Myelodysplasia
In Context

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Myelodysplasia

- Acquired, clonal disorder of the bone marrow stem cells. AKA: smoldering, sub-acute or atypical leukemia
- Usually characterized by cytopenias, a hypercellular bone marrow, and dysplastic morphology
- Incidence: 75/100K over 70yrs. Other ages the same as AML (1/100K at 30yrs to 15/100K at 70)
Myelodysplasia Diagnosis
In “Context”

Diagnosis depends upon clinical/ pathologic/ cytogenetic/
molecular information. Must distinguish from other myeloid
neoplasms and non-neoplastic causes of similar blood or
marrow findings.

<table>
<thead>
<tr>
<th>Category</th>
<th>Blood</th>
<th>Monocytosis?</th>
<th>Blasts?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myelodysplasia</td>
<td>Cytopenias*</td>
<td>Rarely</td>
<td>&lt;20%</td>
</tr>
<tr>
<td>Myeloproliferative</td>
<td>Cythemias</td>
<td>Occasionally</td>
<td>&lt;20%</td>
</tr>
<tr>
<td>Myelodysplasia/myeloprolif.</td>
<td>Variable, usually leukocytosis</td>
<td>Often</td>
<td>&lt;20%</td>
</tr>
<tr>
<td>Acute Leukemia</td>
<td>Variable, usually leukocytosis</td>
<td>Occasionally</td>
<td>&gt;20%</td>
</tr>
</tbody>
</table>

*5q-minus may have thrombocythemia
Myelodysplasia Diagnosis Requires “Context” Cont’d

- Diagnosis depends on clinical/ pathologic/ cytogenetic/ molecular information to distinguish from non-neoplastic disorders:
  - Infections such as HIV/AIDS
  - Nutritional deficiencies such as B12 or folate deficiency; copper deficiency
  - Toxins such as lead poisoning, alcoholism, cytotoxic drugs
  - Marrow failure syndromes/ aplastic anemia
  - Congenital anemias: thalassemias, CDA’s
WHO Classification

- Myelodysplastic Syndromes:
  - Refractory cytopenia with unilineage dysplasia
  - Refractory anemia with ringed sideroblasts (RARS)
  - Refractory cytopenia with multilineage dysplasia (RCMD)
  - Refractory anemia with excess blasts
  - MDS with isolated del (5q)
  - Myelodysplastic syndrome-unclassifiable
  - Childhood MDS
WHO Classification Cont’d

- Myelodysplastic/Myeloproliferative Neoplasms:
  - Chronic myelomonocytic leukemia
  - Atypical CML, BCR-ABL-negative
  - Juvenile myelomonocytic leukemia
  - MDS/MPN, unclassifiable

- Will not discuss MDS/MPN today
- Will focus on only a few MDS categories
WHO Classification Depends Upon:

- Clinical findings
  - History of acquired (non-congenital) cytopenias without other cause
  - History of mutagenic exposure?
    - Prior treatment for neoplasms such as breast cancer or lymphoma
    - Environmental exposures such as benzene
  - Usually no physical findings beyond signs of anemia and thrombocytopenia. In particular, splenomegaly is rare
WHO Classification Depends Upon (Cont’d):

- Morphologic features in blood and marrow. Number of lineages with more than 10% dysplastic cells.
- Percentage of blasts is critical for diagnosis and classification.
- Cytogenetics are important
  - Therapy-related myeloid neoplasms
  - 5q-minus has own WHO category
  - IPSS uses cytogenetics
### Recurring chromosomal abnormalities in adults with myelodysplastic syndrome

<table>
<thead>
<tr>
<th>Disease</th>
<th>Chromosome abnormality</th>
<th>Frequency</th>
<th>Involved genes*</th>
<th>Consequence</th>
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</thead>
<tbody>
<tr>
<td>MDS unbalanced</td>
<td>+8</td>
<td>10 percent</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-7/del(7q)</td>
<td>10 percent</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-5/del(5q)</td>
<td>10 percent</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>del(20q)</td>
<td>5 to 8 percent</td>
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<tr>
<td></td>
<td>-Y</td>
<td>5 percent</td>
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<tr>
<td></td>
<td>i(17p)</td>
<td>3 to 5 percent</td>
<td></td>
<td>TP53</td>
</tr>
<tr>
<td></td>
<td>-13/del(13q)</td>
<td>3 percent</td>
<td></td>
<td>Loss of function</td>
</tr>
<tr>
<td></td>
<td>del(11q)</td>
<td>3 percent</td>
<td></td>
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<tr>
<td></td>
<td>del(12p)/t(12p)</td>
<td>3 percent</td>
<td></td>
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<tr>
<td></td>
<td>del(9q)</td>
<td>1 to 2 percent</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>idic(X)(q13)</td>
<td>1 to 2 percent</td>
<td></td>
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</tr>
<tr>
<td>Balanced</td>
<td>t(1;3)(p36.3;q21)</td>
<td>1 percent</td>
<td>PRDM16</td>
<td>Deregulation of PRDM16 - transcriptional activation?</td>
</tr>
<tr>
<td></td>
<td>t(2;11)(p21;q23)/t(11q23)</td>
<td>1 percent</td>
<td>RPN1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>inv(3)(q21q26.2)</td>
<td>1 percent</td>
<td>MLL</td>
<td>MLL fusion protein - altered transcriptional regulation</td>
</tr>
<tr>
<td></td>
<td>t(8;9)(p23;q34)</td>
<td>1 percent</td>
<td>RPN1</td>
<td>MDS1/EVI1 - Fusion protein</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>DEK</td>
<td>NUP214</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fusion protein - nuclear pore protein</td>
</tr>
<tr>
<td>Therapy-related MDS</td>
<td>-7/del(7q)</td>
<td>50 percent</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>-5/del(5q)</td>
<td>40 to 45 percent</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>dic(5;17)(q11.1-13;p11.1-13)</td>
<td>5 percent</td>
<td>TPS3</td>
<td>Loss of function, DNA damage response</td>
</tr>
<tr>
<td></td>
<td>der(1;7)(q10;p10)</td>
<td>3 percent</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>t(3;21)(q26.2;q22.1)</td>
<td>2 percent</td>
<td>RPL22L1</td>
<td>RUNX1 fusion protein - altered transcriptional regulation</td>
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<tr>
<td></td>
<td>t(11;16)(q23;p13.3)/t(11q23)</td>
<td>3 percent</td>
<td>MLL</td>
<td>MLL fusion protein - altered transcriptional regulation</td>
</tr>
</tbody>
</table>

Refractory Cytopenia with Unilineage Dysplasia

- >10% of cells in a lineage show dysplasia.
- Uni or bi cytopenia
  - Cut off 10g hgb, 1.8K/ul neutrophils, 100K/ul platelets
  - Usually anemia; refractory thrombocytopenia or neutropenia is rare
  - BM blasts <5%; No blasts in PB
- Must exclude other causes of cytopenia
- 25% have abnormal cytogenetics.
- If cytogenetics normal, then must observe patient for 6 months to see if anemia resolves spontaneously.
Morphologic Features of MDS in Erythroids

- Megaloblastic changes; How assess percentage?
- *Sideroblasts. >15% for RARS
- Nuclear dysplasia including binuclearity, multinuclearity, irregular nuclear outlines, nuclear fragmentation (karyorrhexis).
  - *somewhat diagnostic; **very diagnostic
RBC precursors with irregular nuclear outlines
RBC precursors and Megas with multinucleation
B12 Deficiency with Dysplastic Erythroids and Giant Band
Copper Deficiency with Vacuolization of Erythroid and Granulocyte Precursors
Alcohol Induced Erythroid Vacuolization
Case Study 1

- 80 year old woman with relapsed acute promyelocytic leukemia 32 months after initial diagnosis and treatment and one month after starting treatment that included arsenic.

- WBC 1.5K/uL, HGB 7.9 gm/dL, MCV 95fL, RDW 16.9% PLT 65K/uL. 17% neutrophils, 74% lymphs, 9% monos
Marrow Findings

- 70% cellular marrow with a G:E ratio of 1:6
- Flow less than 1% abnormal promyelocytes.
- Cytogenetics normal
- FISH negative for the t(15;17)
Irregular nuclei, karyorrhexis, and coarse basophilic stippling
Diagnosis for Case 1

- Dysplastic erythroid precursors and increased coarse basophilic stippling of erythrocytes secondary to arsenic
Case Study 2

- 52 year old woman with subdural hematoma and platelet <5K/ul
- WBC 14K/ul, HGB 9.3 gm/dL, MCV 90.4fL, RDW 14.1%, PLT <5K/ul: 73% neutrophils, 3% IG’s, 18% lymphs 5% monos, 1% basos.
- Platelet count did not respond well to transfusions suggestive of peripheral destruction/ sequestration
Marrow Findings

- 70% cellular marrow with G:E ratio of 1.7:1
- 30% of erythroid precursors are binucleate
- 4% of erythroid precursors show karyorrhexis
- Normal karyotype and MDS FISH
Marrow Aspirate

Erythroid binucleation and karryorhexis
Diagnosis for Case 2: Congenital Dyserythropoietic Anemia II

- Rare autosomal recessive
- Median diagnosis age: 27 (95% 19-34)
- >10% binucleate erythroids and >2% karyorrhexis very specific
- Biallelic mutation of SEC23B gene that is a component of the coat protein (COP)II complex involved in transport of secretory proteins.
Refractory Anemia with Ringed Sideroblasts

- Greater than 15% of erythroid precursors are ringed sideroblasts (1/3 of nucleus with >5 granules)
- Characteristic “dimorphic” blood smear; often with basophilic stippling and Pappenheimer bodies
- Usually has normal cytogenetics and dysplasia limited to erythroids.
- Mutation of SF3B1 spliceosome protein (>60%)
RARS Peripheral Blood showing Dimorphic RBC’s and Pappenheimer Body
RARS Marrow with “poor hemoglobinization”
RARS Marrow, Prussian Blue stain
Ringed Sideroblasts
Other causes of sideroblasts include alcohol, other toxins such as lead, drugs such as isoniazid, and congenital
5q- Syndrome (WHO)

- If sole cytogenetic abnormality and normal blasts, then prognosis good
- Symptoms are macrocytic anemia with normal to increased platelets normal to slightly elevated WBC.
- Bone marrow shows increased megas, many with round or non-lobated nuclei.
- Lenalidomide (Revlimid) is FDA approved for treatment
Classic 5q- mega
Morphologic Features of MDS: Megas and Platelets

- *micromegas
- **many monolobated megas
- **multiple separate nuclei megas
- *agranular platelets
- *platelets with giant granules

*somewhat diagnostic; **very diagnostic
Binucleate mega
Small, unilobate mega “micro megakaryocyte”
Mega with Multiple Separate Nuclei
AKA “Pawn Ball” or “Koala Mega”
Cloud-Like and Hyperchromatic Megas in PMF
Mega Cluster in PMF
Dwarf Megas CML
Morphologic Features of Granulocytes in MDS

- *Hypogranularity: primary or secondary
- *Pelger-Huet anomaly
  - Inherited has no clinical significance
  - Drug associated: mostly anti-virals, immunosupp.
- Maturation arrest
- Abnormal granulation
- *ALIP: abnormal localization of immature precursors
- **Auer rods
  *somewhat diagnostic; **very diagnostic
Dysplastic Granulocytes

Hypogranular  pseudo Pelger-Huet  Auer rod
Case Study 3

- 53 year old woman with a history of acute megakaryoblastic leukemia with +8/ +11/ 20q-minus.
- Now 150 days post MUD Allo SCT while in CR1.
- WBC 4.6K/uL, HGB 10.7gm/dL, MCV 100.3FL, RDW 20.1%, PLT 23K/uL. 41% neutrophils, 53% lymphocytes, 6% monocytes.
Marrow findings:
-20% cellular marrow, reduced megakaryocytes
- Full maturation of all lineages; G:E ratio of 1.2:1.
- Hyposegmentation of the neutrophils was the only dysplastic morphology.
Case 3 Diagnosis: Drug-Induced Hyposegmented Neutrophils

- Higher proportion of circulating hyposegs than in MDS (47% vs 12%).
- More clumped chromatin and more round, non-segmented nuclei
- Implicated drugs: mycophenolate mofetil, tacrolimus, ganciclovir
- Transient. Normalizes off drug
- No other lineages show dysplasia
- Role of lamin B receptor (LBR) gene?
Summary

- MDS is a clinical, pathologic, and cytogenetic (molecular?) diagnosis
- Cytogenetics, blast percentage, and cytopenias are best prognostic features
- Morphology can help distinguish MDS from:
  - Other myeloid neoplasms
  - non-neoplastic causes of cytopenias with similar blood or marrow morphology
1.) Which of the following statements is true?

A. If untreated, myelodysplasia almost always progresses to acute myeloid leukemia
B. B12 deficiency can cause marrow changes with similar morphology to myelodysplasia
C. High grade myelofibrosis is a frequent complication of myelodysplasia
D. Cytogenetic translocations detectable by karyotype occur in the majority of myelodysplasia cases
B. B12 deficiency can cause marrow changes with similar morphology to myelodysplasia. Only a minority of myelodysplasia cases progress to acute leukemia. Most patients die of cytopenias. MDS frequently has low grade myelofibrosis, but MDS rarely progresses to high grade fibrosis. Cytogenetic translocations occur in a minority of MDS cases. Most genetic alterations detectable by karyotype in MDS are loss or duplications of chromosomes or parts of chromosomes. A minority of MDS have balanced translocations detectable by karyotype.
CME Questions Cont’d

2. ) All of the following EXCEPT can cause increased erythroid precursor vacuoles:

A. Mycophenolate
B. Chloramphenicol
C. Alcohol
D. Copper deficiency
A. Mycophenolate is associated with hyposegmented neutrophils

Alcohol and chloramphenicol can cause vacuolation of erythroid precursors. Copper deficiency can cause vacuolation of both erythroid and granulocyte precursors.
3.) Which of the following findings in MDS indicates a worse than average prognosis:

A. 5q-minus as the sole cytogenetic abnormality
B. Increased blasts, greater than 5%, but less than 10%.
C. 20q-minus as the sole cytogenetic abnormality
D. Many hypolobated neutrophils (pseudo Pelger-Huet anomaly)
Answer to Question 3

B. Increased blasts, greater than 5%, but less than 10%.

Blast percentages above normal (2%) correlate with worse prognosis. 5q-minus or 20q-minus as the sole cytogenetic abnormality have better than average prognosis. Pseudo Pelger-Huet anomaly has no prognostic significance on its own.