EOSINOPHILIA: A PRAGMATIC APPROACH TO DIAGNOSIS AND TREATMENT

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Disclosures

• No financial disclosures
• None of the therapies discussed are FDA-approved for the treatment of hypereosinophilic disorders except for imatinib
• I am not a hematologist
Objectives

• Describe the spectrum of eosinophilic disorders, from benign eosinophilia to eosinophilic leukemia
• Discuss the mechanisms of eosinophil-associated pathogenesis and general approaches to treatment
Clinical disorders associated with eosinophilia

- Allergy/Asthma
- Drug hypersensitivity
- Connective tissue disorders
- Parasitic infection
- Neoplasm
- Rare hypereosinophilic syndromes
- Other (hypoadrenalism, HIV...)
Eosinophil life cycle

1-2% of peripheral blood leukocytes; $t_{1/2}$ in blood = 18 hours

>90% of eosinophils are found in the tissues, particularly those tissues which interface with the environment (BM, lymphoid tissue, lower GI tract, and uterus)

(from Rothenberg 1998 NEJM)
Eosinophils and pathology

Direct cytotoxic effects
- Eosinophil granule proteins
- Reactive oxygen intermediates
Recruitment of other inflammatory cells
Fibrogenesis
Hypercoagulability
Secondary causes of eosinophilia can mimic idiopathic HES

- 50 year old Iraqi rug salesman with pruritus and erythematous total body rash, AEC 30,000/mm³
- 76 year old man with CLL referred for unexplained asymptomatic eosinophilia, AEC 4,000/mm³

Diagram:
- HES: 87%
- HELMINTH
- DRUG
- NEOPLASM
- OTHER
What is hypereosinophilic syndrome?
Loeffler’s endocarditis

FIBROPLASTIC ENDOCARDITIS WITH EOSINOPHILIA (LÖFFLER’S ENDOCARDITIS PARIELTALIS FIBROPLASTICA): CASE REPORT AND REVIEW OF LITERATURE*

By F. G. Hoffman, Lt. Colonel, USAF (M.C.), Waterloo, N. Y., David Rosenbaum, M.D., and P. D. Genovese, M.D., Indianapolis, Indiana

In 1936 Löffler published a report of two patients with a hitherto unclassified type of endocarditis. This entity, subsequently referred to as fibroplastic endocarditis or Löffler’s endocarditis parietalis fibroplastica, is characterized by an afebrile course, progressive, refractory congestive failure and a striking eosinophilia. The cases reported by Löffler, in addition, exhibited signs of mitral valvulitis, though these were inadequate to account for the clinical picture.

(Hoffman, Rosenbaum and Genovese 1955 Ann Intern Med)
Idiopathic Hypereosinophilic Syndrome

- Blood eosinophilia $\geq 1500/$mm$^3$ 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

(Chusid, Dale, West and Wolff 1975 Medicine (Baltimore))

“We accept the point of view of Engfeldt and Zetterström, Hardy and Anderson, and Roberts that there is a continuum of hypereosinophilic disease with eosinophilic leukemia at one pole”
End Organ Involvement in HES

(Ogbogu et al. 2009 JACI)
Hypereosinophilia and hypereosinophilic syndromes

- Blood eosinophilia $\geq 1500/\text{mm}^3$ on at least two occasions or evidence of prominent tissue eosinophilia associated with symptoms and marked blood eosinophilia
- Evidence of end organ damage attributable to eosinophilia

NOTE: Secondary causes of eosinophilia, such as parasitic or viral infection, allergic diseases, drug- or chemical-induced eosinophilia, hypoadrenalism and neoplasms, can cause HE or HES, but are approached differently

(Klion et al. JACI 2006; Simon et al. JACI 2010; Valent JACI 2012)
Clinical subtypes of HES

NIH COHORT (n=263)

- MYELOPROLIFERATIVE
- LYMPHOCYTIC
- OVERLAP
- ASSOCIATED
- FAMILIAL
- IDIOPATHIC
Elevated serum tryptase identifies a myeloproliferative subtype of HES

- Male gender
- Anemia and/or thrombocytopenia
- Dysplastic eosinophils and myeloid precursors in periphery
- Splenomegaly
- Hypercellular marrow
- Increased serum B12 levels
- 30% mortality at 3 years

(Klion et al. 2003 Blood)
**PDGFRA-associated MPN**

- Caused by an interstitial deletion in chromosome 4 that leads to a constitutively activated fusion tyrosine kinase that is sensitive to imatinib (Cools et al. NEJM 2003)

- Can be detected by nested RT-PCR or FISH

- A number of additional fusion partners, as well as point mutations, have now been identified

(Gotlib 2004 Blood)
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)

(Thurny JAEDV 2010)  
(McPherson BrJDERM 2008)
Myeloproliferative variant HES

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

*Marked eosinophilia occurs in a variety of myeloid neoplasms and myeloproliferative disorders, including those associated with PDGFRB, FGFR1, KIT, and JAK2, but the clinical features are often due to the involvement of other lineages.
Lymphocytic variant HES

- Associated with populations of phenotypically aberrant or clonal T cells secreting eosinophilopoietic cytokines
- Equally common in men and women
- Predominance of skin manifestations
- Often associated with elevated serum IgE, TARC levels
- May progress to lymphoma
  - <3%; usually preceded by cytogenetic abnormalities and lymphocytosis
- No response to imatinib
Production of IL-4 and IL-5, and not IFN-γ, by CD3-CD4+ T cells in LHES
Novel variants of LHES

- EBV-driven LHES

63 year old man with a 2 year history of ulcerative lesions

Bright field

FISH-EBV (594)

EBV-transformed B cells (X50-7)
EBV-negative B cells (BJAB)
Vβ 5.1 positive patient cells

EBV copies

EBV copies

0 5000 10000 200000 300000

LHES Normal Volunteers
Novel variants of LHES

- Episodic angioedema and eosinophilia (EAE; Gleich’s syndrome)

36 year old man with recurrent episodes of bilateral hand and foot swelling x 3 months

Additional features

- CD3-CD4+ clonal T cell population
- Elevated IgM
- Multilineage cycling

(Katzen Am J Dis Child 1986; Khoury et al. Allergy 2016)
Idiopathic HES

- Despite extensive evaluation, in >50% of patients with eosinophilia >1500/mm$^3$, no etiology is apparent and the clinical picture does not fit one of the defined subtypes.

- A subset of these patients are completely asymptomatic and have no evidence of end organ involvement (hypereosinophilia of unknown significance; HE$_{US}$)

(Chen JACI 2013)
Overlap HES

- Single organ eosinophilic disorders that overlap in presentation with idiopathic HES and may be associated with marked peripheral eosinophilia
- Examples include EGID, EGPA, chronic eosinophilic pneumonia, atopic dermatitis
- Important to recognize since the therapeutic approach may be different
Treatment

• Potentially life-threatening?
• Secondary treatable cause?
• Most likely clinical subtype?
Conventional therapy for HES

- Prednisone
- Hydroxyurea
- Interferon-α
- Imatinib (FDA-approved for HES in 2006)

Response at 1 month

(Ogbogu et al. 2009 JACI)
Conventional therapy for HES is unsatisfactory

Discontinuation of Therapy

PRED 42%
HU 76%
IFN 84%
Clinical subtype predicts steroid-responsiveness

- Retrospective analysis of 164 PDGFRA-negative HES subjects who received steroids for at least 2 weeks as a single agent and for whom response data was available

- Response was defined as the minimum clinically effective dose of GC for which AEC<1000/mm3 and symptoms improved for at least 1 week

- A multivariate logistical model was used to determine predictors of responsiveness

(Khoury et al. JACI:In Pract, submitted)
Imatinib and *PDGFRA*-associated MPN

- Imatinib has a rapid (weeks) and dramatic effect on eosinophilia
  - Assess eosinophil counts, signs and symptoms weekly for at least 1 month
  - **Consider drug failure if minimal response at 4 weeks on 400 mg daily**
- Acute necrotizing myocarditis has been reported with initiation of treatment in the setting of cardiac involvement
- Resistance and relapse are rare, but incidence and mechanisms are probably similar to CML
- Despite high remission rate, documented cures are exceedingly rare
### Imatinib response rates in idiopathic (FIP1L1/PDGFRA-negative) HES

<table>
<thead>
<tr>
<th>Outcome*</th>
<th>Time frame (months)</th>
<th>Response</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>NA</td>
<td>3/5 (60%)</td>
<td>Cools 2003</td>
</tr>
<tr>
<td>C at 1 month</td>
<td>4-118</td>
<td>2/8 (24%)</td>
<td>Pardanani 2004</td>
</tr>
<tr>
<td>C at 1 month</td>
<td>1-15</td>
<td>5/36 (14%) all transient</td>
<td>Baccarani 2007</td>
</tr>
<tr>
<td>C at 1 month</td>
<td>NA</td>
<td>10/43 (17%) partial in 4</td>
<td>Ogbogu 2009</td>
</tr>
<tr>
<td>C at 1 week</td>
<td>2-88</td>
<td>4/8 (50%) transient in 2</td>
<td>Helbig 2011</td>
</tr>
</tbody>
</table>

*C= resolution of clinical symptoms and eosinophilia, H=normalization of bone marrow, M=molecular remission*
Imatinib response in steroid-resistant HES

(Khoury, Desmond, submitted)
Case

• 36 year old obese man presents with pre-syncope.
  • Evaluation in ER notable for mildly elevated troponin at 0.11, normal EKG and AEC 12,456/mm³
  • Bone marrow: hypercellular with dysplastic eosinophils, no increase in blasts, FISH for JAK2, PDGFRA and B negative, cytogenetics and flow cytometry normal
  • Echo and treadmill were normal and he was discharged

• Two months later, he presents with chest discomfort
  • Troponin is now 2.8 and EKG shows inversion in anterior leads
  • Echo shows right ventricular dilatation, CXR with patchy hilar infiltrates
  • AEC 11,382/mm³

• Treated with 100 mg prednisone + ivermectin (history of travel to China) with minimal response (AEC 8640/mm³)
What would you do next?

(A) Chest, abdomen, pelvis CT
(B) Cardiac biopsy
(C) Bronchoscopy with biopsy
(D) Begin empiric therapy with imatinib
(E) Repeat bone marrow biopsy

Repeat FIP1L1/PDGFRA testing by PCR was positive prior to therapy
Targeted therapies for eosinophilic disorders

Active and theoretical eosinophil-selective therapeutic targets

Tyrosine kinases

(Bochner et al. JACI 2012)
HES and mepolizumab: outcomes

(Rothenberg NEJM 2009) (Roufosse JACI 2012)
Clinical subgroup may affect response to mepolizumab

(LHES subgroup analysis)

% Response
PDN≤10 for ≥8 wk
Off PDN until study end
AEC≤600 for ≥8 wk
AEC≤600 until study end

*P

Compassionate use analysis

IHES n=20
MHES n=3
LHES n=6
EGPA OVERLAP n=6

Non-Responders
Partial
Complete

(Roufosse JACI 2010)

(Kuang, unpublished)
Dexpramipexole

• An oral agent developed for the treatment for ALS
• Failed phase 3 trial in ALS, but was found to lower eosinophil count in 75% of subjects
• Met primary endpoint (steroid-sparing) in a recent proof of concept study in HES, reducing AEC to 0 in blood, bone marrow and tissue of responders
Conclusions

• HES is a heterogeneous group of disorders
• HES subtypes differ in etiology, clinical presentation, and treatment
• With the availability of new targeted therapies, the etiology of the eosinophilia is becoming increasingly important in determining therapeutic options