Integrated Diagnostic Approach to the Classification of Myeloid Neoplasms

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What is an integrated approach?
What is an integrated approach?

• Incorporating all diagnostic data related to a single patient sample into a single report
What is an integrated approach?

• Incorporating all diagnostic data related to a single patient sample into a single report

• Models
  – Surgical pathology
  – Lymph node pathology
The Lymph Node Model

• 68 year-old woman with skin rashes and lymphadenopathy. A cervical lymph node is biopsied.
The Lymph Node Model

Images courtesy of Dr. Roger Warnke
The Lymph Node Model

Images courtesy of Dr. Roger Warnke
The Lymph Node Model

Images courtesy of Dr. Roger Warnke
The Lymph Node Model

CD21

Images courtesy of Dr. Roger Warnke
The Lymph Node Model

Images courtesy of Dr. Roger Warnke
The Lymph Node Model

• Additional studies
  – *TCRG* PCR clonal
  – *IGH* PCR clonal
  – EBV EBER1 ISH negative
The Lymph Node Model

• Diagnosis
  – Angioimmunoblastic T cell lymphoma complicated by a monotypic plasmacytoid B cell population
The Old Myeloid Disorder Model
The Old Myeloid Disorder Model
The Old Myeloid Disorder Model
The Old Myeloid Disorder Model

- Descriptive diagnosis, r/o MDS
- Dysplastic megas, r/o MDS
The Old Myeloid Disorder Model

- Descriptive diagnosis, r/o MDS
- del(5q) as sole abnormality

- Dysplastic megas, r/o MDS
- inv(3)
Why do we need an integrated approach to myeloid disorders?
Myeloproliferative Neoplasms

- Chronic myelogenous leukemia, \textit{BCR-ABL1}+
- Chronic neutrophilic leukemia
- Polycythemia vera
- Primary myelofibrosis
- Essential thrombocythemia
- Chronic eosinophilic leukemia
- Myeloid neoplasms associated with \textit{PDGFRA}, \textit{PDGFRB} and \textit{FGFR1} rearrangements
- Mast cell disease
- Myeloproliferative neoplasms, unclassified
Myeloproliferative disorders

Molecularly defined

Clinicopathologically assigned

CML
MPD-eos
PV
SM
EMS
ET
CIMF
MPD-RS
JMML
CMML
CNL
CEL
HES
CBL
UMP
Diagnostic Algorithm for Suspected Polycythemia Vera

BM biopsy, reticulin stain, cytogenetic studies & mutation screening for JAK2V617F

- Ph chromosome (+) → CML
- V617F (+) or del(13q) → PMF likely but use histology to exclude other myeloid neoplasm
- Other cytogenetic abnormalities → Could be PMF but also MDS or other myeloid neoplasm
- Normal cytogenetics and V617F (-) → If megakaryocytes dwarf consider FISH for BCR-ABL otherwise use histology for specific diagnosis

From Tefferi and Vardiman. Leukemia, Sep 20 Epub, 2007
Diagnostic Algorithm for Primary Eosinophilia

Bone marrow biopsy, tryptase stain, T cell clonality studies,* & cytogenetic studies and FISH or RT-PCR for FIP1L1-PDGFRα

If FIP1L1-PDGFRα positive

- PDGFRα rearranged myeloid neoplasm with eosinophilia

If 5q33 translocations

- PDGFRβ rearranged myeloid neoplasm with eosinophilia

If 8p11 translocations

- FGFR1 rearranged myeloid neoplasm with eosinophilia

If BM histology shows abnormalities other than eosinophilia

- Use histology to make specific diagnosis

- PB blast > 2% or BM blast > 5% or Abnormal cytogenetics

- CEL

- HES

From Tefferi and Vardiman Leukemia, Sep 20 Epub, 2007
Myelodysplastic Syndromes

- Refractory cytopenia
- Refractory anemia with ring sideroblasts
- Refractory cytopenia with multilineage dysplasia
- Refractory anemia with excess blasts
- Myelodysplastic syndrome with isolated del(5q)
- Myelodysplastic syndrome, unclassifiable
Diagnostic Algorithm for Myelodysplastic Syndromes

Step 1: Determine the presence of dysplasia?

Step 2: Are bone marrow blasts > 20%?
- Yes → AML
- No →
  - Step 3: Are monocytes > 1 x 10^3?
    - Yes → CMML (MDS/MP)
    - No →
      - Step 4: What is the percentage of blasts?
        - 10–19% → RAEB II
        - 5–9% → RAEB I
        - <5% →
          - Step 5: What is the percentage of ring sideroblasts?
            - >15% → Multi-lineage dysplasia? 2 or more cell lines with > 10% dysplasia
              - Yes → Refractory cytopenia with multilineage dysplasia and ring sideroblasts (RCMD-RS)
              - No → Refractory anemia with ring sideroblasts (RARS)
            - <15% → Multi-lineage dysplasia? 2 or more cell lines with > 10% dysplasia
              - Yes → Refractory cytopenia with multilineage dysplasia (RCMD)
              - No → Refractory anemia (RA)

# International Prognostic Scoring System for MDS

<table>
<thead>
<tr>
<th>Prognostic variable</th>
<th>Score</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>0 0.5 1.0 1.5 2.0</td>
</tr>
<tr>
<td>BM blasts (%)</td>
<td>≤5 5–10 11–20 21–30</td>
</tr>
<tr>
<td>Karyotype\textsuperscript{a}</td>
<td>Good Intermediate Poor</td>
</tr>
<tr>
<td>Cytopenias\textsuperscript{b}</td>
<td>0–1 2–3</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Karyotype:  
- Good = normal, del(5q), del(20q) or –Y  
- Intermediate = others  
- Poor = complex, -7

\textsuperscript{b} Cytopenias:  
- 0–1  
- 2–3

<table>
<thead>
<tr>
<th>Karyotype</th>
<th>Risk Group</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td>Low</td>
<td>0</td>
</tr>
<tr>
<td>del(5q), del(20q) or –Y</td>
<td>Int-1</td>
<td>0.5–1</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Int-2</td>
<td>1.5–2</td>
</tr>
<tr>
<td>Poor</td>
<td>High</td>
<td>≥2.5</td>
</tr>
</tbody>
</table>
Myelodysplastic/Myeloproliferative Neoplasms

- Chronic myelomonocytic leukemia
- Atypical chronic myeloid leukemia
- Juvenile myelomonocytic leukemia
- Myelodysplastic/myeloproliferative neoplasms, unclassified
Key Elements for a Bone Marrow Diagnosis

- Peripheral blood findings
- Marrow aspirate
- Marrow trephine/clot biopsy
- Immunophenotyping
  - Flow cytometry
  - Immunohistochemistry
- Karyotype analysis
- Molecular analysis
  - FISH
    - Translocations
    - Chromosome gains or loss
  - PCR
    - Translocations
    - Mutations
Who are the players?

- Peripheral blood - Instruments, MT/CLS
- Marrow aspirate
- Marrow trephine/clot biopsy
- Immunophenotyping
- Karyotype analysis
- Molecular analysis
Who are the players?

- Peripheral blood - Instruments, MT/CLS
- Marrow aspirate – Hematologist and/or Pathologist
- Marrow trephine/clot biopsy
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• Marrow trephine/clot biopsy - Pathologist
• Immunophenotyping – Flow lab/Reference lab

• Karyotype analysis – Cytogenetics lab/Reference lab
• Molecular analysis
Who are the players?

- Peripheral blood - Instruments, MT/CLS
- Marrow aspirate - Hematologist and/or Pathologist
- Marrow trephine/clot biopsy - Pathologist
- Immunophenotyping – Flow lab/Reference lab
- Karyotype analysis – Cytogenetics lab/Reference lab
- Molecular analysis – Molecular lab/Reference lab
Who is best qualified to put it all together?
Who is best qualified to put it all together?

The clinician?
Who is best qualified to put it all together?

The clinician?

Clinicians will do what is needed to take care of their patients and will fill the void if one is created in the lab.
Who is best qualified to put it all together?

The clinician?
The pathologist?
Who is best qualified to put it all together?

The clinician?
The pathologist?

When pathologists correlate findings, they become a critical and visible part of the care giving team.
Who is best qualified to put it all together?

The clinician?
The pathologist?
The pathologist and the clinician together?
Who is best qualified to put it all together?

The clinician?
The pathologist?
The pathologist and the clinician together?
The pathologist can assist the clinician in ordering the appropriate tests, can make sense of different results, and even explain the reason for discrepancies.
The Pathologist Role

- Consult with clinician
  - Recommend tests, explain specimen requirements, etc
- Spot inappropriate orders
  - i.e. Flow for Hodgkin lymphoma staging
- Recommend and implement additional tests
  - i.e. Adding FISH to a PB with flow cytometry suggestive of mantle cell lymphoma
- Address all testing in a single report
Case 1

- 48 year old woman with diarrhea. A CBC is performed.
  - A peripheral blood smear review is performed due to instrument flag for white cell abnormalities
Case 1

• CLS Hematology Specialist notes increase basophils and some dysplastic neutrophils. Suggests accelerated phase of CML and correlation with studies for t(9;22).
Case 1

- CLS Hematology Specialist notes increase basophils and some dysplastic neutrophils. Suggests accelerated phase of CML and correlation with studies for t(9;22).
  - Bone marrow, flow cytometry, karyotype and PCR for $BCR-ABL1$ are ordered.
Case 1

- D816V mutation of \textit{KIT} detected by PCR
- \textit{BCR-ABL1} negative

From Gotlib J. Immunol Allergy Clin N Am, 26:575, 2006
Case 1

- Mast cell leukemia
- Mast cells with aberrant expression of CD25 detected
- D816V KIT mutation positive
Case 2

• 28 year old man with history of bipolar disorder
• Presents to psychiatrist with worsening of psychiatric symptoms, mild fatigue and night sweats

Courtesy Dita Gratzinger
Case 2

- Physical exam reveals marked splenomegaly, no lymphadenopathy
- CT scan shows 24 cm spleen, no other significant findings

Courtesy Dita Gratzinger
Case 2

- $BCR-ABL1$ negative
- No $KIT$ mutation detected
- FISH for $CHIC2$ deletion (surrogate for $FIP1L1$-$PDGFRA$ fusion) positive
Case 2
Case 2

- Chronic eosinophilic leukemia (Myeloid neoplasm associated with \textit{PDGFRA} rearrangement)
- \textit{CHIC2} deletion positive
- \textit{TCRG} gene rearrangement of unknown significance detected
The Bone Marrow Report

- Standardized reporting?
- Synoptic reporting?
  - Improves report completeness
  - A training tool?
- College of American Pathologists Cancer Protocols and Checklists for Bone Marrow
The Bone Marrow Report

- Clinical information
- Aspirate and biopsy sites
- Peripheral blood
- Marrow aspirate/touch preps
- Marrow biopsy/clot
- Immunophenotyping
- Cytogenetics
- Molecular genetics
- Other ancillary tests
- Diagnosis
The Bone Marrow Report

• Clinical information
  – Patient ID information
  – Ordering physician
  – Indication for procedure
  – Prior/current therapy (including growth factors)

• Aspirate and biopsy sites
The Bone Marrow Report

• Peripheral Blood
  – CBC data, including units and reference ranges
  – Morphologic description
The Bone Marrow Report

- Marrow aspirate/touch preps
  - Adequacy
  - Differential cell count
  - Morphologic findings
The Bone Marrow Report

• Marrow biopsy/clot
  – Adequacy for the questioned asked
  – Morphologic description
The Bone Marrow Report

• Immunophenotyping
  – Method(s) used
  – Where studies performed
  – Antibodies used
  – Interpretation
The Bone Marrow Report

- Cytogenetics
  - Testing performed
  - Where studies were performed
  - Interpretation
The Bone Marrow Report

- Molecular genetics
  - Testing performed
  - Where studies were performed
  - Interpretation
The Bone Marrow Report

• Other ancillary tests
  – Iron stain
  – Other cytochemistry
  – AFB, GMS
  – Reticulin, etc
The Bone Marrow Report

- **Diagnosis**
  - WHO classification where appropriate
  - Address the question asked in the clinical information in a comment if only a descriptive diagnosis is rendered
Pathologists as the Gate-Keepers

- Stop unnecessary tests
- Suggest more appropriate tests to get to the correct diagnosis
- Put all the information together
Do we really need to do everything on every case?
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- PB, BM aspirate and biopsy should be reviewed together
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- Increased utility of karyotype and molecular genetic testing in myeloid disorders
Do we really need to do everything on every case?

• PB, BM aspirate and biopsy should be reviewed together
• Increased utility of karyotype and molecular genetic testing in myeloid disorders
• Does every case of CML need karyotype and BCR-ABL1?
Do we really need to do everything on every case?

- PB, BM aspirate and biopsy should be reviewed together
- Increased utility of karyotype and molecular genetic testing in myeloid disorders
- Does every case need karyotype and $BCR-ABL1$?
- Is routine flow cytometry necessary for most MDS and MPNs?
Do we really need to do everything on every case?

- PB, BM aspirate and biopsy should be reviewed together
- Increased utility of karyotype and molecular genetic testing in myeloid disorders
- Does every case need karyotype and BCR-ABL1?
- Is routine flow cytometry necessary for most MDS and MPNs?
- When do you perform both immunohistochemistry and flow cytometry immunophenotyping?
“In life there are drivers and passengers….”
• “In life there are drivers and passengers. Everyone else is just roadkill.”