CLINICAL VIGNETTE

Hematuria and Hemolysis: A 50-Year-Old Male with Paroxysmal Nocturnal Hemoglobinuria

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Case

A 50-year-old male with chronic pancytopenia presented to the emergency department with hematuria. Four weeks prior to admission, he noted one day of brown urine, which gradually lightened to pink before returning to a normal yellow color. This pattern recurred several times over the weeks preceding admission. With each episode he denied pain or additional symptoms. He presented to urgent care and given his intermittent hematuria in the setting of known thrombocytopenia, was referred to the emergency department for additional evaluation.

He was first diagnosed with isolated mild thrombocytopenia at least 10 years prior with platelet counts of 110,000 to 120,000/µL. He was evaluated by his primary care physician (PCP) without establishing a definitive diagnosis. He recently, established care with a different PCP, and subsequent laboratory evaluation was notable for new pancytopenia, with a white blood cell (WBC) count of 3.2/µL, hemoglobin 11.5 g/dL, and platelet count of 67,000/µL. He was referred to a hematologist but did not seek further medical care due to the COVID-19 pandemic. Extended review of systems was otherwise negative, without fevers, night sweats, weight loss, chest pain, shortness of breath, rash, nausea, abdominal pain, diarrhea, bloody stools, dysuria, flank pain, or foamy urine.

On admission, the patient was hemodynamically stable without abnormal vital signs. He appeared pale and fatigued, though in no acute distress. His physical exam was notable for conjunctival pallor and a palpable spleen tip below the costal margin. There was no petechiae or purpura and no appreciable cervical, axillary, or inguinal lymphadenopathy. The remainder of his exam, including was normal. Initial laboratory testing included a WBC count of 2.46/µL with an absolute neutrophil count of 1,130/µL, hemoglobin 9 g/dL, platelets 49,000/µL, creatinine 1.68 mg/dL (baseline 0.8 mg/dL), AST 133 U/L, and total bilirubin 2 mg/dL. Urinalysis had brown color, 3+ blood, 3+ protein, > 210 RBC/HPF, and granular casts. Further laboratory testing revealed a lactate dehydrogenase (LDH) of 3,625 U/L and a haptoglobin < 10 mg/dL.

Hematology was consulted for ongoing evaluation of pancytopenia and concern for non-immune mediated hemolytic anemia. Coombs testing was negative. Peripheral smear was negative for schistocytes, blasts, teardrop cells, target cells, or spherocytes. His vitamin B12, folate, zinc, and copper levels were normal. Infectious studies, including EBV and CMV PCR, HIV, and hepatitis panels were also negative. CT imaging of the chest, abdomen, and pelvis confirmed mild splenomegaly but did not demonstrate lymphadenopathy, cirrhosis, or masses. Peripheral flow cytometry and flow cytometry for paroxysmal nocturnal hemoglobinuria (PNH) detected a PNH clone within granulocytes (96.35%), monocytes (83.29%), and RBCs (6.7%).

Given the patient's severe pancytopenia, he also underwent bone marrow biopsy to evaluate for a primary bone marrow disorder. Biopsy demonstrated macronormoblastic erythroid maturation and dysplastic forms, in addition to dysplastic megakaryocytes as well as hypogranular and hypolobated neutrophils, suspicious for underlying myelodysplastic syndrome (MDS).

Diagnosis of PNH with possible MDS was established. The patient started on folate supplementation in the setting of ongoing hemolysis and received the meningococcal vaccine in anticipation of starting eculizumab. His counts and renal function remained stable throughout his hospitalization, and he was discharged with close hematology follow-up with plan to start eculizumab 2 weeks after meningococcal vaccination.

Discussion

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired disorder of clonal hematopoietic stem cells (HSC) that presents with non-immune mediated hemolytic anemia, thrombosis, smooth muscle dystonias, and bone marrow failure.[1,2] The annual incidence of PNH is estimated at 0.35 per 100,000 people, with a prevalence rate of 3.81 per 100,000 people.[3] The reported age range at diagnosis is broad, though most commonly diagnosed between 30-59 years. No significant gender predilection has been reported with PNH.[1] While treatment with complement inhibition therapy and bone marrow transplantation have greatly improved prognosis, the 10-year PNH survival rates from date of diagnosis is 68.4%, versus 85.8% amongst age matched controls.[4]

The pathophysiology of PNH involves an acquired somatic mutation in the X-linked phosphatidylinositol glycan class A (PIG-A) in one or more long-lasting multipotent HSC, followed

by subsequent expansion of these HSC clones.[1,2,5] The PIG-A gene product is required for the biosynthesis of glycosyl phosphatidylinositol (GPI), which is necessary for anchoring proteins to the cell membrane.[5] This mutation leads to a severe under expression of GPI-anchored proteins, specifically the complement inhibitory proteins CD55 and CD59, which in turn causes chronic complement-mediated intravascular hemolysis of GPI-deficient erythrocytes due to a continuous state of complement activation.[2,5]

Free hemoglobin is released as a result of the intravascular hemolysis, causing rapid depletion of nitric oxide (NO), which is crucial in regulation of smooth muscle tone and vasodilation.[6] NO depletion causes smooth muscle dystonias which lead to dysphagia, esophageal spasm, abdominal pain, and erectile dysfunction, as well as arterial vasoconstriction which can contribute to renal failure and pulmonary hypertension.[5,6] NO depletion can also lead to platelet activation and aggregation, which, along with other factors, predisposes to thrombophilia.[2] Thrombosis is a significant cause of morbidity and mortality and occurs in up to 40% of PNH patients that are not on complement inhibition therapy.[5] Venous thromboses are most commonly seen in the hepatic vein (Budd-Chiari syndrome), followed by the intraabdominal and cerebral veins.[1,2]

The clinical presentation in PNH is primarily related to hemolytic anemia, bone marrow failure, and thrombophilia.[7] Symptoms of anemia (35% of patients) and hemoglobinuria (26% of patients) are the most common presenting features, though patients often present with non-specific symptoms such as fatigue, abdominal pain, or unexplained thromboses. Hemolysis and subsequent hemoglobinuria may be precipitated by acute stressors such as infection, trauma, or surgery.[7]

As in our patient, laboratory evaluation typically reveals classic features of hemolysis, with elevated bilirubin, LDH, and reticulocyte count in the setting of anemia with low haptoglobin. Gross hemoglobinuria may be present as well. Diagnosis is confirmed with peripheral blood flow cytometry demonstrating the absence of CD55 and CD59 on at least 2 blood cell lineages.[1,2,8] While not required for the diagnosis of PNH, bone marrow biopsy should also be performed in patients with severe pancytopenia in order to appropriately classify disease and evaluate for underlying bone marrow disorders.[1] The different categories of PNH are 1) classical PNH, with evidence of PNH in the absence of an additional bone marrow disorder; 2) PNH in the setting of a primary BM disorder such as aplastic anemia or myelodysplastic syndrome (MDS); and 3) subclinical PNH, with abnormalities on flow cytometry but no clinical or laboratory signs of hemolysis.[2,8]

The treatment of PNH is multifaceted, focusing on managing hemolysis, preventing thrombotic events, and addressing bone marrow failure. The mainstay of therapy is using terminal complement inhibitors such as eculizumab and ravulizumab. These are monoclonal antibodies that bind complement C5 and prevent formation of the membrane attack complex. The downregulation of complement activation significantly reduces the degree of intravascular hemolysis and thrombosis, in turn improving survival in PNH.[1,2] However, terminal complement inhibition can predispose to life-threatening infections, specifically Neisserial meningitis. Patients with PNH should receive a quadrivalent meningococcal vaccine at least 2 weeks prior to their first dose.[8] Treatment with complement inhibitors has also been shown to decrease the risk of thrombosis by up to 80%. Thus, while thromboembolism was the leading cause of death in patients with PNH prior to the introduction of eculizumab, primary thromboprophylaxis for such patients is no longer recommended.[8,9]

Despite remarkable advances in the care of PNH patients, allogeneic stem cell transplantation (ASCT) is sometimes necessary for with eculizumab therapy failure, severe cytopenias, or an underlying bone marrow disease such as MDS or aplastic anemia.[8] Due to the high risk of transplant-related complications and mortality, ASCT is considered on a case-by-case basis.

This patient demonstrates many of the classic epidemiologic, clinical, and laboratory findings of PNH, as well as the treatment options that have transformed management and prognosis. Further, it exemplifies the importance of a thorough history, physical exam, and laboratory evaluation to obtain an accurate diagnosis so that appropriate prompt treatment can be initiated to avoid complications of PNH and improve patients' quality of life.

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