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Paroxysmal nocturnal haemoglobinuria: Atypical presentation in a 13-year old Chinese and a Malay adult.

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Introduction

PAROXYSMAL NOCTURNAL HAEMOGLOBINURIA (PNH) is a rare acquired disorder of red cells, the cause of which is unknown. These cells have an intrinsic red cell membrane defect resulting in a shortened life span, and show increased sensitivity to lysis by complement, activated probably through the alternative pathway of the complement sequence resulting clinically in a chronic haemolytic anaemia and haemoglobinuria occurring during sleep. Additional characteristics of these cells include excessive antibody binding, and low or absent acetylcholinesterase activity. Red cell survival studies using 51Cr isotope in this condition show a double population of red cells (Dacie, 1967).

Though a few cases have been diagnosed in Malaysia, there have been no documented cases in the literature so far. We describe here two such cases.

Case Reports

Case 1 – C.W.S., a 13-year old Chinese boy was admitted into hospital on 16.5.77 with fever, chills and rigors of a few days duration. There was no associated sternal, abdominal or lumbar pains. The fever persisted for 4 days when he started to have polyuria, the urine passed being uniformly reddish-brown in colour. There had been no similar episodes before though he had noticed a gradual deterioration in his effort tolerance in the past 2 months.

On examination, he had a low grade fever and was pale and mildly jaundiced. There was no lymphadenopathy. The liver was enlarged to 2 cm. below the costal margin. The spleen was not palpable. Other systems were normal.

The peripheral blood showed a pancytopenia. The bone marrow was normocellular, with increased erythropoiesis. The iron stores were depleted. The urine was noted to be very dark in colour and was later found to be positive for haemosiderin and haemoglobin. Bile was absent but urobilinogen was present in increased quantities. The serum bilirubin was 4.0 mg/100 ml with a predominance of the indirect form. LE cells was negative on three occasions. Blood film for malaria was negative on six occasions. VDRL and anti-human globulin tests were negative. Red cell G.6.P.D. activity was normal. Haemoglobin analysis showed normal components of Hb.A, Hb.A_2 (2.5%) and Hb.F (1.7%). Ham's (Acidified Serum) test and the sucrose lysis test were positive. Leucocyte Alkaline Phosphatase Score was 10 while serum haptoglobin was 17.5 mg/100 ml (30 – 200 mg% normal). RBC acetylcholinesterase activity was 50% of normal.

The patient was initially observed in the ward. Later he complained of blurring of vision and abdominal pain. Funduscopy showed bilateral retinal haemorrhages. His haemoglobin dropped from 5.0 gm/100 ml to 2.1 gm/100 ml. He was given a short-course of prednisolone for his retinal haemorrhages which cleared up quite well. Two units of washed red cells brought up his haemoglobin to 12.9 gm/100 ml (Table I) and resulted in a temporary improvement of the patient's clinical status. He was readmitted into hospital on 21.8.77 with a further complaint of abdominal pains. The blood picture again showed pancytopenia (Table I). He also had fresh bilateral retinal haemorrhages. He was subsequently started on oxymethalone 60 mg daily.

Table I

Haematological Investigations of Case I

	17/5/77	25/6/77	29/6/77	12/7/77	3/8/77
Hb. Gms%	5.0	2.1	7.4	12.9	5.5
Platelets/cu.mm.	2020	8080	14,140	51,510	11,110
Reticulocytes %	2.1	4.0	1.8	0.5	4.8
Total White Count/cu.mm.	2750	2582	3706	4549	2897
Neutrophils Count/cu.mm.	2007	749	2483	1820	1014

Case 2 – A.I.R., a 36-year old Malay male was admitted on 1.6.77 with a history of high fever and cough with white sputum for 4 days. He also complained of left sided chest pain for 2 days and yellowing of skin.

On examination, he was febrile and toxic. He was very pale and markedly jaundiced and had a tachycaria of 100 beats/min. Auscultation of the heart revealed an ejection systolic murmur all over the praecordium. Examination of the chest revealed signs of left lung consolidation. There was a tender liver enlarged to 4 cm. below the costal margin, but the spleen was not palpable, and there was no lymphadenopathy.

Urinalysis showed only a trace of urobilinogen. ESR was 120 mm/1st hr. Blood film for malaria was negative. The serum bilirubin was 5.5 mg/100 ml with a predominance of the indirect component. The other parameters of the liver function tests were normal. A chest Xray showed a wedge shaped opacity in the left upper lobe. The peripheral blood showed a pancytopenia, details of which are shown in Table II. A bone marrow aspiration on 5.6.77 revealed a hypercellular marrow with increased erythropoiesis and adequate iron stores. Blood cultures on 3 occasions were negative.

The patient was given a short-course of ampicillin resulting in rapid improvement. He was put on oral iron and vitamins supplements and his haemoglobin steadily rose to 7.7 gm/100 ml. However, the patient remained persistently jaundiced and his peripheral blood still showed a pancytopenia. A repeat bone marrow aspiration on 8.7.77 revealed a normocellular marrow with depleted iron stores.

Haemoglobin analysis was normal and LE cells were negative on three occasions. VDRL and anti-human globulin test were negative. Red cell G.6.P.D. activity was normal. Ham's (Acidified Serum) test and the sucrose lysis test were positive. LAP score was 0. Serum haptoglobin was 15 mg/100 ml (normal 30 – 200 mg/100 ml). Red cell acetylcholinesterase activity was 25% of normal. Urine haemosiderin and urine haemoglobin were positive. There were no red cells in the urine.

On 2.9.77, he was readmitted because of epigastric pain. His blood counts are given in Table II. Two units of washed red cells were given. His Hb. then improved to 10.4 gm/100 ml and platelets to 111,100/cu.mm. blood.

Discussion

Both patients presented with symptoms not readily recognized initially as manifestations of PNH. Case 1 was diagnosed as iron deficiency anaemia from the bone marrow examination which showed depletion of iron stores. As severe iron deficiency is unusual in a young Chinese male, the manifestations were reviewed and further investi-

Table II

Haematological Investigations of Case II

	2/6/77	21/6/77	13/7/77	8/8/77	2/9/77	8/9/77
Hb. Gms%	3.3	5.8	8.3	7.4	6.8	10.4
Platelets/cu.mm.	45,450	<83,830	104,030	88,880	–	111,100
Reticulocytes %	7.3	23.5	16.5	20	–	18
Total White Count/cu.mm.	2409	2372	4073	4809	–	4579
Neutrophils Count/cu.mm.	1807	1660	2688	3510	–	3892

gations were carried out. The significant abnormalities in the urine together with a pancytopenia in the peripheral blood suggested PNH which was confirmed by a positive Ham's acidified serum and sucrose lysis tests. The low alkaline phosphatase score and low acetylcholinesterase activity provided further evidence of this disorder. The recurrent bleeding in the fundi was probably a manifestation of the thrombocytopenia.

Case 2 on the other hand presented with high fever, chest symptoms and jaundice. The chest Xray appearance of a wedge shaped consolidation suggested an infarct. Investigations showed a pancytopenia in the peripheral blood with active erythropoiesis in the marrow suggesting a response to haemolysis. A month later the bone marrow showed depletion of iron stores. Urine examination at this stage was found to be strongly positive for haemosiderin. Other investigations then confirmed diagnosis of PNH.

As illustrated by these two cases, the typical symptomatology of PNH – haemoglobinuria occurring particularly in the morning on waking and haemolytic anaemia, may be masked by other features. However both manifested the chronic intermittemt course of this condition probably precipitated in Case 2 by a fairly severe infection.

In this disorder, the severity of the haemolysis is correlated with the degrees of abnormality of the PNH erythrocytes and the proportion of the sensitive abnormal cells present (Hinz *et al.,* 1956). Haemolysis is easily precipitated by infections, surgery, inoculation and parenteral iron therapy (Dacie, 1967). Whole blood transfusions because of complement activation initiated probably by the serum factor properdin (Hinz *et al.,* 1956) and the acid pH of the anti-coagulant can cause an immediate haemolytic episode.

Venous thrombosis and thromboembolism occur frequently (Dacie, 1967). The abdominal pain which both of the patients experienced and the lung complication in Case 2 may have been caused by thrombosis. Haemorrhages due to thrombocytopenia or recurrent infections associated with granulocytopenia can also occur. These features were noted particularly in Case 1. Hypoplastic anaemia or even aplastic anaemia is not infrequently encountered in PNH cases either at the onset or later in the course of the illness. Both our patients showed a pancytopenia but the bone marrow was either normocellular or hypercellular. It has been postulated that the change (? a somatic mutation) leading to PNH is particularly likely to occur when haemopoietic regeneration takes place in a marrow which has undergone aplasia or hypoplasia, leading to its partial repopulation by a clone of abnormal haemocytoblasts. It has therefore been suggested that PNH is a stem cell disorder (Lewis and Dacie, 1967). It has also been suggested that leucocytes are also probably affected in the same way as shown by the low alkaline phosphatase score (Lewis and Dacie, 1967), which is usually normal in typical cases of aplastic anaemia.

The management of this disease can be a difficult problem. Frequent transfusions of washed red cells may be required to sustain life and improve anaemia. When an iron deficiency state develops, due to loss of large amounts of haemosiderin in the urine, as in the two cases described, the loss must be replaced with oral iron. Steroids may be useful under certain circumstances (Firkin *et al.,* 1968). In one of the two patients described, fundal haemorrhages improved with steroid therapy. Oxymethalone was given to the same patient whose anaemia was a serious problem, as it has been reported that high dose, long term androgen therapy may be beneficial (Hartman *et al.,* 1966).

Summary

Two patients, one a 13-year old Chinese male and the other an adult Malay male, presenting with a typical features of paroxysmal nocturnal haemoglobinuria are described. The first patient was initially diagnosed as iron deficiency anaemia. The second presented with a haemolytic anaemia, fever and a lung infarct. The complications and management in these two cases are discussed.

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References

Dacie, J.V. (1967) The haemolytic anaemias, Congenital and Acquired, Part IV. New York. Grune and Stratton. 2nd Edition.

Firkin, F., Goldberg H., and B.G. Firkin (1968) Glucocorticoid management of paroxysmal nocturnal haemoglobinuria. *Aust. Ann. Med.* **17,** 127.

Hartman, R.C., Jenkins D.E. Jr., McKee L.C., and Heyssel R.M. (1966) Paroxysmal nocturnal haemoglobinuria: Clinical and laboratory studies relating to iron metabolism and therapy with androgen and iron. *Medicine* **45,** 331.

Hinz C.F. J., Jordan W.S., & Pillemer L. (1956) The properdin system and immunity. IV. The haemolysis of erythrocytes from patients with paroxysmal nocturnal haemoglobinuria. *J. Clin. Invest.* **35,** 453.

Lewis, S.M. and Dacie, J.V. (1967) The Aplastic Anaemia – Paroxysmal nocturnal haemoglobinuria syndrome. *Brit. J. Haematology,* **13,** 236.