Hematopathology Preview: Bleeding Disorders, RBCs, Leukemia, and Lymphoma

10-27-2014
A. Inman
Bleeding Disorders

• Increased fragility of vessels
• Platelet deficiency or dysfunction
• Derangement of coagulation
• Drugs
Figure 4-5 Platelet adhesion and aggregation. Von Willebrand factor functions as an adhesion bridge between subendothelial collagen and the glycoprotein Ib (GpIb) platelet receptor. Aggregation is accomplished by fibrinogen bridging GpIIb-IIIa receptors on different platelets. Congenital deficiencies in the various receptors or bridging molecules lead to the diseases indicated in the colored boxes. ADP, adenosine diphosphate.

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Tests to Evaluate Bleeding Disorders

• Prothrombin time (PT):
  – Tests extrinsic and common coagulation pathways

• Partial thromboplastin time (PTT):
  – Tests intrinsic and common coagulation pathways

• Platelet counts

• Tests of platelet function:
  – Platelet aggregation test
  – Von Willebrand factor
  – Bleeding time
Primary Hemostasis Disorder
Secondary Hemostasis Disorders

Figure 2. Lower limb ecchymosis.
Thrombus in small Blood vessel
Stay tuned for more on specific disorders.......
Translocations

- t (9;22)  CML (bcr-abl)
- t (8;14)  Burkitt’s lymphoma (c-myc)
- t (14;18) Follicular lymphoma (bcl-2)
- t (15;17) AML M3
- t (1;14)  T-cell Lymphoblastic lymphoma
Translocations cont.

- $t\ (11;\ 22)$  Ewing’s sarcoma
- $t\ (11;\ 14)$  Mantle cell lymphoma (bcl-1)
- $t\ (11;\ 18)$  MALT lymphoma (API-2)
- $t\ (1;\ 14)$  MALT lymphoma (bcl-10)
### Complete Blood Count (CBC)

<table>
<thead>
<tr>
<th>Test</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cells ((10^3/\mu L))</td>
<td>4.5-11.00</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin ((gm/dL))</td>
<td>13.6-17.2</td>
<td>12.0-15.0</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>39-49</td>
<td>33-43</td>
</tr>
<tr>
<td>Red cell count ((10^6/\mu L))</td>
<td>4.3-5.9</td>
<td>3.5-5.0</td>
</tr>
<tr>
<td>Reticulocyte count (%)</td>
<td>0.5-1.5</td>
<td></td>
</tr>
<tr>
<td>Mean cell volume (\mu m^3)</td>
<td>82-96</td>
<td></td>
</tr>
<tr>
<td>Mean corpuscular hemoglobin (pg)</td>
<td>27-33</td>
<td></td>
</tr>
<tr>
<td>Mean corpuscular hemoglobin concentration ((gm/dL))</td>
<td>33-37</td>
<td></td>
</tr>
<tr>
<td>RBC distribution width (RDW)</td>
<td>11.5-14.5</td>
<td></td>
</tr>
<tr>
<td>Platelets ((10^3/\mu L))</td>
<td>150-450</td>
<td></td>
</tr>
</tbody>
</table>

Modified from Robbins and Cotran Pathologic Basis of Disease 7th edition
“Goldilocks” zone
Red Blood Cell Terms

• Size
  – Normocytic
  – Microcytic
  – Macrocytic

• Color
  – Normochromic
  – Hypochromic

• Anisocytosis = variation of size
• Poikilocytosis = variation of shape
Beta-thalassemia / Hb. E Post splenectomy
Megaloblastic anemia
Case 1

70 y.o. female with fatigue. No hemoptosis or vaginal bleeding. Normal physical exam except for pallor.
CBC

- Hgb 5.9
- MCV 56.2
- RDW 20.2
- WBC 5,900
- Plt 383,000
1a. The RBCs show?

A. Macrocytosis
B. Hyperchromasia
C. Spherocytosis
D. Schistocytosis
E. Anisopoikilocytosis
1b. What lab result would you expect?

A. Elevated serum ferritin
B. Elevated serum iron
C. High serum iron and low TIBC
D. Low serum iron and high TIBC
E. Low serum iron and low TIBC
1c. Before the patient leaves your office you should?

A. Order TSH and T3
B. Order TSH and T4
C. Prescribe multivitamins with iron
D. Perform stool exam for occult blood
E. Perform stool exam for hookworms and other parasites
Case 2
34 y.o. female with 2-day history of fever, petechiae and hematuria; also headaches and mental confusion.
CBC

- Hgb 7.0
- MCV 77
- RDW 23
- WBC 17,000
- Plt 14,000
2a. Describe the RBCs

A. Normochromic  
B. Microcytic  
C. Spherocytes and schistocytes  
D. Drepanocytes and schistocytes  
E. Howell-Jolly bodies
2b. Diagnosis?

A. Sickle cell anemia
B. Hereditary spherocytosis
C. Thrombotic thrombocytopenic purpura (TTP)
D. Anemia of chronic disease secondary to hypothyroidism
E. Folate deficiency
Case 3

34 y.o. male in for routine physical has pallor and icterus; splenomegaly on PE
CBC

- Hgb 11
- MCV 84
- WBC 6,000
- Plt 350,000
3a. Describe the RBCs

A. Normochromic
B. Schistocytosis
C. Microcytic
D. Spherocytosis
E. Hypochromic
3b. What test should you order to confirm your diagnosis?

A. Serum iron
B. Osmotic fragility
C. Reticulocyte count
D. Malaria screen
E. D dimer
Case 4
37 y.o. female treated lifelong for a seizure disorder complains of fatigue and lightheadedness
CBC

- Hgb 6
- MCV 130
- WBC 6,000
- Plt 220,000
4a. All of the following correctly describe the RBCs EXCEPT:

A. Normochromic
B. Macrocytic
C. Anisocytosis
D. Ovalocytosis
E. Spherocytosis
A bone marrow aspirate was performed
Bone marrow aspirate smear

**Morphology:**

- Assessment of cellularity best performed on the biopsy (% hematopoietic cells vs adipose tissue)

- Evaluation of maturation and composition of hematopoietic elements
  - Initial evaluation on the biopsy
  - Detailed evaluation using bone marrow aspirate smear
Acute leukemia
Normal bone marrow

Bone marrow biopsy

Acute leukemia
Bone marrow biopsy

Normal bone marrow

Aplastic anemia
Bone marrow aspirate from case 4 patient
4b. What findings on the bone marrow aspirate suggest folate deficiency?

A. Hyposegmented neutrophils
B. Hypocellularity
C. Giant bands and hypersegmented neutrophils
D. Miniature bands and hypersegmented neutrophils
E. Hypersegmented blasts and promyelocytes
Leukemia
Figure 13-1  Differentiation of blood cells. CFU, Colony forming unit; LIN−, negative for lineage-specific markers.

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LEUKEMIA

**Acute**
- ALL and AML
- Hi/Low WBC
- Rapidly fatal if untreated; anemic and thrombocytopenic
- Curable

**Chronic**
- CLL and CML
- Always high WBC
- Slowly progressive- patient lives many years
- Difficult to cure
Acute Leukemias

- Lymphoblast
- Myeloblast
- Monoblast
- Promyelocyte
5a. In Acute Leukemias you will almost always find:

A. Normal hct, normal platelets
B. Normal hct, decreased platelets
C. Decreased hct, increased platelets
D. Anemia, thrombocytopenia
E. WBC count >100,000
5b. In Chronic Leukemias you will almost always find:

A. Anemia, thrombocytopenia
B. WBC count >50,000
C. Normal hct, increased platelets
D. Anemia, thrombocytosis
E. Circulating blasts
lymphoblasts
ALL (PAS stain)
Myeloid Precursors
Leukamoid Reaction
Immature granulocytes present ("LEFT SHIFT")
CML
LAP (leukemoid)  LAP (CML)
Many Blasts
<table>
<thead>
<tr>
<th>FAB subtype</th>
<th>Description</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>Undifferentiated</td>
<td>Myeloperoxidase negative; myeloid markers positive</td>
</tr>
<tr>
<td>M1</td>
<td>Myeloblastic without maturation</td>
<td>Some evidence of granulocytic differentiation</td>
</tr>
<tr>
<td>M2</td>
<td>Myeloblastic with maturation</td>
<td>Maturation at or beyond the promyelocytic stage of differentiation; can be divided into those with t(8;21) AML1–ETO fusion and those without</td>
</tr>
<tr>
<td>M3</td>
<td>Promyelocytic</td>
<td>APL; most cases have t(15;17) PML–RARα or another translocation involving RARα</td>
</tr>
<tr>
<td>M4</td>
<td>Myelomonocytic</td>
<td></td>
</tr>
<tr>
<td>M4&lt;sub&gt;Eo&lt;/sub&gt;</td>
<td>Myelomonocytic with bone-marrow eosinophilia</td>
<td>Characterized by inversion of chromosome 16 involving CBFβ, which normally forms a heterodimer with AML1</td>
</tr>
<tr>
<td>M5</td>
<td>Monocytic</td>
<td></td>
</tr>
<tr>
<td>M6</td>
<td>Erythroleukaemia</td>
<td></td>
</tr>
<tr>
<td>M7</td>
<td>Megakaryoblastic</td>
<td>GATA1 mutations in those associated with Down's syndrome</td>
</tr>
</tbody>
</table>

AML1, acute myeloid leukaemia 1; APL, acute promyelocytic leukaemia; PML, promyelocytic leukaemia; RARα, retinoic-acid receptor-α. Modified from REF.65.
Myeloperoxidase (MPO)
Sudan black B
Nonspecific esterase
Case 6
25 y.o. male with fever, recurrent URIs and submandibular swelling; also poor wound healing
CBC

• Hgb 9.9
• MCV 106.3
• WBC 7.9 (70% “abnormal cells”)
• Plt 50,000
6a. Diagnosis?

A. ALL
B. AML
C. CLL
D. CML
E. Hereditary spherocytosis
6b. Which test on a bone marrow aspirate confirms your diagnosis?

A. MPO (-)
B. MPO (+)
C. PAS (+)
D. Iron stain (Prussian blue)
E. Leukocyte alkaline phosphatase = 20
Case 7
6 y.o. male with URIs, headache, bone pain and easy bruising; axillary and cervical lymphadenopathy; hepatosplenomegaly.
CBC

- Hgb 9
- MCV 82
- WBC 92,000 (86% abnormal)
- Plt 18,000
7a. Diagnosis?

A. ALL
B. AML
C. CLL
D. CML
7b. What test results are expected on a bone marrow aspirate?

A. MPO (+), PAS (+)
B. MPO (-), PAS (-)
C. TdT (+), Precursor B cell (+)
D. TdT (-), Precursor T cell (+)
E. Sudan black B (+); CD 10 (-)
Case 8
15 y.o. male with flulike symptoms; axillary and cervical lymphadenopathy; gums are thick and bleeding
CBC

- HGB 9
- MCV 90
- WBC 42,000 (88% abnormal)
- Plt 22,000
BM Bx results

- MPO (-)
- PAS (-)
- Sudan Black B (-)
- Non-specific esterase (++)
- Serum lysozyme 162 (4-15 normal)
8. Diagnosis

A. AML (FAB M1)
B. AML (FAB M3)
C. AML (FAB M5)
D. ALL (L1)
E. Infectious mononucleosis
Case 9
39-year-old female has routine workup for fibrocystic disease of breast; splenomegaly present
CBC

- Hgb  13
- MCV  96
- WBC  133,000 (seg 56, band 15, meta 13, myelo 4, pro 3, blast 3); baso 1, eo 1
- Plt  130,000
9a. What test should you order on a bone marrow aspirate?

A. MPO
B. PAS
C. Sudan black B
D. LAP
E. TRAP
10. 30-y.-o. female; anemia, thrombocytopenia; CBC- blasts w. Auer rods, schistocytes. Diagnosis?

A. ALL
B. AML, M1
C. AML, M3
D. AML, M5
E. TTP
Quick Look at Lymphomas
Architecture of normal lymph node
Benign lymph node enlargement (lymphadenopathy): most common pattern - follicular hyperplasia

- Infections
- Autoimmune disorders
- Non-specific
Lymphomas

Hodgkin:
• RS Cells
• Often curable

Non-Hodgkin Lymphoma:
• Low grade- slowly progressive, rare cure
• High grade- rapidly progressive; a minority are curable
HD vs NHL

**Hodgkin:**
- Stage important
- Few malignant cells
- Def. cell-mediated
- Localized- radiation

**Non-Hodgkin:**
- Grade important
- Mostly lymphoma
- Def. humoral
- Systemic- chemotherapy
Follicular Hyperplasia, Lymph Node (10X)

- Benign Follicle
- Mantle Zone
Follicular Hyperplasia, Lymph Node (40X)

- Follicle
- T-cell rich area
- B-cell area
- Follicle center
- Marginal zone
- T-cell zone
- B-cell zone
- Histiocyte
- Plasma cell
- Follicle sheath
- Sinusoidal tissue
- Capsule

Legend:
- Blue: Lymphocytes
- Pink: Plasma cells
- Yellow: Histocytes
- Green: Follicles
- Black: Lines
- Red: Arrows
Follicular Lymphoma, Lymph Node (4X)
Follicular Lymphoma, Lymph Node (10X)
Nodular Sclerosis Hodgkin Lymphoma, Lymph Node (4X)
Plasma Cell (Multiple) Myeloma, Bone (Radiograph)

“Punched Out” Lesions

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Figure 13-18 M protein detection in multiple myeloma. Serum protein electrophoresis (SP) is used to screen for a monoclonal immunoglobulin (M protein). Polyclonal IgG in normal serum (arrow) appears as a broad band; in contrast, serum from a patient with multiple myeloma contains a single sharp protein band (arrowhead) in this region of the electropherogram. The suspected monoclonal Ig is confirmed and characterized by immunofixation. In this procedure, proteins separated by electrophoresis within a gel are reacted with specific antisera. After extensive washing, proteins that are cross-linked by antisera are retained and detected with a protein stain. Note the sharp band in the patient serum is cross-linked by antisera specific for IgG heavy chain (G) and kappa light chain (κ), indicating the presence of an IgGκ M protein. Levels of polyclonal IgG, IgA (A), and lambda light chain (λ) are also decreased in the patient serum relative to normal, a finding typical of multiple myeloma.

Courtesy Dr. David Sacks, Department of Pathology, Brigham and Women's Hospital, Boston, Mass.