Hypereosinophilic Syndrome

Fellow: Eunpi Cho
Faculty Discussant: Michael Linenberger
Case

- 19 yo M admitted to Evergreen Hospital after cardiac arrest.
- Troponin 8.41, BNP 12,087
- Utox pos for amphetamines (was on lisdexamfetamine for Aspergers/ADHD)
- TTE – EF 15-20%, severe concentric LVH, severe hypokineses, and ballooning at apex
# Case

<table>
<thead>
<tr>
<th>Date</th>
<th>11/5/2012</th>
<th>11/6/2012</th>
<th>11/7/2012</th>
<th>10/4/2012</th>
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<tbody>
<tr>
<td>WBC</td>
<td>14.70</td>
<td>17.65</td>
<td>18.74</td>
<td>25</td>
</tr>
<tr>
<td>Hg</td>
<td>11.3</td>
<td>15.8</td>
<td>16.4</td>
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<tr>
<td>HCT</td>
<td>31</td>
<td>43</td>
<td>46</td>
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<tr>
<td>PLT</td>
<td>116</td>
<td>171</td>
<td>236</td>
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<tr>
<td>% Neutrophils</td>
<td>36</td>
<td>43</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>% Lymphocytes</td>
<td>14</td>
<td>8</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>% Monocytes</td>
<td>6</td>
<td>10</td>
<td>8</td>
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<tr>
<td>% Eosinophils</td>
<td>44</td>
<td>38</td>
<td>40</td>
<td>69</td>
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<tr>
<td>% Basophils</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Abs. Eos</td>
<td>6.4</td>
<td>6.65</td>
<td>7.53</td>
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</table>
Hypereosinophilic syndrome

- Persistent eosinophilia of $1.5 \times 10^9/L$ or more eosinophils for longer than 6 months, or death before 6 months associated with signs and symptoms of hypereosinophilic disease
- Lack of evidence for parasites, allergies, or other known causes of eosinophilia
- Presumptive signs and symptoms of organ involvement
Other causes of marked eosinophilia

- Neoplasm
  - Leukemia, lymphoma, solid organ adenocarcinoma
- Addisons
- Allergy
  - Asthma, atopic dermatitis
- Collagen vascular disease
  - Sarcoid, IBD, CSS
- Parasites
  - Strongyloides, filaria, hookworm, scabies, isospora
- Other causes
  - Chronic TB, ABPA, HIV, coccidiomycosis, cholesterol embolus, systemic mastocytosis

American College of Rheumatology (ACR) criteria for the diagnosis of Churg-Strauss syndrome.
1. Asthma (wheezing, expiratory rhonchi)
2. Eosinophilia of more than 10% in peripheral blood
3. Paranasal sinusitis
4. Pulmonary infiltrates (may be transient)
5. Histological proof of vasculitis with extravascular eosinophils
6. Mononeuritis multiplex or polyneuropathy.

Differentiating HES

• Myeloproliferative (clonal population of eosinophils)
  – PDGFRA-associated
  – Myeloproliferative w/o PDGFRA (clonality demonstrated by HUMARA or ≥ 4 of the following: dysplastic peripheral eosinophils, B12 > 1000 pg/mL, tryptase ≥ 12, anemia and/or thrombocytopenia, HSM, bone marrow cellularity > 80%, spindle-shaped mast cells, myelofibrosis)

• Lymphocyte variant (abnormal clonal population of T-cells)
  – Eosinophilia thought to be 2/2 to T cell production of cytokines

• Familial

• Idiopathic

• Overlap (EGID, eosinophilic pneumonia, eosinophilia myalgia syndrome, etc)

HES evaluation

- CBC with differential
- Serum tryptase
- Serum B12
- FIP1L1/PDGFRα analysis (also PDGFRB, FGFR1)
- BCR-ABL, Jak2 V617F, KIT D816V
- Lymphocyte clonality studies
- Bone marrow biopsy with cytogenetics
- CT CAP
- Echocardiogram
- Pulmonary function tests
- Biopsy of affected tissues
Case diagnostic workup

Abnormal values
- IgE = 5070 (nl 0-300)
- ESR=58, RF=35, CRP 30.7 (0-10)
- C5=30.2 (10.6-26.3)
- CXR with bilateral infiltrates
- Cardiac MRI: Mild diffuse increased left ventricular wall thickening with patchy diffuse subendocardial, mid-myocardial and subepicardial T2 signal with corresponding delayed contrast enhancement.
- Endomyocardial bx: acute myocarditis, eosinophil rich, no large vessels in biopsy, no granulomas
- Bone marrow: normocellular, trilineage hematopoiesis with increased eosinophils and eosinophil precursors. No dysplasia.

Normal values
- IgA, IgG, IgM
- antiPR3=neg, ANA neg, antiMPO=neg,
- Total complement, C1, C3, C4
- B12=591 (nl)
- Negative for stool O&P, parvo, Mono, Hep C, Quantiferon
- SPEP normal
- TCR – no clonal population
- BCR-ABL neg, Jak2 neg, KIT D816V

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Cardiac biopsy & bone marrow biopsy
Bone marrow aspirate
M-HES

- Imatinib used in 5 patients with idiopathic HES, reported by Gleich et al Lancet 2002
  - 4 patients responded, all with normal IL-5 levels. Started at 100 mg daily, reduced to 200 mg/week

- FIP1L1-PDGFRA fusion gene reported as therapeutic target of imatinib (Cools et al NEJM 2003)
FIP1L1-PDGFRA

- 16 patients with HES, 1 pt with AML that progressed from HES
  - 11 patients received imatinib (100-400 mg daily).
- 9 of 11 achieved durable remission (>3 mo) after median 4 weeks, mean duration 7 mo
- 1 patient with known t(1;4)(q44;q12) mutation led to discovery of fusion gene with previously unnamed Fip1-like 1 (FIP1L1) through sequencing, gene upstream of PGDRFA on 4q12
- 9 patients were sequenced & 5 had fusion gene, 4 did not
- 1 patient developed resistance and had new T647I mutation (occurring at ATP-binding region) of PDGFRA at same position as BCR-ABL T315I

Cools et al. NEJM 2003
Treatment of non-FIP1L1/PDGFRA-HES

- Corticosteroids (initial dose ≥ 40 mg/d with slow taper)
- Vincristine 1-2 mg IV for rapid reduction (consider if counts >100,000/µL)
- Hydroxyurea 1-3g/d
- IFN-alpha 1-2 mU sq/d, or peg IFN-alpha
- Other cytotoxic agents such as cytoxan, 6-TG, MTX, ara-C, 2-CDA
- Other immunomodulatory tx (IVIG, cyclosporine)
- Mepolizumab (available for compassionate use)
- Stem cell transplant

Adapted from Klion AD et al. J of Allergy and Clin Immunol 2006
Treatment course

![Graph showing the treatment course with Absolute eosinophil count in thousand/µL and Troponin in ng/mL over time. The graph includes two lines: one for Eosinophils (red) and one for Troponin (blue). The x-axis represents dates from 11/3/12 to 12/7/12. The y-axes are labeled Absolute eosinophil count in thousand/µL on the left and Troponin in ng/mL on the right.]

- Prednisone 60 mg/day
- Prednisone 40 mg/day
Treatment course

Absolute eosinophil count in thousand/µL

Troponin in ng/mL

Prednisone 40mg/day
Pred 30 ->25 ->20 /day
Pred 60/day x 10 days -> taper; currently 2 mg/day
Imatinib
azathioprine
mepolizumab
Mepolizumab in HES

• fully-humanized, anti-IL-5 monoclonal IgG1 antibody with $\frac{1}{2}$ life of approx 19 days
• 85 patients with HES (FIP1L1/PDGFRα neg) requiring pred 20-60 mg/d
• Mepolizumab 750 mg IV q4wk x 32wk vs placebo (1:1 randomization)
• 1° endpoint: time to pred to 10 mg/d or less for 8 or more consecutive weeks
• 2° endpoint: eosinophil $\leq$ 600/µL for 8 or more weeks, TTF (clinical worsening, pred $>$ 60 mg/d, withdrawal from study), prednisone dose $\leq$ 7.5 mg/d, no prednisone for 1 or more days, mean daily prednisone dose at 36 wk, pred dose of 10 mg/d or less by week 20 for 8 or more weeks
• Weekly clinic visits and blood counts: tapering of prednisone based on symptoms and absolute eo count.

Rothenberg et al. NEJM 2008
## Mepolizumab in HES

<table>
<thead>
<tr>
<th>1° end point</th>
<th>mepolizumab</th>
<th>placebo</th>
<th>Odds ratio</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>All pts</td>
<td>36/43 (84%)</td>
<td>18/42 (43%)</td>
<td>8.0 (2.7-3.8)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>≤ 30 mg pred</td>
<td>26/30 (87%)</td>
<td>17/30 (57%)</td>
<td>5.0 (1.4-17.8)</td>
<td>0.01</td>
</tr>
<tr>
<td>&gt; 30 mg pred</td>
<td>10/13 (77%)</td>
<td>1/12 (8%)</td>
<td>36.7 (3.3 to 412.3)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Rothenberg et al. NEJM 2008
Long-term safety

- Open label extension study: 78 subjects who received between 1-66 mepolizumab infusions. Mean exposure 251 weeks (4-302)
- Mean daily dose of pred dec from 20 to 0 mg over 24 wks
- 1° endpoint = safety. AE: cough (33%), fatigue (31%), headache (29%), URI (29%), sinusitis (28%). SAE: arthralgia & PNA, nausea, abdominal pain, dyspnea, pruritis, pyrexia. 1 death from AITL possibly attributable to drug.
- 2° endpoint = efficacy, frequency of dosing

**FIG 2.** Initial decline in corticosteroid use in the first 6 months of the study.

Roufosse et al. J Allergy Clin Immunol 2013
Hypereosinophilia

Screen for reactive causes

Reactive Eosinophilia

Treat underlying cause

Screen for FIP1L1-PDGFRA by FISH or RT-PCR; bone marrow aspirate and biopsy with cytogenetic analysis; evaluate for reciprocal translocations involving 4q12 (PDGFRα), 5q31-33 (PDGFRβ), or 8p11-13 (FGFR1)

Positive

Other clonal or molecular abnormality, clonal eosinophil, and/or increased marrow blasts (>5 - <20%)?

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

Idiopathic hypereosinophilic syndrome

Lymphocyte-variant hypereosinophilia

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

If organ damage present

Gotlib J. Am J Hematol 2012