World Allergy Forum Symposium:
Eosinophilia and Co-Morbid Conditions

2012 EAACI Congress
Tuesday, 19 June 2012
10:30 – 12:00
Geneva, Switzerland

Moderators:
Ruby Pawankar (Japan)
Cezmi Akdis (Switzerland)

Differential Diagnosis of Eosinophilic Conditions
Hans-Uwe Simon (Switzerland)

Eosinophilic Esophagitis
Marc Rothenberg (United States)

Hypereosinophilic Syndrome
Amy Klion (United States)

www.worldallergy.org

The World Allergy Organization (WAO) is an international organization of 89 regional and national allergy and clinical immunology societies. WAO’s mission is to be a global resource and advocate in the field of allergy, advancing excellence in clinical care through education, research and training as a world-wide alliance of allergy and clinical immunology societies. WAF is an educational program of the World Allergy Organization.
WISC 2012
2012 WAO International Scientific Conference

Severe Allergies, Severe Asthma:
New Strategies for Optimal Treatment & Prevention

Hyderabad, India
6-9 December 2012

www.worldallergy.org/wisc2012
“Eosinophilia and Co-Morbid Conditions”

Program

Moderators:
Ruby Pawankar
Nippon Medical School
Tokyo, Japan

Cezmi Akdis
Swiss Institute of Allergy and Asthma
Davos, Switzerland

1. Welcome to the World Allergy Forum Symposium and Introduction to “Eosinophilia and Co-Morbid Conditions”
   Ruby Pawankar and Cezmi Akdis

2. Differential Diagnosis of Eosinophilic Conditions
   Hans-Uwe Simon
   Institute of Pharmacology
   University of Bern
   Bern, Switzerland

3. Eosinophilic Esophagitis
   Marc Rothenberg
   Director, Division of Allergy and Immunology
   Director, Cincinnati Center for Eosinophilic Disorders
   Cincinnati, OH, United States

4. Hypereosinophilic Syndrome
   Amy D. Klion
   Eosinophil Pathology Unit
   Laboratory of Parasitic Diseases
   National Institute of Health
   Bethesda, MD, United States

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Mission of the World Allergy Organization

WAO’s mission is to be a global resource and advocate in the field of allergy, advancing excellence in clinical care through education, research and training as a world-wide alliance of allergy and clinical immunology societies.

WAO Meetings

World Allergy Congress™ (WAC)

WAO hosts the World Allergy Congress™ (WAC) — its main scientific meeting — biennially in different regions of the world. Please join us in Milan, Italy in 2013 and Seoul, South Korea in 2015.

WAO International Scientific Conference (WISC)

In 2010, WAO launched its theme-based scientific conferences alternating with and complementing WAO’s biennial World Allergy Congresses. The 2nd WAO International Scientific Conference on Severe Allergies, Severe Asthma: New Strategies for Optimal Treatment and Prevention will be held in Hyderabad, India — 6-9 December 2012. The 2012 Conference will provide a forum for the most useful combination of the latest research, review of current theory and practice, and hands-on, problem-based learning. For more information, visit www.worldallergy.org/wisc2012.

World Allergy Organization Journal

The World Allergy Organization Journal (WAO Journal) provides a global forum for the exchange of research and information on allergy, asthma, and clinical immunology. The journal supports this scientific interaction among members of the World Allergy Organization, an alliance of 89 societies worldwide, through publication of original research, clinical reviews, position papers, and epidemiological studies that contribute to current knowledge in patient care. Articles cover diagnosis, therapeutic options, crisis management, and treatment efficacy. Authors and reviewers represent all geographic regions, providing a truly global perspective. Published monthly online, with access on computers and mobile devices, the journal ensures the widest availability of practice-relevant science at the point of care. In 2010, the WAO Journal launched a new feature, Chief Editor Podcasts, consisting of audio downloads of interviews with authors of recently published articles on the latest research. www.waojournal.org

WAO Online Resources

As a leading global online destination for allergy, asthma and clinical immunology the WAO website supports and enhances WAO educational activities and provides materials specifically designed for continued medical training.

Popular resources include:

- Specially commissioned educational synopses on major topics posted in the Allergic Diseases Resource Center
- Interactive case studies that challenge allergists to diagnose unusual cases
- Online learning programs including the Immunology Online Lecture Series, Asthma and Allergic Rhinitis Online Lecture Series, and the interactive learning modules with CME on Food Allergy and Drug Allergy
- An archive of webinars recorded at major meetings, and audio recordings of interviews with key opinion leaders around the world
- A special section, Defining the Specialty, which provides easy access to WAO publications and other resources that help to define the specialty of allergy and immunology including the WAO White Book on Allergy
- Disease-specific sections of the website including the Allergic Rhinitis Working Group, Small Airways Working Group, and HAE Alliance.

The WAO website is HONcode certified. www.worldallergy.org

WAO Programs for Education, Research and Patient Care

Global Resources in Allergy™ (GLORIA)

GLORIA promotes best practices in the management of allergic disease through programs developed by international advisory expert panels. Modules are created from established guidelines and recommendations to address different aspects of allergy-related patient care. GLORIA is presented at national and regional allergy society meetings throughout the world and also at regional, state and local society meetings within the United States. All current GLORIA modules are available for free download at www.worldallergy.org/gloria.

World Allergy Forum ® (WAF)

The World Allergy Forum ® (WAF) program brings cutting edge symposia to major allergy meetings throughout the world. Developed by international expert advisory panels, the symposia provide up-to-the-minute presentations on scientific and clinical developments in the field of allergic disease. WAF is the longest running educational program series sponsored by WAO and currently provides two or three placements a year with up to 1,000 attendees at each program. WAF is supported by an unrestricted educational grant from Novartis. View presentations for free at www.worldallergy.org/waf.
WAO Programs for Education, Research and Patient Care (continued)

Emerging Societies Program (ESP)
In order to advance the WAO mission of supporting developments that will enable allergists to better serve patients now and in the future, the Emerging Societies Program (ESP) aims to disseminate information on and share experiences about new treatments for allergic disease and about new indications for available therapies. As a response to an area of need identified by ESP Delegates, the ESP has also started to offer World Allergy Training Schools (WATS) in various regions of the world. All ESP meetings and training schools are conducted with the help and support of WAO Member Societies and held in conjunction with a Member Society’s annual meeting and in partnership with the American College of Allergy, Asthma and Immunology (ACAAI). View all ESP activities at www.worldallergy.org/esp.

WAO Publications
WAO papers support and promote the specialty of allergy and help set standards for clinical practice and training. A full bibliography is available at www.worldallergy.org/publications/.

World Allergy Week
In 2011, based on feedback from WAO Member Societies over recent years, WAO inaugurated the first annual World Allergy Week as a way for WAO Member Societies to collaborate in a global effort to disseminate information of worldwide importance about allergic and immunologic diseases and asthma. Participation covered a wide spectrum of activities including promotions through websites and social media avenues, patient information sessions, and interviews for radio and television programs. Watch for updates and view last year’s activities at www.worldallergy.org/worldallergyweek/.

WAO Junior Members Group
www.worldallergy.org/juniormembers/
The WAO Junior Members Group aims to support and encourage young scientists and clinicians by providing the opportunity for them to contribute to the ongoing work of the WAO - and become future WAO leaders! Applicants must be working in the field of allergy/clinical immunology, be 35 years of age or under and/or within 5-years of their latest degree, and a current member of a WAO Member Society. Visit www.worldallergy.org/juniormembers/ for further information or to apply.
The World Allergy Organization (WAO), a world federation of allergy, asthma, and clinical immunology societies, consists of 89 Member Societies. All active members of dues-paying Member Societies are Individual Members of WAO.

**WAO Member Societies**

- Albanian Society of Allergology and Clinical Immunology
- National Association for Private Algerian Allergists
- American Academy of Allergy, Asthma and Immunology
- Argentine Association of Allergy and Immunology
- Argentine Society of Allergy and Immunopathology
- Australasian Society of Clinical Immunology and Allergy
- Austrian Society of Allergology and Immunology
- Azerbaijani Society for Asthma, Allergy and Clinical Immunology
- Bangladesh Society of Allergy and Immunology
- Belgian Society for Allergy and Clinical Immunology
- Brazilian Society of Allergy and Immunopathology
- British Society for Allergy and Clinical Immunology
- Bulgarian Society of Allergology
- Canadian Society of Allergy and Clinical Immunology
- Chilean Society of Allergy and Immunology
- Chinese Society of Allergy and Immunology
- Colombian Society of Allergy, Asthma, and Immunology Association
- Croatian Society of Allergology and Clinical Immunology
- Cuban Society of Allergology
- Czech Society of Allergology and Clinical Immunology
- Danish Society of Allergology
- Egyptian Society of Allergy and Clinical Immunology
- Egyptian Society of Pediatric Allergy and Immunology
- Finnish Society of Allergology and Clinical Immunology
- French Society of Allergology
- Georgian Association of Allergology and Clinical Immunology
- German Society for Allergy and Clinical Immunology
- Hellenic Society of Allergology and Clinical Immunology
- Honduran Society of Allergy and Clinical Immunology
- Hong Kong Institute of Allergy
- Hungarian Society of Allergology and Clinical Immunology
- Icelandic Society of Allergy and Immunology
- Indian College of Allergy, Asthma and Applied Immunology (ICAAI)
- Indonesian Society for Allergy and Immunology
- Israel Association of Allergy and Clinical Immunology
- Italian Association of Territorial and Hospital Allergists
- Italian Society of Allergy and Clinical Immunology
- Japanese Society of Allergology
- Jordanian Society for Allergy and Clinical Immunology
- Korean Academy of Allergy, Asthma and Clinical Immunology
- Kuwait Society of Allergy and Clinical Immunology
- Latvian Association of Allergists
- Lebanese Society of Allergy and Immunology
- Malaysian Society of Allergy and Immunology
- Mexican College of Clinical Immunology and Allergy
- Mexican College of Pediatricians in Allergy and Clinical Immunology
- Mongolian Society of Allergology
- Moroccan Society of Allergology and Clinical Immunology
- Netherlands Society of Allergology
- Norwegian Society of Allergology and Immunopathology
- Panamanian Association of Allergology and Clinical Immunology
- Paraguayan Society of Immunology and Allergy
- Peruvian Society of Allergy and Immunology
- Philippine Society of Allergy, Asthma and Immunology
- Polish Society of Allergology
- Portuguese Society of Allergology and Clinical Immunology
- Romanian Society of Allergology and Clinical Immunology
- Russian Association of Allergology and Clinical Immunology
- Serbian Association of Allergologists and Clinical Immunologists
- Allergy and Clinical Immunology Society (Singapore)
- Slovenian Association for Allergology and Clinical Immunology
- Allergy Society of South Africa
- Spanish Society of Allergology and Clinical Immunology
- Swiss Society for Allergology and Immunology
- Allergy, Asthma and Immunology Society of Thailand
- Turkish National Society of Allergy and Clinical Immunology
- Ukrainian Association of Allergologists and Clinical Immunologists
- Uruguayan Society of Allergology
- Vietnamese Society of Allergy and Immunology
- Zimbabwe Allergy Society

**Associate Member Societies**

- Belarus Association of Allergology & Clinical Immunology
- Ecuadorian Society of Allergy and Immunology
- Ecuadorian Society of Allergology and Affiliated Sciences
- Iranian Society of Asthma and Allergy
- Moldavian Society of Allergology and Immunology
- Swedish Association for Allergology
- Tunisian Society of Respiratory Diseases and Allergology
- British Society for Immunology
- GA2LEN (Global Allergy and Asthma European Network)
- International Association of Asthma

**Regional Organizations**

- Asian Pacific Association of Allergy, Asthma and Clinical Immunology
- Commonwealth of Independent States Society of Immunology and Allergology
- European Academy of Allergology and Clinical Immunology
- Latin American Society of Allergy and Immunology

**Affiliate Organizations**

- International Primary Care Respiratory Group
- Southern European Allergy Societies

Apply for your National Allergy Society to become a WAO Member Society at www.worldallergy.org/wao_societies/apply.php.

For WAO membership information please contact the Secretariat

**World Allergy Organization (WAO)**

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Dear Colleagues,

A warm welcome to the forty-second symposium in the World Allergy Forum (WAF) series: Eosinophilia and Co-morbid Conditions. Recognizing the importance of Eosinophilia, the World Allergy Organization (WAO) is delighted to bring this symposium to the 2012 Annual EAACI Congress in Geneva, Switzerland. WAO is proud and appreciative that this symposium is an annual event at the Congress, with the EAACI hosting the World Allergy Forum every year since this major educational program commenced fifteen years ago and continues as a sign of very long term collaboration with the EAACI.

WAO is proud to announce that the year 2012 marks the 15th anniversary of the World Allergy Forum. The first WAF was presented in 1997 and WAO is appreciative that this symposium is an annual event at the EAACI Congress. Since 1997, WAF has flourished and become the longest continuing educational program of World Allergy Organization (WAO).

The eosinophil is an often misunderstood cell - it plays a central role in defense against parasitic infections, but when present in excess numbers, it may cause significant disease and disability. This WAF Symposium will address the eosinophil and the disorders of this interesting blood cell. Today’s symposium is composed of world renowned experts on this subject. Prof. Hans-Uwe Simon will review current concepts in the pathogenesis of eosinophilia and eosinophil-related organ damage in neoplastic and non-neoplastic conditions. Dr. Marc Rothenberg will discuss the recent advances in understanding the intrinsic (genetic) and extrinsic (environmental) components and the key molecular pathways and antigenic triggers that illustrate the complex nature of this emerging disease. Dr. Amy Klion will conclude today’s symposium by examining hypereosinophilic syndrome. There will be an open discussion following the formal lectures.

The WAO Board hopes that you enjoy today’s program with its wealth of information which can be used in your everyday clinical practice. If you would like to access the faculty materials after the session they will be available at: http://www.worldallergy.org/educational_programs/world_allergy_forum/

WAO gratefully acknowledges the educational grant from Novartis that supports educations programs such as this conjoint program at the EAACI meeting.

With best regards,

Symposium Chairs

Ruby Pawankar, MD, PhD, FAAAAI
President
World Allergy Organization

Cezmi Akdis, MD
President
European Academy of Allergy and Clinical Immunology
Eosinophils and their products play an essential role in the pathogenesis of various reactive and neoplastic disorders. Depending on the underlying disease, molecular defect and involved cytokines, eosinophilia may develop that subsequently could lead to organ damage. In other patients, persistent eosinophilia is accompanied by typical clinical findings, but the causative role and impact on eosinophilia remain uncertain. For patients with eosinophil-mediated organ pathology, early therapeutic intervention with agents reducing eosinophil counts can be effective in limiting or preventing irreversible organ damage. Therefore, it is important to approach eosinophil disorders and related syndromes early by using established criteria, to perform all appropriate staging investigations, and to search for molecular targets of therapy. Here, I will review current concepts in the pathogenesis of eosinophilia and eosinophil-related organ damage in neoplastic and non-neoplastic conditions. I will also discuss possible diagnostic algorithms.

Key references:

Differential diagnosis of eosinophilic conditions

Hans-Uwe Simon, MD, PhD
Professor and Chairman

EAACI 2012
World Allergy Forum
Geneva, June 19, 2012

Roles of eosinophils

Defense
Parasites
Bacteria
Viruses

Tissue damage
MBP
ECP
EDN
EPO
Respiratory burst

Immunomodulation
T helper 2 cytokines
IL-10, TNF-α
Leukotrienes
Antigen presentation

Fibrosis/remodeling
TGF-β, MMP-9
FGF-2, NGF, VEGF
IL-4, IL-6, IL-11
IL-13, IL-17, IL-25

What is (hyper)eosinophilia?

- Normal values
  < 0.4 x 10⁹ cells/l
  1 to 5% of leukocytes

- Eosinophilia
  - Mild: 0.4 – 1.5 x 10⁹ cells/l
  - Moderate: >1.5 – 5.0 x 10⁹ cells/l
  - Severe: >5.0 x 10⁹ cells/l
Eosinophilia

Intrinsic eosinophilic disorders
- Chronic eosinophilic leukemia
- Acute eosinophilic leukemia
- Idiopathic HES

Extrinsic eosinophilic disorders
- Allergic diseases
- Autoimmune diseases
- Infectious diseases
- GVHD
- Immunoosuppressive therapies
- Chronic T cell diseases
- Drug-induced disease
- Idiopathic HES
- Hodgkin's lymphoma
- Cutaneous T cell lymphoma
- Acute lymphoblastic-lymphoblastic leukemia
- Langerhans cell histiocytosis
- Rhabdomyosarcoma

Mutations in hematopoietic stem cells
- Pluripotent:
  - Chromosomal translocation (8p11)
  - Deletion/gene fusion: PDGFRA
- Multipotent:
  - Chronic myeloid leukemia associated with PDGFRB, ABL, ETI6, Jak2 fusion genes
  - Myelodysplastic syndromes

Detection of FIP1L1-PDGFR fusion gene
- Encodes tyrosine kinase
- Found in eosinophils, also in neutrophils, monocytes, lymphocytes, mast cells


T cell-mediated eosinophilia

- Allergic diseases
  - EGID, EoE, asthma, allergic rhinitis, atopic eczema
- Autoimmune diseases
  - Bullous pemphigoid, pemphigus, PBC, systemic sclerosis, Le: dermatomyositis
- Infectious diseases
  - Parasites, ectoparasites (scabies), fungi, viruses (HIV)
- Immunodeficiency: HIV, Omenn, Hyper-IgE, CGD
- Drug-induced: hypersensitivity, DRESS, IL-2, GM-CSF (stimulation), α-CD52, rituximab (immunodeficiency)
- Inflammatory clonal T-cell disease (HES lymphocytic variant)
  - Abnormal T cell clones

T cell-mediated eosinophilia

Drugs
Allergens
Microbes

Th2
IL-4
IL-5
IL-13

Immunodeficiency
Reactive abnormal T cell clones

Tumor cell-mediated eosinophilia

Solid tumors
Thyroid, lung, stomach, testis, bladder

ALL
Hodgkin's disease
Cutaneous T cell lymphoma

GM-CSF
IL-3
IL-5

LHC histiocytosis
(Hyper)eosinophilia

Organ manifestation?

- Skin
  - Biopsy
- Heart
  - Echocardiography
- Nervous system
  - Electromyogram, functional tests, biopsy
- Lungs
  - X-ray, functional tests
- Liver
  - Enzymes, ultrasound
- Pancreas
  - Enzymes, ultrasound
- G/I/T
  - Endoscopy, biopsy
  - Intestine
  - Esophagus

Exclude secondary causes of eosinophilia

- IgE-mediated allergy
  - Serum IgE, skin tests
- Parasitic/viral infection
  - Serology, biopsy
- Drug-/chemical-induced history, skin test, LT
- Malignancy
  - CT, serologic parameters
- Autoimmune diseases
  - Serum Ab, biopsy, DIF

Exclusion of secondary causes

No → yes

Extrinsic or intrinsic?

IL-5, IL-3 and GM-CSF analysis
in serum, T cell supernatants,
immunohistochemistry
(Hyper)eosinophilia

Organ manifestation?

Search for common triggers

Extrinsic or intrinsic?

Extrinsic?

Work up for underlying disease

- Non-IgE-mediated allergy
- Clonal T cell disease (lymphocytic forms)
- Immunodeficiency
- Tumor-associated
- Idiopathic

Intrinsic?

IL-5, IL-3, GM-CSF

Hematological workup

- Stem cell disorder (myeloproliferative forms)
- Idiopathic

Main diagnostic problems

1. No simple cytokine assays
   - Cytokines in blood: low levels
   - Problems before analysis: treatment initiated, transport
2. FIP1L1-PDGFRα negative myeloproliferative forms
3. Increased IL-5 levels can occur in myeloproliferative forms
4. T cell clones can be found in myeloproliferative forms
5. T cell clones can often not be detected
   (non-clonal lymphocytic form of HES)
Eosinophilic Esophagitis

Marc E. Rothenberg MD, PhD
Professor of Pediatrics
Director, Division of Allergy and Immunology
Director, Cincinnati Center for Eosinophilic Disorders
Cincinnati, OH, United States

Eosinophilic Esophagitis is a chronic allergic inflammatory disorder of the esophagus that is compounded by both genetic predisposition and aberrant responses to environmental antigens, particularly those derived from food. Recent advances in understanding the intrinsic (genetic) and extrinsic (environmental) components and the key molecular pathways and antigenic triggers illustrate the complex nature of this emerging disease. Expression profiling of mRNA and microRNA transcripts, as well as whole genome analysis of high-density genetic variants, have identified key etiological steps that provide novel insight into disease mechanisms and entry points for therapeutic strategies. Emerging data demonstrate the interplay of epithelial cells, mast cells and eosinophils, Th2-associated cytokines including IL-13 and TSLP, as well as acquired and inherited impairment of barrier function.
miR-21 critically regulates a set of allergen-induced transcripts.

This empirical analysis has reinforced our hypothesis that miR-21 has a critical, dominant and relatively specific role in regulating IFNγ/IL-12 responses.
EE risk variants on 5q22

Multiple SNPs at 5q22 replicate and reach genome wide significance as risk factors for EE.

Linkage Disequilibrium in the 5q22 locus

SNPs in TSLP and WDR36 are inherited in a single haplotype block.

TSLP Expression in the EE esophagus

EE patients have higher levels of TSLP mRNA expression in the esophagus.
Phenotypic Refinement: is the association of TSLP SNPs simply dependent on atopy?

- Is TSLP a susceptibility locus specifically for EE and not atopy in general?

- Candidate gene approach using a custom Illumina SNP chip containing 732 SNPs in 53 known atopy-associated genes.

- Genotyped 738 EE patients and compared allele frequencies with control groups of various atopic histories:
  - non-atopic (n=246)
  - atopic (n=220)
  - asthmatic (n=312)
  - atopic/asthmatic (n=332)

Shevick, Hinds, Hirstoey et al., JACC 2010
Therapeutic Options for EGID

- Allergen elimination-dietary and airborne antigens
- Anti-inflammatory agents (parenteral or “inhaled” glucocorticoids)
- Elemental Diet
- Systemic Glucocorticoids
- (Anti-GIL Rx and anti-LTs)
- Anti-IL-5 and/or anti-CCR3/betaxin
- Anti-IL-13
- Imatinib (Gleevec)

Eosinophilic Esophagitis
Dietary Management

Before

After

Retrospective Comparative Effectiveness of Different Dietary Approaches (Elemental [amino acid formula], Six Food Elimination [SPEED] and Skin Test Directed

These results show effectiveness of dietary therapy, but that diets based on skin testing do not have superiority compared with an empiric diet that eliminates the top six most common food allergens.
Effect of Fluticasone propionate Treatment in a double blind placebo controlled trial

Fluticasone propionate (FP) or dietary treatment improves gene expression profile of EE patients (~5% genes). The sustained gene patterns during remission point to an abnormal epithelial differentiation pathway.

Effect of treatment on EE transcript profile

Gene expression: 1% of the genome

Epithelial cell

Allergens

Antibodies

IL-13

Type I and II TNF

Sustained expression

Immunodeficiency

mRNA expression

Sustained gene expression

miR21

Enoxin-3
Hypereosinophilic Syndromes (HES)

Amy Klion, MD
Eosinophil Pathology Unit
Laboratory of Parasitic Diseases
National Institute of Health
Bethesda, MD, United States

Hypereosinophilic syndromes (HES) are a heterogeneous group of disorders defined by the presence of peripheral eosinophilia and eosinophil-related pathology. In recent years, a number of clinical variants of HES have been described. For some of these, including PDGFRA-positive myeloproliferative neoplasm and lymphocytic variant HES, the etiology has been identified. Although this has simplified treatment and led to improved outcomes for some variants, these advances have created confusion in the definition of HES. Similarly, although the development of a wide variety of therapeutic agents targeting specific pathways or aspects of eosinophilia and eosinophil activation is adding to the armamentarium of agents available to treat patients with HES, our lack of understanding of the mechanisms of pathogenesis in the different clinical variants of idiopathic disease makes selection of the most appropriate agent for an individual patient difficult. Recent advances in HES classification and therapeutic choices will be discussed.
Hypereosinophilic Syndrome

Amy Kison, MD
Laboratory of Parasitic Diseases
NIAMID, NIH

Disclosure

- Employment
  - National Institutes of Health
- Financial Interests
  - None
- Research Interests
  - CitriClinics, Medimmune, Teva, Kalorieks
- Organizational Interests
  - Member of ASHAll, IES, EDA
- Gifts
  - Nothing to Disclose
- Other Interests
  - Nothing to Disclose

Eosinophilia: Case 1

- 28 year old Hispanic man with history of intravenous cocaine use presents with signs and symptoms of severe right-sided congestive heart failure in the setting of marked eosinophilia

  - WBC 14,400 with 63% eosinophils (9.0/72/mm3); anemia, platelets 10k
  - Echocardiogram: dilated cardiomyopathy, fibrotic material filling the right ventricle, moderate to severe MV and TV, small pericardial effusion
  - Endomyocardial biopsy: focal fibrosis
  - Bone marrow: hypercellular with marked eosinophilia, no blasts, mild fibrosis
Eosinophilia and endomyocardial fibrosis

- Drug hypersensitivity
- Churg Strauss Syndrome
- Paracitic infection
- Hypereosinophilic Syndrome

Case 1 (continued)

- A diagnosis of hypereosinophilic syndrome was made and he was treated with high dose steroids and hydration without response.
- Approximately 10 months after he presented, Imatinib mesylate therapy was started with complete hematologic remission.
- One month later he developed hemoptysis, fever and chills and died of presumed sepsis.

Loeffler's endocarditis

**FIBROPLASTIC ENDOCARDITIS WITH EOSINOPHILIA (LOEFFLER'S ENDOCARDITIS PARENCHYAL FIBROPLASTICA): CASE REPORT AND REVIEW OF LITERATURE**

By F. G. Hazama, Lt. Colonel, USAF (M.C.), Watertown, K. V. Davis, M.D., and P. D. Genovese, M.D., Indianapolis, Indiana

In 1930 Löffler published a report of two patients with a histiocytic undiagnosed type of endocarditis. This entity, subsequently referred to as fibroplastic endocarditis or Löffler's endocarditis parenchylal fibroplasia, is characterized by an acute or subacute, progressive, anatomic, and clinical picture of eosinophilia. The cases reported by Löffler, in addition, exhibited signs of mitral valvulitis, though these were inadequate to account for the clinical picture.
Idiopathic Hypereosinophilic Syndrome

- Blood eosinophilia ≥ 1,500/mm³ for longer than 6 months (or death before 6 months associated with signs and symptoms of HES)
- Lack of evidence for parasitic or other known causes of eosinophilia
- Presumptive signs of organ involvement, such as heart failure, gastrointestinal dysfunction, central nervous system abnormalities, fever or weight loss

 Orozco, D., West and Whitfield Medicine (2014)

"We accept the point of view of Engefeldt and Zellerstein, Hardy and Anderson, and Roberts that there is a continuum of hypereosinophilic disease with eosinophilic leukemia at one pole."

End Organ Involvement in HES

Ogbeu et al. 2006 JACI

Treatment of HES

- Corticosteroid
- Hydroxyurea
- Interferon-α
- Imatinib

Ogbeu et al. JACI 2006
Hypereosinophilic syndromes

- Blood eosinophilia ≥ 1.500/mm³ on at least two occasions or evidence of prominent tissue eosinophilia associated with symptoms and marked blood eosinophilia
- Exclusion of secondary causes of eosinophilia, such as parasitic or viral infection, allergic diseases, drug- or chemical-induced eosinophilia, hypoadrenalinism and neoplasms

![Image of HES subtypes]

- Myeloproliferative
  - PDGF-associated
  - CML NOS
- Lymphocytic variant
  - constant
  - intermittent
  - episodic
- Overlap (single organ)
  - EGID, CEP, ...

- Associated
  - CID
  - steroid
  - others
- Familial
- Idiopathic
  - benign H/E of unknown significance
  - multisystem
  - with myeloproliferative features

Elevated serum tryptase identifies a myeloproliferative subtype of HES

- Male gender
- Anemia and/or thrombocytopenia
- Dysplastic eosinophils and myelodysplasia in periphery
- Splenomegaly
- Hypercellular marrow
- Increased serum B12 levels
- 38% mortality at 3 years

![Graph of tryptase levels]
PDGFRA-associated MPN

- Caused by an interstitial deletion in chromosome 4 that leads to a constitutively activated fusion tyrosine kinase


- Can be detected by nested RT-PCR or FISH
- A number of additional fusion partners have now been identified

Additional clinical features of PDGFRA-associated MPN

- Fibrotic complications, including endomyocardial fibrosis, appear to be more common
- Bone marrow mastocytosis is usually, but not always seen, but without classic symptoms of mast cell activation (i.e. anaphylaxis, flushing, diarrhea)
- Unusual dermatologic presentations have been reported
  - Mucosal ulcerations
  - Lymphomatoid papulosis (LyP)

Myeloproliferative HES

- PDGFRA-positive MPN (>80%)
- CEL-NOS
- Idiopathic HES with myeloproliferative features

NOTE: myeloid neoplasms and myeloproliferative disorders, including those associated with PDGFRA and KIT, are included in a separate category in this classification system since marked eosinophilia can be present, but the clinical features are due primarily to the involvement of other lineages
Clinical, molecular and hematologic remission is common, if not universal, with imatinib treatment at doses of 100-400 mg daily.

What’s new in MHES?
- Although imatinib does not appear to be curative in the vast majority of patients, doses as low as 100 mg weekly can lead to durable responses.
- Primary and secondary resistance to imatinib are rare, but have been reported.
- Newer tyrosine kinase inhibitors (dasatinib, sorafenib, nilotinib) appear to be useful in cases of imatinib intolerance, but to date have been relatively ineffective in imatinib resistant disease.

Lymphocytic variant HES
- Associated with the presence of clonal lymphocyte populations with aberrant phenotypes (e.g., CD3+CD4+CD8+ or CD3+CD4+) that produce eosinophilic and cytotoxic granules.
- Equally common in men and women.
- Predominance of skin manifestations.
- Often associated with elevated serum IgE, TARC levels.
- May progress to lymphoma.
- No response to imatinib.
Production of IL-4 and IL-5, and not IFN-γ, by CD3-CD4+ T cells in LHES

What's new in LHES?
- Eosinophilic eosinophilia and eosinophilia (Gleich's syndrome) is associated with a clonal lymphocyte population
- Chronic active EBV and LHES?
- Mepolizumab is effective and does not appear to lead to outgrowth of the clone (Raufosse et al. JACI 20)

Familial eosinophilia
- Autosomal dominant
- Gene mapped to chromosome 5q31-33
- Eosinophilia begins at birth, but only a small subset develop end-organ damage
- Lack of clinical manifestations is associated with a relative lack of eosinophil activation compared to other eosinophilic disorders (Kuhn et al. Blood 2004)
Idiopathic HES

- Benign
  - prolonged asymptomatic eosinophilia >1500/mm³
- Single organ involvement?
- Complex
  - signs and symptoms of multiorgan involvement

Anti-IL-5 antibody therapy for HES

- Pilot studies of both reslizumab and mepolizumab showed efficacy in HES
- Placebo-controlled, randomized, multicenter trial of mepolizumab (150 mg monthly for up to 9 months) in 65 PDGRCA-negative patients with stable HES on 30-60 mg prednisone daily demonstrated safety and efficacy as a steroid-sparing agent (Schleimer et al. NEJM 2010)
- A long term extension study showed that mepolizumab continued to be effective over a period of time that is clinically relevant in the management of a chronic disease and no new safety concerns were identified (abstract presented at AAAAI 2013)

Conclusions

- The diagnosis of HES and its variants continues to be a matter of considerable debate
- An understanding of the underlying etiology of the eosinophilia has profound therapeutic implications
- These implications will become more and more important with the increasing availability of novel targeted therapies.
Abstract Submission Deadline: 21 January 2013