CLINICAL VIGNETTE

A Case of Paroxysmal Cold Hemoglobinuria

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Introduction

Paroxsymal cold hemoglobinuria (PCH) is a rare condition characterized by hemolytic anemia and hemoglobinuria. It is caused by autoimmune polyclonal immunoglobulin G (IgG) reacting with red blood cells (RBCs) during cold temperatures.[1] The infrequency with which it is encountered makes recognizing and managing PCH a diagnostic and therapeutic challenge.

Case Description

A 65-year-old male with a history of non-insulin dependent diabetes mellitus type 2 presented to the emergency room with a chief complaint of "blood in my urine" as well as generalized fatigue for 3 days. The patient was in his usual state of health until 10 days prior to presentation when he developed signs and symptoms consistent with a viral upper respiratory infection, including fevers, chills, nasal congestion, productive cough, and sore throat. The patient's upper respiratory symptoms quickly improved, but approximately 3 days prior to presentation, he began to notice dark urine, which eventually appeared "bloody." The patient noted a similar appearance of his urine several years ago, but this episode was self-limiting and resolved in 1-2 days. The patient's current symptoms continued for more than 3 days. He also developed fatigue and presyncopal symptoms, prompting him to go to the emergency department for evaluation.

Physical examination was notable for skin pallor but was otherwise unremarkable. Urine was red in color. Laboratory studies revealed an elevated creatinine (1.7 mg/dL; reference range: 0.6-1.3 mg/dL) suggesting acute kidney injury, as well as anemia (hematocrit 17.2%; reference range 38.5-52%) with elevated unconjugated bilirubin and lactate dehydrogenase (LDH) levels suggesting hemolysis. Urinanalysis showed 3+ blood but only 5 RBCs on microscopy. Urine hemoglobin was positive. Peripheral blood smear revealed multiple spherocytes and erythrophagocytosis by neutrophils. The direct Coombs test was positive using anti-C3. Donath-Landsteiner assay was positive. A diagnosis of PCH was made.

The patient was initially treated with conservative measures including warming the body with blankets and using warm intravenous fluids and blood products. Worsening anemia

(Figure 1) despite transfusion prompted initiation of prednisone on hospital day 2, followed by rituximab infusion on hospital day 3 and intravenous immunoglobulins on hospital day 8. The patient's hematocrit stabilized on hospital day 15 with no further transfusion requirements. His acute kidney injury was attributed to pigment-induced acute tubular necrosis. This was managed with intravenous fluids using sodium bicarbonate to alkalinize the urine and treatment of the underlying hemolysis. His creatinine peaked on hospital day 9 to 2.7 mg/dL, and then improved towards baseline.

Discussion

PCH is a type of autoimmune hemolytic anemia caused by cold-reacting polyclonal IgG autoantibodies. As blood circulates through the distal extremities and becomes exposed to cold temperatures, these autoantibodies bind to various antigens (particularly the P-antigen) on the RBC membrane and begin fixing complement proteins.[1,2] Later as the blood returns to the body's core and the temperature increases, the complement cascade is completed and complement-mediated hemolysis ensues. The resulting intravascular hemolysis may lead to hemoglobinuria. The disease was first described in the mid-1800s, but the pathophysiology was better understood in the early 1900s when Julius Donath and Karl Landsteiner demonstrated that hemoglobuinuria was the result of intravascular hemolysis.[3] They described a procedure (known today as the Donath-Landsteiner assay), which proved that antibody binding is temperature-dependent and that complement-binding is necessary for hemolysis.[3]

PCH is a rare diagnosis. Sokol et al [2,4,5] estimates the annual incidence of PCH at 0.4 cases per 100,000 people. It accounts for about 5% of all adult hemolytic anemias.[2] PCH is more common in young children (median age 5 years); however, the condition can affect patients of all ages with one study reporting cases in patients with ages that ranged from 1 to 82 years.[6] PCH may occur following a variety of infectious illnesses such as secondary and tertiary syphilis, mumps, measles, varicella zoster, Epstein-Barr virus, cytomegalovirus, influenza, parvovirus B19, coxsackievirus A9, adenovirus, *Haemophilus influenza*, *Mycoplasma pneumoniae*, *Klebsiella pneumonia*, and visceral leishmaniasis.[1,7,8] PCH has also been associated with hematologic and solid organ malignancies such as chronic lymphocytic leukemia, diffuse large B-cell lymphoma, and small cell lung cancer.[1,2] Evaluation into the

underlying cause should be explored for every patient with a diagnosis of PCH, especially when a chronic infection or underlying malignancy are of concern.

The typical presentation is that of a patient with sudden onset of fever, rigors, and chills followed by red to brown urine within minutes to a few hours after exposure to cold temperature.[2] These symptoms signify the process of intravascular hemolysis and resulting hemoglobinuria. Additional symptoms may include abdominal cramping, back and leg pain, pallor, headaches, nausea, vomiting, diarrhea, esophageal spasm, Raynaud's phenomenon, and urticaria.[2] Transient hepatomegaly with jaundice and splenomegaly may also occur.[2] Symptoms may be preceded by an upper respiratory infection 1-2 weeks prior to presentation.[1]

Patients can have severe and rapidly progressive anemia with hemoglobin levels at hospital admission ranging from 2.5 to 12.5 g/dL based on a series of published case reports.[1,9] Peripheral blood smears may reveal abnormal RBC morphologies, including spherocytes, anisocytosis, poikilocytosis, fragmented RBCs, basophilic stippling, polychromatophilia, autoagglutination, and erythrophagocytosis by neutrophils and monocytes.[1,9] Additional laboratory abnormalities that signify hemolysis may include increased LDH, indirect bilirubinemia, decreased haptoglobin, free plasma hemoglobin, and hemoglobinuria.[1,10] Low serum complement levels (C2, C3, C4) may also be seen.[2] The direct Coombs test is positive for complement and negative for IgG. Acute kidney injury from pigment-induced acute tubular necrosis may result in elevated blood urea nitrogen and creatinine levels.[1,10]

The Donath-Landsteiner assay can be used to support the diagnosis of PCH.[1,11] In this test, three samples of the patient's serum is incubated with washed group O-cells that express the P-antigen and fresh normal serum (a source of complement proteins).[11] One sample is incubated at 0-4°C, a second at 37°C, and a third at 0-4°C initially and then rewarmed to 37°C.[11] The test is positive if hemolysis occurs only in the specimen group that is incubated first at 0-4°C and then rewarmed to 37°C, but not the other two groups.[11] This diagnostic test is not very sensitive, and the entire clinical picture should be considered. A more sensitive test involves incubating radiolabeled monoclonal anti-IgG antibodies with the patient's serum and donor RBCs at 4°C.[2] The level of radioactivity on separated RBCs in this sample will be elevated in PCH compared to a control sample incubated at 37°C.[2] This assay, however, is not generally available at most institutions.

Treatment is largely supportive and the prognosis is highly favorable.[1] Patients should be maintained in a warm environment and frequent assessment of blood counts should be performed as anemia may be sudden and severe. RBC transfusion may be necessary. P-antigen negative donor units are preferred but may be difficult to procure due to its rarity. Corticosteroids (at the equivalent dose of 1mg/kg of prednisone per day) may be given to help reduce antibody production and complement-mediated phagocytosis; however, data regarding the effectiveness of these drugs in the clinical setting are limited and difficult to evaluate given their transient effects on hemolysis.[1,7,12] Cyclophosphamide or azathioprine may be considered if corticosteroids fail to achieve remission.[7,13] The use of rituximab (an anti-CD20 antibody) and plasmapheresis have also been reported in limited case reports.[7,14,15] Intravenous immunoglobulin therapy is often used to treat autoimmune hemolytic anemia, but there are little data available concerning its use specifically for cold antibody autoimmune hemolytic anemias.[7] Splenectomy is not indicated in the treatment of PCH as the spleen has no role in the pathogenesis of hemolysis in this disease.[2] Data regarding the efficacy of eculizumab, a monoclonal antibody that targets complement component 5, is lacking, and it is therefore not routinely employed.[2] The most common non-hematologic complication in PCH is pigment-induced acute tubular necrosis which can be managed with hydration and possible alkalinization of the urine.[2]

Conclusion

This clinical vignette highlights many classic clinical, laboratory, and diagnostic features of PCH as well as its management. The patient presented with fatigue and hemoglobinuria, preceded by a viral upper respiratory infection 10 days prior to presentation, which suggests a post-infectious etiology to his disease pathophysiology. Laboratory studies demonstrated a significant hemolytic anemia and urinalysis revealed a discrepancy between the qualitative (3+ blood) and quantitative (only 5 RBCs on microscopy) assessment for RBCs in the urine, suggesting a diagnosis of hemoglobinuria. Additional features from the peripheral smear (which was notable for multiple spherocytes and erythrophagocytosis by neutrophils), a positive direct Coombs test for complement, and a positive Donath-Landsteiner assay supported a diagnosis of PCH. Along with supportive measures and RBC transfusion, the patient was treated with prednisone and rituximab, followed later in the hospitalization by IVIG with improvement and stabilization in his anemia. Furthermore, the patient's acute kidney injury – attributed to pigment-induced acute tubular necrosis from ongoing hemolysis – improved with treatment of the underlying hemolysis as well as hydration and alkalization of the urine using intravenous sodium bicarbonate.

Figures

FIGURE 1: Hematocrit and creatinine during the patient's hospitalization.
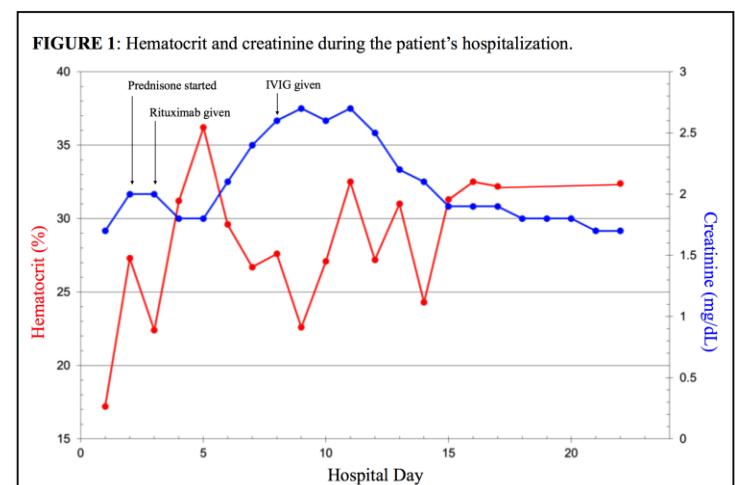
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