Systemic Mastocytosis
A brief case and disease overview

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Hematology Fellows Conference Series

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Jesse Salk MD, PhD
jjssalk@uw.edu
The Story of Mr D.

- 74 y/o, generally healthy, CAD/CABG
- 1.5 months fevers to 102, weight loss, cough, diarrhea, abdominal pain
- Diff: monos 18%, meta 3%, myelo 5%, pro 2%, no blasts, giant platelets, vaculated monos, toxic granulations
- LFT: AP 825, otherwise normal.
- CT abdomen: innumerable retroperitoneal LN <2 cm, splenomegally (17.6 cm), “diffuse mottling of axial skeletal, consider metastatic disease.”
- PSA 2.6, SPEP polyclonal, FLC normal.
The Story of Mr D.

- **Heme consult:** BCR-ABL, JAK2, CALR, MPL (negative)
  - Peripheral flow (left shifted, 0.06% circulating mast cells)
  - PET-CT (splenomegally with some uptake, no uptake nodes, diffuse uptake throughout marrow)

**Heme clinic:** “I feel all better!”

**Bone marrow:** 3 months later, uneventful. WBC 35.

**OSH ER:** Fatigue, rapidly increasing abdominal girth, para x4, admitted AKI Cr 3, AP 1000, Tbili 2.5. US “cirrhosis”, portal HTN.
Mr D’s Marrow

Morphology: “Markedly hypercellular (100%) marrow with granulocytic hyperplasia and megakaryocytic atypia in background of marked reticulin fibrosis (2-3+). Multifocal dense infiltrates of mast cells (>15 cells per aggregate) occupying 30-40% of marrow space. Touch imprints reveal >25% of mast cells have atypical morphologic features.

Cytogenetics: Normal XY

FISH: No MDS-associated findings

Molecular: POSITIVE for D816V mutation

http://dx.doi.org/10.1590/1516-3180.2013.1313460
Where does this fit into hematology?

<table>
<thead>
<tr>
<th>MYELOPROLIFERATIVES</th>
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<tbody>
<tr>
<td>• Chronic myeloid leukemia</td>
<td>BCR/ABL, Ph+</td>
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<td>• Polycythemia vera</td>
<td>JAK2 V617F</td>
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<td>• Essential thrombocytosis</td>
<td>JAK2 &gt; CALR &gt; MPL</td>
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<td>PDGFRA-FIP1L1</td>
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<td>D816V KIT &gt; other KIT</td>
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MYELOPROLIFERATIVES

- Chronic myeloid leukemia
- Polycythemia vera
- Essential thrombocytosis
- Primary myelofibrosis
- Chronic eosinophilic leukemia
- Chronic neutrophilic leukemia
- Mastocytosis

- Cutaneous mastocytosis
- Isolated mast cell tumors
- Systemic mastocytosis (SM)
Cutaneous mastocytosis

- Primarily children, often infancy
- Excellent prognosis, most often spontaneously regresses in teens
- Variably serious allergic & anaphylactic reactions
- Genetics: KIT mutations 75% but only ¼ are D816V
Cutaneous mastocytosis

Some kids have spots, some don't!

To learn why, please read the back of this card.

Mastocytosis and Mast Cell Activation Disorder

Some people have spots and some don't. I would like to explain why.

Some people have a rare disease called mastocytosis. This disease can cause mild to severe allergic-type reactions to everyday things like heat, food or emotions. It can also cause spots. Mastocytosis can be life threatening, and at this time there is no known cure. For many children the disease goes away before they become teenagers.

Some other people have mast cell activation disorder. Even if they don't have spots, they can have many of the same symptoms as people with mastocytosis. Please don't worry! With or without spots, mast cell disorders are NOT CONTAGIOUS. That means you cannot 'catch' them. If you have any other questions, please feel free to ask.

To learn more, please visit The Mastocytosis Society, Inc. website at: www.tmsforacure.org

Mastocytosis Society
Systemic Mastocytosis

MAJOR CRITERIA (need 1):

• Multifocal infiltration of >25% abnormal looking mast cells into marrow or other major organs as evidenced by tryptase staining.

MINOR CRITERIA (need 3):

• Atypical morphology of mast cells in tissues
• Persistent elevation of serum tryptase
• Aberrant expression of CD2 or CD25 on mast cells
• Presence of activating D816V mutation
Where does this fit into hematology?

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- Mastocytosis

- Cutaneous mastocytosis
- Isolated mast cell tumors
- Systemic mastocytosis (SM)

- Indolent SM
- Aggressive SM
- Mast cell leukemia
- Systemic mastocytosis associated with clonal hematological non-mast cell lineage disease (AHNMD)
Systemic Mastocytosis

- **Indolent SM**
  - No severe cytopenias
  - No major skeletal involvement
  - No overt liver dysfunction, portal hypertension
  - No GI malabsorption with weight loss

- **Aggressive SM**
  - Any of the above

- **Mast cell leukemia**
  - Diffuse infiltration in marrow, often circulating

- **Systemic mastocytosis associated with clonal hematological non-mast cell lineage disease (SM-AHNMD)**

  SM with any one of other heme malignancies. Myeloid >lymphoid. Often other MPNs.
Spectrum of survival

Pardanani, Blood 2013. PMID: 23426950
KIT and other genetics

Aroch, EJH 2015
KIT and other genetics

- TET 2 39%
- DNMT 3A 12%
- ASXL1 20%
- RUNX 1 23%

Aroch, EJH 2015
Clonality of mastocytosis

ISM: KIT mutation outside mast compartment = increased risk of progression to ASM

AHNMD: Often in NMD compartment, varies with subtype (90% CMML, 30% AML)
Management

• Symptomatic, generally palliative

• Indolent
  
  Trigger avoidance
  
  H1, H2 blockade, leukotrine antagonists, steroids, epi

• Aggressive
  
  Steroids
  
  IFN + Steroids
  
  Cladrabine + Steroids
  
  Dasatinib?

• AHNMD
  
  Treat underlying disorder
  
  Hydroxyurea
  
  Allo transplant
Emerging and experimental treatments

- Midostaurin (multikinase inhibitor, FLT3 activity)
- Brentuximab vedotin (Anti CD-30)
- Denileukin diftitox (IL2 MAB + diptheria toxin)
- SL-401 (IL3 receptor)
- MK 2206 (AKT inhibitor, PI3K/AKT pathway)
- Obatoclax (BCL-2)
- Everolimus
- Ibrutinib
- Cladribine + IFN
- Thalidamide
- Dasatinib
- Nilotinib
- Sunitinib
- Tamoxifen
Mr D’s course

• OSH, started on prednisone 60 mg Qday, DC script for hydrea given

• Heme clinic: ECOG 3, requiring para EOD x 1 week, WBC 48, 1% circulating blasts, PLT 61, TB 2.6, Cr 2.

• Continued prednisone, started dose reduced ruxolitinib in lieu of hydrea, palliative para scheduled, gentle diuresis, hospice requested

• 3 day f/u: GI clinic w/o ascites.

• 1 month f/u: weight dropped, pain abated, ECOG 2, WBC 15, PLT 50, Cr 1.4, returned hospice bed.

• 2 month f/u: weight and pain increase when tapered to prednisone 5, increased TB remains 2.5. CD30 negative

• Future: Cladrabine, IFN, dasatinib, IDA Midostaurin?


Bob Richard and Paul Hendrie