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Case Report

PAROXYSMAL NOCTURNAL HEMOGLOBINURIA TRANSFORMING TO APLASTIC ANAEMIA WITHIN TWO YEARS: RARE IN CHILDHOOD

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ABSTRACT
A ten years old boy presented with severe anemia. Complete blood count showed pancytopenia and mild reticulocytosis. Bone marrow was hypocellular and PNH clone was present which subsequently on two years follow up revealed aplastic bone marrow with PNH clone being absent this time. In this case within two years such a transformation took place which is rare in childhood.

Key Words: *Paroxysmal Nocturnal Hemoglobinuria, Aplastic Anemia, Pancytopenia*

INTRODUCTION
Paroxysmal nocturnal hemoglobinuria (PNH) is a rare acquired clonal hematologic disorder classified as hemolytic anemia. It is also associated with a component of bone marrow failure and a liability for venous thrombosis. So it is a triad of hemolytic anemia, pancytopenia and thrombosis (Luzzatto and Notaro, 2003). Presence of PNH type cells in cases of bone marrow failure syndromes suggests a relatively benign nature of the disease (Wang *et al.,* 2002). There can be either sequential or concurrent appearance of aplastic anemia and PNH in an individual patient 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 (Dolzel *et al.,* 2004; Wainright *et al.,* 2003).

CASES
A 10 years old male child presented with progressive pallor and generalised weakness with hypoplastic right thumb without bleeding, jaundice, hepatosplenomegaly or lymphadenopathy with Hb 2, WBC 6,600 TPC 80,000, reticulocyte count 4% DCT neg, LDH 804,and normal serum ferritin, no hemoglobinuria or thrombosis. Bone marrow of this child was hypoplastic with decreased erythropoesis and megakaryopoesis. Subsequently Flow cytometry was done which revealed presence of PNH clone. 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. The child was given supportive treatment with packed red cells and platelet transfusion alone as he could not afford treatment with antithymocyte globulin and cyclosporine A. Two years later in follow up, the child again presented with similar complaints and had pancytopenia. Repeat PNH clone was absent this time so marrow was repeated which revealed aplastic anaemia.

DISCUSSION
PNH is related to a somatic mutation in the phosphatidylinositol glycan class A *(PIG-A)*, X-linked gene, responsible for a deficiency in glycosyl phosphatidylinositol–anchored proteins (GPI-APs) (Takeda *et al.,* 1993). The lack of one of the GPI-AP complement regulatory proteins (CD59) leads to hemolysis. Recent studies have focused on inhibiting the complement cascade, with encouraging clinical results using eculizumab, a C5-inhibitor humanized monoclonal antibody (Hillmen *et al.,* 2004).
PNH diagnosis has evolved over time. Prior to the past 3 decades, Ham test was used. It was based on the increased sensitivity of PNH-affected erythrocytes to complement mediated lysis. In the late 1980s, flow cytometry (FC) allowed direct quantification of the GPI-AP–deficient cells. FC, the current standard for

diagnosis, is a reliable quantitative test, and is more sensitive than Ham test for the identification of small populations of GPI-AP–deficient cells.

Although significant advances have been reported in the detection of the GPI-AP–deficient cells, as well as in the pathophysiology of the disease, the natural history and the identification of survival prognostic factors have been rarely described (Hillmen *et al.,* 1995; Socie *et al.*, 1996). 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 (Zhao *et al.,* 2002). 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 (Ware *et al.,* 1991). 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 (Luzzatto and Notaro, 2003). 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.

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) has been tried. Results of a combination treatment (ATG + Cy A) are better than Cyclosporine alone. Allogenic haemopoietic cell transplantation has been tried successfully.

The course of the disease in 80 patients referred to Hammer- smith Hospital, London, between 1940 and 1970 revealed a median survival of approximately 10 years (Peter *et al.,* 1995). Twenty-five years after the diagnosis, 58 patients (72 percent) had died, and 22 (28 percent) were alive. The median age at the time of death was 56 years (range, 20 to 84), with a median interval of 10 years (range, 0 to 48) between diagnosis and death. In five patients the disorder progressed from hemolytic PNH to aplasia on ten years of follow up. Ham's test remained positive in four of these patients.

Here we present a rare case of PNH in childhood which within two years without treatment progressed to aplastic anaemia with absent PNH clone.

Conclusion

PNH is rare disease in childhood and known to transform into aplastic anemia, leukemia, myelodysplasia or spontaneous remission. This must be kept in mind and regular investigations must be repeated on follow up as it influences the outcome.

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