Update on Diagnosis of Myelodysplastic Syndromes

Jay L. Patel, MD
Disclosure

• None
Objectives

• Review current diagnostic criteria pertaining to myelodysplastic syndromes

• Understand the relevance of selected somatic gene mutations in the diagnosis and prognostication of myelodysplastic syndromes
<table>
<thead>
<tr>
<th>WHO 2016</th>
<th>WHO 2008</th>
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<tbody>
<tr>
<td>MDS with single lineage dysplasia</td>
<td>Refractory cytopenia</td>
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<tr>
<td>MDS with multilineage dysplasia</td>
<td>Refractory cytopenia with multilineage dysplasia</td>
</tr>
<tr>
<td>MDS with ring sideroblasts*</td>
<td>Refractory anemia with ring sideroblasts</td>
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<tr>
<td>- Single lineage dysplasia</td>
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<tr>
<td>- Multilineage dysplasia</td>
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<tr>
<td>MDS with isolated del(5q)*</td>
<td>MDS with isolated del(5q)</td>
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<tr>
<td>MDS with excess blasts</td>
<td>Refractory anemia with excess blasts</td>
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<tr>
<td>MDS, unclassifiable</td>
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CBC

Cytogenetics

Morphology
Cytopenia?

• Hemoglobin: <10 g/dL
• ANC: <1.8 x10⁹/L
• Platelets: <100 x10⁹/L
Representative examples of morphologic abnormalities in myelodysplasia

<table>
<thead>
<tr>
<th>Erythroid hyperplasia</th>
<th>Megaloblastoid changes</th>
<th>Multinuclearity</th>
<th>Nuclear pycnosis</th>
</tr>
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<tbody>
<tr>
<td>Nuclear lobulation</td>
<td>Cytoplasmic fraying</td>
<td>Ferritin sideroblast</td>
<td>Ring sideroblasts</td>
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<tr>
<th>Micromegakaryocyte</th>
<th>Multiple separated nuclei</th>
<th>Small binucleated cell</th>
<th>Monolobar cell</th>
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<tr>
<th>Pseudo-Pelger anomaly</th>
<th>Abnormal nuclear shape</th>
<th>Hypo-degranulation</th>
<th>Myeloblasts</th>
</tr>
</thead>
</table>

Mario Cazzola et al. Blood 2013;122:4021-4034
Limits of morphology

• Patients with MDS may not show definitive morphologic evidence of dysplasia
• Significant dysplasia may accompany non-neoplastic cytopenias
• Dysplasia is not entirely reproducible among pathologists
• Sample quality
### MDS-related cytogenetic abnormalities

- **Complex karyotype**
- **Unbalanced abnormalities**
  - -7/del(7q)
  - -5/del(5q)
  - i(17q)/t(17p)
  - -13/del(13q)
  - del(11q)
  - del(12p)/t(12p)
  - del(9q)
  - idic(X)(q13)

- **Balanced abnormalities**
  - t(11;16)(q23;p13.3)
  - t(3;21)(q26.2;q22.1)
  - t(1;3)(p36.3;q21.1)
  - t(2;11)(p21;q23)
  - t(5;12)(q33;p12)
  - t(5;7)(q33;q11.2)
  - t(5;17)(q33;p13)
  - t(5;10)(q33;q21)
  - t(3;5)(q25;q34)

- May allow for a diagnosis of MDS in the absence of morphologic dysplasia
Limits of Cytogenetics

• Up to 50% of patients with MDS have a normal karyotype
• Non-specific abnormalities (e.g. del20q, trisomy 8, -Y)
• May not be available
Ribosomal proteins: RPS14
Epigenetic regulators: TET2, ASXL1
RNA splicing: SF3B1, SRSF2, U2AF1
Transcription factors: RUNX1, ETV6
Tyrosine kinase signaling: RAS
Tumor suppressor genes: TP53

Blood. 2013 Dec 12;122(25):4021-34.
Genotype-phenotype relationships

Various combinations of founding driver mutations involving genes of RNA splicing (SRF2, U2AF1) or DNA methylation (TET2, DNMT3A), and subclonal driver mutations involving genes like ASXL1, EZH2, RUNX1, or TP53

SF3B1 mutation: refractory anemia with ring sideroblasts

Miscellaneous driver mutations: refractory cytopenia with unilineage dysplasia (refractory anemia)

Refractory cytopenia with multilineage dysplasia

Refractory anemia with excess blasts

TET2/SRSF2 co-mutation: chronic myelomonocytic leukemia

Various founding mutations plus subclonal SETBP1 mutation: atypical chronic myeloid leukemia

SF3B1/JAK2 or SF3B1/MPL co-mutation: refractory anemia with ring sideroblasts associated with marked thrombocytosis

Activating GSF3R mutation: chronic neutrophilic leukemia

Blood. 2013 Dec 12;122(25):4021-34.
Age-Related Clonal Hematopoiesis Associated with Adverse Outcomes

Siddhartha Jaiswal, M.D., Ph.D., Pierre Fontanillas, Ph.D., Jason Flannick, Ph.D., Alisa Manning, Ph.D., Peter V. Grauman, B.A., Brenton G. Mar, M.D., Ph.D., R. Coleman Lindsley, M.D., Ph.D., Craig H. Mermel, M.D., Ph.D., Noel Burtt, B.S., Alejandro Chavez, M.D., Ph.D., John M. Higgins, M.D., Vladislav Moltchanov, Ph.D., Frank C. Kuo, M.D., Ph.D., Michael J. Kluk, M.D., Ph.D., Brian Henderson, M.D., Leena Kinnunen M.Sc., Heikki A. Koistinen, M.D., Ph.D., Gad Getz, Ph.D., Adolfo Correa, M.D., Ph.D., Benjamin Reiter, Ph.D., Stacey Gabriel, Ph.D., Sekar Kathiresan, M.D., Heath J. Bader, Mark I. McCarthy, M.D.,* Michael Boehnke, Ph.D.,** Jaakko Tuimala, Ph.D., Yael Gurosky, Ph.D., Christopher Haiman, Sc.D., Leif Groop, M.D., Ph.D., James G. Wilson, M.D., Donna Neuberg, Sc.D., David Spangler, M.D., and Benjamin L. Ebert, M.D., Ph.D.

Clonal Hematopoiesis and Blood-Cancer Risk Inferred from Blood DNA Sequence

Giulio Genovese, Ph.D., Anna K. Kähler, Ph.D., Robert E. Handsaker, B.S., Johan Lindberg, Ph.D., Samuel A. Rose, B.S., Samuel F. Bakhour, M.D., Ph.D., Kimberly Chambert, M.S., Eran Mick, B.S., Benjamin M. Neale, Ph.D., Menachem Fromer, Ph.D., Shaun M. Purcell, Ph.D., Oscar Svanstedt, M.S., Mikael Landén, Ph.D., Martin Högblad, M.D., Ph.D., Sören Lehmann, M.D., Ph.D., Stacey B. Gabriel, Ph.D., Jennifer L. Moran, Ph.D., Eric S. Lander, Ph.D., Patrick F. Sullivan, M.D., Pamela Sklar, M.D., Ph.D., Henrik Grönberg, M.D., Ph.D., Christina M. Hultman, Ph.D., and Steven A. McCarroll, Ph.D.
Mutation happens

Consider mutation frequency vs. disease incidence

Clonal hematopoiesis of indeterminate potential (CHIP)

- No morphologic evidence of malignancy
- Exclude PNH, MGUS, MBL
- Presence of a somatic mutation associated with myeloid malignancies
  - $DNMT3A$, $TET2$, $ASXL1$, $SF3B1$, $TP53$, $JAK2$, $CBL$, $BCOR$, $BCORL1$, $SRSF2$
  - Variant frequency at least 2%
- Risk of progression $\sim$0.5-1.0% per year

If included as MDS, incidence could double!

Blood. 2015 Jul 2;126(1):9-16.
Negative predictive value

- Greater than 85% of patients with MDS have one or more somatic mutations (Papaemmanuil et al, Blood 2013)
- If diagnosing MDS, a negative NGS result should prompt re-evaluation for other causes of cytopenia.
Do Variant Allele Frequencies help?

- Somatic vs. germline
- Cutoff for clinical relevancy?
- VAF > 30% appears less common in CHIP

Take home

• Sequencing capabilities have advanced much faster than our understanding of genomics
• Detection of somatic variant(s) alone is insufficient to diagnose MDS
• For patients with possible MDS, integration of clinical history, CBC, morphology, conventional cytogenetics, and mutation data is essential
• Data is accumulating…stay tuned (i.e. ‘MDS-related somatic mutations’? ‘IPSS-Mol’?)