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Paroxysmal nocturnal hemoglobinuria: rare cause of acute renal failure

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ABSTRACT

Paroxysmal nocturnal hemoglobinuria is a rare acquired disease, characterized by hemolytic anemia, recurrent infections, cytopenias, and vascular thrombosis. It occurs by non-malignant clonal expansion of one or more hematopoietic stem cells that acquired somatic mutations in *PIG-A* gene linked to chromosome X. This mutation results in lower erythrocyte expression of CD55 and CD59 surface proteins and consequently increased susceptibility to the complement system. The renal involvement is generally benign, resulting in mild impairment in urinary concentration. Acute renal failure requiring hemodialytic support accompanying PNH is rarely observed. The authors report a case of a 37-year-old male who presented with bicytopenia (hemolytic anemia and thrombocytopenia) associated with acute renal failure requiring dialysis. Diagnosis was challenging because of the rarity and unfamiliarity with this entity, but was confirmed by flow cytometry. In the course of the disease, acute pyelonephritis with multiple renal abscesses was diagnosed requiring prolonged antibiotic therapy. Patient outcome was favorable after the control of hemolysis and the infection treatment.

Keywords: Hemoglobinuria, Paroxysmal; Anemia, Hemolytic; Acute kidney injury; Flow cytometry.

CASE REPORT

A 37-year-old male patient, a farmer, born and resident in a small town of northeast Brazil, sought medical attention complaining of recurrent episodes of gross hematuria alternating with brownish urine for 5 months. This symptom worsened 2 weeks ago, becoming continuous. Concurrently, he complained of asthenia, abdominal pain, nausea, and vomiting, which prevented him from exercising his daily activities. He denied the use of toxic substances or accidents with poisonous animals. The admission physical examination showed a well-looking patient, but pale, anicteric, and afebrile; no edema was evidenced. Pulse rate = 80 beats per minute, blood pressure = 130/70 mm Hg, respiratory rate = 18 breaths per minute, room air oximetry = 97%. Cardiac, pulmonary, and abdominal examination was normal. The initial laboratory tests showed the presence of uremia (BUN = 197 mg/dL and creatinine = 25.9 mg/dL), hyperkalemia (potassium = 8.6 mEq/L) with electrocardiographic changes, and bicytopenia (anemia with hemoglobin = 6.5 g/dL and platelet

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count = 51,600/mm^3). The patient underwent hemodialysis, received packed blood red cells transfusion, and hyperkalemia was promptly treated. The urinary tract ultrasound was normal except for cortical enhanced echogenicity. Colored Doppler echography of the renal arteries and veins were normal. Proceeding the lab workup, urinalysis showed 76,000 leukocytes/mL, 93,000 erythrocytes/mL, but casts were absent; 24-hours proteinuria was 411 mg in a 2475 mL volume. Urine culture failed to show any bacterial growth. Serum total protein was 5.5 g/dL, albumin 3.2 g/dL and globulins = 2.3 g/dL. Hepatitis B antigen (HBsAg), antibodies to HIV, HCV and HBsAg, as well as antinuclear antibody (ANA) were negative; complement fractions C3 and C4 were normal. The search for schistocytes as well as direct and indirect Coombs was negative. Total bilirubin was normal but the lactate dehydrogenase was elevated (LDH = 940 U/L), reticulocytes count was reduced (0.3% and absolute = 8310/mm^3) and myelogram showed slight hypercellularity with no atypical elements. Renal biopsy was not performed due to thrombocytopenia.

The patient was discharged and referred to chronic hemodialysis treatment and a follow up in an outpatient clinic.

One month later, the patient returned to the emergency department complaining of back pain and fever. Urinalysis showed marked leukocyturia and urine culture showed growth of more than 10^5 colony-forming units of *Escherichia coli,* and blood culture was positive for the same pathogen. Diagnosis of acute pyelonephritis was done and ceftazidime was initiated and lasted 14 days. On this occasion, BUN = 40 mg/dL, creatinine = 3.2 mg/dL, hemoglobin 7.7 g/dL, hematocrit = 22.8%; leukocytes = 10.100/mm^3 and platelets = 50,400/mm^3. Approximately 3 days after the end of antimicrobial therapy, the patient presented with asthenia, chills, and anorexia, progressing to right flank pain, fever (38 ˚C), and gross hematuria. Although he had already lost 8 kg since the very beginning of symptoms, the patient still presented well-looking, anicteric but pale. Blood pressure was 88 × 62 mm Hg, pulse rate = 90 beats per minute, respiratory rate = 18 breaths per minute. Examination of the heart and lung remained unchanged, but costovertebral angle tenderness was detected on the right. The computed angiotomography of the abdomen showed signs of pyelonephritis in the right kidney with multiple small abscesses, homogeneous hepatomegaly, but no signs of renal arterial or venous thrombosis. New antibiotic regimen with cefepime and vancomycin was started. A new laboratory workup disclosed the recovery of renal function (BUN = 21 mg/dL and creatinine = 1.2 mg/dL) allowing the removal of the temporary dialysis catheter. Reviewing the whole case the diagnosis of paroxysmal nocturnal hemoglobinuria (PNH) was considered. Flow cytometry showed a CD55 negativity in 58% of granulocytes, CD59 negativity in 65% of granulocytes and CD14 negativity in 56,4% of monocytes. Red blood cells failed to express CD55 in 17,8% of cells and 12,3% of cells for CD59. Red blood cells results should be interpreted with caution, because the cytometry was undertaken after hemotransfusion. These results were consistent with the diagnosis of paroxysmal nocturnal hemoglobinuria (PNH). The patient received a packed red blood cells transfusion and 30 mg of prednisone daily aiming at hemolysis control. Joint evaluation with the urologist ruled out surgical intervention, opting for conservative treatment for 6 weeks. The patient presented a satisfactory outcome, weight gain, and fever defervescence. He was again discharged and was prescribed warfarin and folic acid.

DISCUSSION

PNH is a rare hemolytic anemia, caused by non-malignant clonal expansion of one or more hematopoietic stem cells that have acquired somatic mutations in the *PIG-A* gene linked to chromosome X. These mutations result in a defect of synthesizing glycosylphosphatidylinositol (GPI) anchors, and thus, several proteins with specific functions, typically anchored by GPI on the cell surface, exhibit partial or complete absence. Among these are the CD55 (decay accelerating factor) and CD59 (membrane inhibitor of reactive lysis) that play an important role in regulating the activation of the complement system. In patients with PNH, red blood cell clone that are CD55 and CD59 deficient are sensitive to the action of complement, thus subjected to chronic intravascular hemolysis.[1]

The main clinical manifestations of PNH are related to abnormalities in hematopoietic function including hemolytic anemia, hypercoagulability, bone marrow aplasia or hypoplasia, and progression to myelodysplasia and/or acute leukemia. Recurrent infections are also described.[1,2] Renal lesions are usually benign and related to chronic hemosiderin deposition in the renal tubules.[3] The occurrence of acute and chronic kidney injury are observed in recurrent hemolysis as observed in PNH.

The initial clinical presentation, including asthenia, nausea, vomiting and abdominal pain, was initially interpreted as resulting from anemia and uremia. The investigation of anemia showed elevated LDH compatible with hemolysis. Other findings, which could reinforce the diagnosis of hemolysis, were not present, like hyperbilirubinemia and reticulocytosis. Besides anemia, the patient developed thrombocytopenia and the reduced reticulocyte count pointed towards relative bone marrow failure.

Common causes of renal failure, like diabetes and hypertension, and other such infections (HIV, hepatitis B and C), systemic lupus erythematosus, drug toxicity, and venomous animal accidents were ruled out. The absence of schizocytes excluded the possibility of hemolytic uremic syndrome and thrombotic thrombocytopenic purpura. Autoimmune hemolytic anemia was eliminated because the negative result for Coombs test. Kidney biopsy was not undertaken because of the thrombocytopenia. Initially, the patient was misdiagnosed with chronic kidney disease of unknown etiology and treated with hemodialysis.

As the renal function recovered after a few sessions of hemodialysis, the case was reviewed. The association of paroxysmal reddish or brownish urine suggestive of hemoglobinuria, hemolytic anemia, abdominal pain and acute renal failure, raised the hypothesis of PNH, and prednisone was administered. Although there is no consensus on the use of corticosteroids in PNH, prednisone can assist in the reduction of hemolytic complement activation. Although the patient already presented a clinical picture compatible with PNH since the first hospitalization, the delay in accurate diagnosis was due to its rarity and the unfamiliarity with this entity.

Flow cytometry to study the expression of CD55 and CD59 is the choice test because of its high sensitivity and specificity in confirming the diagnosis of PNH. Ham's test and the sucrose test, which have been used in the past, are currently replaced by cytometry.[1,2]

The reduction of hematopoiesis occurs in all patients with PNH and, in the patient of this report, was demonstrated by the presence of thrombocytopenia and reticulocytopenia.

The renal lesion is usually benign and is secondary to hemosiderin deposition in the proximal renal tubules causing mild dysfunction recognized by impaired urinary concentration. Acute kidney injury with PNH patients who recovered renal function after a period of dialysis has been described. The renal biopsy of these cases shows acute tubular necrosis and intense deposition of hemosiderin in renal tubular cells. Although we have not performed a renal biopsy, we believe the patient had tubular injury secondary to massive hemolysis.[3-6]

Another important factor was the treatment of acute pyelonephritis and multiple renal abscesses. Recurrent infections also occur frequently in PNH and deserve special attention. In the case reported here, the infection treatment was responsible for the hemolytic control as well as general clinical improvement.

Regarding thrombophilia, PNH has a predilection for intra-abdominal venous thrombosis, especially the hepatic veins. In this case report, the renal venous and arterial thrombosis was ruled out as the cause of renal failure. Thromboembolism is a leading cause of morbidity and mortality associated with PNH. It is estimated that approximately 40% of patients with PNH submit any thrombotic event during life and those with a larger clone are at higher risk for thromboembolism. Thus, patients with PNH and granulocytes clone greater than 50% that do not have contraindications for chronic anticoagulation should receive warfarin for thromboembolic disease prophylaxis.[1,7]

We must consider that the only curative treatment available for PNH is hematopoietic stem cells transplantation.[1,2,8] All other modalities are available for the control of clinical manifestations. Currently, transplantation is indicated only in patients with bone marrow failure syndromes with severe cytopenias because of their considerable morbidity and mortality. Eculizumab, another available treatment, is a monoclonal antibody that binds to complement component C5 and inhibits complement terminal activation.[1,2,9] This treatment is indicated in selected patients, namely: a) those that depend on frequent hemo transfusion; b) those who have refractory symptoms (fatigue, pain, and paroxysmal intense and frequent target organ damage); and c) for those who presented with thrombosis of unknown cause, despite the PNH clone size. Other immunosuppressive schemes (cyclosporine and anti-thymocyte globulin) may also be considered for patients with aplastic anemia or myelodysplasia related to the HPN.[10,11]

This report illustrates a case of acute kidney injury primarily considered to be of unknown etiology, but when it is associated with hematuria, hemolytic

anemia, and/or other cytopenias, the possibility of PNH should always be considered.

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