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Paroxysmal Nocturnal Hemoglobinuria

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SUMMARY

Three cases with Paroxysmal Nocturnal Hematuria (PNH) with different presentations are reported. The first case presented as chronic hemolytic anemia, the second as acute renal failure and third as hepatic vein thrombosis. Their diagnosis and management is discussed.

INTRODUCTION

Paroxysmal Nocturnal Hemoglobinuria (PNH) is an acquired clonal disorder[1] characterized by the formation of defective platelets, granulocytes and red cells. The central diagnostic feature of PNH is the increased sensitivity of red cells to complement.

PNH can manifest itself in many different ways. These include the passage of dark urine, iron deficiency anemia, bleeding disorders, thrombotic episodes, neurological manifestations and renal failure.

Over the last one year three cases of PNH presented to our institution. The various modes of presentation and our diagnosis and management are discussed.

Case I

A nineteen year old male presented with two and a half years history of pallor, generalized weakness, malaise and palpitations. Physical examination revealed a pale young man with mild scleral icterus. His liver was 4 centimeters below costal margin. Laboratory investigations revealed Hb 3.8 gm/dl, Hct 11.4%, WBC 2.7×10^9/l and platelet count of 27,000. Reticulocyte count was 12%. Urine analysis showed blood in urine but no RBCs. The liver function tests showed total bilirubin 2.5 mg/dl, indirect bilirubin 1.2 mg/dl, SGPT 80 U/L, SGOT 87 U/L, alkaline phosphatase 166 U/L. RBC morphology revealed a mixed population of macrocytes, and tear drop cells. A direct and indirect Coomb's test were performed and both were negative. Urine for hemosiderin was positive. Bone marrow aspirate revealed erythroid hyperplasia. Hemoglobin electrophoresis was done which was normal. G6PD level was normal. Ham's test was positive. Neutrophil alkaline phosphatase (NAP) was done and revealed a low score compared to normal control.

Case II

A 32 years old male who came in with oliguria, nausea, vomiting and generalized swelling of the body. His complaints started one week prior to admission when he was given a unit of blood for anemia. Immediately after the transfusion he developed coca cola colored urine. Past history revealed that the patient had been taking iron and blood transfusions often for anemia. He would develop dark urine after blood transfusions or iron therapy. Physical examination revealed a pale young male with mild scleral icterus. Other positive physical findings included enlarged liver and spleen. Lab findings showed Hb of 3.5 gm/dl, TLC was 3.5×10^9/L and platelets were 18,000/m^3. Reticulocyte count was 12%. PT, APTT were normal. BUN was 180 mg/dl and creatinine was 10 mg/dl. Urine analysis was positive for blood. Serum LDH was elevated 707 U/L. Urine for hemosiderin was positive. Serum haptoglobins were low 20 mg/dl Direct Coomb's test was negative while indirect Coombs test was positive. A Ham's test was performed which was positive. NAP score was low with control of 107 and patient was 11. A diagnosis of paroxysmal nocturnal hemoglobinuria was made with alloimmune hemolytic anemia presenting as pigment nephropathy.

Case III

A 24 year old male presented with severe abdominal pain nausea and vomiting. He gave a past history of vague abdominal pain on and off for the last six months. He also gave a history of passing

dark urine on and off for one year. On examination the patients was in severe pain. He was pale. Conjunctiva showed mild scleral icterus. He had a pulse of 120/min and a BP of 90/70. Other positive physical finding was an enlarged and a very tender liver. Laboratory examination revealed Hb of 4.0 gm/dl, TLC 2.5×10^9/L with neutrophil 72%, lymphocytes 20%, monocytes 05%, eosinophils 02 %, basophils 01%, platelets were 40,000. The reticulocyte count was 14%. Peripheral smear was normocytic normochromic with few macrocytes. Bone marrow aspirate was performed which revealed a hypocellular marrow with erythroid hyperplasia and no iron stores. Coomb's test both direct and indirect were negative. Urine for hemosiderin was positive. A Ham's test was done which was positive. Liver biopsy revealed centrilobular congestion and sinusoidal congestion with no evidence of right heart failure. Liver scan revealed only the caudate lobe of the liver. The NAP score was low thus confirming the diagnosis of PNH and Budd Chiari syndrome.

DISCUSSION

PNH is an acquired clonal disorder. The red cell show increased sensitivity to compliment which may be activated both by classical or alternate pathway[2]. The defect in the membranes of granulocytes and platelets is less known but they also show increased sensitivity to complement[3]. Chemotactic response of PNH granulocytes is also abnormal. The abnormal cells are derived from a somatic mutation arising in a damaged marrow and have selective growth advantage over normal cells.

PNH generally runs a chronic course. There are different modes of presentation. Chronic hemolysis is a common presenting problem. Hemolysis is usually irregular and may be precipitated by infections, surgery and even strenuous exercise[4]. The patients manifest all the clinical and laboratory signs of chronic hemolytic anemia as seen in patient 1 and 2.

Iron deficiency anemia may be a presenting feature. This is because of iron loss both as hemosiderin and hemoglobin in urine. Iron administration results in hemolysis[5] indicating that there is increased production of both normal and abnormal clone of red cells. The new abnormal cells undergo hemolysis.

Severe bleeding tendencies due to low platelet count may be a prominent clinical manifestation.

Venous thrombosis is associated with grave prognosis. The Budd-Chiari syndrome results from hepatic vein thrombosis[6] and presents as colicky abdominal pain. Small venous occlusions may occur in the brain[7] with or without any objective neurologic findings. The reason for increased thrombotic complications may be related to activation of platelets by complement or to intravascular release of ADP from aging red cells causing platelet aggregation.

Budd-Chiari syndrome results from occlusion of the hepatic veins due to thrombosis. In this condition the liver is grossly enlarged tender and severe intractable ascites is present. However signs and symptoms of right heart failure are absent.

A patient with PNH may present with acute renal failure[8] like our case 2. During hemolytic episode free hemoglobin is released into circulation. This will bind to Haptoglobin in the blood. If the concentration exceeds the binding capicity of haptoglobin which is about 100 mg/dl of plasma, free hemoglobin circulates in the blood and is cleared from the circulation rapidly within hours by glomerular filtration. Renal tubular epithelial cells are then exposed to it. This free hemoglobin appears to result in acute renal failure when some other systemic abnormalities like acidosis, dehydration, shock or other conditions associated with decreased renal perfusion are present[9]. Under these circmstances hemoglobin becomes toxic to the renal tubule and also causes heodynamic abnormalities which result in acute renal failure. During acidosis hemoglobin is converted to ferrihemmate which is toxic. During ischemia or anoxia renal tubular cell are damaged and become more vulnerable to toxic effects of hemoglobin. Intratubular obstruction from cellular debris and pigment casts can also result in acute renal failure. Altered cortical and glomerular hemodynamics mediated through increased sympathetic activity, increased renin angiotensin activity, decreased synthesis of vasodilatory prostaglandins and or increase in plasma vasopressin may also contribute to development of acute renal failure in these patients[10]. Clinical course of acute renal failure due to hemoglobinuria is often like other cases of acute renal failure. A phase of oliguria is followed by diuretic phase. Following an episode of intrvascular hemolysis patient will pass urine of dark color. Urine output drops and renal function decreases. During this oliguric phase

patient may need dialysis therapy. Recovery starts invariably within 2 to 4 weeks as was seen in our case.

The diagnosis of PNH should be considered in any patient with pancytopenia of unknown origin particularly when accompanied by reticulocytosis.

Laboratory investigations usually reveal anemia, pancytopenia, a mild reticulocytosis and a low neutrophil alkaline phosphatase(NAP) Bone marrow may reveal hypoplasia of all cell lines or erythroid hyperplasia. Hemosiderinurea is usually present during the hemolytic episode.

The most convenient tests are examination of urine for hemosiderin and Ham acid hemolysis test. This test establishes the sensitivity of the patients red cells to complement especially in the presence of acidification. Hemolysis is usually initated by infections, surgery and even strenuous exercise.

Treatment of PNH is generally supportive. Transfusions with red cells is often done in severe cases. Chronic transfusions are associated with problems of transfusion reactions.Iron supplements and folates are necessary. The former because of development of iron deficiency anemia.

The use of steroids is associated with its attendant problems. It should be reserved for severe cases only. The principal role of anticoagulants is in the managment of thrombotic complications. Bone marrow transplantations is highly effective but a high risk method for treatment[11].

The clinical course of this disorder is extremely variable. It generally runs a chronic course in which the severity of the disease may wax and wane as the normal and PNH done alternately appear to gain ascendancy. Sometimes the abnormal clone may disappear altogether. Initial reports tended to emphasize the more severely affected patients so the prognosis was generally grave. Now with a higher index of suspicion concerning this disorder and with simplified methods of diagnosis milder cases are being diagnosed which tend to have a better outlook. Nonetheless even today the disease must be considered a serious one as most patients eventually die due to the complications of PNH. The most lethal complications are thrombotic episodes, complications of pancytopenia and rarely termination into acute leukemia.

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