Myelodysplastic Syndromes

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Current Issues in Anatomic Pathology
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Lecture Outline

- MDS and Classification
- Morphologic dysplasia
- Reactive conditions with dysplasia
- Cytogenetics/FISH
- Flow Cytometry
- Hypocellular MDS

2008 WHO Classification of Myeloid Neoplasms

- Acute Myeloid Leukemia
- Myelodysplastic Syndromes
  - Refractory cytopenia with multilineage dysplasia (RCUD)
  - Refractory anemia with ring sideroblasts (RARS)
  - Refractory cytopenia with multilineage dysplasia (RCMD)
  - Refractory anemia with excess blasts (RAEB)
  - Myelodysplastic syndrome with isolated del(5q)
  - Myelodysplastic syndrome, unclassified
  - Refractory cytopenia of childhood
- MDS/MPN
- Myeloproliferative Neoplasms
  - Chronic Myelomonocytic Leukemia
  - Atypical Chronic Myeloid Leukemia, BCR-ABL-negative
  - Juvenile Myelomonocytic Leukemia
  - MDS/MPN, unclassifiable
- Myeloid or lymphoid neoplasms associated with eosinophilia and abnormalities of PDGFRA, PDGFRB, or FGFR1

Myelodysplastic Syndrome

- Clonal hematopoietic stem cell disorders characterized by:
  - Ineffective hematopoiesis
  - Peripheral blood cytopenia(s)*
    - Hemoglobin < 10 g/dL
    - Absolute neutrophil count < 1.8 × 10⁹/L
    - Platelets < 100 × 10⁹/L
  - Dysplasia in one or more myeloid lineages
  - Increased risk of acute myeloid leukemia

*Values above these levels are not exclusionary for a diagnosis of MDS if definitive dysplasia and/or cytogenetic findings are present.
Myelodysplastic Syndrome

• Incidence of 3-5/100,000 with male predominance
• Occurs primarily in older adults with median age of ~70 years
• ~10,000 new MDS cases diagnosed annually in the United States
• Many of us encounter bone marrow evaluations to “rule out” MDS in cytopenic patients! (if only it were that easy….)

Myelodysplastic Syndrome

• Diagnostic features:
  – Morphologic dysplasia: at least 10% of cells in one or more lineages, ring sideroblasts
  – Clonal cytogenetic abnormality (50% of cases)
    • can be used as presumptive evidence of MDS if dysplasia lacking
  – Increased blasts (if not on G-CSF)

• Other causes of dysplasia should be excluded (especially if a cytogenetic abnormality is lacking)

MDS Challenges

• Dysplasia is required for diagnosis but is not specific…..
  – Requires careful correlation with clinical information to exclude non-neoplastic causes:
    • Medications/chemotherapy
    • Nutritional status
    • Infections, including HIV
    • Autoimmune conditions
  – If unilineage dysplasia and absence of a clonal cytogenetic abnormality, 6 month observation is recommended by WHO before a definitive diagnosis of MDS

MDS Challenges

• MDS may lack sufficient morphologic dysplasia to allow definitive diagnosis
  – Defined cytogenetic abnormalities provide presumptive evidence of MDS; patients should be monitored for emerging morphologic evidence of MDS
  – Some lack dysplasia and cytogenetic abnormality at initial presentation; continued monitoring and repeat evaluation may be required
    • “Idiopathic cytopenia of undetermined significance” (does not meet minimal criteria for MDS by WHO)
  • Cytogenetic abnormalities seen in other disorders (e.g. aplastic anemia)
### WHO MDS Classification

**Dysplasia without increased blasts***:
- Refractory cytopenia with unilineage dysplasia (RCUD)
- Refractory anemia, neutropenia, or thrombocytopenia
- Refractory anemia with ring sideroblasts* (RARS)
- Refractory cytopenia with multilineage* dysplasia (RCMD)

**Increased blasts**:
- RAEB-1 (2-4% blood; 5-9% marrow)
- RAEB-2 (≥5% blood; 10-19% marrow; Auer rods)

*Dysplasia must be present in ≥ 10% of cells within a lineage (erythroid, granulocytic, megakaryocytic); “multilineage” dysplasia is at least 2 lineages
Without increased blasts: <1% PB, <5% marrow
Ring sideroblasts must account for ≥15% of erythroid precursors in RARS

Of note, CMML (MDS/MPN overlap) may appear more myelodysplastic than myeloproliferative.

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### MDS associated with isolated del(5q)

- Female predominance
- Anemia (usually marked macrocytic)
- Usually normal or increased platelet count
- Normal to increased hypolobulated megakaryocytes
- Usually lack erythroid and granulocytic dysplasia
- Long survival (145 months median)
- Transformation to AML <10%

“5q- syndrome” designates subset with macrocytic anemia, normal or elevated platelet count, and marrow erythroid hypoplasia.

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### Refractory Cytopenia of Childhood (provisional)

- Persistent cytopenia(s)
- Dysplasia in two myeloid cell lineages or >10% of a single lineage
- Requires <2% circulating blasts and less than 5% marrow blasts
- Frequent bone marrow hypocellularity; must distinguish from aplastic anemia
- Monosomy 7 most common cytogenetic abnormality
WHO MDS Classification
MDS, unclassified

3 situations for MDS-U:
• RCUD or RCMD but with 1% peripheral blasts
• Unilineage dysplasia with pancytopenia
• Cytopenia(s), <1% blood and <5% marrow blasts, equivocal dysplasia (in <10% of cells in one or more lineages), cytogenetic abnormality considered presumptive evidence of MDS

Erythroid dysplasia

• Nuclear:
  – Budding
  – Bridging
  – Karyorrhexis
  – Multinuclearity
  – Nuclear hyperlobation
  – Megaloblastic changes
• Cytoplasmic
  – Ring sideroblasts
  – Vacuolization
  – PAS positivity
Neutrophil dysplasia

- Hypo-, agranularity
- Nuclear hypolobation (pseudo Pelger-Huet)
- Irregular hypersegmentation
- Pseudo Chediak-Higashi granules
- Megaloblastic maturation
- Small or large size
- Auer rods (neoplastic!)

Megakaryocytic dysplasia

- Micromegakaryocytes
- Nuclear hypolobation
- Multinucleation (normal megs are uninuclear with lobation)
The patient is a 62-year-old man who presents with increasing fatigue and bruising over several months. The patient is on no medications.

CBC analysis shows:
- WBC 2.7 x 10^9/L
- Neuts 1.1 x 10^9/L
- HGB 9.1 g/dL
- MCV 96 fl
- PLTS 47 x 10^9/L

Cytogenetics: Normal

Ring sideroblasts:
- MDS
- Alcohol/toxins
- Drugs (e.g. INH)
- Zinc toxicity
- Copper deficiency
- Pyridoxine deficiency
- Congenital sideroblastic anemia
- Mitochondrial cytopathy (Pearson syndrome)

In this case, features suggest copper deficiency (in some cases due to zinc toxicity)
MDS cytogenetics

Presumptive diagnosis in patients with persistent cytopenias of undetermined origin but lacking diagnostic morphologic dysplasia (should be followed for definitive dysplasia before unequivocal dx)

*Alone NOT considered definitive evidence for MDS (in absence of dysplasia):
  +8  del(20q)  -Y

WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, 2008.

Abnormality | Frequency (diagnosis)
---|---
**Unbalanced**
-7 or del(7q) | 10% (50% t-MDS)
-5 or del(5q) | 10% (40% t-MDS)
+8* | 10%
del(20q)* | 5-8%
y* | 5%
t(15q) or t(17p) | 3-5%
del(11q) | 3%
del(12p) or t(12p) | 3%
-13 or del(13q) | 3%
del(9q) | 1-2%
sdel(X)(q13) | 1-2%

**Balanced**
t(1;16)(q23;p13.3) | (3% t-MDS)
t(3;21)(q26.2;q22.1) | (2% t-MDS)
t(1;3)(p36.3;q21.2) | 1%
t(2;11)(p21;q23) | 1%
in(3)(q121q36.2) | 1%
t(6;9)(p23;q34) | 1%

FISH Analysis

- Panels often include -5/del(5q), -7/del(7q), +8, and del(20q)
- FISH correlates with karyotypic findings
- FISH detects few (0-6%) additional abnormalities if karyotype is adequate and generally not needed in this setting
- FISH useful if:
  - suboptimal metaphase analysis; detects up to 15% more abnormalities
  - morphology suggests a specific abnormality that was not detected by cytogenetics
- Sensitivity for residual disease following treatment is not much better than routine karyotype

Flow Cytometry in MDS

- Presently not routinely used for diagnosis or classification
- Evaluation of previously diagnosed MDS by highly experienced flow labs with numerous myeloid markers and objective criteria for "abnormal" show:
  - Sensitivity: ~70-90%
  - Specificity: ~90%
- ~10% flow abnormal with non-diagnostic morphology and cytogenetics
  - Insufficient data to determine whether these biologically behave like MDS (true or false pos?)

Flow Cytometry in MDS Cautions

- Reactive conditions (marrow recovery, G-CSF therapy, infection) can cause mild phenotypic alterations.
- Insufficient literature to fully understand myeloid phenotypic change in reactive conditions that may mimic MDS
- Blast assessment can be useful, but...morphologic blast count required for diagnosis and classification because:
  - Some blasts do not express stem cell antigens (CD34, CD117)
  - Processing for flow lyses erythroid precursors
  - Blasts can be fragile with a subset lost during processing
8% blasts (CD34, CD117)
75% monocytic cells

Remember: promonocytes are blast equivalents

International Prognostic Scoring System (IPSS)

<table>
<thead>
<tr>
<th>Prognostic variable</th>
<th>Score Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BM blasts (%)</td>
<td>0 0.5 1.0 1.5 2.0</td>
</tr>
<tr>
<td>Karyotype</td>
<td>Good Intermediate Poor</td>
</tr>
<tr>
<td>Cytopenias</td>
<td>0/1 2/3</td>
</tr>
<tr>
<td>Cytogenetics</td>
<td>Good: normal, Y, del(5q), del(20q)</td>
</tr>
<tr>
<td></td>
<td>Poor: complex (&gt;3 abnormalities) or abnormalities of chromosome 7</td>
</tr>
<tr>
<td></td>
<td>Intermediate: other abnormalities</td>
</tr>
</tbody>
</table>

Risk groups are as follows:
- Low: 0
- Intermediate-1: 0.5-1.0
- Intermediate-2: 1.5-2.0
- High: >2.5

WHO Classification-Based Prognostic Scoring System for MDS

<table>
<thead>
<tr>
<th>Prognostic Variable</th>
<th>Score Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO category</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>Karyotype</td>
<td>RA, RARS,5q- RCMD RAEB-1 RAEB-2</td>
</tr>
<tr>
<td>Transfusion*</td>
<td>Good Intermediate Poor</td>
</tr>
<tr>
<td>Risk groups</td>
<td>Score AML</td>
</tr>
<tr>
<td>Very low</td>
<td>0 3-6%</td>
</tr>
<tr>
<td>Low</td>
<td>1 14-24%</td>
</tr>
<tr>
<td>Intermediate</td>
<td>2 33-48%</td>
</tr>
<tr>
<td>High</td>
<td>3-4 54-63%</td>
</tr>
<tr>
<td>Very high</td>
<td>5-6 84-100%</td>
</tr>
<tr>
<td>Median follow up</td>
<td>27-30 months</td>
</tr>
</tbody>
</table>

Hypocellular MDS

- ~5-10% of MDS are hypocellular (<30% cellularity in younger patients, <20% in older patients)
- Same diagnostic criteria and classification should be applied
  - Morphologic dysplasia
  - Cytogenetic abnormality
  - Evaluation for blasts
- Should be classified in appropriate MDS category and qualified as hypocellular
- Prognostic scoring schemes apply
- Most cases RA (low IPSS); some progress to AML
- Some will respond to immunosuppression, similar to aplastic anemia
Hypocellular MDS

• Proper classification usually accomplished by:
  – Careful exam of blood/aspirate smears for dysplasia and blasts
  – estimation of CD34+ blasts on the biopsy (IHC or flow cytometry)
  – cytogenetics (e.g. abnormality of 5 or 7)
• May be useful: iron stain, reticulin stain, PNH markers
• Similar to RCUD, if unilineage dysplasia and no cytogenetic abnormality or increase in blasts, 6 month observation is appropriate
• If you can’t call it— don’t!

• Differential diagnosis includes:
  – Acute myeloid leukemia (AML)
  – Hairy cell leukemia
  – T-large granular lymphocytic leukemia
  – Toxic effects
  – Aplastic anemia
  – Paroxysmal nocturnal hemoglobinuria (PNH)
• Hypocellular MDS has higher risk of AML than AA and PNH
Acquired Aplastic anemia

- Aplastic anemia (AA)
  - Peripheral cytopenias and marrow hypoplasia (<25% normal for age or 25-50% with <30% hematopoietic; often 5-10% cellularity)
  - Often best to diagnose markedly hypocellular marrow or marrow aplasia (with comment)
  - May demonstrate cytogenetic abnormalities, such as +8, that do not predict MDS-like biologic behavior (“aplastic anemia with cytogenetic abnormalities”)
  - Generally responds to immunosuppression
  - Minority subset “evolve” to MDS/AML

Summary

- MDS is a clonal myeloid neoplasm characterized by cytopenias, dysplasia, ineffective hematopoiesis and increased risk of AML
- MDS diagnosis and classification is based on morphologic dysplasia, cytogenetic abnormalities, and blast proportion
- Reactive conditions can demonstrate dysplasia; clinical correlation is essential
- WHO defined cytogenetic abnormalities allow a presumptive diagnosis of MDS if dysplasia is not definitive
- Hypocellular MDS can be difficult, but should be distinguished from AA and PNH if possible

Questions?
Panyoxysmal Nocturnal Hemoglobinuria (PNH)

- Lack of GPI anchor proteins (e.g., CD55 and CD59) resulting in hemolysis and other clinical complications
- Can evolve to marrow failure syndrome with hypocellularity similar to AA or hypocellular MDS
- Some postulate PNH is a manifestation of aplasia/myelodysplasia spectrum since all can demonstrate PNH-like cells

Myelodysplastic Syndrome

- Diagnostic workup should include:
  - Comprehensive history and physical exam
  - CBC with differential
  - Nutritional studies if indicated (B12, folate, iron)
  - Reticulocyte count (if anemia)
  - BM aspiration and biopsy
  - Iron stain
  - Cytogenetics

WHO MDS Classification

Refractory cytopenia with unilineage dysplasia
- Refractory anemia (RA)
- Refractory neutropenia
- Refractory thrombocytopenia

- Requires one (or two) cytopenias and unilineage dysplasia (in ≥10% of one lineage); blasts not increased
- Dysplasia may not be overt (can be difficult to diagnose…)
- Cytogenetic abnormalities in up to 50%
- Median survival ~66 months

WHO MDS Classification

Refractory anemia with ring sideroblasts
- Erythroid dysplasia only; blasts not increased (<5%)
- ≥15% ring sideroblasts
  - 5 or more granules encircling at least 1/3 of the nucleus
  - Ring sideroblasts can be seen in other categories of MDS
- Cytogenetic abnormalities in 5-20%
- Median survival ~69-108 months
- Must exclude non-neoplastic causes of ring sideroblasts (alcohol, toxins, drugs (e.g., INH), zinc, copper deficiency, and congenital sideroblastic anemia)
WHO MDS Classification

- Refractory cytopenia with multilineage dysplasia
  - Dysplasia in \( \geq 10\% \) of cells in 2 lineages
  - Blasts <5\% (marrow) and <1\% (blood)

- Cytogenetic abnormalities in up to 50\%
- Median survival ~30 months (shorter if complex karyotype)

WHO MDS Classification

MDS associated with isolated del(5q)

- Anemia (usually marked macrocytic)
- Usually normal or increased platelet count
- Normal to increased hypolobulated megakaryocytes
- Usually lack erythroid and granulocytic dysplasia
- Isolated del(5q)

WHO MDS Classification

- Refractory anemia with excess blasts
  - Type 1 (RAEB-1):
    - 2-4\% peripheral blood blasts
    - 5-9\% bone marrow blasts
    - No Auer rods
  - Type 2 (RAEB-2):
    - >5\% peripheral blood blasts
    - 10-19\% bone marrow blasts
    - +/- Auer rods

*Table 5.94 Reporting chromosomal abnormalities their frequency in the myelodysplastic syndrome diagnosis.*

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>MDS</th>
<th>iMDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>t(15;17)</td>
<td>5%</td>
<td>1%</td>
</tr>
<tr>
<td>t(8;21)</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>t(9;11)</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>inv(16)(p13)</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>del(5q)</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>del(20q)</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>del(12)(q14)</td>
<td>1%</td>
<td>1%</td>
</tr>
</tbody>
</table>

*The presence of these abnormalities as the cytogenetic abnormality in the absence of morphologic criteria is not considered definitive evidence of MDS, in the setting of persistent cytopenia unexplained, in the other abnormalities are considered prescriptive evidence of MDS, absence of definitive morphologic features.*
The patient is a 32 year old taxi driver who presents with a 4 month history of increasing fatigue. He is transferred with a presumed diagnosis of MDS or acute leukemia.

CBC shows:
- WBC 3.6 x10^9/L
- Neuts 1.6 x10^9/L
- Hgb 6.1 g/dL
- Hct 17.3%
- MCV 102 fl
- Platelets 190 x10^9/L

Megaloblastic anemia
(associated with vitamin B12 or folate def)

- Peripheral blood smear:
  - Macro-ovalocytes
  - Hypersegmented neutrophils

- Bone marrow:
  - Megaloblastic change in erythroid, and granulocytic precursors
  - Erythroid hyperplasia and left shift
  - Mild dyserythropoiesis
  - With or without mild megakaryocytic dysplasia

In this patient reticulocytes and NRBC were seen on the blood smear 4 days following vitamin B12 replacement.
**Acquired Pelger-Huet Anomaly associated with drugs**

- A predominance of uni-lobed neutrophils (with occasional bi-lobed forms present); in some cases many band forms may also be seen
- Abnormally coarse nuclear chromatin
- Uniformity in appearance of the neutrophil population
- ABSENCE OF OTHER MORPHOLOGIC DYSPLASIA

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**Copper Deficiency**

- **Granulocytes:**
  - Left shifted
  - Vacuolization of precursors

- **Erythroid series:**
  - Left shifted with mild megaloblastic changes and terminal dyserythropoiesis
  - Vacuolated cytoplasm
  - Ringed sideroblasts

- Megakaryocytes: usually normal
- Variable marrow cellularity
- Blasts are generally NOT increased.

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<table>
<thead>
<tr>
<th>Dyserythropoiesis</th>
<th>Dysgranulopoiesis</th>
<th>Dysmegakaryopoiesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy/bone marrow regeneration</td>
<td>Chemotherapy/bone marrow regeneration</td>
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</tr>
<tr>
<td>Vitamin B12/folate deficiency, and rarely pyridoxine (B6) deficiency</td>
<td>Vitamin B12/folate deficiency, and rarely pyridoxine (B6) deficiency (some cases)</td>
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</tr>
<tr>
<td>Infections (parvovirus, HIV)</td>
<td>Infections (HIV)</td>
<td>Infections (HIV)</td>
</tr>
<tr>
<td>Autoimmune conditions</td>
<td>Autoimmune myelofibrosis</td>
<td>Autoimmune myelofibrosis</td>
</tr>
<tr>
<td>Post-transplant</td>
<td>Post-transplant</td>
<td>Post-transplant</td>
</tr>
<tr>
<td>Paraneoplastic</td>
<td>Paraneoplastic</td>
<td>Paraneoplastic</td>
</tr>
<tr>
<td>Medications, alcohol and other toxins, heavy metals (e.g. arsenic) etc.</td>
<td>Medications (e.g. tacrolimus, mycophenolate mofetil, gancyclovir, purine analogs)</td>
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</tr>
<tr>
<td>Rapid erythroid proliferation in response to anemia; erythropoietin therapy</td>
<td>Exogenous (G-CSF) or endogenous (e.g. sepsis) cytokines</td>
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</tr>
<tr>
<td>Aplastic anemia/PNH</td>
<td>Hemophagocytic lymphohistiocytosis</td>
<td>Hemophagocytic lymphohistiocytosis</td>
</tr>
<tr>
<td>Congenital dyserythropoietic anemias</td>
<td>Congenital (e.g. Fanconi anemia)</td>
<td>Transient abnormal myeloipoiesis of Down syndrome; other congenital disorders</td>
</tr>
</tbody>
</table>

G-CSF may result in increased blasts and neutrophil dysplasia
The patient is a 56 year old man who is 2 years post orthotopic liver transplant. The patient is receiving tacrolimus and mycophenolate mofetil for immunosuppression.

CBC shows:
- WBC 2.6 x10^9/L
- Neuts 1.5 x10^9/L
- Hgb 8.9 g/dL
- MCV 79 fL
- Platelets 170x10^9/L

Pelger-Huet Neutrophils

- Inherited Pelger-Huet anomaly
- Myeloid neoplasm, such as MDS or AML
- Recent chemotherapy
- Other medications, including mycophenolate mofetil, tacrolimus, gancyclovir, and even trimethoprim-sulfamethoxazole
- Infection associated (uncommon, but occurs)

In this case, neutropenia resolved 4 weeks after decreasing mycophenolate mofetil dose