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Unraveling the Connection: PNH Induced Budd-Chiari Syndrome - A Case Study and Early Detection Emphasis

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Abstract: ***PNH is acquired disorder of hematopoietic stem cell which is characterized by acquired intravascular hemolytic anemia, bone marrow failure with pancytopenia and high incidence of life threatening thrombosis. A serious complication of PNH is hepatic venous thrombosis leading to Budd Chiari syndrome. Budd-Chiari syndrome (BCS) is an uncommon disorder characterized by obstruction of hepatic venous outflow. The obstruction may be thrombotic or non-thrombotic anywhere along the venous course from the hepatic venules to junction of the inferior vena cava (IVC) to the right atrium. Budd-Chiari syndrome is a congestive hepatopathy caused by blockage of hepatic veins. This syndrome occurs in 1/100 000 in the general population. We present a rare case of PNH in a 23 year old man clinically presenting with Budd Chiari syndrome that on detailed investigations actually turned out to be complication of PNH. This article emphasizes on early detection of PNH to prevent life threatening complications like Budd Chiari syndrome.***

Keywords: PNH, Budd Chiari Syndrome, Hepatic Venous Thrombosis

1. Introduction

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare disease that presents clinically with a variety of symptoms, the most prevalent of which are hemolytic anemia, hemoglobinuria, and somatic symptoms including fatigue and shortness of breath. Other findings associated with PNH include thrombosis, renal insufficiency, and in the later course of the disease, even bone marrow failure. The condition is genetic, with the mutations occurring on the X linked gene.[1]

Paroxysmal nocturnal hemoglobinuria occurs due to the development of a genetic mutation in hematopoietic stem cells. This mutation of the X-linked gene phosphatidylinositol glycan class A (PIGA), produces a deficiency in the glycosylphosphatidylinositol (GPI) protein, which is responsible for anchoring other protein moieties to the surface of erythrocytes. The GPI anchor protein defect created by a PIGA gene mutation enhances platelet activation and aggregation in addition to causing hemolysis of red cells. Nitric oxide depletion and complement activation also promote thrombosis by enhancing platelet aggregation and inflammatory cytokine release, respectively. Finally, the thrombophilia found in PNH is enhanced by defective fibrinolysis. Deficiency or absence of a GPI anchored protein responsible for plasminogen activation is suspected. [2]

A serious complication of Paroxysmal Nocturnal Hemoglobinuria (PNH) is hepatic venous thrombosis leading to Budd-Chiari Syndrome (BCS).[3]. Obstruction of the hepatic venous outflow tract, either at the level of hepatic veins or the inferior vena cava, is referred to as the Budd Chiari Syndrome.(4). Budd- Chiari Syndrome is a rare and a potentially life threatening disorder associated with thrombogenic conditions such as myeloproliferative neoplasms or inherited deficiencies in protein C, protein S, and antithrombin in atleast75%of the patients.(5).

2. Case Presentation

A 23 year old male presented with chief complaints of dull aching abdominal pain, fatigue, weight loss and loss of appetite since 2 months. He had no complaints of fever, diarrhoea, vomiting , bleeding from any site or breathlessness.

On examination, he was vitally stable with temperature in normal range, pulse rate of 76 beats per minute ,blood pressure of 110/70 mm Hg and respiratory rate of 14/min.

His general and systemic examination including that of abdomen was unremarkable.

Based on this our differential diagnosis ware chronic liver disease, abdominal tuberculosis and chronic hemolytic anemia list of investigation are in following order

Routine blood investigations:
CBC: Hb 7 gm/dl,
TLC: 4,500/cmm

Plat: 81,000/cmm
Urine R/M: 5-10 RBCs/hpf with trace blood.no blie salt and bile pigment present
LFT: Total bilirubin:3.29mg/dl
Indirect bilirubin:2.16mg/dl
Direct bilirubin: 1.13mg/dl
S LDH:1960 IU/L
S Vitamin B12: >1500 pg/ml
LA: absent
Dengue IgM: negative
Chikangunya IgM: negative
Widal: negative
MP: negative
HIV: negative
HBsAg: negative
DAT and IAT: negative
Sickle solubility test: negative

Considering dull aching pain in abdomen , the patient was also further subjected to routine imaging :

On ultrasonography of abdomen and pelvis , portal venous thrombosis was noted. On CECT Abdomen, occlusion of the hepatic veins, portal vein, distal splenic vein and inferior vena cava thrombosis with borderline splenomegaly was noted. Further, this patient was subjected to flow cytometry which showed decreased expression of GPI linked CD59 on 33% of gated RBCs.

Image 1

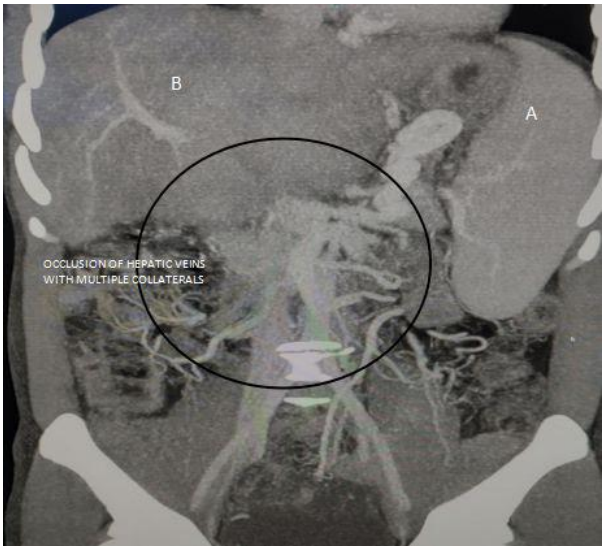

Image 2

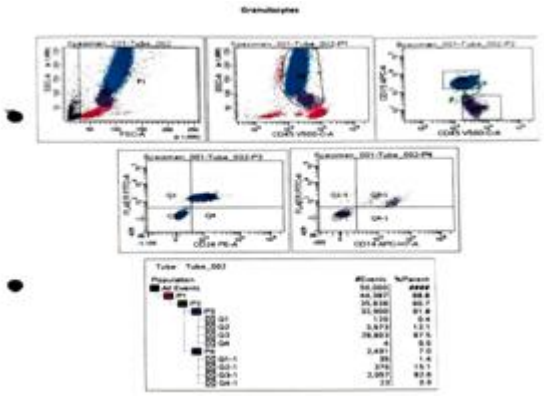

Image 3

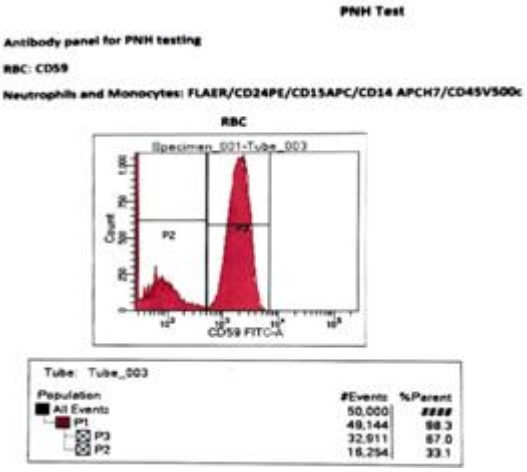

Image 4

3. Discussion

Paroxysmal nocturnal hemoglobinuria (PNH) is a clonal hematopoietic stem cell disease manifested by chronic intravascular hemolysis findings, bone marrow failure and thrombosis. It has is an acquired defect of the glycosylphosphatidylinositol associated proteins CD55 and CD59. These protein deficiencies lead to complement-mediated cell lysis and other clinical manifestations. Flow cytometry analysis of antibodies directed against CD55 and CD59 is the gold standard technique for the diagnosis [6]

Poor survival is associated with the occurrence of thromboembolic complications (relative risk at 8 years, 10.2) [7,8,9]]

Patients with thrombosis at presentation have only a 40% survival rate at 4 years.[7] The relative risk of death is increased five- to 15.4-fold [10]

Explanation for thrombotic state is given by the fact that this patients also have decreased expression of UPAR (Urokinase Plasminogen Activator receptor) leading to decreased thrombolysis and subsequent thrombotic events like BCS as in our patient.

This rate of thrombosis in PNH is likely to be underestimated, because a study using sensitive imaging techniques detected abnormalities suggestive of previous subclinical pulmonary thromboses in 6 of 10 patients with PNH (with no known prior thrombosis), even in patients with apparent recent disease onset. There was also evidence of subclinical myocardial damage in 2 of 10 patients. These subclinical thromboses are able to lead to long-term organ damage as reflected by compromised cardiac function in the majority of these patients. [11]

BCS should be suspected in patients with:

(1) Abrupt onset of ascites and painful hepatomegaly; (2) Massive ascites with relatively preserved liver functions; (3) Sinusoidal dilation in liver biopsy without heart disease; (4) Fulminant hepatic failure associated with hepatomegaly and ascites; (5) Unexplained chronic liver disease; (6) Liver disease with thrombogenic disorder.

Serum transferase levels may be more than five times the upper limit of the normal range, especially in the fulminant and acute forms of BCS. Serum alkaline phosphatase and bilirubin levels also increase. Serum albumin level decreases moderately.

Doppler ultrasonography of the liver, with a sensitivity and specificity of 85% or more, is the technique of choice for initial investigation when BCS is suspected [12]

4. Treatment

Patient was started on tablet warfarin with injection LMWH as bridging therapy; along with multivitamins and folic acid supplements for venous thrombosis.

Patient was further referred to gastrosurgeon for TIPSS (transjugular intrahepatic porto systemic shunt) and hematologist for bone marrow transplant.

He was explained regular follow up with periodic monitering of CBC and serum iron levels.

Eculizumab, a monoclonal antibody targeted against C5 complement is available as an excellent option for treatment of these patients but in countries like India, cost and low socioeconomic status is a major issue.

5. Conclusion

Paroxysmal Nocturnal Hemoglobinuria should always be suspected in a patient presenting with thrombotic state as in this case, after ruling out other causes of hypercoagulability. Early detection of this disease offers benefit of periodic monitoring with supportive treatment and prevention of complications.

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Author Profile

Prachi Parikh did her MBBS from Maharaja Sayajirao University in February 2023. She is currently doing compulsory internship in GMERS Medical College. She is looking for clinical experience in the USA.