

Case Report

PNH is a debilitating, fatal but treatable disease: same disease, different clinical presentations

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Abstract: Paroxysmal nocturnal hemoglobinuria (PNH) is a disease characterized by chronic persistent hemolysis, multi-organ damage and eventually multiple organ failure. PNH develops as a result of increased sensitivity to complement due to an acquired deficiency of certain glycosylphosphatidylinositol (GPI)-linked proteins. The clinical presentation of PNH varies greatly from one patient to another. We present three cases of PNH with different clinical presentations to illustrate the debilitating nature of the disease, possible fatal outcomes, and the need to timely diagnosis and targeted therapy. These cases also underline the need for increased awareness of PNH among relevant healthcare specialties. PNH should be considered as a differential diagnosis in patients with unexplained abdominal pain, dyspnea, renal failure, thrombosis and non-immune hemolytic anemia.

Keywords: Paroxysmal nocturnal hemoglobinuria (PNH), thrombosis, abdominal pain, eculizumab

Introduction

Paroxysmal nocturnal hemoglobinuria (PNH) is a chronic hemolytic disease characterized by a mutation in the phosphatidylinositol glycan class A (PIG-A) gene that results in the partial or complete absence of certain glycosylphosphatidylinositol (GPI)-linked proteins [1]. This mutation results in uncontrolled complement-mediated hemolysis and platelet activation due to the absence of CD55 (DAF: decay accelerating factor) and CD59 (MIRL; membrane inhibitor of reactive lysis) proteins, which are normally linked to blood cell membranes by the GPI anchor protein [2].

The clinical manifestations of PNH are diverse at initial presentation, and this clinical heterogeneity persists through the course of the disease. However, clinical signs and symptoms that are commonly seen include anemia, dyspnea, abdominal pain, thrombosis, end-organ damage, and bone marrow failure with cytopenias [3]. In particular, thromboembolism is one of the most common causes of mortality and morbidity in PNH [4]. Other causes of death include hemorrhage, renal failure, cardiac failure, infections, myelodysplastic syndrome or

aplastic anemia [5, 6]. Even in the absence of symptoms and diagnosis, ongoing hemolysis can be destructive and the consequences may be sudden and life threatening.

Historically, therapy for PNH was mainly restricted to the treatment and prevention of complications (e.g., red blood cell transfusions for anemia), but did not address ongoing hemolysis and related symptoms [3]. Eculizumab is a humanized monoclonal antibody that blocks the activation of terminal complement at C5 and prevents the formation of C5a and the terminal complement complex, C5b-9 [7]. In clinical trials, this agent has been shown to substantially reduce intravascular hemolysis and abrogate the need for blood transfusions in most patients with PNH [8-11]. In spite of rare spontaneous remissions, a benign course with controlled hemolysis can usually be observed in symptomatic patients during treatment with eculizumab [12].

Three cases with different presentations and courses of PNH was reported to illustrate the debilitating and sometimes fatal nature of the disease and variability of clinical presentation and outcomes.

Case 1: Debilitating PNH presenting with chronic anemia and abdominal signs

A 58 year-old female was admitted to the emergency department due to nausea, vomiting, and abdominal pain. On physical examination she had rebound and defense, and laboratory tests revealed anemia (hemoglobin, 9.0 g/dL), and thrombocytopenia (platelet count, 75,000/mm³). Aspartate aminotransferase (AST) and potassium levels could not be measured due to hemolysis. Mesenteric ischemia was observed at abdominal computed tomography (CT), and ileum resection and end-to-end anastomosis were performed. There was no documented predisposition to thrombophilia.

The patient was transferred to the hematology department due to her anemia and thrombocytopenia. Her medical history revealed chronic anemia that was unresponsive to iron replacement therapy and was compatible with non-immune hemolytic anemia. Plasma lactate dehydrogenase (LDH) level was 1075 IU (range 135-214), haptoglobin, <20 mg/dl, and indirect bilirubin was 1 mg/dl. PNH was suggested as diagnosis based on the chronic hemolytic anemia with thrombosis, and subsequent testing revealed a PNH clone of 60% in granulocytes and 35% in monocytes.

Eculizumab treatment was initiated, and hemolysis was controlled; hemoglobin elevated to 12.6 g/dL and plasma LDH decreased to 270 IU. No other thrombotic episodes were observed, and the patient has continued on maintenance therapy with eculizumab without any further symptoms or hemolysis.

Case 2: Fatal PNH associated with Budd-Chiari syndrome

A 61 year-old female was admitted to the emergency department due to progressive icterus, fatigue and poor performance status. Splenomegaly, abdominal pain and icterus were documented with physical examination. Laboratory tests revealed high bilirubin (total bilirubin, 50.9 mg/dL; indirect bilirubin, 26.7 mg/dL), and LDH (2904 IU) levels and anemia (hemoglobin, 6.7 g/dL; hematocrit, 19.9%; haptoglobin, <20 mg/dL) with normal alanine aminotransferase (ALT), alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT) levels. Potassium and AST could not be measured due to hemolysis. Multiple stones were found in the gall bladder, and abdominal ultra-

sonography revealed splenomegaly. Magnetic resonance cholangiography was normal without evidence of choledocolithiasis.

The patient was diagnosed with hemolytic anemia with probable Budd-Chiari syndrome. However, Budd-Chiari syndrome could not be definitively documented because the patient deteriorated rapidly and died due to progressive hepatic failure. Post-mortem testing revealed a PNH clone size of 27% in erythrocytes (types 2 and 3). Although autopsy could not be performed due to religious reasons, the possible cause of death was recorded as thrombosis and liver failure due to PNH.

Case 3: Treatment of PNH in a patient with mild anemia and pulmonary hypertension

A 48-year-old male was admitted to hospital with mild fatigue, and was initially diagnosed with iron deficiency anemia and Iron replacement therapy was initiated. After 2 months anemia persisted and accompanied by leukopenia and thrombocytopenia. Anemia was compatible with Coombs-negative hemolytic anemia (haptoglobin <20 mg/dL; LDH, 1680 IU; reticulocytes, 5.6%; and spherocytes remarkable on a peripheral blood smear). Hypercellular bone marrow with remarkable erythroid precursor cells was documented on bone marrow aspiration and biopsy. PNH was suggested as diagnosis on this basis, and further testing revealed PNH clone of 68% in granulocytes and 63% in monocytes. The patient had mild symptoms related to anemia, and echocardiography indicated mild pulmonary hypertension.

Eculizumab was initiated, and the patient's quality of life was measurably improved after 1 month of treatment. LDH level decreased to within the normal range by the second month, and hemoglobin increased to >13 g/dL by the fourth month of treatment.

Discussion

PNH is a clonal hematopoietic stem cell disease that is characterized by hemolysis, thrombosis and cytopenias, and has a diverse clinical presentation and disease course [5]. As a result, clinical outcomes can vary widely, as demonstrated in these three different cases [3]. Hemolysis can be ongoing even in the absence of overt symptoms, and chronic hemolysis and platelet activation cause susceptibility to destructive, sudden and potentially fatal

Variability in paroxysmal nocturnal hemoglobinuria

thrombosis affecting vital organs [3, 5]. Thrombosis causes 40-67% of deaths among PNH patient with a known etiology [4]. It also impairs quality of life and is associated with substantial morbidity [13].

Why some PNH patients have debilitating clinical symptoms and life-threatening complications such as thromboembolism cannot currently be clarified accurately. While the course of PNH has been shown to be mostly independent of the size of the PNH clone, a multivariate analysis has revealed that ongoing hemolysis and symptoms increased the risk of thromboembolism, and that a history of thromboembolism increases the risk of mortality [14]. Additionally, a multivariate analysis in a Chinese cohort revealed that age, history of thromboembolism, recurrent infections, and evolution to MDS or AML affect survival [15].

Although a relatively benign course can be observed, especially in patients treated with eculizumab as case 3, catastrophic and often fatal thrombosis can be the first sign of the disease, as observed in case 2. Chronic hemolysis results in free hemoglobin release, depletion of nitric oxide and vaso-occlusion that lead to morbidities such as fatigue, abdominal pain, transfusion dependence, dyspnea (due to pulmonary hypertension), dysphagia, and erectile dysfunction [5, 13]. Chronic hemolysis and platelet activation may also lead to chronic renal failure and dialysis, as well as recurrent nonfatal thrombotic events, as in case 1 where thrombosis resulted in severe morbidity and organ loss [6, 14].

The wide clinical spectrum of PNH, with a benign course at one end and severe morbidity and a high risk of mortality at the other, leads to highly variable clinical outcomes. One of the most important factors affecting the course of the disease is delay to diagnosis and initiation of targeted treatment. Case 3 illustrates that adverse outcomes can be prevented and a good quality of life can be achieved in patients who are diagnosed in sufficient time, and treated appropriately [10, 11].

In conclusion, the course of PNH is unpredictable, although some risk factors have been associated with a raised risk of morbidity and mortality. However, larger, prospective studies are required to confirm these findings. Increased awareness of the disease among clini-

cians should enable more rapid clinical recognition of suggestive signs and symptoms, enabling more effective diagnosis and earlier treatment with eculizumab.

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Variability in paroxysmal nocturnal hemoglobinuria

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