Overview of the Hypereosinophilic Syndromes

Hematology Fellows Conference
Emily Stevens MD, PhD
February 12, 2016

Discussant: Michael Linenberger
Patients

1. 28 yof w/ questions regarding safety of pregnancy in the setting of hypereosinophilia
   – Eos 5,000-18,000 and plt 500-700 x 6y. Previously normal CBC.
   – GERD, nausea, abdominal pain x 13y

2. 45 yof w/ progressive RUQ pain & n/v/d x 1m
   – duplex u/s: non-occlusive thrombi in SMV and LPV; b/l DVT
   – CT: PE; SMV, IMV, and LPV thrombosis, colitis, heterogeneous liver
   – Eos 8000, plt 60. Previously normal CBC.

3. 22 yom screening CBC w/ Eos 3500, asymptomatic
   – 20% Eos in marrow, cbc and marrow otherwise normal; lost to f/u
   – 3y later: HTN, nephritic syndrome (Cr 2.4); severe pulm HTN, MV & AV insufficiency; plt 87, Eos 6000
Outline

• Eosinophil Biology
• Diagnostic Criteria and Classification of Hypereosinophilic Syndromes (HES)
• Diagnostic Approach
• End-organ Sequelae of HES
• Treatment Options for HES
• Patient Examples
Eosinophils

- Granulocytes with cytotoxic proteins, lipid mediators, chemotactic peptides and cytokines
- Mediate parasite defense, allergy, inflammation and immune modulation
- Growth factors: GM-CSF, IL3, IL5. made by T-cells, mast cells, stromal cells, dendritic cells and by eos themselves
- PB Eos 500-1500/µl not uncommon—allergy/infection
- PB Eos >1500/µl is rare--should prompt a thorough evaluation
Eosinophil Activation

Hypereosinophilic Syndromes

• Hypereosinophilia (HE): >1500/μl PB Eos on 2 occasions

• Hypereosinophilic syndrome (HES):
  – Hypereosinophilia
  \textit{AND}
  – Symptomatic eosinophil tissue infiltration
    \begin{itemize}
    \item >20% eos in marrow
    \item pathologist opinion of “markedly increased eosinophils”
    \item extracellular deposition of eos-derived proteins in tissues by IHC
  \end{itemize}

• Hypereosinophilia of Unknown Significance (HEUS)
  – No symptoms
  – No evidence of tissue infiltration on evaluation

• Familial Hypereosinophilia
Eosinophil Activation

Hypereosinophilic Syndromes

Primary organs affected by HES:

- Skin
- Lungs
- GI tract
- Heart (endocardial damage with mural thrombus, then fibrotic stage that can progress to restrictive cardiomyopathy and valvular insufficiency)
- Nervous system
- Vascular (Raynauds)
- Angioedema (predominantly in CD3-/CD4+ subtypes)
- Spleen
Hypereosinophilic Syndromes

Primary HES:

– Myeloproliferative HES
  • Myeloid and lymphoid neoplasms with eosinophilia & abnormalities in PDGFRA, PDGFRB, or FGFR1
  • Chronic Eosinophilic Leukemia, not otherwise specified (CEL-NOS)

– Lymphocytic HES

– Idiopathic HES
Overview: Primary HES

Hypereosinophilic Syndrome Variants (HES)

Myeloproliferative (M-HES)
- Clinical
  - Hepatomegaly
  - Splenomegaly
- Blood
  - Myeloid precursors
  - Anemia/thrombopenia
- Serum
  - Increased vitamin B12/tryptase

Lymphocytic (L-HES)
- Bone marrow
  - Fibrosis
  - Left shift maturation
  - Atypical mast cells (spindle-shaped)
- Cytogenetic abnormalities
- Response to TK inhibitors (imatinib)

Idiopathic (I-HES)
- Eosinophil expansion driven by Th2 cytokine-secreting T cells (IL-5)
- Exclusion of T-cell malignancies (e.g., lymphoma)

PDGFRA/B & FGFR1
- Features of MPN AND
  - FIP1L1-PDGFRα (F/P+)
  - OR
  - PDGFRB translocation
  - OR
  - FGFR1 translocation

CEL-NOS
- Not another MPN or AML,
  - Eos >1500,
  - No PDGFRA/B, FGFR1 translocation,
  - PB blasts >2%,
  - OR
  - BM blasts >5%,
  - OR
  - Evidence of clonality

L-HES
- T-cell subset with abnormal phenotype
  - CD3+CD4+ (most common)
  - CD3+CD4+CD8-
  - CD3+CD4+CD7-
  - Clonal TCR gene rearrangement

OTHER
- Gleich’s syndrome
  - Cyclic angioedema with eosinophilia
- T-cell abnormalities sometimes detected
- Suspected role of IL-5

I-HES
- Exclusion of:
  - Reactive eosinophilia
  - L-HES
  - CEL-NOS
  - MDS, MPN, AML
  - PDGFRA/B and FGFR1

Hypereosinophilic Syndromes

• Secondary HES
  – Infectious: strongyloidiasis, trichinellosis, filariasis, schistosomiasis, hookworm, scabies, isosporiasis, coccidiomycosis, histoplasmosis, HIV
  – Drug-mediated (DRESS): allopurinol, cephalosporins, etc
  – Paraneoplastic: Myeloid stem cell neoplasms, lymphoid neoplasms, adenocarcinoma
  – Immunodeficiency
  – Autoimmune: sarcoid, IBD, IgG4 related disease, “GVHD”

• Overlap HES (single-organ system)
  – Eosinophilic esophagitis
  – Eosinophilic gastroenteritis
  – Churg-Strauss (vascular)
  – Eosinophilic fasciitis (scleroderma-like illness)
Etiology of HE in NIH Cohort

- Idiopathic
- MPN
- Familial
- HEUS
- Lymph
- Other
- Overlap
- Secondary/Associated

Diagnostic Approach

- Hypereosinophilia
  - Screen for reactive causes
    - Reactive Eosinophilia
      - Treat underlying cause
        - Positive
          - Screen for FIP1L1-PDGFRA by FISH or RT-PCR; bone marrow aspirate and biopsy with cytogenetic analysis; evaluate for reciprocal translocations involving 4q12 (PDGFRA), 5q31-q33 (PDGFRB), or 8p11-13 (FGFR1)
        - Negative
          - Stop O&P, "strongy serology", stop meds, CRP, ESR, ANCA, ANA, HIV

Diagnostic Approach

Screen for FIP1L1-PDGFRα by FISH or RT-PCR; bone marrow aspirate and biopsy with cytogenetic analysis; evaluate for reciprocal translocations involving 4q12 (PDGFRA), 5q31-q33 (PDGFRB), or 8p11-13 (FGFR1).

- Negative
- Other clonal or molecular abnormality, clonal eosinophils, and/or increased marrow blasts (>5 - <20%)?
  - Yes: Chronic Eosinophilic Leukemia, NOS or WHO-defined myeloid neoplasm with associated eosinophilia (e.g. MDS, MPN, MDS/MPN)
  - No: Abnormal T-cell immunophenotype and/or in vitro Th2 cytokine production?
    - Yes: Idiopathic hypereosinophilia
    - No: Lymphocyte-variant hypereosinophilia
      - If organ damage present: Idiopathic hypereosinophilic syndrome

IgE, T-cell clonality and T-cell immunophenotyping (CD3-/CD4+ or CD3+/CD4+/CD7-)

B12, Tryptase, JAK2 V617F, cKIT D816V, CALR

Evaluate for Tissue Infiltration

- CBC with differential and marrow evaluation
- Renal and hepatic panel
- Skin exam
- Serum troponin, BNP, EKG, Echo +/- cardiac MRI
- PFTs, bronchoscopy
- CT chest, abdomen & pelvis (lymphoma, malignancy)
- EGD +/- colonoscopy
Treatments - Primary HES

**Myeloid and lymphoid neoplasms with eosinophilia and abnormalities of PDGFRA, PDGFRB or FGFR1**

**Chronic Eosinophilic Leukemia, NOS or WHO-defined myeloid neoplasm with associated eosinophilia (e.g. MDS, MPN, MDS/MPN)**

**Idiopathic hypereosinophilia**

If organ damage present

**Idiopathic hypereosinophilic syndrome**

**Lymphocyte-variant hypereosinophilia**

- **Imatinib** for PDGFRA/B rearranged disease; ALL or AML-type induction chemotherapy for FGFR1-rearranged myeloid/lymphoid neoplasm followed by transplantation

- For CEL, NOS: hydroxyurea or interferon-α; 2nd line: imatinib; other chemotherapeutics; clinical trial; transplantation

- **Steroids**
  - 2nd line: hydroxyurea or interferon-α; imatinib; mepolizumab or alemtuzumab; other chemotherapeutics; clinical trial; transplantation

- **Steroids**
  - 2nd line: steroid-sparing drugs or other anti-immune agents; interferon-α; mepolizumab or alemtuzumab; clinical trial

Key Points

- Regardless of underlying etiology of eosinophilia, organ damage = HES
- Must evaluate for tissue infiltration in addition to symptom assessment
- HES is hypercoagulable state
- Close clinical f/u of all cases of HEUS to monitor for HES and occult organ infiltration UNLESS M-HES
- Treat according to underlying etiology to best ability
1. 28 yof w/ questions regarding safety of pregnancy in the setting of hypereosinophilia
   - Eos 5,000-18,000 and plt 500-700 x 6y. Previously normal CBC.
   - GERD, nausea, abdominal pain x 13y
   - Negative stool O&P, JAK2, BCR-ABL
   - Marrow: 80% cellular, ↓storage iron, ↑Eos; negative JAK2, BCR-ABL, MDS, and MPN FISH
   - Oral iron, Ranitidine, Magic Mouthwash, Pretzels

   - CBC: eosinophilia, thrombocytosis, basophilia and monocytosis
   - Marrow: normocellular, no fibrosis, normal cytogenetics, 2 TP53 variants
   - normal B12 and tryptase
   - EGD with marked eosinophilia in esophagus and stomach
   - Started high dose steroids
Patient 1

Eosinophils

thousand/microL


Generalized Normal High
Generalized Normal Low
2. 45 yof w/ progressive RUQ pain & n/v/d x 1m
   • duplex u/s: non-occlusive thrombi in SMV and LPV; b/l DVT
   • CT: PE; SMV, IMV, and LPV thrombosis, colitis, heterogeneous liver
   • Eos 8000, plt 60. Previously normal CBC.
   • Colon biopsy: > 25Eos/HPF

   • Treated with high dose steroids and anticoagulation
   • Persistent thrombocytopenia on warfarin→LMWH
Patient 2

PLT

Eosinophils

D-Dimer Quant

mcg/mL FEU
Patient 3

3. 22 yom screening CBC w/ Eos 3500, asymptomatic
   - 20% Eos in marrow, cbc and marrow otherwise normal; lost to f/u
   - 3y later: HTN, nephritic syndrome (Cr 2.4); severe pulm HTN, MV & AV insufficiency; plt 87, Eos 6000
   - Marrow with Eos, otherwise normal
   - Imatinib + steroids x 3m; no response
   - Mepolizumab + steroids x 3m; no response
   - Hydrea; no response
   - Peg-IFNα x 6w; no response, but ↑ LFTs

   - Referred for transplant
Patient 3

- Severe AV and MV regurgitation and severe pulmonary hypertension
- Large LV thrombus
Patient 3

- Now with normal eosinophil count, full engraftment
- Resolved pulmonary hypertension, improved AV and MV regurgitation
- Still chronic oral GVHD, no joint or skin symptoms
- Newly elevated liver enzymes likely liver GVHD


