Bone marrow morphology in reactive conditions

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Conflict of Interest

• Nothing to disclose
Outline of Presentation

• Brief introduction
  – General categories (cytosis/cytoses, cytopenia(s), hypercellular, hypocellular, dysplastic-appearing changes, histiocytic, hypoplasia
  – Types of conditions (post treatment, drug-associated, idiopathic AA, nutritional deficiency, paraneoplastic, infectious)

• Specific examples

• Recognize and suggest possible etiologies in your report
Overview

• **Reactive bone marrow changes**
  – Common
  – Nonspecific
    • Perhaps more specifically interpretable in the proper clinical context
  – Important differential diagnostic considerations
    • May mimic neoplastic process
    • May mask an underlying neoplastic process
General patterns

• Quantitative changes in the hematopoietic compartment
• Qualitative changes in the hematopoietic compartment
• Lymphoid-, plasma cell- and histioeyctic proliferations
• Stromal changes
• Abnormal bony trabeculae
Clinical considerations

- Patient age: Expected normal BM cellularity for age
- CBC
  - Reference range for age
    - Varies; particularly in pediatric population
  - Compare to previous if known
- Medical conditions, drug history

Bone marrow cellularity changes with age
Specimen considerations

• Adequate
  – Preferably PB and BM
  – BMA cellular, not hemodilute
  – PB, BMA well-stained
  – Core: appropriate length, not subcortical

• Absence of artifacts
  – Aspiration/crush
  – Formalin vapor exposure
Specimen considerations

Subcortical

Formalin vapor exposure
Quantitative changes in the hematopoietic compartment:
Bone marrow hyperplasia

- Panhyperplasia
- Granulocytic hyperplasia
- Megakaryocytic hyperplasia
- Erythroid hyperplasia
- Eosinophilia
Panhyperplasia

- Regeneration after chemotherapy
- Paraneoplastic
Granulocytic hyperplasia

GCSF

Paraneoplastic due to underlying plasma cell disorder
Erythroid hyperplasia

AIHA

Megaloblastic anemia
Megakaryocytic hyperplasia

ITP

Thrombopoietin receptor agonist therapy
## Eosinophilia Etiology

<table>
<thead>
<tr>
<th>Primary (clonal)</th>
<th>Secondary to underlying neoplasm</th>
<th>Secondary to non-neoplastic disorder</th>
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</table>
| - Chronic eosinophilic leukemia (CEL, NOS) | - Lymphoma  
  - T-cell lymphoma  
  - Classical Hodgkin lymphoma  
  - Lymphoblastic leukemia  
  - Carcinoma  
  - Lymphocytic variant of hypereosinophilia | - Infection  
  - Allergic disorders  
  - Drug reaction  
  - Rheumatologic disorders  
  - Immunodeficiency |
| - Myelodendroid and lymphoid neoplasms with eosinophilia and rearrangements of PDGFRα, PDGFRβ, FGFR1, and JAK2 | | |
| - AML [particularity inv(16)] | | |
| - CML | | |
| - MDS | | |
| - MPN | | |
| - Systemic mastocytosis | | |
Quantitative changes in the hematopoietic compartment: Bone marrow hypoplasia

- Aplastic anemia
- Red blood cell aplasia
- Granulocytic maturation arrest
- Megakaryocytic hypoplasia
  - Rare; postinfectious, paraneoplastic, autoimmune
Aplastic Anemia

- Diagnosis of exclusion
- Etiologies
  - Toxins
  - Drugs
  - Infection
  - Hypocellular neoplasm
    - MDS/AML, T-LGL, HCL
  - Bone marrow failure syndrome
Pure red blood cell aplasia

- Etiologies
  - Medications
  - Infections
    - Parvovirus B19
  - Collagen vascular disease
  - Neoplasms
    - T-cell LGL, Thymoma, CLL
  - Immune-mediated
  - Other

[Images: CD71, Parvoviral inclusions]
Pure red blood cell aplasia

Paraneoplastic due to T-LGL
Granulocytic maturation arrest

• Etiologies
  – Direct toxic/drug effect
  – Autimmune process
  – Infection (with direct suppression of myeloid progenitors)

• Initial distinction from APL may be challenging
Granulocytic maturation arrest

Unknown etiology
Qualitative Changes in Hematopoietic Cells

- Granulocytes
- Megakaryocytes
- Erythroid precursors
Granulocytic qualitative changes

- GCSF
- HIV
- Tacrolimus
Stress dyserythropoiesis

Autoimmune hemolysis

Systemic infection
Copper deficiency

- Variably cellular bone marrow
- Distinctive cytoplasmic vacuoles in both early granulocytic and erythroid precursors
- Ring sideroblasts are also common
Vitamin B12 deficiency

- Bone marrow is most often hypercellular with the erythroid lineage being most prominent
- Left-shifted erythroid lineage with “sieve-like” chromatin
- Giant bands and metamylocytes
Drug-related erythroid lineage changes

Arsenic

Colchicine
Azathioprine-related atypical megakaryopoiesis
Lymphocytoses

• Hematogones
  – Postchemotherapy or bone marrow transplantation; autoimmune disorders, congenital cytopenias, neoplasms, viral infections and immunodeficiency states

• Nodular B- and T-cell aggregates
  – Increase with age

• T-cell lymphocytoses
  – CD8/LGL skewed in virus infections and autoimmunity
  – CD4 skewed in drug reactions
Hematogones

- Normal B-lymphocyte precursors (arrows)
- May pose a diagnostic challenge with B-lymphoblasts
- Show a consistent and predictable spectrum of sequential antigen expression
Hematogones

- Cyan - Early stage
- Dark Blue - Middle stage
- Magenta - Naïve B-cells
Benign lymphoid aggregates

- Increasing incidence with age
- Small, nodular, well-circumscribed
- Variable combination of small lymphoid cells, histiocytes and plasma cells
- Nonclonal
Lymphoid aggregates in BM

Germinal center formation

Benign lymphoid aggregate in myeloid malignancy
Histiocytic proliferations

• General increase
  – Cell turnover
  – Storage disorders

• Granulomas
  – Caseating-/non-caseating
  – Lipogranulomas, fibrin ring granulomas
  – Foreign body granulomas

• Hemophagocytosis
Increased histiocytes

- Sea-blue histiocytes
- Crystal-storing histiocytes (Ig in myeloma)
- Post myeloablative chemotherapy, early
- Post myeloablative chemotherapy, late
Fibrin ring granulomas

- a.k.a. “doughnut” ring granulomas or ring granulomas
- Considered a subtype of epithelioid granuloma
- Rarely encountered in routine bone marrow examination
- Distinctive morphologic appearance
- Reported with a number of infectious agents
  - some more common: Q fever, brucellosis, CMV, EBV, hepatitis viruses
Histiocytic proliferations

Post allogeneic stem cell transplant

Masking classical Hodgkin lymphoma
Hemophagocytosis

• Life-threatening condition characterized by overstimulation of the immune system leading to hypercytokinemia and multi-organ system failure
Hemophagocytosis

• Hemophagocytic syndromes are referred to as hemophagocytic lymphohistiocytosis (HLH) based on satisfaction of multiple criteria.

• HLH can be classified into a primary (genetic) and a secondary form.
Polyclonal plasmacytosis

- Increase in polyclonal plasma cells above normal range
- No significant nuclear immaturity
- Perivascular distribution
- Etiologies: chronic viral infections, autoimmune disorders, after chemotherapy, systemic immune reactions
Stromal alterations

- Fibrosis
- Serous fat atrophy
- Fibrinoid necrosis
- Necrosis
Fibrosis

• Reticulin and collagen fibrosis

• Non-neoplastic associations:
  – autoimmune myelofibrosis, HIV-associated myelopathy, metabolic disorders (renal), grey platelet syndrome

• Neoplastic associations:
  – MPN, hairy cell leukemia, mastocytosis, lymphomas, metastatic tumors
Serous fat atrophy

- Associated conditions:
  - Malnutrition
  - Anorexia nervosa
  - AIDS
  - Metabolic disorders
  - Malignancy

- Altered stroma composed of hyaluronic acid and increased glycosaminoglycans
Fibrinoid necrosis

- Seen following myeloablative chemotherapy
- Eosinophilic granular stroma
Necrosis

- Secondary to vascular insufficiency
- Associated conditions:
  - Malignancy
  - DIC
  - Infection
- Granular matrix with ghost cells
Bony alterations

• Note age and gender-related normal variations

• Bony trabeculae
  – Composed of central and peripheral bone
  – Provide support for BM microenvironment and hematopoietic cellular meshwork
Bony Alterations

Osteosclerosis

Osteonecrosis
Bony Alterations

Renal osteodystrophy

Paget’s disease
Special considerations

• Post myeloablative chemotherapy
• Certain medications/drugs
• Autoimmune myelofibrosis
Bone marrow changes in reactive conditions: summary

• Recognize common alteration patterns and potential etiologies
• Derive a systematic approach to consider and exclude potential reactive mimics
• In a particular clinicopathological context, specific etiology may be unveiled
• After careful workup, a descriptive report is ideal
Questions?