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Brief report

A patient with fatal cold haemagglutinins

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Abstract

We describe a patient with an acute fatal autoimmune haemolytic anaemia (AIHA) due to idiopathic cold haemagglutinins. According to the literature the dramatic course of this cold haemagglutinin disease is uncommon.

Keywords: Anaemia; Cold haemagglutinin; Fatal; Haemolysis

1. Case history

In June 1994 a 64-year-old male was admitted because of jaundice. He had a pneumonia in 1946, urinary tract infection in 1970, nasal polyps since 1980 and prostatism in 1994. Two days before presentation he had dark urine and bilateral lumbar pain. His general practitioner prescribed amoxicillin for suspected urinary tract infection. The next day fever and jaundice appeared. Physical examination showed a moderately ill icteric man with a temperature of 38.2°C without further abnormalities. Later he developed acrocyanosis. His serum was brown coloured. Remarkably his blood already agglutinated several seconds after removal. Only after heating the blood to 37°C could laboratory tests be performed. The erythrocyte sedimentation rate was 88 mm after 1 h, haemoglobin 3.6 mmol/l with normal cell indices, reticulocytes were 52‰, leukocytes $19.2 \times 1 \times 10^9$/l, platelets 211×10^{12}/l, lactate dehydrogenase 6672 U/l, bilirubin 186 μmol/l, and haptoglobin was 0.3 g/l. No paraprotein was found. Analysis of arterial blood gases showed an incomplete respiratory compensated metabolic acidosis (pH 7.24, Po_2 133 mmHg, Pco_2 17 mmHg, bicarbonate 7 mmol/l, base excess −20 mmol/l, O_2 saturation 100%). The direct antiglobulin test was negative with anti-IgG, anti-IgM and anti-IgA, but positive with anti-complement (C3c, C4) serum, indicating the presence of IgM auto-antibodies. Neither erythrocyte-bound antibodies nor allo-antibodies were found. Warm haemolysins were absent, but aspecific cold auto-antibodies were present. These cold agglutinins reacted equally strongly with I-positive adult donor erythrocytes as with I-negative adult donor erythrocytes and with cord cells. We did not find anti-Pr antibodies. Even at a temperature of 30°C the cold agglutinins were strongly reactive, indicating a wide thermal amplitude. The cold agglutinin titre (CAT) was 16 at 4°C, 8 at room temperature and negative at 37°C.

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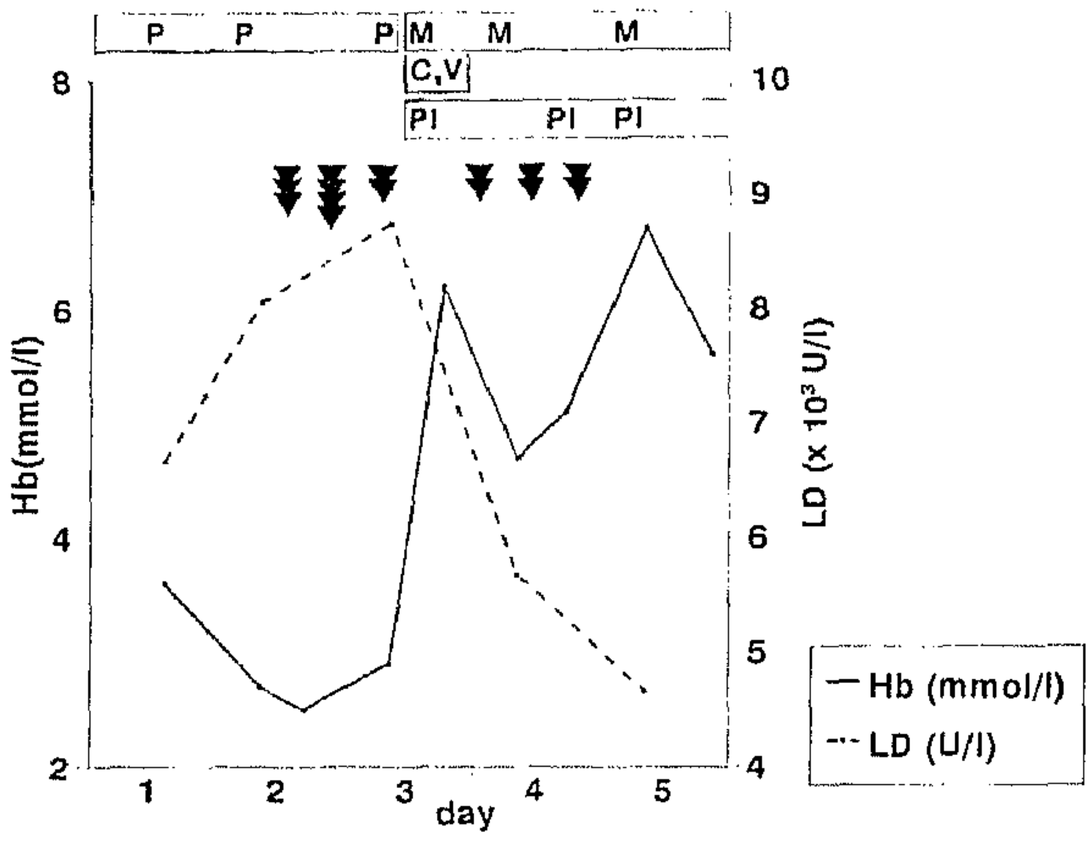

Fig. 1. Course of haemolysis and therapy of the patient. P = prednisone 60 mg (orally); M = methylprednisolone 1000 mg (i.v.); C = cyclophosphamide 1000 mg (i.v.); V = vincristine 2 mg (i.v.); PI = plasmapheresis; Hb = haemoglobin (normal 8.5–10.7 mmol/l); LD = lactate dehydrogenase (normal < 290 U/l); ▼ = blood transfusion.

Serological testing did not reveal a recent infection with *Mycoplasma pneumoniae*, Epstein-Barr virus or cytomegalovirus. Electrocardiography, chest X-ray and ultrasonography of the abdomen were all normal.

A diagnosis of acute auto-immune haemolytic anaemia (AIHA) due to low-titre IgM cold haemagglutinins with wide thermal range was made. Despite treatment with warm covers, corticosteroids and transfusions at 37°C of 3 times washed leukocyte-depleted blood the fulminant haemolysis continued (Fig. 1). High-dose corticosteroids, several plasmaphereses and cytostatics (cyclophosphamide and vincristine) were unable to stop haemolysis and multi-organ failure developed. The patient required inotropic medication, artificial ventilation and renal replacement therapy. Four days after admission he died. Autopsy confirmed multi-organ failure; no underlying malignancy was found, nor signs of a primary pneumonia or other infections. The diagnosis, therefore, is 'fatal acute AIHA due to idiopathic IgM cold haemagglutinins'.

2. Discussion

In 1925 a possible association between acrocyanosis in Raynaud's disease and cold haemagglutinins was described for the first time [1]. Cold haemagglutinins may occur idiopathically and cause the cold haemagglutinin disease (CHAD) [2] which affected our patient. Furthermore, cold haemagglutinins can occur secondarily to infections (especially *Mycoplasma pneumoniae* and infectious mononucleosis), chronic lymphatic leukaemia and malignant lymphoma, solid tumours, cirrhosis of the liver, sarcoidosis and systemic diseases, all being beyond the scope of this case report.

CHAD affects males and females equally and occurs mainly above the age of 60 years. In CHAD for not yet elucidated reasons monoclonal cold haemagglutinins are formed, usually of the IgM class and directed against the I-antigen (seldom the i- or H-antigen) of the erythrocytes. Haemolysis due to cold haemagglutinins mainly occurs intravascularly after activation of complement [2,3].

The predominant characteristic of a patient with CHAD is acrocyanosis in cold, which appears reversible after warming. Laboratory investigations are crucial to diagnose CHAD. Rapid macroscopic auto-agglutination is characteristic, being reversible after heating the blood to 37°C. At 37°C the erythrocytes usually look normal at 37°C, but at lower temperatures there may be anisocytosis, poikilocytosis and spherocytosis.

In CHAD the direct antiglobulin test is positive using anticomplement serum, while it is negative with anti-gammaglobulin sera. The IgM cold agglutinin in itself is rarely detected as it disappears readily from the cell, especially during warming. Usually the CAT is strongly positive at 4°C, varying from 1024 to 512000. The CAT falls with rising temperatures, especially at temperatures above 20°C. The CAT may remain stable or increase gradually over years, or decrease after treatment of the patient with cytostatics, parallelling the clinical response. The appearance of clinical symptoms in CHAD not only depends on the titre of cold haemagglutinins, but also and more importantly on their thermal amplitude, which is the range of temperatures over which they cause haemagglutination [2,3].

Treatment of a patient with CHAD is determined by the seriousness of the symptoms. If slight acrocyanosis in the cold is the only symptom, avoidance of cold will suffice. However, in more serious cases additional treatment will be necessary. Medical ther-

apy may consist of corticosteroids to inhibit the production of cold haemagglutinins [2]. Furthermore, alkylating agents and antimetabolites are recommended [2]. Finally α-interferon [4,5] and danazol [6] are mentioned. Blood transfusions are seldomly required. Compatible blood can hardly be found since the cold haemagglutinins are usually directed against the I-antigen present on erythrocytes of almost all adults. Blood must be only transfused after heating to 37°C. Plasmapheresis has been mentioned to remove the cold haemagglutinins from the blood [2,7], but it will not inhibit the monoclonal production of cold haemagglutinins. Finally, splenectomy has been reported with ambiguous results [2].

The prognosis of CHAD is good. Usually it is a chronic disease stable for years, but gradual progression and spontaneous remission have also been described.

Only 2 other cases of fatal AIHA due to idiopathic cold haemagglutinins have been described. The first patient had idiopathic cold IgM haemagglutinins in low titre (64 at 4°C and 16 at 37°C) with a wide thermal range causing fatal haemolysis [8]. The other patient died from haemolytic anaemia caused by idiopathic anti-Pr cold IgM agglutinins with high thermal amplitude at very low titres [9].

Our patient also presented with acute, rapidly progressive AIHA caused by idiopathic cold IgM haemagglutinins in low titre and with a wide thermal amplitude, and did not respond to corticosteroids, cytostatics, blood transfusions and plasmapheresis. Remarkable was the absence of monoclonality of the cold haemagglutinins, as well as the fulminant course of the haemolysis, both reported in haemolysis due to cold haemagglutinins secondary to infections [10,11]. We are in need of new therapeutic strategies to manage cases like ours.

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