Episode 65

Problem Representation
A 25-year-old man with a history of Gilbert syndrome and sickle cell disease requiring monthly red blood cell (RBC) exchange transfusions presented with acute-onset fevers, chills, and night sweats, as well as evidence of worsening hemolysis.

Schemas
In the CPSer's schema, causes of hemolytic anemia can be localized to the RBC's extracellular environment (e.g., microangiopathic hemolytic anemias), membrane, or internal environment. Membrane and intracellular issues can be caused by intrinsic defects (e.g., hereditary spherocytosis or hemoglobinopathies) or extrinsic factors (e.g., autoimmune hemolytic anemias or infection). Findings on peripheral blood smear can further help determine the cause.

Diagnosis
Laboratory data were notable for anemia, indirect hyperbilirubinemia, elevated lactate dehydrogenase, and low haptoglobin, raising concern for hemolysis. No schistocytes were visualized on the peripheral blood smear. The patient initially improved on empiric ceftriaxone and azithromycin, but then his fevers recurred. A thin and thick smear led to the diagnosis of Babesiosis. He was started on azithromycin and atovaquone, and his symptoms resolved.

Teaching points

- Sickle cell disease[1] (SCD) results from mutations in the beta-globin gene which cause hemoglobin polymerization and RBC sickling. Vaso-occlusion[2], a consequence of RBC sickling, leads to a number of complications, including tissue ischemia and acute chest syndrome. In adults, the acute chest syndrome[3], a leading cause of death in SCD, is thought to be caused by vaso-occlusion of the pulmonary microvasculature from pulmonary (e.g., infection, hypoventilation) or extrapulmonary processes (e.g., fat emboli released from ischemic bone marrow during vaso-occlusive episodes that cause pulmonary vascular obstruction and inflammation).
- Babesiosis[4] is caused by parasites of the genus *Babesia* and most commonly occurs in the Northeast and upper Midwest regions of the United States. While the majority of cases[5] are transmitted by ticks, *Babesia* spp. can also be transmitted by blood transfusion and represent the most common transfusion-related infection in the United States. Laboratory findings often include hemolytic anemia, thrombocytopenia, and elevated liver enzymes. Diagnosis is made by PCR or thin smear (thick smear often misses these small organisms). Treatment for patients with mild to moderate symptoms involves a 7-10 day course of azithromycin and atovaquone[5].
- Gilbert syndrome[6] is an autosomal dominant genetic disease caused by a mutation in the gene for UDP-glucuronosyltransferase 1A1 (UGT1A1) that leads to an unconjugated hyperbilirubinemia. It typically presents during adolescence with intermittent jaundice triggered by dehydration, fasting, acute illness, or overexertion. No specific treatment is indicated for this benign condition.

Clinical Reasoning Pearl

Use treatment to help with diagnosis. When taking a diagnostic pause, the response to treatment can help inform your clinical reasoning.

<u>For example:</u>
In this case, the patient's fevers briefly improved with azithromycin and ceftriaxone, which helped focus on an atypical infection as a possible cause.

References

1. Rees DC, Williams TN, Gladwin MT. Sickle-cell disease. Lancet. 2010 Dec 11;376(9757):2018-31.
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3. Novelli EM, Gladwin MT. Crises in Sickle Cell Disease. Chest. 2016 Apr;149(4):1082-93.
4. Vannier E, Krause PJ. Human babesiosis. N Engl J Med. 2012 Jun 21;366(25):2397-407.
5. Lobo CA, et al. The clinical assessment, treatment, and prevention of lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis. 2006 Nov 1;43(9):1089-134.
6. Fretzayas A, et al. Gilbert syndrome. Eur J Pediatr. 2012 Jan;171(1):11-5.