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CASE REPORT

A rare cause of haemolytic anaemia: paroxysmal nocturnal haemoglobinuria in an elderly patient

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ABSTRACT

Paroxysmal nocturnal haemoglobinuria (PNH) is an acquired haemopoietic stem cell disorder characterised clinically by chronic haemolytic anaemia with acute episodes, thrombosis and bone marrow failure. It is a rare condition, which usually occurs in younger people. Immunophenotyping and flow cytometry play a key role in diagnosing PNH. Treatment is mainly supportive. Because it is so rare, delay in diagnosis is not uncommon in patients with PNH, which has a considerable impact on patient management and prognosis.
We present this case to draw attention to this rare cause of haemolytic anaemia, which should be considered in any patient, of any age, who has signs of chronic haemolysis.

INTRODUCTION

Paroxysmal nocturnal haemoglobinuria, also known as the Marchiafava-Micheli syndrome, is an uncommon acquired clonal disorder characterised by chronic haemolysis with acute exacerbations, cytopenias of varying extent and a tendency to venous thrombosis.[1-3] It is associated with a somatic mutation in the PIG-A gene of a totipotent haemopoietic stem cell causing the blood cells of the PNH clone to be deficient in glycosyl phosphatidyl inositol anchored membrane proteins. Deficiency of these proteins leads to an increased sensitivity of PNH cells to complement-mediated lysis, which is responsible for chronic intravascular haemolysis and probably also for thrombosis.[3-5] The haemolysis usually occurs at night, although not in all patients. The reasons for this nightly occurrence are unclear but a lowering of blood pH at night may play a role. There is a close relation to aplastic anaemia and PNH may convert into acute leukaemia.[6-8] PNH usually occurs in young adults. In the present case, we report a Caucasian woman of older age with haemolytic anaemia in whom PNH was diagnosed.

CASE REPORT

A 67-year-old Caucasian woman presented with a history of progressive fatigue, dizziness and presumed haematuria, for which she had already seen a urologist who diagnosed an asymptomatic urinary tract infection. Her medical history revealed hysterectomy, angina pectoris and a frozen shoulder. Her mother died of chronic leukaemia at the age of 80. Her medication consisted of nitrofurantoin, ramipril and celiprolol. Physical examination showed a pale, tired-looking woman with normal blood pressure, pulse and temperature. No pathological lymph nodes were found. Heart, lungs and abdomen revealed no abnormalities. She had vitiligo over the upper extremities. The ECG and chest X-ray were both normal.
Laboratory tests showed the following results: ESR 31 mm/h (N. 2-20), haemoglobin 5.4 mmol/l (N. 7.5-10.5), Ht 0.27 l/l (N. 0.36-0.50), MCV 101 fl (N. 82-100), leucocytes 4.7 x 10^9/l (N. 4.0-10.0), platelet count 154 x 10^9/l (N. 130-340), haptoglobin <0.1 mmol/l (N. 0.28-2.00), LDH 8609 U/l (N. <450), bilirubin 36 µmol/l (N. <17), serum iron 15 µmol/l (N. 10-30) and reticulocyte count 70% (N. 0.7-2.4). Urine analysis showed haemoglobin and haemosiderin. Apparently, the patient was suffering from intravascular

haemolysis. A direct Coombs' test was negative. The blood smear showed no spherocytes, elliptocytes or fragmentocytes. Erythrocyte enzymes, such as G-6-PD, were normal as was haemoglobin electrophoresis. The following step in Coombs-negative haemolysis is the Ham's test and sucrose haemolysis test. Both these tests can confirm haemolysis in red cells of a patient's serum by activating complement, the first by lowering serum pH and the second by reducing ionic strength. The Ham's test was positive in our patient. To confirm the diagnosis, flow cytometry was then performed, which provided immunological evidence for the existence of PNH in our patient. This test uses monoclonal antibodies against phosphatidyl inositol (PI) anchored proteins on granulocytes, which under normal circumstances protect cells against complement-mediated lysis. In PNH, expression of these proteins is significantly reduced or absent, as in our patient, causing lysis of red cells.

Our patient was treated with blood transfusion, and iron and folic acid suppletion. In addition, we started with acenocoumarol as a prophylaxis against thrombosis which, after infections, is the main cause of death in patients with PNH. Our patient was readmitted after six months for another transfusion but is doing very well at the moment.

DISCUSSION

We present here a case of PNH in a 67-year-old woman. There was a delay in diagnosis because her haemoglobinuria was first thought to be haematuria. Doctors tend to overlook the diagnosis of PNH in patients with chronic haemolysis. Our patient was remarkable because of her age at presentation. Most patients diagnosed with this condition are young adults, the main symptoms usually first appearing in the third and fourth decades of life.[9]

The clinical course of PNH is highly variable, ranging from a mild defect to a lethal process. As previously stated, the main clinical features consist of haemoglobinuria, episodic haemolysis, marrow hypoplasia and thrombotic disease.[1-3] Renal failure occurs rarely in PNH.[10] There is a close relation to aplastic anaemia and conversion into acute leukaemia occurs in 5 to 15% of all patients.[6-8] PNH should

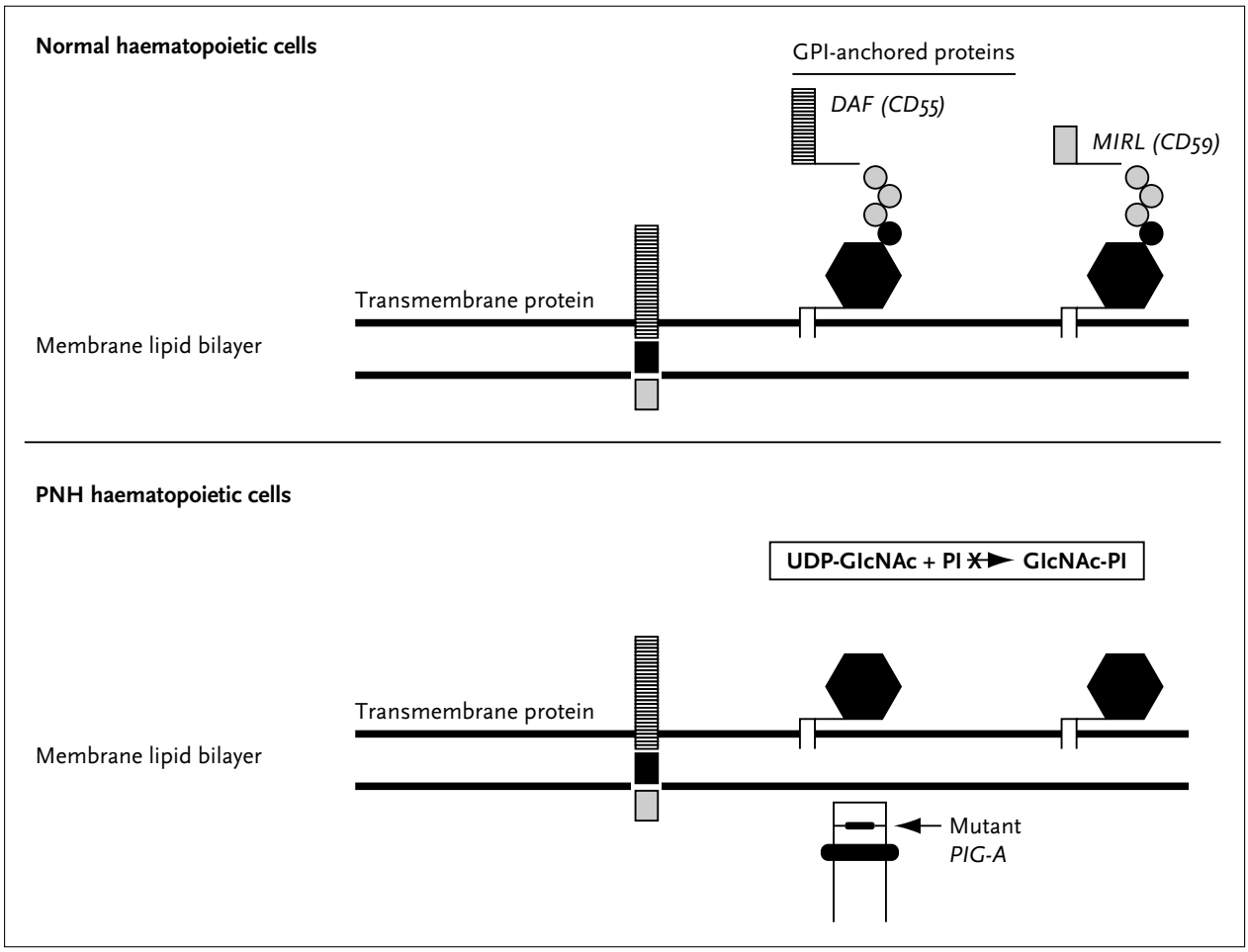

Figure 1
Normal and PNH haemotopoietic cells

be considered a very serious disease, the complications of which can be fatal. Nowadays, however, even mild cases can be detected because of new techniques such as flow cytometry, which is a specific diagnostic test for PNH.[11] In PNH, expression of PI-anchored proteins is significantly reduced or absent due to a mutation of the PIG-A gene, causing absence of PI-anchored proteins. In normal circumstances these proteins protect against complement-mediated lysis of red cells (*figure 1*). Flow cytometric analysis can exactly measure the expression of antigens on each cell membrane and estimate the percentage of deficient cells by using monoclonal antibodies. In our patient, only 5% of the granulocytes reacted with CD59, CD24 and CD16 antibodies, which recognise PI-anchored proteins. Erythrocytes of PNH patients are most deficient for DAF (CD55), MIRL (CD59) and AchE (CLBgran/5Ag).

PNH must be differentiated from antibody-mediated haemolytic anaemias (AIHA), especially paroxysmal cold haemoglobinuria and the cold agglutinin syndrome. This was done in our patient by performing a direct Coombs' test, which was negative. Warm and cold antibodies were also negative. Other causes of chronic haemolysis, such as corpuscular defects, were ruled out as well. Molecular analysis of haemoglobin showed no abnormalities. Erythrocyte enzyme values were normal.

With the exception of bone marrow transplantation, there is no curative therapy available.[12] Treatment depends on the clinical picture and consists of supportive measures, such as transfusion, antibiotics and anticoagulants.[1,2] Thrombosis occurs frequently and accounts for 50% of all deaths in PNH. Beneficial effects of steroids and splenectomy have been reported. We describe a patient with chronic haemolytic anaemia caused by PNH, which was diagnosed by flow cytometry. She was treated with blood transfusions, iron and folic acid suppletion, and a prophylaxis against thrombotic complications.

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