CLINICAL VIGNETTE

A Commonly Overlooked Cause of Anemia and Thrombocytopenia

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Case Vignette

A 20-year-old female presented to the hospital with fevers, rhinorrhea, fatigue, and severe intermittent abdominal pain. She reported that six months prior, her primary care doctor had noted anemia and thrombocytopenia on routine labs. She was referred to a hematologist who performed a bone marrow biopsy that demonstrated no abnormalities, and she was told that her underlying diagnosis was unclear.

At the time of presentation to the hospital, she was febrile, hypotensive, and tachycardic. Her physical exam was notable for obesity, conjunctival pallor, and a non-acute abdomen with mild diffuse tenderness. Her labs showed a Hg of 6.4 with an MCV of 116 and platelets of 34. Urinalysis showed only two red blood cells. A chest x ray showed no evidence of infection or abnormalities. A CT angiogram of the abdomen/pelvis was negative for internal hemorrhage, infection, ischemia, and thrombosis. The patient was started on broad-spectrum antibiotics and multiple consultants were involved, including infectious disease and hematology-oncology.

A broad infectious and autoimmune workup was unremarkable. Throughout the hospitalization, her hemoglobin continued to intermittently decrease and she remained thrombocytopenic. Her labs persistently showed a slight increase in LDH and normal bilirubin with undetectable haptoglobin levels. Her reticulocyte count remained lower than expected given her degree of anemia, and her peripheral smear showed non-specific increased polychromasia. Direct antibody testing (DAT) and G6PD testing were negative. Vitamin B12, methylmalonic acid, and folate levels were within normal limits.

Several days into her hospitalization, a PNH flow cytometry panel was sent, which demonstrated loss of CD55 and CD59 expression, diagnostic of PNH. Her hemolysis, likely triggered in the setting of an upper respiratory tract infection, stabilized prior to discharge. Her treatment plan is to start eculizumab as an outpatient.

Discussion

Paroxysmal Nocturnal Hemoglobinuria (PNH) is a rare, acquired cause of hemolytic anemia with a variable clinical presentation, commonly leading to a delay in diagnosis. PNH is caused by an acquired clonal stem cell mutation resulting in abnormal sensitivity of the red blood cell membrane to undergo lysis by complement. More specifically, the complement regulating proteins CD55 and CD59 are deficient, causing the unregulated formation of the membrane attack complex on red blood cell membranes and ultimately leading to intravascular hemolysis.[1]

Despite the name, the disease is not necessarily paroxysmal or nocturnal, nor does it frequently involve hemoglobinuria. In fact, less than 30% of patients have episodic hemoglobinuria.[2] More commonly patients will experience non-specific complaints including dysphagia (from esophageal spasm), chest pain, abdominal pain, or erectile dysfunction. These symptoms are theorized to result from free hemoglobin released into the blood during hemolysis, which acts as a scavenger for nitric oxide and therefore promotes increased smooth muscle tone and contraction throughout the body.[3] In our vignette, the patient's vague recurrent abdominal pain with unremarkable imaging was likely secondary to this relative deficiency in nitric oxide and resultant smooth muscle cramping.

Thrombosis is another important occurrence in roughly 40% of patients with PNH.[3] This may be due to the relative deficiency of nitric oxide and subsequent increase in platelet aggregation.[4] Thrombosis is important to recognize as part of the disorder because it is the leading cause of death in patients with PNH.[3] The mesenteric, hepatic, and CNS veins are particularly prone to thrombosis,[1] and therefore, complaints such as abdominal pain or headache in these patients should be investigated.

In addition to the physical signs and symptoms discussed, the diagnosis is also suggested by anemia of variable frequency and severity. Although the peripheral smear is often non-diagnostic as it was in our case, laboratory workup will often show signs of hemolysis including elevated LDH and reduced haptoglobin.[1] Interestingly, in our patient LDH was repeatedly only mildly high, though haptoglobin remained undetectable. Leukopenia and thrombocytopenia may also be present in the setting of marrow failure from impaired hematopoiesis. Marrow failure may even progress to aplastic anemia in some PNH patients.[4]

Once PNH is suspected, the definitive diagnosis is made by flow cytometry, which will document deficiency of CD55 and CD59. As in our case, bone marrow biopsy is often not helpful as the morphology is variable and nonspecific (it may show generalized hypoplasia or erythroid hyperplasia).[1]

Mild disease does not necessarily require intervention. However, if there is thrombosis or severe hemolysis requiring

transfusions, as in our patient, the hallmark of therapy is treatment with eculizumab. Eculizumab is a monoclonal antibody that works directly against the complement C5, preventing its cleavage so that the membrane attack complex cannot assemble. Although the treatment is expensive, it has been shown to improve quality of life and reduce hemolysis and thrombosis risk in PNH patients.[4] For patients who do not respond to eculizumab, bone marrow transplant may be considered.[3]

This case serves as a reminder that the classically taught clinical findings of paroxysmal hemoglobinuria and thrombosis in PNH are often absent at the time of presentation. It highlights the difficulty of diagnosing PNH given that the presenting complaints are often vague and non-specific. Given its variability and ill-defined symptoms, PNH should be considered in any confusing or undiagnosed cases of anemia and thrombocytopenia (or pancytopenia), regardless of the clinical presentation.

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