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Case Report

Beyond the heart: unveiling paroxysmal nocturnal hemoglobinuria in a patient with rheumatic heart disease

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ABSTRACT

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare acquired clonal disorder caused by a PIGA gene mutation, leading to glycosylphosphatidylinositol (GPI) anchor deficiency and uncontrolled complement activation. It causes intravascular hemolysis (IVH), thrombosis, and systemic complications. Rheumatic heart disease (RHD), associated with severe valvular pathology, can cause hemolytic anemia. Herein this case reports a 46-year female with RHD-associated aortic stenosis, regurgitation, chronic anemia, jaundice, and hemoglobinuria. Investigations showed hemolysis with elevated lactate dehydrogenase, indirect bilirubin, and reticulocytosis. Chronicity and severity prompted further evaluation. Flow cytometry revealed a significant PNH clone (40.15% in RBCs, >89% in WBCs), confirming complement-mediated hemolysis coexisting with RHD. This case highlights the diagnostic complexity of overlapping hemolytic mechanisms and underscores the importance of considering PNH in unexplained anemia and hemolysis, with early evaluation critical for optimizing outcomes in such rare clinical scenarios.

Keywords: Paroxysmal nocturnal hemoglobinuria, Rheumatic heart disease, Haemolytic anemia

INTRODUCTION

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired clonal disorder of the hematopoietic stem cells with an incidence rate of 0.35 cases per 100,000 people per year, driven by a somatic mutation in the PIGA gene.[1] This mutation results in the absence of the glycosylphosphatidylinositol (GPI) anchors and the GPI-anchored proteins (GPI-AP) they support, such as CD55 (decay-accelerating factor) and CD59 (membrane inhibitor of reactive lysis). Without these regulatory proteins, the complement system becomes unregulated on the surface of the hematopoietic cells, leading to the formation of membrane attack complexes. This uncontrolled complement activation results in intravascular hemolysis (IVH) of erythrocytes and activation of leukocytes and platelets, contributing to thrombotic risk, systemic complications, and reduced life expectancy.[2]

Intravascular hemolysis, a condition in which red blood cells are destroyed within the vasculature, may also occur through other mechanisms, including mechanical damage from turbulent blood flow across diseased heart valves, as seen in rheumatic heart disease (RHD). RHD, with an annual incidence of 37.4 per 100,000, can cause severe valve damage, most common being mitral stenosis, which may lead to mechanical hemolysis of red blood cells.[3,4]

We describe a case of chronic anemia, recurrent jaundice, and hemoglobinuria requiring frequent transfusions. While mechanical hemolysis was initially suspected due to her severe valvular disease, the chronicity and gradually increasing severity of her anemia necessitated further investigation. Flow cytometry confirmed a significant PNH clone, providing evidence of concurrent complement-mediated hemolysis.

This case highlights the diagnostic complexity of identifying coexisting mechanisms of intravascular

hemolysis and the critical role of advanced diagnostic tools like flow cytometry. Recognizing the dual contribution of RHD and PNH significantly influenced the therapeutic approach and emphasized the need for targeted management strategies in such rare clinical scenarios.

CASE REPORT

A 46-year female with RHD, including severe aortic stenosis and moderate aortic regurgitation, with an ejection fraction of 60%, presented with a three-year history of episodic jaundice, hemoglobinuria, nausea, generalized weakness, and exertional dyspnea. Over the past two months, her symptoms worsened with increased fatigability, palpitations, and occasional loss of consciousness. She also had a history of multiple transfusions over three years.

On examination, the patient was vitally stable with a blood pressure of 110/78 mmHg, pulse rate of 88 beats per minute, respiratory rate of 18/minute, body temperature of 98.4 ^{0}F. She was pale, with a grade 4 ejection systolic murmur and a palpable thrill at the mitral and aortic areas along with systolic pressure gradient of 64 mmHg. Investigations revealed a haemoglobin level of 65 g/l (normal: 120–160 g/l), total leukocyte count of 8×109/l (4-10×109/l), platelets 250×109/ (280±130×109/l) and a reticulocyte count of 7% (0.5-2.5%). Peripheral blood smear showed anisopoikilocytosis, normocytic normochromic to microcytic hypochromic red cells, polychromatophils, few elliptocytes and schistocytes. Biochemical tests indicated evidence of hemolysis, elevated indirect bilirubin 59.8 umol/l (3.4-12.0 umol/l), LDH: 850 U/l (<248 U/l).

Imaging revealed mild cardiomegaly and multiple axial skeletal lytic lesions. Frequent transfusions led to a weak positive Coombs test and patient was managed with pulse steroids in early 2024 considering it was Coombs-positive autoimmune hemolytic anemia (AIHA), however, chronicity and persistent anemia prompted further evaluation. Repeat Coombs test was negative and flow cytometry for detection of PNH clone was performed. It showed presence of a PNH clone on red cells with 4.13% type II RBCs and 36.02% type III red cell clone. The PNH clone (double negative for CD157 and FLAER) identified in monocytes and granulocytes were 89.44% and 93.14%, respectively (Figure 1).

The presence of a significant PNH clone, an unexpected observation, significantly altered the treatment approach. Bone marrow aspiration revealed marked erythroid hyperplasia with normoblastic to megaloblastic maturation with normal myeloid cells and megakaryocytes. Bone marrow biopsy was cellular for age and revealed all haematopoietic components with erythroid prominence (Figure 2). No increase in plasma cells was noted. Serum protein electrophoresis (SPEP) showed no M-spike.

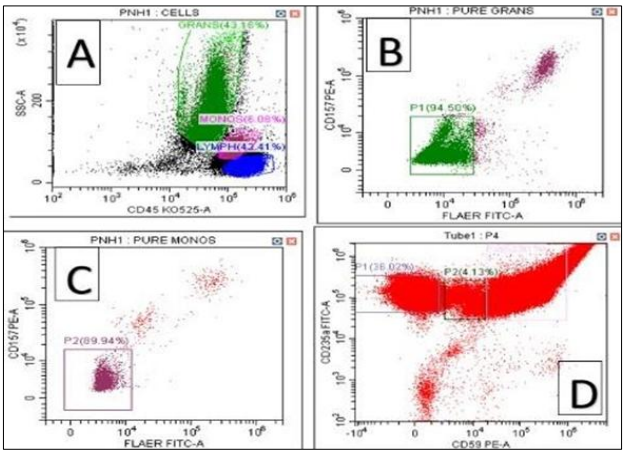

Figure 1: Flow cytometric immonophenotyping revealing (A) side scatter versus CD45 plot, (B) double negative for CD157 and FLAER on granulocytes, (C) double negative for CD157 and FLAER on monocytes, and (D) PNH clone on red cells with 4.13% type II RBCs and 36.02% type III RBCs.

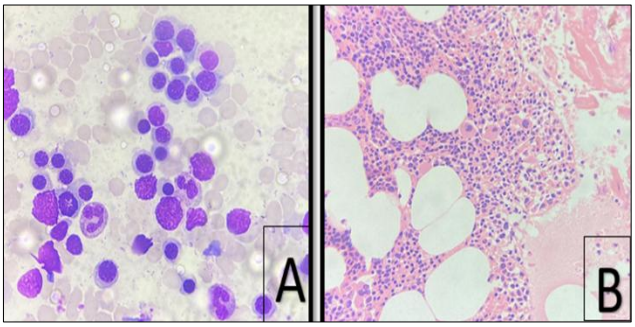

Figure 2: (A) Giemsa stain, bone marrow aspiration revealed marked erythroid hyperplasia with normoblastic to megaloblastic maturation (1000x), and (B) hematoxylin and eosin stain, cellular bone marrow biopsy revealing all haematopoietic components with erythroid prominence (400x).

Diagnosed with PNH, the patient was advised to undergo definitive therapy- stem cell transplantation; however, due to financial constraints and her heart condition, she was unable to pursue this option. Complement inhibiting therapy was not initiated, due to financial constraints. Instead, she was managed with supportive care, which included blood transfusions as needed, treatment for RHD-related complications, and regular monitoring of hemolysis and cardiac function. She was discharged in stable condition and is under regular follow-up.

Bone marrow aspirate smears were stained using the May–Grünwald–Giemsa stain. Bone marrow biopsy was stained with hematoxylin and eosin stain. Immunophenotypic analysis was performed by 10-colour flow cytometry (Beckman Coulter DxFLEX Flow Cytometer). Analysis was done on CytExpert software.

DISCUSSION

PNH typically has an insidious onset, with abrupt, clinically apparent hemoglobinuria as the presenting symptom in only about 25% of cases.[5] The disease usually follows a chronic course, characterized by a stable clinical pattern in an individual. Its severity varies widely, ranging from a mild, clinically stable condition to a chronically debilitating and potentially fatal illness. Most commonly diagnosed in the fourth to fifth decades of life, however PNH can manifest at any age, affecting both genders, with a slight female predominance. It has been observed across various racial groups and exhibits no familial tendency.[6]

The clinical features of PNH are diverse and include anemia, fatigue, shortness of breath, abdominal pain, erectile dysfunction and thrombosis. Additionally, end-organ damage is a significant concern in PNH. Thromboembolism is a leading cause of morbidity and mortality in PNH.[7] The disease may coexist with bone marrow failure, aplastic anemia (AA), and in rare cases, clonal evolution can lead to acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS). Renal failure, cardiac failure, and infections also contribute to the overall disease burden.[8]

PNH diagnosis relies on flow cytometry, the gold standard for detecting CD55- and CD59-deficient cells. Both RBCs and leucocytes must be analyzed, as clone size may be underestimated if only RBCs are assessed due to complement-mediated destruction or recent transfusions. Flow cytometry also identifies PNH phenotypes (the healthy cells are type I, type II has partial deficiency of GPI-APs and type III lack all GPI-Aps and a mosaic of these cells can be seen in most patients). Fluorescein-labeled proaerolysin (FLAER), a fluorescent-tagged bacterial aerolysin, binds to GPI-linked molecules on the surface of normal cells but not on GPI-deficient PNH cells. This binding enables sensitive detection of PNH clones in granulocytes and monocytes.[9] Additional tests include complete blood count (CBC), reticulocyte count, hemolysis markers (LDH, bilirubin, haptoglobin), iron studies, and bone marrow evaluation.[10]

These investigations shed light on the potential overlap between PNH and RHD, suggesting that complement regulatory deficiencies, as seen in PNH, might have a role in the pathophysiology of RHD. The findings highlight the importance of considering PNH as part of the differential diagnosis in patients with unexplained anemia or hemolysis in the context of rheumatic heart disease. In patients with aortic stenosis or heart valve prostheses, monitoring erythrocyte count, hemoglobin, and hematocrit can help detect intravascular hemolysis, particularly when the systolic pressure gradient exceeds 50 mmHg, as higher gradients increase the risk of mechanical hemolysis.[11]

PNH associated hemolysis and mechanical hemolysis can be distinguished by clinical features, laboratory findings, and specialized tests. PNH often presents with episodic hemoglobinuria, markedly elevated LDH, and absent haptoglobin, with flow cytometry confirming GPI-deficient cells. In contrast, mechanical hemolysis is typically chronic, with milder LDH elevation, detectable haptoglobin, and schistocytes on peripheral smear. Flow cytometry remains the key diagnostic tool to confirm PNH.

CONCLUSION

This case highlights the diagnostic complexity arising from overlapping mechanisms of intravascular hemolysis, as seen in the coexistence of PNH and RHD. It emphasizes the need to consider PNH testing in patients presenting with unexplained anemia, hemoglobinuria, or hemolysis, as early identification can significantly impact clinical management. Flow cytometry plays a pivotal role in confirming the diagnosis of PNH by accurately detecting affected cell populations. Recognizing the dual contributions of complement-mediated and mechanical hemolysis calls for a thorough and multidisciplinary approach to diagnosis and treatment. In resource-limited settings where complement inhibitors may be unavailable or unaffordable, the initiation of anticoagulation remains a critical step in mitigating thrombotic complications and improving patient outcomes.

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