INTRODUCTION
Paroxysmal nocturnal haemoglobinuria (PNH) is a rare, acquired, life-threatening haematological disorder. It is caused by a genetic mutation resulting in a deficiency of glycosyl phosphatidylinositol anchor (GPI) required for cell membrane proteins, including complement regulating proteins CD55 and CD59.1 PNH occurs in most ethnicities around the world. However, it remains a rare disease with worldwide prevalence estimated to be up to 1-5 cases per million.2 Based on the degree of GPI deficiency in red blood cells, PNH is classified into three types: type 1 exhibiting normal expression, type 2 with subtotal deficiency of less than 10%, and type 3 exhibiting complete deficiency.3 Furthermore, it has been associated with aplastic anaemia (AA), where PNH clones occur in almost 40% of cases of AA;4 however, no literature to support this frequency has been reported from Pakistan. Patients with PNH experience 40% frequency of thrombotic events, most commonly being venous in origin and occurring in the cerebral, hepatic, portal, mesenteric, splenic, and renal veins and most recently recognised, arterial thrombosis.

Due to the mutation of the molecule GPI in PNH, the red blood cell membranes lack CD55 and CD59. This can be easily detected on flow cytometry allowing it to be an excellent diagnostic test. Flow cytometry can detect lack of CD55 and CD59 on granulocytes, monocytes and platelets as well.

CASE REPORT
Paroxysmal nocturnal haemoglobinuria Type III Presenting as Portal and Mesenteric Vein Thrombosis in a Young Girl
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ABSTRACT
Paroxysmal nocturnal haemoglobinuria (PNH) is a rare, acquired, life-threatening haematological disorder. It is characterised by complement induced haemolytic anaemia, thrombosis and impaired bone marrow function. Thrombosis most commonly occurs in the hepatic, portal, superior mesenteric and cerebral veins. A 22-year female, previously diagnosed with severe aplastic anaemia treated with anti-lymphocyte globulin (ALG) and cyclosporine, had become transfusion independent for more than 10 years. She presented with abdominal pain and vomiting, initially diagnosed with portal and superior mesenteric vein thrombosis. Immunophenotyping by flow cytometry revealed a diagnosis of paroxysmal nocturnal haemoglobinuria type III. She was treated with vitamin K antagonist and platelet transfusion.


INTRODUCTION
A 22-year female with past medical history of aplastic anaemia treated with ALG (anti-lymphocyte globulin) and cyclosporine, presented to the Emergency Department with abdominal pain, vomiting and abdominal distention for two weeks. On examination, she was pale and tachycardic. The abdomen was distended and moderately tender. The liver and spleen were not palpable and gut sounds were absent. The rest of the systemic examination was unremarkable.

Laboratory investigations showed haemoglobin of 8.6 g/dl with MCV of 84 FL, MCH of 27 PG, WBC count of 4.0 x 10^9/L and platelet count of 29 x 10^9/L. Reticulocyte count was 4.4%. Indirect bilirubin was 2.2 mg/dl (normal range: 0.1-0.8 mg/dl). Lactate dehydrogenase (LDH) was 1682 mg/dl (normal range: 208-378 mg/dl). Urine detailed report showed red cells with no casts. Urine for hemosiderin was negative.

An ultrasound abdomen, including kidneys and urinary bladder, was performed which was normal. CT scan of abdomen showed thrombosis of the superior mesenteric vein extending into the portal vein with diffusely thickened, edematous stomach, small and large bowel loops and moderate ascites. Overall appearances were consistent with mesenteric venous ischaemia (Figure 1).

Immunophenotyping by flow cytometry was done which showed type III PNH cells on granulocytes and monocytes while predominant type I on RBCs since she had recently received transfusion with packed red cell blood cells (Figures 2-4).

She responded to supportive measures and anticoagulation therapy with vitamin K antagonist (Warfarin) with close monitoring of INR (range: 1.5-2). Due to thrombocytopenia, she also received platelet transfusions when required to maintain platelet counts above 20 x 10^9/L.
DISCUSSION

PNH is a disorder characterised by a defect in the GPI anchor due to an abnormality in the PIG-A gene. This leads to partial or complete absence of certain GPI-linked proteins, particularly CD59, also called membrane inhibitor of reactive lysis (MIRL) and CD55, which is also known as decay accelerating factor (DAF).

PNH is associated with a marked increase in venous thrombosis in the hepatic and other intra-abdominal and peripheral veins. While this propensity for thrombosis is not understood, it is well known that the activation of complement on the platelet surface stimulates the removal of complement complexes by vesiculation; thus resulting in circulating microparticles that are rich in phosphatidylserine, making them highly thrombogenic.\(^5\) Thrombosis is the most common cause of death in almost 50% of these patients and is attributed to venous thrombosis.\(^6\) The risk of thrombosis appears to be significantly related to the size of the PNH clone.\(^7\) In two series, almost all patients developing thrombosis had more than 50%\(^8\) or more than 61\% PNH granulocytes.

In the past, PNH was diagnosed indirectly, based on the sensitivity of PNH red cells to lysis by complement. The sucrose lysis test and Ham's acid hemolysis test were used as screening and diagnostic tests, respectively. However, the recognition of the deficiency of GPI-linked proteins in PNH has resulted in the development of flow cytometric methods as a diagnostic test, rendering the former methods obsolete.\(^9\) The only potentially curative treatment for PNH is allogeneic hematopoietic cell transplantation. All other treatments are merely supportive.
and directed against the major clinical manifestations of the disease.

The 5-year survival of patients with PNH has drastically improved from 67% to 96% since the introduction of the monoclonal antibody eculizumab. It has also decreased the risk for thrombotic events from 6% to 1% per year. It has been shown that eculizumab therapy, which is effective in decreasing hemolysis, can also decrease the risk for venous thrombosis.\(^\text{10}\) Currently, this agent is not available in Pakistan. Warfarin or heparin may be used in an acute situation; however, their continued use or discontinuation has not yet been established. Prophylaxis in PNH is achieved through long-term anti-coagulation therapy with heparin or warfarin; although it has been seen that despite aggressive management, thrombosis can still occur.

REFERENCES