Conditions that mimic neoplasia in the bone marrow

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Conflict of Interest

• Nothing to disclose
Learning Objectives

• Multiple conditions in bone marrow/peripheral blood that may mimic neoplastic disorders
• Select examples
• Present key tips for discriminating normal from abnormal
Hematogones

• A.k.a. normal B-lymphocyte precursors
• Typically found in small numbers in most adult bone marrow specimens
• Occur in larger numbers
  – In some healthy infants and young children
  – In a variety of disease states in both children and adults
    • particularly prominent in regeneration following chemotherapy or bone marrow transplantation
    • autoimmune disorders, congenital cytopenias, neoplasms, viral infections and immunodeficiency states
  – In some cases, they constitute 5% to 50% of bone marrow cells.
Hematogones
Hematogone maturation

Consistent and predictable spectrum of sequential antigen expression
Hematogones

• Microarchitectural pattern
  – Reside in the bone marrow interstitium in an individually distributed, non-clustered fashion
  – Background trilineage hematopoiesis should be intact and normal
  – With increasing numbers of hematogones, one may encounter cases where they are more closely situated to one another
  – Lack of distinctive clustering of more than 5-10 cells, particularly if they all express TdT
Hematogones may mimic neoplasms

- Lymphoblastic leukemia/lymphoma (LL)
- Lymphomas
- Metastatic neoplasm

Early bone marrow involvement by B-LL
Lymphoblasts

• Share morphologic, and some immunophenotypic features with hematogones

• In particular, distinguishing residual/recurrent B-lymphoblasts from hematogones after treatment for B-lymphoblastic leukemia/lymphoma can be challenging

• Recognition of the typical maturational profile for hematogones and lack of aberrant antigen expression are two useful tools to help with this distinction
B-lymphoblasts
B-lymphoblasts

Aberrant antigen expression
Hematogones may mimic neoplasms

T-cell prolymphocytic leukemia

High grade B-cell lymphoma with MYC and BCL2 rearrangement

Metastatic small cell carcinoma
Quiz

B-lymphoblastic leukemia

Hematogones
Eosinophilia

• Numerous causes, both neoplastic and non-neoplastic
• Broad workup can be daunting
• Methodical algorithmic approach
  – Manage ancillary testing
  – Ensure thorough, appropriate workup
  – Diagnose/exclude specific disease entities
### Eosinophilia Etiology

<table>
<thead>
<tr>
<th>Primary (clonal)</th>
<th>Secondary to underlying neoplasm</th>
<th>Secondary to non-neoplastic disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic eosinophilic leukemia (CEL, NOS)</td>
<td>Lymphoma</td>
<td>Infection</td>
</tr>
<tr>
<td>Myeloid and lymphoid neoplasms with eosinophilia and rearrangements of PDGFRA, PDGFRB, FGFR1, PCM1-JAk2</td>
<td>- T-cell lymphoma</td>
<td>- Allergic disorders</td>
</tr>
<tr>
<td>AML [particularly with inv(16)]</td>
<td>- classical Hodgkin lymphoma</td>
<td>- Drug reaction</td>
</tr>
<tr>
<td>CML</td>
<td>Lymphoblastic leukemia</td>
<td>- Rheumatologic disorders</td>
</tr>
<tr>
<td>MDS</td>
<td>Carcinoma</td>
<td>- Immunodeficiency</td>
</tr>
<tr>
<td>MPN</td>
<td>Lymphocytic variant of hypereosinophilic syndrome (LV-HES)</td>
<td></td>
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</tbody>
</table>
Eosinophilia Assess Morphology

• Increased eosinophils and precursors only
  – Normal bone marrow with increased eosinophils
  – Take care in assessing eosinophil cytology
  – Abnormal forms may be found in secondary causes
  – Eosinophil cytology alone should not be used to indicate clonal eosinophilic disease
Peripheral blood

Idiopathic hypereosinophilia

Images courtesy of M. Howard, MD
Peripheral T-cell lymphoma

Images courtesy of M. Howard, MD

Peripheral blood
Peripheral blood

Chronic eosinophilic leukemia, NOS

Images courtesy of M. Howard, MD
Eosinophilia

- Assess other pathology
  - Monocytosis, dysplasia, increased or abnormal blasts, basophilia
  - Fibrosis
  - Dysplasia
  - Mast cell clusters
  - Lymphoid infiltrates/Hodgkin lymphoma
  - Skin lesions, splenomegaly, known diagnosis, etc.
  - Granulomas
Neoplastic eosinophilia

Myeloid neoplasm with eosinophilia and PDGFRA-FIP1L1
Neoplastic eosinophilia

Chronic myeloid leukemia, *BCR-ABL1* positive
Non-neoplastic eosinophilophilia masking a clonal neoplasm

Peripheral T-cell lymphoma, NOS
Non-neoplastic eosinophilia masking a clonal neoplasm

Abnormal T-cells (in red)

Lymphocytic variant hypereosinophilic syndrome (LV-HES)
Sustained Eosinophilia

Assess/identify secondary causes

No

Assess peripheral blood/bone marrow morphology

No

Morphologic features of other diseases, e.g. mastocytosis, myeloid neoplasm, lymphoma etc.

No

Increased eosinophils and precursors only

Order:
- Immunohistochemistry for tryptase and/or CD117 and CD25
- KIT D816V
- Chromosomes
- FISH for PDGFRα-rearrangement
- T-cell flow cytometry
- Consider T cell receptor gene rearrangement

Do Not Routinely Order:
- JAK2 V617F
- BCR/ABL1 FISH or PCR
- FISH for PDGFRB or FGFR1
- Mast cell flow cytometry

Workup as appropriate

Workup as appropriate for other diseases

Yes

Chromosome and/or FISH result

Positive for:
- PDGFRα rearrangement
- PDGFRβ rearrangement
- FGFR1 rearrangement
- PCM1-JAK2 fusion

Other clonal myeloid abnormality**

No clonal abnormality

Myeloid neoplasm with*:
- PDGFRα rearrangement
- PDGFRβ rearrangement
- FGFR1 rearrangement
- PCM1-JAK2 fusion

Consider chronic eosinophilic leukemia, not otherwise specified

Consider:
- Reactive eosinophilia
- Idiopathic hypereosinophilia
- Idiopathic hypereosinophilic syndrome

Consider lymphocytic variant hypereosinophilic syndrome

Spindled CD25 positive mast cells and KIT D816V mutation

Work up as mastocytosis

Assess peripheral blood/bone marrow morphology

Yes

Morphologic features of other diseases, e.g. mastocytosis, myeloid neoplasm, lymphoma etc.

No

Increased eosinophils and precursors only

Order:
- Immunohistochemistry for tryptase and/or CD117 and CD25
- KIT D816V
- Chromosomes
- FISH for PDGFRα-rearrangement
- T-cell flow cytometry
- Consider T cell receptor gene rearrangement

No clonal abnormality

Consider:
- Reactive eosinophilia
- Idiopathic hypereosinophilia
- Idiopathic hypereosinophilic syndrome

Consider lymphocytic variant hypereosinophilic syndrome

Spindled CD25 positive mast cells and KIT D816V mutation

Work up as mastocytosis

* Bone marrow typically shows additional morphologic abnormalities
** Trisomy 8, deletion 20q, and –Y as sole abnormalities do not necessarily implicate the presence of a clonal myeloid disease
Key: FISH, fluorescence in situ hybridization
Quiz

Drug-induced hypereosinophilia

B-lymphoblastic leukemia with eosinophilia
Post-therapy effect

- Recombinant therapy
- Therapeutic agents
- Selected medications
- Post myeloablative chemotherapy/stem cell transplantation
Granulocyte colony stimulating factor

Peripheral Blood

Leukocytosis with granulocytic left shift, toxic changes, occasional monocytosis and circulating blasts

Bone marrow core biopsy

Hypercellular with granulocytic hyperplasia, prominent left shift and occasional transient increase in blasts and monocytes
G-CSF/GM-CSF may mimic neoplasia

G-CSF administration after delayed hematopoietic recovery for treatment of lymphoma mimics acute leukemia

72 y.o. treated for high grade lymphoma mimics chronic myelomonocytic leukemia
Thrombopoietin receptor agonists (TPO-RAs)

- A number of thrombopoietin-like molecules have been developed to treat thrombocytopenia
- TPO-RAs are being used with increasing frequency to treat thrombocytopenia associated with a variety of conditions such as hepatitis C associated thrombocytopenia, myelodysplastic syndrome, and aplastic anemia.
TPO Receptor Agonists

• Mechanism of Action
  – Stimulate megakaryocyte and platelet production by binding to the TPO receptor
• Generally reserved for third-line therapy
• Recombinant TPO products are not used in the USA due to reports of anti-TPO antibody development
Exemplary case

Peripheral blood

Slight leukocytosis

Occasional basophils and nucleated RBC
Bone Marrow Aspirate

Numerous spicules with megakaryocytic hyperplasia and morphologic spectrum
Bone Marrow Core Biopsy

Megakaryocytic hyperplasia, loose clustering and large, hyperlobulated forms

Reticulin

Mild reticulin fibrosis, grade 1 of 3 (MF-1)
Bone Marrow Pathology with Thrombopoietin Receptor Agonists

- Leukoerythroblastic reaction seen in small number
- Hypercellular with panmyelosis
- ~10% showed erythroid/granulocytic hyperplasia (Brynes)
- Increased megakaryocytes, pleomorphism, cluster formation: “MPN-like” features (ET/PV-like)

Bone Marrow Pathology with Thrombopoietin Receptor Agonists

• Increase in reticulin fibrosis; mainly mild (MF-1), some with MF-2/3; no collagen fibrosis; not clinically relevant
• No significant bone marrow dysfunction
• Karyotype normal
• Nonclonal

TPO-RA neoplastic mimics

• The main diagnostic trap is with myeloproliferative neoplasms
  – Similarities include splenomegaly (particularly if history is ITP), leukoerythroblastosis, transient thrombocytosis, occasional thrombosis, and megakaryocyte hyperplasia with large, hyperlobulated and occasionally bizarre/hyperchromatic forms which may loosely cluster

• Features to help distinguish include history of TPO-RA use, normal karyotype, non-clonal, no mutations in \textit{JAK2, CALR, MPL}
Quiz

TPO-RA

Early MPN (JAK2 V167F 7%)
Drug effect mimicking myelodysplasia

Pseudo–Pelger-Huët abnormalities

• Etiology: number of medications
• Neutrophils demonstrate hyposegmentation with abnormally clumped chromatin; Dohle bodies also
• Cytologic changes typically abate after removal of the offending agent
• Be careful to not over interpret as myelodysplasia!
Drug effect mimicking myelodysplasia

Arsenic induced RBC changes in APL

Dyserythropoiesis due to colchicine
Post myeloblastic chemotherapy changes and neoplastic mimics

- Post-therapy
- Myelodysplastic syndrome
Post myeloblative chemotherapy changes and neoplastic mimics

Post-therapy

Myelodysplastic syndrome
Megaloblastic anemia due to vitamin B12 deficiency

• May be due to inadequate dietary intake
  – At risk populations include the elderly, alcoholics, those with poor diet and pregnant women

• May also be due to absorption defects
  – This includes deficiencies of and antibodies against intrinsic factor including the autoimmune disorder (pernicious anemia)
  – Some medications that may impair absorption (e.g. aminosalicylates)
Peripheral Blood findings

- Macrocytic anemia
- Pancytopenia in severe cases there may be pancytopenia
- Increasing anisopoikilocytosis with increasing severity of the deficiency
  - often includes schistocytes
- Hypersegmented neutrophils
- Oval macrocytes are typical
- Rarely, Howell-Jolly bodies or Cabot rings are seen
Bone Marrow Findings
Megaloblastic anemia may mimic...

• Pure erythroid leukemia
• Myeloid neoplasm with abundant erythroid precursors
• Other neoplasms: lymphoma, carcinoma
• Key tips in megaloblastic anemia:
  – Be careful to not overcall as neoplastic
  – Systematic approach
Neoplastic mimics

DLBCL

MDS-RS-MLD
Quiz

Myelodysplastic syndrome

Megaloblastic anemia
Copper Deficiency

• Definition
  – Decreased serum copper or ceruloplasmin levels

• General features/Etiology
  – Insufficient copper absorption from gastrointestinal tract; long-term TPN without copper supplementation, malabsorption after gastric bypass surgery or celiac disease, excess serum zinc
Copper Deficiency

• Clinical presentation
  – Sensory and motor difficulties, neurocognitive defects, cytopenias (anemia and neutropenia)

• Prognosis
  – Hematologic abnormalities are fully reversible with restoration of serum copper levels
  – Neurologic disorders may not resolve but are less likely to progress
Copper Deficiency

Peripheral blood findings

• Anemia is typical
  – may be normocytic, macrocytic, or microcytic anemia
  – minimal polychromasias

• Neutropenia (which can be marked) is generally also seen
Copper Deficiency

Bone marrow findings

• Variable cellularity
  – May be hypocellular, normocellular, or hypercellular
  – Possible erythroid predominance

• Cytologic
  – Distinctive cytoplasmic vacuoles in granulocytic and erythroid precursors
  – Megakaryocytes may show some slight atypia
  – May be some subtle nuclear-cytoplasmic dyssynchrony in the erythroid or granulocytic precursors
    • No overt dysplastic features
  – Blasts not increased
  – Ring sideroblasts are common
Copper Deficiency
Copper Deficiency

• Main neoplastic differential diagnosis is with low-grade MDS
• Should not see vacuolated granulocytic precursors in MDS
• Clear cut dysplasia in MDS fulfilling WHO criteria
Germline predisposition syndromes

• New category in the WHO 2016 Classification of Haematopoietic neoplasms
• Important to recognize and diagnose for future management
• Be careful not to overinterpret abnormal megakaryocytes in a young patient with thrombocytopenia as MDS
• Recognize different propensities to develop frank hematopoietic malignancies
Bone Marrow Aspirate Smear

Cellular aspirate; intact trilineage hematopoiesis; morphologically unremarkable megakaryocytes (circle), although occasional small, atypical forms (arrow) noted.
Bone Marrow Aspirate Smear

Cellular aspirate; intact trilineage hematopoiesis; occasional small, atypical megakaryocytes (arrow) noted
Occasional small, atypical megakaryocytes (arrow) noted amidst otherwise intact granulopoiesis and erythropoiesis.
# Myeloid neoplasms with germ line predisposition and preexisting platelet disorders

<table>
<thead>
<tr>
<th>Disease</th>
<th>Inheritance</th>
<th>Gene involved</th>
<th>Bleeding tendency</th>
<th>Degree of Thrombocytopenia</th>
<th>Bone marrow morphology</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPDMM</td>
<td>AD</td>
<td><em>RUNX1</em></td>
<td>Mild due to an aspirin-like functional platelet defect</td>
<td>Moderate</td>
<td>Normal number of megakaryocytes with abnormal (small, hypolobated) forms</td>
<td>&gt;40% develop a myeloid neoplasm. Occasional T-LL</td>
</tr>
<tr>
<td>Thrombocytopenia 2</td>
<td>AD</td>
<td><em>ANKRD26</em></td>
<td>None to mild</td>
<td>Moderate</td>
<td>Normal number of megakaryocytes with abnormal (small, hypolobated) forms</td>
<td>~10% develop a myeloid neoplasm. Some patients have ↑hemoglobin.</td>
</tr>
<tr>
<td>ETV6-related thrombocytopenia</td>
<td>AD</td>
<td><em>ETV6</em></td>
<td>None to mild</td>
<td>Mild-moderate</td>
<td>Normal number of megakaryocytes with abnormal (small, hypolobated) forms</td>
<td>Increased risk of lymphoblastic leukemia</td>
</tr>
</tbody>
</table>

**Overlapping features**
Summary

• Numerous bone marrow reactive conditions
• Important to recognize morphologic mimics so as to neither overdiagnose or underdiagnose a neoplastic condition
• A systematic morphologic approach with judicious use of specialized testing technologies along with clinical history is optimal
Questions?