

Case Report

Paroxysmal Nocturnal Hemoglobinuria Presenting with Renal Vein Thrombosis and Pulmonary Embolism

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ABSTRACT

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare hematological disorder. It predisposes to thrombosis at unusual sites. Its long-term prognosis can be complicated with aplastic anemia, myelodysplastic syndrome or leukemia. We present a female patient who was admitted with a tentative diagnosis of pulmonary embolism. She presented initially a diagnostic

dilemma until she developed renal vein thrombosis a few days after admission. She was then investigated for thrombophilia. Ham's test was positive twice. She was successfully managed with anticoagulation that was maintained for life. We discuss the underlying pathophysiology, clinical manifestations and treatment of PNH.

KEYWORDS: paroxysmal nocturnal hemoglobinuria, pulmonary embolism, renal vein thrombosis

INTRODUCTION

Paroxysmal nocturnal hemoglobinuria (PNH) is a clonal, hematopoietic stem cell disorder that results in the formation of defective red cells, white cells, and platelets. It was one of the first hematological disorders given a clear clinical description because of definite symptoms: dark urine at night that was distinctive and easily observed. The pigment was confirmed to be hemoglobin, due to hemolysis of red cells.

The clinical manifestations are mainly related to hemolytic anemia, hypercoagulable state, and bone marrow aplasia. Progression to myelodysplastic syndrome or acute leukemia can also occur^[1]. Diagnosis requires high level of clinical suspicion. It is confirmed by Ham's test, but more recently confirmation can be done simply by analyzing the GPI-anchored proteins CD55 (DAF) and CD59 on hematopoietic cells using monoclonal antibodies and flow cytometry^[2].

In this case report, we describe a female patient who presented with renal vein thrombosis and pulmonary embolism as the first manifestations of PNH. We describe the clinical presentation, diagnosis and treatment of PNH.

CASE PRESENTATION

A 56-year-old Kuwaiti female was admitted to the medical department in March 2001 with a two-week history of progressive shortness of breath, right loin pain and hematuria. She also gave history of productive cough with whitish sputum and low-grade fever. She had no previous medical or surgical illnesses, and was not on any current

medication, including oral contraceptive pills. On physical examination, she was pale and the temperature was 37.8 °C. She was tachypneic with a respiratory rate of 20/minute. Her pulse was 100 per minute, regular and the blood pressure was 160/90 mm Hg.

Cardiovascular, respiratory and neurological examination was unremarkable. Abdominal examination revealed right loin tenderness. There were no signs of deep vein thrombosis in the lower limbs.

Laboratory investigations revealed a Hb of 11.7 gm/l with MCV 78.5 fl, MCH 26.6 pg, platelets 34 x 10⁹/L, and WBC was 13.9 x 10⁹/L. Reticulocytes count was 2.7%, ESR 55 mm in the 1st hour, urea, creatinine and electrolytes were all normal. PT and APTT were normal. Serum Iron 8.5 µmol/L, Transferrin 2.37 gm/L, Transferrin saturation 14.27%, LDH 4.95 U/L, serum haptoglobin 2.16 g/l. Stool occult blood was negative. Urine routine microscopy showed excess RBC and 2++ proteinuria. Repeated urine cultures were negative. Arterial blood gases showed pH 7.5, pCO₂ 3.81 Kpa, PO₂ 6.1 Kpa, O₂ saturation 86.4%. Chest X-ray and abdominal ultrasound were normal. ECG showed S₁, Q₃, T₃, and inverted T wave in the anteroseptal leads.

Tc-99m MAAperfusion lung scan showed multiple large perfusion defects in both lung field. Lower limbs Doppler study was normal. In the view of her condition, she was started on full anticoagulation with intravenous heparin infusion. Bone marrow aspiration to evaluate thrombocytopenia was normocellular and normoblastic with depleted iron stores.

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She was prescribed prednisolone 50 mg orally, and intravenous immunoglobulin 50 g daily for four days. Because of the pulmonary embolism associated with hematuria and loin pain, she was investigated for renal vein thrombosis. Abdominal US Doppler showed minimal fullness of the right renal collecting system. A urologist evaluated her and advised cystoscopy, which was normal. A 24-hour urine for cytology was normal. IVU study demonstrated a faint nephrogram of the right kidney and mildly enlarged right kidney with mild dilatation of the collecting system. CT scan kidneys showed right renal vein thrombosis with poorly functioning right kidney.

Due to the combined presentation of both renal vein thrombosis and pulmonary embolism, she was investigated for thrombophilia. Protein C and S were within normal range. Anti thrombin III level was 111% (84-123), anticardiolipin IgG 4 GPL U/ml ($N < 13.3$ GPL U/ml), anticardiolipin IgM 0.9 MPL U/ml ($N < 9.8$ MPLU / ml), Anti dsDNA6 AU/ml ($N < 26$ AU/ml). Leukocyte alkaline phosphatase score 115 ($N 20-146$). Ham acid hemolysis test was positive (repeated twice). This confirmed the diagnosis of paroxysmal nocturnal hemoglobinuria.

She had uneventful recovery. In addition, her platelet count had steadily increased to $218 \times 10^9/L$. Her initial thrombocytopenia could also be explained on the basis of consumptive coagulopathy. She was discharged on oral coumadin 5 mg daily, folic acid, ferrous sulphate and a tapering dose of prednisolone. We have elected to anticoagulate her indefinitely since she is prone to recurrent thrombosis as well as the seriousness of her initial presentation.

DISCUSSION

This is the first case of reported PNH, to our knowledge to present with renal vein thrombosis. In spite of the absence of hemolysis, which is a cardinal sign of PNH, the diagnosis was suspected due to the unusual combination of thrombocytopenia and thrombosis at unusual sites. The major clinical manifestations of PNH are paroxysmal hemolytic anemia, venous thrombosis, and diminished hematopoiesis, which can lead to cytopenias or aplastic anemia^[1]. The hemolysis is mediated by complement activation. Nocturnal hemolysis has been attributed to the intestinal absorption of lipopolysaccharide, a potent activator of complement^[3]. Hemoglobinuria and hemosiderinuria are present and may eventually lead to iron deficiency anemia and renal failure^[4]. Complements can be activated by viral or bacterial infection. Tendency for thrombosis is markedly increased in PNH. It is mainly at unusual sites, such as hepatic vein^[5], portal or splenic veins, cerebral veins^[6] or other veins.

Most patients with PNH have evidence of diminished hematopoiesis e.g., aplastic anemia, granulocytopenia or thrombocytopenia at some time during the course of the disease. These changes are due to deficient production rather than reduced survival^[7]. Conversely, patient who presents with aplastic anemia may develop PNH^[8].

Because PNH is a disorder of stem cell, it may have other manifestations of stem cell disorder. The incidence of myelodysplastic disorder has ranged from 5-9%^[1], whereas acute leukemia had a reported incidence of less than 1%^[1], most commonly acute myelogenous leukemia. Infection is surprisingly rare in PNH in spite of lymphocyte abnormalities.

The pathogenesis of PNH is now well documented. Molecular studies revealed the absence of GPI anchor, which binds several proteins to the cell membrane, due to an abnormality in the PIG-A gene^[9]. Such proteins, which include leukocyte alkaline phosphatase, acetyl cholinesterase, decay accelerating factor-DAF (also called CD55)^[10] membrane, attack complex inhibitory factor (also known as CD59)^[11], and many other deficient proteins of unknown significance. GPI anchor consists of two molecules, phosphatidylinositol (PI) that is inserted into the cell plasma membrane, and a molecule of ethanolamine (ETN) that binds to the protein molecule^[9].

Both CD55 and CD59 protect red cells from the lytic action of activated complements. Deficiency of CD55 and CD59 lead to the increased sensitivity of red cells and platelets to complement, with resultant hemolysis and thrombosis, respectively.

Diagnosis is confirmed by the Ham acid hemolysis test^[12]. It is almost never positive in any other disease or negative in PNH unless there is an operator error. Sucrose test is less sensitive and specific. Recently, the expression of GPI anchored proteins on hematopoietic cells can be analyzed by a simple method using monoclonal antibodies and flow cytometry with increased sensitivity and specificity^[2].

Treatment of PNH has been largely empirical. Recent understanding of the molecular aspect may eventually lead to more rational therapy. Hemolysis is treated with blood transfusion if clinically required. Supportive treatments include folic acid and iron supplement. The urinary loss of iron is significant because of hemosiderinuria. Prednisone has a rapid beneficial in patients with hemolysis by diminishing complement activation^[13].

Thrombosis is managed similar to other venous thrombosis occurring in other setting. Prednisone is also used, since complement activation probably occurs with thrombosis in PNH. For recurrent episodes of thrombosis, they are generally

managed as other patients with a hypercoagulable state. Bone marrow transplantation^[14] may be indicated in some patients, mainly those with severe life threatening disease or early in the course of the disease in children. Impaired hematopoiesis but not hemolysis, in PNH, may respond to cyclosporine or antithymocyte globulin^[15,16]. With the cloning of the PNH gene (PIG-A), gene therapy may be possible in the future^[17].

In conclusion, PNH is a rare cause of intravascular hemolysis, thrombosis and bone marrow suppression. Diagnosis is easy by using Ham's test, and more recently with monoclonal antibodies against GPI anchored proteins. Treatment is mainly supportive. Selected patients may benefit from bone marrow transplantation.

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