PathMD™: Board Review Letter

Author: Philip Ferguson, M.D. **Peripheral Blood – Part 3** Volume 1, Number 39

Case #1 A 36 y/o Hispanic female presents to the ER seizing with an elevated creatinine, petechiae, and fever on the previous day. Representative images of the blood smear are shown. What is the most likely diagnosis?

A. Disseminated intravascular coagulation
B. Hemolytic uremic syndrome
C. Thrombotic thrombocytopenia purpura
D. Hereditary pyropoikilocytosis
E. Autoimmune hemolytic anemia

Answer: C. The blood smear shows a microangiopathic hemolytic anemia (MAHA) that can be seen in DIC, TTP, and HUS. Additional clues to the diagnosis come from the clinical history and other relevant laboratory data. TTP results from a metalloprotease deficiency (ADAMTS-13), which normally cleaves large molecular weight multimers of von Willebrands factor in the plasma. The large multimers have much more prothrombotic activity and result in platelet rich microthrombi being formed in the microvasculature. The classic pentad of TTP is fever, thrombocytopenia (manifested in this case by petechiae), renal failure, neurologic changes, and MAHA. HUS usually only has MAHA, thrombocytopenia, and renal failure. It is classically associated with *E. coli* infection. Unfortunately, TTP usually doesn't present as a pentad, and therefore there can be a lot of clinical overlap. In DIC the PT and aPTT would be prolonged (not described in this case). Evans' syndrome (autoimmune hemolytic anemia and ITP) does not have the schistocytes, which are present in this case. Hereditary pyropoikilocytosis will have a normal platelet count, but the smear can resemble MAHA. (Kjeldsberg, page 323-325)

Case #2 A 40 y/o patient presents to his primary care physician's office complaining of fatigue. A routine CBC was performed, and representative images of the smear are shown. Based on the findings, what is the next best test for the physician to order?

A. Anti-i antibody
B. Anti-I antibody
C. Direct antibody test (DAT)
D. Serum protein electrophoresis (SPEP)
E. Haptoglobin

Answer: D. These images are representative of rouleaux formation which is the result of decreased zeta potential between erythrocytes, and is caused by increased plasma proteins (most commonly associated with a monoclonal gammopathy). The RBC membrane has a net negative charge. The increased protein levels alter this and decrease the zeta potential (opposing negative charges). Cold agglutinins are the result of IgM antibodies linking erythrocytes in a more ball-like pattern (aggregates). In adults cold agglutinins are commonly the result of anti-I associated with *mycoplasma pneumoniae*. A SPEP would be the best screening test to search for a monoclonal gammopathy or other protein derangement. (Glassy, pages 146-151)

Case #3 A 35 y/o white female presents to her primary care physician to establish care. A routine CBC was performed, which showed a microcystic anemia with a slightly increased MCHC. Upon further questioning, the patient stated that a surgeon wanted to take her spleen out many years ago, but she did not return to see the "quack." Based on the clinical history, laboratory data, and peripheral smear images, what is the best diagnosis?

A. Iron deficiency anemia
B. Hereditary elliptocytosis
C. Alpha thalassemia
D. Beta thalassemia
E. Hereditary spherocytosis

Answer: E. Hereditary spherocytosis (HS) is usually an autosomal dominant disorder (65%) that has many different described RBC membrane cytoskeletal abnormalities. The common denominator is the spleen removes the areas of unsupported RBC membrane, which results in a decreased surface to volume ratio (increased MCHC and microcytosis). Dependent upon the type of defect the clinical significance can vary greatly. Diagnostically, the RBC morphology will show spherocytes. An osmotic fragility test and direct antiglobulin test (r/o autoimmune hemolytic anemia) may also be helpful. (Kjeldsberg, pages 93-98)

Case #4 A 30 y/o African American patient admitted to the burn unit is found to have a decreased Hb and Hct. Peripheral smear review is shown. Haptoglobin is undetectable, and DAT is negative. Based on these findings, which of the following is the best diagnosis?

A. Iron deficiency anemia
B. Autoimmune hemolytic anemia
C. Acute transfusion reaction
D. Hereditary pyropoikilocytosis
E. Thermal injury

Answer: E. Thermal injury can be seen in burn patients or as an artifact from blood specimens exposed to heat (i.e. the dashboard of the lab courier's car). It is characterized by significant anisopoikilocytosis with microspherocytes and small read cell fragments, which are much smaller than seen in usual hematologic diseases. Hereditary pyropoikilocytosis can have very similar morphologic features, but in this case the clinical history is suggestive of direct thermal injury.

Case #5 A 35 y/o male is found to have thrombocytopenia. A bone marrow was performed and the aspirate showed sheets of cells (95% of the non-erythroid cells) shown in the image for this case. Myeloperoxidase was positive in 10% of the cells shown. Flow cytometry demonstrated that the cells expressed CD19, CD13, CD33, CD34, and CD117. Based on these findings, what is the best diagnosis?

A. Precursor B ALL
B. AML – M0
C. AML – M1
D. AML – M2
E. AML – M4
F. AML – M5

Answer: C. AML-M1 is the FAB classification for a minimally differentiated AML (<10% of the non-erythroid) cells mature beyond the blast stage. The flow cytometry shows a myeloid phenotype (CD13,

CD33, and CD117) with aberrant CD19 expression (often seen in cases with t(8;21)). CD34 is a marker of immaturity, but is not specific for myeloid lineage. This case is not an M0 because >3% of the cells are myeloperoxidase positive. There is no evidence of monocytic differentiation to support the diagnosis of an AML-M4 or AML-M5.

Case #6 A 72 year old man presents with fatigue. A CBC was drawn and shows: Hb 9.6 g/dL, TIBC 220 mcg/dL (250-450), iron 25 mcg/dL (50-150), and transferrin 180 mcg/dL (200-400). A representative image of the peripheral smear is shown. What is the best diagnosis?

A. Thalassemia
B. Anemia of chronic disease
C. Hemoglobinopathy
D. Iron deficiency anemia
E. Can not be determined

Answer: D. Iron deficiency anemia is characterized by a hypochromic microcystic anemia (classically). In addition, the Iron level is usually decreased (<40-50 mcg/dL) and the TIBC is increased (>450 mcg/dL). Transferrin can also be increased in iron deficiency anemia. It parallels TIBC, and can be estimated by the following: Transferrin (mg/dL) = 0.7 x TIBC (mcg/dL). In this case, the TIBC and Transferrin is low, but the iron saturation is low (11%). The ratio of serum iron (mcg/dL) divided by TIBC (mcg/dL) is referred to as the % Transferrin Saturation or the Iron Saturation. In iron deficiency anemia, the iron saturation is usually less than 20%. Note that the measured transferrin value is not used in this calculation. (Bakerman, pages 53-59, 243-244, & 332-335)

Case #7 An osmotic fragility test was performed on the blood specimen from a 45-year-old patient who has a microcytic anemia (MCV = 73, RBC = 3.8 x 10^6/mL, Hb = 11.0 g/dL, & Hct. = 33.4%). Based on these laboratory values and the findings on the osmotic fragility test, what is the most likely diagnosis?

A. Hereditary spherocytosis
B. Iron deficiency anemia
C. Alpha thalassemia
D. Beta thalassemia
E. All of the above are diagnostic possibilities

Answer: B. The osmotic fragility test shows a shift to the right, which means the erythrocytes have the ability to expand in a hypo-osmotic environment. Hereditary spherocytosis does not have this ability to expand, and therefore results in a shift to the left on the osmotic fragility diagram because the cells will lyse in a minimally hypo-osmotic environment (0.9% NaCl is approximately iso-osmotic). The shift to the right shown in this case can be seen in conditions that have an increased surface to volume ratio such as thalassemias and iron deficiency anemia, which can tolerate a more hypo-osmotic environment. Iron deficiency anemia is the best answer in this case because a thalassemia would be expected to have a higher RBC count. (Kjeldsberg, pages 100-102) *Unsolicited Advice* In thalassemias, the MCV to RBC ratio is usually <13. Normally, the RBC count multiplied by 3 is approximately equal to the hemoglobin, which multiplied by 3 is approximately equal to the hematocrit. In cases of thalassemia, when the RBC count is multiplied by 3 it is often significantly greater than the hemoglobin concentration, and suspicion of this diagnosis should be raised. In this example the RBC count multiplied by 3 is approximately equal to the hemoglobin, which makes a thalassemia much less likely.

Case #8 An 18 y/o patient presents to his university's football physician for his annual sports physical. He has a CBC drawn for the first time, and representative images are shown. The CBC was repeated at the local hospital with similar findings, and a DAT was negative. If both parents had CBCs drawn, one would most likely have which of the following?

A. Hereditary spherocytosis
B. Autoimmune hemolytic anemia
C. Hereditary elliptocytosis
D. Hereditary pyropoikilocytosis
E. Thermal injury

Answer: C. The image for this case represents hereditary pyropoikiolcytosis. Usually one of the parents will have hereditary elliptocytosis (HE) and the other parent can also have HE or a clinically unrecognized quantitative defect in one of the cytoskeleton components of the RBC membrane (thalassemia-like). The offspring can then have hereditary pyropoikilocytosis. (ASCP Check Path QAH 94-2)

Question #1 Which of the following would most likely give a spuriously low platelet count on an automated CBC analyzer?

A. Ethylenediaminetetraacetic aced (EDTA)
B. Citrate
C. Heparin
D. All of the above
E. None of the above

Answer: A. EDTA can sometimes be associated with platelet clumping or satellitism (platelets adhere to WBCs). The patient can be redrawn in a citrated or heparin tube to correct this artifact. (Kjeldsberg, page 318)

Question #2 What is the iron saturation in case #6?

A. 11%
B. 14%
C. 4%
D. 5%
E. Can not be determined

Answer: A. See explanation in Case #6 for details.

References:

Bakerman's ABC's of Interpretive Laboratory Data. S. Bakerman, et al. Fourth Edition. 2002.

Practical Diagnosis of Hematologic Disorders. CR Kjeldsberg, ASCP 2006.

Color Atlas of Hematology. EF Glassy. College of American Pathologists. 1998.

