Hypereosinophilic syndrome: the highs and lows

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45F hx migraine HAs, depression and mild asthma presents to UWMC ED with CC of progressive abdominal pain with associated nausea/vomiting and occasional diarrhea.

Initial workup in ED reveals:
- PE: VSS, anxious appearing. CTAB, CV wnl, diffuse abdominal tenderness, no peritoneal signs. No palpable nodes. No rashes or skin lesions.
- CTAP: Segmental wall thickening and pericolonic inflammatory changes involving the sigmoid colon, trace ascites. No LAD or masses.
- Ab US with Doppler: Nonocclusive thrombus in the superior mesenteric vein and left portal vein, otherwise normal liver, biliary tree, GB
- Labs:
  - BMP: 134/3.7 109/18 7/0.8 gluc: 73
  - Lipase/amylase: wnl
  - AST/ALT: 21/24, AP: 71, Tbiili: 0.7, Alb: 3.0
  - Coags: wnl, UA: neg
Case: TA

- Admission labs (cont):
  - CBC: 16.5/ 37/ 80 (baseline 230s)
    - WBC diff:
      - N: 29% (4.73)
      - L: 15% (2.59)
      - M: 4% (0.59)
      - E: 51% (8.49)
      - Baso: 0% (0.05)
      - Immature gran: 1% (0.11)
  - PBS: mild normocytic anemia, no NRBCs, rare teardrops. Platelets reduced in number, normal in appearance.
Outline

- A brief overview of eosinophil contents and function
- Definition and classifications of hypereosinophilia
- A diagnostic approach to hypereosinophilia
- Thrombosis in HES
- Thrombocytopenia in HES
- Treatment strategies in HES... Coming in 2015...
Can’t spell eosinophilia without...
Eosinophil: non-dividing, end-stage granular leukocytes derived from CD34+ marrow precursors

- **IL-5, IL-3 and GM-CSF** provide growth stimulus

- Approx 1-3% of circulating cells, 8-18hr half-life in peripheral blood

- >100 fold higher concentration in tissue (lower GI tract, spleen, LNs)

- “Eosin-loving” basic granules, hence bright granular staining on H&E

- Granules contain major basic protein (MBP), eosinophil cationic protein (ECP), eosinophil peroxidase (EPO), eosinophil derived neurotoxin (EDN)

Function/dysfunction:

- Inactivation of tissue invasive helminths and parasites

- "frustrated phagocytosis"

- Role in inflammation (asthma, atopy) and immunoregulation
Definitions:
- Mild: eos >500 and <1500
- Moderate: eos 1500-5000
- Severe: eos >5000

Classification: primary vs. secondary (vs. idiopathic)
- Primary: clonal eosinophil expansion
- Secondary: reactive process
  - infection, esp tissue invasive parasites (eg strongyloides stercoralis, schistosoma spp., toxocara spp., trichinella spp, filaria),
  - allergic/atopic
  - medication associated, DRESS (NSAIDs, PCN, cephalosporins, aspirin, allopurinol, dilantin/ AEDs)
  - autoimmune (Churg Strauss, SLE, other vasculitides)
  - malignancy associated (lymphoma, metastatic carcinoma)
  - lymphocyte variant (clonal T-cell population evolving IL-5 with secondary eosinophilia)
- Idiopathic: ???
Hypereosinophilia: etiologies

### Distribution of Diseases in 1682 Patients With Eosinophilia

<table>
<thead>
<tr>
<th>Disease</th>
<th>Patients, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic diseases</td>
<td>1465 (79.7)</td>
</tr>
<tr>
<td>Asthma</td>
<td>492 (26.4)</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>755 (40.5)</td>
</tr>
<tr>
<td>Rhinocconjunctivitis</td>
<td>215 (11.5)</td>
</tr>
<tr>
<td>Allergic GI</td>
<td>23 (1.2)</td>
</tr>
<tr>
<td>Parasitic infections</td>
<td>152 (8.2)</td>
</tr>
<tr>
<td>Heroinism</td>
<td>146 (7.8)</td>
</tr>
<tr>
<td>Protozoa</td>
<td>6 (0.3)</td>
</tr>
<tr>
<td>Hemolymphoid neoplasms</td>
<td>44 (2.4)</td>
</tr>
<tr>
<td>Hodgkin disease</td>
<td>23 (1.2)</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>12 (0.7)</td>
</tr>
<tr>
<td>LSA myeloma</td>
<td>7 (0.4)</td>
</tr>
<tr>
<td><strong>Idiopathic hypereosinophilic syndrome</strong></td>
<td><strong>7 (0.4)</strong></td>
</tr>
<tr>
<td>Solid tumors</td>
<td>14 (0.8)</td>
</tr>
<tr>
<td>NSCL cancer</td>
<td>3 (0.2)</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>6 (0.3)</td>
</tr>
<tr>
<td>Colorectal carcinoma</td>
<td>10 (0.5)</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>3 (0.1)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (0.1)</td>
</tr>
<tr>
<td>GI diseases</td>
<td>29 (1.6)</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>11 (0.6)</td>
</tr>
<tr>
<td>Crohn disease</td>
<td>5 (0.3)</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>9 (0.5)</td>
</tr>
<tr>
<td>Eosinophilic GE</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Skin diseases</td>
<td>40 (2.1)</td>
</tr>
<tr>
<td>Chronic idiopathic urticaria</td>
<td>14 (0.8)</td>
</tr>
<tr>
<td>Atopic dermatitis</td>
<td>1 (0.05)</td>
</tr>
<tr>
<td>Well syndrome</td>
<td>14 (0.8)</td>
</tr>
<tr>
<td>Lung diseases</td>
<td>14 (0.8)</td>
</tr>
<tr>
<td>Pulmonary aspergillosis</td>
<td>5 (0.3)</td>
</tr>
<tr>
<td>ChronicStrauss syndrome</td>
<td>2 (0.1)</td>
</tr>
<tr>
<td>Wegener disease</td>
<td>1 (0.05)</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>5 (0.3)</td>
</tr>
<tr>
<td>Eosinophilic pneumonia</td>
<td>1 (0.05)</td>
</tr>
<tr>
<td>Autoimmune diseases</td>
<td>12 (0.6)</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>6 (0.3)</td>
</tr>
<tr>
<td>Sjogren syndrome</td>
<td>3 (0.1)</td>
</tr>
<tr>
<td>Rheumatic polymyagia</td>
<td>2 (0.1)</td>
</tr>
<tr>
<td>Behcet syndrome</td>
<td>1 (0.05)</td>
</tr>
<tr>
<td>Eosinophilia of unknown signif</td>
<td>51 (2.7)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1682 (100)</strong></td>
</tr>
</tbody>
</table>

Abbreviations: GE, gastroenteritis; GI, gastrointestinal; NSCL, non-small cell lung.
Primary eosinophilia: WHO classifications

| Table 11: 2008 World Health Organization Classification of Eosinophilic Disorders |
|--------------------------------|---------------------------------|
| Myeloid and lymphoid neoplasms with eosinophilia and abnormalities of PDGFRA, PDGFRB, or FGFR1 | Diagnostic criteria of an MPN* with eosinophilia associated with FIP1L1-PDGFR
| Myeloid, lymphoid, and hematopoietic stem cell neoplasms* with HE and a recurrent somatic gene defect | |
| A. PDGFR-A rearranged neoplasms | |
| B. PDGFR-B rearranged neoplasms | |
| C. FGFR1 rearranged neoplasms | |
| D. Other defects: JAK2 fusion gene, FLT3 fusion gene | |
| 2. Eosinophilic leukemia without a recurrent somatic gene defect (listed above) | |
| A. No gene defect and no chromosome defect detectable | |
| B. With a nonspecific chromosome/gene abnormality (other than listed in 1 and 3) | |
| 3. WHO-defined myeloid neoplasm with HE (MN-eo): | |
| A. Ph (BCR/ABL) chronic myeloid leukemia (CML-eo) | |
| B. JAK2 V617F myeloproliferative neoplasms (MPN-eo) | |
| C. KIT D816V systemic mastocytosis (SM-eo) | |
| D. CBFβ-fusion gene-related acute myeloid leukemia (AML-eo; eg, AML-M4-eo) | |
| E. Myelodysplastic syndromes with HE (MDS-eo) | |
| F. Other WHO-defined myeloid neoplasms with HE | |
| Idiopathic Hypereosinophilic Syndrome (HES) | |
| Exclusion of the following: | |
| 1. Reactive eosinophilia | |
| 2. Lymphocyte-variant hypereosinophilia (cytokine-producing, immunophenotypically aberrant T-cell population) | |
| 3. Chronic eosinophilic leukemia, HOS | |
| 4. WHO-defined myeloid malignancies associated eosinophilia (e.g., MDS, MPNs, MDS/MPNs, or AML) | |
| 5. Eosinophilia-associated MPNs or AML/ALL with rearrangements of PDGFRA, PDGFRB, or FGFR1 | |
| 6. The absolute eosinophil count of >1500/mm³ must persist for at least 6 months and tissue damage must be present. If there is no tissue damage, idiopathic hypereosinophilia is the preferred diagnosis. | |
Hypereosinophilia: a diagnostic approach

Tefferi et al, 2010
Started on lovenox 1mg/kg BID in the ED and admitted to UWMC

Additional history:
- PMH: migraine HAs (well controlled), mild asthma (dx 20 yrs ago) has been worse lately, depression/PTSD
- ROS: increased anxiety, weight loss due to decreased appetite
- Meds: No new meds. Chronic meds: clonazepam, prazosin, topiramate, rizatriptan, lunesta, albuterol
- Allergies: Sulfa drugs (rash)
- Family: No known hx of eosinophilic disorders, rheumatological disease or malignancy (although son w recent dx of aggressive lymphoma).
Back to the case: TA

- Additional workup:
  - CT chest notable for left lower lobe segmental and subsegmental PEs, no LAD or pulm interstitial disease
  - EKG: ST, otherwise normal, TTE unremarkable, TnT flat
  - LDH: 158, CRP: 57
  - Giardia Ag neg, H. pylori breath test neg
  - Hepatitis panel neg, HIV neg
  - Stool O&P neg x2
  - Antiphospholipid Abs neg
  - B12 wnl, tryptase non-elevated
  - CA 19.9, CEA wnl
  - ANA, ANCA, RF, immunoglobulins—all wnl

- A diagnostic procedure was performed...
Back to the case: TA

Bone marrow aspirate:
Bone marrow aspirate/biopsy:
- Normal trilineage hematopoiesis with prominent eosinophilia
- Flow cytometry with no evidence of myeloid stem cell disorder
- FISH neg for FIP1L1, PDG FRA, PDG FRB, FG FR1, KIT, CBFB rearrangements
- JAK-2 negative, BCR/ABL negative
- T-cell subsets: wnl

(Another) diagnostic procedure was performed...
Back to the case: TA

- EGD/colonoscopy with mild esophagitis/gastritis, mild luminal narrowing at 23-30 cm from anal verge, otherwise normal appearing mucosa
- Multiple biopsies taken:
  - Gastric antrum/ fundus: 40 eos per HPF, otherwise wnl
  - Esophagus: 2 eos per HPF, otherwise wnl
  - Sigmoid colon: submucosal cluster of eos (>25 per HPF)
  - No e/o mucosal damage
  - **Flow panel negative for B/T lymphoma**
Back to the case: TA

- Diagnosis?
  - Idiopathic hypereosinophilic syndrome (HES)
  - aka...
Later that evening…

- Acute SOB at rest → CTPE:
  - Interval worsening of the acute pulmonary thromboembolic disease. **New pulmonary emboli are identified in the left main pulmonary artery, segmental and subsegmental branches in the left upper lobe and right lower lobe with persistent clots in the left lower lobe segmental and subsegmental branches.**

- LE duplex (next AM):
  - Right: Non-occlusive **deep venous thrombosis is present in the right proximal femoral vein.** Superficial venous thrombosis is present in the right great saphenous vein from mid calf to distal thigh.
  - Left: Non-occlusive **deep venous thrombosis is present in the left common femoral and proximal main thigh femoral veins. Occlusive deep venous thrombosis is present in two left gastrocnemius veins.**

- Repeat abdominal US with doppler (next AM):
  - Compared to study of 3/7/14, evidence for progression includes **new non-occlusive thrombus in the posterior branch of the right portal vein, main portal vein, and new bidirectional flow in the left portal vein,** which was previously hepatopetal.

- Methylpred 1g QD initiated
- Transferred to ICU for close monitoring
HES and thrombosis

- Well, it happens...
  - Approximately 25-30% of HES patients have associated thromboembolic events with approx 5-10% associated mortality (Ogbogu, et al 2007)

- “eosinophilia” AND “thrombosis”; “idiopathic” AND “hypereosinophilia” AND “thrombosis”
HES and thrombosis

HES and thrombosis: potential mechanisms

- MBP and ECP
- EPO stimulate
- MPO + EPO
- MBP/ECP inhibit
- ECP neutralize


Slungaard et al, J Clin Invest. 1993
Giromlami et al, J Thromb & Thrombolysis. 2004
Fredens et al, Allergy. 1991
MBP and ECP binding of thrombomodulin, preventing activation of protein C

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Figure 2. Impaired APC generation by endothelial monolayers exposed to cationic EO granule proteins. 2-cm² endothelial cell mono-

Figure 3. Recovery of APC generation capacity by porcine aortic endothelial cells; time course and requirement for intact protein synthetic capacity. Results of two experiments are shown. In the first,
HES and thrombosis: potential mechanisms

- EPO stimulated release of tissue factor

MPO and EPO → platelet activation

**Figure 1.** Dose-response curves for the secretion of platelet 5-HT by eosinophil granule proteins. Shown are the dose-dependencies for secretion of [14C]5-HT from washed human platelets mediated by MBP (●), EPO (○), ECP (□), and EDN (△). The secretion is expressed as a percentage of the total platelet [14C]5-HT. The values shown represent the
HES and thrombosis: redux
HES and thrombosis: therapeutic implications

- Prophylactic anticoagulation in HES?
- DTI vs heparinoids for acute management (i.e., bival gtt vs heparin gtt)?
- Long-term management—warfarin vs LMWH vs Xa inhibitors vs DTI?
- Role of anti-platelet agents?
Meanwhile...

- Baseline plt: 230s
- Additional labs: Fibrinogen, PTT/PT wnl. Peripheral smear unchanged from admission (no signs of MAHA)
Well, it happens...

- Thrombocytopenia noted in approx 30% of HES cases (Flaum, et al)
- ‘hypereosinophilic syndrome’ AND ‘thrombocytopenia’; ‘eosinophilia’ AND ‘platelets’
HES and thrombocytopenia: potential mechanisms

- MBP/ECP mediated direct platelet activation → consumption
- Eosinophil mediated TF release → thrombin generation → consumption
- Eosinophil mediated endothelial injury → DIC/consumption
- Portal vein thrombus → portal hypertension → splenomegaly → sequestration
HES and thrombocytopenia: therapeutic implications

- Correct underlying process (hypereosinophilia)
- Vigilant DIC/MAHA monitoring
- Role of immune modulation
Back to the case...

- Eosinophil count down to 0 after first dose solumedrol 1g
- Transitioned to pred 1mg/kg, eosinophils reappear but at very low levels
- Repeat LE duplex with stable clot burden
- Initiated on slow pred taper
- Discharged home on LMWH + warfarin
- Thrombocytopenia persistent at discharge
And then...

- Hematology follow up 1 week after discharge
  - Looks well, no new complaints.
  - Tapered to pred 70mg QD
  - Abs eosinophil count at 110
  - Plt count stable-low at 62
- A/P
  - Transitioned from warfarin to dalteparin
  - Hold at current pred dose
  - Repeat US imaging planned to assess clot burden
  - Discussion of aspirin...holding for now
  - Discussion of IVIG...holding for now
  - Close hematology follow up
First line: corticosteroids
- 1mg/kg pred x 2-3 weeks followed by extended taper (2-3 months)

If resistant to pred or relapse with taper, add hydrea vs IFNa
- If eosinophilia persists → trial higher dose imatinib at 400-800mg/d
  - (Butterfield et al, “Success of short term, higher dose imatinib mesylate to induce clinical response in FIP1L1-PDGFRα negative hypereosinophilic syndrome.” Leuk Res, 2009.)

Still? mepolizumab vs alemtuzumab
- Rothenberg, et al. NEJM 2008

Still?? RIC alloHSCT
Eosinophils are a terrible beauty

HE classification (big buckets):
- primary (clonal) vs secondary (reactive) vs idiopathic (please research me)

Hypereosinophilia causes thrombosis, potentially life threatening

Hypereosinophilia is associated with thrombocytopenia; significance undetermined

Treatment of HES should be tailored to account for these potential complications
Thank you


References


Hypereosinophilia: therapeutic options

- **Myeloid and lymphoid neoplasms with eosinophilia and abnormalities of PDGFRα, PDGFRβ, or FGFR1**
- **Chronic Eosinophilic Leukemia, NOS or WHO-defined myeloid neoplasm with associated eosinophilia (e.g. MDS, MPN, MDS/MPN)**
- **Idiopathic hypereosinophilia**
- **Lymphocyte-variant hypereosinophilia**

**Idiopathic hypereosinophilic syndrome**
- Imatinib for PDGFRα/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
Mepolizumab

- Fully humanized, anti-interleukin-5 monoclonal immunoglobulin G1 antibody

- Rothenberg, et al. NEJM 2008
  - randomized, double-blind, placebo-controlled, parallel-group, multicenter study
Mepolizumab

- Duration of remission?
- Role of maintenance?