CLINICAL VIGNETTE

Presentation of Paroxysmal Nocturnal Hemoglobinuria in a 26-Year-Old Male

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Case Presentation

A 26-year-old male with no known significant past medical history, presented to the Emergency Department with worsening dyspnea on exertion and multiple episodes of near syncope. His exercise tolerance decreased significantly over two months and he presented to the ED after nearly passing out. He did not have any chest pain, nausea, vomiting, fevers, or chills. He denied any abnormal bleeding or easy bruising. He was fully vaccinated for COVID-19 and was not taking any medications. He had no medical evaluations for several years, and no family history of bleeding disorders.

In the ED the patient was afebrile, with normal stable vital signs including heart rates 70s-90s and normal blood pressures. Physical exam was remarkable for significant conjunctival and palmar pallor. His abdomen was non-distended abdomen without guarding or hepatosplenomegaly. Stool was hemoccult negative. Labs included Hemoglobin of 4.7 with MCV 97, WBC 4.5, platelets 51, and normal electrolytes. Total bilirubin was elevated at 1.7 with normal transaminases. D-Dimer was elevated at 1.3 with normal fibrinogen and INR. The emergency department obtained CT abdomen/pelvis as well as CT Angio Chest to assess for pulmonary embolism and both tests were unremarkable. Patient was transfused 2 units packed red blood cells with appropriate response of hemoglobin to 7 and admitted for evaluation.

Hematology was consulted and requested additional laboratories including haptoglobin < 10, direct coombs test negative, mononucleosis screen negative, normal ADAMTS13 activity, elevated reticulocyte count. Other unremarkable tests included ANA, pANCA, cANCA, Immunoglobulin IgA, IgG, and IgM, myeloperoxidase antibody, proteinase 3 antibody, B12 and folate. Peripheral smear showed no schistcocytes, but noted microcytic red blood cells, and markedly reduced platelets. The working diagnosis was chronic coombs negative microangiopathic hemolytic anemia, possibly due to paroxysmal nocturnal hemoglobinuria (PNH). PNH flow cytometry returned positive CD16 population and associated GPI anchor for CD55/59, consistent with diagnosis of PNH.

Patient was discharged with hematology follow up. Bone marrow biopsy showed normocellular marrow without signs of aplastic anemia and no need for expedited transplant evaluation. Repeat laboratories were consistent with active hemolysis. He started on eculizumab infusion with hemoglobin levels stable and downtrending LDH and is currently doing well with outpatient management. Since initiation of treatment, patient has noted less dyspnea and has not required any transfusions.

Discussion

Paroxysmal nocturnal hemoglobinuria is a rare, complement-mediated microangiopathic hemolytic anemia where red blood cells and their progenitors either lack or have decreased amounts of glycosylphosphatidylinositol (GPI) anchor proteins located on the surface of the cells.[1] Due to this, the cells lack complement inhibitors associated with GPI, specifically CD55 and CD59, leading to the intravascular hemolysis as well as increased likelihood of thrombosis. The presentation of PNH can be variable including a hemolytic anemia as in our patient, bone marrow failure with aplastic anemia, or thrombosis. PNH usually presents in adults with no known risk factors and is often underdiagnosed given the variable and indolent presentation.[2] It equally affects males and females. Most cases of PNH are caused by an acquired mutation in the hematopoietic stem cells of red blood cells. Given the pathophysiology of PNH, the mainstay of treatment of treating intravascular hemolysis is terminal complement inhibitors.[1]

The clinical presentation of PNH is very variable and may be indolent, but most present with sequela of anemia including fatigue and dyspnea as in our patient. Other presenting findings include hemoglobinuria, abdominal pain, chest pain, pancytopenia, and thrombosis. Patients with hemoglobinuria, may report coca-cola colored urine.[3] Hemolysis usually occurs at all times throughout the day, but increases at night, hence the name. The degree of hemolysis is determined by the percentage of red blood cells having abnormalities in their GPI anchor proteins. Typical laboratory findings for PNH include anemia, elevated reticulocyte count, negative coombs test, and elevated LDH level as seen in our patient.[1]

Bone marrow failure is an important consideration in patients with PNH as aplastic anemia or overlap with myelodysplastic syndrome can develop. In one study, bone marrow failure was seen in 15% of patients. Bone marrow dysfunction in PNH patients may be mild and asymptomatic, but can be severe, with aplastic anemia. Patients with bone marrow failure and PNH more often have lower PNH population blood cells, and less intravascular hemolysis. Over time, PNH may progress, with increased hemolysis.[4] PNH is classified into three types: classical, subclinical, and associated with bone marrow failure.

The classical presents with intravascular hemolysis with little to no bone marrow failure. Subclinical PNH is found on flow cytometry, but without clinical nor bone marrow findings. PNH with bone marrow failure can have a certain degree of myelodysplastic syndrome and/or aplastic anemia.[5]

When PNH is suspected, the preferred method for diagnosis is flow cytometry or FLAER analysis. Flow cytometry uses labeled monoclonal antibodies that bind specifically to CD59 and CD55, the GPI-anchored proteins. FLAER is a reagent that also binds to the GPI anchor, further improving the diagnostic value. When performing these studies, definitive diagnosis requires two independent flow cytometry reagents used on two different cell lineages. These studies are also able to show the percentage of PNH cells in the sample.[6] Bone marrow biopsy is also indicated to evaluate for any bone marrow failure. Imaging including ultrasound is also routinely performed to evaluate for thrombosis.

Symptomatic PNH includes symptomatic anemia as in our patient or thrombosis, without significant bone marrow failure, are recommended for treatment with a complement inhibitor. C5 complement inhibitors include eculizumab and ravulizumab which control the hemolysis and prevent any thrombosis.[7,8] Treatment will be indefinite and studies have shown that those treated with complement inhibitors have higher for transfusion independence and improved quality of life, which has seen in our patient who initiated eculizumab. Choice of agent varies and ravulizumab may be preferred over eculizumab due to longer time periods between treatments, lower cost, and fewer episodes of breakthrough hemolysis. Both of these agents are noninferior to each other with similar toxicity. Their mechanism of action is to bind C5 and inhibit the complement activity by cleaving C5 into segments. Subclinical PNH does not need treatment, but will need to be monitored for progression. Another important consideration is the inhibition of terminal complement significantly increases risk of Neisseria infections, with > 1000-fold increased risk, even in vaccinated individuals. All patients need to be vaccinated against Neisseria and also considered for penicillin prophylaxis for patients less than 45 years of age. Lastly, PNH patients with significant bone marrow failure will need evaluation for allogenic hematopoietic cell transplantation.[1]

Conclusion

Microangiopathic hemolytic anemia should be considered in patients presenting with anemia not due to other causes such as bleeding, renal disease, malignancy, or other known chronic conditions. Laboratory findings such as significant anemia, elevated reticulocyte count, negative coombs test, elevated LDH, and evidence of hemolysis such as D-Dimer elevation and low haptoglobin, suggest this diagnosis, but mainstay is flow cytometry. Earlier diagnosis and initiation of complement inhibitors in symptomatic PNH patients can prevent further complications including transfusion related iron overload, thrombosis, and improve quality of life.[5]

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