Paroxysmal Nocturnal Haemoglobinuria in the Differential Diagnosis of Unresponsive Iron Deficiency Anemia: A Case Report

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ABSTRACT

A 16-year-old male patient who was on oral iron treatment for iron deficiency anemia for the last one year was seen at the Haematology clinic with complaints of weakness, pallor, and jaundice. A complete blood count revealed Hb of 4.2 mmol/L, Hct of 0.14, and MCV of 76 fl. A blood smear showed 50% neutrophils, 40% lymphocytes, and 10% monocytes with anisocytosis, poikilocytosis, polichromasia in erythrocytes and normoblasts. Reticulocyte count was under 1%. There was a slight erythroid hyperplasia in the bone marrow aspiration. Biochemical examinations showed total bilirubin of 3.9 mg/dL, indirect bilirubin of 3.4 mg/dL, and lactate dehydrogenase (LDH) of 6085 U/L (220-450). In re-evaluating the history of the patient, he was seen to be complaining of dark discoloration of morning urine. Perl's reaction was found to be positive for hemosiderin in the urine sediment. Because Ham's test was positive, the levels of CD55, 58, and 59 proteins on erythrocyte membranes were found to be lower. The patient was started 32 mg of methylprednisolone and his anaemia was improved by the 14th day of treatment. When evaluating iron deficiency anemia resistant to iron supplementation, PNH should be kept in mind.

Key Words: Paroxysmal nocturnal haemoglobinuria, Iron deficiency anemia.

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INTRODUCTION

Paroxysmal nocturnal hemoglobinuria (PNH) is an uncommon, but not rare, disorder of insidious onset and chronic course. It is characterised by attacks of intravascular hemolysis and hemoglobinuria that occur chiefly at night while the patient is asleep. Consequently, the attention of the patient is captured the following morning by the startlingly abnormal appearance of the first voided urine although it occurs only in 25% of the cases[1]. Iron deficiency anemia (IDA) was seen only in 6% in patients with PNH as a presenting feature[2]. In this case report, we presented a young male patient with poorly explained IDA who was finally diagnosed as PNH.

CASE REPORT

A 16-year-old male patient who was on iron supplementation treatment for iron deficiency anemia for the last one year was seen at the Haematology clinic with complaints of weakness, pallor, and jaundice. His physical examination was otherwise normal except a 2/6 systolic murmur on auscultation of the apex. A complete blood count examination revealed Hb of 4.2 mmol/L, Hct of 0.14, WBC of 4.4 x 10^9/L, platelet count of 106 x 10^9/L, MCV of 76 fl, MCH of 27.1 pg, and MCHC of 0.32. A blood smear examination showed 50% of neutrophils, 40% of lymphocytes, and 10% of monocytes with anisocytosis, poikilocytosis, polichromasia in erythrocytes and normoblasts. Reticulocyte count was under 1%. Bone marrow aspiration and biopsy examination did not reveal aplastic anemia, myelodysplastic syndrome, or myeloproliferative diseases. There was only erythroid hyperplasia in the bone marrow aspiration. Biochemical examinations showed AST of 69 U/L, ALT of 14 U/L, total bilirubin of 3.9 mg/dL, indirect bilirubin of 3.4 mg/dL, alkaline phosphatase of 80 U/L (38-155), lactate dehydrogenase (LDH) of 6085 U/L (220-450), total iron of 77 g/dL (49-167), ferritin of 9 ng/mL (10-250), transferrin of 348 mg/dL (200-360) and haptoglobulin of 7 mg/dL (30-200). In re-evaluating the history of the patient, he was seen to be complaining of dark discoloration of morning urine. A day after, cytologic examination of the urine was performed. Perl's reaction (Prussian blue) was found to be positive for hemosiderin in the urinary sediment (Figure 1). In order to rule out PNH, Ham's test (acid hemolysin test) was performed. Hemolysis was detected when blood was acidified with HCl. Finally, the levels of CD 55, 58, and 59 proteins on erythrocyte membranes were examined. Since the positivity of proteins was below normal, the diagnosis of PNH has become definite (8%, 22%, and 22%, respectively). The patient was started 32 mg of methylprednisolone. On the 14th day of treatment, Hb was 8.5 mmol/L, Hct was 0.27, WBC was 6.3 x 10^9/L, platelet count was 147 x 10^9/L and LDH was 1445 U/L. The reticulocyte count was also reverted to normal. The patient was in good health with no side effect of methylprednisolone as the dosage was tapered off every two weeks.

DISCUSSION

PNH, also known as Marchiafava-Micheli syndrome, is a rare disorder characterised by episodes of hemolysis and hemoglobinuria. The chronic intravascular hemolysis results from the abnormal sensitivity of the erythrocytes to complement-mediated lysis. There is a failure to regulate alternative pathway activation on the erythrocyte surface. PNH erythrocytes are deficient in the two most important membrane regulators of complement, one at regulation of the C_3 convertases and a second at regulation of the membrane attack complex, and consequently, they are subject to chronic hemolysis in vivo[1]. In the absence of CD55, the factor that inhibits the formation and stability of the C_3 convertases of complement, there is a greater binding of activated C_3 to PNH erythrocytes. The other factor, CD59, inhibits complement mediated lysis by blocking the assembly of the membrane attack complex[3,4-7]. The diagnosis is made most often in the fourth to fifth decades of life with a range of 16 to 75 and 6 to 82 in two large series, but PNH is also encountered in childhood and in old age. The average interval between the onset of symptoms and the correct diagnosis was 2.5 to 3 years[8-11]. The diagnosis of PNH must be considered in patients with poorly explained iron deficiency anemia accompanied by hemolysis. In patients with nocturnal hemoglobinuria, the urine is usually darkly discoloured in the morning and clears during the day

which was pointed out by Strübing in 1882[12]. The continuos loss of large amounts of iron in the urine may produce iron deficiency. The half life of complement-sensitive PNH cells is only about 6 days[1]. Quantification of serum LDH is particularly informative because intravascular hemolysis results in markedly elevated values. In our case, LDH values decreased from 6085 to 1445 U/L in two weeks' time. Androgenic steroids and prednisone have been used in the treatment of PNH. Androgens appear to be most effective in cases with prominent marrow hypoplasia, whereas prednisone is most useful in patients with overt hemolysis[1]. Empiric use of steroids (prednisone 20 to 40 mg/day) has resulted in controlling symptoms and stabilizing RBC values in > 50% of patients[13]. In our case, we started 32 mg of methylprednisolone and Hb level was found to be 8.5 mmol/L two weeks later. Hemolytic episodes can also be precipitated by oral iron therapy[1].

Multiple proteins were found to be deficient in PNH cells besides CD55 and CD59. These are urokinase recptor [CD87], endotoxin binding protein receptor [CD14], and lymphocyte function-associated antigen 3 [CD58]. In our patient, we had also detected lower levels of CD58.

PNH is associated with a striking predisposition to intravascular thromboses, especially within the venous circulation involving portal, mesenteric, and hepatic veins. In our patient, we did not detect venous thrombosis.

When evaluating iron deficiency anemia resistant to iron supplementation, PNH should be kept in mind.

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