2007 Workshop of Society for Hematopathology & European Association for Hematopathology
Indianapolis, IN, USA
Case # 228

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11/03/07
Case 228:

- **Clinical History:**
  - This 65 year old female with three month history of abdominal bloating and weakness.
  - Labs (CBC): Mild leukocytosis (14k/ul) with monocytosis (2940 absolute monocyte count), mild anemia (HB 11.5) and thrombocytopenia (90 k/ul).
  - Bone marrow biopsy: Hypercellular marrow (>75%) with several early myeloid / monocytic elements and few cell clusters with granular cytoplasm
  - Physical examination was negative for hepatosplenomegaly and skin rash.
- RBC with moderate anisopoikilocytosis and rare NRBC
- Few hypogranular / hyposegmented PMN’s
- Monocytosis (absolute count 2940 / cmm)
- Mild myeloid left-shift
- Rare degranulated mast cells (feather edge)
Peripheral Blood
Peripheral Blood
BM Aspirate Smear
BM Aspirate Smear
BM Biopsy Imprint
BM Biopsy Imprint
BM Biopsy
BM Biopsy
BM Biopsy

CD117

CD14
BM Biopsy
Bone Marrow Morphology

- Marrow cellularity 80-90%
- Marked myeloid left-shift and focal immature cell clusters
- Mast cells (aggregates and diffuse scattering)
- Mild dyserythropoiesis and normal megakaryocytic morphology
- Focal paratrabecular fibrosis
- Benign lymphoid aggregate

- Serum tryptase levels increased (outside lab report)
<table>
<thead>
<tr>
<th>Bone Marrow Aspirate</th>
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<tbody>
<tr>
<td>Blasts</td>
<td>7 %</td>
</tr>
<tr>
<td>Pro/Mye/M/PMN</td>
<td>40 %</td>
</tr>
<tr>
<td>Monocytes</td>
<td>9 %</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>5 %</td>
</tr>
<tr>
<td>Erythroid</td>
<td>21 %</td>
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<tr>
<td>Mast cells</td>
<td>~15 %</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Flow Cytometry</th>
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<tbody>
<tr>
<td>Mast: CD117+, CD33dim+</td>
<td></td>
</tr>
<tr>
<td>My/Mo: CD33/CD13+, CD14+, CD117+</td>
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<thead>
<tr>
<th>Immunohistochemistry</th>
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<tbody>
<tr>
<td>Mast cells: CD21+, CD117+, CD34-, CD2- CD25-, Tryptase+</td>
<td></td>
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<tr>
<td>Mono: NSE+, CD14</td>
<td></td>
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<tr>
<td>Myeloid: MPO+, CD117+, CD15+</td>
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Differential Diagnosis:
- Myelodysplastic syndrome ? CMML
- Reactive mastocytosis

Diagnosis: Systemic Mast cell Disease with Associated clonal Hematologic non-Mast Cell Lineage Disease (SM-AHNMD)

Panel Diagnosis: Differential diagnosis includes SM/mast cell leukemia and SM-AHNMD
- Studies by panel: WT c-kit CD25-
MC Characteristics in Mastocytosis

- Mature MC with variant morphology in indolent SM
  - MC with cytoplasmic extensions
  - Oval to spindle nuclei, hypogranular / degranulated cytoplasm and normal appearance

- BM histological patterns
  - Type I = Focal infiltrates
  - Type II = Focal infiltrates / hypercellular marrow in non MC areas and osteoclerosis (SM-AHNMD)
  - Type III = Diffuse infiltration (ASM or MCL)

- Immature MC (promastocytes / blasts) seen in aggressive SM and mast cell leukemia

- Immunophenotype
  - Immature = CD34+, CD13+ and CD117+
  - MC in SM = CD117+, CD2+ and CD25+
Indolent Systemic Mastocytosis
<table>
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<tr>
<th>WHO Classification of Mastocytosis</th>
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<tbody>
<tr>
<td>Cutaneous mastocytosis</td>
<td>CM</td>
</tr>
<tr>
<td>• Maculopapular CM</td>
<td>MPCM</td>
</tr>
<tr>
<td>• Diffuse CM</td>
<td>DCM</td>
</tr>
<tr>
<td>• Mastocytoma of skin</td>
<td></td>
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<tr>
<td>Indolent systemic mastocytosis</td>
<td>ISM</td>
</tr>
<tr>
<td>Smoldering SM</td>
<td>SSM</td>
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<tr>
<td>• Isolated bone marrow mastocytosis</td>
<td>BMM</td>
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<tr>
<td>Systemic mastocytosis with an associated clonal hematologic non MC lineage disease</td>
<td>SM-AHNMD</td>
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<tr>
<td>Aggressive systemic mastocytosis</td>
<td>ASM</td>
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<tr>
<td>• With eosinophilia</td>
<td></td>
</tr>
<tr>
<td>Mast cell leukemia</td>
<td>MCL</td>
</tr>
<tr>
<td>• Aleukemic MCL</td>
<td></td>
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<tr>
<td>Mast cell sarcoma</td>
<td>MCS</td>
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<td>Extra-cutaneous mastocytoma</td>
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SM-AHNMD

- Clonal hematopoietic non-MC neoplasms associated with systemic mast (SM) cell disease
- AML, CMML, MDS, CML<sup>ph+</sup>, HES etc.
- In most cases SM is obvious, however, in some it may be masked by *non-MC neoplasm*

**Clues**

- MC aggregates
- Variant MC morphology (spindle, lobed nuclei and lack of granules) *Bm touch imprint > aspirate smear*
- CD2+/CD25+ (IPOX)
- C-kit mutation for confirmation
SM-AHNMD

- Second most frequent subtype of SM
- >80% are myeloid – MDS/MPS, AML, CEL and CML (CMML is the most common association)
- Associated lymphatic malignancies (10-20%)
  - Plasma cell myeloma
  - ALL, CLL and hairy cell leukemia (rare cases)
  - CD25+ in hairy cells?
  - No case reports with Hodgkin lymphoma
BM Presentation

- Hypercellular marrow
- Normo or hypocellular areas
- “Occult” mastocytosis unmasked after chemotherapy

Prognosis depends on the “AHNMD component”

- Type of MDS/MPD or AL type
- 5 year survival: SM-AHNMD 17-28%, compared to MCD alone 75% and 61% (Travis et al)

Pullarkat VA et al Am J Hem. 2003;73:12-17
Agis H et al, Leuk Res. 2005;29:1227-1232
Diagnostic Workup

- Tissue biopsies (BM, skin & other tissues)
  - Routine H&E, Giemsa and toluidine blue (pH 1.5-2.5)
  - Reactive increase in MPD and lymphoproliferative disorders

- Flow / Immunohistochemistry
  - CD2, CD25, CD117, CD35, CD14, CD15, CD33 and CD34
  - Flow – Quick processing, stain lyse method over Ficoll separation, double step acquisition i.e. all nucleated cells followed by selective gating on CD117

- Serum
  - Elevated tryptase levels (note: higher levels are also seen in AML, MDS, MPD & hypereosinophilic syndrome)

- Molecular
  - C-kit (D816V), bcr/abl and FIPL1-PDGFRα

- Pediatric patients
  - Skin biopsy > tryptase levels and D816V

- Adults
  - Bone marrow biopsy > serum tryptase and c-kit mutation ?
Case 228 – 6 month followup

- White blood cell count 55.1/ul with 15 bands, 7 myelocytes, 4 metamyelocytes, 9 lymphocytes and 10 monocytes. No circulating blasts. Hemoglobin 10.3 and platelet count had decreased to 78,000.
- Continued diarrhea and weight loss
- Chemotherapy (outside follow-up, no details about the exact treatment regimen)