PAROXYSMAL NOCTURNAL HAEMOGLOBINURIA AND ITS ASSOCIATION WITH MARROW APLASIA - A CASE REPORT

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Paroxysmal Nocturnal Haemoglobinuria is an acquired disorder characterized by the production of an abnormal line of red cells which are unusually prone to lysis by activated complement. These cells are continually haemolysed intravascularly, causing anaemia, haemoglobinuria and haemosiderin urea. There is increased tendency to thrombosis and it may complicate aplastic anaemia. In this article, a case of aplastic anaemia, subsequently developing classical features of paroxysmal Nocturnal haemoglobinuria is presented.

CASE REPORT

A 35 years old carpenter from Dir District was well when in June 1982, he developed fever, headache and body aches, for which he took paracetamol. Four days later he started complaining of weakness, palpitation, breathlessness on exertion, dark colour urine and black colour stool and his local doctor noticed yellow discolouration of his sclera. On investigations he was anaemie with malena stools on rectal examination. There was no jaundice or hepato-splenomegaly. His blood count showed pancytopenia, liver function tests were normaland bone marrow aspirate showed marrow hypoplasia. He received 6 pints of blood and was discharged as a case of aplastic anaemia, on dexamethasone 0.5 mg thrice daily which he continued and remained well. In March 1986, he again developed fever, headache, backache, body aches, abdominal pain and dark coloured urine. This time he was admitted in another unit of the same hospital. He was pale with mild jaundice and hepatosplenomegaly each one finger breadth. Investigations showed haemoglobin of 6.2gm%. Total leucocyte count of 11800/mm^3, L-58%, P-40%, Reticulocyte count- 20%, Platelet count-80,000/mm^3, Urine for haemoglobin was positive, Total serum billirubin was 4.2mg% with conjugated of 1.2 mg% and unconjugated of 3.mg%, with normal SGPT, serum protein and Alkaline phosphatase. Malaria parasite, Coomb's test and sickling test were negative and haemoglobin electrophoresis and G6PD levels were normal. Bone marrow showed moderately depressed granulopoiesis and thrombopoiesis, with mild normoblastic hyperplasia. A diagnosis of Haemolytic anaemia of unknown cause was made and the patient was commenced on dexamethasone (0.5mg) 2 tablets thrice daily after he was transfused 2 pints of blood He improved and was discharged on the same dose of dexamethasone. In February 1988, he once again developed fever, abdominal pain, headache, backache and passage of dark colour urine. On examination he was jaundiced, pale and cushinoid. Liver was palpable 2 finger breadth and spleen 3 finger breadth below the costal margins. Haemoglobin was 10.8 gm%, total leucocyte count was 17800/ mm3 P-77%, L-20%, platelet count 100,000/mm^3, reticulocyte count-20%, Total serum billirubin was 4mg% with conjugated of 1.Smg%, unconjugated of 2.5mg% with normal SGPT, alk. phosphatase and protein. Urine was positive for haemoglobin, Coomb's test negative, G6PD level and Hb. electrophoresis were normal. Peripheral smear showed marked anisocystosis and malarial parasite was negative. Bone marrowwas markedly active, showing moderate erythroid hyperplasia and depressed thronibopoiesis. Ham's test was positive. A diagnosis of paroxysmal nocturnal haemoglobinuria was made and he was commenced on prednisolone (5mg) 2 tablets thrice daily and

was transfused one pint of blood. His fever and jaundice subsided and urine colour became clear. Prednisolone was decreased to 10 mgtwice daily after aweek and hewas discharged on this dose and remained well. In summary this was a case who initially had bone marrow hypoplasia but subsequently developed classical features of paroxysmal nocturnal Haemoglobinuria documented by haemoglobinuria, reticulocytosis, positive Ham's test and excluding other causes of intravascular haemolysis. His episodes of haemolysis are precipitated by minor infections and responded well to steroids.

DISCUSSION

The underlying abnormality in PNH is the production of an abnormal line of red cells by the pleuripotent marrow stem cells, which are unusually sensitive to complement and these abnormal PNH red cells can be demonstrated bylysis in acidified serum (Ham's test) [1,2]. These red cells vary in their complement sensitivity and three populations of abnormal red cells can be demonstrated in most patients. The clinical manifestations relate directly to the proportion of highly complement sensitive red cells that are produced. Recent work has shown that the nature of the lesion in the red cell leading to this increased complement sensitivity is a deficiency of the delay accelerating factor (DAF) of red cell stromawhich normally protects red cells from damage by C3b deposition[3]. The abnormal stem cells clone in the bone marrow which generate these PNH red cells, Granulocytes and platelets, develops due to bone marrow injuction, aplasia, hypoplasia or spontaneous mutation[4]. The haemolysis in PNH is primarily intravascular, producing haemoglobinaemia, haemoglobinuria and the long continued haemosiderinuria. The invivo haemolysis is determined by the continuing activation of the alternative complement pathway which occurs normally and the PNH red cells pick up small amounts of activated C3 (Csb) which are sufficient to cause lysis of the sensitive PNH cells although not causing lysis of normal red cells. The increase in haemolysis during sleep resulting in nocturnal haemoglobinuria, characteristically seen in severely affected patients, is due to activation of the alternative pathway during sleep, resulting in increased uptake of C3 by the red cells or the delivery from the bone marrow during sleep of cohorts of very sensitive red cells. The acute haemolysis which may be precipitated by infections, inoculations, transfusion, medicinal iron or surgical interventions also probably depends ypon the activation of the alternate pathway. [1,2] Venous thrombosis are common complications of this disorder and thrombosis and thromboembolism are the most frequent immediate cause of death in PNH patients. [1,2] The cause of the association between PNH and aplastic anaemia is not known but the hypothesis of common stem cell dysfunction explains this relation and PNFI has developed subsequent to marrow aplasia of idiopathic origin, due to drugs or chemicals and even after aplasia of genetic origin (Fanconi's anaemia) [2,4,5]. Possibly the marrow aplasia facilitates the growth of the not very vigorous PNH clone by reducing competition by normal stem cells. Many patients of PNH are initially diagnosed as aplastic anaemia and subsequently develop features of PNH. In one series of 80 cases of PNH[1], aplastic anaemia was the first diagnosis in 23 of them and in 3 cases, PNH had preceded by mylosclerosis. This relationship takes several forms. Most commonly marrow hypoplasia is present at the onset, then a significant recovery of marrow function occurs, afterwards classic haemolytic PNH develops. Less commonly marrow hypoplasiais present and persists without recovery but tests for PNH become positive. Least commonly, haemolytic PNH is present at the onset and marrow hypoplasia subsequently develops. In small number of patients, PNH has been complicated by development of leukaemia[1,2]. In the reported case of ours, aplastic anaemia was documented initially and subsequently classic haemolytic PNH developed. PNH is underdiagnosed because the classic feature of haemoglobinuria is present only intermittently and in some cases chronic haemolytic process continues without gross haemoglobinuria. Therefore, diagnosis such as haemolytic anaemia of unknown etiology (as was in the case under report), refractory anaemia and pancytopenia of unknown cause are

subsequently proven to have PNH. At present there is no known treatment to correct the basic defect in the PNH cells but patients can be helped in a number of ways. Blood transfusions are the mainstay of treatment during acute haemolysis, not only for raising of Nb level but also for suppressing the marrow production of the abnormal PNH red cells. Corticosteroids reduce haemolysis in acutely ill patients but their side effects limit their use in patients with long continuing disease as was demonstrated by our case. Androgens are particularly useful if the marrow is hypoplastic and they may suppress haemolysis. Oral anticoagulants are usually given to patients with thrombosis. Splenectomy is not recommended. Several patients have been treated successfullybyallogenic transplantation of normal bone marrow. [6] PNH is a chronic disorder and some patients have survived for more than 20 years after diagnosis. The median survival of 80 patients was 10 year[1]. The same author reported complete recovery in 10-15% of his cases. The severity of the disease is variable and some patients may lead a normal life. The major morbidity relates to venous thrombosis. Fortunately the case under report has, so far, not developed major thrombotic episode, leukaemia or mylosclerosis.

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