a heterozygous mutation in exon 1 of CTLA4. This variant has not been previously reported in the literature in individuals with CTLA4-related disease. The patient remains in active treatment, and treatment with abatacept is being initiated. The protein cytotoxic T lymphocyte antigen-4 (CTLA-4) is an essential negative regulator of T cells. Heterozygous mutations in CTLA4 cause a disease of immune dysregulation. Clinical presentation is variable and may be characterized by enteropathy, hypogammaglobulinemia, granulomatous lymphocytic interstitial lung disease, lymphocytic organ infiltration in non-lymphoid organs, autoimmune cytopenias, and recurrent infections. Inflammatory bowel disease may be associated with certain variants in CTLA4, but the literature remains limited, both by number of papers published as well as by ethnic subsets studied. Clinicians who are presented with children who have early-onset colitis, and particularly inflammatory bowel disease that is difficult to treat, should consider possible genetic abnormalities, such as CTLA-4 haploinsufficiency, as these can impact therapeutic decision-making and outcomes.

Patient Presentation and Testing:  
This is a 2-year-old boy with cloacal exstrophy of the urinary bladder, omphalocele, imperforate anus, polydactyly, and sacral agenesis who was diagnosed with very early-onset inflammatory bowel disease at six months of age. He underwent cloacal exstrophy closure, omphalocele repair, and colostomy placement in the first week of life. At six months of age, he presented with dark tarry stools. Upper endoscopy and colonoscopy revealed polyps, ileitis, and colitis. He was p-ANCA positive and started on sulfasalazine. Unfortunately, he continued to have symptoms suggestive of active colitis, prompting a change to prednisone and azathioprine. Despite therapy, his colitis persisted leading to chronic bloody diarrhea and growth failure. Initial immune evaluation consisted of a normal complete blood count, serum immunoglobulin, lymphocyte subsets, and neutrophil oxidase burst assay. FOXP3 analysis by flow cytometry showed a moderately elevated percentage of FOXP3+CD25+ cells in the CD4+ T cell population, but the regulatory T cell immunophenotype was normal. Because suspicion was high for a monogenic immunologic disease to explain his symptoms, genetic sequencing was performed. A candidate gene panel was sequenced by Next Generation Sequencing, and a heterozygous mutation in exon 1 of CTLA4 (c.23G>A; p.Arg8Gln) was found. This variant has not been previously reported but is predicted to be pathogenic in Exac and PolyPhen databases.

Diagnosis, Treatment and Patient Outcomes:  
The patient’s diagnosis of CTLA-4 haploinsufficiency associated with very early-onset inflammatory bowel disease has provided opportunity for targeted treatment of his specific molecular defect. Given his poor response to treatment thus far, the patient will be started on abatacept. Abatacept is FDA approved for the treatment of rheumatoid arthritis but has been used successfully for the treatment of disease-related manifestations of CTLA-4 haploinsufficiency. Abatacept is a CTLA-4 fusion protein formed by the IgG1 Fc region linked with the extracellular domain of CTLA-4; it replaces the defective protein in CTLA-4 haploinsufficiency. In addition, given other manifestations of CTLA-4 haploinsufficiency including lymphoproliferative disease in non-lymphoid organs, particularly the brain and lung, we have initiated further evaluation of these organs to evaluate for disease-specific manifestations.
Summary and Lessons Learned:
Abnormal skin may be a presenting sign of a number of primary immunodeficiencies, therefore, early immunologic diagnostic work up of patient with skin lesions should be considered. We describe a case of an infant boy who presented with generalized erythroderma and severe epidermal desquamation since birth. It was believed that he had congenital ichthyosis and no primary immunodeficiency was considered until after the second episode of Staphylococcal sepsis, when the child was already 70-days old. He also had developed severe failure to thrive and milk intolerance. Laboratory evaluation indicated probable Netherton Syndrome, which was eventually confirmed by the finding of SPINK5 gene mutation.

Patients with Netherton Syndrome have very high mortality in infancy due to susceptibility to Staphylococcal sepsis, pneumonia, chronic enteropathy, failure to thrive and electrolyte abnormalities (1), thus, early treatment is essential for successful patient care. The list of diseases presenting with erythroderma in infancy is not extensive; it includes Sjögren-Larsson Syndrome, KID Syndrome, SCID in the form of Omenn Syndrome or GvH, Wiskott-Aldrich Syndrome, and Netherton Syndrome (2). Thus, if in our patient’s case a diagnostic work up had focused on the key finding of erythroderma, the diagnosis of primary immunodeficiency could had been achieved before the onset of its florid telltale signs such as severe infections and failure to thrive. Implementation of appropriate skin care and infusions of IVIG improved our patient’s skin condition and weight gain.

Patient Presentation and Testing:
The infant was born at term gestation to consanguineous parents via C-section performed due to presence of fetal tachycardia. Baby was noticed to have generalized epidermal desquamation, underlying erythema, alopecia, and foul-smelling skin. His birth weight was 3300 grams. The baby was admitted to NICU due to respiratory distress which resolved after 1 week of mechanical ventilation followed by 1 week of CPAP. Initially the skin rash was thought to be infectious in nature. The rash was then diagnosed as seborrheic dermatitis, and was treated for 3 weeks with topical steroids without improvement. Subsequently, a diagnosis of ichthyosis was suggested, for which a non-syndromic ichthyosis genetic panel was requested to support this diagnosis, yet it came back negative.

The patient also displayed poor sucking and was fed through an NG tube. He had poor weight gain despite receiving additional calories by fortifying human breast milk. This was later replaced by high caloric cow’s milk formula. By 2 months of age the baby had gained only 75g since birth and the decision was made to place a gastrostomy tube. Throughout his NICU course, the baby developed one UTI with E. cloacae, two Staphylococcal bacteremias, one episode of Influenza and one episode of Para-Influenza, which prompted Immunology consultation.
Immunology service evaluated the infant at 70 days of life. Due to the failure to thrive, infectious history and parental consanguinity, a primary immunodeficiency was suspected. Due to the skin appearance, Netherton syndrome (NS) was considered the most likely diagnosis. Given our patient’s alopecia it was not possible to evaluate for the presence of trichorrhexis invaginata (bamboo hair), a sign frequently found in patients with NS, however the suspicion of NS was further enhanced when it was noted that patient had eosinophilia, albeit transient. Eosinophilia appeared to be related to the source of nutrition, starting in the first week of life while the child was on breast milk, worsened when Human Milk Fortifier, a cow’s milk-based product, was added to his diet, and resolved after starting hydrolyzed formula. This suggested a non IgE-mediated cow’s milk allergy. Commonly observed in NS IgE-sensitization to milk, egg white, peanut, soy, wheat, and cod fish was not found on his RAST test.

Furthermore the patient also displayed significantly elevated IgE 378 IU/ml (0-15) and IgA 121 mg% (4.4-73); both common findings in NS.

He was found to have normal counts of lymphocytes -T, -B and NK cells, normal IgG and IgM, and normal NK cells functions. This last finding was unexpected, since NK functions are often impaired in patients with NS. The majority of patients with NS have antibody deficiency, manifested as the inability to respond to polysaccharide antigens. This immune response is T-cell independent and is typically weak until age of 2 years, and as such was not evaluated in our patent.

**Diagnosis, Treatment and Patient Outcomes:**

Diagnosis was made by single gene sequencing. It revealed that the patient is homozygous in the SPINK5 gene for a variant designated c.238dup, which is predicted to result in a frameshift and premature protein termination (p.Ala80Glyfs*19). This variant has been reported to be causative for Netherton Syndrome.

Patients with NS have very high mortality during the first year of life for which the decision was made to start the administration of IVIG without waiting for the genetic confirmation of the diagnosis. The patient received 400 mg/kg of IVIG every 2 weeks twice, and subsequently every three weeks.

Patients with NS have severe skin barrier defect for which we decided to apply meticulous skin care using our experience with the care for patients with atopic dermatitis. It consisted of soaking of the whole body in water for 10 minutes once daily, using liquid cleanser with pH 5 at the end of the bath, immediately followed by the application of Petrolatum, spread (in only one movement) from head to toes. Petrolatum administration was repeated every 4 hours around o’clock.

The skin appearance improved after two weeks of treatment, having much less desquamation, yet with no significant change in the erythroderma.

Enteral feeding pathway (G-tube) with hydrolyzed formula, better skin care, and IVIG provided the appropriate setting for better weight gain. The baby was discharged from the NICU on his 91st day of life gaining 200 grams since the beginning of treatment 3 weeks earlier.

Skin care and infusion of IVIG every 3 weeks continued as outpatient. There has been remarkable improvement in skin appearance and increased weight gain velocity, although he remains below the 3rd percentile at 9 months of age.

**REFERENCES:**

**Case Title:**
Asymptomatic Granulomatous and Lymphocytic Interstitial Lung Disease (GLILD) in Common Variable Immunodeficiency (CVID)

**Summary and Lessons Learned:**
We report a 30 year old female diagnosed with common variable immunodeficiency (CVID) and biopsy proven granulomatous and lymphocytic interstitial lung disease (GLILD). She has had chest CTs that showed persistent mediastinal lymphadenopathy and patchy reticulonodular infiltrates in both lungs. She has been completely asymptomatic without any respiratory symptoms and her pulmonary function testing has shown no evidence of restrictive or obstructive defect.

GLILD is associated with reduced survival rates and is a risk factor for the development of B cell lymphomas. There are a few published reports regarding the treatment strategies for GLILD. Combination chemotherapy with Rituximab and Azathioprine improved pulmonary function and decreased radiographic abnormalities in patients. However, the lack of pulmonary symptoms and her normal pulmonary function testing with normal diffusion capacity of carbon monoxide (DLCO) posed a dilemma on whether to treat her at this point or to closely monitor her. Given lower survival rates in CVID patients with GLILD compared to CVID patients without GLILD, an argument was made for active treatment. However, it remained unclear if treatment would improve survival. Given patient’s younger age, treatment of GLILD and possible prevention of future complications was an important consideration. Ultimately, the decision was made to closely observe the patient with serial imaging, PFTs, and close clinical monitoring by Immunology, Pulmonology, and Hematology.

This case provided several notable and interesting teaching points:
- CVID patients are at risk for noninfectious complications due to immune dysregulation.
- The differential diagnosis of the above pulmonary imaging findings include infection, malignancy (lymphoma), GLILD and sarcoidosis. It is important to obtain tissue biopsy to have the correct diagnosis to recommend the appropriate treatment.
- There is no published literature regarding the decisions to actively treat or observe asymptomatic GLILD in CVID patients. Any decision regarding treatment or observation may need to be made on a case-by-case basis.

**Patient Presentation and Testing:**
We report a 30 year old female who was referred to our clinic for evaluation of immunodeficiency. Her medical history was significant for recurrent sinopulmonary infections. Laboratory evaluation was significant for IgG of <70 mg/dl, IgA of <10 mg/dl, IgM of <20 mg/dl, undetectable tetanus and pneumococcal antibody titers, and normal T cell proliferation response to mitogens and tetanus antigen. Flow cytometry showed a slightly low B cell number and percentage (4.5% B cells, 50 B cells). She was diagnosed with CVID and started on immunoglobulin replacement.

Previous chest x-rays have shown persistent bibasilar opacities, so a chest CT was obtained to evaluate for bronchiectasis. This showed mediastinal lymphadenopathy and patchy reticulonodular infiltrates in both lungs. These findings persisted after treatment with antibiotics. Given concern for GLILD or lymphoma, an open lung biopsy was obtained. The pathology showed lymphocytic interstitial pneumonitis, acute and organizing pneumonia, and sarcoid-like granulomas. These are all findings consistent with CVID associated GLILD. Interestingly, cultures from the open lung
biopsy showed slow growing Mycobacterium Avium-Intracellulare (MAI). Ziehl-Neelsen staining was performed and no definitive acid-fast bacilli were visualized. Evaluation by Infectious Diseases recommended no treatment and closer observation of the MAI given that she was asymptomatic (no fevers, weight loss, cough, sputum production or shortness of breath).

Given the discordance between the microbiology results and the staining results, the pathologist decided to further investigate the nature of the lymphoid proliferation in the lung tissue. A clonal B-cell population was detected. Epstein Barr Virus (EBV) encoding region in situ hybridization and Human Herpesvirus 8 (HHV-8) immunohistochemistry were performed on biopsy specimen and were both negative. Given the clonal B-cell population and concern for lymphoma, a PET CT scan was performed which showed diffuse lymphadenopathy with fluorodeoxyglucose (FDG) uptake in the thoracic, cervical, and abdominal regions. A fine needle aspiration of a retroperitoneal lymph node with high FDG uptake showed pathology favoring reactive process. Follow-up CT scans showed that the lymphadenopathy is stable. PFTs and DLCO have been normal. She remains asymptomatic from a pulmonary standpoint.

**Diagnosis, Treatment and Patient Outcomes:**
The patient was diagnosed with CVID with GLILD. GLILD is a term used to describe a variety of noninfectious pulmonary pathology findings found in CVID patients, which includes lymphocytic interstitial pneumonia, follicular bronchiolitis, non-necrotizing granulomatous disease, and lymphoid hyperplasia. Common presenting symptoms of GLILD include dyspnea, splenomegaly, and a restrictive defect found on pulmonary function testing. Patients with GLILD exhibit reduced survival and higher morbidity. Although no established guidelines exist for treatment of GLILD, successful therapies have include corticosteroids, steroid sparing agents such as cyclosporine, azathioprine, methotrexate, and rituximab. These therapies showed improvement in clinical symptoms and radiographic abnormalities for symptomatic patients. Combination chemotherapy with Rituximab and Azathioprine improved pulmonary function and decreased radiographic abnormalities in patients with CVID and GLILD.

Although this patient exhibited abnormal radiographic findings, she did not have any pulmonary symptoms (no cough, dyspnea, wheezing, or chest tightness). Her pulmonary function testing did not show any restrictive or obstructive defect. Her DLCO remains normal.

Given that she was totally asymptomatic from a pulmonary standpoint, we debated whether to treat the patient with combination chemotherapy or to carefully observe the patient. Given her younger age of presentation, active treatment of her GLILD was considered, with the goal of preventing future pulmonary complications related to GLILD. GLILD is a risk factor for the development of B cell lymphomas and there was a clonal B cell population detected on her lung biopsy. After careful discussion with the patient and multiple specialty providers (pulmonology, hematology), the decision was made to closely observe her and follow her clinical status, perform serial imaging and periodic complete PFTs with DLCO.
Case Title:
A Tale of Two Diseases: LRBA Deficiency and Sickle Cell Disease

Summary and Lessons Learned:
Our patient was a 16-year-old African-American female with history of sickle cell disease diagnosed at birth by newborn screen. Her medical history was complicated by recurrent acute chest syndrome and sickle cell pain crises as well as recurrent strep pharyngitis leading to tonsillectomy. The patient was doing well on hydroxyurea (hemoglobin 7 g/dl) until the age of 15 when she began to have very resistant anemia (hemoglobin nadir 4.6 g/dl) and lymphadenopathy. Her recurrent anemia was treated with prednisone, IVIG, and packed red blood cell transfusions without significant improvement. When she was 16 years old she underwent further work-up of her anemia and was found to be direct antiglobulin test (DAT) positive. She began receiving rituximab and prolonged corticosteroid tapers with only mild improvement in anemia. Because of the resistant anemia, and evidence of autoimmunity, immunological workup was pursued and revealed elevated IgG of 5390 mg/dL. Physical exam revealed hepatosplenomegaly which was confirmed by CT scan of the abdomen. It was also surmised that her spleen was relatively enlarged when compared to other patients with sickle cell disease. Bone marrow biopsy was performed and showed no evidence of malignancy; cytogenetics were normal. Lymph node biopsy was also performed and showed reactive hyperplasia without evidence of Epstein Barr virus infection. Flow cytometry revealed low memory B cells and decreased class switched and non-class switched memory B cells. Ultimately ion torrent gene sequencing revealed two LRBA (Lipopolysaccharide-responsive vesicle trafficking, beach and anchor-containing) mutations (heterozygous missense and heterozygous splicing) that were predicted to be deleterious. The patient was trialed on mycophenolate mofetil but ultimately placed on abatacept to increase CTLA4 levels and ultimately target her underlying LRBA deficiency. This patient serves as an atypical example of a patient with LRBA deficiency in addition to sickle cell disease, thus representing a rare group of patients born with two underlying genetic mutations. The lesson learned from this case is that if a patient’s presentation seems atypical or uncharacteristically severe (as was her lymphadenopathy, elevated IgG, hepatosplenomegaly and anemia), one should further investigate whether other disease processes could potentially be contributing.

Patient Presentation and Testing:
The patient is a 16 yo African-American female with history of sickle cell disease diagnosed via newborn screening and recurrent strep pharyngitis resulting in tonsillectomy that presented to us with new onset resistant anemia, lymphadenopathy, elevated IgG, and hepatosplenomegaly. Past medical history also included recurrent acute chest syndrome and pain crises. Family history is significant for a mother and father with sickle cell trait. The patient does not drink, smoke, or do illicit drugs.

Due to the autoimmune cytopenias, further anemia workup revealed direct antiglobulin test positivity as well as evidence of hemolysis (elevated reticulocyte count, indirect bilirubin, and LDH along with low levels of haptoglobin). Immunoglobulin levels were performed due to history of recurrent strep pharyngitis and evidence of autoimmunity and revealed elevated IgG level. Flow cytometry revealed low memory B cells and decreased class switched and non-class switched memory B cells. Ultimately ion torrent gene sequencing revealed two LRBA (Lipopolysaccharide-responsive vesicle trafficking, beach and anchor-containing)
mutations (heterozygous missense and heterozygous splicing) that were predicted to be deleterious. These mutations were thought to be the cause of her new onset autoimmune hemolytic anemia, lymphadenopathy, and hepatosplenomegaly. Though she had a history of recurrent pharyngeal infections consistent with LRBA deficiency, these resolved with tonsillectomy. She lacked the characteristic low immunoglobulins that accompany LRBA deficiency, and this was thought to be secondary to one mutation being a splicing mutation.

**Diagnosis, Treatment and Patient Outcomes:**
The patient was diagnosed with LRBA deficiency, which explains her autoimmune hemolytic anemia, infections, lymphadenopathy, and hepatosplenomegaly. The patient was initially placed on mycophenolate mofetil as a general immunosuppressant. The patient was unable to reach therapeutic levels of this drug and anemic episodes continued. Because it is known that LRBA protein helps with trafficking of CTLA4 protein; the patient was ultimately placed on abatacept infusions to increase levels of CTLA4. While on abatacept, the patient’s hemoglobin stabilized and rate of hospitalization improved significantly. Her relative splenomegaly improved as well.
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Case Title:
Hypogammaglobulinemia Associated with Salmonella Infection During Infancy

Summary and Lessons Learned:
Patient A is a 20-month-old female with recurrent sinopulmonary infections. Initial immunoglobulins at 20 months of age were, in mg/dL (normal range): IgG 309 (345-1213), IgA 20 (14-106), IgM 47 (34-206). She had protective titers to diphtheria, tetanus, H. influenza. Her case was managed conservatively. She continued to develop recurrent sinopulmonary infections. Vomiting and diarrhea at 30 months of age led to hospital admission, with stool PCR positive for Salmonella. She was treated with antibiotics and IVIG 6 gm was initiated, and later switched to SQIG with significant improvement. After 16 months, Ig levels normalized and Ig replacement therapy was successfully discontinued.

Patient B is a 10-month-old male evaluated for a chronic cough and a family history of a possible immunodeficiency. Initial immunoglobulins at presentation, in mg/dL (normal range): IgG 130 (246-904), IgA <15 (27-66), IgM 16 (40-143). B and T lymphocyte subsets were within normal limits. Poor responses to Pneumococcus (Prevnar) but protective titers to diphtheria and tetanus were noted. Amoxicillin prophylaxis 200 mg/day was started. Bloody stool developed at 13 months of age, culture positive for Salmonella montevideo, requiring ED evaluation and hospital admission. Blood cultures also grew Salmonella montevideo. Repeat immunoglobulins during this hospitalization were as follows, mg/dL (reference range as above): IgG 217, IgA 22, IgM 52. IVIG 5 gm was initiated in hospital. Sequence analysis of the X-linked BTK gene was negative. Upon 4 week follow up his IgG was 549, IgA <15, IgM 33.

Multiple questions are raised by these cases: the unique gastrointestinal pathogen, when most appropriate to initiate replacement Ig, and how to define the duration of replacement therapy.

Patient Presentation and Testing:
Both patients were initially managed conservatively. Once a severe infection developed, IVIG was initiated. Important tests included measurement of immunoglobulins (University Health Care System, Children’s Hospital of Georgia), bacterial cultures and PCR, lymphocyte studies (Children’s Hospital of Georgia), and BTK gene sequence analysis (GeneDx).

Diagnosis, Treatment and Patient Outcomes:
Our patients each presented with serious Salmonella infections with presumptive transient hypogammaglobulinemia of infancy, managed conservatively. During hospitalization, immunoglobulin replacement was started, stabilizing these clinical courses. Patient A was able to discontinue Ig replacement after Ig normalization; Patient B continues to be followed, on replacement Ig.
Case Title: Should X-linked HyperIgM Syndrome patient be transplanted?

Summary and Lessons Learned:
A 7 months old male presented at age of 3 months with severe disseminated viral infection. Extensive immunological work-up showed low T cells numbers and function, absent isotype-switched memory B cells and low immunoglobulins except normal IgM. Genetic testing revealed pathogenic mutation in CD40LG gene. Patient diagnosed with XHIGM and started on IVIG with ganciclovir and Cytogam for CMV pneumonitis and viremia and prophylactic antibiotics for complications that may occur with XHIGM syndrome. CMV-specific cytotoxic T cells therapy was considered before elective bone marrow transplantation.

XHIGM is a combined immunodeficiency caused by pathogenic mutations in the CD40LG gene. CD40L abnormalities effect T cell interaction with B, dendritic and natural killer cells and neutrophils and result in abnormal B cell class switching, cytokine secretion and neutrophils maturation. It should be suspected in any patient with features of combined immunodeficiency even in case of normal IgM level. Diagnosis is made by gene sequencing and flow cytometry for expression of CD40L on stimulated T cells. Indication and timing of HSCT is unclear. It is published that overall survival between patients treated with or without HSCT is similar with improvement quality of life for those transplanted before 5 years (de La Morena). Untransplanted, patients may develop sclerosing cholangitis or malignancy that is associated with worse outcome. Here, we are considering elective HSCT once lung disease is improved, as fully matched sibling is available. The implications of transplant from a donor sister with carrier state should be taken into consideration.

Patient Presentation and Testing:
A full-term 3 month-old was brought to medical attention for rhinorrhea and cough and respiratory panel detected rhinovirus and RSV. Progressive respiratory distress resulted in hospitalization and need for mechanical ventilation. Disseminated cytomegalovirus (CMV) was present in bronchoalveolar lavage (BAL) of lung, retina and blood and patient was started on ganciclovir and Cytogam. Due to the extent of CMV dissemination, primary immunodeficiency was suspected. Two male family members died with early childhood infections on the mother side suggestive of an X-linked inheritance.

Based on history and presentation, differential diagnosis included X-linked combined immunodeficiencies such as severe combined immunodeficiency (SCID), NEMO, IPEX and XHIGM syndrome. Workup was notable for neutropenia and lymphopenia; immunoglobulin levels were very low except for normal IgM; lymphocytes enumeration showed low number of T cells and natural killer (NK) cells but normal for B cells; Proliferation with mitogens and antigen were low. NK cell function was persistently low with normal CD107a mobilization assay. Genetic testing for NEMO was normal. Newborn screening for SCID was normal. Flow cytometry confirmed normal number and FOXP3 expression of regulatory T cells. However, B cell compartment showed absent isotype-switched memory B cells and pointed towards X-linked hyperIgM syndrome (XHIGM). Flow cytometry for CD40L after T cell stimulation test was abnormal and highly suggestive for HIGM. Sanger sequencing of CD40LG revealed a pathogenic intronic splice site mutation c.288+1G>A. Both sister and mother are carriers for the same CD40LG mutation.

Diagnosis, Treatment and Patient Outcomes:
Patient was diagnosed with X-HIGM syndrome. He was placed on immunoglobulin replacement therapy and continued on ganciclovir. Currently lung disease with cystic bronchiectasis is extensive, partly related to CMV infection.
and partly to barotrauma on ventilator. CMV-specific cytotoxic T cells therapy was considered to maximize lung CMV clearance but follow up BAL became negative and therefore this therapy is currently in hold. In preparation for elective bone marrow transplantation from sister as donor (10/10 HLA match), patient continues prophylaxis for Pneumocystis jirovecii, Mycobacterium avium and cryptosporidium to prevent sclerosing cholangitis. Filgrastim is given intermittently for neutropenia. The timing of hematopoietic stem cell transplant (HSCT) depends on improvement in lung disease and function.
Case Title:
A crossroad between immunodeficiency and autoinflammation: PAPA syndrome

Summary and Lessons Learned:
Our patient was referred for possible immunodeficiency with history of recurrent purulent otitis media, septic arthritis and osteomyelitis, cutaneous abscesses, and preseptal cellulitis. Given synovial fluid and abscess cultures were repeatedly negative and lack of antimicrobial response, an autoinflammatory disorder was considered. PSTPIP1 sequencing revealed a pathogenic heterozygous mutation, confirming a diagnosis of pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome. Our patient achieved clinical remission with the TNF-alpha inhibitor adalimumab.

Our case emphasizes that providers need a high index of suspicion for an autoinflammatory disorder, particularly when sites of inflammation are sterile. Our case also highlights the possibility of ocular involvement, not previously well-described in PAPA syndrome, and adds to the existing few reports on the effectiveness of TNF-alpha inhibition in PAPA syndrome.

Patient Presentation and Testing:
A 12-year-old female was referred for possible immunodeficiency. She experienced recurrent purulent otitis media, requiring multiple PE tube placements. At 6-years-old, she had 3 episodes of presumed elbow septic arthritis and osteomyelitis. Synovial fluid analyses had >100,000 WBC/mcL with >95% neutrophils. Cultures remained negative. She was treated with antimicrobials without response. At 9-years-old, she developed cutaneous abscesses and preseptal cellulitis refractory to antimicrobials. Cultures again remained negative. Her medical history was notable for juvenile arthritis and cystic acne. Social and family histories were otherwise unremarkable.

Given the lack of antimicrobial response, a lesional skin biopsy was performed. It demonstrated areas of dense dermal neutrophilic inflammation suggestive of a neutrophilic dermatosis. With her history of pyogenic sterile arthritis, neutrophilic dermatosis, and acne, an autoinflammatory condition was considered. Her phenotype seemed most consistent with PAPA syndrome. PSTPIP1 sequencing demonstrated a previously described pathogenic heterozygous mutation c.688G>A in exon 10 leading to A230T.

Diagnosis, Treatment and Patient Outcomes:
Our patient was diagnosed with PAPA syndrome, a rare autoinflammatory disorder characterized by sterile, erosive arthritis, neutrophilic dermatosis, and cystic acne. As in our patient, the natural history is cutaneous features dominate and arthritis subsides during adolescence. Given its rarity, there are no adequate trials regarding treatment. Data has demonstrated that PSTPIP1 mutations result in dysregulated IL-1 production. Anakinra, a recombinant IL-1 receptor antagonist, has been effective, but requires daily subcutaneous injections. Data has also shown increased TNF-alpha production by stimulated PBMCs from patients, and there are cases where TNF-alpha inhibition has been successful. Our patient was treated with the TNF-alpha inhibitor adalimumab, resulting in clearing of acne and pyoderma gangrenosum lesions. Moreover, she has not developed any new pyoderma gangrenosum lesions, preseptal inflammation, or arthritis.
Case Title:
Successful Heart and Lung Transplantation in Common Variable Immunodeficiency

Summary and Lessons Learned:
The first case is a 60-year-old female with refractory cough, decreased total lung capacity and markedly decreased diffusion capacity on pulmonary function tests, diagnosed with interstitial lung disease of unknown etiology. Echocardiogram demonstrated left ventricular dilatation and severe dysfunction with restrictive diastolic filling and reduced ejection fraction. She was diagnosed with nonischemic cardiomyopathy secondary to probable viral etiology. Due to history of recurrent pneumonia, she was referred to the Allergy and Immunology Department for suspected immunodeficiency. IgG, IgA and IgM levels were all decreased and she was diagnosed with common variable immunodeficiency (CVID) and started on monthly intravenous immunoglobulin infusions (IVIG). Over the next four years she developed worsening congestive heart failure and underwent heart transplant.

The second case is a 38-year-old old male, previously diagnosed with non-specific interstitial pneumonia by lung biopsy. He had progressively worsening dyspnea and cough and steadily declining lung function measured by spirometry. Two years prior to presenting to the Allergy and Immunology Department, he developed recurrent pneumonia and worsening symptoms requiring intermittent use of supplemental oxygen. Due to frequency of infections, immunoglobulin levels were ordered and IgG and IgA were low. He was found to have low pneumococcal titers despite having received polyvalent pneumococcal vaccine 2 years prior and showed complete lack of response to booster vaccine. He was diagnosed with CVID and started on monthly IVIG. Although the frequency of infections decreased, his dyspnea drastically worsened over the following 6 months and he underwent successful bilateral lung transplant at the age of 42.

Following organ transplantation, both patients continue to receive monthly IVIG while on immunosuppressive therapy. Although their risk of infection is increased, neither patient has had any major infections, complications or hospitalizations following transplant. This case series was written with the intention of elucidating the potential complications that can arise from the diagnosis of the CVID and highlight the role of organ transplantation with this particular primary immunodeficiency. Very few cases of solid organ transplant associated with CVID have been reported in the literature. This case series suggests that organ failure may have been due to CVID. Despite treatment of CVID with IVIG, organ damage was irreversible but CVID did not preclude successful organ transplantation. These patients should be followed closely to determine their long term outcomes. Further research within the practice of Allergy and Immunology will be an essential tool in diagnosis and management of CVID associated with organ transplantation.

Patient Presentation and Testing:
In the case regarding the female who underwent heart transplant, she was referred to Allergy and Immunology Department for the evaluation of possible immune deficiency after 10 months of cough and dyspnea, following a pneumonia treated with multiple courses of antibiotics, inhalers and systemic steroids. Prior to her initial encounter, she had been evaluated by Pulmonary and Cardiology consults. Chest radiograph showed an interstitial pattern and pulmonary function tests revealed decreased total lung capacity (56%) and markedly decreased diffusion capacity (49%), and she was diagnosed with interstitial lung disease of unknown etiology. An echocardiogram demonstrated a severely dysfunctional and dilated left ventricle, restricted diastolic filling, and a reduced ejection fraction of 20%. Cardiology evaluation led to a diagnosis of nonischemic cardiomyopathy secondary to probable viral etiology. Her course was
complicated by coronary artery disease with stent placement in LAD artery, subsequent ventricular fibrillation with cardiac arrest during a hospitalization for pancreatitis requiring defibrillator (AICD) placement and recurrent pneumonia.

At the time of her initial encounter it was unclear if recurrent pneumonias were infectious or inflammatory in nature. If the etiology was infectious, immune deficiency was probable. If recurrent pneumonias were due to an inflammatory process, an autoimmune or vasculitic process was more likely. Her past medical history was only significant for partial colectomy secondary to diverticulosis and there was no history of recurrent infections prior to her onset of symptoms. Laboratory evaluation was ordered to help distinguish between an immune deficiency versus an autoimmune or vasculitic process, including complete blood count, inflammatory markers, metabolic chemistries, protein electrophoresis, immunoglobulin levels, total complement, rheumatoid factor, anti-nuclear antigen, cryoglobulin, hepatitis B surface antibody, hepatitis C antibody and anti-neutrophil cytoplasmic antibody. IgG, IgA and IgM levels were all decreased and remainder of laboratory workup was otherwise unremarkable. These findings suggested the recurrent pneumonias and cardiomyopathy were likely secondary to an immune deficiency, specifically CVID.

The second case described the male who received bilateral lung transplant and was referred to Allergy and Immunology Department for the evaluation of recurrent infections, with the prior diagnosis of non-specific interstitial pneumonia made 8 years prior by lung biopsy. Yearly pulmonary function tests demonstrated steadily declining lung function. He was referred to Rheumatology Department for an elevated rheumatoid factor and family history significant for a sister with juvenile idiopathic arthritis. He developed myalgias, daily low grade fevers and paresthesias raising suspicion of a connective tissue disease. His symptoms had significantly deteriorated over the previous year requiring supplemental oxygen and he was on immunosuppressant therapy with mycophenolate mofetil and prednisone. Due to recurrent upper respiratory tract infections, immunoglobulins were ordered by the Pulmonary Department. IgG and IgA levels were found to be decreased.

At his initial encounter, his recurrent respiratory infections were thought to be due to his underlying lung disease and/or use of immunosuppressant therapy. In order to evaluate for possible immune deficiency pneumococcal serotypes were ordered to measure response to polyvalent pneumococcal vaccine he had received 2 years prior. Serotypes were found to be low and he was given pneumococcal booster vaccine to which he showed complete lack of response. This confirmed the diagnosis of CVID as the etiology of recurrent infections.

Diagnosis, Treatment and Patient Outcomes:
In both cases, the patients were diagnosed with CVID by Allergy and Immunology Department after months of recurrent respiratory infections, and close follow up with multiple sub-specialists. Following the diagnosis of CVID, they were started on monthly IVIG therapy which reduced their infection rates. Despite this, both patients continued to have worsening organ function, requiring solid organ transplants. Since their transplants, the patients have been on immunosuppressive therapy, in addition to IVIG, and neither patient has had any major complication, infection or hospitalization. These cases highlight the delicate balance which must be achieved in the management of this unique subset of CVID patients: the use of IVIG to prevent infection/protect donor organs and immunosuppressive therapy to avoid graft versus host disease.
Case Title:
Monogenic cause of lupus requiring individualized treatment

Summary and Lessons Learned:
A case of a 12-year old male with developmental regression, progressive spastic quadriplegia and a history of multiple inflammatory and autoimmune disorders including Kawasaki Disease, idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia and monogenic lupus. There is a strong family history of autoimmune diseases; Mother has ulcerative colitis, spondyloarthritis, eczema, and autoimmune thyroiditis. His progressive CNS changes and the diagnosis of monogenic lupus prompted the investigation for an interferonopathy as numerous autoinflammatory syndromes are now known to be due to excessive interferon production. His particular presentation was suggestive of Aicardi-Goutières Syndrome (AGS). A AGS gene panel demonstrated a ADAR mutation indicating his diagnosis is AGS with a ADAR mutation. This gene events degradation of double stranded RNA causing an anti-viral RNA-like interferon response and autoimmunity. This case demonstrates the importance of considering monogenic immune dysregulatory disorders and early investigations to improve patient care.

Patient Presentation and Testing:
Patient at 14 months of age had regression of motor and verbal skills, he was diagnosed with cerebral palsy. At 2 years of age he had Kawasaki with coronary involvement. Between 2 and 5 years of age he had pneumonia 4 times, 3 times required IV antibiotics. At 5 years old he had idiopathic thrombocytopenic purpura and at 10 years of age influenza virus induced autoimmune hemolytic anemia. At 12 years of age he was diagnosed with systemic lupus erythematosus (SLE): active, Class IV diffuse, global proliferative lupus nephritis, chilblain lupus and seizures. A cat scan of his brain showed bilateral periventricular calcification and calcification in the frontal cortex. His investigations demonstrated polyclonal hypergammaglobulinemia on immunofixation. Vaccine-specific ab production was impaired to measles, rubella vaccines after MMRV booster and pneumococcal after Prevnair 13. Chronic COOMBS positivity. Lymphocyte subsets are normal by immune phenotyping, with elevated 3% of double negative T cells (CD4-/8-/αβ TCR). Repeatedly borderline low naïve T cell production (CD4/45/RA 55%) and of early thymic emigrant cells (CD4+/45RA/CD31 23%). Good lymphocyte proliferation response to mitogens, anti-CD3 and in mixed lymphocyte culture. Genetic testing showed a normal karyotype. NGS panel for 180 PID-related genes: Likely pathogenic variance in 3 genes: NOD2, NLRP3 and NCF2 which all may contribute to an increased risk of autoimmune disease.

Array CGH ruled out big deletions/homozygosity. His presentation of developmental regression and monogenic lupus prompted a Aicardi-Goutières syndrome NGS gene panel at Fulgent (incl. only TREX1, SAMHD1, RNASEH2C, RNASEH2B, RNASEH2A) neg. Single gene testing at Fulgent: ADAR: pathogenic heterozygous variant c.3019G>A(p.Gly1007Arg). This was a de novo mutation as his parents do not carry variant.

Diagnosis, Treatment and Patient Outcomes:
Current treatment includes prednisone and mycophenolate which is standard treatment for lupus, however, there has been no remission
of lupus nephritis. Improvement was seen after starting 1g/kg of IVIG monthly, there was no protocol but was tried as standard treatment was ineffective. The ADAR mutation causes a amplified interferon response, targeted therapy against the interferon receptor signaling molecule JAK1/2 is the current treatment of choice. Our patient will start JAX1/2 inhibitor once funding is secured, this will occur in the next month.
Case Title:
Skin Ulcers procreating Hypopigmented lesions and Failure to Thrive: An unusual presentation of Ataxic Telangiectasia case.

Summary and Lessons Learned:
Ataxia Telangiectasia (AT) is a progressive neurological disease with possible wide variability in presentation. Including a panel of lymphopenia, an investigation can clinch the diagnosis of AT and might be life-saving.

Patient Presentation and Testing:
A 4-year-old Pakistani female, the birth of a first degree consanguineous marriage, presented with generalized vesicular rash mainly on the abdomen and scalp which eventually became ulcers procreating residual hypopigmented lesions. The patient also presented with chronic diarrhea, short stature, failure to thrive (Weight and height < 5th percentile). There was no previous infection or family history of primary immunodeficiency diseases (PID). As for development, the patient was meeting milestones except for a mild delay in speech. Immunizations were up-to-date including bacille Calmette-Guerin (BCG). On physical examination, the patient has had mild ocular telangiectasia but no cutaneous involvement. Investigations revealed lymphopenia (1.6 109 cells/liter) and eosinophilia. As part of the diarrhea workup duodenoscopy revealed subtotal villous atrophy. Biomarkers for celiac disease were negative. Immune system workup: high IgG, normal IgA, IgE and IgM. IgG Subclasses: low IgG 2, and 3 , antibody titers to Haemophilus Influenza and Pneumococcus vaccine were low. Lymphocyte subsets showed low CD4, CD19 and high NK cells (40%), low naïve T cells (2%) and inverted CD4/CD8 ratio. T cell function with post phytohaemagglutinin (PHA) was 18.7% but with normal response to CD3. Alfa Feto Protein was requested due to the continued low CD4, level was high: 260.9 IU/ml.

Diagnosis, Treatment and Patient Outcomes:
Next Generation Sequencing (NGS) showed homozygous mutation for Trp1750fs in chromosome 11 of ATM gene confirmed by whole exome sequencing. Intravenous immunoglobulins (IVIG) were administered and diarrhea, lesions, and growth improved.
**Case Title:**
Skin Ulcers procreating Hypopigmented lesions and Failure to Thrive: An unusual presentation of Ataxic Telangiectasia case.

**Summary and Lessons Learned:**
Ataxia Telangiectasia (AT) is a progressive neurological disease with possible wide variability in presentation. Including a panel of lymphopenia investigation can clinch the diagnosis of AT and might be lifesaving.

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**Diagnosis, Treatment and Patient Outcomes:**
Next Generation Sequencing (NGS) showed homozygous mutation for Trp1750fs in chromosome 11 of ATM gene confirmed by whole exome sequencing. Intravenous immunoglobulins (IVIG) were administered and diarrhea, lesions and growth improved.
Case Title:
CGD due to absent p47phox expression without pathogenic exonic mutations in NCF1

Summary and Lessons Learned:
A 4-year-old female was referred for evaluation of a chronic right cervical fistula since age 1 and chronic diarrhea. She had a prior history of left inguinal lymphadenitis. Physical examination revealed a draining fistula at the base of the neck, diffuse cervical lymphadenopathy and 2 healed inguinal scars. Laboratory evaluation included a normal CBC with differential, quantitative immunoglobulins and lymphocyte subsets. Dihydrorhodamine (DHR) assay demonstrated a greatly reduced, but not absent respiratory burst. Cultures of the draining fistula yielded skin flora. MRI demonstrated a right cervical fistula connecting with a retropharyngeal phlegmon. Colonoscopy revealed mild inflammatory bowel disease.

Based on the result of the DHR assay, the patient was diagnosed with Chronic Granulomatous Disease. She was started on antibiotics and low dose corticosteroids. The patient had a complete resolution of the fistula and diarrhea. She is currently undergoing reduced intensity conditioning in preparation for hematopoietic stem cell transplantation (HSCT). DNA sequencing of CYBA (encodes p22phox), NCF1 (encodes p47 phox), and NCF2 gene (encodes p67 phox), which is >99% sensitive in delineating known autosomal recessive (AR) causes of CGD, did not reveal pathogenic mutations. There are reported rare cases of CGD in which DNA sequencing does not reveal pathogenic mutations but protein expression of one of the subunits of the NADPH oxidase complex is abnormal. Consequently, Western blot analysis of p22phox, p47phox and p67phox demonstrated undetectable p47phox expression, confirming the diagnosis of CGD. CGD is a primary immunodeficiency due to pathogenic mutations in one of the subunits of NADPH oxidase, which is responsible for the respiratory burst in monocytes and neutrophils. In the absence of a respiratory burst, phagocytic cells are unable to kill catalase positive bacteria and fungi leading to recurrent pyogenic infections. 65% of CGD is due to pathogenic mutations in the CYBB (encodes p91 phox) gene, which is the cause of X-linked CGD. The AR forms of CGD are due to pathogenic mutations in one of three other genes encoding subunits of NADPH oxidase: NCF1, NCF2 and CYBA.

It is a unique and rare case because the patient presented with classic CGD with an abnormal DHR assay, DNA sequencing for all of the autosomal recessive CGD variants was negative, yet Western blot analysis of the NADPH oxidase complex revealed absent p47 phox expression. We speculate that her mutation is likely in one of the regulatory genes (such as the promoter region) which is quite unusual.

Patient Presentation and Testing:
A 4-year-old Chinese female, adopted and brought to the United States at age 3, was referred for evaluation of a chronic right cervical fistula since age 1 and chronic diarrhea. She had a prior history of left inguinal lymphadenitis and chronic diarrhea. Family history and vaccination history were unknown. Physical examination at the time of arrival revealed a draining fistula at the base of the right neck, diffuse cervical lymphadenopathy and 2 healed scars in the left inguinal region.
Based on the clinical presentation, chronic granulomatous disease (CGD) was felt to be the most likely diagnosis. However, in the absence of culture data, chronic mycobacterial infection due to defects in the IL-12/IFN-γ pathway (Mendelian susceptibility to mycobacterial disease) was also high in the differential diagnosis. Other considerations included other defects in neutrophils as well as combined immunodeficiencies.

Laboratory evaluation included a normal CBC with differential, quantitative immunoglobulins and lymphocyte subsets. The expression of IFNGR1 and IL-12RB1 receptors and IFN-γ-induced STAT1 phosphorylation were normal by flow cytometry. Dihydrorhodamine (DHR) assay demonstrated a greatly reduced, but not absent respiratory burst. Cultures of the draining fistula yielded skin flora. MRI demonstrated a right cervical fistula connecting with a retropharyngeal phlegmon. Colonoscopy revealed mild inflammatory bowel disease.

Based on the result of the DHR assay, the patient was diagnosed with CGD. Subsequently, DNA sequencing of CYBA (encodes p22pohox), NCF1 (encodes p47 phox), and NCF2 gene (encodes p67 phox), which is >99% sensitive in delineating known autosomal recessive (AR) causes of GCD (GeneDx), did not reveal pathogenic mutations. There are reported rare cases of CGD in which DNA sequencing does not reveal pathogenic mutations but protein expression of one of the subunits of the NADPH oxidase complex is abnormal. Consequently, Western blot analysis of p22phox, p47phox and p67phox was performed and demonstrated undetectable p47phox expression, confirming the diagnosis of CGD.

**Diagnosis, Treatment and Patient Outcomes:**

Dihydrorhodamine (DHR) assay demonstrated a greatly reduced, but not absent respiratory burst. Based on the result of the DHR assay, the patient was diagnosed with CGD and started on empiric antibiotics (ciprofloxacin and clindamycin), prophylactic trimethoprim-sulfamethoxazole and itraconazole and low dose corticosteroids. The patient had a complete resolution of the fistula and diarrhea. She is currently undergoing reduced intensity conditioning in preparation for hematopoietic stem cell transplantation (HSCT).

CGD is a primary immunodeficiency due to pathogenic mutations in one of the subunits of NADPH oxidase, which is responsible for the respiratory burst in monocytes and neutrophils. In the absence of a respiratory burst, phagocytic cells are unable to kill catalase positive bacteria and fungi leading to recurrent pyogenic infections. Approximately 65% of CGD is due to pathogenic mutations in the CYBB (encodes p91 phox) gene, which is the cause of X-linked CGD. The autosomal recessive (AR) CGD forms of CGD are due to pathogenic mutations in one of the three other genes encoding subunits of NADPH oxidase: NCF1, NCF2 and CYBA. Of these, mutations in NCF1 (p47) account for 25% of CGD, and NCF2 (p67) and CYBA (p22) account for 5% of CGD each. The c75_76delGT pathogenic variant is the most common cause of autosomal recessive CGD and accounts for >95% of NCF1 gene pathogenic variants (Noack et al., 2001). AR forms of CGD tend to have a milder course of disease due to hypomorphic mutations in the causative genes leading to residual NADPH oxidase function, which was seen in this case. In contrast, mutations in CYBB are usually null leading to absent NADPH oxidase activity and a more severe phenotype. Apart from increased infections, CGD is also characterized by a dysregulated inflammatory response, which leads to poor wound healing and propensity for inflammatory bowel disease. Glucocorticoid therapy can be useful in these situations and was beneficial in the treatment of both the fistula and inflammatory bowel disease in this case.

The optimal treatment of CGD has undergone significant changes in the last decade. In the past, prophylaxis with antimicrobials (trimethoprim-sulfamethoxazole, itraconazole) in conjunction with IFN-γ was the predominant therapy. However, there has been significant advances in the outcomes of HSCT for CGD and HSCT is the currently the recommended treatment if a well-matched HLA donor is identified.
Recent diagnosis of common variable immunodeficiency syndrome in a teenager years after Mycoplasma encephalitis

Summary and Lessons Learned:
Common variable immunodeficiency (CVID) is a heterogeneous group of disorders, leading to recurrent and often severe bacterial infections. Primary antibody deficiency syndromes and CVID are the most common immunodeficiency in all age groups. Here we present 17 year old male with combined immunodeficiency whose diagnosis was made 6 years after mycoplasma encephalitis.

17-year-old male presented to PID clinic with history of recurrent upper and lower respiratory infections. He had complex past medical history of intractable focal onset epilepsy, swallow dysfunction and anger disorder which began in February 2011 after encephalitis secondary to mycoplasma infection. On presentation, Immunoglobin (Ig) levels were all decreased. The specific levels included: IgA and IgE were not detectable, IgG was 166 mg/dL (694–1618 mg/dL), IgM was 6 mg/dL (48–271 mg/dL). Absolute cell counts of CD19 and CD4 (both memory and naïve subsets) were all low. CD19 count was 26 cells/mL, CD4 count was 400 cells/mL. He also had absent pneumococcal (in 14/14 serotypes) and tetanus antibody titers.

The diagnosis of combined immunodeficiency was made and the patient was started on subcutaneous immunoglobulin therapy. Few months after treatment he had significant clinical improvement.

Here we describe a 17-year old boy, who presented with severe complications of mycoplasma encephalitis at age 11 secondary to undiagnosed combined immunodeficiency at the time of presentation. His significant past medical history and recurrent infections led to the diagnosis of combined immunodeficiency. Most of the cases with antibody deficiency present with recurrent bacterial infections. This case report illustrates the importance of considering an underlying immune deficiency in patients with severe or recurrent infections regardless of their age. Early diagnosis and therapy are essential to prevent long term morbidity and mortality in patients with immunodeficiency.

Patient Presentation and Testing:
The 17-year-old male presented to UNM Pediatric Immunodeficiency Clinic with recurrent episodes of pneumonia, throat infections and upper respiratory infections. He reported that he has been very tired many years now. His past medical history was significant for history of encephalitis and intractable focal onset epilepsy, which began in February 2011 after acute febrile illness. At that time, he was diagnosed with mycoplasma encephalitis.

Family history was negative for immunodeficiency diseases.
Patient was evaluated at primary immunodeficiency clinic due to history of recurrent sinopulmonary infections and mycoplasma encephalitis. Screening tests of serum immunoglobulins showed decreased concentrations of four types of immunoglobulins: IgA< 7 mg/dL, IgM=6 mg/dL, IgG=166 mg/dL, IgE< Intl_Unit/mL. Lymphocyte immunophenotyping revealed CD19 absolute count of 52 cells/µL, CD4+ T cell count of 400 cells/µL. He also had absent tetanus and pneumococcal IgG titers. No evidence of genetic defects was established.

As he carried very high risk for severe infections due to lack of immunoglobulins and immune cells, we initiated treatment with IgG replacement therapy.

Diagnosis, Treatment and Patient Outcomes:
The diagnosis of CVID was made and the patient was started on IgG replacement therapy with subcutaneous immunoglobulin at four weekly intervals at dosage of 500 mg/kg. Four months later, the patient was free of infection and the IgG level was consistently higher than 800 mg/dL.
Genetic testing for multiple mutations causing CVID and agammaglobulinemia including BTK gene were negative. Whole exome sequencing data is still pending. The patient is followed at Immunodeficiency Center clinic every 3 months and screened for complications of CVID periodically.
Summary and Lessons Learned:
We present the case of a previously healthy 19yo female, who was first diagnosed with EBV-associated lymphoproliferative disease in October 2015 following excisional biopsy of an enlarged and tender supraclavicular lymph node. Over the next 1.5 years, she underwent biopsies of her lung, appendix and lacrimal duct, which all demonstrated EBV-associated lymphoproliferative disorder. She developed new rapidly enlarging pre-auricular lymphadenopathy in July 2017 demonstrating B-cell lymphoma with morphological features of marginal zone lymphoma, likely secondary to EBV infection. Her exam is notable for height of 56 inches, 8 inches below her expected mid-parental height, along with fine slow-growing hair and prior history of alopecia. Immune studies were notable for mild lymphopenia with genetic testing revealing a pathogenic variant and a novel mutation leading to RNA changes in the RMRP gene, consistent with cartilage-hair hypoplasia (CHH). CHH is a rare autosomal recessive condition characterized by metaphyseal dysplasia, bone marrow failure, increased risk of hematologic malignancy and variable immune deficiency, with increased susceptibility to pathogens that are typically cleared by T- and NK-cell mediated mechanisms including varicella, EBV and HHV-6. CHH presents with a wide range of phenotypic variability, even within the same family, however 100% of patients present with disproportionate short-limb short stature, 88% of patients demonstrate impaired lymphocyte proliferation and T-cell function with 35-65% demonstrating infections in infancy and early childhood and about 5-10% developing neoplasms, including lymphoma and leukemia. As a child, our patient demonstrated short stature (<1% for age) and fine hair, however lacked recurrent infections concerning for a combined immunodeficiency, which likely led to her delayed diagnosis. Her EBV-driven lymphoproliferation raised new concerns for a primary immunodeficiency leading to cytotoxic cell dysfunction and inability to clear EBV. Differential includes syndromes associated with lymphoproliferation including MST-1 deficiency, ITK deficiency and CD27 deficiency. Treatment for CHH is based largely on the phenotypic presentation, however the immunodeficiency aspect is variable and little data exists regarding the immune function of CHH patients as they enter adulthood. BMT/HSCT in children has resulted in normalization of T-cell numbers and function and resolution of autoimmune manifestations, with reported survival rates ranging between 60-80% depending on donor match. There is little data or specific recommendations for management of associated malignancies, though poor prognosis has been reported in patients with non-Hodgkin lymphoma, even with conventional cytotoxic protocols.

Patient Presentation and Testing:
We present the case of a 19yo female of mixed Hispanic/Italian heritage who presents for evaluation at our clinic. Mother describes a routine pregnancy and delivery and patient was otherwise healthy during childhood, aside from Varicella infection at age 9mo (did not require hospitalization) and now-resolved alopecia. While mother did state that patient caught infections “more easily” than her siblings, she had no reported history of recurrent otitis media, sinusitis, diarrheal illnesses, thrush or skin infections as a child. As she approached her teenage years, she received outpatient treatment for several illnesses including E. coli UTI treated with Bactrim in December 2010, right lower lobe pneumonia in August 2012 requiring 5 day course of azithromycin followed by a 10 day course of amoxicillin due to persistent symptoms and clinical findings of left lower lobe pneumonia on subsequent exam as well as an atypical pneumonia with hazy left infiltrate in January 2014, which resolved with another course of azithromycin. She was first noted to have cervical lymphadenopathy in March 2014, with reassuring lab workup at that time, including CBC, ESR, CRP and Heterophile antibodies. Lymphadenopathy resolved, however she developed a tender mass near her left clavicle in October 2015. Labs at that time including LDH, Uric acid, Bartonella and Cocci serologies were negative.
She underwent fine needle aspiration with subsequent supraclavicular lymph node excisional biopsy in October 2015, which demonstrated atypical EBV-associated lymphoproliferative disorder. Follow up PET scan in November 2015 demonstrated areas of abnormal uptake including a 23mmx18mm mass in her left lower lobe, R posterior rib, 8mm substernal lymph node, a 15mmx15mm mass near her stomach and 18mmx13mm area near her right mid-pelvis. In December 2015, she was noted to have a positive EBV PCR. She had a mucocele appendectomy in January 2016, which pathology revealed IGH and IGK positivity consistent with a B-cell clonal process in one biopsy and IGH+ in the second biopsy, which was overall consistent with EBV-associated lymphoproliferative disorder. In February 2016, she underwent IR guided biopsy of her left lower lobe mass, again demonstrating atypical EBV-positive lymphoproliferation. EBV PCR was negative in March 2016. She was well in the interim, receiving Tamiflu in December 2016 for presumed flu. In April 2017, she developed a conjunctival lesion in her right eye. MRI revealed enlargement of the right lacrimal gland with associated focal nodular enhancement and biopsy of the lesion in May 2017 was again consistent with EBV-associated lymphoproliferative disorder. Repeat HIV and EBV PCR were negative at that time. She developed new, rapidly enlarging left pre-auricular lymphadenopathy, with excisional biopsy in July 2017 revealing B-cell lymphoma with morphologic features of marginal zone lymphoma. Most recent EBV titers in July 2017 were consistent with past infection, though she was noted to have active viremia, with elevated EBV DNA PCR in both July and August 2017. Of note, her physical exam is notable for height of 56 inches (mid parental height estimate 64 inches) and she is the shortest of her siblings. She also has fine hair that is slow growing, having received only 3 haircuts in her lifetime. Prior immune workup was notable for decreased pneumococcal titers (revaccination records unavailable) with normal diphtheria and tetanus titers. Prior subsets with mildly decreased CD3, CD4 and CD19 counts. ITK sequencing was also obtained given history of lymphoproliferative disorder, and was normal. As part of our workup, repeat immunoglobulins, lymphocyte proliferation studies, vaccine titers, inflammatory markers, B-cell phenotyping and genetic panel for immunodeficiency was obtained.

**Diagnosis, Treatment and Patient Outcomes:**

Lab workup was significant for T-cell (Cd3 719, CD4 352, CD8 347) and CD19+ B-cell (41) lymphopenia and normal immunoglobulin subsets along with elevated ESR (25). HIV testing was negative. Lymphocyte proliferation studies and vaccine titers were pending at time of submission. Gene panel was significant for a pathogenic variant change in n.147G>A (RNA change) along with a novel mutation at n.257_266 deletion (RNA change) of the RMRP gene, consistent with cartilage-hair hypoplasia (CHH). She recently underwent bone marrow biopsy (results pending at submission) and is currently being evaluated for chemotherapy treatment (rituximab monotherapy or bendamustine-rituximab) vs RCHOP as treatment for her stage 1 marginal zone lymphoma along with consideration for bone marrow transplantation given her new diagnosis of CHH.
A Rare Case of Acute Mastoiditis causing Meningitis

Summary and Lessons Learned:
Introduction: Acute mastoiditis, which is usually seen in children is a rare occurrence in adults. While acute otitis media complications have declined due to antibiotic use, complications can be fatal. According to studies at two hospitals done in Sweden, 3 out of 42 patients with acute otitis media were adults. Symptomatic mastoiditis is an infrequent complication of both acute and chronic otitis media but can be serious due to the proximity of the mastoid to the posterior cranial fossa, lateral sinuses, semicircular canals, facial nerve canal, and the petrous tip of the temporal bone. Otitic meningitis, although the most common complication of chronic otitis media, is an uncommon occurrence in acute otitis media and mastoiditis.

Patient Presentation and Testing:
We report a case of 33-year-old male with recent past medical history of sinus congestion, recurrent sinusitis, and acute otitis media. He was admitted after he developed acute mastoiditis complicated with meningitis. Symptoms included severe headache, fevers, photophobia, altered mental status, rhinorrhea, and right ear pain. Lumbar puncture was notable for WBC 17,619, PMN 88% with negative CSF culture. CT of the Orbital/ Sella/ Posterior Fossa confirmed mastoiditis and MRI of the brain showed right mastoiditis with underlying abscess and diffuse leptomeningeal enhancement concerning for meningitis. Patient underwent mastoidectomy and tymphanostomy tube placement with ENT. Ear culture was remarkable for Klebsiella, but blood cultures were negative. He was managed aggressively and successfully with antibiotics and fluids.

Diagnosis, Treatment and Patient Outcomes:
Discussion: Although mastoiditis is associated with a spectrum of disease, meningitis associated with acute otitis and mastoiditis is a rare complication. Most acute mastoiditis cases occur in children but have dramatically declined with the routine use of antibiotics. In adult cases, it has been linked to prior cranial surgery. Mastoiditis generally presents with fever, posterior ear pain, and edema of the pinna. The dangerous consequence of mastoiditis is otitis meningitis presenting with fever, neck pain, photophobia and mental status changes. CT scan should always be performed when mastoiditis is suspected, with an MRI if there is concern for intracranial processes. It is imperative to start IV antibiotics early. Prompt recognition and treatment is critical, which can involve IV antibiotics and if necessary mastoidectomy for debridement of necrotic bone. Common organisms can be S. pneumoniaiae and Haemophilus influenza for acute mastoiditis and S. aureus, Pseudomonas, and enteric Gram-negative rods for chronic otitis media. As antibiotics have improved overtime, the aggressive complications of acute otitis media have declined. Very few cases of adult otitis media have been reported. Primary care physicians, hospitalists in consultation with ear nose throat specialists need to be cautious so as not to miss this potentially fatal complication of acute otitis media. It should also prompt physicians to look for immune deficiencies and allergy related causes in patients with recurrent disease.
Case Title:
An Uncommon Case of Common Variable Immunodeficiency

Summary and Lessons Learned:
A 40 year old male with a history of infections since childhood, autoimmune disorders, and hematologic dyscrasias was referred to Allergy Immunology to evaluate for Common Variable Immunodeficiency (CVID). Our patient was noted to have borderline low IgG levels, protective protein vaccine titers and a recent diagnosis of insulin dependent diabetes mellitus (IDDM), all findings that are not generally associated with CVID. Approximately 25 percent of people with CVID have an autoimmune disorder. A review of the literature showed that CVID patients with autoimmune disorders tend to have immunoglobulin levels that are closer to normal. The literature also revealed that a total of 5 CVID patients have been reported to have IDDM, the oldest of which was 31 years of age. Our patient adds to the literature, further associating CVID and IDDM.

Patient Presentation and Testing:
The initial interview with our patient revealed that he was evaluated for cystic fibrosis as a child, presumably due to a history of recurrent infections. In his late teens, our patient was diagnosed with alopecia universalis, an autoimmune disorder that is more commonly associated with CVID. During an overseas deployment in his fourth decade of life, our patient was diagnosed with two lobar pneumonias and revealed that he suffered from significant symptoms of gastroenteropathy nearly that entire time. The immunology work up showed consistently low IgA and IgM levels with a very poor response to the PPSV23 vaccine. The persistent finding of leukopenia and thrombocytopenia was also noted.

Diagnosis, Treatment and Patient Outcomes:
Given the borderline low IgG, low IgA and IgM levels, a history of recurrent bacterial infections, multiple autoimmune disorders, hematologic dyscrasias and a poor response to a polysaccharide vaccine, a diagnosis of CVID was established. After the diagnosis was made, monthly IVIG infusions were initiated which have thus far resulted in a better overall energy level for the patient while keeping him free of any serious infections.
A patient with GATA-2 deficiency presenting with pancytopenia, vasculitis and fever of unknown origin

Summary and Lessons Learned:
GATA2 deficiency is a primary immunodeficiency that may present heterogeneously with infections, myelodysplasia, autoimmune disease, or leukemia. It presents most often in adolescence and early adulthood, and may require coordinated evaluation by multiple subspecialists for diagnosis. Haploinsufficiency with heterozygous mutations cause disease with autosomal dominant inheritance, similar to other diseases conferred by transcription factor mutations. The presence of monocytemia in a young adult with myelodysplasia and chronic viral infections or nontuberculous mycobacterial infection is concerning for GATA-2 deficiency. NTM infections in GATA-2 deficiency are relatively common and require a high index of suspicion. M. kansasii infection may cause false positive PPD and negative IGRA in the setting of pulmonary symptoms. Bone marrow transplant and genetic testing of siblings is indicated in severe deficiencies.

Patient Presentation and Testing:
A 20 year old Caucasian-Filipino female was admitted from Heme clinic after presenting with a history of EBV mononucleosis a year ago, a persistent rash since, and pancytopenia and fever of unknown origin of 5 months duration. She was admitted to an outside hospital 5 months ago for fever and pancytopenia; after bone marrow biopsy and mediastinal lymph node aspirate she had been diagnosed with pulmonary and bone marrow sarcoid and started on prednisone 40 mg daily without improvement in her symptoms. She continued to decline and require transfusions in spite of prednisone, then was admitted 3 months ago with fever and treated with IV antibiotics. Prior to her clinic appointment she developed epistaxis, oral ulcers, thrush, and 17 pound unintentional weight loss in the setting of drenching night sweats. She was admitted to UAB, where she briefly required ICU care for uncontrolled epistaxis with hemorrhagic shock in the setting of thrombocytopenia. She was started empirically on RIPE therapy for LTBI (PPD 12 mm and negative IGRA). She underwent mediastinoscopy for evaluation of pulmonary adenopathy and a small pleural effusion; mediastinal lymph node biopsy contained extensive necrosis and nonspecific inflammation. Her skin biopsy demonstrated medium vessel vasculitis. She was found to be pancytopenic with hypocellular bone marrow with dysplastic changes with reduced numbers of hematogones (CD10+CD20+) and atypical megakaryocytes. Circulating B cells, NK cells, and monocytes were reduced. She had hypergammaglobulinemia with normal vaccine responses. Due to NK cell deficiency, monocyte deficiency, and dysplastic changes with reduced CD10+CD20+ hematogones she underwent genetic testing of her bone marrow, with findings of a novel variant in GATA-2 (c.1024_1025insGCCG; p.A342Gfs*43) causing a frameshift mutation with an early stop codon.

Diagnosis, Treatment and Patient Outcomes:
This patient was diagnosed with GATA-2 deficiency based on her genetic testing and flow cytometry results. Throughout her hospitalization she required multiple transfusions of blood products, and had a recurrence of epistaxis requiring transfusions. She was started on empiric RIPE therapy in the setting of lymphadenopathy and B symptoms; although her cultures and PCR from skin and lung biopsies were negative for TB she continued on empiric M. kansasii treatment with ethambutol/rifampin/azithromycin after conferring with Dr. Holland (NIH). She had been treated with anakinra for HLH while inpatient but this was discontinued due to neutropenia and a maximal ferritin level of 1850. She was referred to the NIH for evaluation and has undergone bone marrow transplant. Her sisters will undergo genetic testing for her GATA-2 mutation, as one has pulmonary infections and the other has recurrent epistaxis.
Schimke Immuno-Osseous Dysplasia (SIOD) is an autosomal recessive disorder caused by biallelic mutations in the SMARCAL1 gene (SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily A-like protein 1). The clinical phenotype includes T-cell immunodeficiency, early-onset nephropathy progressing to renal failure, spondyloepiphyseal dysplasia, and vasculopathy. We evaluated telomere length at the single-cell level in two siblings with SIOD and found remarkably reduced telomere length in their circulating T cells. Although recent studies using cell lines manipulated to have SMARCAL1 deficiency associate SMARCAL1 deficiency with telomere damage,(1) this is the first evaluation of whether telomere abnormalities occur in patients with SIOD.

In both patients, prior SMARCAL1 sequencing revealed three variants: c.[395_411del;416dup], p.[Glu132Alafs*5;Leu139Phefs*4], and c.[2459G>A p.Arg820His]. Parental SMARCAL1 gene analysis confirmed biallelic involvement. Patient 1 presented at three-years-old with height less than the first percentile, T-cell lymphopenia (absolute CD3 count of 346/µL, CD45RA+ count of 108/µL, CD45RO+ count of 97/µL), hypertension, proteinuria, hypercholesterolemia, recurrent otitis media and respiratory infections including one pneumonia. Patient 2, the younger sibling, presented at two-years-old with milder disease including height at the fifth percentile for age and T-cell lymphopenia (absolute CD3 count of 731/µL, CD45RA+ count of 323µL, CD45RO+ count of 170/µL). Due to progressive nephrotic syndrome, Patient 1 underwent renal transplant evaluation and both patients underwent hematopoietic stem cell transplant (HSCT) evaluation. We pursued telomere length analysis because the results could impact the HSCT conditioning regimen; non-myeloablative and reduced intensity conditioning has been used in patients with Dyskeratosis congenita, a disease of impaired telomere maintenance.(2) Additionally, we wanted to determine whether telomere defects occur in patients with SIOD.

Patient samples were analyzed at Repeat Diagnostics via a CLIA-approved Flow-FISH telomere length assay. Mean telomere length was measured in lymphocytes, CD45RA+ T-cells, CD45RO+ T-cells, CD20 cells, and CD57 cells (mainly NK cells) and compared to age-matched controls. Despite differing in their disease severity, both patients had mean telomere lengths less than the first percentile and more than two standard deviations below the mean in all measured lymphocyte subsets. These findings are significant as they support the notion of a telomere replication defect in SIOD lymphocytes. To date, neither patient has received a stem cell transplant. However, we are currently investigating the role of telomere replication in SIOD. This area of research could present possible new therapies in SIOD. For example, patients with Dyskeratosis Congenita had telomere elongation in circulating leukocytes with danazol therapy.(3)

References:
1. Poole, LA et al. SMARCAL1 maintains telomere integrity during DNA replication. Proc Natl Acad Sci U S A 2015; 112 (48): 14864-9
Expanding the clinical phenotype of chronic granulomatous disease (CGD): a female patient with a de novo mutation in CYBB

Summary and Lessons Learned:
A 16-year-old female was referred for an autoinflammatory disorder with a history of various cutaneous manifestations, most notably pyoderma gangrenosum, hidradenitis suppurativa, and scarring acne. Lesional cultures were negative. Her history seemed most suggestive of pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome. She was empirically treated with the TNF inhibitor adalimumab. Shortly after, she developed a cutaneous ulcer infected with Serratia marascens. She died of complications from Providencia stuartii sepsis and macrophage activation syndrome (MAS).
PSTPIP1 sequencing for PAPA syndrome was negative. Whole exome sequencing (WES) identified a novel mutation in the X-linked CGD-causing gene CYBB. Functional experiments demonstrated extremely skewed X-chromosome inactivation.
We have identified a female patient with a potentially lethal X-linked mutation in CYBB and confirmed the immunodeficiency. Our case expands the spectrum of symptoms associated with CGD to include severe neutrophilic dermatoses, which was misleading the clinical diagnosis. Our case adds to prior observations that TNF inhibition is not beneficial in CGD.

Patient Presentation and Testing:
A 16-year-old female presented with an 8-year history of mucocutaneous manifestations, including pustular scalp psoriasis, pyoderma gangrenosum, hidradenitis suppurativa, scarring acne, oral ulcers, recurrent hordeolum and chalazion, and pustules of the nose and fingertips. Her lesions were steroid-responsive. Previous therapy included methotrexate and the TNF inhibitor etanercept without response or adverse effects. She briefly tried the TNF inhibitor adalimumab also without adverse effects. Her medical history, including a thorough infectious work-up, was otherwise unremarkable. Family history was negative. Her phenotype was most consistent with PAPA syndrome. She was tested for mutations in two exons of the PSTPIP1 gene associated with PAPA and tested negative. Her DNA sample was submitted for WES to identify a possible disease-causing gene. She was not expected to have an X-linked disease. WES analysis confirmed an unexpected diagnosis of CGD. Functional experiments shed light on an unusual mechanism of her disease due to skewed X-linked inactivation.

Diagnosis, Treatment and Patient Outcomes:
After ~2 months on adalimumab, our patient developed fever and malodorous drainage from a leg ulcer. Cultures isolated Serratia marascens. Shortly after, she died of complications from Providencia stuartii sepsis, MAS, and multi-organ failure.
Analysis of WES data revealed a novel mutation in the X-linked CGD-causing gene CYBB (c.935T>G, p.M312R). Her mother and two unaffected siblings did not carry this mutation. Although we were unable to evaluate NADPH oxidase activity, the mutation is presumed pathogenic since it occurs in a domain where all previously identified missense mutations have been pathologic in X-linked CGD.
Cutaneous granulomas are common clinical finding in certain primary immunodeficiency (PID) one defect recently described is associated with PLAID (PLCG2 associated antibody deficiency and immune dysregulation) was discovered after investigating a patient who had diffuse granulomatous dermatitis which gradually worsened from birth. We present a male patient who started at 2 months that disseminated dermatosis that fades to the finger pressure in the perioral region, back of hands, side of arms, scrotum and soles of the feet; some small pustules with fine whitish scales on the surface can be observed; pathology discards the diagnosis of histiocytosis since a marked inflammatory dermatitis with mixed infiltrate (eosinophils, neutrophils, lymphocytes, histiocytes and plasma cells) and significant edema in the dermis was observed. The Wartin-Starry staining revealed negative conjunctival erythema assessed by ophthalmology without alterations.

At 4 months of persistent lesions in the skin, a biopsy of left forearm skin demonstrating "chronic non-caseiform granulomatous dermatitis" showed numerous histiocytes grouped in granulomatous forms without, some of them with giant-cell forms associated with discrete lymphocytic infiltrate, without evidence of vasculitis, with staining for negative microorganisms. The studies revealed neutropenia 1000 / mm3, with the presence of hypogammaglobulinemia: IgG 113mg/dL (p3 = 338), IgM 6.58 mg/dL (p3 = 25), IgA <6.7 mg/dL, normal complement level c3 127, c4 15, ANA and ANCA negative. Lymphocyte subpopulations: LT 5610 cells x mm3 (3000-5000), CD3+ 5386 cells x mm3, CD4+ 4264 cells x mm3 (2800-3900), CD8+1066 (350-2200), CD19+ 122 cells x mm3 (430-3300), CD16+56+ 122 cells x mm3 (220-720). US in both hips in which it is observed that it presents lack of development of the acetabular posterior wall.

As a result of the suspicion of Blau syndrome with the persistence of skin granulomas, treatment with Infliximab was initiated at 3 mg/kg dose but after the infusion the neutrophil count diminished to 1000 cells x mm3. Therefore, AMO was performed, it was normocellular with borderline neutrophil production (11%).

At 10 months of age, the patient presented neurological deterioration with sudden onset characterized by loss of strength and mobility, decreased sensitivity and presence of paroxysmal and involuntary clonic movements of the entire extremity and duration of 30 to 40 seconds. An EEG was performed, reporting a general slowdown with epileptiform. A brain MRI is performed: Leptomeningitis and right parietal cerebritis. Discrete cortical-subcortical cerebral atrophy and a small left temporal arachnoid cyst. At 11 months, he had chickenpox, dermatosis and chronic conjunctivitis.
revealed neutropenia 1000 / mm3, with the presence of hypogammaglobulinemia: IgG 113mg/dL (p3 = 338), IgM 6.58 mg/dL (p3 = 25), IgA <6.7 mg/dL, normal complement level c3 127, c4 15, ANA and ANCA negative. Lymphocyte subpopulations: LT 5610 cells x mm3 (3000-5000), CD3+ 5386 cells x mm3, CD4+ 4264 cells x mm3 (2800-3900), CD8+ 1066 (350-2200), CD19+ 122 cells x mm3 (430-3300), CD16+ 122 cells x mm3 (220-720). US in both hips in which it is observed that it presents lack of development of the acetabular posterior wall. At 6 months, the laboratory exams revealed folates 18.7, vitamin b12 less than 150 ng/dL, FE21μg/dL, Fixation 448, saturation index 5%. As a result of the suspicion of Blau syndrome with the persistence of skin granulomas, treatment with Infliximab was initiated at 3 mgkg/dosis but after the infusion the neutrophil count diminished to 1000 cells x mm3. Therefore, AMO was performed, it was normocellular with borderline neutrophil production (11%). He presented deficiency of iron and B12 vitamine; we started ferrous sulfate and IM B12. At 10 months of age, the patient presented neurological deterioration with sudden onset characterized by loss of strength and mobility, decreased sensitivity and presence of paroxysmal and involuntary clonic movements of the entire extremity and duration of 30 to 40 seconds. An EEG was performed, reporting a general slowdown with epileptiform activity in isolated waves; subsequently presented 2 epileptic seizures not associated with fever. A brain MRI is performed: Leptomeningitis and right parietal cerebritis. Probable internal carotid arteritis and its terminal branches. Discrete cortical-subcortical cerebral atrophy and a small left temporal arachnoid cyst. Mucosal thickening pansinusa, At 11 months, he had chickenpox and continued with dermatosis and chronic conjunctivitis.

**Diagnosis, Treatment and Patient Outcomes:**

- **Immunology approach:** autoinflammatory syndrome - Hypogammaglobulinemia - Cerebritis + Leptomeningitis vs CNS vasculitis - Symptomatic seizures - Iron deficiency anemia. Current treatment: immunoglobulin Subcutaneous fortnightly - Prednisone 5 mg every 24 hours (0.6 mg / kg) - Talidomine 25 mg every 24 hours - Levetiracetam 1.5 every 24 hours - TMP / SMX 5 ml every 24 hours - Itraconazole 25 mg every 24 hours.
- We suspected APLAID Syndrome because of cutaneous granulomas, hypogammaglobulinemia, diminished B cells as a feature of the newly described PID, PLCG2-associated antibody deficiency and immune dysregulation, caused by genomic deletions in PLCG2. A syndrome associated with a missense mutation in PLCG2 characterized by systemic auto inflammation, immune abnormalities, and bullous and granulomatous skin disease.
Immunodeficiency syndromes such as IPEX, IPEX-like syndromes, DOCK8 deficiency, Comel-Netherton syndrome, and SAM (severe dermatitis, multiple allergies, and metabolic wasting) syndrome present with eosinophilia, severe atopy, enteropathy, and dermatitis. Patients can have significant failure to thrive secondary to diarrhea, eosinophilia, and endocrinopathies such as early onset type-1 diabetes mellitus.

Our patient was a 10-month-old admitted to the PICU for hyponatremia, chronic diarrhea, emesis, severe eczema, and cellulitis with significant failure to thrive and hypothyroidism. Immunologic and genetic assays including whole exome sequencing did not identify a diagnosis. After treatment of the underlying severe malnutrition and neglect, the patient’s eosinophilia, hypogammaglobulinemia, eczema and hypothyroidism dramatically improved.

Immunologists should consider severe malnutrition when evaluating a patient with immune dysregulation. Although this degree of malnutrition is rare, this case illustrates the impact of nutrition on the immune system.

Patient Presentation and Testing:
10-month-old admitted to the PICU for chronic diarrhea, emesis, hyponatremia, severe eczema, and cellulitis. Patient’s weight on admission was only 4.4 kg. He was born at term with a birth weight of 2.84 kg and developed eczema with diarrhea at four months of age. The diarrhea was temporarily improved with elemental amino acid nutrition; however, his mother unrestricted his diet under the care of a homeopathic provider. His brothers had a history of food allergies and eczema. Physical exam was significant for severe developmental delay, failure to thrive, and severe eczema. Initial laboratory evaluation upon admission included WBC 17,300 cells/mm3, AEC 3979 cells/mm3, platelets 990 cells/mm3, MPV 7.0 fl, sodium 122 meq/L, TSH 11.37 mcIU/ml, IgG<300 mg/dL, IgA 28 mg/dL, IgM<25 mg/dL, IgE 4522 IU/mL, fecal A1-AT >1.13 mg/g and prealbumin was 13.0 mg/dL. No mutation was found in FOXP3 sequencing, but FOXP3 flow cytometry was abnormal with a large population of CD25- FOXP3+ cells. Flow cytometry evaluating WASp was normal. Whole exome sequencing was performed, but did not reveal any disease variant with his reported phenotype.

Diagnosis, Treatment and Patient Outcomes:
Initial medical management focused on treatment of severe malnutrition and electrolyte abnormalities. The patient’s atopic dermatitis was aggressively treated with topical emollients and corticosteroids along with IV antibiotics. He was given bowel rest with total parenteral nutrition and transitioned to elemental formula with a gastric tube. Within weeks, the patient had remarkable growth, improved skin dermatitis, and his laboratory values including AEC, TSH, IgG, IgA, and IgM normalized. The history of severe malnutrition and parental neglect necessitated removal from the household by Child Protective Services. Currently, the child continues to thrive.
Summary and Lessons Learned:
The aim of our study is to highlight the rare, but sometimes life-threatening side reaction occurring during the administration of intravenous immunoglobulin (IVIG) therapy in patients with a humoral immune deficit. Thereby, awareness should be raised regarding the body response to the intravenous substitution therapy, ranging from subtle early symptoms, that normally disappear rapidly when the infusion rate is slowed down or stopped, to hypersensitivity reactions, such as anaphylactic shock, requiring an immediate stop of the infusion and appropriate, prompt treatment to be initiated.

Method: We performed a retrospective analysis of 35 patients diagnosed with a primary immunodeficiency at the Ph.D. MD Octavian Fodor Regional Institute of Gastro-Enterology and Hepatology in Cluj-Napoca, included in a National Program and treated monthly with 400-600 mg/kg with IVIG. Of all clinical cases with an immunodeficiency, we will focus on four patients with a medical history of other immune dysregulation (eg. allergies and autoimmune diseases) developing a rapid onset of severe reactions after infusion of IVIG. Those 4 pts developed at the first administration of IVIG a severe systemic reaction with itch on extremities, generalized rush, severe dyspnea with wheeze and hypotension during 10 minutes. The IVIG where stopped and anaphylactic therapy started (epinephrine, oxygen, iv solution, antihistamine and corticotherapy) with improvement during 30 minutes. In 2 patients onother IVIG administration was introduce after a month (with same IVIG) and the reaction appeared again. The same protocol for therapy was applied. All this pts where change on another brand of IVIG (low in IgA) which was well tolerated.

Patient Presentation and Testing:
The pts where skin tested with IVIG and developed an edema with pseudopodes (larger diameter 7 mm/small diameter 5,mm). Primary immunodeficiency include a variety of disorders that render patients more susceptible to infections due to a dysfunction or lack of one component of the immune system. Without long-term therapy, these infections may produce irreversible changes in the function of various organs or could be fatal. Early recognition, diagnosis, and treatment with intravenous replacement, especially for humor deficit, can alter the course of the disease and have a positive effect on patient outcome. Therefore the main option for long-term therapy in this group of primary humoral immunodeficiency diseases remains immunoglobulin substitution therapy, either iv or subcutaneous-

Diagnosis, Treatment and Patient Outcomes:
Conclusion. Although anaphylactic reactions to the therapy are not frequent, patients with severe IgA deficiency and other immune dysfunction, such as previous allergic reactions or hypersensitivities, are at increased risk.
Summary and Lessons Learned:
This is a 45-year-old Caucasian woman with past medical history of anxiety and diarrhea predominant Irritable Bowel Syndrome (IBS-D) who recently moved into the area and presented for an appointment with her Primary Care Physician for urticarial rash unremitting to therapy. The patient was subsequently referred to Dermatology with further failure to therapy. One year later, the urticarial rash had not improved and the patient noticed vitiligo patches on the dorsal aspect of her hands for which she was further evaluated by Dermatology and referred to Allergy. Six months later, she followed up with her Gastroenterologist for poorly controlled IBS-D. On exam, the patient's skin exam showed vitiligo patches and a diffuse urticarial rash. One month later, the patient was admitted to the hospital with community acquired Pneumococcal pneumonia and on further questioning, the patient reported multiple episodes of sinus infections in the past couple of months. Her Gastroenterologist pursued laboratory analysis which showed normal complete metabolic panel, CBC, ANA, and cryoglobulins. Immunoglobulin levels were also ordered in the setting of recurrent infections, urticaria, and vitiligo. Total IgA level was less than 5mg/dL (normal 66-344 mg/dL), IgG level was 254 mg/dL (normal 716-1554 mg/dL) and IgM was 10 mg/dL (45 - 250 mg/dl). Skin biopsy of the rash showed a perivascular inflammatory infiltrate with eosinophils and neutrophils consistent with urticaria. The patient was subsequently diagnosed with CVID and initiated on monthly IVIG infusions which resolved her urticarial rash, diarrhea, and vitiligo.

This case illustrates an unusual presentation of CVID that caused a delay in diagnosis of three years. Sinopulmonary infections are the most well-known presentation of CVID and many times clinicians tend to look for sinopulmonary infections as a hint for the possibility of CVID. Because our patient presented with an unusual combination of symptoms to different specialists (Dermatologist, Allergist, Gastroenterologist) over a prolonged time course, her disease remained undiagnosed for three years. This case highlighted many lessons for all of us – a reminder of the importance of a thorough history and reevaluating your differential diagnosis each time you see a patient.

Patient Presentation and Testing:
The patient presented for an annual physical with worsening vitiligo and urticaria which was unremitting to therapy. Shortly thereafter she was admitted to the hospital with an episode of community acquired Pneumococcal pneumonia and it was noted that she had experienced recurrent sinus infections over the preceding two years. Her history and a chart review were negative for malignancy or a thymoma making secondary hypogammaglobulinemia an unlikely source of her symptoms. Further past history of the patient revealed that she was prone to sinopulmonary infections as a child but only in the past two years began to experience symptoms again.

The patient has no smoking history, rare alcohol use, and no recreational drug use. She denies other episodes of pneumonia, sinus infections, or ear infections before these recent occurrences. There is no family history of autoimmune conditions. On examination, she appeared in no acute distress and vital signs were normal. Skin showed vitiligo patches specifically on the dorsal aspect of her hands bilaterally and an erythematous papular urticarial rash noted extensively throughout her body. Cardiac examination was regular in rate and rhythm and no murmurs or gallops were heard. Lung auscultation revealed no crackles, wheezing, or rales. Abdominal examination was nontender with no hepatosplenomegaly. Laboratory analysis revealed mildly low T3 of 2.3 pg/ml and normal T4 level. Complete metabolic panel, CBC, ANA, and cryoglobulins were all normal. Due to the patient's history of diarrhea, a tissue transglutaminase IgA, along with a total IgA level, were performed in order to screen for Celiac Disease. Her total IgA level was less than 5mg/dL (normal 66-344 mg/dL). Additional immunoglobulin levels were checked and showed an IgG
level of 254 mg/dL (normal 716-1554 mg/dL) and IgM of 10 mg/dL (45 - 250 mg/dl). Skin biopsy showed a perivascular inflammatory infiltrate with eosinophils and neutrophils which was consistent with urticaria and is highly suggestive of an allergic response.

**Diagnosis, Treatment and Patient Outcomes:**
Suspicion of CVID in a patient would warrant checking serum immunoglobulin levels and, if abnormal, a repeat check of immunoglobulin levels would be needed to confirm that the hypogammaglobulinemia is not due to an error. Based on lab results showing hypogammaglobulinemia, the next best step for our patient was to refer to a clinical immunologist who could proceed with checking the patient’s response to vaccines and exclude other causes of hypogammaglobulinemia. Our patient’s response to vaccine was minimal which met another diagnostic criterion of CVID. At this point, the next step was to decide the need for prophylactic antibiotics and/or immune globulin replacement therapy. In our patient, due to her proven vulnerability as seen through her recurrent infections, it was decided to proceed with immune globulin replacement therapy.
Because our patient presented with an unusual combination of symptoms to different specialists (Dermatologist, Allergist, Gastroenterologist) over a prolonged time course, her disease remained undiagnosed for three years. Ultimately immunoglobulin levels were ordered by her Gastroenterologist when the patient presented for an annual physical and mentioned diarrhea, vitiligo, urticaria, and sinus infections. Since her diagnosis a year ago, she has been treated with monthly IVIG infusions which normalized her IgG level and resolved her urticarial rash. She has not had any further episodes of pneumonia or sinus infections and vitiligo has not advanced.
Case Title:
Highlighting the Variability in the Treatment Options and Response in Patients with Hyper IgD Syndrome

Summary and Lessons Learned:
Hyper IgD is a rare autosomal recessive subtype of periodic fever syndrome. The goals of management are to alleviate symptoms and improve quality of life however there remains limited available data on the best approach to treatment. Here we present two cases with similar presentations where both patients had elevated IgD levels with negative periodic genetic fever panels, yet they had very different responses to treatment.

Patient Presentation and Testing:
The first patient is an eight year old boy of Scottish and Italian descent with no significant past medical history presenting with recurrent fevers every six weeks for several years. He is usually debilitated for a one week duration with the fevers accompanied by severe abdominal pain, aphthous ulcers, conjunctivitis, pruritic rashes, and cervical adenitis. His laboratory work up is significant for a normal CRP, ESR and white blood cell count without any neutropenia. His IgD level is elevated at 195 mg/dL (upper limit of normal for age: 41.4 mg/dL). He was prescribed prednisone to begin at the onset of episodes and had a remarkable response, with almost immediate improvement in his symptoms and quality of life.

The second patient is a three year old boy of Portuguese and Irish decent with past medical history of failure to thrive, multiple episodes of sinusitis with recurrent fevers every four weeks lasting five days to temperatures of 106F. The fevers are accompanied by abdominal pain, aphthous ulcers, diffuse joint pain and lymphadenopathy. His laboratory work up revealed slightly elevated inflammatory markers and his IgD level is elevated at 38 mg/dL (upper limit of normal for age: 20 mg/dL). He completed nine courses of oral steroids over twelve month period which did not improve his symptoms. He was placed on meloxicam daily, also without any relief. The next step in management is anakinra for abortive therapy, and we are still awaiting these results. Unfortunately, his multiple courses of oral steroids have already resulted in effects on his growth and development.

Diagnosis, Treatment and Patient Outcomes:
Our cases are to make the medical community aware of similar clinical picture yet very different response to treatment and the new treatment options available for Hyper IgD Syndrome. This is an important aspect to be cognizant of considering the significant morbidity associated with this syndrome.
Case Title:
Chronic Granulomatous Disease due to Novel Variants in NCF2

Summary and Lessons Learned:
A 3-year-old boy presents with infections suspicious for neutrophil dysfunction. The diagnostic evaluation reveals evidence of impaired NADPH oxidase activity via dihydrorhodamine (DHR) flow cytometric analyses. After considering and assessing clinical (and technical) scenarios that could result in abnormal DHR findings, the patient is found to have two novel variants in NCF2 consistent with a rare form of autosomal recessive chronic granulomatous disease (CGD) affecting the p67-phox subunit of the NAPDH oxidase complex. For the practicing allergist-immunologist, this case highlights causes of abnormal DHR findings and details necessary testing for an accurate diagnosis.

Patient Presentation and Testing:
A 3-year-old biracial boy with unremarkable family and social histories presents with a medical history of recurrent infections. His most concerning illnesses have been 3 episodes of lymphadenitis, affecting his cervical and submandibular nodes, two of which required surgical intervention despite oral antibiotic therapy. With the surgical intervention, bacterial culture revealed growth of methicillin-sensitive Staphylococcus aureus (MSSA). An evaluation of his immune system is performed revealing no abnormalities in his absolute neutrophil count, serum immunoglobulin levels, or lymphocyte enumeration. While ill, he has a DHR study that reveals a significantly diminished burst. Though suggestive of CGD, abnormal DHR findings can result in the setting of laboratory error, pre-activated specimens, acute illness, glutathione synthetase deficiency, myeloperoxidase (MPO) deficiency, glucose-6-phosphate dehydrogenase deficiency, SAPHO (syndrome of synovitis, acne, pustulosis, hyperostosis, and osteitis) and Rac2 deficiency (if N-formyl-methionyl-leucyl-phenylalanine is used for stimulation). Addressing these scenarios, he underwent subsequent testing:
- Repeat DHR analyses (while healthy) revealed consistent results without evidence of pre-activation.
- A peripheral blood smear revealed decreased primary granules but intact MPO enzymatic activity.
- Expression of chemotaxis markers was normal and neutrophil chemotaxis was intact.
- Neutrophil bactericidal activity against Staphylococcus aureus colonies was decreased.
- Ferricytochrome c reduction assays revealed decreased superoxide production.

The results detailed above and the clinical history were consistent with CGD. Additional considerations for testing included nitroblue tetrazolium testing as well as DHR analysis of the patient’s mother to assess for carrier status (X-linked CGD).

Diagnosis, Treatment and Patient Outcomes:
A gene sequencing panel assessing CYBA, CYBB, G6PD, NCF1, NCF2, NCF4 and NOD2 revealed two previously undescribed heterozygous variants with deleterious characteristics in NCF2 consistent with a rare form of autosomal recessive CGD affecting the p67-phox subunit of the NAPDH oxidase complex. The patient began prophylactic antibacterial and antifungal therapy and is under consideration for interferon gamma therapy versus hematopoietic stem cell transplantation.
Case Title:
Sideroblastic anemia, immunodeficiency, fever and developmental delay (SIFD): case report and therapy

Summary and Lessons Learned:
Introduction: The number of primary immunodeficiencies described has increased over the years counting more than 300. SIFD is characterized by sideroblastic anemia, B cell immunodeficiency, periodic fever and neurological development delay. It is associated with mutation of TRNT1 gene and it was previously described in 14 patients. Mean survival is 48 months and cardiac problems are reported as cause of death. Etanercept has been used to treat autoinflammatory diseases. We report a patient with SIFD under treatment with anti-TNF alpha.

Case report: A 6 month old girl of a nonconsanguineous family, was referred with recurrent fever, most of the times unrelated to infection. She was a premature baby, 34 weeks, 2.140g, with laryngomalatia. Intensive Care was necessary for 14 days due to decreased oxigen saturation during breastfeeding. Extended neonatal screening was normal. Umbilical cord fall occurred after 20 days. Fever and local reaction were reported after each vaccination. Cutaneous lesions were previously diagnosed as insect bite and skin biopsy was reported as leukemia cutis. The patient was referred to Oncology in order to exclude leukemia. The following infections were diagnosed: paniculitis, herpes stomatitis, tonsilitis, lobar pneumonia, viral traqueitis due to Metapneumovirus. Recurrent high fever episodes associated with anemia occurred in the first year and blood transfusion was done during acute episodes (3-6 months old). Severe failure to thrive and delay on neurological development were also present. No hearing loss was confirmed. Acute phase proteins were persistently elevated (CRP, Ferritin). Immunoglobulin levels were: IgG= 147 mg/dL, IgA=14 mg/dL, IgM 24,2 mg/dL and CD19: 17.4%. TRNT1 mutation was identified after whole exome sequencing. Nowadays, the patient is being treated with anti-TNF alpha with good response.

Discussion: We report a patient with recurrent fever, elevated inflammatory markers, hypogammaglobulinemia and developmental delay, as defined by the SIFD and a biallelic mutation in nucleotidiltransferase RNAt1 (TRNT1). This report emphasizes the clinical presentation and the variable severity. Molecular diagnosis not only helped with final defect finding but it could also orient therapy.

Patient Presentation and Testing:
A 6 month old female patient was referred due to recurrent fever and severe anemia. Cutaneous lesions were seen at that evaluation and skin biopsy described as leukemia cutis. Oncology excluded this diagnosis and she was referred again for evaluation of the immunologist. Considering recurrent fever, failure to thrive and no infection site identified, auto inflammatory disease was suspected. Acute phase proteins were persistently elevated and hypogammaglobulinemia was also diagnosed. Benign autoinflammatory diseases were excluded and WES looking for definitive diagnosis.

Diagnosis, Treatment and Patient Outcomes:
TRNT1 mutation was identified after whole exome sequencing characterizing Sideroblastic anemia, immunodeficiency, fever and developmental delay (SIFD). The molecular diagnosis was done by Translational Autoinflammatory Disease Studies Unit, National Institute of Health, Bethesda, USA and we worked all together to establish the best therapy for
this patient. Anti-TNF alpha was prescribed and the frequency and intensity of the fever improved as well as the patient’s development.
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Case Title:
Terminal Complement Deficiency in an Active Duty Navy Submariner

Summary and Lessons Learned:
Complement proteins are critical components of the immune system. Inherited and acquired deficiencies of such proteins can create clinically significant susceptibility to infection, most commonly by encapsulated bacteria such as Streptococcus pneumoniae, Haemophilus influenza type b, and Neisseria meningitidis.

A 22 year old previously healthy bisexual male active duty submariner presented with fevers, chills, myalgias, sore throat, headache, and a painful vesicular rash which spread from his face to diffusely cover his neck, chest, and back. On exam, the patient was noted to be febrile and tachycardic with significant neck pain and stiffness. Both Kernig and Brudzinski signs were positive. In addition, he demonstrated a leukocytosis of over 20,000 and elevated inflammatory markers. PCR of the patient’s rash was positive for herpes-simplex virus type I (HSV-1). A lumbar puncture was performed, and yielded a positive PCR result for Neisseria meningitidis (non-groupable). The patient was diagnosed with both cutaneous HSV-1 and Neisseria meningitis. He was started on intravenous acyclovir and ceftriaxone and improved significantly over the course of several days, discharging approximately a week after admission. HIV serology was obtained and returned negative. On further history, the patient and his mother both confirmed that he had previously experienced similar vesicular rashes when he was younger, and his sister had suffered from disseminated meningococcal disease as a child. Given the family history, the patient was tested for an inherited immune deficiency and found to have very low or undetectable CH50 on three separate occasions. Additional laboratory tests, to include C2, C3, C4, IgA, IgM, and IgG all returned within normal limits. The patient then underwent specific testing for a suspected deficiency of terminal complement (C5-C9) and was found to have undetectable levels of C5.

An inherited deficiency of the complement system can predispose patients to infections with encapsulated bacteria such as Neisseria meningitidis. While the scientific literature describes correlations between specific complement deficiencies and mammalian humoral response to herpesvirus infection, the presence of co-morbid disseminated HSV-1 in this patient cannot be definitively attributed to such a deficiency and may simply reflect activation of latent virus during a state of acute physiologic stress. Providers should perform careful interviews to obtain personal or family history suspicious for inherited immune deficiencies and understand the laboratory analysis required for diagnosis, as such patients are at increased risk of death from infection and should receive targeted vaccination and education.

Patient Presentation and Testing:
The patient’s initial presentation consisted of significant headache, meningismus with positive Kernig and Brudzinski signs, fever, and tachycardia. He noted that he had developed a sore throat, fever, headache, and myalgias five days prior to presentation. Initially, he thought that these symptoms were consistent with the common cold. Three days prior to admission, he presented to a healthcare clinic due to persistent symptoms and received a single injection of intramuscular penicillin for presumed streptococcus pharyngitis. When he again worsened over the course of the next few days and subsequently developed a painful vesicular rash, he decided to present to the urgent care clinic and was then transferred to our care. Of note, the patient was bisexual and reported multiple recent sexual contacts with men and women. He reported using condoms infrequently.

Given his clinical picture on presentation, primary concern was for a cutaneous infection (herpes simplex or varicella zoster) which had disseminated to cause a viral meningitis or for infection with a bacterial pathogen. Lumbar puncture was performed, and showed greater than 6,000 white blood cells, low glucose (3), and elevated protein (181) with a positive result for "non-groupable" Neisseria meningitidis. Other considerations, given his initial complaint of sore
throat, included complications of infectious mononucleosis or streptococcus pharyngitis. Monospot, rapid strep test, and throat culture all returned negative. Bacteremia was considered given the systemic nature of his clinical presentation with tachycardia, fever, myalgias, and profound leukocytosis. Blood cultures were obtained and returned negative. Given the patient's recent risky sexual behavior, an acute presentation of HIV was considered. Multiple late generation laboratory tests, to include HIV-1 RNA returned negative for human immunodeficiency virus. Given his history, other sexually transmitted infections, such as syphilis, gonorrhea, and chlamydia were tested for as well (even though no discharge or lesions were noted on genital exam). All of these tests returned negative. PCR of the contents of his vesicular skin lesions returned positive for HSV-1.

The patient informed us that he had previously experienced a similar vesicular rash on his face as an adolescent, but he had otherwise been very healthy, never suffering from recurrent infections. However, he also informed us that his sister had suffered from severe disseminated meningococcal disease at a very young age. Both his mother and his prior pediatrician (who had treated both children) corroborated this information. Because of the family history, we decided to test the patient for an inherited immunodeficiency. Given the increased incidence of Neisseria infection in those with complement protein deficiencies, the first test we obtained was CH50, which returned very low. To confirm this result, we tested the patient a second time, and CH50 levels were undetectable. Noting that complement may be low in the setting of acute infection due to physiologic consumption rather than true deficiency, we waited more than a week after his hospital discharge to test the patient a third time. The result was undetectable CH50.

At this point, we decided to investigate the specific complement proteins. Given that terminal complement is essential for immune defense against Neisseria infections, C5-C9 were each specifically tested. Ultimately, the patient was found to be completely deficient in C5.

**Diagnosis, Treatment and Patient Outcomes:**
While admitted, the patient was treated with intravenous acyclovir and ceftriaxone for his acute infections. His symptoms quickly improved.

However, the ultimate diagnosis was a deficiency in complement protein C5, one of the terminal complement components (C5-C9) critical in the formation of the membrane attack complex and subsequent defense against the Neisseria species of bacteria. As this lab has just resulted, we are in the process of contacting the patient to notify him. Since this patient is an active duty submariner, he has already been vaccinated against meningococcus. Our goal is to ensure that he has also received both the pneumococcal and Haemophilus influenzae type b conjugated vaccinations, as these are indicated in all individuals with terminal complement deficiency. In addition, we plan to have further discussions with this patient regarding his condition. These will include the need to be vigilant regarding the early signs of infection, the importance of wearing a medical identification badge, and the potential benefit of antibiotic prophylaxis with monthly injections of benzocaine penicillin.
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Case Title:
Candidal Granulomatous Disease: A Unique Presentation of Chronic Granulomatous Disease (CGD) with a Novel Mutation

Summary and Lessons Learned:
A four day old female born at 40 2/7 weeks of gestational age to consanguineous parents with a profound rash at the
time of birth, Candida funisitis presented with clinical sepsis. She was noted to have oral thrush, worsening rash and
fever which prompted her presentation to the hospital. Initially, urine cultures grew Group B Streptococcus, but
eventually, her tracheal cultures and skin scrapings grew Candida albicans. She clinically declined and passed away
despite double coverage for gram negative, gram positive bacteria and fungi. Initial immunological work up was
unrevealing as Chronic Granulomatous Disease (CGD) was not suspected. After information about her skin scrapings,
placental and umbilical cord pathology results, fungal tracheal cultures, CGD was suspected and a dihydrorhodamine
(DHR) flow cytometry assay was sent. It came back consistent with autosomal recessive CGD with postmortem genetics
consistent with NFC2 mutation. This case defines the importance of suspecting autosomal recessive CGD in patients with
a history of consanguinity with disseminated candidiasis. With a high index of suspicion, early diagnosis can lead to
potentially lifesaving treatments such hematopoietic stem cell transplant (HSCT). However, in our patient, this was not
an option given her lack of response to antimicrobials with continued pressor refractory septic shock. In addition, it is
important to identify autosomal recessive CGD for future family planning.

Patient Presentation and Testing:
A four day old female born at 40 2/7 weeks gestational age to consanguineous parents and no family history of
immunodeficiency presented with septic clinical features and rash. At birth, she was noted to have a rash and required
oxygen for presumed meconium aspiration. On day of life four, she developed oral thrush, a worsening erythematous
papular rash and fevers prompting hospitalization. Blood and cerebrospinal fluid cultures were negative at presentation
and urine grew Group B Streptococcus. Despite adequate treatment with penicillin and gentamicin, she decompensated
and required intubation and vasopressor support. Antimicrobial coverage was broadened, including double fungal
coverage. Skin scrapings grew Candida albicans with pathology showing folliculitis with microabscesses containing fungal
hyphae. Tracheal culture cultures grew Candida albicans.
Immunological workup revealed low-normal IgG, normal IgA and IgM. T, B and NK cells were mildly low. Lymphocyte
mitogen proliferation was normal. DHR was ordered as other immunological work up unrevealing which showed 5.2 %
neutrophil activity. This was ordered due to growth of catalase positive fungal organism (Candida albicans). On day of
life 47, she expired from vasopressor refractory shock with persistent hypoxemia despite double coverage with
antifungals. Postmortem examination showed disseminated candida infection with severe involvement of lungs with
confluent necrotizing granulomatous bronchopneumonia. Granulomatous inflammatory foci were also present in the
skin, mediastinal lymph nodes, liver, small bowel and spleen. Pathology records confirmed the presence of Candida
funisitis with fungal yeasts. Genetic testing revealed Q374X nonsense variant in the NCF2 gene which is a pathogenic
variant not previously reported, but consistent with autosomal recessive CGD.

Diagnosis, Treatment and Patient Outcomes:
With the postmortem pathology and DHR consistent with autosomal recessive CGD, genetic testing was pursued to
confirm diagnosis for future family planning. This identified a Q374X nonsense variant in the NCF2 gene consistent with
autosomal recessive CGD. Due to delay in diagnosis for various circumstances, her disease was identified after the patient expired. This mutation appears to be lethal variant as the baby did not clinically improve despite appropriate therapy. Unfortunately, she was too ill for definitive therapy such as HSCT. This case exemplifies the need to have high suspicion for CGD in disseminated candidiasis with or without granulomatous inflammation. Early diagnosis and antifungal treatment immediately after birth may have altered her clinical course.

p67phox is one of the five nicotinamide adenine dinucleotide phosphate (NADPH) oxidase units encoded by the NFC2 gene with mutations seen in up to 5% of CGD cases. According to Ben-Farhat et al., seven out of eleven patients in their Tunisian cohort presented with invasive Aspergillosis and six with mycobacterial infection. Five died despite adequate treatment. Cohen et al. found that 55 out of 250 CGD patients had severe fungal infections with 43 cases attributable to Aspergillus species, eight to Candida albicans, three to Candida glabrata and one to Haememila polymorpha. Severity of clinical outcome depends on the mutation and amount of residual NADPH oxidase activity. While there are reports of primary candidal infections suspected to be from CGD, only one other definitive case of NFC2 gene mutation is reported with a presentation of disseminated candidemia and granulomatous lung disease. We report a novel pathogenic variant, Q374X nonsense variant (c. 1120 C>T) that has not been previously reported, as a potentially lethal variant of NFC2 gene-associated autosomal recessive CGD.
Case Title:
Chronic Mucocutaneous Candidiasis in Otherwise Healthy Hosts

Summary and Lessons Learned:
This is a case series on 3 patients with isolated Chronic Mucocutaneous Candidiasis without any other clinical manifestations. Chronic Mucocutaneous Candidiasis Syndrome (CMCS) is a heterogeneous group of disorders of chronic superficial candidiasis, usually accompanied by other infections and/or autoimmunity. It has been well described in the literature. Isolated Mucocutaneous Candidiasis, also known as Chronic Mucocutaneous Candidiasis Disease (CMCD), is a more recently described entity. All three of our patients went through a significant period of time where treatment was solely based on symptomatic control versus discovering an underlying etiology. This is likely due to decreased awareness of CMCD in the medical community. This case series highlights the need for an increase in awareness by physicians regarding CMCD. By recognizing this disease, physicians can start implementing a targeted treatment approach, instead of symptomatic control with anti-fungals. Despite the efficacy of anti-fungals, they are not the definitive treatment as it does not treat the underlying immunodeficiency and frequent use has been associated with resistance.

Patient Presentation and Testing:
Our first patient is a 10 y/o boy with recurrent oral/genital candidiasis since infancy. Second is a 16 y/o girl with recurrent esophageal candidiasis and third, a 52 y/o female (mother of patient 2) with persistent vaginal candidiasis for over 30 years. They responded to oral antifungals, but relapsed after discontinuation. CBC, CMP, and T/B/NK cell subsets were normal. Two of the patients had slightly low serum Immunoglobulin G levels. Lymphocyte proliferation assay was normal, but nonreactive to Candida. Delayed-type hypersensitivity skin testing to Candida was also nonreactive. This suggested a Candida specific defect, which led to cytokine analysis of the patients. IL-17A was absent in all patients, while IL-17F was present only in one patient. Genetic testing for common CMCS/CMCD mutations was negative.

Diagnosis, Treatment and Patient Outcomes:
The patients were diagnosed with CMCD. Several endotypic and genotypic alterations are responsible for the lack of immunity towards candida. However, the absence of IL-17 A is unique to our patients and also plays an important role in immunity against Candida. Our patients presented with CMCD and lacked other immunological alterations normally seen with CMCS. Whether the absence of IL-17 A alone is responsible for their disease manifestation is yet to be determined. Our patients are doing well on antifungals as needed. However, cases on effective treatment with immune modulators have been reported and can be considered for our patients in the future.
Summary and Lessons Learned:
The use of Whole Exome Sequencing (WES) in our patient identified two novel mutations in the LRBA gene resulting in a severe phenotype of autoimmunity and immunodeficiency. His symptoms were poorly controlled on traditional therapies for CVID and autoimmunity. Only with WES were we able to identify his specific immunodeficiency and an effective therapy. Abatacept therapy resulted in life-changing improvement in his symptoms. Using WES to further define CVID can have both diagnostic and therapeutic benefits for patients and should be actively pursued when primary immunodeficiency is suspected.

Patient Presentation and Testing:
The patient presented in 2007 at age 2 with TPN dependent intractable diarrhea, FTT, immune cytopenias and profound hypogammaglobulinemia. He had an extensive immune work-up, the rest of which was unremarkable. With the presumptive diagnosis of CVID, he was started on Ig replacement. He went on to develop a refractory Evan’s syndrome, autoimmune hepatitis and lymphocytic interstitial pneumonitis. Managed with a variety of immunosuppressive regimes, his condition remained unstable, requiring multiple hospitalizations for respiratory infections, worsening anemia and electrolyte abnormalities. WES performed in 2016 showed compound heterozygous variants (c.1161+1G>A, c.1931dupC) in the LRBA gene.

Diagnosis, Treatment and Patient Outcomes:
LRBA (lipopolysaccharide responsive beige-like anchor protein) deficiency is caused by bi-allelic mutations in the LRBA gene resulting in autoimmunity, lymphoproliferation and immunodeficiency presumably through failure of CTLA4-mediated regulation. Abatacept (CTLA4-Ig) has been recently shown to be an effective treatment for symptoms of autoimmunity due to LRBA deficiency.
Patient was started on Abatacept (422 mg = 20 mg/kg every 4 weeks). Within two months of instituting this therapy, the diarrhea completely resolved, he had no more episodes of hemolysis and no significant infections. Both his nutritional status and his growth curve improved. He is currently 12 years old and remains on IVIG but is no longer on any immunosuppressant medications.
Case Title:
The use of ion torrent assay to identify a novel combined-immunodeficiency in a 2-year-old boy with Pseudomonal meningitis.

Summary and Lessons Learned:
This case involves a previously healthy 2-year-old boy who was admitted for pan-susceptible Pseudomonas aeruginosa bacteremia and cefepime-resistant Pseudomonal meningitis, which is typically seen only in an immunocompromised host. He was hospitalized for a total of 3 months and received a total 9 week course of antibiotics with meropenem and tobramycin.

Our patient’s initial immunologic workup was essentially negative, which led us to investigate the options available for genetic testing. An ion torrent gene chip assay was used for the detection of 300 immune dysregulation genes from the patient’s whole blood specimen was performed at the National Institutes of Health (NIH). This technology allows for rapid gene sequencing and identification of mutations. In the case of our patient, the assay performed a targeted capture of exons from a panel of immune related genes. Although no obvious causative agents were identified out of the captured regions screened, one novel heterozygous, missense variant was identified in ERBB2IP, and six uncommon, heterozygous, nonsynonymous, variants of unknown significance, with a CADD-PHRED score greater than 15 were found in RAD50, PTPN13, TRNT1, SLC11A1 and TYK2. Many of these mutations have been linked to other known immunodeficiency syndromes.

Although our patient had no overt immunodeficiency identified by routine immunologic screening, an ion torrent assay analysis revealed nonsynonymous mutations in seven genes related to immune dysregulation. This suggests a possible novel combined-immunodeficiency syndrome, in particular atypical autosomal recessive hyper-IgE syndrome (AR HIES) or a less severe form of radiosensitive combined-immunodeficiencies. This indicates that genetic testing is paramount in the identification and diagnosis of rare immunodeficiencies, especially in the identification of new and novel mutations. Identification of new mutations can assist in earlier diagnosis for other children with similar stigmata, earlier treatment and prevention of poor outcomes, morbidity and mortality.

Patient Presentation and Testing:
Our patient is a previously healthy 2-year-old boy of Asian Indian heritage, who presented to the hospital with one day of fever, status epilepticus and respiratory failure. Initial workup revealed that he was bacteremic with pan-susceptible Pseudomonas aeruginosa, and his cerebrospinal fluid (CSF) culture grew cefepime-resistant Pseudomonas aeruginosa. The patient suffered an ischemic stroke secondary to septic emboli and CNS vasculitis. Brain MRI localized the septic emboli to the right occipitoparietal region with ventriculitis. He developed hydrocephalus and an external ventricular drain was placed, which was later replaced by a ventriculoperitoneal shunt. The patient completed an extensive 9-week course of antibiotics with meropenem and tobramycin, and showed long strides towards recovery at the end of his 3-month hospitalization.

This 2-year old had no significant past medical history. He had never been on antibiotics in the past. His parents reported that he had 1-2 colds per year, but otherwise he had no significant illnesses or hospitalizations. His immunizations were up to date. His growth and development were appropriate for his age. His parents are first cousins. There was no personal or family history of HIV, miscarriages, chronic diarrhea, heart defects, facial defects, eczema, abnormal teeth, fractures, delayed umbilical cord separation or delayed teeth eruption. There was no family history of immunodeficiency, cystic fibrosis, autoimmune disease or frequent/recurrent infections.

The initial evaluation included a complete blood count which showed leukocytosis with marked left shift and thrombocytopenia. His metabolic panel showed stable electrolytes with good kidney function. The C-reactive protein
was elevated. Urinalysis and urine culture were negative. Blood culture drawn prior to initiation of antibiotics showed pan-susceptible Pseudomonas aeruginosa, however, the initial CSF culture grew Pseudomonas aeruginosa resistant to cefepime.

Initial immunology workup revealed normal immunoglobulins, and normal T, B and natural killer (NK) cell enumerations (percentage and total counts). Pneumococcal, diphtheria and tetanus titers were protective. The mitogen proliferation assays to phytohaemagglutinin (PHA), concanavalin A (conA) and pokeweed mitogen (PWM) were adequate. HIV 1/2 antibody test was negative, oxidative burst was normal, and complement C3, C4 and CH50 were normal. Alternate complement pathway (AH50) was normal as well. Sweat chloride testing was unable to be performed due to an inadequate specimen, however, our patient’s newborn screen was negative for cystic fibrosis. CD11 and CD18 were also normal.

An ion torrent gene chip assay used for the detection of 300 immune dysregulation genes from the patient’s whole blood specimen was performed at the National Institutes of Health (NIH). The ion torrent assay is a type of DNA sequencing technology that breaks down DNA into fragments which are then amplified with adapters containing complementary base pairs to which they will bind. This technology allows for rapid gene sequencing and identification of mutations. In the case of our patient, the assay performed a targeted capture of exons from a panel of immune related genes. Although no obvious causative agents were identified out of the captured regions screened, one novel heterozygous, missense variant was identified in ERBB2IP, and six uncommon, heterozygous, nonsynonymous, variants of unknown significance, with a CADD-PHRED score greater than 15 were found in RAD50, PTPN13, TRNT1, SLC11A1 and TYK2. These genes are related to immune dysregulation and have been linked to other known immunodeficiencies.

**Diagnosis, Treatment and Patient Outcomes:**
The results of the ion torrent gene assay revealed a possible novel combined-immunodeficiency syndrome, in particular atypical autosomal recessive hyper IgE-Syndrome (AR HIES) or a less severe form of radiosensitive combined-immunodeficiencies. Our patient remained hospitalized for 3 months but showed significant strides towards recovery at the time of discharge. During his hospitalization he was treated for 9 weeks with meropenem and tobramycin for Pseudomonal sepsis, meningoencephalitis and presumed ventriculitis. He was discharged to an inpatient rehab facility and continues to follow up with the Immunology team for ongoing investigation into the etiology of his severe infection. Currently, he is maintained on antibiotic and antifungal prophylaxis for AR HIES with sulfamethoxazole/trimethoprim and itraconazole, respectively.
A brain biopsy is necessary to diagnose enteroviral meningoencephalitis in patients with Bruton’s agammaglobulinemia.

Summary and Lessons Learned:
We describe a case of a male with Bruton’s agammaglobulinemia (XLA) diagnosed at 16 months of age and treated with IVIG who presented at 3 1/2 year of age with a 4-month history of poor linear growth, obesity, increasing clumsiness, stumbling and falling as well as refusal to climb stairs. In addition he started having difficulty talking. A brain MRI showed features of demyelinating brain disease. We suspected that his condition was caused by infection rather than by inflammatory process such as acute demyelinating meningoencephalitis (ADEM), multiple sclerosis (MS) - like disease or by congenital leukodystrophy. Enteroviral infections were reported as a cause of chronic meningoencephalitis in agammaglobulinemia (CEMA), but we haven’t found it in CSF tested by RT PCR on two separate occasions (1). The CSF was also negative for other viruses and bacteria. On the other hand the CSF contained high myelin basic protein (MBP) and, surprisingly, there was IgG and 5 oligoclonal bands, which were absent in the serum.

As we were conducting patient’s work up a report was published in NEJM showing that the next generation sequencing (NGS) successfully identified neuroleptospirosis not detectable by the conventional CSF tests in another patient with immunodeficiency, which encouraged us to use this diagnostic method in our patient (2). Applying metagenomic NGS allows for identification of all genetic material in the sample and characterization of known pathogens and of novel pathogens that elude conventional testing. The unbiased NGS was performed by Dr. Charles Chiu at the University of California, San Francisco, but no infectious material was detected.
The patient’s clinical condition continued to deteriorate and we consulted Dr. Waldman at Children’s Hospital of Philadelphia. She found no evidence of leukodystrophy, but in brain biopsy performed there Enterovirus was identified by PCR.

In the recently published review Bearden et al., recommend brain biopsy if there is a high index of suspicion of enteroviral infection and progressive neurologic deterioration in patients with XLA (3). However, as a base for this recommendation they described only one case. Our case is different that in addition to RT PCR, we also performed the NGS, which may be perceived (not necessarily proven) to have a higher sensitivity than PCR.

Brain biopsy is obviously an invasive procedure. Thus, those taking care of patients similar to ours might lean towards less invasive testing like the NGS in CSF, as erroneously as we did.

**Patient Presentation and Testing:**

We describe a case of a male with Bruton’s agammaglobulinemia (XLA) diagnosed at 16 months of age. Prior to the diagnosis the patient had frequent ear and upper respiratory infections, which were attributed to his attendance at day care. He presented for evaluation after he was found to be neutropenic with ANC 100 cells/mm3. This prompted measurement of immunoglobulins, which were as follows: IgG < 304 mg% (345-1213), IgM 45 mg% (43-173), IgA< 53 (14-106) and IgE 4 IU/ml. Flow cytometry revealed no CD19+ cells, and normal –T and -NK cells. A BTK gene sequencing revealed a novel variant c.1185G>A (p.Trp395X), which was predicted to lead to a nonsense mutation and had been scored as probably associated with X-linked agammaglobulinemia. The family history revealed no consanguinity or immunodeficiency. Patient has been growing normally and achieved developmental milestones as expected.

We started replacement with 500 mg/kg of IVIG, which initially was infused every 3 weeks and then monthly. A through of IgG was maintained > 600 mg%. Neutropenia and ear infections resolved.

He was well till age 3-year-and- 8 months when he presented with a 4-month history of poor linear growth and obesity. He was noticed to refuse to climb chairs, became clumsy, was easily stumbling and falling. In addition he started having difficulty talking. A MRI revealed: “multifocal white matter abnormalities in the supratentorial compartment and slightly seen in the pons with and increased signal along the undersurface of the corpus callosum. Findings may represent dysmyelination or demyelination rather than a delayed myelination.”

We suspected that this condition was caused by primary infection rather than by inflammatory process, like acute demyelinating meningoencephalitis (ADEM), multiple sclerosis (MS) - like disease or by congenital leukodystrophy. We performed a spinal tap, which showed 3 WBC ( neutrophils 8 %, limphocytes 72% and monocytes 20 %), glucose 47 mg% and protein 48 mg% (range: 15-45). Myelin base protein (MBP) was elevated at 2.3 ng/ml (range: 0.0-1.2).

Surprisingly, there were also five oligoclonal bands, which were present in the CSF, but were not detected in the serum. On a repeat CSF analysis performed a month later there was 3.9 mg% of IgG (range: 0-8.6 mg %), albumin 4.6 mg% (range: 3.5-5.5). CSF IgG index was 0.5 (range: 0.0-0.7) and CSF/Serum albumin index was 4 (range: 0-8) , which is consistent with intact blood-brain barrier. This indicated that IgG in the CSF was not from IVIG, but probably of intrinsic origin. No commercial laboratory agreed to look for B lymphocytes in the CSF.

On both spinal taps, the CSF tested by RT PCR was negative for Enterovirus. It was also negative for JVC, HSV 1, HSV 2, EBV, and Mycoplasma by PCR. Bacterial and mycobacterial cultures, were negative. Hoping that it might be helpful in diagnosis we measured cytokines in CSF, and the results were as follow: All results are in the pg/ml. IL-1 Beta : 7 ( range<5), IL-2 : 3 (range: <2, IL-4: 18 (range: <5), IL-5: <1 (range: <6), IL-6: 12 (range: <26), IL-8: 167 (range: <182), IL-10: <1 (range: <3), INFγ: 6 (range: <4), TNFα: 15 (range: <3), GM-CSF: 3 (range<1). The results are not easy to interpret. Increased cytokines indicated primarily activation of Th1 cells T (TNFα and INFγ), but also activation of macrophages (IL-1 Beta and GM-CSF) as well as of Th2 cells (IL-4).

The results of other tests were as follows: CBC: WBC 4.7, Hb 11.8, Hct 34.5, Platelets 290,000, S 45%, L 39%, M11%, ESR 14, CRP<1, and normal comprehensive metabolic panel.

MRI of the cervical spine did not show any signal abnormalities.

Consulting neurogeneticist initiated work up for, in her opinion, an unlikely leukodystrophy. The results were as follows: Normal: arylsulfatase A, β galactosidase, Normal in plasma: hydroxlysine, ornitine, hydroxyproline, taurine and ammonia. Normal: lactate, pyruvate, total free carnitine, VLCFA and urine organic acids.

During the time we were conducting the patient’s work up a report was published in NEJM showing that the next generation sequencing (NGS) successfully identified neuroleptospirosis not detectable by the conventional CSF tests in another patient with immunodeficiency. This encouraged us to use this diagnostic method in our patient (2). Applying metagenomic NGS allows identification of all genetic material in the sample and characterization of known pathogens and of novel pathogens that elude conventional testing.
Diagnosis, Treatment and Patient Outcomes:
Despite negative CSF studies we worried that we are missing an enteroviral infection. Even though, currently there is no specific therapy for enetroviral infections, as our patient continued to neurologically worsen, we decided to treat him with high doses of immunoglobulins, as has been done previously by others for chronic enteroviral myeloencephalitis. We treated our patient with 2 g/kg IVIG, and started weekly infusions of SCIG. We aimed to keep through level at 2000 mg%. However, the patient continued to worsen.
A follow up MRI revealed development of extensive atrophy with dysmyelination or worsening demyelination and demonstrated a large bilateral chronic subdural hematoma. Therefore, we decided to treat a potentially developing ADEM, and the patient received a high dose (30 mg/kg) of IV solumedrol daily for 5 days. However, no improvement in the patient’s condition was appreciated, and in fact he has been progressively deteriorating further. His speech became reduced to monosyllables and later no language at all. He lost his toilet training. His gait which was initially wide-based progressed to a non-ambulatory state and later to spastic quadriplegia. He lost head control, and was having difficulty feeding, choking with liquid and solid food, in addition he developed persistent horizontal nystagmus.
In this situation, a year after he presented with neurological symptoms, we decided to consider treatment with Rituximab anti-CD20 monoclonal antibody. This idea might seem counterintuitive in the patient who had no B lymphocytes. However, we knew the findings by Nonoyama et al., who reported that patients with XLA have small number of “leaky B cells” which can proliferate, undergo isotype switching, and differentiation into specific Ab-producing cells (4). There was also evidence that B cells play the role in multiple sclerosis (MS), the prototypical inflammatory demyelinating disease. In addition, there were reports of some benefit from B-cell depletion in MS (5, 6). Thus, our patient received IV Rituximab once weekly 375 mg/m² for 4 weeks. However, again no measurable improvement of his condition was noticed.
Eventually, fifteen months after presenting with neurological symptoms, a brain biopsy was performed at Children’s Hospital of Philadelphia. Microscopic examination of dura showed no significant pathologic changes. There was leptomeningeal chronic inflammation with lymphocytes and macrophages highlighted by CD68, CD163, CD45 and CD3. The gray matter demonstrated loss of neurons, reactive astrogliosis and microglial nodules. A chronic inflammatory process involved the white matter with perivascular cuffs and wide spread T-lymphocytes. No B lymphocytes were present, but note that the brain biopsy was performed a month after the last dose of Ruitiximab. Subdural membrane demonstrated fibrous tissue with granulation tissue and meningeal cells hyperplasia. There were numerous macrophages highlighted by CD163 and CD68 and T lymphocytes. Scattered hemosiderin deposits were identified and iron stain was highlighted them.
The morphological features were those of severe, non-necrotizing, chronic meningoencephalitis and in keeping with enteroviral meningoencephalitis.
Brain tissue was positive for Enterovirus (by PCR).
There is currently no specific treatment for enteroviral infections, but new promising antiviral drugs are in development. Thus, if there is a high index of suspicion of enteroviral infection and progressive neurologic deterioration in patients with XLA, a brain biopsy should be considered.
References:
3. David Bearden et al., Enteroviruses in X-linked Agammaglobulinemia: Update on Epidemiology and Therapy. JACI in Practice 2016;4:1059-1065
A Case of Congenital Agammaglobulinemia Without a Clear Genetic Cause.

Summary and Lessons Learned:
Rationale: Congenital Agammaglobulinemia is a primary immunodeficiency usually caused by defects in B cell development. Patients typically present with recurrent sinopulmonary or invasive infections with encapsulated bacteria. Immune system evaluation frequently demonstrates absent immunoglobulins and a paucity of B lymphocytes. X-linked agammaglobulinemia with detectable pathogenic variants in the Bruton Tyrosine Kinase (BTK) gene is the most common genetic variant identified (approximately 90%). We describe a unique case of a school aged male with a history of Haemophilus influenza meningitis as well as absent immunoglobulins and B cells without a recognized genetic defect after extensive testing.

Methods: Genetic testing was performed by Invitae Corporation. Immunologic testing was performed by ARUP Laboratories as well as Cincinnati Children’s Hospital Diagnostic Immunology lab.

Results: Patient is a nine year old immunized male with history of polymicrogyria, ADHD, seizures and mild recurrent sinopulmonary infections who presented with two serious infections within the past year. He had no history of serious infections until the age of nine years. At that time, he presented with headache, altered mental status and fever. He was subsequently diagnosed with Haemophilus influenza meningitis. After an uneventful recovery, he presented two months later with an intra-abdominal soft tissue infection. Subsequent immunological studies revealed absent immunoglobulins and B cells. He also had no responses to his previous vaccinations. Testing for BTK pathogenic variants was negative. Secondary testing for agammaglobulinemia, hypogammaglobulinemia, as well as common variable immune deficiency associated genes was also negative for any pathogenic variants (30 genes).

Conclusions: X-linked agammaglobulinemia is the most common cause of congenital agammaglobulinemia occurring in 1 in 250,000 persons. While there have been other reported cases of autosomal recessive forms of agammaglobulinemia, these cases still remain relatively rare. We report a patient with history and labs consistent with congenital agammaglobulinemia without a clear genetic etiology. Determining the genetic etiology of an immunodeficiency is important in terms of assisting with future prognostic factors as well as with any future genetic counseling regarding potential offspring. Whole exome sequencing is being pursued in this patient to establish a genetic cause. This will allow us to potentially uncover new genetic causes for agammaglobulinemia which will benefit the community of allergy immunology by providing information to continue to expand the knowledge base for immunodeficiency. In addition, it is important to realize that agammaglobulinemia can present at varying ages and to remember to always keep it as a differential diagnosis.

Patient Presentation and Testing:
The patient initially presented to the emergency department with two days of fevers to 102-103F, headache, neck pain, sore throat as well as one day of altered mental status. The patient had been evaluated by his Pediatrician on the day of presentation to the emergency department, was diagnosed with strep pharyngitis, and given an IM injection of Rocephin. Rapid flu testing at the Pediatrician’s office was negative. The patient then presented to the emergency department later that day secondary to increasing alteration of his mental status. In the emergency department, the patient was noted to have a physical exam consistent with meningitis signs including a positive Kernig, positive Brudzinski, and altered mental status with GCS of 11-12. Lumbar puncture was obtained which returned grossly
purulent fluid significant for 10,240 WBC, glucose of 25, and elevated protein. Procalcitonin was elevated to 48.9. Other pertinent lab findings include thrombocytopenia as well as mild hyponatremia. CT of the head/sinus was obtained which was negative for abscess but positive for mild paranasal sinus mucosal thickening. Chest x-ray was negative for any radiographic abnormality. Patient was subsequently admitted to the PICU, started on empiric antibiotic therapy with rocephin, vancomycin, and acyclovir. CSF cultures ultimately returned positive for Haemophilus influenza, patient was treated with a ten day course of rocephin. Thrombocytopenia and hyponatremia self-resolved prior to discharge. The patient presented with a second serious infection two months later. The patient presented to the emergency department with seven days of worsening left sided abdominal, hip, and back pain. The patient had daily fevers to 102.5F. The patient had presented to the emergency department once prior as well as to his pediatrician’s for one visit. The patient had been started on miralax for a moderate stool burden visualized on abdominal x-ray. Patient was found to be positive for coronavirus, Rhino/enterovirus by respiratory swab at the pediatrician’s office. Further work up was initiated when the patient presented to the emergency department for the second time on day seven of illness. A CBC, CMP, lipase, CRP, mono screen, EBV antibodies, rapid strep, throat culture, urinalysis, urine culture, blood culture, ultrasound of appendix, CT abdomen and pelvis were obtained. Imaging returned normal. Labs were significant for leukocytosis to 15.6 with a predominance of neutrophils, and CRP elevated to 24.4. Patient was admitted for an ultrasound of appendix, CT abdomen and pelvis were obtained. Imaging returned normal. Labs were significant for leukocytosis to 15.6 with a predominance of neutrophils, and CRP elevated to 24.4. Patient was admitted for abdominal pain and started on medications for pain control. MRI of the spine/pelvis were then obtained with concern for an increased dose of T2 signal intensity in the left iliacus muscle extending along the psoas. Repeat MRI of the pelvis was obtained to clarify the area of involvement of T2 intensity which returned consistent with myositis/fasciitis. Vancomycin was started and then later changed to ceftarol. Patient recovered without incident. Initial immunoglobulins were undetectable. Immunoglobulin levels were repeated and confirmed as absent IgA, IgG, and IgM. At follow up he was found to have absent responses to diphtheria and tetanus. Subsequent lymphocyte subsets revealed absent B cells. T cell absolute number was within normal limits. Bruton Tyrosine Kinase (BTK) genetic testing was sent to Cincinnati Children’s Hospital. BTK testing returned negative for a mutation. Additional genetic panel for 30 genes associated with common variable immunodeficiency, hypogammaglobulinemia, and agammaglobulinemia were sent to invitae. This panel also returned negative for any mutations. Patient is currently following with genetics and allergy immunology to pursue whole exome sequencing.

**Diagnosis, Treatment and Patient Outcomes:**
The patient having two serious invasive infections within a couple of months of each other prompted screening immunoglobulin levels to be obtained during the patient’s second hospitalization course. Since the screening levels returned low, repeat immunoglobulin levels were obtained from a more sensitive testing modality. These values returned absent. The labs were concerning for an immunodeficiency therefore further investigation ensued. Lymphocyte subsets were obtained to try to help differentiate between deficiencies of B versus T cells versus both. Lymphocyte subset results of absent B cells with normal number of absolute T cells. This combined with lack of response to immunization titers lead to a pattern consistent with congenital agammaglobulinemia. The most common genetic defect for congenital agammaglobulinemia is a mutation in BTK, which occurs in 90% of males with agammaglobulinemia. The BTK testing was therefore obtained which returned negative. Subsequently a panel of 30 genes associated with common variable immunodeficiency, hypogammaglobulinemia, and agammaglobulinemia was obtained which also returned negative. Whole exome sequencing is now being pursued with allergy immunology as well as genetics department to try to determine if the patient has an undiscovered genetic cause for his agammaglobulinemia. The patient was also started on weekly home subcutaneous injections of immunoglobulin therapy, after the patient was recognized as having lack of immunoglobulins and B cells. The patient has remained infection free for four months since initiating therapy and the patient’s mother reported that the patient has also not had any upper respiratory symptoms which he had frequently at baseline throughout his life. Repeat trough levels of IgG were obtained which revealed improvement which assisted verification of adequate replacement therapy being achieved. In conclusion, the patient’s history, immunologic work up, and response to subcutaneous immunoglobulin therapy is most consistent with a form of congenital agammaglobulinemia. At this time the genetic cause for his congenital agammaglobulinemia is unknown which is why we are continuing to pursue whole exome genetic sequencing. BTK which is the most common genetic cause was negative. The other more rare autosomal recessive forms that have been discovered as causes for congenital agammaglobulinemia are less consistent with the patient’s presentation as well given that the patient does have other significant past medical history including seizures, polymicrogyra as well as that he presented later than most at 9 years of age.
Introduction:
Cardiofaciocutaneous Syndrome (CFC) is a rare autosomal dominant (AD) disorder arising from mutations in several genes, which lead to defects in the RAS/MAPK pathway, similar to Noonan Syndrome and Costello Syndrome. CFC is associated with heart defects (pulmonic stenosis or atrial septal defect), distinct facial features (hypertelorism, ptosis, micrognathia and low set ears) and skin abnormalities (eczema, ichthiosis, nevi, keratosis pilaris and thin, curly hair, along with curly, sparse or absent eyelashes and eyebrows). There have been case reports of lymphatic dysplasia, leukoproliferative disease and autoimmune disease in patients with associated RASopathies, however immunodeficiencies including hypogammaglobulinemia have not been described in CFC.

Case Report:
A 4-year-old female with history of CFC per genetic testing, presented with recurrent infections including frequent viral infections requiring hospitalization, and frequent severe gastrointestinal infections including Clostridium difficile and Hafnia alvei, as well as recurrent otitis media. Upon presentation, she was found to be lymphopenic, with normal albumin levels, and hypogammaglobulinemic with IgG of 308 and IgA of 17.9 were noted. Pneumococcal titers were obtained and found to be protective to 0 of 14 strains tested, despite having received full childhood vaccination series, including pneumococcal 13-valent conjugate vaccine. She developed borderline protective titers to only 5 of 14 serotypes after receiving the pneumococcal 23-valent polysaccharide vaccine. Flow cytometry was completed which revealed low B and T cell numbers, with normal natural killer cells. Switched memory B switch cells were also low. She also had a history of seizures, which are a known association of CFC and was also being worked up for possible mitochondrial disorder with history of acidosis. Further evaluation and treatment with IVIG are pending.

Discussion:
Our patient presented clinically with recurrent infections, and was found to have persistent hypogammaglobulinemia, along with low CD4 and CD8 T cells. Low switch memory B cells on flow cytometry were also noted, possibly associated with her blunted response to Pneumovax. As previously mentioned there are reports of lymphatic defects, predisposition toward cancers including leukoproliferative diseases, and autoimmune disease with RASopathies, however immunodeficiencies, including hypogammaglobulinemia have not been reported with CFC. Her clinical phenotype can in part be explained by her documented humoral immunodeficiency.

Conclusion:
CFC is rare syndrome, affecting multiple organ systems including the immune system. While there are known associations with lymphatic dysplasia and leukoproliferative disease, other immune deficiency such as hypogammaglobulinemia had not previously been described, and should be considered in these patients.

Patient Presentation and Testing:
The patient presented as a consult during hospitalization under the gastroenterology service for bloody diarrhea, and was also noted to have recurrent viral infections requiring hospitalization, recurrent otitis media and severe GI infections including Clostridium difficile and Hafnia alvei requiring hospitalization. Upon presentation she had already been diagnoses with CFC per genetic testing. Immunology service was consulted and records revealed lymphopenia on multiple occasions. Hypogammaglobulinemia with IgG of 308 and IgA of 17.9 were revealed. Pneumococcal titers were obtained and found to be protective to 0 of 14 strains tested, despite having received full childhood vaccination series,
including pneumococcal 13-valent conjugate vaccine. She developed borderline protective titers to only 5 of 14 serotypes after receiving the pneumococcal 23-valent polysaccharide vaccine. Flow cytometry was completed which revealed low B and T cell numbers, with normal natural killer cells. Switched memory B switch cells were also low. Labs were repeated including when child was well and IgG remained low. Patient continued to get recurrent infections, so decision was made to treat with IVIG which is currently pending.

**Diagnosis, Treatment and Patient Outcomes:**
Our diagnoses is hypogammaglobulinemia based on persistently low immunoglobulin levels. CFC diagnoses was already in place upon presentation and was initially based off of clinical phenotype and confirmed by genetic testing. Treatment with IVIG is pending due to frequency and severity of infections with persistently low immunoglobulin levels along with sub-optimal response to pneumococcal 23-valent polysaccharide vaccine.
Case Title: Delayed Diagnosis of DOCK8 Deficiency

Summary and Lessons Learned: Dedicator of cytokinesis 8 (DOCK8) deficiency is a rare, autosomal recessive, combined immunodeficiency characterized by severe atopy, increased susceptibility to cutaneous viral infections, Staphylococcus skin abscesses, and sinopulmonary infections. Typically, eczema presents during infancy and other symptoms develop throughout childhood. Here we present a case of DOCK8 deficiency with delayed diagnosis at age 12 that originally manifested with diffuse eczema and a severe genitorectal HPV infection during infancy. Unusually severe viral skin infections, especially in infants with atopic dermatitis, should prompt primary care physicians and immunologists to consider DOCK8 deficiency in the differential. Case reports of rare diseases help elucidate variable pathogenesis. In the case of DOCK8 deficiency, early diagnosis may prevent life threatening infections and malignancies.

Patient Presentation and Testing: The patient was referred to immunology at 12 years of age after developing vesicular lesions in the cranial V1 distribution consistent with herpes zoster that required hospitalization for IV acyclovir. Upon review of his medical history, the patient was born to unrelated parents at full term. He exhibited diffuse eczematous changes within a few weeks of birth. By 8 months of age, he developed a severe genitorectal HPV infection, requiring multiple surgical debridements to resect the lesions. He later developed recurrent skin abscesses, oral candidiasis, and MRSA impetigo. Additional atopic comorbidities include allergic rhinitis, asthma, and food allergies. Due to the severity of his herpes zoster episode and history of recurrent infections, immunology work up was initiated at age 12. Laboratory analysis was significant for eosinophilia, low CD4+ (300/mm3) and CD8+ (332/mm3) total lymphocyte counts, and elevated IgE (1315 IU/mL) with normal IgM, IgG, and IgA levels. Lymphocyte mitogen and antigen stimulation studies revealed absent response to candida and tetanus. Given his history of atopy and severe viral cutaneous infections, along with eosinophilia, lymphphenia, and T cell dysfunction, DOCK8 deficiency was highly suspected. DOCK8 protein expression was markedly reduced on flow cytometry. Sequencing of the DOCK8 gene revealed a pathogenic point mutation (c.2971-1G > A).

Diagnosis, Treatment and Patient Outcomes: The patient was diagnosed with DOCK8 deficiency. He recently underwent a myeloablative allogenic stem cell transplant from a matched, unrelated donor (10/10). Hematopoietic stem cell transplant is the only curative therapy for DOCK8 deficiency. Currently, the patient remains hospitalized after his transplant due to complications of acute kidney injury and acquired anemia.
Summary and Lessons Learned:
Our patient is a 13 year-old Hispanic male who carried a diagnosis of warm autoimmune hemolytic anemia and immune-mediated thrombocytopenia with antiplatelet antibodies consistent with Evan’s syndrome. His symptoms began when he was 11 years old. He presented initially with intermittent fevers, fatigue, pallor, and scattered petechiae on the extremities. He was found to have pancytopenia with reticulocytopenia. Bone marrow biopsy was significant for hypocellular marrow with marked erythroid hypoplasia. He also had parvovirus viremia with a viral load greater than 1 million copies/mL. Despite treatment with recurrent steroid pulses, blood transfusions, and mycophenolate mofetil, he continued to have autoimmune hemolytic anemia and thrombocytopenia and was treated with rituximab. Hemoglobin and platelets recovered within a few months post rituximab treatment. Over the next six months, he developed severe polyarticular arthritis and occasional dyspnea. He was treated with abatacept and had significant improvement in arthritis and dyspnea. Immunologic evaluation was initiated and he was ultimately found to have a heterozygous splice site (c.567+1G>A) mutation in CTLA-4 consistent with CTLA-4 haploinsufficiency.

This case demonstrates that CTLA-4 haploinsufficiency has many autoimmune manifestations that can develop at different times mimicking isolated rheumatologic conditions. CTLA-4 haploinsufficiency is characterized by lymphoid proliferation in non-lymphoid organs including intestine, brain, and lung. Patients can also present with hematologic cytopenias and immunodeficiency. Our patient had many of the features of CTLA-4 haploinsufficiency. Most remarkably, he also had polyarticular arthritis, which has not been previously described with CTLA-4 haploinsufficiency.

Patient Presentation and Testing:
Our patient is a 13 year-old male with history of warm autoimmune hemolytic anemia and immune-mediated thrombocytopenia with antiplatelet antibodies consistent with Evan’s syndrome who presented to our immune dysregulation clinic for evaluation. He was diagnosed at age 11. Prior to presentation in our clinic, he had been treated with multiple courses of steroids and mycophenolate mofetil in addition to a 4-week course of rituximab. However, he continued to have frequent relapses of anemia and thrombocytopenia. On presentation to our clinic, he complained of severe joint pain and swelling despite continued treatment with mycophenolate mofetil. Joints affected included bilateral knees, ankles, wrists, and all small joints of the fingers. Based on his history of Evan’s syndrome and systemic juvenile arthritis, primary immunodeficiency disease was suspected. Immune evaluation revealed normal T, B, NK cell populations, normal T cell proliferative responses, and immunoglobulin quantities. An evaluation for autoimmune lymphoproliferative disease was unyielding and he had normal quantities of CD4-CD8- T cells. Because of systemic arthritis, he was referred to rheumatology. Because of high suspicion of an immunodysregulatory primary immunodeficiency disease, genetic testing was performed. A deleterious splice site mutation was found indicating CTLA-4 haploinsufficiency.

Diagnosis, Treatment and Patient Outcomes:
In patients with CTLA-4 haploinsufficiency, there is usually a history of antibody mediated cytopenias in addition to a constellation of other immune mediated diseases. Abatacept is as CTLA-4 fusion protein composed of the Fc region of IgG1 bound to the extracellular domain of CTLA-4. Abatacept was initiated in our patient and he had significant improvement in arthritis and pulmonary symptoms within 2 infusions. Further studies to assess for manifestations of CTLA-4 deficiency have including imaging of the brain, lungs, and serologic assessment for insulin resistance have been normal.

References:
DiGeorge Syndrome (DGS) Variant and Immune Manifestations in an Infant of a Diabetic Mother (IDM)

Summary and Lessons Learned:
Rationale: DGS is classically caused by a mutation on chromosome 22q11. DGS variant or DGS phenotype are terms used to describe patients presenting with a typical DGS phenotype but lack a 22q11 mutation. DGS variants are caused by other genetic abnormalities and teratogens including retinoic acids, alcohol, and maternal diabetes. The phenotype and immunological manifestations of DGS variants are extremely heterogeneous. We present a case of a DGS variant in an infant born to a diabetic mother.

Methods: Case Description
Results: A term male infant born to a 28-year-old mother with insulin-dependent diabetes was found to have hypocalcemia, hypoparathyroidism, butterfly vertebrae, cardiac abnormalities, and an involuted thymus. Newborn screen was notable for repeatedly abnormal TREC. SCID panel revealed heterozygous mutations for Ligase-4, STIM4 and DOCK8. Whole exome sequencing did not reveal any further immunologic mutations. Laboratory evaluation revealed normal FISH for 22q11.2 and a normal microarray. Isohemagglutinin at birth was negative. Initial subsets showed CD4% and CD8% as low as 23% and 9%, respectively, with a total count of 265 and 100. He was placed on prophylactic Bactrim and is avoiding live vaccines. IgG, IgA, and IgM levels have been normal. The patient demonstrated loss of antibody protection to tetanus. B cell panel showed normal percentages of CD45RA/RO. Currently 17 months old, the patient has shown a slow increase in his lymphocyte subsets, with his most recent CD4 count being 897 (normal range 1300-3400 in children age 12-23 months) and CD8 count being 660 (normal range 620 -2000 in children age 12-23 months). Conclusions: DGS variant in infants born to diabetic mothers is rare but has been described. Immunodeficiency usually improves gradually in these variants. We describe a case of a DGS variant, his phenotypic manifestation, and his immunological findings. We note that he interestingly carries heterozygous mutations for multiple SCID-associated genes. Whether these genes are involved with the slow improvement in his lymphocyte subsets or the inability to maintain specific antibody protection is unknown. It is important to increase awareness of DGS variants and closely follow these patients' immune function, which can be highly variable.

Patient Presentation and Testing:
The patient initially presented as a full-term baby born to a diabetic mother. In the newborn nursery, he developed respiratory distress. A chest x-ray revealed cardiomegaly and vertebral body abnormalities. An echocardiogram showed VSD, ASD and PFO. There were no limb abnormalities, esophageal abnormalities, or anal atresia on exam. Renal ultrasound showed mild hydronephrosis. He did not meet criteria for VACTERL, and his findings were likely the result of uncontrolled maternal diabetes before and soon after conception. In order to rule out an underlying chromosomal abnormality, a microarray was sent and was within normal limits. Patient was then noted to have persistent hypocalcemia raising concern for the possibility of DiGeorge Syndrome, for which FISH analysis of 22q11 was sent. During this time, his newborn screen panel resulted with abnormal TREC values, at which point our service was consulted. We suggested lymphocyte subsets, mitogenic and antigenic responses, CD45 RA/RO and SCID panel. We also suggested a chest ultrasound to assess for thymic tissue, which revealed an involuted thymus. Given that genetic testing for 22q11 was negative, our service was suspicious for either a genetic DiGeorge variant or a variant secondary to being an infant of a diabetic mother. TBX1 genetic testing for DiGeorge variants was negative. SCID panel revealed non-pathogenic heterozygous mutation for DOCK8, Ligase 4 and STIM4. Lymphocyte subsets revealed low CD4 and CD8 T cells. Given that an underlying diagnosis was not reached and the patient had multiple abnormalities, whole exome sequencing was sent and did not reveal any further mutations. The diagnosis of DiGeorge variant secondary to being an Infant of a Diabetic mother was made.
Diagnosis, Treatment and Patient Outcomes:
This patient's constellation of anatomic anomalies, endocrine derangements, and immunodeficiency was suggestive of a classic DiGeorge Syndrome. FISH analysis for 22q11 and microarray were normal, implying that this patient is a DiGeorge variant. TBX1 genetic testing was negative, confirming a teratogenic cause for DiGeorge variant, specifically being an infant of a diabetic mother. Given this diagnosis and the variability of immune function in these patients, he had a full immunological workup and was noted to have CD4 and CD8 lymphopenia. He was managed with prophylactic Bactrim and avoidance of live vaccines. The patient follows with our immunology clinic every few months to undergo testing of his immune function, which is described to improve in variants, in contrast to classic DiGeorge Syndrome. As his lymphocyte subsets improve, we hope to vaccinate him with live vaccines and discontinue prophylaxis with Bactrim.
Case Title:
Stem Cell Transplant to Treat Warsaw Breakage Syndrome and ITK deficiency in the Setting of Recovered Hodgkin's Lymphoma

Summary and Lessons Learned:
We report the case of a pediatric patient diagnosed with Interleukin-2 tyrosine inducible tyrosine kinase (ITK) deficiency and Warsaw breakage syndrome (WABS) following an initial presentation with a suspicious neck mass subsequently found to be lymphoma. Interestingly, this patient was diagnosed with WABS and ITK deficiency following his Hodgkin’s diagnosis. There are no published reports of patients with both WABS and ITK deficiency. This case reinforces the fact that primary immunodeficiency may initially present with symptoms other than chronic infection.

Patient Presentation and Testing:
An eight year-old male was referred for evaluation due to a 4 month history of a waxing and waning unilateral neck mass. The mass had first been noted following an episode of febrile tonsillitis. The patient’s medical history as significant for poor weight gain and mild intellectual disability. Family history was significant for parental consanguinity (first cousins). Following an excisional biopsy, bone marrow aspiration, and scans, classic Hodgkin’s stage IIB was diagnosed. The patient enrolled in the experimental arm of the COG:AHOD1331 study in November of 2015. The chemotherapy agents used were Brentuximab, Etoposide, Doxorubicin, and Cyclophosphamide with Prednisone. Due to microcephaly, bilateral hearing loss, intellectual disability, and the recent Hodgkin’s diagnosis patient was evaluated by genetics with whole exome sequencing. A homozygous pathogenic c.223C>T mutation in DDX11 gene associated with Warsaw breakage syndrome and a homozygous pathogenic terminal deletion mutation in interleukin-2-inducible T cell kinase gene (ITK) associated with lymphoproliferative syndrome 1 were identified. The patient’s sister was heterozygous for DDX11 and ITK genes.

Diagnosis, Treatment and Patient Outcomes:
This patient was diagnosed via whole exome sequencing with both ITK deficiency and Warsaw breakage syndrome. Subsequently, the patient was found to have persistent Epstein-Barr Virus viremia, for which he was started on viral thymidine kinase inhibitors. Due to the known risk of recurrent lymphoproliferative malignancy in the setting of ITK with EBV viremia the patient underwent allogenic stem cell transplant in February of 2017, utilizing a conditioning regimen of Fludarabine, Melphalan, and Thymoglobulin and Rituximab. Engraftment was rapid however the patient developed respiratory symptoms and tested positive for human metapneumovirus in the immediate period following his transplant. High dose IVIG was administered, however viral infection persisted for several weeks. Post-transplant prophylaxis for graft versus host disease with Methotrexate and Tacrolimus was also administered, however, the patient developed steroid refractory acute GVHD of the skin, gut, and liver with a maximum acuity of grade IV. Twelve mesenchymal stem cell (MSC) infusions were used to treat the acute GVHD with complete recovery. His human metapneumovirus infection also resolved and the patient continues to do well just over one year out from transplant.
Case Title:
A Unique Presentation of Common Variable Immunodeficiency and

Summary and Lessons Learned
Common variable immunodeficiency (CVID) is one of the most commonly diagnosed primary immune deficiency. Patients generally have hypogammaglobinemia, recurrent sinopulmonary infections, impaired functional antibody response, inflammatory, and autoimmune manifestations. Posner-Schlossman syndrome (PSS) is a recurrent inflammatory glaucoma with increased intraocular pressure. It more commonly presents unilaterally and typically lasts days to weeks. Ocular complications have been described in patients with CVID; However, PSS has not been associated. We report the case of a patient with CVID who developed decreased vision and headaches secondary to PSS. This is a rare presentation of a woman with a primary immunodeficiency of CVID and an inflammatory disease of PSS. A distinct relationship still needs to be established; However, this case might draw attention to possible ocular findings in this rare disorder.

Patient Presentation and Testing
A 36 year old woman with a history of recurrent sinopulmonary infections underwent blood testing which revealed very low levels of immunoglobulins with poor response to polysaccharide vaccine, and a diagnosis of CVID was made. The patient began receiving intravenous immunoglobulin therapy. In February 2017, patient presented to an ophthalmologist for problems with blurred vision, mild eye discomfort, and headaches. The symptoms came on in the morning and lasted 1-2 weeks for the past two months and are associated with light flashes and disorientation. Tonometry revealed bilateral increased intraocular pressure (OD 34 mmHg and OS 42 mmHg) and slit lamp examination revealed stellate keratic precipitates; a diagnosis of PSS was made.

Diagnosis, Treatment, and Patient Outcomes
For the treatment of PSS the patient was started on Lotemax 0.5% suspension: 1 drop into both eyes twice a day. Within two months of treatment, the patient noticed an improvement in her symptoms. Follow up ocular slit lamp examination revealed a few faint keratic precipitates and tonometry showed bilateral decreased intraocular pressure (OD 15 mmHg and OS 9 mmHg). Patient continues to follow up with the ophthalmologist with no further complaints.
Summary and Lessons Learned
This is a unique case of a patient who had multiple years of musculoskeletal weakness and gluteal atrophy without a known diagnosis despite extensive medical workup including negative anti-GAD 65 antibodies. During this period, the patient began to develop recurrent sinopulmonary infections. With a thorough immunologic workup, the patient was diagnosed with Common Variable Immunodeficiency (CVID) and started on immunoglobulin therapy. Multiple years later, repeat testing for anti-GAD 65 antibodies was positive leading to the diagnosis of Stiff-Person Syndrome (SPS). The SPS disease is characterized by rigidity, stiffness, and weakness of the truncal muscles due to autoantibody production against glutamic acid decarboxylase 65 kD isoform (GAD65). Autoimmune diseases involving many organ systems are associated with CVID including rheumatologic, hematologic, dermatologic, and gastrointestinal; however, the neurologic system is less commonly associated.

Diagnostic evaluation to identify autoimmune disorders in patients with CVID can be difficult. To make the clinical diagnosis in the setting of CVID is not ideal as necessary serology testing may likely be altered and may not be helpful with the decrease antibody presence due to the immunodeficiency. As with our patient, both protective and self-antibodies were affected due to decreased antibody production capability of CVID. It is important to note that with our patient the workup and eventual diagnosis of her autoimmune disease took many years to obtain.

As immunologists, diagnosing and treating associated autoimmune diseases in patients with CVID can be difficult and imperative that a high clinical index of suspicion is maintained. Repeat testing may be necessary to identify the cause of the autoimmune symptoms. It took many years before the ultimate underlying cause of her weakness was fully elucidated. This patient represents the first reported case of SPS in a patient with CVID. Though it is extremely rare, clinicians might consider the diagnosis of SPS in a patient with CVID with musculoskeletal weakness and atrophy when other autoimmune disorders have been ruled out.

Patient Presentation and Testing
The patient was a physically active 50-year old woman with a five-year history of right-sided pelvic and low back pain that was accompanied by gluteal muscle atrophy. During this period she also developed recurrent sinopulmonary infections and required antibiotic courses on a monthly basis for more than one year. Before presenting to the immunology clinic, she had already been completing intensive physical therapy without improvement of her symptoms. An extensive workup was performed, which included normal electromyography and repeatedly absent anti-GAD65 antibodies. An extensive rheumatologic and neurologic laboratory workup was negative. When she presented to the immunology office her immune evaluation demonstrate low IgG at 551 mg/dL (reference range: 694-1618 mg/dL) and IgA at 54 mg/dL (reference range: 81-463 mg/dL) with normal IgM at 113 mg/dL (reference range: 48-271 mg/dL). The patient had absent pneumococcal antibody titers after both a pneumococcal polysaccharide and conjugate vaccinations.

Diagnosis, Treatment, and Patient Outcomes
With the laboratory findings, she was subsequently diagnosed with Common Variable Immunodeficiency. The patient was started on standard 400 mg/kg monthly dosing of Intravenous Immunoglobulin (IVIG) infusions for which began to improve recurrent infections substantially. Unexpectedly with the initiation of IVIG, her muscle weakness showed slight
improvement; however, no complete resolution was seen. Three years after initial testing, the patient had repeat anti-GAD65 antibody testing, which was positive at 41.2 IU/mL (reference range: < 5.0 IU/mL). With the patient’s constellation of musculoskeletal symptoms and the positive anti-GAD65 testing, the patient was diagnosed with Stiff-Person Syndrome. After this diagnosis and with her persistent musculoskeletal symptoms her IVIG dosing was increased to 1g/kg for immune modulatory effect. With this dose increase, the patient has seen an improvement in her musculoskeletal manifestations. This case IVIG describes the first patient with CVID and Stiff-person Syndrome.
Summary and Lessons Learned
Epstein Barr Virus (EBV) causes lymphoid hyperplasia due to its ability to immortalize B-cells, leading to lymphocyte proliferation. This process is augmented in immunocompromised individuals including those with primary immunodeficiencies and those on immunosuppressive therapy. Uncontrolled lymphoproliferation can compromise critical physiologic functions and require invasive treatment. Here we present a case of critical airway compromise requiring tracheotomy due to EBV-associated non-malignant lymphoproliferation in a patient with Crohn’s disease and mannose binding lectin (MBL) deficiency, with complete resolution following rituximab treatment, an anti-CD20 monoclonal antibody. This case highlights that targeting B-cells with rituximab can reduce non-neoplastic EBV-associated lymphoproliferation in individuals with reduced ability to mitigate EBV-driven lymphoid organ infiltration.

Patient Presentation and Testing
A 17 year-old female on 0.75mg/kg of 6-mercaptopurine (6MP) daily for Crohn’s disease presented with fevers, malaise, and persistent tonsillitis. She had an unremarkable family, social, and surgical history. She had no acute sick contacts. She was hospitalized for progressive respiratory distress and required tracheotomy due to severe lymphoid hyperplasia. Immunologic and infectious evaluation included serum cell and immunoglobulin counts, viral detection assays, genetic screening, and tonsillar biopsies to determine etiology of her fevers and lymphoid hyperplasia. Biopsies were also used to rule out neoplasm.

Diagnosis, Treatment, and Patient Outcomes
EBV panels detected rapidly increasing viral load (range 3,674 - 96,401 IU/ML) with positive IgM viral capsid antibodies. Biopsies revealed EBV-positive florid immunoblastic proliferation with extensive necrosis. Pathology was negative for malignancy, ruling out B-cell lymphoma. Serum evaluation noted absolute pan-lymphopenia; mildly elevated ferritin (781ng/mL); decreased mannose binding lectin (11); normal quantitative immunoglobulins; negative coccidiomycosis, cryptococcal, cytomegalovirus, human immunodeficiency virus (HIV) serology, and negative quantiferon gold. Natural Killer cell function and soluble IL-2-receptor levels were within normal limits, making hemophagocytic lymphohistiocytosis (HLH) unlikely. Genetic testing for primary immunodeficiencies was sent. 6MP was discontinued and she was started on rituximab weekly to mitigate B-cell proliferation and reduce lymphoid organ hyperplasia. EBV viral load was undetectable after seven weeks of treatment and airway narrowing markedly improved, allowing for decannulization. All cell lines and inflammatory markers normalized after completion of therapy. She has remained in good health since decannulization without evidence of infectious, immunologic, or oncologic sequelae of EBV infection or rituximab therapy.
Summary and Lessons Learned:
We present a case of a 14 year old male with cystic fibrosis who presented to the allergy/immunology clinic two years ago after multiple cystic fibrosis exacerbations with worsening pulmonary symptoms after multiple IV antibiotic treatments. He had high serum IgE, positive Aspergillus IgE, new pulmonary infiltrates, and positive skin testing, and was started on oral steroid therapy for allergic bronchopulmonary aspergillosis (ABPA). Due to history of steroid induced hyperglycemia, omalizumab therapy was trialed. This anti-IgE therapy has been used sporadically in children with CF as treatment for ABPA, and has been seen to decrease frequency of respiratory symptoms, reduce use of systemic corticosteroids, and improve expiratory flow function. One year later, our patient has noticed significant improvement in his respiratory symptoms, less cough, increased exercise tolerance, and improved sleep. His FEV1 has returned to baseline, and his steroid therapy has been tapered.

Steroids are the mainstay of ABPA therapy. However, due to well-known side effects of long term use of systemic steroids including immune suppression, infections, hypertension, adrenal insufficiency, weight gain, osteoporosis and steroid induced diabetes, other treatments have been explored, including omalizumab. Omalizumab is a monoclonal anti-IgE antibody, with proven efficacy in severe allergic asthma. Since ABPA has increased IgE production, there have been multiple cases describing positive results using omalizumab for treatment, however there have been no randomized, blinded, controlled multicenter trials. Our case adds further data to suggest using omalizumab as treatment for allergic bronchopulmonary aspergillosis in patients with cystic fibrosis.

Patient Presentation and Testing:
A well-known patient to the pulmonology clinic, a 12-year-old male with cystic fibrosis who had a sudden decline in his pulmonary function tests (PFTs), and failed oral antibiotic treatment was admitted to the hospital for worsening cough and sputum production. He complained of watery eyes, sinus pain behind his eyes and over his maxillary bones. He denied fevers and shortness of breath. Mom attributed his worsening lung function to increased pollen in the environment. At the time, PFTs showed FEV1 78 with a baseline of high 80s, low 90s. He was started on meropenem, IV tobramycin and trimethoprim-sulfamethoxazole on admission. Due to concerns for allergic bronchopulmonary aspergillosis, IgE was obtained and was noted to be 621 kU/L (normal <25). Chest x-ray also showed new opacities in right upper lobe, right lower lobe, and left perihilar region. Thus additional testing was sent for aspergillus. M3 A. Fumigatus AB Quant was elevated at 10.9 KUa/L (normal < 0.35).

Diagnosis, Treatment and Patient Outcomes:
Due lack of significant improvement of respiratory symptoms on antibiotic therapy, there were significant concerns for allergic bronchopulmonary aspergillosis. Despite changing IV antibiotics, FEV1 remained unchanged, thus leading to unlikely cause of bacterial exacerbation and most likely ABPA. He was referred to allergy/immunology clinic where he was positive for aspergillus skin testing sensitivity. He was started on oral steroid therapy which ameliorated his respiratory symptoms and improved his nighttime sleep. However, due to a history of steroid induced hyperglycemia, omalizumab was suggested. His increased pulmonary exacerbations delayed his injections for almost a year. His FEV1 prior to omalizumab was 81 A year after receiving omalizumab therapy every two weeks, FEV1 is at 96. He states improvement in is respiratory symptoms, less cough, increased exercise tolerance, and improved sleep. His steroid therapy has been tapered and his IgE level has decreased to 200 kU/L from 1200 kU/L prior to treatment.
Case Title: Nivolumab-Associated Posterior Reversible Encephalopathy Syndrome and Encephalitis

Summary and Lessons Learned:
Immune checkpoint inhibitors have shown promise as cancer therapeutics. Nivolumab is a human monoclonal antibody against surface protein programmed death 1 (PD-1), which blocks the interaction between PD-1 and its ligand on T cells, inhibiting apoptosis and promoting tumor-targeted T cell activation. Immune-related adverse events associated with checkpoint inhibitors are well described. We report a case of posterior reversible encephalopathy syndrome (PRES) and encephalitis associated with nivolumab. A 67 year old man with end-stage renal disease, ulcerative colitis, and metastatic renal cell carcinoma presented with nausea, vomiting, and word-finding difficulty two weeks after his fourth treatment with nivolumab. In the emergency department, he was hypertensive and became unresponsive with agonal breathing. Brain MRI revealed vasogenic and cytotoxic edema involving the bilateral parieto-occipital, temporal, and superior frontal lobes suggesting both PRES and encephalitis secondary to nivolumab. He was started on high dose steroids. Though his neurological examination improved transiently, profound visuospatial defects, left hemiparesis, and slow cognitive processing persisted. During this time, his blood pressure remained elevated and difficult to control. Repeat brain MRI showed worsening foci of restricted diffusion in the bilateral sensory and motor cortices, temporal and parieto-occipital lobes, and cerebellar hemispheres. He communicated a desire to focus on comfort and passed away shortly thereafter.

Increased capillary leakage due to T cell-mediated toxicity to the vascular endothelium is the proposed mechanism of nivolumab-associated encephalitis. The PRES-like findings in this case were likely multifactorial due to both the autoimmune process and malignant hypertension. However, the cerebral edema was more widespread than in typical PRES, accompanied by cortical infarction, and responsive to steroids, suggesting severe encephalitis due to nivolumab. The interaction between PD-1 and PD-Ligand 1 or 2 normally serves the immunoregulatory function of inhibiting T cell activation and proliferation. The disruption of PD-1/PD-Ligand binding by nivolumab enhances T cell activity with anti-tumor effects. However, this increased T cell function has been linked to a wide range of inflammatory adverse events. Specific risk factors for immune-related neurologic complications are unknown. In our patient, endothelial dysfunction due to chronic renal failure along with pre-existing ulcerative colitis could have increased his risk of developing an adverse event from nivolumab. Inviting further research, pre-existing autoimmune conditions have not been established as risk factors for immune-related adverse effects of checkpoint inhibitors. This description of nivolumab-induced encephalitis increases awareness of immune-mediated adverse reactions to checkpoint inhibitors and is important when considering the broader impact of immunotherapy.

Patient Presentation and Testing:
A 67 year old man with end-stage renal disease, ulcerative colitis, and metastatic renal cell carcinoma presented with nausea, vomiting, and word-finding difficulty two weeks after his fourth treatment with nivolumab. He had previously undergone unilateral nephrectomy, bilateral adrenalectomy, and treatment with sorafenib with progression of liver and lung metastases. Upon initial assessment, he was afebrile and hypertensive, with normal oxygen saturation and work of breathing. Physical examination revealed mild expressive aphasia, but no other abnormalities. CT head was ordered to evaluate for stroke or mass lesion. While in the CT scanner, he became unresponsive with agonal breathing. Code blue was called for respiratory failure, and he was promptly intubated and admitted to the intensive care unit. Head CT scan
and plain chest film showed no acute abnormalities. Brain MRI was obtained to further evaluate for neurologic etiologies for his respiratory compromise. Brain MRI revealed vasogenic and cytotoxic edema involving the bilateral parieto-occipital, temporal, and superior frontal lobes. EEG was also ordered to evaluate for seizure-like activity, but no epileptiform waves were seen.

**Diagnosis, Treatment and Patient Outcomes:**
The MRI findings were concerning for posterior reversible encephalopathy syndrome given involvement of the bilateral parieto-occipital lobes, however the widespread distribution of cerebral edema suggested that the PRES was part of a larger, severe encephalitis secondary to nivolumab. As corticosteroids are the mainstay of treatment for autoimmune side effects of checkpoint inhibitors, the patient was started on methylprednisolone 125mg daily. He initially remained unresponsive with rigid extremities, however, after increasing the dose of methylprednisolone to 500 mg daily, he became awake and alert, followed commands, and responded to questions. However, left hemiparesis and slow cognitive processing persisted. Additionally, visual testing demonstrated oculomotor apraxia, optic ataxia, and simultagnosia consistent with Balint’s syndrome in the setting of normal visual fields and acuity. During this time, his systolic blood pressure also rose to a peak of 190 mmHg and remained difficult to control on a nicardipine drip. As his neurologic exam plateaued, repeat brain MRI was obtained and showed worsening foci of restricted diffusion in the bilateral sensory and motor cortices, temporal and parieto-occipital lobes, and cerebellar hemispheres suggesting cortical infarction. The patient was able to communicate a desire to focus on comfort without further dialysis, and he transitioned to a palliative care unit where he passed away.
Summary and Lessons Learned:

Introduction: Hereditary angioedema (HAE) is a potentially life-threatening disease for which effective medications are currently available. Preferred first-line therapy include C1 inhibitor (C1INH) replacement or inhibition of bradykinin production or function. However, despite the availability of targeted therapy, a number of HAE patients may be incorrectly treated and/or do not have access to rescue medication.

Patient Presentation and Testing:

Case 1: A 10 year-old male with HAE presented with angioedema involving the face and airway after a minor bicycle injury. Mother administered prednisolone and diphenhydramine immediately because she had been instructed to give systemic steroids and antihistamines for rescue during a previous visit to a local children’s hospital emergency department (ED). Patient’s angioedema progressed to respiratory compromise, so he was emergently intubated and received plasma-derived C1 inhibitor (pdC1INH) in our ED. Labs obtained after pdC1INH were significant for a low C4 level 4.5 mg/dL (normal 10-40 mg/dL) and low C1INH protein level 17 mg/dL (normal 21-39 mg/dL), consistent with Type 1 HAE. Patient’s mother and sister were also previously diagnosed with HAE, yet none had access to on-demand treatment. The patient was successfully extubated and discharged after HAE education, arrangement for C1INH prophylaxis, and follow-up with his pediatrician. One month later, during time of submission, he was intubated again at another ED and is pending transfer to our PICU.

Case 2: A 17 year-old incarcerated female with HAE was brought to our ED with 2 days of head and neck angioedema and profuse drooling after fighting. Despite immediate administration of pdC1INH, patient required intubation due to significant airway compromise. Labs were significant for a low C4 level < 2 mg/dL and low C1INH protein level < 3 mg/dL, consistent with Type 1 HAE. The patient had a long history swelling since early childhood after trauma and had been seen by multiple ED’s and providers, yet rescue medication was never arranged for her. She was successfully extubated and is receiving C1INH prophylaxis at her institution. Arrangements have been made to test her 2 year old son for HAE.

Diagnosis, Treatment and Patient Outcomes:

Conclusion: These cases highlight the importance of patient education and availability of rescue medicine for HAE patients. Both of our patients had a known diagnosis of HAE, multiple family members with HAE, and numerous encounters with the healthcare system but received delayed and incorrect care resulting in serious morbidity. Further studies investigating the disparities in access and delivery of healthcare would be beneficial to all HAE patients.
Summary and Lessons Learned:
Allergen Immunotherapy (AIT) is a common treatment for individuals with allergic rhinitis and conjunctivitis. Given that AIT requires injections of small quantities of allergens in gradually increasing doses, some individuals may experience anxiety related to potential allergic reactions.

A 12-year-old male was receiving AIT for allergic rhinoconjunctivitis induced by mold, pollen, and grass allergens. During the build-up phase of AIT, the patient reported symptoms of an allergic reaction including chest and abdominal pain accompanied by shortness of breath that occurred after hospital discharge. The medical team extended the 30-minute observation period in order to assess these reported symptoms, but objective findings of an allergic reaction were not observed. The medical team suspected that the patient was experiencing anxiety related to AIT and it was unclear if continuing AIT was in the best interest of the patient.

Subsequently, during AIT the patient concurrently participated in 18 Cognitive Behavioral Therapy (CBT) sessions that addressed both general and allergy-specific anxiety management. CBT began with psychoeducation about allergies, AIT, and anxiety. Intervention then included identification of automatic thoughts and distortions related to allergic reactions from AIT and cognitive restructuring. The patient engaged in systematic desensitization through relaxation training and deep breathing while utilizing planned behavioral distractions during AIT. The therapist attended an AIT appointment with the patient to observe his symptoms and model appropriate use of the interventions. In addition, the patient and therapist developed personal goals regarding AIT and tracked progress on a weekly calendar. CBT was completed in conjunction with consultation with the allergy medical team in order to ensure accurate assessment of the patient’s AIT experiences. Over time, the patient reported decreased chest and abdominal pain and denied respiratory concerns following AIT, and the patient was able to continue with the recommended course of AIT without concern and is currently receiving monthly AIT injections without the presence of the psychology team.

This case highlights the relevance of CBT interventions in differentiating between symptoms of an allergic reaction versus anxiety during AIT. More broadly, this case highlights the importance of psychological services for children with anxiety related to allergic and immunologic conditions and interventions. Communication between medical and mental health providers may facilitate patients’ adherence to medical recommendations and increase their overall quality of life.

Patient Presentation and Testing:
The patient was 10 years old when he first presented to the Allergy Clinic at Children’s National Medical Center (CNMC). He was previously diagnosed by an outside provider with allergic rhinoconjunctivitis (ARC), asthma, eczema, food allergies (peanuts, shellfish), and eosinophilic esophagitis (EoE). The patient was prescribed Zyrtec, Alaway eyedrops, and Flonase for ARC management, Flovent daily and albuterol prior to physical activity for asthma management, Westcort cream for eczema management, and Prevacid for EoE management. The patient was compliant with shellfish and peanut avoidance.

The patient was started on weekly allergen AIT to treat ARC. After receiving the fourth dose of AIT (0.2 mL of red-top vials A and B), the patient reported coughing, watery eyes, and difficulty breathing 30-40 minutes after his injection. Notably, these symptoms occurred after the patient left the hospital following his observation period and were not examined by medical personnel. As a result of these reported symptoms, the subsequent AIT dosage was decreased to
0.15 mL of the red top vials A and B and the patient continued to report coughing, chest pain, runny nose, and fatigue after he left the hospital. The patient was administered Benadryl by his mother and the symptoms were not reported to the medical team until the following visit. The medical team elected to repeat this dose and extend the observation period to 60 minutes. At this appointment, the patient experienced runny nose, mild swelling at the injection site, and itching but there were no objective signs of wheezing or shortness of breath. Following these reactions, the patient’s dose was reduced to 0.1 ml of the red top vials A and B; however, the patient began missing appointments and there was continued report of adverse symptoms following AIT which limited progression of the intervention.

Based on the patient’s reported symptoms, lack of physical evidence of an allergic reaction, and resulting missed AIT appointments, the medical team referred the patient to the Allergy Psychology team at CNMC. At that time, the therapist conducted a comprehensive evaluation of the patient’s developmental, social, and educational history and diagnosed with patient with Psychological Factors Affecting a Medical Condition and Generalized Anxiety Disorder. Based on these diagnoses, the therapist developed a treatment plan that included Cognitive Behavioral Therapy for social anxiety and AIT-specific anxiety. The medical and psychosocial teams collaborated to develop a treatment plan for the patient’s AIT progression. Specifically, the team agreed to prolonged observation periods following AIT (60 minutes), weekly communication between medical personnel and the patient’s therapist following AIT appointments, and presence of the therapist at one or more AIT appointments to observe the patient’s symptoms and model appropriate anxiety-reducing interventions.

**Diagnosis, Treatment and Patient Outcomes:**
The patient received a diagnosis of Psychological Factors Affecting Other Medical Conditions which is defined as the presence of either psychological or behavioral factors that negatively impact a medical condition or its management. In the current case, the patient’s physiological symptoms of anxiety were misattributed to an allergic reaction and were negatively impacting the treatment of his allergic rhinoconjunctivitis. Additionally, assessment of other psychosocial functioning revealed symptoms that warranted a co-morbid diagnosis of Generalized Anxiety Disorder (GAD), including (1) excessive worry about topics such as social interactions, separation, school performance, and safety of family members, (2) difficulty controlling worry, and (3) physical symptoms of anxiety including impaired concentration, fatigue, and inability to carry out developmentally appropriate activities.

Cognitive Behavioral Therapy (CBT), a short-term, goal-oriented psychotherapy treatment that aims to change patients’ patterns of thinking and behavior through practical problem-solving and skill building, was recommended, as it is the treatment of choice for patients with these diagnoses. Individual sessions with the patient were held weekly, and the medical team and therapist communicated following the patient’s AIT appointments regarding symptom presentation. After sufficient preparation and skill-building, the therapist attended one of the patient’s AIT appointments in order to facilitate the use of CBT skills developed during therapy. During this appointment, the therapist completed frequent assessments of the patient’s anxiety symptoms, identified when coping strategies could be implemented (e.g., deep breathing and relaxation when patient began to feel chest discomfort), and provided prompts for the patient to engage in distracting activities. The therapist also helped the patient identify negative thoughts and distortions, challenge those thoughts, and identify positive replacement thoughts in-vivo. This portion of the CBT intervention was particularly helpful as reported by the patient as he felt he could use the interventions more effectively in subsequent appointments.

The patient achieved complete remission of AIT-related anxiety as evidenced by the absence of patient-reported symptoms (e.g., chest pain, difficulty breathing), a decrease in anxiety rating scores, and an ability to continue AIT treatment as recommended by the medical team. The patient continued CBT sessions to address GAD symptoms and achieved remission for these symptoms as well.
Case Title: Efficacy of immunotherapy in ant bite allergy

Summary and Lessons Learned
It is reported in the literature that from 0.8% to 5.0% of the human population has developed allergic reactions in skin or systemic, after a sting by Hymenoptera, approximately 50 people die each year in EE. As a result of severe anaphylaxis after a bite by these insects (bee, wasp and ants). The fire ant (Solenopsis invicta and S. richteri). Bite with their jaws while they bite. This allows them to remove the stinger, to rotate and to prick again. A single ant can inflict several bites on very little time.

Patient Presentation and Testing
A 13-year-old male patient diagnosed with anaphylaxis secondary to ant stinging at a second exposure was decided on treatment with specific immunotherapy (ITE), his laboratory studies with 7500 leukocytes 5.4% eosinophils and 400 cells, IgE 750 IU / ml.

Diagnosis, Treatment, and Patient Outcomes
Diagnostic testing was performed in vivo using prick with ant antigen. ESPIA questionnaire is applied, the patient refers, improvement of symptoms at 3 months of ITE administration to exposure to new ant pickets, overall rating of 67 points, which translates into a good efficacy of the same. Immunotherapy is an effective treatment for allergy to ant bite and is an excellent therapeutic option in patients who trigger anaphylactic reactions that put their lives in risk.
Case Title:
Childhood Chronic Spontaneous Urticaria: Rapid Response to Omalizumab

Summary and Lessons Learned:
A 7 year old female with a past history of mild intermittent allergic asthma presented with a 13 month history of chronic spontaneous urticaria without angioedema. All known etiologies of chronic childhood urticaria were ruled out. The patient reported an initial UAS7 score of 42 points and a Total Serum IGE measured 125 IU/ml. After 3 months of refractory treatment to multiple Nonsedating antihistamines at 3-4 times the usual dosing and Montelukast 5 mg po daily the patient was initiated on Omalizumab 150 mg SC q monthly. The patient responded after the first dose reaching a UAS7 score of 0 points within 1 month of treatment. The patient remains antihistamine and symptom free after 6 months of Omalizumab 150 mg SC q monthly and without reported adverse events. Omalizumab is approved for children >12 years for refractory Chronic Urticaria; however, there is a lack of evidence based studies in children under 12 with poorly controlled Chronic Urticaria. This case demonstrates the safety and efficacy of Omalizumab in the management of a patient with Childhood Chronic Spontaneous Urticaria and reflects the need for further studies to support our understanding and use of Omalizumab in this pediatric patient population.

Patient Presentation and Testing:
The patient is a 7 year old girl with a 13 month history of daily episodes of urticaria and dermatographism without angioedema. She denied any specific food and food additive, drug, contact, infectious, nutritional or autoimmune trigger. Past allergy history was significant for well controlled mild intermittent allergic asthma. She reported a history of an adverse drug reaction to amoxicillin. Her mother is diagnosed with severe persistent allergic asthma and is presently receiving Omalizumab 225 mg SC q 2 weeks. Total Serum IGE measured 125 IU/ml with High Specific IGE sensitivity to Birch Pollen, Cat and Dog Dander and Apple. Treatment was initiated with multiple high dose nonsedating antihistamines including Cetirizine 10 mg BID, Fexofenadine 180 mg BID and subsequently Levocetirizine 10 mg BID, Loratadine 10 mg BID and Montelukast 5 mg qd without significant clinical response. The patient reported an initial UAS7 score of 42 points. After 3 months of refractory treatment to aforementioned antihistamines and montelukast 5 mg per day, the patient was initiated on Omalizumab 150 mg SC every 4 weeks.

Diagnosis, Treatment and Patient Outcomes:
The diagnosis of chronic spontaneous urticaria was based on a 13 month history of persistent daily urticaria without angioedema unresponsive to multiple high dose nonsedating antihistamines (3-4 times the recommended dose of cetirizine, fexofenadine, loratadine and levocetirizine) and montelukast 5 mg qd. Known etiologies of childhood chronic urticaria including infectious, nutritional, autoimmune, food, food additive and drug hypersensitivity and inducible stimuli were ruled out. The patient reported an initial UAS7 score of 42 points. Total Serum IGE measured 125 IU/ml. Due to symptom severity and poor response from the above treatments the patient was initiated on Omalizumab 150 mg SC q monthly and responded after the first dose reaching a UAS7 score of 0 points within 1 month of Omalizumab treatment. All prior nonsedating antihistamines have been discontinued and after 6 months of Omalizumab treatment the patient remains in clinical remission without reported adverse events.
Case Title:
Systemic Mastocytosis Masquerading as Eosinophilic Gastroenteritis

Summary and Lessons Learned:
A 56-year-old female presents with gastrointestinal symptoms and profound peripheral eosinophilia. Work-up reveals eosinophil and mast cell infiltration of the upper and lower gastrointestinal tract with tryptasemia. Bone marrow is normocellular with eosinophilia and without mast cells. Her diagnosis is indolent systemic mastocytosis. This case illustrates the differential diagnosis of peripheral eosinophilia, which includes mastocytosis. Systemic mastocytosis may uncommonly present with normal bone marrow and mast cell infiltration of extracutaneous organ(s).

Patient Presentation and Testing:
A 56-year-old female with a history of diabetes mellitus, gastroesophageal reflux disease, and allergic rhinitis presents with 2-3 weeks of diffuse abdominal pain, bloating, watery diarrhea (10 episodes/day), non-bloody emesis, and intermittent dysphagia with odynophagia. She is a former 30 pack-year smoker. Apart from the addition of exenatide 2 months prior, there are no changes to her medications. Physical examination is normal except for diffuse abdominal fullness and tenderness to palpation without guarding. Liver and spleen are not palpable. Laboratory evaluation shows peripheral eosinophilia which increased from 1,320 cells/µL (0-610) on admission to 12,770 cells/µL on day 7. Upper and lower gastrointestinal biopsies show >400 eosinophils/high-power field (HPF) and 80-120 mast cells/HPF in the gastric tissue, duodenum, terminal ileum, and colon. The mast cells are arranged in dense infiltrates and >25% are atypical or spindle-shaped. They express CD2 and CD25 in addition to CD117. Laboratory evaluation reveals no cytopenias and normal liver and kidney function with the exception of albumin 3.0 gm/dL (3.5-5.0). Tryptase and total serum immunoglobulin IgE are elevated at 37 ng/mL (<11) and 11,021 kU/L (≤114), respectively. Exenatide is discontinued. Strongyloides serology and anti-neutrophil cytoplasmic antibodies are negative. Peripheral blood flow cytometry, IgG, IgA, and IgM are normal. Bone marrow biopsy shows a normocellular marrow without mast cells and with mildly myeloid-predominant trilineage hematopoiesis and eosinophilia. Genetic testing for KIT (D816V), platelet-derived growth factor receptor alpha and beta (PDGFRA, PDGFRB), and fibroblast growth factor receptor 1 (FGFR1) is negative. Serum tryptase and peripheral eosinophils remain elevated 6 weeks later, at 45 ng/mL and 1,020 cells/µL, respectively. Albumin normalizes.

Diagnosis, Treatment and Patient Outcomes:
Her diagnosis is indolent systemic mastocytosis given the mast cell infiltration of her gastrointestinal tract and persistently elevated serum tryptase. Medication-induced eosinophilia is considered, but exenatide cessation did not resolve her eosinophilia or symptoms. She is discharged on loratadine, famotidine, montelukast, and pantoprazole, and recommended to start cromolyn. She is given self-injectable epinephrine, instructed to have a bone densitometry scan, and continues to have gastrointestinal symptoms.
SUCCESSFUL TREATMENT OF ADULT-ONSET MACULOPAPULAR CUTANEOUS MASTOCYTOSIS WITH OMALIZUMAB

Case Title:
SUCCESSFUL TREATMENT OF ADULT-ONSET MACULOPAPULAR CUTANEOUS MASTOCYTOSIS WITH OMALIZUMAB

Summary and Lessons Learned:
Female, 36 years-old, with a history of maculopapular, brownish, fixed and intensely pruritic skin lesions which had started 17 years ago. She had a positive Darier sign. Treatment with different types of antihistamines, targeting both H1 (including ketotifen) and H2 receptors, as well as second generation H1 antihistamines used at fourfold the regular dose, had no effect. Total IgE level was 94,7 UI/mL. Skin biopsy showed accumulation of perivascular mast cells in the superficial dermis. No involvement of any other organ was evidenced. Diagnosis of adult-onset maculopapular cutaneous mastocytosis (MPCM) was established, based on current criteria which include presence of typical skin lesions; a positive Darier’s sign; and a biopsy showing increased infiltration of mast cells in the dermis. Due to unresponsiveness to treatment, she was started on omalizumab in January 2017. Omalizumab injections were administered initially at a dose of 150 mg every 2 weeks for the first three months of treatment, and subsequently at a dose of 300 mg every 4 weeks for the following two months, to June 2017. After the first 3 months of therapy with omalizumab, the patient presented marked improvement of her symptoms, particularly with disappearance of pruritus and considerable reduction of the color intensity of the skin lesions. No new skin pruritic maculopapular lesions appeared. There was a decrease in Mastocytosis Quality of Life questionnaire scores 81% and 52% at baseline and post-treatment, respectively; increase in the Urticaria Control Tests UCT scores (4 and 14, respectively; controled disease >12); decrease of Chronic Urticaria Quality of Life CU-QoL scores (79 and 50, respectively); and zero score for pruritus. Dermatology Life Quality Index DLQI scores were also reduced 25 and 14 at baseline and after treatment, respectively. Baseline serum tryptase level was 12.3 mcg/L, and after 3 months of Omalizumab treatment it decreased to 10.2 mcg/L, with a 17.2% reduction.

Mastocytosis is a rare disease characterized by proliferation and accumulation of mast cells in the skin and/or internal organs. It can be divided into cutaneous and systemic. The aim of treatment is to control the signs and symptoms caused by the release of mast cell mediators. It is important to avoid factors that trigger degranulation of mast cells, including heat, cold, pressure, stress, anxiety, infections, and drugs. Omalizumab has been shown to control objective and subjective symptoms of mastocytosis. Although Omalizumab use is not approved for use in cutaneous mastocytosis, being licensed only for chronic spontaneous urticaria and difficult to control asthma, this therapy has proven to be a good option for patients with this rare cutaneous disease.

Patient Presentation and Testing:
Patient presenting with maculopapular, brownish, fixed and intensely pruritic skin lesions which were worse in times of stress, since she was 19 years-old. She demonstrated major concern of her appearance, affecting her social life, due to the presence of the skin lesions, and complained of intense pruritus which had a profound impact on her sleep, work
and daily activities. She has never complained of abdominal pain, diarrhea, hypotension, syncope, musculoskeletal pain, or any allergic reactions including anaphylaxis or reactions to hymenoptera stings. She presented a positive Darier sign. No liver, spleen or lymphnode enlargement was found on physical examination. Skin biopsy showed massive infiltration of mast cells in the dermis.

**Diagnosis, Treatment and Patient Outcomes:**

Diagnosis of adult-onset maculopapular cutaneous mastocytosis (MPCM) was established by current criteria. Patient was unresponsive to different types of antihistamines, targeting both H1 and H2 receptors, including second generation H1 antihistamines at fourfold the regular dose. After the third application of Omalizumab the patient noticed a considerable reduction in the intensity of the lesions and complete disappearance of the pruritus. Objective measures including UCT, CU-QoL and DLQI indicated improvement, and tryptase levels were reduced by 17.2% after 3 months of treatment. The patient’s subjective judgement was of a marked improvement of her symptoms, and therefore therapy with omalizumab was maintained. Omalizumab has proven to be a good option for patients with this rare cutaneous disease.
Case Title:
Motor Stereotypies and Allergy – Are they cousins?

Summary and Lessons Learned:
Introduction- Motor Stereotypies (MS) are heterogeneous self-directed, repetitive, rhythmic, involuntary, coordinated, often bilateral purposeless movements which can be usually halted by distraction. Such types of behavioural disorders are often described with autism, tics and obsessive compulsive disorders, though they may be seen in isolation. MS can be associated with relative or absolute increase in stimulatory chemicals like dopamine or reduction in inhibitory mediators like δ-Aminobutyric acid and Acetylcholine. Pharmacological and behavioural therapies are mostly ineffective in controlling MS, highlighting the possibility of additional pathogenetic pathways.

Case- A 10 year girl presented with abnormal body movements since the age of 18 months, which began as to-and-fro body rocking while crawling and sitting, gradually progressed during brushing, standing and watching television over next year. She started having repetitive rhythmic head banging, at age 3, while subjected to stress or just prior to sleep. These movements were controlled with distraction or parental interruption. She was prescribed with Risperidone along with behaviour therapy, for years, with some control over body-rocking but head banging was still problematic. Neuroimaging, sleep and electroencephalographic studies were normal. She was referred to allergy clinic with complaints of seasonal cough and nasal block since early childhood requiring frequent over-the-counter anti-allergic medications. Head banging duration and intensity used to become worse during these episodes. Physical examination revealed bilateral inferior turbinate hypertrophy and wheeze in chest. Spirometry showed reversible obstructive pattern. Her total and specific IgE levels were significantly high (1435 IU/mL and 53.7 kUA/L respectively) with positive skin prick test for few aeroallergens (Eragrostis, Pennisetum, Brassica and Holoptela). She was started on Mometasone nasal spray (50 microgram twice daily), Salmeterol-Fluticasone (25-125 microgram twice daily) inhaler with Montelukast (5 milligram at night) along with salbutamol inhaler (200 microgram) as-and-when required. She was also advised for allergen avoidance measures. Her respiratory symptoms resolved in 2 weeks along with significant improvement in head banging resulted in weaning of psychotropic medications by the end of 4 weeks. During 1 year follow up, her allergic and stereotypic symptoms were adequately controlled on anti-allergic medications only.

Conclusion- There are evidences of mast cell-microglia-neuron interaction in the pathogenesis of ASD and autoimmune diseases but the role of mast cells in MS has never been previously reported. In our child, an isolated MS responding to anti-allergic medications is discussed, suggesting the possibility of mast cell induced pathogenesis as a common link, warranting prospective studies for establishment of casual relationship.

Patient Presentation and Testing:
A 10 year girl presented with abnormal body movements since the age of 18 months, which began as to-and-fro body rocking while crawling and sitting, gradually progressed during brushing, standing and watching television over next year. She started having repetitive rhythmic head banging, at age 3, while subjected to stress or just prior to sleep. These movements were controlled with distraction or parental interruption. She was prescribed with Risperidone along with behaviour therapy, for years, with some control over body-rocking but head banging was still problematic. Neuroimaging, sleep and electroencephalographic studies were normal. She was referred to allergy clinic with complaints of seasonal cough and nasal block since early childhood requiring frequent over-the-counter anti-allergic medications. Head banging duration and intensity used to become worse during these episodes. Physical examination revealed bilateral inferior turbinate hypertrophy and wheeze in chest. Spirometry showed reversible obstructive pattern. Her total and specific IgE levels were significantly high (1435 IU/mL and 53.7 kUA/L respectively) with positive skin prick test for few aeroallergens (Eragrostis, Pennisetum, Brassica and Holoptela).
Diagnosis, Treatment and Patient Outcomes:
She was started on Mometasone nasal spray (50 microgram twice daily), Salmeterol-Fluticasone (25-125 microgram twice daily) inhaler with Montelukast (5 milligram at night) along with salbutamol inhaler (200 microgram) as-and-when required. She was also advised for allergen avoidance measures. Her respiratory symptoms resolved in 2 weeks along with significant improvement in head banging resulted in weaning of psychotropic medications by the end of 4 weeks. During 1 year follow up, her allergic and stereotypic symptoms were adequately controlled on anti-allergic medications only.
Patient Presentation and Testing:
A 36 year old man presents for further evaluation after receiving a diagnosis of stinging insect venom hypersensitivity. Initially diagnosed after paper wasp sting induced anaphylaxis at age 4, he subsequently tested positive on venom skin testing, but only received venom immunotherapy (VIT) for three years. However, he then went on to have unprovoked anaphylaxis at ages 16 and 29.

After elevated serum tryptase levels (22.1 and 24.1 ng/ml) on 2 separate clinic visits, a bone-marrow biopsy revealed 1% mast cells, positive for D816V mutation of the c-KIT gene, without aberrant CD2 or CD25 expression. No extracutaneous mast cell disease was noted on either CT of the neck/chest/abdomen and pelvis or gastrointestinal endoscopy-guided biopsy.

Diagnosis, Treatment and Patient Outcomes:
Our patient did not meet the WHO criteria for SM and was diagnosed with MMAS. A rare clonal mast cell activation disorder, MMAS is diagnosed if only minor clonality criteria for SM are present without meeting full criteria. Hymenoptera stings are common triggers. Lifelong VIT is recommended if venom hypersensitivity is detected. The patient described had repeat venom skin testing and was positive to yellow jacket, wasp and white faced hornet. However, he declined lifelong VIT despite strong counseling. At last follow-up, he had not had any further episodes of anaphylaxis.
Summary and Lessons Learned
The patient had a longstanding history of constipation alternating with diarrhea, suggesting a diagnosis of IBS. However, symptoms became progressively worse with intermittent abdominal pain and diarrhea occurring up to eight times per day. History and diet changes did not reveal an identifiable cause. Finally, colonoscopy with immunostain for mast cell tryptase (MCT) revealed increased mast cell infiltration, suggesting a diagnosis of mastocytic enterocolitis. The patient was started on loratadine 10 mg and famotidine 20 mg, both BID. Due to marginal effect on symptoms, a trial of oral budesonide 9 mg daily was instituted. At one month follow up, the patient reported a marked decrease in symptom frequency and severity. To our knowledge, this is the first case of ME successfully managed with oral budesonide. The most common diagnoses in patients with chronic diarrhea are irritable bowel syndrome, inflammatory bowel disease, malabsorption syndrome, infection, and idiopathic secretory diarrhea. However, in some patients, laboratory workup for these diagnoses is negative, histologic appearances on routine staining are unremarkable, and treatment is ineffective. In a subset of patients with chronic diarrhea, increased mast cells in the gut mucosa is revealed by immunohistochemical analysis for MCT and has been observed to be the primary morphologic abnormality. This condition is described as mastocytic enterocolitis, and most patients with this condition respond to mast cell stabilizers and histamine H1 and H2 receptor antagonists. Incorporation of endoscopy, colonic or duodenal mucosal sampling, and MCT immunostaining as part of investigation in chronic intractable diarrhea can help to identify mastocytosis earlier, allowing for earlier administration of appropriate treatment and alleviation of symptoms. Therapies for mastocytic enterocolitis include antihistamines, such as ranitidine and famotidine. Cromolyn has been shown to provide improvement in gastrointestinal symptoms while antileukotrienes have shown improvement in pruritis and flushing. If these therapies fail, budesonide can serve as an alternative treatment. This case report provides support for considering budesonide in patients with mastocytic enterocolitis who have shown no improvement with antihistamines, cromolyn, and antileukotrienes.

Patient Presentation and Testing
The patient is a 39 year old male with a PMH of enterocolitis, GERD, epilepsy, Asperger syndrome, MDD, and OSA who presented on August 23, 2017, for evaluation of a recent diagnosis of mastocytic enterocolitis. The patient has had a longstanding history of constipation alternating with diarrhea, suggestive for IBS. Five months prior to presentation, these symptoms had become progressively worse, with intermittent sharp abdominal pain, bloating, and diarrhea occurring up to eight times per day. There were no identifiable food triggers to suggest food allergy. Reduced gluten diet had no effect on symptoms, which would have otherwise suggested Celiac disease. Four months prior to presentation, CT with contrast showed fatty pancreas and mildly dilated small bowel concerning for enteritis. One month prior to presentation, colonoscopy with mast cell tryptase immunostain showed increased mast cell infiltration (20.2 per high power field). Based on these findings, the patient was diagnosed with mastocytic enterocolitis. There was no definite increase in chronic inflammatory cells, intraepithelial lymphocytes, neutrophilic infiltrates, granulomas, subepithelial collagen, dysplasia, malignancy, viral changes, or parasites. Baseline tryptase and serum IgE levels were normal, which pointed away from systemic mastocytosis and food allergy. Evaluation for the c-kit mutation was not pursued since history was unremarkable for systemic mastocytosis. Of note, the patient has history of chronic seasonal allergic rhinitis with marked exacerbation during spring and fall. His symptoms are managed with intranasal spray and oral antihistamines. He has no other history of cutaneous symptoms, recurrent anaphylaxis, or symptoms suggestive of mast cell activation disorder. He has allergies to penicillin and sulfa drugs. Social and family histories are noncontributory.

Diagnosis, Treatment, and Patient Outcomes
There were no identifiable food triggers to suggest food allergy. Reduced gluten diet had no effect on symptoms, which would have otherwise suggested Celiac disease. CT with contrast showed fatty pancreas and mildly dilated small bowel
concerning for enteritis. Colonoscopy with mast cell tryptase immunostain showed increased mast cell infiltration (20.2 per high power field), which led to diagnosis of mastocytic enterocolitis. Baseline tryptase and serum IgE levels were normal, which pointed away from systemic mastocytosis and food allergy. Evaluation for the c-kit mutation was not pursued since history was unremarkable for systemic mastocytosis. The patient was then started on loratadine BID and famotidine BID, which has been shown to reduce symptoms in mastocytic enterocolitis. However, they had had minimal effect in this patient. The patient was then started on budesonide 3 mg, TID. The patient stated that he continued to have abdominal pain and diarrhea, but symptoms had decreased in frequency and severity.
Successful Use of Tiotropium Bromide Nasal Spray for Gustatory Rhinitis

**Summary and Lessons Learned:**
This case highlights that using a long acting anti-cholinergic in the treatment of gustatory rhinitis is both effective and safe. Presently, tiotropium bromide monohydrate is a long acting anticholinergic with specificity for muscarinic receptors indicated for maintenance treatment of bronchospasm associated with COPD and asthma. It is an aqueous solution available in an inhalation device and can effectively be sprayed into the nose to be used off label for gustatory rhinitis.

**Patient Presentation and Testing:**
We present a case of 91-year-old male with history of gustatory rhinitis for the past 7 years. Within 15 minutes of ingestion of any kind of food whether it was hot, cold, spicy or bland, he developed symptoms of clear watery rhinorrhea and sneezing, which would persist for 15 minutes or more. He was seen by an allergist in the past and had tried nasal and oral antihistamines, nasal steroids, and leukotriene inhibitors without relief. Anti-cholinergic nasal spray, ipratropium bromide helped him to an extent but did not completely resolve his symptoms. His symptoms were negatively impacting his social life and he could no longer go on dates to dinner.

**Diagnosis, Treatment and Patient Outcomes:**
Because his symptoms were consistent with gustatory rhinitis and ipratropium provided some relief, though minimal, we decided to try a long acting anti-cholinergic drug. We prescribed Tiotropium Respimat to use 1 spray in each nostril once a day. It was an off label indication for gustatory rhinitis and risks and benefits were discussed with the patient and his son in detail. He was seen for follow up in 2 months and his rhinorrhea had improved significantly since starting the tiotropium. He was able to do his routine activities and enjoy his social life without any restriction. He resumed having dinner dates.
Case Title:
Successful aspirin desensitization for polyposis in a omalizumab non-responder patient.

Summary and Lessons Learned:
A 51 year-old male with personal history of rhinitis and nasal polyposis was sent three years ago to our allergy unit. He referred runny nose, nasal congestion, hyposmia and trouble sleeping. All his symptoms got worst after taking ibuprofen. No wheezing or bronchospasm was recognized. After a complete anamnesis NSAID challenges were performed with positive results for ASA(Anaphylaxis) and negative for etoricoxib. He was diagnosed of aspirin-exacerbated respiratory disease-AERD
He was follow-up by the otolaryngology unit where he was diagnosed with bilateral grade 3 Nasal Polyps. Treatment with Nasal washes with salty water, intranasal corticosteroid and montelukast was initiated with bad response. Course of oral prednisolone was added with a temporary improvement. One year later nasal congestion reappears with grade 2-3 of nasal polyps. Nasal smear: 400 eosinophils. After a few courses of corticosteroids treatment with omalizumab, 300mg/4 weeks, was initiated. At first it was effective with clinical improvement (decrease in polyp size and subjective progress in nasal breathing), but after a year of treatment polyps grew to grade 4 and a new course of corticoids was needed. Omalizumab was discontinued without worsening.
Few months later ASA desensitization was done. Basal peak flow:580, spirometry: FVC: 5.300(98%), FEV1:3.740(92%) FEV1/FVC: 71(74%). Premedication:montelukast, nasal corticosteroid. We follow the next protocol: Day 1: 10mg--15mg--25mg--50 mg--100 mg--125mg, total accumulated 325mg. After the 1stdose he present rhinitis and peak flow decrease to 410; was treated with 200mg hydrocortisone, 5mg dexclorfeniramine and salbutamol nebulization, persisting runny nose that improves after 20mg ebastine, 50mg ranitidine and 40mg methylprednisolone. Following doses were given without new symptoms till the 5th. After it, he presented nauseas vomiting and sweating that was treated with 0.3cc adrenaline and 4mg ondansetron, with good response and tolerating the last dose.
Day 2 passes off in normal conditions: 100mg--200mg-325mg--650mg. Premedication:60mg methylprednisolone.
A dose of 650mg of ASA every 12hs was given during the first month with improvement of rhinitis, hyposmia, snore and breath. Nasal endoscopy demonstrate a reduction on the polyps to grade 2. ASA dose was reduced to 350mg/12hs with a deterioration of the rhinitis, the 650mg dose was restore.
In conclusion, ASA desensitization protocols may be safely performed and can be useful to treat polyposis even in those cases that biological treatment was ineffective. Each case must be considered individually.

Patient Presentation and Testing:
A 51 year-old male with personal history of rhinitis and nasal polyposis, without other medical history, was sent three years ago to our allergy unit. He did not have any relevant allergy family history.
In that time he refereed runny nose, nasal congestion, hyposmia and trouble sleeping. No wheezing or bronchospasm were recognized by the patient. At least every two weeks he had an episode of severe nasal congestion, during that days he needed to sleep propped up or sitting up.
All his symptoms got worse every time he consumed an ibuprofen.
After a complete anamnesis our team associated the worsening with the intake of ibuprofen. Until that moment he didn’t realized that the drug was de cause of his severe nasal congestion. Because of this we decided to do drug challenge tests in our outpatient care area.
NSAID challenges were performed. The ASA challenge test was positive: ten minutes after the second dose (25mg—50mg, accumulated 75mg), the patient presented nasal congestion, rhinorrhea and dyspnea. He received treatment with dexchlorfeniramine, methylprednisolone and adrenaline. The challenge test with etoricoxib was well tolerated. Finally he was diagnosed of chronic rhinosinusitis and NSAIDs intolerance --->aspirin-exacerbated respiratory disease, AERD

**Diagnosis, Treatment and Patient Outcomes:**
After the diagnosis of AERD he was follow-up by the otolaryngology unit where they saw bilateral grade 3 Nasal Polyps. Treatment with Nasal washes with salty water, intranasal corticosteroid and montelukast was initiated with bad response. Course of oral prednisolone was added with a temporary improvement. Because of the poor response surgery for nasal polyposis was done with improvement of symptoms, but one year later nasal congestion reappeared with grade 2-3 of nasal polyps. A nasal smear showed 400 eosinophils and endoscopy grade 3-4 polyps.

He was then sent to the allergy unit where after a few courses of corticosteroids, off-label treatment with omalizumab was established. The dose, was 300mg every four weeks. At first it was effective with clinical improvement and subjective progress in nasal breathing. Nasal endoscopy examination showed a decrease in polyp size, with bilateral grade 2 polyps.

After a year of treatment polyps grew to grade 4 and a new course of corticoids was needed. Omalizumab was discontinued without worsening.

A few months later, and after studying the case in our Severe Asthma Unit with pulmonologist and otolaryngologist, ASA desensitization was done. Before starting with de desensitization protocol we measure basal peak flow, 580, and basal spirometry, FVC: 5.300(98%). FEV1:3.740(92%) FEV1/FVC: 71(74%).

The patient got montelukast and nasal corticosteroid spray as pretreatment. We follow the next protocol in two days.
- **Day 1:** 1stdose 10mg, 2nd 15mg, 3rd 25mg, 4th 50 mg, 5th 100 mg, 6th 125mg, total accumulated 325mg. After the 1stdose he present rhinitis and peak flow decrease to 410; was treated with 200mg hydrocortisone, 5mg dexchlorfeniramine and salbutamol nebulization, persisting runny nose that improves after 20mg ebastine, 50mg ranitidine and 40mg methylprednisolone. Following doses were given without new symptoms till the 5th. After it, he presented nauseas vomiting and sweating that was treated with 0.3cc adrenaline and 4mg ondansetron, with good response and tolerating the last dose.
- **Day 2** passes off in normal conditions with the following doses: 1st 100mg, 2nd 200mg, 3rd 325mg, 4th 650 mg. Before the first dose was given he received 60mg methylprednisolone because during the night he got a severe hives. A dose of 650mg of ASA every 12hs was given during the first month with improvement of rhinitis, hyposmia, snore and breath. Nasal endoscopy demonstrated a reduction on the polyps to grade 2.

ASA dose was reduced to 350mg/12hs with a deterioration of the rhinitis, the 650mg dose was restored. In conclusion, ASA desensitization protocols may be safely performed and can be useful to treat polyposis even in those cases that biological treatment was ineffective. Each case must be considered individually.
Case Title:
The benefit of Mepolizumab in the treatment of allergic rhinitis in patients with eosinophilia

Summary and Lessons Learned:
Mepolizumab is a humanized interleukin-5 antagonist monoclonal antibody. It is currently approved for asthma as it affects the pathway responsible for maturation and release of eosinophils in the bone marrow. Eosinophils are associated with airway allergic disease. The reduction of the amount of eosinophils in the blood has been shown to be effective in decreasing pulmonary inflammation. Eosinophils have also been shown to be a key effector cell in nasal inflammation that is seen in allergic rhinitis. While not currently approved for allergic rhinitis, due to the pathway involved and the subsequent decrease in eosinophils, Mepolizumab could be further investigated as a possible treatment for allergic rhinitis and other diseases in which eosinophilia is present.

Patient Presentation and Testing:
A 63 year old female presented with a chief complaint of chronic cough secondary to moderate persistent asthma for years. The cough was constant throughout the day and responded poorly to medication. The patient also complained of allergic rhinitis symptoms most notably runny nose and nasal congestion. The patient was evaluated using the total nasal symptom score. She had severe rhinorrhea, severe nasal congestion and severe nasal itching. She stated that the symptoms interfered with her sleep. She denied sneezing. The patient had used nasal corticosteroid inhalers in the past with small improvements in symptoms. Chest CT was negative for significant findings, however laboratory testing repeatedly showed eosinophilia.

Diagnosis, Treatment and Patient Outcomes:
Due to the patient’s persistent cough and asthma symptoms, Mepolizumab was initiated. The patient’s cough symptoms decreased dramatically. After repeated injections, it was noted that the patient’s allergic rhinitis symptoms began to improve also. The patient was evaluated by a total nasal symptom score and had scores of 0 for nasal congestion, rhinorrhea, nasal itching, and sneezing. The patient’s nasal symptoms did not interfere with sleep after the Mepolizumab was initiated. The patient’s eosinophil level decreased from a level of 2261 prior to Mepolizumab to an eosinophil level of 138 after treatment.
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Case Title:  
The one that did not go away: adenoid hypertrophy as a rare cause of upper airway impairment in adults

Summary and Lessons Learned:  
Adenoid hypertrophy is a rare, or underreported, cause of nasal congestion in adults. In severe cases, symptoms could progress to cause upper airway impairment and mouth breathing. Unlike palatine tonsils, adenoid cannot be visualized directly due to its anatomical location, therefore, imaging studies such as computed tomography (CT) are often indicated. It is important to recognize adenoid hypertrophy as a rare cause of upper airway impairment and mouth breathing in adults, and consider appropriate investigation and therapy when indicated. Adenoid hypertrophy persistence should be considered in the differential diagnosis of therapy-resistant chronic rhinitis in adults.

Patient Presentation and Testing:  
A 50-year-old male presented was referred to allergy clinic after an initial evaluation at otolaryngology department for bilateral tinnitus, chronic sinusitis and allergic rhinitis. Symptoms have been present for longer than 5 years. The patient reported chronic hoarseness and a history of smoking 40 years for pack a day. Allergic rhinitis symptoms were not responsive intranasal steroid and antihistamine sprays used twice daily. CT of the neck and sinuses showed prominence of nasopharyngeal adenoidal tissue measuring 3.5 x 2.7 cm in cross-section, left maxillary sinus polyp versus mucus retention cyst, and mild paranasal sinusitis. The prominent adenoidal tissue of the posterior nasopharynx was considered to be secondary to infectious, inflammatory or neoplastic process.

Diagnosis, Treatment and Patient Outcomes:  
Patient did not obtain adequate symptom improvement with medical therapy. Due to the large nasopharyngeal mass blocking the nasopharynx, surgical correction was planned and implemented. The patient reported improvement after adenoidectomy. The biopsy of the mass showed respiratory mucosa with benign prominent lymphoid infiltrates, no malignancy was seen. The patient was attempting smoking cessation during the most recent follow-up visit.
Case Title:
An Unusual Cause of Sinusitis

Summary and Lessons Learned:
Chronic nasal congestion and chronic sinus symptoms may be the result of a more serious underlying condition. If symptoms do not respond to standard empirical therapy in a timely fashion, further investigation with an imaging study should not be delayed. Tumors of the nasopharynx are not rare and must be diagnosed promptly to allow the patient maximal opportunity for the best possible outcome.

Patient Presentation and Testing:
33 year old, previously healthy female, presents with a four month history of nasal congestion, sinus pressure, and anosmia of an unrelenting nature. She denied rhinorrhea, sneezing, sniffing, nasal pruritis or ocular itch or tearing. She had been treated empirically with three different courses of antibiotic, consecutively, for presumed sinusitis with no imaging study. She got no relief with cetirizine or fluticasone nasal spray. She did get brief relief with oxymetazoline nasal spray. She presented for allergy evaluation as she was not improving on the current treatment provided her. Past medical history was noted for childhood asthma until age thirteen. She was otherwise in excellent health and on no medications. Family history is noted for asthma and allergic rhinitis in her mother. Her son has asthma, atopic dermatitis, and egg allergy.
Examination of her nose revealed extremely edematous nasal membranes, almost completely obstructed, and bilateral nasal polyps. No cervical or submandibular lymphadenopathy. The remainder of her exam is unremarkable.

Diagnosis, Treatment and Patient Outcomes:
Prick and intradermal inhalant skin testing were all negative, with appropriate controls. A sinus CT showed complete opacification of the right maxillary sinus, bilateral frontal sinuses and bilateral ethmoid air cells. There was complete opacification of the nasal passages with bowing of both lamina papyracea laterally into the orbits. The CT study was very suggestive of a malignancy, so an urgent ENT consultation was arranged. The ENT surgeon removed a few nasal polyps revealing tumor tissue. A biopsy obtained for frozen section returned with the diagnosis of Esthesioneuroblastoma, a rare tumor of neuroectodermal origin arising in the olfactory lobe of the brain. The tumor was extensive on subsequent MRI, threatening both optic nerves, but was considered surgically resectable. She was referred to Mass Eye & Ear Infirmary for surgery and post operative cancer care.
Case Title:
Identifying the Root of the Problem: A Case of Recurrent Sinusitis due to Oroantral Communication

Summary and Lessons Learned:
This is a case of recurrent sinusitis due to an oroantral communication (OAC). OACs can occur secondary to a root canal and result in recurrent sinusitis. The diagnosis of an OAC is based on clinical symptoms even though a panoramic dental radiograph or computer tomography (CT) scan of the sinuses can help diagnose it. An OAC should be suspected in subjects with recurrent sinusitis following a dental procedure or a sinus culture yielding oral flora. Identification of an anatomical cause for recurrent sinusitis will prevent an unnecessary and costly immunodeficiency evaluation.

Patient Presentation and Testing:
A 53 year old female presents to allergy/immunology clinic for evaluation of recurrent sinus infections and suspected immunodeficiency. She has experienced up to four sinus infections per year during the past six years, signs and symptoms of which include: purulent nasal discharge, post nasal drip, right facial swelling, cough, fevers and night sweats, and cervical lymphadenopathy. She required multiple courses of antibiotics and states that her susceptibility to sinus infections became more frequent after undergoing root canals of her second and third right maxillary molars approximately six years ago. Her sinus infections also seem to be more likely to occur one to three weeks after dental cleanings. She denies any other history or family history of immunodeficiency or recurrent infections. Physical exam revealed normal vital signs and tenderness over the right maxillary sinus, ipsilateral anterior cervical lymphadenopathy, and purulent drainage in the posterior oropharynx. Medical records document cervical lymphadenitis two years prior complicated by a right carotid artery dissection. Cultures from her sinuses and fine needle aspiration of a cervical lymph node yielded Propionibacterium acne, an anaerobic bacterium common to the oral cavity.

Diagnosis, Treatment and Patient Outcomes:
An OAC between the oral cavity and maxillary sinus was suspected. A complete blood count with differential, quantitative immunoglobulins, pneumococcal and tetanus/diphtheria antibody titers, and lymphocyte subsets and proliferation studies were normal. A maxillary sinus CT was normal aside from changes suggestive of chronic sinusitis. However, her dentist indicated that she experienced a sensation of fluid entering her maxillary sinus while drinking liquids and of air entering her maxillary sinus during a valsava, consistent with an OAC. Extraction of her crowns and her right second and third molars elicited pus from the operative site, consistent with an OAC. Her symptoms resolved after extraction surgery and a six month course of oral clindamycin. She has been symptom free for the past eighteen months.
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Case Title:
Recurrent Swelling in a Patient with Marginal Zone Lymphoma: Acquired C1 Inhibitor Deficiency

Summary and Lessons Learned:
Acquired C1 inhibitor deficiency is rare and potentially life threatening. We present a patient with indolent marginal zone lymphoma who developed multiple episodes of angioedema without urticaria. This case highlights the importance of diagnosing acquired C1 inhibitor deficiency. Once the diagnosis is made the patient must receive bradykinin targeting therapy for episodes of angioedema as well as treatment of the underlying condition. All allergy/immunology providers should maintain a high level of suspicion for acquired C1 inhibitor deficiency in patients with recurrent angioedema and underlying malignancy, particularly non-Hodgkins lymphoma.

Patient Presentation and Testing:
68-year-old female presented with lip and cheek swelling without urticaria or pruritus. In the last one year, she described multiple similar episodes of intermittent lip, tongue and face swelling. Ten months prior she reported severe tongue swelling that required intubation. NSAIDs were suspected to be the cause and were discontinued, but frequent episodes of angioedema continued. Each episode lasts for several days and no other triggers can be identified. Anti-histamine therapy did not improve the angioedema.
Past medical history includes invasive ductal carcinoma of the breast in remission, hypothyroidism, arthritis with possible lupus, and marginal zone lymphoma diagnosed one year prior. No treatment had been administered for indolent lymphoma. There is no family history of angioedema. She has never taken ACE-inhibitors.
Laboratory testing showed a decreased C1 esterase inhibitor level of 4 (reference range 19-37 mg/dL), C1 esterase functional level decreased at 18% (reference range >41%), C1Q decreased at 3 (reference range 12-22 mg/dL), undetectable C4, undetectable C2 and normal C3. ANA positive at 1:160 with homogenous pattern. Double stranded DNA antibody negative. Similar results were obtained from an outside hospital 10 months prior.

Diagnosis, Treatment and Patient Outcomes:
The diagnosis is acquired C1 inhibitor deficiency based on decreased levels of C4, C1Q, C1 inhibitor level and function. The acute angioedema at presentation was treated with icatibant (bradykinin receptor antagonist) with rapid improvement of angioedema.
Acquired C1 inhibitor deficiency is often caused by an underlying condition, most commonly B cell malignancy and autoimmune disorders. Treatment should include therapy directed at the predisposing condition as well as bradykinin targeting therapies for acute episodes of swelling. The predisposing condition in this case is indolent marginal zone lymphoma. Thus, rituximab was initiated biweekly. After 6 weeks of therapy with rituximab the patient had a marked decrease in acute attacks of angioedema.
Case Title:
Acrodermatitis enteropathica: utility of a zinc level in refractory atopic dermatitis

Summary and Lessons Learned:
Acrodermatitis enteropathica, a rare autosomal recessive disorder, results in impaired zinc absorption from the diet due to a mutation in the intestinal zinc-specific transporter gene SLC39A4. Symptoms usually develop in the first few months of life and often begin after weaning from breast milk to cow’s milk. The triad of alopecia, diarrhea, and dermatitis is classically described as an indication of zinc deficiency. The rash can be eczematous and may be misdiagnosed as atopic dermatitis. Here we present an infant initially diagnosed with refractory eczema that was later determined to have severe zinc deficiency associated with acrodermatitis enteropathica, highlighting the need to maintain this on the list of differential diagnoses for eczema.

Patient Presentation and Testing:
This patient presented to the Allergy and Immunology clinic as a 19 month old male born at 39 weeks via spontaneous vaginal delivery to a gravida 2 para 1 healthy mother who was found to have severe eczematous dermatitis, hair loss, and diarrhea that started around 1.5 months of age and rapidly progressed. In addition, he had recurrent viral induced upper respiratory tract infections, wheezing, and chronic rhinitis. The patient’s newborn screen was negative for cystic fibrosis, metabolic or endocrinologic abnormalities; and a sweat chloride was negative. A celiac panel was negative, thyroid studies were within normal limits, pancreatic enzyme levels were low, and immunoglobulins were within normal limits for age. He remained breast fed and his growth is maintained around the 35th percentile. He has incidentally also been diagnosed with a milk protein sensitivity, but IgE to cow’s milk is negative. The only pertinent family history was colitis in the patient’s father.

Diagnosis, Treatment and Patient Outcomes:
He was initially treated for eczema but failed treatment with topical corticosteroids and emollients. He was referred to dermatology, who made the diagnosis of acrodermatitis enteropathica. He had a serum zinc level of < 25 mcg/dL (reference 75-150 mcg/dL). Although genetic testing was recommended (SLC39A4), his family was unable to afford the expense. However, he was started on zinc supplementation presumptively at 3 mg/kg/day by mouth daily, had complete resolution of his symptoms, and normalization of his serum zinc levels. This case highlights the need to consider acrodermatitis enteropathica in a patient with refractory dermatitis to avoid misdiagnosis. We must also consider the financial barriers when considering confirmatory testing for congenital zinc deficiency and explore treatment options of presumptive zinc supplementation, when testing is not feasible.
Case Title:
There's Something in the Air: Allergic Contact Dermatitis to Wood Dust

Summary and Lessons Learned:
While occupational respiratory disorders related to wood dust are well described in the literature, there is a paucity of data surrounding cases of contact dermatitis. Here we present a previously non-atopic adult male carpenter with new onset dermatitis. Initial symptoms consisted of a mild rash and concurrent eye irritation, progressing over 2-3 months to increased eye irritation, associated periorbital edema, and significant dermatitis on exposed areas of skin. Distribution suggested an airborne contact dermatitis. Symptoms consistently and completely resolved with avoidance of his wood fabrication shop. Skin patch testing revealed positive reactions to several woods, formaldehyde, and fabrication gloss. The patient was instructed to avoid allergens and, when unavoidable, increase skin protection measures. He was offered treatment with topical tacrolimus and triamcinolone for symptomatic control.

Providers should be aware of occupational contact dermatitis from wood dusts. Diagnosis can be challenging given the multiple potential agents and lack of guidance regarding wood-based testing. Treatment is challenging when avoidance is not sustainable, particularly with regard to impact on quality of life and livelihood.

Patient Presentation and Testing:
24 yo previously non-atopic adult male carpenter with new onset dermatitis. Typical protective equipment covered most of his body with the exception of neck, face, and arms from the elbows distally. Eye protection was perforated. Initial symptoms were eye itching and mild redness on the hands that worsened with scratching/itching. Topical emollients and triamcinolone were ineffective. Over 2-3 months, symptoms progressed to include worsening eye itch, periorbital edema at the margin of his protective glasses, and increasingly severe rash from the fingers to the antecubital fossa. Additional pharmacologic treatment with cetirizine, ranitidine was ineffective. Avoidance was associated with complete resolution of symptoms. Skin patch testing to include North American Standard, Plastic and Glues, as well as assorted woods and glues from patient’s wood fabrication shop was performed and diagnostic for contact dermatitis. To avoid contaminants, thinly planed wood samples were prepared for patch testing rather than collected wood dust. Patch testing revealed strong positive reactions to mahogany, fishtail, formaldehyde and weakly positive reactions to cherry, walnut, paduk, maple and fabrication gloss.

Diagnosis, Treatment and Patient Outcomes:
The patient was diagnosed with occupational allergic contact dermatitis, supported by the distribution of affected skin, consistent resolution of symptoms with avoidance of the wood fabrication shop, and positive patch testing. The patient was counseled regarding avoidance and skin protection measures to optimize safety and to comfortably continue in his profession.
Oral Crohn’s Disease, a Very Rare Cause of Isolated Lip Angioedema:

**BACKGROUND:**
Oral localization of Crohn’s disease is uncommon but can present with labial or buccal swelling that can be mistaken for isolated lip angioedema. Oral Crohn’s can present before or after the onset of GI disease and it appears to affect a different patient population and manifests particular tropicity for squamous cell epithelium. In the meantime, orofacial angioedema is frequently consulted to A&I sub-specialists therefore awareness of rare diseases for differential diagnosis is important.

**CASE REPORT:**
We present a 74-year-old lady with Oral Crohn’s syndrome who presented with chronic indurated swelling of her lower lip, painful, angular cheilitis, deep linear ulcerations of the tongue, and no evidence of facial palsy or digestive symptoms. She developed esophageal strictures and had a history of perforation 9 years before she presented to our clinic that required surgical repair. She also had a history of abdominal and perianal abscesses that required I&D 6 years ago. Never diagnosed with Crohn’s. She had a history of DM –II, hypothyroidism, GERD, hypercholesterolemia, allergic rhino-sinusitis, Vit D deficiency and hypertension. She did not have a family history of HAE and had no one else in the family with a similar problem. She was never placed on ACEI. At the time of presentation review of symptoms revealed unintentional weigh loss and low grade fevers noted by the patient as well as random abdominal pains. Her exam revealed tense lower lip edema, with painless and non-pruriginous swelling that was 2-3 times normal lip size, poor dentition, deep longitudinal fissures of the tongue and angular cheilitis. Her labs at the time of her initial visit was significant for elevated ESR (84, reference range -15mm/hr), low hemoglobinm and hematocrit values (10.1 g/dl and 32.3%), low iron levels (39ug/dl), low TIBC (257 mcg/dl). She had an initial work up assessed her quantitative C1 esterase inhibitor values and function as well as her C1q levels. A derm consult was also requested for lower lip biopsy with the concern of cheilitis granulomatosa. Her C1 esterase inhibitor levels were elevated (41mg/dl) and her C1 esterase inhibitor functional study was 102% of mean normal. Her C1q levels were within normal range (21mg/dl). Patient was seen at Duke Dermatology clinic and changed her mind not to have biopsy and upon follow up p-ANCA (Anti-Myeloperoxidase Antibody), IgG and IgA ASCA testing was requested and her p-ANCA levels came back as within normal (6 units) and both her IgA and IgG ASCA was elevated (29 and 38 U respectively). Patient was lost to follow up after her second visit.

**DISCUSSION:**
Oral Crohn’s disease is characterized by a very low prevalence (0% to 9%), male predominance, protracted course with high prevalence of associated anal and esophageal involvement (suggesting a tropicity for squamous cell epithelium). Melkersson-Rosenthal syndrome (MRS) is the main differential diagnosis as both entities have associated edema, induration, angular cheilitis, chronic protracted evolution, and granulomatous histologic features. Facial palsy and absence of digestive symptoms are suggestive of MRS. A&I sub-specialist are frequently consulted for both cases of indurated edema, mistaken to be angioedema, hence knowledge of these rare diseases are essential.

**Patient Presentation and Testing:**
Patient presented with chronic indurated swelling of her lower lip, painful, angular cheilitis, deep linear ulcerations of the tongue, that was mistaken for isolated lip angioedema. Had GI problems for the past 9 years including esophageal strictures that required dilatation, and perianal abscess that required incison and drainage. She had no history of HAE
and was never placed on ACEI despite being hypertensive. Had low RBC indices and iron and elevated ESR and her tests for HAE type I and II as well as AAE was negative. A lip biopsy was requested but patient declined the procedure at Dermatology office and did not want any interventional diagnostic procedure later on. Based on her past history of GI problems that was consistent with Crohn’s, her review of systems that was positive for low grade fever and intermittent abdominal pains as well as weight loss and her exam findings as well as lab data that was supportive of Cronh’s including ASCA IgG and IgA in the presence of negative p-ANCA, patient was considered to be a case of oral Crohn’s disease.

**Diagnosis, Treatment and Patient Outcomes:**
The diagnosis of the patient based on very characteristic oral exam findings, past history, lab data and review of symptoms is oral Crohn’s disease which appears to have a peculiar tropism for squamous cell epithelium, frequently involving anal, esophageal and orolabial mucosa compared to Crohn’s in general. Patient was lost to follow up however and did not respond our calls. A treatment plan at this stage of Crohn’s appear to involve biologic agents that would include TNF inhibitors such as Adalimumab, Infliximab and Certolizumab as well as monoclonal antibody against the cell adhesion molecule α4-integrin Natalizumab.
Case Title:
AQUAGENIC URTICARIA: CASE REPORT

Summary and Lessons Learned:
Aquagenic urticaria is a rare, familial, sporadic dermatosis characterized by formation of pruritic wheals due to contact with water.
OBJECTIVE: To describe clinical and diagnostic aspects of a patient with aquagenic urticaria treated in the allergy outpatient clinic at the CUBM of Ribeirão Preto (Brazil).

Patient Presentation and Testing:
A 12-year-old boy reported the appearance of pruriginous punctiformis after bathing or swimming in a pool 4 months earlier. The lesions lasted for approximately 30 min. Regardless of modifications in water temperature and soap, the episodes occurred several times a week. The patient denied any association with type of clothing or food or other systemic manifestations. Personal antecedents included allergic rhinitis. Familial antecedents included a father with porphyria and a mother with allergic rhinitis. Physical examination revealed no lesions. Dermographometry and tests for cold urticaria using ice cubes and cholinergic urticaria were negative. Water compresses at 37°C resulted in urticariform lesions on his back and trunk, confirming the diagnosis. The total IgE level was 386.0 UI/mL, and a hemogram showed 6.3% eosinophils.

Diagnosis, Treatment and Patient Outcomes:
The diagnosis was Aquagenic urticaria and the treatment with antihistamines was effective for 6 months, when intensely pruriginous lesions reappeared. The dosage of antihistamines was quadrupled, and 10 mg/day antileukotriene was initiated. After 2 months, the condition improved, with a progressive reduction in medication until complete withdrawal after 5 months. For 2 years, a total remission of symptoms has been maintained. Clinical manifestations and age of onset were similar to those described in the literature. Diagnosis and correct treatment are important for good prognosis.
Case Title: Disseminated Tinea Corporis due to Zoonotic Transmission Masquerading as Recalcitrant Urticaria

Summary and Lessons Learned:
Disseminated tinea corporis (DTC) in an immunocompetent patient is a rare entity. Based on the differing clinical presentation and histologic findings, urticaria and tinea corporis (TC) are two distinct entities that shouldn’t be confused, as treatment of one can exacerbate the other. We present a young woman with TC likely from zoonotic transmission which became disseminated with evidence of Majocchis Granuloma (MG) secondary to immunosuppressive treatment for suspected urticaria. DTC and MG are uncommon entities and should be differentiated from urticaria. Proper diagnosis is important as each entity is treated differently. In general, the most common cause of TC is Trichophyton rubrum but zoonotic transmission may be from Trichophyton mentagrophytes.

Patient Presentation and Testing:
Our patient was a 16 year old female with pet rats who presented for a rash consisting of annular, non-blanching plaques with central clearing. She was seen by ER, allergy, and dermatology physicians, and diagnosed repeatedly with urticaria. She was treated initially with anti-histamines, then later with IV corticosteroids due to recalcitrance. The central clearing of multiple lesions was more characteristic of TC, so repeat biopsy was performed, which confirmed diagnosis. We suspect immunosuppression from corticosteroids blunted the immune response leading to DTC and MG. Patient was treated with oral anti-fungals. We suspect she contracted the infection from her pet rats. Infection with Trichophyton mentagrophytes has been described in laboratory animals.

Diagnosis, Treatment and Patient Outcomes:
Shave skin biopsy was performed which demonstrated perivascular dermatitis, parakeratosis, and spongiosis. Notably, there was fungal hyphae in the epidermis and the hair follicle consistent with MG.
Sensitization to vespids venoms after immunotherapy with bee venom

Summary and Lessons Learned:
Up to 50% of patients with allergy to hymenoptera may be positively affected by cross-reactivity. Cross-reactivity between bees and wasps by specific IgE is frequent between 30-60% of cases and it is mainly due to hyaluronidase (Api m2 / Ves v2, Pol d 2), to dipeptidylpeptidase IV (Api m5 / Ves v3) or to vitellogenins (Api m12 / Ves v6). However, cross-reactivity between vespids and bee phospholipases has not been described because they do not share common structures. But in our case the Cross-reactive Carbohydrate Determinants (CCDs) plays an important role in the sensitization found after immunotherapy with bee venom.

Patient Presentation and Testing:
We report the case of a 29 - year - old male with a history of allergic rhinitis caused by house dust mites and a history of severe local bee sting reaction. Denies stings by other hymenoptera. That he occasionally helped his beekeeper father. Which in 2010 immediately after a bee sting he initiates generalized pruritic erythema, rapidly progressive malaise and dizziness, without loss of consciousness. He consulted at a primary health center and was treated with methylprednisolone 60 mg and dexchlorpheniramine 5 mg intramuscularly with improvement of symptoms within a few hours. He was not treated with adrenaline.
After performing the allergy study 2 months after the reaction, he had normal tryptase; positive intradermal tests to bee venom and negative to vespids venoms; specific IgE to bee, Vespula and Polistes venoms of 0.66, 0.11 and 0.05 kU/L respectively; and positive basophils activation test (BAT) only to bee venom, he initiated Pharmalgen® Apis mellifera immunotherapy (ALK Abelló).

Diagnosis, Treatment and Patient Outcomes:
After 3 years of treatment he had specific IgE of 3.65; 7.56 and 6.15kU/L respectively, in the absence of new stings. A decrease in BAT positivity to bee venom and a negative sting challenge test with good tolerance to bee sting.
To differentiate between sensitization and cross-reactivity an immunoCAP-inhibition study was performed to Apis mellifera, Vespula and Polistes venoms and different molecular allergens, including CCDs. It was possible to demonstrate cross-reactivity between venoms and CCDs and between vespids phospholipases and CCDs.

Conclusions
We suspect that sensitization to CCDs is responsible for sensitization found to vespids venoms after immunotherapy with bee venom. No other allergen from bee venom was found responsible for cross-reactivity by the molecular study performed. We did not find publications of similar cases.