Bone Marrow Failure Disorders in Adults: Diagnostic Approach

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University of Nebraska

Objectives

1. Review Bone Marrow Failure and Aplastic Anemia

2. Establish a diagnostic algorithm for suspected cases of Bone Marrow Failure and Aplastic Anemia
Case 1

- 40 y/o male being evaluated for pancytopenia
- No significant PMH or FH
- No medications or exposure to environmental toxins
- Physical examination – unremarkable

<table>
<thead>
<tr>
<th>CBC</th>
<th>Differential</th>
<th>%</th>
<th>k/µL</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC</td>
<td>3.0k/µL</td>
<td>33.0</td>
<td>990</td>
</tr>
<tr>
<td>Hgb</td>
<td>11.9g/dL</td>
<td>65.0</td>
<td>1950</td>
</tr>
<tr>
<td>HCT</td>
<td>34.3%</td>
<td>1.0</td>
<td>30</td>
</tr>
<tr>
<td>MCV</td>
<td>109.0 fl</td>
<td>1.0</td>
<td>30</td>
</tr>
<tr>
<td>PLT</td>
<td>80.0k/µL</td>
<td>0</td>
<td>0</td>
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Bone Marrow Core Biopsy
Case 2

- 52 y/o female being evaluated for pancytopenia
- No significant PMH or FH
- No medications or exposure to environmental toxins
- Physical examination – unremarkable

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<thead>
<tr>
<th>CBC</th>
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<tr>
<td>WBC 2.9k/uL (normal differential)</td>
<td></td>
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<td>MCV 102.0 fL</td>
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<td>PLT 80k/uL</td>
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Bone Marrow Core Biopsy and Aspirate
Bone Marrow Failure: Definition

- Failure of bone marrow to provide adequate hematopoiesis
- Results in pancytopenia
- Variety of different mechanisms
  - Neoplastic
  - Congenital/genetic
  - Environmental (medications, toxins)
  - Other

BM Failure

- Malignancy
  - MDS
  - Lymphoma
  - ALL
  - AML
  - Carcinoma
- Non-malignancy
  - Single Lineage Aplasia
  - Multilineage Aplasia

- Acquired
  - Medication
  - Parvovirus
  - Thymoma

- Congenital
  - Diamond-Blackfan
  - Shwachman-Diamond
  - Severe congenital neutropenia
  - TAR, CAMT

- Constitutional AA (mainly children)
- Idiopathic Acquired AA
- Secondary Acquired AA
Aplastic Anemia: Definition

1. Diminished or absent bone marrow hematopoietic precursors = **Aplasia**

2. Presence of **Pancytopenia**

   - Confusing terminology
     - Misnomer: Aplastic Anemia is defined by pancytopenia (not anemia)
     - Aplastic anemia is frequently used as a “shorthand” for idiopathic acquired aplastic anemia

Constitutional Aplastic Anemia

- Mainly in pediatric population
- Inherited disorder
- Multiple described gene mutations
- Occasionally late-onset presentation into early adulthood
  - Dyskeratosis Congenita (most common in adults)
  - Fanconi Anemia
Secondary Acquired Aplastic Anemia

- Minority of cases <5%
- Difficult to establish causality, but well-documented associations
  - Drugs
    - Anticonvulsants (CBZ, hydantoin, phenacemide)
    - Antibiotics (sulfonamides, chloramphenicol)
    - NSAIDs (phenylbutazone, indomethacin)
    - Anti-thyroid drugs (methimazole, PTU)
  - Toxins
    - Solvents/degreasing agents
    - Industrial chemical (eg. benzene in rubbers/shoe factories)
    - Pesticides/insecticides (eg. benzene hexachloride: lindane)
  - Viral infection
    - Parvovirus B19 (often RBC aplasia)
    - Hepatitis viruses (non-A through -G)
    - HIV
  - Immune disorders
    - Eosinophilic fasciitis
    - SLE
  - Miscellaneous
    - Pregnancy (self-limited, ends with delivery)
    - Anorexia Nervosa (reversible)
    - Thymoma (often RBC aplasia)


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    - SLE

  - **Miscellaneous**
    - Pregnancy (self-limited, ends with delivery)
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Idiopathic Acquired Aplastic Anemia

- An etiologic cause cannot be identified

- **Most common** (80% of adult onset Aplastic Anemia)

- Mechanism not entirely elucidated
  - Hypothesized to be immune-mediated stem cell destruction (autoreactive T-cells)
  - Frequent response to immunosuppressive therapy
    - 70% of patients responded antithymocyte globulin (ATG) and cyclosporine
Diagnostic Work-up of Bone Marrow Failure in Adults

- Bone marrow biopsy
  - Single lineage aplasia
  - Malignancy
  - Megaloblastic maturation

Acquired or Congenital SLBMF

Cytopenias of alternate etiologies

Suspected Aplastic Anemia

Pancytopenia
+ BM Aplasia

Aspirate smear
Core biopsy
+/-Flow cytometry
+/-Cytogenetic studies
+/-Peripheral blood smear

Diagnostic Work-up of Bone Marrow Failure in Adults

- Bone marrow biopsy
  - Pancytopenia
    + BM Aplasia

Suspected Aplastic Anemia
Peripheral Blood in Aplastic Anemia

- Pancytopenia
- Reticulocytopenia
- No dysplasia
- No blasts
- No lymphoma cells

BM Core Biopsy and Aspirate in AA

Core Biopsy
- Hypocellular BM
- Empty marrow (fat cell replacement)
- No abnormal infiltrate

Aspirate
- Particles only stromal cells, lymphocytes and plasma cells
- No abnormal infiltrates
- Not significant dysplasia (isolated to erythroid lineage)
Cytogenetic Abnormalities in AA

- Normal karyotype in most cases (90%)

- Cytogenetic abnormalities in 5-10% of AA
  - Non-described in myeloid neoplasms (+6 and +15)
  - Described in AML & MDS (+8, -7): Line between MDS and AA in some cases is blurry
Diagnostic Work-up of Bone Marrow Failure in Adults

Bone marrow biopsy

Pancytopenia + BM Aplasia

Suspected Aplastic Anemia

Exclude “subtle” causes

Evaluate for concomitant PNH

Investigate etiology

Exclude “Subtle” Malignancies that Present with Pancytopenia and Hypocellular BM

- Most common entities in the pathologic DDx:

<table>
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<tr>
<th>Entity</th>
<th>Frequency</th>
<th>Characteristics</th>
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<tr>
<td>Hypoplastic Hairy cell leukemia</td>
<td>10% of HCL</td>
<td>Monocytopenia, ‘fried egg’ morphology, Clonal B-cell population</td>
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<tr>
<td>Hypoplastic AML</td>
<td>5% of AML</td>
<td>Abnormal myeloblast population, Recurrent CG abnormalities</td>
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<td>Hypoplastic ALL</td>
<td>1-2% of ALL</td>
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<td>Hypoplastic MDS</td>
<td>10% of MDS</td>
<td>Dysplastic megakaryocytes and neutrophils, Cytogenetic abnormalities in 50% of cases</td>
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Diagnostic Work-up of Bone Marrow Failure in Adults

Bone marrow biopsy

Pancytopenia + BM Aplasia

Suspected Aplastic Anemia

Exclude hidden causes

Investigate etiology

Evaluate for concomitant PNH

Investigate the Etiology: Clinicopathological Correlation

**“Clues”**

Clinical

- Younger age
- Family HX
- Bone deformities, skin lesions
- Toxin exposure
- Recent viral illness
- Viral inclusions/giant erythroblasts

Pathologic

- Serous atrophy/gelatinous transformation
- Proteinaceous edema, fat necrosis

**Suspected etiology**

- Late presentation of Constitutional AA
- Secondary Acquired AA to toxin
- Secondary Acquired AA to virus
- Secondary Acquired AA to virus
- Secondary Acquired AA to malnutrition

**Next Step**

- Chromosomal breakage analysis – Fanconi
- TERT, TERC mutations/telomere length – DC
- Viral serologies
- Parvovirus PCR
- If “no clues” are present and confirmatory test are negative: Idiopathic Acquired Aplastic Anemia
Diagnostic Work-up of Bone Marrow Failure in Adults

- Bone marrow biopsy
  - Pancytopenia + BM Aplasia
  - Suspected Aplastic Anemia
  - Exclude hidden causes
    - Investigate etiology
    - Evaluate for concomitant PNH

Evaluate for Concomitant PNH

- PNH and AA closely related
  - PNH clones seen in 60% of AA
  - Clinically relevant PNH develops in 15-20% of AA after treatment

- PNH clones confer a poor prognosis
  - 48% of AA with PNH-clone vs. 91% of AA with absent PNH clone R/ to ATG/cyclosporine
Example Cases

Case 1

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- No significant PMH or FH
- Physical examination – unremarkable

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Bone Marrow Core Biopsy

Flow Cytometry

Clonal B-cell population: CD19+, CD20+, CD103+, CD11c+, CD25+
DX: Hypocellular BM (10%) with Hairy Cell Leukemia

**Case of BM failure secondary to neoplasm**

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**Case 2**

- 52 y/o female being evaluated for pancytopenia
- No significant PMH or FH
- Physical examination – unremarkable

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Bone Marrow Core Biopsy and Aspirate

- No significant dyspoiesis
- Negative Flow Cytometry
- Negative cytogenetic studies

Bone Marrow Core Biopsy and Aspirate

Path Dx: Hypocellular bone marrow (10%) with panhypoplasia
- No significant PMHx or FHx
- No drugs, toxins
- No malignancy identified on BMBx (including ancillary studies)

Case of idiopathic acquired aplastic anemia
Questions?

References


Questions?