Myelodysplasia: Low Grade vs. Benign High Grade vs. AML

UCSF: Current Issues in Anatomic Pathology
Kathryn Foucar, MD
kfoucar@salud.unm.edu
May 2013

Objectives
• Key clues to MDS and mimics
• Logical approach to cytopenias in elderly
• Distinguish MDS from AML

Disclosure:
• Nothing to disclose

Outline
• MDS – Key tips
• Risk stratification in MDS
• Unexplained cytopenia in elderly
• Pancytopenia
• MDS vs. AML
**Myelodysplasia**
- Ineffective HP results in cytopenias despite hypercellular BM
- Hallmark of cytopenias with dysplasia
- Variable % blasts in blood and BM
- Dysplasia may involve 1, 2, or 3 HP lineages

**MDS: Incidence**
- Primarily disease of elderly; can occur at all ages
- 40 per one million adults
- Incidence increases with age: 15-50 per 100,000 in elderly patients (> 70 years)
- MDS in infants/children linked to either constitutional disorders or prior chemotherapy

**Pathophysiologic Mechanisms of MDS**
- Multistep pathogenesis
- Acquired stem cell abnormality resulting in clonal hematopoiesis
- Stem cell and BM microenvironmental defects (complex interplay)
- Increased BM apoptosis (bld/BM paradox)
- Acquisition of clonal abnormalities linked to disease progression and/or transformation

**MDS: Key Considerations**
**Clinical:**
- Prolonged, unexplained cytopenia (usually symptomatic)
- Stable vs. progressive cytopenia(s)
- Search for causes, risk factors, exposures, medications
- Exclude collagen vascular disease, chronic viral infection
- ↑ in frequency of therapy-related MDS (30% MDS)
**MDS: Key Features**

**Blood:**
- Cytopenias
- Variable dysplasia (assess all hematopoietic lineages)
- Variable blasts (low)

**Bone Marrow:**
- Hypercellular
- Dysplasia (one or more lineages); ringed sideroblasts, coarse Fe granules
- Variable blast % (often ↑ for patient age)

- Neutropenia; assess qual/quant all lineages
- Normal and abnormal neutrophils
- MDS: pseudo Pelger-Hüet dysplasia
MDS: erythroid dysplasia

Bone Marrow Aspirate in MDS

Megakaryocyte abnormalities; small, pawnball

Clot section in MDS

Hypercellular, inc small megas

IHC in MDS

CD42b

CD34
## MDS: Practical Approach/Key Tips

- Careful blast enumeration (do not use CD34 by flow as surrogate for blast %)
- Assess bone marrow architecture by immunohistochemistry
- Full karyotyping recommended (targeted FISH may be useful)

## WHO Classification of MDS

<table>
<thead>
<tr>
<th>Disease</th>
<th>Blood Findings</th>
<th>BM Findings</th>
<th>Freq. of Cytog. Abnls*</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA</td>
<td>Anemia</td>
<td>Erythroid dysplasia only</td>
<td>24%</td>
</tr>
<tr>
<td></td>
<td>No or rare blasts</td>
<td>&lt; 5% blasts</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt; 15% ringed sideroblasts</td>
<td></td>
</tr>
<tr>
<td>RARS</td>
<td>Anemia</td>
<td>Erythroid dysplasia only</td>
<td>9%</td>
</tr>
<tr>
<td></td>
<td>No or rare blasts</td>
<td>&lt; 5% blasts</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ 15% ringed sideroblasts</td>
<td></td>
</tr>
<tr>
<td>RCMD</td>
<td>Bi- or pancytopenia</td>
<td>Dysplasia in 10% cells of ≥ 2 myeloid lineages</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>No or rare blasts</td>
<td>&lt; 5% blasts</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
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<th>Blood Findings</th>
<th>BM Findings</th>
<th>Freq. of Cytog. Abnls*</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAEB-1</td>
<td>Cytopenias</td>
<td>Unilineage or multilineage dysplasia</td>
<td>55%</td>
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<tr>
<td></td>
<td>&lt; 5% blasts</td>
<td>5 – 9% blasts</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>No Auer rods</td>
<td></td>
</tr>
<tr>
<td>RAEB-2</td>
<td>Cytopenias</td>
<td>Unilineage or multilineage dysplasia</td>
<td>38%</td>
</tr>
<tr>
<td></td>
<td>5-19% blasts</td>
<td>10 – 19% blasts</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Auer rods +/-</td>
<td></td>
</tr>
<tr>
<td>Sq-syndrome</td>
<td>Anemia</td>
<td>NI in ↑ megas w/ hypolobated nuclei</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>Usu. nl or ↑ platelets</td>
<td>&lt; 5% blasts</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt; 5% blasts</td>
<td>del(5q) only cytog. abnormality</td>
<td></td>
</tr>
</tbody>
</table>

## Conventional Karyotype/FISH

- Normal conventional cytogenetics in > 40% of 1º MDS; abnormal karyotype in > 95% T-MDS
- Frequency of cytogenetic abnormalities linked to WHO subtype (lowest in RARS; highest in RCMD)
- Whole or partial deletions of chromosomes 5, 7, 20, 8
- Translocations very uncommon
Conventional Cytogenetics

46,XX,del(5)(q31q33)[19]/46,XX[1]

Cytogenetic Abnormalities in MDS

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Frequency</th>
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<tbody>
<tr>
<td>de novo MDS</td>
<td></td>
</tr>
<tr>
<td>-5/del(5q)</td>
<td>10-20%</td>
</tr>
<tr>
<td>+8</td>
<td>10%</td>
</tr>
<tr>
<td>-7/del(7q)</td>
<td>5-10%</td>
</tr>
<tr>
<td>17p-</td>
<td>7%</td>
</tr>
<tr>
<td>del(20q)</td>
<td>5%</td>
</tr>
<tr>
<td>complex abnls</td>
<td>10-20%</td>
</tr>
<tr>
<td>translocations</td>
<td>rare</td>
</tr>
<tr>
<td>Therapy-related</td>
<td></td>
</tr>
<tr>
<td>-5/del(5q) or -7/del(7q)</td>
<td>90%</td>
</tr>
<tr>
<td>complex abnls</td>
<td>90%</td>
</tr>
<tr>
<td>Translocation</td>
<td>&lt; 5%</td>
</tr>
</tbody>
</table>

MDS: Risk Stratification (IPSS-R)

<table>
<thead>
<tr>
<th>Prognostic Variable</th>
<th>0</th>
<th>0.5</th>
<th>1</th>
<th>1.5</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytogenetics</td>
<td>Very Good</td>
<td>Good</td>
<td>Intermediate</td>
<td>Poor</td>
<td>Very Poor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BM Blast %</td>
<td>≤ 2</td>
<td>&lt;2-&lt;5</td>
<td>5-10</td>
<td>&gt;10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>≥ 10</td>
<td>8-&lt;10</td>
<td>&lt;8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets</td>
<td>≥ 100</td>
<td>50-&lt;100</td>
<td>&lt;50</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANC</td>
<td>≥ 0.8</td>
<td>&lt;0.8</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>


MDS: Diagnostic Criteria

**Definitive**
- Sustained cytopenia
- Dysplasia ≥1 lineage
- Other causes excluded
- With/without clonal CC

**Presumptive**
- Sustained cytopenia
- Other causes excluded
- Abnormal CC or flow

**ICUS**
- Sustained cytopenia without dysplasia
- Lack of presumptive criteria
**Elderly Patient with Unexplained Cytopenia(s)**

- Common problem
- All the usual causes of anemia excluded
- Must distinguish MDS from non-neoplastic
- Low grade MDS very challenging
  - Minimal (so-so) dysplasia
  - Normal cytogenetics

**Case**

71-yr-old female w/ fatigue, weight loss; lung cancer in 1998; neutropenia, progressive anemia requiring transfusions

**Clinical dx:** Myelodysplasia

**CBC:** WBC 2,600; Hgb 10.9; Hct 31.4%; Plt 341,000 (blood smear NA)
**Diagnosis?**

1. Low grade MDS
2. Megaloblastic anemia
3. Copper deficiency
4. Magnesium deficiency

![Bar chart showing percentages of conditions](chart)

**Copper Deficiency: BM Features**

- Discrete vacuoles in myeloid (granulocytic), erythroid precursors
- Rare ringed sideroblasts
- No typical dysplastic features
- Normal blast count

**Zinc-Induced Copper Deficiency**

- Becoming more common!!
- Linked to zinc supplements, denture paste, and even zinc lozenges
- Also noted with prolonged TPN, medications

**Denture Cream Dangers Claimed**

"I think a lot of people out there have neuropathy and don’t know it could be connected to their dentures."
**Pancytopenia**

- Hematopoietic failure
- Not diagnostic endpoint
- Assess all lineages
- Scan for rare abnormal cells (any clues)
- Age is critical factor

**Pancytopenia**

- Constitutional
- Acquired
- Ineffective HP
- BM effacement/fibrosis
- BM hypocellular

**Pancytopenia Hypocellular BM**

- Aplastic anemia
- HCL/T-LGL
- MDS/AML
- Starvation
- Injury, toxin, inf., CVD
- PNH

**Pancytopenia Hypercellular BM**

- Megaloblastic anemia
- Infection/immunoregulatory disease
- MDS/Acute Leukemia
- Effacement by 2° tumor
- Rare constitutional disorders
**Pancytopenia Fibrotic BM**

- Chronic renal failure
- Metastatic tumors/lymphoma
- MPN (mastocytosis/PMF)
- Fibrotic MDS, AML, MPN (late stage)
- Chronic infection/CVD
- HCL

**Case:** 57 year old female with new onset of pancytopenia

**CBC:**
- WBC 1.5
- H/H 11.2/33%
- MCV 89
- RDW 19.2
- Plt 123

![Blood](57_year_old_female_with_pancytopenia)

![BM Aspirate](57_year_old_female_with_pancytopenia)
57 year old female with pancytopenia

**Diagnosis?**

1. Low grade MDS
2. Copper deficiency
3. Megaloblastic anemia
4. Magnesium deficiency

**Megaloblastic Anemia Key Tips**

- Vitamin $B_{12}$ deficiency fairly common
- *Diverse* manifestations (neurologic, psychiatric, hematologic)
- Blood and BM features may be “non-classic”
- High index of suspicion-lab testing a **must** (including MMA)
Blood Findings in Megaloblastic Anemia

- Most cases exhibit “classic profile”
- MCV may be normal (assess for other co-factors)
- Search for NRBC’s—check chromatin
- Hypersegmentation may be absent
- May mimic MDS
- Pancytopenia common

Bone Marrow Findings in Megaloblastic Anemia

- Bone marrow usually (not always) markedly hypercellular
- Blasts not increased
- Dysplasia restricted to megaloblastic changes
- Megaloblastic features of granulocytic lineage may persist in absence of comparable erythroid lineage changes

Laboratory Testing Issues

- Falsely normal serum cobalamin levels due to IF ab interference!!
- Essential to measure methylmalonic acid and homocysteine levels
- Intrinsic factor antibodies sensitive and specific for pernicious anemia

Tips to Assess Dysplasia

- Focus on specific dysplastic features such as hypogranular cytoplasm of neutrophils and neutrophil nuclear hypo- or hypersegmentation
- Megakaryocytes small in MDS
- Be aware that many non-neoplastic conditions are associated with anisopoikilocytosis of RBC’s and nuclear aberrations of erythroid elements in BM
MDS Diagnostic Challenges

Distinction between true dysplasia vs. “abnormal” morphology

- G-CSF or EPO-driven BM
- Medication-related dyspoiesis
- Significance of low frequency, subtle findings

Familial P-H/ Medication effect.

MDS Diagnostic Challenges

MDS vs. low blast count AML

- Most frequently issue with t(8;21), inv(16), t(15;17) AMLs
- Morphologic “clues” to distinct AML subtypes
- Careful delineation of blasts, blast equivalents
- 20% blasts (blast equivalent) threshold

15% blasts, t(8;21)

Low Blast Count AML

- Cases of AML with t(8;21) or inv(16) may present with < 20% blasts
- Clinical course is that of overt AML and AML therapy warranted
- Assess for morphologic “clues” for t(8;21) and inv(16)
- Clue: Auer rods in cases with <20% blasts
  (May be MDS but must be sure)
**MDS: Key Tips**

- Exclude lookalikes
- Low grade MDS dx of exclusion
- Count blasts in blood and BM
- Assess architecture of core bx
- Conventional cytogenetics key
- Exclude low blast count AML

**Summary**

- MDS incidence higher in elderly but non-neoplastic causes of cytopenia more common
- MDS in younger patients likely therapy-related
- Copper deficiency (often zinc-induced) closely mimics MDS
- “MDS” with Auer rods likely low blast count AML
- Value of cytogenetics clear-cut