PAROXYSMAL NOCTURNAL HEMOGLOBINURIA IN CHILDHOOD: AN UNCOMMON PRESENTATION

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ABSTRACT

An eight year old boy presented with severe anemia and bleeding spots. Complete blood count showed pancytopenia. There was mild reticulocytosis. Bone marrow was hypocellular with normoblastic erythroid hyperplasia. Ham's test (acidified serum test) was positive which confirmed the diagnosis of Paroxysmal nocturnal hemoglobinuria (PNH). Although PNH is rare in childhood, it should be considered as a diagnostic possibility in cases of aplastic anemia as the two conditions can coexist. The presence of PNH in association with aplastic anemia can influence the outcome of the latter.

Key words: Paroxysmal nocturnal hemoglobinuria, aplastic anemia, pancytopenia

INTRODUCTION

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired clonal hematologic disorder which has been traditionally classified as hemolytic anemia. However, it is also associated with a component of bone marrow failure and a liability for venous thrombosis. It is a unique disorder characterized by a triad of hemolytic anemia, pancytopenia and thrombosis.[1] There can be either sequential or concurrent appearance of aplastic anemia and PNH in an individual patient. Presence of PNH type cells in cases of bone marrow failure syndromes suggests a relatively benign nature of the disease.[2] An attempt should be made to identify the condition before starting therapy. Majority of the cases occur in adulthood with isolated case reports in children.[3,4] An extensive literature search revealed only one case report from India in a child[5] which prompted us to report an interesting case of severe anemia in an eight year old boy which turned out to be PNH with aplastic anemia.

CASE REPORT

An eight year old boy presented to Pediatric out-patient department in January 2004 with the complaints of progressively increasing pallor and fatigability for 2 months and bleeding spots all over the body for 1 month duration. On, examination, the child had

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severe pallor with petechial and purpuric spots all over the body. The liver was palpable 2 cm below the costal margin and spleen was 1 cm. There was no significant lymphadenopathy. On investigation, the hemoglobin was 6.2 gm%, total leucocyte count was 3550/mm^3 with a differential count of 38% neutrophils, 2% eosinophils and 60% lymphocytes. The platelet count was 18000/mm$^{3.}$ There were no abnormal cells in the peripheral smear. Bone marrow aspiration was hypocellular with normoblastic erythroid hyperplasia. The trephine biopsy showed decreased cellularity. The leucopoeisis and thrombopoeisis were depressed with a myeloid to erythroid ratio of 1.5:1. The reticulocyte count was 2.5% with a negative Coomb's test. The serum LDH was 700 IU/L. Serum bilirubin was within normal limits and urine examination was negative for hemoglobinuria. In view of the normoblastic erythroid hyperplasia in the bone marrow and reticulocytosis against a backdrop of pancytopenia, a diagnosis of Paroxysmal nocturnal hemoglobinuria was considered. Ham's test (acidified serum test) was carried out which was positive. The final diagnosis was PNH with aplastic anemia. The child was given supportive treatment with packed red cells and platelet transfusion and was started on oral cyclosporine A alone as he could not afford treatment with antithymocyte globulin. Two months in follow up, the child continued to have anemia and pancytopenia but there was some improvement in the thrombocytopenia. The platelet count rose to 46,000/mm^3. Unfortunately, the child was lost to follow up subsequently.

DISCUSSION

PNH was first described a century ago but the molecular defects have been identified only recently. Because of a somatic mutation in the phosphatidyl inositol glycan complementation group-A (PIG-A) gene, a number of proteins such as membrane inhibitor of reactive lysis (MIRL, CD59) and decay accelerating factor (DAF, CD55) are absent from the surface of red blood cells.[1] This renders the cells susceptible to lysis by complement resulting in intravascular hemolysis and hemoglobinuria. The hemoglobinuria may be intermittent on awakening in the morning or may be continuous throughout the day. However, some patients may never develop it.

PNH is a disease of adults presenting in 3rd to 5th decade. In a large series of 78 cases of PNH diagnosed in 10 years, the mean age of diagnosis was 34 years.[6] In the largest series of 26 cases of PNH with onset in childhood the age ranged from 8 months to 21 years and only 3.8% cases were younger than 10 years.[7] There was significant difference between young patients with PNH and adult patients. Hemoglobinuria as the presenting complaint was seen in only 15% of children as against 50% in adults. In contrast, bone marrow failure was much more common in young than in the adults (58% versus 25%).

PNH and aplastic anemia are clinically related. The disorders may present simultaneously or one may evolve into

another. The cause of bone marrow failure in PNH is not very clear. The possible explanations are that PNH clone suppresses the normal marrow progenitors or it has an intrinsic growth and proliferative advantage compared to normal stem cells.[1] The high prevalence of bone marrow failure frequently leads to an initial diagnosis of aplastic anemia rather than PNH as happened in the present case. He was initially diagnosed as a case of aplastic anemia but because of the presence of normoblastic erythroid hyperplasia in the bone marrow and mild reticulocytosis, the possibility of PNH was thought of. The reticulocyte count in these cases is not parallel with the extent of hemolysis and this reflects the underlying bone marrow failure which always coexists with PNH.[1] Venous thrombosis is the third component of this condition, the pathophysiology of which is not very clear. The possible reasons are impaired fibrinolysis, hypercoagulability and hyperactivity of platelets because of the lack of CD59 on PNH platelets. However, a thrombotic complication was not present in our case.

Ham's test is a highly sensitive test for the diagnosis of PNH. It may miss the diagnosis initially if the PNH clone is small. Therefore it is important to repeat the Ham's test at regular intervals to avoid missing the diagnosis. The availability of flow-cytometry has further improved the diagnosis of PNH. In the series of 78 cases of PNH by Zhao et al[6] Ham's test was positive in 65.8% cases whereas CD59 and CD55 were found deficient in 100% of cases.

Treatment of the condition depends upon the clinical presentation. In patients presenting with the features of aplastic anemia, either cyclosporine (Cy A) alone or in combination with antithymocyte globulin (ATG) have been tried. Results of a combination treatment (ATG + Cy A) are better than Cyclosporine alone.[8,9] Allogenic haemopoietic cell transplantation has been tried successfully.[10] In the present case cyclosporine was used alone because of financial constraints. In cases with recurrent hemolytic episodes short courses of oral prednisolone have been tried around the time of hemolysis.[1]

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