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Case Report

Paroxysmal Nocturnal Hemoglobinuria Causing Budd Chiari Syndrome - A Rare Case Report

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Abstract: Paroxysmal nocturnal hemoglobinuria (PNH) is a rare acquired disorder of hematopoietic stem cells characterized by hemolytic anemia, marrow failure, and a high incidence of life-threatening thrombosis. PNH can be diagnosed with a single blood test and has a poor prognosis if untreated. It is an important cause of intra-abdominal thrombosis and therapy with the anti-complement drug, eculizumab, is very effective. Eculizumab usually prevents further thrombotic complications, thus emphasizing, that early diagnosis is critical. We report a case of a young female who presented with Budd Chiari syndrome and pancytopenia and on further evaluation turned out to be a case of PNH.
Keywords: paroxysmal nocturnal hemglobinuria, hemolytic anemia, thrombosis, Budd Chiari Syndrome

INTRODUCTION

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired, intracorpuscular type of hemolytic anemia, in which uncontrolled complement activity leads to intravascular hemolysis and platelet activation. It occurs due to a somatic mutation of the phosphatidylinositol glycan A (PIG-A) gene in the hematopoietic stem cells, inhibiting the synthesis of glycosyl phosphatidylinositol (GPI) [1, 2]. This in turn leads to a deficiency of all GPI anchored proteins, especially complement regulatory proteins CD55 and CD59 on the cell membrane. This renders the PNH cells more prone to complement-mediated intravascular hemolysis, leading to presentation of inflammatory mediators and systemic hemoglobin release [3].

The symptoms and the clinical course of the disease are highly variable, that often makes the diagnosis of this rare disease difficult. It generally presents in the early adulthood. Although the passage of dark brown morning urine is the classical manifestation of PNH, this typical history is seen in only 26% of patients. Most of the patients present with symptoms of anemia, mainly tiredness, dyspnea and palpitation. This disease is characterized by a triad of hemolysis, bone marrow failure and thrombosis. Among these, the most frequent and most life threatening complication is thrombosis. It occurs once in 29-44% [4] of the patients with PNH and accounts for mortality in 40-67% patients [5]. Intra-abdominal veins and cerebral veins are the two main sites of thrombosis in PNH. So keeping a high index of suspicion and considering PNH as one of the differential diagnosis of a patient presenting with thrombosis and pancytopenia, one can make a timely diagnosis of this rare, yet treatable disorder. Here we present a case report of a young female who presented with chronic right upper quadrant abdominal pain and anemia, and on evaluation, turned out to be a case of Budd Chiari Syndrome secondary to PNH.

CASE REPORT

A 26 year old female presented to the outpatient department of our hospital with the complaints of easy fatigability, breathlessness, and palpitations along with dull right hypochondriac pain from last two months. On clinical examination, she had pallor, mild icterus and tender hepatomegaly. Besides hemoglobin of 7 g/dl, patient also had leucopenia (white blood cell count of 3000/mm^3) and thrombocytopenia (platelet count of 1, 07,000/mm^3). Peripheral blood film showed pancytopenia with normocytic anemia. All the other routine biochemical tests were normal except for elevated serum bilirubin (3.0 mg/dl) and mildly elevated transaminases (aspartate transaminase 56 IU/L and alanine transaminase 68 IU/L). Chest X-ray and electrocardiogram were normal. Bone marrow aspiration and biopsy showed hypocellular marrow, suggestive of aplastic anaemia. Ultrasound of the abdomen revealed hepatomegaly with possibility of hepatic vein thrombosis. Further confirmation was made by Contrast Enhanced Computed Tomography (CECT) of the abdomen, which revealed mild hepatomegaly with areas of in homogenous enhancement, narrowing of the caliber of intrahepatic inferior vena cava and improper visualization of hepatic vein, suggesting Budd Chiari Syndrome. Screening tests for congenital thrombophilias (antithrombin III, protein C, protein S and factor V Leiden mutation) were found to be negative. Antinuclear antibody (ANA), lupus anticoagulant and anti-phospholipid antibodies were also negative. In view of pancytopenia and thrombosis, flow cytometry was performed suspecting PNH, which revealed 12.5% of CD55 negative red cells, 21% of CD55 negative granulocytes, and 22.3% of CD59 negative red cells and 25.5% of CD59 negative granulocytes. The above clinical findings and laboratory evaluation led to the diagnosis of PNH with Budd Chiari syndrome in our patient. She was started on low molecular heparin and then shifted to oral anticoagulation. The patient was then referred to hematology and hepatology departments of a higher centre for further management.

DISCUSSION

PNH is an acquired, life threatening clonal disorder of the hematopoietic stem cells characterized by lysis of red blood cells by the complement system. It occurs due to the somatic mutation of PIG-A gene, disrupting the biosynthesis of GPI, and thus resulting in deficiency of GPI-anchored proteins. The two main GPI-anchored proteins which are deficient in PNH are CD55 (decay accelerating factor) and CD59 (membrane inhibitor of reactive lysis), and their deficiency accounts for the complement mediated intravascular hemolysis [1-3].

Although early morning dark brown urine is the telltale presenting sign of this disease, it is present only in one fourth of the patients. All these patients have anemia, and they generally present with non-specific complaints like easy fatigability, weakness, dyspnea and palpitations. Some patients experience symptoms like intermittent esophageal spasms, chest pain, dysphagia and rarely erectile dysfunction. These symptoms are probably related to the red cell breakdown products, which cause spasm of the smooth muscles [6]. At the time of hemolytic crisis, the patients experience moderate to severe intensity pains, in particular back pain, muscle and abdominal pain. This has been hypothesized to be caused by enhanced degradation of nitric oxide associated with intravascular hemolysis leading to deregulation of endothelial and smooth muscle cells in the blood vessels (vasculopathy) [7].

There is a close clinico-pathological correlation between aplastic anemia, myelodysplasia (MDS) and PNH. At initial presentation, more than 20% of the patients with aplastic anemia show evidence of deficient GPI-anchored proteins [8]. 10-20% patients of aplastic anemia develop mylodysplasia during the course of their disease [9]. Hence, PNH and MDS (secondary clonal disorders) may constitute the natural course of aplastic anemia. Apart from above presentations, some patients of PNH are diagnosed when they present with one of the complications associated with the disease, of which the most frequent and most serious is thrombosis. It occurs at least once during the course of disease in 29-44% of patients [4]. In 19% of the patients, intra-abdominal thrombosis precedes the diagnosis of PNH [10]. Similar presentation was seen in our case where the young female patient presented with right hypochondriac pain secondary to hepatic vein thrombosis (Budd-Chiari syndrome). Apart from being one of the most common site of thrombosis (affecting 7.5 to 25% of PNH patients), hepatic vein thrombosis (Budd Chiari syndrome) is recognized as a common cause of hepatic failure and mortality in PNH patients [11]. Although the common presenting feature of Budd Chiari syndrome is acute or chronic abdominal pain, increasing number of cases have also been reported with silent thrombosis. So, every patient of spontaneous Budd Chiari syndrome should be screened for PNH [11].

Apart from hepatic veins, the other common veins involved intra-abdominally are mesenteric veins, portal vein, splenic vein and inferior vena cava. Cerebral veins are next commonest sites of thrombosis in PNH and the

patients generally present with neurological symptoms and signs such as severe headache, vomiting, seizures, altered level of consciousness, papilloedema, sixth and seventh cranial nerve palsies, etc [12]. Occurrence of thromboembolic complications is associated with poor survival rate in PNH patients. In patients having thrombosis at the time of initial presentation, the relative risk of death is increased 5 to 15.4 fold [13]. Deep venous thrombosis is also quite common in these patients. Apart from venous involvement, arterial thrombosis is also reported in PNH and most frequently involves the cerebral and coronary arteries [14].

The gold standard for diagnosis of PNH is flow cytometry for CD55 and CD59 on white and red blood cells. At least 5% of total red cells and 20% of total granulocytes should be CD59 and CD55 negative for making a diagnosis of PNH [15]. Screening for PNH should be undertaken in all patients with unexplained thrombosis who are young, have thrombosis in an unusual site (e.g., intra-abdominal veins, cerebral veins, dermal veins), have evidence of intravascular hemolysis or have any cytopenia [4]. Thrombosis in a patient with PNH requires urgent intervention because of high morbidity and mortality associated with it. Physician needs to balance between the risk of bleeding (because of underlying bone marrow failure) and the highly thrombotic tendencies in PNH. The optimal treatment of acute thrombotic events requires full anticoagulation (in the absence of major contraindications) beginning with heparin therapy and the commencement of monoclonal antibody eculizumab. Continuing anticoagulation with oral vitamin K antagonists is generally recommended in the long term if there are no contraindications. Recurrent thromboses and extension of existing thromboses are frequent complications in PNH.

Eculizumab binds to complement component C5, inhibits its cleavage and thus the formation of membrane attack complex (MAC), protecting the PNH red cells from intravascular hemolysis [15]. The development of any thrombosis in a patient with PNH is now considered one of the primary indications to start eculizumab therapy without delay. It also prevents the propagation of thrombosis or the occurrence of further discrete thromboses in PNH after the initial clot [16].

The management of Budd-Chiari syndrome in PNH, which may occur despite anticoagulant prophylaxis, is usually complex. As with other thrombotic events in this condition, immediate commencement of eculizumab is recommended. Anticoagulation alone may not restore hepatic blood flow. When portal hypertension is predominant, a transjugular intrahepatic portosystemic shunt (TIPS) procedure is often helpful [17]. Liver transplantation is contraindicated because of the risk of recurrent thrombosis; however, most of the data pertaining to this belongs to the pre-eculizumab era [18].

CONCLUSION

PNH is a rare but important condition that physicians should consider when a patient presents with anemia or pancytopenia with thrombosis at any site. Thrombosis in the setting of PNH is an urgent indication to commence eculizumab in addition to anti-coagulant therapy. The poor outcomes seen in untreated PNH, and the significant improvements once treated appropriately, makes it a diagnosis not to be missed.

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