Case report on spontaneous remission in paroxysmal nocturnal hemoglobinuria: a rare phenomenon

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ABSTRACT

Background: Paroxysmal nocturnal hemoglobinuria (PNH) is a rare hematologic disorder characterized by a deficiency of GPI-anchored proteins in blood cells. It is associated with hemolysis, thromboembolic events, and bone marrow failure. Management includes complement inhibitors, anticoagulation, and stem cell transplantation. Spontaneous remission of PNH is rarely reported.

Case Presentation: A 28-year-old male initially diagnosed with aplastic anemia developed portal vein thrombosis and was subsequently diagnosed with PNH. Due to the unavailability of complement inhibitors, anticoagulation therapy and supportive care were employed. Splenectomy with splenorenal shunt was performed for chronic thrombosis and associated complications. The patient achieved spontaneous remission with normalized blood counts and diminished PNH clone.

Conclusion: Managing PNH in resource-limited settings presents challenges due to the unavailability of complement inhibitors. Spontaneous remission of PNH is rarely reported and needs further research. A multidisciplinary approach, accessibility to diagnostic tests, and advanced treatments will enhance PNH management in resource-limited settings.

Keywords: Aplastic anemia, paroxysmal nocturnal hemoglobinuria, portal vein thrombosis, splenectomy.

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Background

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare hematological disorder caused by a mutation in the PIG-A gene, leading to a deficiency of the glycosylphosphatidylinositol (GPI) anchor. This deficiency renders PNH cells sensitive to complement-mediated hemolysis [1]. PNH is classified into three types based on the degree of GPI deficiency in red blood cells. Type 1 exhibits normal expression, type 2 shows subtotal deficiency (less than 10%), and type 3 presents complete deficiency [2]. Its incidence is estimated at 1-10 cases per million in the population, affecting both adults and children with a median age of onset in the 30s [3].

There is no known racial or ethnic association with PNH, and the condition has been documented worldwide [4], specific data regarding PNH prevalence in Pakistan is lacking. The clinical presentation of PNH varies, with subtypes including subclinical PNH (evidence of PNH cells in the blood but no significant symptoms), hemolytic PNH (chronic hemolysis resulting in fatigue, jaundice, and dark-colored urine), and PNH with bone marrow failure (leading to recurrent infections, bleeding tendencies, and fatigue). PNH can occur de novo or in the presence of underlying bone marrow disorders, such as aplastic anemia (AA), myelodysplastic syndrome, or primary myelofibrosis [2].

Thrombosis is a significant concern, especially in resource-limited countries like Pakistan where access to comprehensive PNH management may be limited. Before the availability of complement inhibitors, thrombosis occurred in up to 40% of PNH patients. However, with the advent of treatment options, the risk of thrombosis in treated patients appears to be similar to age-matched controls [5]. Intra-abdominal sites of thrombosis (e.g., hepatic, portal, and mesenteric veins) account for two-thirds of clots in PNH patients, followed by intracerebral sites (10%-20%), and other locations (e.g., skin and lower extremity) [6].

Spontaneous remission, which was previously reported to occur in 15%-30% of PNH patients, has recently been indicated to have a lower rate of around 3% [7].

The management of PNH includes supportive care and the use of complement inhibitors such as eculizumab and ravulizumab, primarily aimed at preventing intravascular hemolysis [8]. Newer agents such as iptacopan and pegcetacoplan have shown promise in preventing both intravascular and extravascular hemolysis [9]. In cases of PNH with thrombosis, anticoagulation therapy is

recommended. For individuals with PNH and bone marrow failure, hematopoietic stem cell transplant is considered a curative treatment option [10].

Further research is necessary to better understand the factors influencing disease course, treatment options, and spontaneous remission in PNH.

Case Presentation

A 28-year-old male resident of Lahore, Pakistan, the eldest among his siblings, had nonconsanguineous parents and remained healthy until the age of 17. In October 2011, he experienced generalized fatigue, shortness of breath, and palpitations. Upon examination, he was pale with no organomegaly and lymphadenopathy. A complete blood count revealed pancytopenia. Viral screening, autoimmune profile, and Fanconi screening were negative. Bone marrow examination confirmed a diagnosis of nonsevere AA. Considering hematopoietic stem-cell transplantation as a curative treatment, HLA matching with siblings was performed, but no HLA-matched donor was available. As a result, the patient was treated with anti-thymocyte globulin (ATG) and cyclosporine, which led to the normalization of blood counts and transfusion independence for nearly a year.

In December 2012, the patient developed fever, abdominal pain, and loose motions, which were initially treated as gastroenteritis without proper investigation. He experienced repeated episodes of abdominal pain, nausea, and black-colored stools. Further workup, including a Doppler ultrasound of the abdomen, revealed portal vein thrombosis. Due to the patient's history of AA and portal vein thrombosis, a workup for PNH was advised. Flow cytometry for CD55 and CD59 revealed PNH. As complement inhibitors were not available, the patient was started only on low-molecular-weight heparin and later switched to warfarin with regular international normalized ratio (INR) monitoring. Symptomatic improvement was observed; however, repeated Doppler ultrasounds showed partial recanalization with collaterals and splenomegaly findings suggestive of chronic portal vein thrombosis (PVT).

In October 2016, the patient presented to the emergency department with black-colored stools, low hemoglobin levels, and raised INR. No evidence of hemolysis was found. Warfarin was withheld, and vitamin K and fresh frozen plasma were administered. Endoscopy revealed esophageal varices, and band ligation was performed. The patient was also started on beta-blockers. Due to labile INR and the patient's unwillingness to have repeated sampling for INR monitoring, warfarin was shifted to rivaroxaban 20mg once daily. The patient's cytopenias worsened over time. Repeat PNH testing by flow cytometry was normal, and no RBC clone was detected. Massive splenomegaly due to underlying chronic PVT was observed, leading to the referral of the patient to a hepatobiliary surgeon for consideration of splenectomy and splenorenal shunt. Workup for hemolysis was negative, and the patient underwent splenectomy with splenorenal shunt with gastric de-vascularization after vaccination in March 2023. The surgery was uneventful, and the patient was started on a low dose of apixaban. Repeat PNH testing after 2 months of splenectomy by Flow cytometry revealed no evidence of PNH. Currently, the patient maintains normal blood counts with no evidence of clinical hemolysis, normal LDH, bilirubin, and reticulocyte counts. The patient is considered to be in spontaneous remission. He continues taking amoxicillin for prophylaxis of post-splenectomy overwhelming sepsis, apixaban, and hematopoietic support medications, along with regular follow-up.

Discussion

PNH is a rare acquired hematopoietic stem cell disorder characterized by complement-mediated hemolysis, thrombosis, and bone marrow failure. It is caused by a mutation in the PIG-A gene, leading to a deficiency in GPI-anchored proteins on blood cells, including erythrocytes, leukocytes, and platelets [1].

The case presented highlights the complex nature of diagnosing and managing patients with rare hematological disorders in resource-limited countries like Pakistan. PNH can arise de novo or in the setting of acquired AA [2]. In this case, the patient was initially treated as a case of AA with immunosuppressive therapy, and he responded with maintained blood counts for 1 year. However, due to resource limitations, a workup for PNH was not conducted at the initial diagnosis. Subsequently, the patient developed portal vein thrombosis, and reevaluation revealed underlying PNH, posing new challenges in the management of the patient.

Venous thrombosis, especially hepatic vein thrombosis, is a common cause of death in patients with PNH before the availability of complement inhibitors, and its occurrence is directly related to the size of the PNH clone. Studies have reported that in 3.6% of patients with portal vein thrombosis, the underlying cause was PNH [11]. The pathogenesis of thrombosis in PNH is multifactorial including depletion of nitric oxide due to free hemoglobin, procoagulant particles released from platelets, deficiency of anticoagulant and fibrinolytic factors, and increased levels of C5a [12].

The management of PNH depends on the clinical type. For classical Hemolytic PNH, complement inhibitors with supportive care are recommended options. Ravulizumab is the preferred complement inhibitor due to its more convenient treatment schedule and similar efficacy and toxicity profile compared with eculizumab [8]. Hematopoietic stem cell transplantation is a curative treatment option for PNH in the context of bone marrow failure. PNH with thrombosis should be treated with combinations of anticoagulation and complement inhibitors, and the duration

of anticoagulation depends on individual risk factors for thrombosis [13].

In this particular case, since complement inhibitors were not available, the patient was managed with anticoagulation and supportive care. However, the thrombosis became chronic, and the patient developed massive splenomegaly, pancytopenia, and esophageal and gastric varices due to underlying chronic PVT. The management of PVT in PNH involves a combination of complement inhibitors and anticoagulation therapy or thrombolytic therapy to prevent further thrombus formation and promote recanalization of the portal vein [13]. Sparse data exist on performing the transjugular portosystemic shunt procedure in patients with chronic portal vein thrombosis and esophageal and gastric varices. Surgical procedures like splenectomy with splenorenal shunt have shown promising results in patients with chronic portal vein thrombosis. However, it is important to consider potential risks and complications associated with the procedure [14]. In this case, the patient underwent splenectomy with a splenorenal shunt and gastric devascularization due to pancytopenia and recurrent hematemesis. Currently, the patient is maintaining blood counts.

Spontaneous remission in PNH represents a rare phenomenon where the abnormal PNH clone undergoes a spontaneous reduction or disappearance, leading to improvements in hematological parameters and clinical symptoms. The exact mechanisms driving this remission are not fully elucidated, but genetic mutations, immune modulation, and immunosurveillance may play significant roles. Previous studies reported spontaneous remission in 15% of patients; however, possible misdiagnoses with the earlier, less specific Ham's test cannot be excluded. Recent studies have shown that the rate of spontaneous remission in PNH was 6 patients in 106 patients. Among the six patients, one transformed into acute myeloid leukemia, and another into chronic myelomonocytic leukemia [15]. In this case, the patient experienced spontaneous remission as evidenced by normalization of blood counts, no evidence of clinical hemolysis, normal LDH, and bilirubin levels, and a diminished PNH clone on flow cytometry. Close monitoring of blood counts, liver function, and imaging studies is necessary to assess the response to treatment and detect any signs of disease progression or recurrence. Long-term anticoagulation therapy may be required to prevent further thrombotic events.

Conclusion

The case presented highlights the complex nature of diagnosing and managing patients with rare hematological disorders in resource-limited countries like Pakistan. The availability of comprehensive diagnostic tests and advanced treatment options may be limited, leading to challenges in accurate and timely diagnosis. In this case, due to resource limitations, a workup for PNH was not conducted at the initial diagnosis. The lack of access to complement inhibitors, such as Ravulizumab and eculizumab, further complicated the management of the patient. The case demonstrates the use of anticoagulation therapy, the role of splenectomy and splenorenal shunt in massive splenomegaly due to portal vein thrombosis, and the concept of spontaneous remission in PNH. Long-term monitoring and multidisciplinary management are essential in optimizing outcomes and ensuring appropriate follow-up care for patients with PNH.

What is new?

The case report highlights the diagnostic challenges and resource limitations in diagnosing and managing PNH in a resource-limited country like Pakistan. The case underscores the need for improved accessibility to diagnostic tests for PNH in such regions. It presents a rare case of PNH initially misdiagnosed as aplastic anemia and later complicated by portal vein thrombosis, providing insights into the management of PNH with limited resources. The case showcases the use of anticoagulation therapy and surgical procedures such as splenectomy and splenorenal shunt in managing complications of PNH. It emphasizes the occurrence of spontaneous remission, a rare phenomenon in PNH, and the importance of close monitoring and multidisciplinary management in optimizing patient outcomes.

List of Abbreviations

AML	Acute myeloid leukemia
ATG	Anti-thymocyte globulin
CBC	Complete blood count
CSA	Cyclosporine
FFP	Fresh frozen plasma
GPI	Glycosylphosphatidylinositol
HSCT	Hematopoietic stem cell transplantation
INR	International normalized ratio
LDH	Lactate dehydrogenase
LMWH	Low-molecular-weight heparin
MDS	Myelodysplastic syndrome
PIG-A	Phosphatidylinositol glycan class A
PMF	Primary myelofibrosis
PNH	Paroxysmal nocturnal hemoglobinuria

Conflicts of interest

The authors declare that they have no conflict of interest regarding the publication of this case report.

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Consent for publication

Written consent was obtained from the patient.

Ethical approval

Ethical approval is not required at our institution to publish an anonymous case report.

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Summary of the case

1	**Patient (gender, age)**	Male, 28 years
2	**Final diagnosis**	Paroxysmal nocturnal hemoglobinuria
3	**Symptoms**	Shortness of breath, palpitations, melena, abdominal pain
4	**Medications**	Ciclosporine, ATG, apixaban, amoxicillin
5	**Clinical procedure**	Splenectomy, splenorenal shunt with gastric devascularization
6	**Specialty**	Hematology