Deep Venous Thrombosis Caused by Paroxysmal Nocturnal Hemoglobinuria in a Young Man

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Abstract

Background: Paroxysmal nocturnal hemoglobinuria is a rare acquired autoimmune disease relation to defect of hematopoietic stem, and is often associated with high rate of life-threatening venous thrombosis.

Method: Lower extremity vein thrombosis is rarer than cerebral and hepatic veins in terms of thrombosis localization. Patients are exposed to intravascular hemolysis, smooth muscle dystonia, renal failure, arterial and pulmonary hypertension, recurrent infectious diseases and an increased risk of especially terrible thrombotic complications. The diagnosis is made by flow cytometry. Deficiency of the glycosphosphatidylinositol - anchored complement regulatory proteins CD55 and CD59 accounts for the intravascular hemolysis that is the primary clinical manifestation of the disease. Besides, paroxysmal nocturnal hemoglobinuria is frequently associated with aplastic anemia or low-risk myelodysplasia and may be asymptomatic.

Result: A patient, who developed thrombosis of the bilateral common iliac veins with the diagnosis of paroxysmal nocturnal hemoglobinuria, is described.

Conclusion: Treatment with heparin and thrombolytic, followed by oral anticoagulant, was effective in resolving thrombosis symptoms.

Keywords: Deep Venous Thrombosis; Hemoglobinuria; Autoimmune

Introduction

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare chronic disorder that most frequently presents in early adulthood and generally continuous along the patient’s life. PNH results in the death of approximately 50% of affected individuals due to thrombotic complications. The name of the disorder is an illustrative term for the clinical consequence of red blood cell deterioration with release of hemoglobin into the urine, and patients make urinate as dark-colored in the morning.

PNH is a condition, in which out of control complement activity causes systemic complications, mainly owing to intravascular hemolysis and platelet activation. It arises through a somatic mutation of the phosphatidylinositol glycan A (PIG-A) gene in bone marrow stem cells, resulting in disruption to glycosphosphatidylinositol (GPI) biosynthesis and thereby a lack of all GPI-anchored proteins on the cell membrane. The deficient proteins are the complement regulatory proteins CD55 and CD59, resulting in increased complement sensitivity of PNH cells, intravascular hemolysis, presentation of inflammatory mediators, and systemic hemoglobin release [1-3].

The devastation of red blood cells results in an inadequacy of these cells in the blood (hemolytic anemia), which can cause signs and symptoms such as fatigue, weakness, paleness of the skin, shortness of breath, and an increased heart rate. People with PNH may also be prone to infections due to a lack of white blood cells. On the other hand, it may cause aplastic anemia and other myelodysplastic syndromes, and if this happens, then it is deadly.

The most frequent and frightening complication of PNH is thrombosis, although the exact pathogenesis is unknown. Most commonly affected vessels are the portal, hepatic, cerebral, or mesenteric veins, and interference of the abdominal aorta or other arteries is rare [4-6] as our case.

A patient with PNH presenting with thrombosis of the bilateral common iliac veins is reported. The patient was treated successfully with anticoagulation and thrombolytic therapy.

Figure 1A: A longitudinal image through the common iliac vein shows a thrombus in Doppler ultrasound (arrows).
Serum biochemical examination demonstrated as glucose: 98 mg/dL, blood urea nitrogen: 15 mg/dL, creatinine: 0.7 mg/dL, sodium: 137 mmol/L, potassium: 3.8 mmol/L, calcium: 9.3 mg/dL, aspartate aminotransferase: 17 U/L, alanine aminotransferase: 8 U/L, and alcalen fosfatase: 100 U/L. Laboratory results showed reticulocytosis (0.9%), increased LDH (1416 U/L) and indirect bilirubin (1.2 mg/dL) and decreased serum haptoglobin levels, aspartat aminotranspherase: 17 U/L, alanine aminotransferase: 137 mmol/L, potassium: 3.8 mmol/L, calcium: 9.3 mg/dL, blood urea nitrogena: 15 mg/dL, creatinine: 0.7 mg/dL, sodium: 137 mmol/L, potassium: 3.8 mmol/L, calcium: 9.3 mg/dL, aspartate aminotransferase: 17 U/L, alanine aminotransferase: 8 U/L, and alcalen fosfatase: 100 U/L. Laboratory results showed reticulocytosis (0.9%), increased LDH (1416 U/L) and indirect bilirubin (1.2 mg/dL) and decreased serum haptoglobin concentration. Besides, leukopenia (3200/mm³), decreased hematocrit (28%) and thrombocytopenia (33000/mm³) levels, coombs negative non-spherocytic hemolytic anemia (9.7 g/dl) were determined. Erythrocyte sedimentation rate was 71 mm/h, ferritin level was 4 ng/ml and renal function was within normal limits. Brucella agglutination was negative. Screenings for congenital (antithrombin, protein C, protein S, factor V Leiden) and acquired (Lupus anticoagulant, antiphospholipid antibodies) thrombophilic abnormalities were negative. The hepatitis viral markers, ANA, APLA were negative; homocysteine, ceruloplasmin and iron studies were normal. Hemoglobin electrophoresis, bone marrow, osmotic fragility test, glucose-6-phosphate dehydrogenase were normal. Cytofluorimetric investigation of peripheral blood cell immunophenotype showed abnormalities of complement regulatory proteins, consistent with the diagnosis of PNH. The CD 55 and CD 59 levels on the erythrocytes and granulocytes were decreased (CD 55 was 15% on the erythrocytes and 10% on the granulocytes and CD 59 levels of 99% on the erythrocytes and 70% on the granulocytes, respectively) for the diagnostic of PNH. Because patient had complaints of abdominal pain and darkening of urine, urinary examination was made. The hemoglobinuria was detected. To make the distinction lymphoproliferative disorders, the chest and abdominal CT were performed, and didnt reveal any pathology.

After putting the diagnosis of PNH, an infusion of heparin (100 IU/kg) with urokinase was started immediately following placing vena cava inferior filter via right jugular vein. The pain was caused by leg edema, subsided within 10 days, gradually. Oral anticoagulation was begun and heparin therapy was tapered. Repeat CT revealed residual thrombus in the iliac veins. The patient’s leg edema had decreased dramatically. With these findings, the patient was transferred to the hematology department for treatment of PNH. Patient who started treatment with eculizumab is kept under monitored for hematological problems and thrombosis.

**Discussion**

Paroxysmal nocturnal hemoglobinuria (PNH), previously Marchiafava–Micheli syndrome, is a rare [7], life-threatening disease of the blood characterized by demolition of red blood cells by the complement system, a part of the body’s immune system. PNH have acquired a somatic mutation of the X-chromosome gene PIG-A which is required for synthesis of the GPI piece that anchors some proteins to the cell surface. As a consequence of mutant PIG-A, the progeniture of touched stem cells (erythrocytes, granulocytes, monocytes, platelets, and lymphocytes) are deficient in all GPI-anchored proteins that are normally expressed on hematopoietic cells. The GPI-anchored proteins, which are deficient in PNH, are CD55 and CD59, the two primary erythrocyte membrane regulators of complement. Deficiency of CD55 and CD59 accounts for the complement-mediated intravascular hemolysis that is the assay mark of the disease [8,9]. Their absence on PNH red cells is responsible for the complement-mediated intravascular hemolysis, leading to the release of free hemoglobin, which contributes too many of the clinical manifestations of PNH including fatigue, pain, esophageal spasm and possibly serious thrombotic episodes [8]. The diagnosis of PNH is made when a patient exhibits paroxysmal hemolysis associated with a defect of CD 55 and 59 [10,11]. Other key features of the disease, notably the high incidence of thrombosis, are not totally understood [12].

The hemolysis findings are frequently detected in the blood test. The normocytic normocromic anemia, non-spherocytic hemolytic anemia, increased indirect bilirubin, lactate dehydrogenase, reticulocytes, and decreased levels of haptoglobin can be seen in the patients with PNH. The direct antitglobulin test (DAT or direct Coombs’ test) is negative, as the hemolysis of PNH is not caused by antibodies. If the PNH occurs in the setting of known (or suspected) aplastic anemia, abnormal white blood cell counts and decreased platelet counts may be seen at this. In our case, anemia may be caused by insufficient red blood cell production in addition to the hemolysis. Today, the gold standard is flow cytometry for CD55 and CD59 on white and red blood cells. Based on the levels of these cell proteins, erythrocytes may be classified as type I, II, or III PNH cells. Type I cells have normal levels of CD55 and CD59, the two primary erythrocyte membrane regulators of complement. Deficiency of CD55 and CD59 accounts for the complement-mediated intravascular hemolysis that is the assay mark of the disease [8,9]. The diagnosis of PNH is made when a patient exhibits paroxysmal hemolysis associated with a defect of CD 55 and 59 [10,11]. Other key features of the disease, notably the high incidence of thrombosis, are not totally understood [12].

The fatal outcome indicates the severity of PNH. While the depth of the anemia is not life-threatening, most deaths are due to venous thrombosis or hemorrhage [13]. Major morbidity and mortality with PNH are often attributed to the development of venous thromboembolism (VTE) [8,14-17]. Thrombotic events exist...
in 40% of PNH patients and describe the major cause of death in this disease. Really, 40–67% of PNH patients will die owing to thrombotic complications. A thrombotic event increases the relative risk of death by 5 to 10 fold [18]. Thrombotic events are caused by venous origin in 85% of the cases, but arterial thrombosis is not so uncommon (15%) [19]. VTE in PNH patients occurs mostly at extraordinary sites. Data from a recent review report hepatic vein thrombosis, leading to Budd-Chiari syndrome, as the most frequent (40.7–44.0% of PNH patients with thrombosis) thrombotic complication [20], followed by cerebral vein and sinus thromboses, mesenteric veins, cavernous sinus, dural veins, superior sagittal sinus being the most frequently involved site [20], and it affects rarely deep vein system. The affection of the abdominal aorta and its branches are relatively rare as our case. Our patient had thrombosis of the bilateral common iliac veins, and this aortic branch venous thrombosis is interesting and differs from other cases presented in the literature.

The complement inhibitor eculizumab, a humanized monoclonal antibody against C5, that inhibits terminal complement activation, approved in the US by the US FDA and the European Medicine Agency in 2007, has been shown to reduce hemolysis, has decreased the erythrocyte transfusion requirements and the risk for thrombosis [12,14,15]. Besides, Hillmen et al. show that eculizumab treatment reduces the risk of clinical thromboembolism in patients with PNH and to improve quality of life of PNH patients [21].

In patients experiencing VTE, early anti-thrombotic therapy aimed to limit the extension of thrombosis, or to dissolve formed thrombi, should improve the prognosis of this severe complication. The successful thrombotic treatment has been shown in many articles. The thrombolytic drugs such as urokinase and tPA were preventing the symptoms of thrombosis occurred in different parts of the body. Abdominal, cerebral and peripheral venous thrombosis life threatening associated with PNH was treated successfully with thrombolytic therapy [22-24]. After thrombolysis treating, administration of heparin is the treatment of choice in acute venous thrombosis. Surgical thrombectomy is an option, but it is highly invasive and carries the risk of pulmonary embolism during manipulation of the IVC. Thus, we preferred to the pharmacologic therapy in this patient after vena cava inferior filter. Lifelong manipulation of the IVC is highly invasive and carries the risk of pulmonary embolism during manipulation of the IVC. Therefore, we preferred to the pharmacologic therapy in this patient after vena cava inferior filter. Lifelong manipulation of the IVC.

Abdominal pain in patients with PNH should be investigated thoroughly as it has been associated with the onset of myelodysplastic syndrome and acute leukemia [25]. Patients with PNH present a therapeutic challenge that requires close monitoring of the disease process and a high index of suspicion for the development of other types of hematologic complications.

In conclusion, our case report emphasis that PNH should be considered in patients with venous thrombosis at unusual sites, especially if associated with haemocromocytometric abnormalities. Antithrombotic treatment in this setting is mandatory, but a careful risk-to-benefit ratio evaluation should be taken into account. Paroxysmal nocturnal haemoglobinuria causes hepatic, splenic, mesenteries, renal and portal vein thrombosis, and also can be caused thrombosis of the deep vein as our case. The patient with deep vein thrombosis should be considered in terms of paroxysmal nocturnal haemoglobinuria.

References


