Case 167

SYSTEMIC MASTOCYTOSIS WITH EOSINOPHILIA

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Clinical History

- Forty seven-year-old male presented with episodic diarrhea, hepatosplenomegaly and hypereosinophilia
- No signs of impairment of cardiac, pulmonary or liver function
- No hypersplenism
- No skin lesions
- CBC data:
  - WBC 13.9, Hgb/HCT 13.8/43.3, PLT 605
  - WBC differential: 44% polys/bands, 34% lymphocytes, 8.8% monocytes, 13.1% eosinophils
  - Absolute eosinophil count 1821, absolute monocyte count 1223
  - Serum tryptase 334 ng/ml
Peripheral Blood Smear

- RBC: mild anisopoikilocytosis with target cells
- WBC: leukocytosis, eosinophilia, mild monocytosis
  No significant left shift or dysplastic changes in myeloid elements
- Thrombocytosis with platelet clumps
- No circulating mast cells or blasts
Bone Marrow Biopsy

- Hypercellular marrow
- Multiple paratrabecular and perivascular mast cell aggregates, involving 20-30% of marrow biopsy
- Interstitial eosinophilia
Bone Marrow Immunohistochemistry

- Tryptase immuno-staining shows more than 25% of spindle-shaped mast cells
Bone Marrow Aspirate Smear

- Differential: 52% granulocytic precursors, 2% monocytes, 12% erythroid precursors, 21% lymphocytes, 10% eosinophils, 4% atypical mast cells
- Mast cells large, spindle-shaped or hypogranular
- No significant dysplastic changes, except for few hypolobulated megakaryocytes
Flow Cytometric Analysis

- Flow cytometric analysis of the bone marrow aspirate:
  - 0.3% blasts, 2.4% monocytes, 6.4% eosinophils 0.04% mast cells

- Mast cells
  - positive for CD117, CD25, CD11c, CD35, CD59, CD63, CD69
  - negative for CD2, CD34
Molecular and Cytogenetic Analysis

- **Molecular analysis:**
  - RT-PCR/RFLP analysis for KIT D816V mutation: positive
  - Nested RT-PCR for FIP1L1-PDGFRα fusion gene: negative
  - RT-PCR/RFLP analysis for JAK-2 V617F mutation: negative

- **Cytogenetics:**
  - Normal
The patient fulfilled WHO criteria for diagnosis of systemic mastocytosis with eosinophilia (SM-eo), smoldering. Patient receives only symptomatic therapy and no cytoreductive therapy. Yearly follow-up shows essentially the same clinical picture, CBC data, tryptase levels and bone marrow findings. In view of pathological findings and clinical course, diagnosis of chronic myelomonocytic leukemia (CMML) was not rendered.
Diagnostic Challenge

- Using the currently accepted WHO diagnostic criteria for SM and HES, classification of patients with increased bone marrow mast cells and unexplained peripheral eosinophilia is problematic.

- Two distinct mutations, KIT D816V and FIP1L1/PDGFRα, are both associated with increased eosinophils and atypical mast cells in bone marrow samples.
  - Mast cells are spindle-shaped.
  - Mast cells are CD25 positive.
  - Serum tryptase is increased.
KITD816V Positive Patient

FIP1L1/PDGFRα Positive Patient

H&E

Tryptase IHS
Patients carrying either KIT or FIP1L1/PDGFRa mutations can be diagnosed as systemic mastocytosis with eosinophilia (SM-eo) by the WHO criteria.

However, pathogenesis, prognosis and treatment of the disorders associated with these two mutations are markedly different.
Hypereosinophilic patients positive for KIT D816V

- No eosinophil-associated end-organ damage. Usually chronic non-life threatening condition
- Both major and minor WHO criteria for diagnosis of SM are usually fulfilled
- Patients show no response to treatment with imatinib mesylate
- In our opinion, these patients should be diagnosed as a systemic mastocytosis with eosinophilia (SM-eo)

Hypereosinophilic patients positive for FIP1L1-PDGFRa

- Clinical presentation, course and major findings (end-organ damage) are associated with the eosinophilic component of the disorder
- Usually only minor WHO criteria for diagnosis of SM are fulfilled
- Patients show dramatic response to treatment with imatinib mesylate
- In our opinion, these patients should be diagnosed as a primary eosinophilic disorder, i.e. FIP1L1-PDGFRa-associated CEL
KIT D816V-associated SM-eo versus FIP1L1/PDGFRa-associated CEL

- We retrospectively sought to identify clinical and laboratory features that could be used to distinguish these two diagnoses.
- 12 hypereosinophilic patients who met WHO criteria for SM-eo (including the presence of D816V KIT mutation) were compared to 17 hypereosinophilic patients with FIP1L1/PDGFRa mutation.
- Based on the differences in clinical and laboratory findings, a risk factor scoring system was devised for distinguishing between these two disorders.
<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>KIT D816V-SM-eo</th>
<th>FIP1L1/PDGFRa-CEL</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patients</td>
<td>12</td>
<td>17</td>
</tr>
<tr>
<td>Age</td>
<td>40 (2-64)</td>
<td>35 (17-77)</td>
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<tr>
<td>Male/Female</td>
<td>7/5</td>
<td>17/0</td>
</tr>
<tr>
<td>GI symptoms</td>
<td>9/12</td>
<td>1/17</td>
</tr>
<tr>
<td>Cardiac symptoms</td>
<td>0/12</td>
<td>7/17</td>
</tr>
<tr>
<td>Pulmonary symptoms</td>
<td>0/12</td>
<td>8/17</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>0/12</td>
<td>0/17</td>
</tr>
<tr>
<td>UP</td>
<td>7/12</td>
<td>0/17</td>
</tr>
<tr>
<td>Pruritus</td>
<td>7/12</td>
<td>8/17</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5/12</td>
<td>13/16</td>
</tr>
<tr>
<td>Joint/bone pain</td>
<td>2/12</td>
<td>0/17</td>
</tr>
<tr>
<td>Mucosal ulcers</td>
<td>0/12</td>
<td>3/17</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>6/12</td>
<td>3/17</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>8/12</td>
<td>14/17</td>
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<tr>
<td>Lymphadenopathy</td>
<td>5/12</td>
<td>4/17</td>
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<tr>
<td>Monocytosis</td>
<td>4/12</td>
<td>1/17</td>
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<tr>
<td>Thrombocytosis</td>
<td>5/12</td>
<td>0/17</td>
</tr>
<tr>
<td>Anemia</td>
<td>5/12</td>
<td>8/17</td>
</tr>
<tr>
<td>Neutrophilia</td>
<td>5/12</td>
<td>5/17</td>
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<tr>
<td>Median serum tryptase (ng/ml)</td>
<td>207</td>
<td>24</td>
</tr>
<tr>
<td>Median peak AEC (/mm³)</td>
<td>2187</td>
<td>12474</td>
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<tr>
<td>ET ratio</td>
<td>12</td>
<td>699 (n=15)</td>
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<tr>
<td>Dense mast cell aggregates in BM</td>
<td>12/12</td>
<td>1/11</td>
</tr>
<tr>
<td>Serum B12 elevated</td>
<td>3/9</td>
<td>16/17</td>
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KIT D816V-associated SM-eo versus FIP1L1/PDGFRa-associated CEL
## Risk Factor Scoring System for Distinguishing Between KIT D816V-eosinophilia and FIP1L1/PDGFRa-eosinophilia

<table>
<thead>
<tr>
<th>Score</th>
<th>Risk factors for FIP1L1/PDGFRa eosinophilia</th>
<th>Score</th>
<th>Risk factors for KIT D816V eosinophilia</th>
</tr>
</thead>
<tbody>
<tr>
<td>+3</td>
<td>AEC/tryptase &gt; 100</td>
<td>-3</td>
<td>AEC/tryptase ≤ 100</td>
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<tr>
<td>+3</td>
<td>Dense mast cell aggregates in BM absent</td>
<td>-3</td>
<td>Dense mast cell aggregates in BM present</td>
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<tr>
<td>+3</td>
<td>Peak AEC &gt; 10,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+2</td>
<td>Serum B12 elevated</td>
<td>-2</td>
<td>GI symptoms</td>
</tr>
<tr>
<td>+1</td>
<td>Pulmonary symptoms</td>
<td>-2</td>
<td>UP</td>
</tr>
<tr>
<td>+1</td>
<td>Cardiac symptoms</td>
<td>-1</td>
<td>Female gender</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-1</td>
<td>Thrombocytosis</td>
</tr>
</tbody>
</table>

Positive total score denotes FIP1L1/PDGFRa-CEL
Negative total score denotes KIT D816V-associated SM-eo
KIT D816V-associated SM-eo and FIP1L1/PDGFRa-associated CEL are Two Distinct Entities

- Risk factor scoring system correctly predicted the molecular status of all 12 KIT D816V-positive SM-eo patients and 16/17 FIP1L1/PDGFRa-positive CEL patients
- These results reinforce the hypothesis that KIT D816V mutation and FIP1L1/PDGFRa gene fusion cause distinct clinical syndromes
- Our novel scoring approach should prove helpful in clinical practice in the evaluation of patients with increased BM mast cells and peripheral eosinophilia
Collaborators

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