A case of cranial venous sinus thrombosis and proteinuria

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An 18-year-old male, presented with history of dyspnoea on exertion, intermittent icterus, colicky abdominal pain, and cola-colored urine (of 6 months duration). There was no history of fever, bleeding, intake of drugs or exposure to radiation. Past history and family history were non-contributory. Examination showed heart rate of 110/minute, respiratory rate of 22/minute, blood pressure of 120/80 mm of Hg, severe pallor and icterus. There was absence of lymphadenopathy, hepato-splenomegaly, skin purpura or bone tenderness.

Q. What is the most likely diagnosis?

Answer: The clinical presentation is suggestive of intravascular haemolysis. Various causes of intravascular haemolysis include:
1) enzyme deficiencies in the red blood cells (RBC); Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency, pyruvate kinase deficiency, and glutathione deficiency,
2) defect in the microvasculature leading to microangiopathic haemolytic anaemia (MHA); prosthetic valve, arterio-venous anastomosis, disseminated intravascular coagulation (DIC), thrombotic thrombocytopenic purpura (TTP), haemolytic uraemic syndrome (HUS),
3) complement activating antibodies; paroxysmal cold haemoglobinuria (PCH) and
4) acquired defect on the RBC membrane; paroxysmal nocturnal haemoglobinuria (PNH).

His G6PD enzyme in the RBC and osmotic fragility were normal. Direct and indirect Coombs test and cold antibodies were negative.

Q. How will you confirm the diagnosis of PNH?

Answer: The gold standard laboratory test is to detect CD59 and CD55 on the red blood cells by flowcytometry.† Absence of these CD markers is diagnostic of PNH. However, in centres where flowcytometry is not available, Ham’s test or sucrose lysis tests coupled with the classical presentation will suggest the diagnosis.

Ham’s test and Sucrose lysis test were positive in the patient. Flow cytometric analysis of RBCs revealed deficiency of CD59 on more than 80% of the RBCs.

Q. What is PNH and how does it present?

Answer: Paroxysmal nocturnal haemoglobinuria (PNH) is an acquired clonal haematological disorder, which manifests by complement-mediated intravascular haemolysis, venous thrombosis and bone marrow failure.†‡ PNH can have diverse clinical presentations varying from iron deficiency anaemia to severe intravascular haemolysis, aplastic anaemia,
hypercoagulable state, acute renal failure, and nephrotic syndrome.[2]

**Q. Why are red blood cells prone for complement-mediated intravascular haemolysis?**

**Answer:** In PNH there is an acquired mutation in the X-linked phosphatidylinositol glycan class-A (PIG-A) gene in the pluripotent hematopoietic stem cell. PIG-A protein is required for the synthesis of the glycosylphosphatidylinositol (GPI) anchor.[1,2] Due to deficiency of the GPI anchor there is deficiency of CD55 (decay accelerating factor) and CD59 (membrane inhibitor of reactive lysis) on the surface of erythrocytes making them prone to lysis by the spontaneously activating products of the complement cascade. Normally, alternative complement cascade is in a constant state of low-level activation. It generates C5b, which further cleaves C5 to C5b and initiates the formation of membrane attack complex (C5b-C9) and polymerization of the C9 into molecular tubes that puncture the cell membrane and cause cell lysis. On the surface of the erythrocyte membrane CD55 binds to the C5b and prevents further activation of the complement cascade. CD59 inhibits the insertion of C9 into the erythrocyte membrane, thereby preventing the complement-mediated lysis of the erythrocytes.[2]

**Q. How common is it in adolescence?**

**Answer:** PNH is usually a disease of adulthood, though it has been described in young children and adolescents occasionally.[3,4]

The patient was treated with prednisolone 60 mg/day along with iron and folate supplements. Two weeks later he developed headache not associated with fever, altered sensorium, seizures, or neurological deficit. Examination of the fundus and the central nervous system revealed absence of any abnormality.

**Q. What has happened in the present case?**

**Answer:** Thrombosis is a frequent complication of PNH and contributes significantly to morbidity and mortality. The common sites of thrombosis include cortical, hepatic and mesenteric veins. A few cases with cerebral arterial and coronary vessel thrombosis have been described.[2,5-11] Cranial venous sinus thrombosis (CVT), though rare, is a strong possibility. However, in a comprehensive review of 38 cases, Bousser et al failed to list PNH among the possible causes of CVT.[12] Benign intracranial hypertension may present similarly.

Investigation revealed bilateral infarcts in the parieto-occipital region on non-contrast computerized tomogram. Magnetic resonance imaging showed the infarcts (Figure 1) along with bilateral transverse and left sigmoid sinus thrombosis. Urine microscopy showed albumin 3+ without any cells or casts. Twenty-four hour urine albumin was 3.5 gm. Ultrasound of abdomen and colour Doppler for renal veins were normal.

**Q. What are the mechanisms postulated for thrombosis in PNH?**

**Answer:** The proposed mechanisms of thrombosis are: increased platelet activation with platelet microparticle formation and depression of cell surface-mediated fibrinolysis.[13] Increased production of the thrombin during the haemolytic process has been reported to be a predisposing factor for thrombosis. In our case, this being the cause could not be ruled out.

**Q. How common is proteinuria in PNH and what are the other renal manifestations of PNH?**

**Answer:** Proteinuria is extremely uncommon in PNH. Few documented causes include focal segmental glomerular disease,[14] antigelomerular basement disease,[15] and thrombosis of the renal vessels.[16] Kidneys in PNH have been reported to be larger than normal, presumably due to venous congestion and sludging. Marked haemosiderin deposit in the proximal tubule is a common feature. Renal failure has been reported concomitant to pre-existing renal disease or transfusion reactions. Clark et al, in a study evaluating 21 patients of PNH with renal dysfunction, have reported that urinary had microscopic haematuria and intermittent proteinuria in addition to haemoglobinuria at some or the other time during the course of the disease. In the same report, cortical infarcts, papillary necrosis, decreased glomerular filtration rate, failure to visualize cortical arterioles and prolonged venous phase on renal angiograms and defect in the concentrating ability have also been reported.[16] Since nephrotic range proteinuria is distinctly uncommon in PNH one should rule out other disorders such as antineutrophil antibody-associated vasculitis, systemic lupus erythematosus and Goodpasture syndrome.

In our patient, the serology for antinuclear, antineutrophil cytoplasmic and antiglomerular basement antibodies were negative. A renal biopsy revealed deposition of haemosiderin in the tubules without any evidence of glomerular or interstitial pathology.

**Q. What could have been the cause of renal involvement in this patient?**

**Answer:** In this case the exact cause remained unknown. However, since the renal pathology was noticed at the time of CVT...
and improved with glucocorticoid and anticoagulant therapy, a possibility of microvascular thrombosis[16] being the cause of renal dysfunction cannot be excluded.

**Q. How is PNH treated?**
**Answer:** During acute haemolytic episodes transfusion therapy is helpful in raising the haemoglobin level and suppressing the bone marrow production of RBC. Glucocorticoids and danazol have been reported to reduce the rate of haemolysis. Patients presenting with acute thrombosis require urgent thrombolytic/anticoagulant therapy. Long-term oral anticoagulation therapy is required in cases with cerebral thrombosis or Budd-Chiari syndrome.[4] Bone marrow transplantation should be considered early in the disease course in patients with either bone marrow failure or thrombosis.

**Q. How is response to therapy monitored?**
**Answer:** Response to therapy is monitored by normalization of haemoglobin level, reticulocyte count, platelet count, plasma haemoglobin levels and proteinuria.

Two weeks later his haemogram normalized. Six weeks later urine examination showed albuminuria to be within the normal range [Figure 2]. Computerized tomogram, 11 months later, did not reveal any infarct in the brain or thrombus in the cranial venous sinus. He did not have any more episodes of thrombosis during the past 12 months.

**Q. How common is bone marrow failure in PNH?**
**Answer:** The exact cause of bone marrow failure in PNH is not known. In about 10% of patients, aplastic anaemia evolves and 5% of the known aplastic anaemia patients eventually develop PNH.[2]

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**References**