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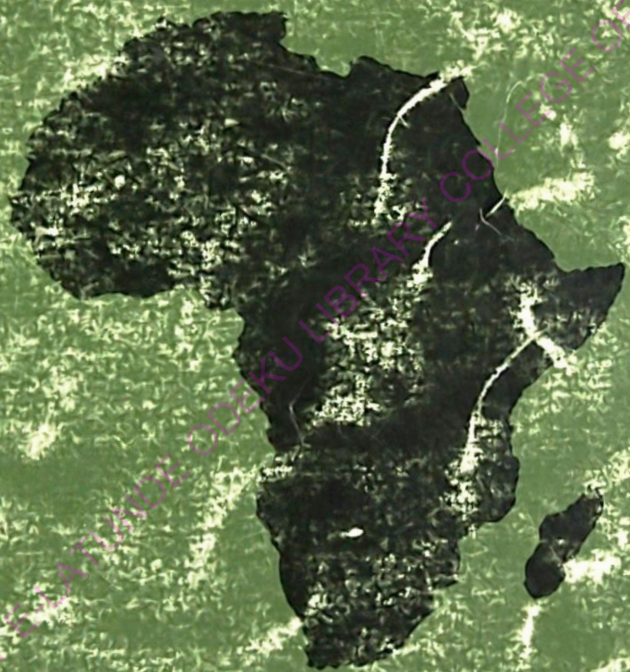

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maturation. The lupus erythematosus cell preparation was negative. The haemoglobin genotype was AA and the glucose-6-phosphate dehydrogenase screening test was negative. Total bilirubin was 5.3 mg% with 4.6 mg% unconjugated. Urobilinogen was present in excess in the urine, while bilirubin was absent. Total serum protein was 7.7 g/100 ml, of which albumin was 4.8 g/100 ml, and globulin 2.9 g/100 ml. The serum sample was negative for hepatitis B surface antigen. The monospot test for infectious mononucleosis was negative, the Donath–Lansteiner test and the serological test for syphilis (VDRL) were both negative.

Blood group serological investigations

The blood group was O, rhesus positive. Other red cell groups were: MS/Ms; P,+ve; Lu(a^-); K-K+; Le (a^-b^-); Fy(a+b+); Go(a^-); Js(a^-). The direct antiglobulin (Coombs) test was positive, the cells reacting with specific anti-complement (anti-C3).

To determine the specificity and titre of the cold antibody the patient's serum was tested neat and up to a dilution of 1 in 512 against (a) a pool of O positive cells chosen to contain the common antigens, and (b) a pool of O umbilical cord cells. The patient's red cells were included as auto-control. The cell–serum mixtures were left at 4°C for 90 min and reading made under a microscope in a cold room at that temperature. The results are shown in Table 1.

It was then necessary to determine the thermal amplitude of the cold agglutinins: a master series of doubling dilutions of patient's serum was made in 0.9% saline from 1 in 1 to 1 in 512. From these dilutions replicate samples were pipetted so that the three red cell samples — pooled normal adult group O red cells, pooled group O cord red cells, and patient red cells — were tested at four different temperatures: 4°C, 10°C, 25°C and 37°C. The serological reactions are indicated in Table 2.

The conclusions from the serological reactions were that the patient had a low-titre cold reacting antibody with i specificity.

At this initial admission a diagnosis of autoimmune haemolytic anaemia due to anti-i cold antibody was made. The patient was started on prednisolone orally, and had a transfusion of 3 units of packed red cells. From then until 2 years later, she was hospitalized on four occasions and received 11 additional units of packed red cells, as well as oral prednisolone. On her last admission she was found to be very ill, dyspnoeic, pale and jaundiced. Her Hb was 2.7 g/dl, Hct was 0.07 l/l. The white cell count was 13.7 × 10^9/l. In spite of transfusion with 3 units of packed red cells, her condition deteriorated and she died; permission for autopsy was not granted.

Discussion

Autoimmune haemolytic anaemia represents a

Table 1. Titre of cold antibody (temperature 4°C)

	Adult cells (I+)	Cord cells (i+)	Auto-control
Titre	1 in 32	1 in 512	1 in 8

Table 2. Thermal amplitude of cold antibody

Cells	4°C	10°C	25°C	37°C
Patient (auto-control)	1 in 8	1 in 32	1 in 16	—
Normal adult (I)	1 in 32	1 in 16	—	—
Normal cord (i)	1 in 512	1 in 512	1 in 64	1 in 32

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Autoimmune haemolytic anaemia associated with low-titre anti-i cold agglutinins in a Nigerian. A case report

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Summary

A case of autoimmune haemolytic anaemia due to low-titre anti-i cold agglutinin in a Nigerian is described. The patient presented with chronic haemolytic anaemia with a positive direct antiglobulin test, the cells reacting with anti-complement (anti-C3). Further tests showed that the antibody was a low titre (1 in 512) cold anti-i antibody with a wide thermal amplitude. The case reported appears to be the first case of cold haemagglutinin disease in a Nigerian.

Résumé

Un cas d'anémie hémolytique attribuable à l'auto-anticorps froid dans un Nigérien est décrit. Le patient présentait du syndrome hémolytique chronique. Le test de Coombs direct était positif; les globules rouges réagissent d'un anti-complément (anti-C3). Les autres tests montrent que l'anti-corps était anti-i anticorps froid de titre bas et l'amplitude thermal large. Il semble que le cas décrit est le premier au Nigéria.

Introduction

Haemolytic anaemia due to cold agglutinins is uncommon; when it occurs it is usually associated with very high levels of cold agglutinins of autoimmune type [1–3]. The haemolysis may be acute or chronic; the acute variety is usually transient and often related to primary atypical pneumonia due to *Mycoplasma pneumoniae* [2], or to infectious mononucleosis [3]. The chronic form is more representative of the classic cold haemagglutinin disease, characterized in temperate climates by acrocyanosis and a variable degree of haemolytic anaemia, and is sometimes associated with malignant lymphoma [2]. Clearly the nature of the disease indicates the greater frequency in colder climates. Autoimmune haemolytic anaemia has been reported in Nigerians but has been of the warm IgG type [4]. Similarly, autoimmune haemolytic anaemia has been reported in Kenya by Barr [5]. No reports appear so far of autoimmune haemolytic anaemia associated with cold agglutinins either in Nigerians or in other Africans of negroid stock. We describe here a case of chronic haemolytic anaemia associated with low-titre cold antibody with the rare anti-i specificity.

Case report

A 30-year-old Nigerian housewife was initially seen at the University of Nigeria Teaching Hospital, having been referred from a private hospital. Her main complaints were weakness, tiredness and yellowness of the eyes, all of 2 months' duration. She had been admitted to this hospital for the same complaints on three occasions over the previous 3 years. Physical examination revealed marked conjunctival pallor and jaundice. The liver was palpable 3 cm below the right costal margin and the spleen 4 cm below the left costal margin. There was no detectable lymphadenopathy.

The haemoglobin (Hb) was 6 g/dl, the haematocrit (Hct) 0.19 l/l; white cell count was 4.5×10^9/l with normal differential leucocyte count. The reticulocyte count was 9% and the peripheral blood film showed several spherocytes, and polychromasia. Bone marrow showed erythroid hyperplasia with normal

assistance, and to Mr John Harrison, Chief Technician of North London Blood Transfusion Centre, for detailed blood group typing of the patient and helpful suggestions for investigation of the patient. I also thank Mr C. Irojiogu for typing the manuscript.

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wide range of haemolytic anaemias in which there is some association with conditions of altered immune status. The demonstrable antibodies may be cold or warm depending on the temperature at which they are maximally reactive. Cold antibody haemolytic anaemia is much less common than the warm variety [3]. It may present as haemolytic anaemia associated with Raynaud's phenomenon and acrocyanosis or may present only with a chronic haemolytic state of varying degree [3].

Our case was shown to have a cold autoantibody by a positive reaction of the patient's red cells with not only a broad-spectrum anti-human globulin reagent, but also reaction with a specific anti-complement (anti-C3). It was not possible to elute the coating antibody further. Another feature of the antibody worthy of note was the titre of the cold antibody. It has been observed that high titres of cold antibody are usually found in chronic haemagglutinin disease. Schubothe [2] observed that the titre at 0°C may vary from 1 in 4000 to 1 in 128,000, while one of the cases reported by Evans *et al.* [6] had a titre of 1 in 500,000. Our patient, however, was unusual in that she had a low titre of cold antibody (1 in 512) at 4°C. This titre compares with the two patients described by Schreiber *et al.* [1], whose cold agglutinin titre at 4°C was 1 in 256, and another reported by Evans *et al.* [6] with a low titre of 1 in 512. The reactivity and haemolytic effect in our case must be related to the observation that the degree of red cell breakdown is greater in those patients in whom the thermal amplitude of antibody activity reaches 37°C [1]. Another unusual aspect of this case was that the antibody detected was anti-i. This antibody has been observed rarely to be the cause of cold haemagglutinin disease [7–9]. Clinically this patient presented classically with chronic haemolytic anaemia. However, other features of cold agglutinin disease were not present. There was neither acrocyanosis nor the manifestations of Raynaud's phenomenon. These were obviously absent in this case because, in relatively warmer climates, as has been observed by Schubothe [2], the symptoms of acrocyanosis or cold intolerance may be absent.

Cold haemagglutinin disease is caused by an IgM complement-fixing antibody whose optimum temperature of activity is 4°C [10]. The titre of the antibody is usually not below 1 in 1000 [1,10,11]. The upper level titre in this condition may be as high as 1 in 100,000 [10]; a titre of 1 in 500,000 has been recorded [6].

The pathophysiology of cold antibody-mediated haemolysis has been clearly defined. On exposure to a cold environment the temperature of the blood in areas close to the surface, such as the skin, drops. This transient reduction of the temperature sets off the complement sequence [10]. The complement fixation by the cold antibody is very rapid, proceeding to the C9 stage, with direct lysis of the red cell within the circulation [10]. Often, however, the fixation of complement is not complete as the red cell leaves the surface structures and returns to body temperatures. The cold IgM antibody detaches from the red cell, but leaves the complement at the stage of C3b still bound to the red cell surface. Since the macrophages in the liver and spleen have C3b receptors, these bind the C3b components and cause the phagocytosis of the C3b-coated erythrocytes [10,12].

This extravascular type of haemolysis forms the more important form of red cell breakdown in complement-mediated cold antibody disease. Thermal amplitude is obviously important in determining the extent of haemolysis in chronic haemagglutinin disease. Even at a relatively lower level or titre of cold antibody, the patient with the higher temperature amplitude of antibody might still have considerable haemolysis [1,10,12].

The case described in this paper appears to be the first such described case of cold haemagglutinin disease in a Nigerian, although warm auto-immune haemolytic anaemias have been described in Nigerians [4] and in Kenyans [5].

The cold antibody haemolytic anaemias, because of the circumstances of a warm environment, would appear to be much less common in persons of negroid stock. But we feel that, with the improved diagnostic expertise available at the University Hospital Centres, and with increased clinical awareness, it should be possible to reveal any cases of this unusual condition which may otherwise have been missed.

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