

COLD ANTIBODIES: an uncommon factor in transfusion safety in a tropical country: a report of two cases

ANTICORPS FROID : un facteur rare dans sécurité transfusionnelle dans un pays tropical : un rapport de deux cas

Mamman Aisha, Suleiman AM, Ijei IP
*Ahmadu Bello University Teaching Hospital
Zaria, Nigeria.*

CORRESPONDENCE

*Aisha Mamman
Department of Haematology
Ahmadu Bello University Teaching Hospital
Zaria, Nigeria
Email: aishamamman@yahoo.com*

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ABSTRACT

BACKGROUND

Cold reacting antibodies with a thermal optimum at 0°C are an uncommon occurrence, and the clinical manifestations are rarely observed in the warm climate of the tropical countries of sub-Saharan Africa.

OBJECTIVE

The objective of this presentation is to report two cases in which cold-reacting antibodies were detected, and to draw attention to the challenge posed to blood transfusion practice by this occurrence in a tropical developing country.

METHOD

Two cases are presented of the detection of cold-reacting antibodies at crossmatch. One was a 30 year old pregnant patient with sickle cell anaemia, who was followed up for nine years. The other was a 76 year old patient with colonic carcinoma, who was successfully managed and followed up for three years.

RESULTS

The sickle cell anaemia patient was successfully transfused with warmed blood, but represented nine years later with acrocyanosis and ulcers on the hands and feet. The colonic carcinoma patient was also successfully transfused, and received chemotherapy following surgery. Remission of the malignancy was achieved and thereafter, the cold antibodies disappeared over a follow-up period of three years.

RESUME

CONTEXTE

L'apparition des anticorps réagissant à froid à un optimum thermique de 0°C est un événement rare, et les manifestations cliniques associées sont rarement observées dans les climats chauds des pays tropicaux d'Afrique sub-saharienne.

OBJECTIF

L'objectif de ce travail de recherche est de rapporter deux cas dans lesquels des anticorps froids ont été détectés, et à attirer l'attention sur le défi posé par cet événement à la pratique de la transfusion sanguine dans un pays tropical en développement.

MÉTHODE

Deux cas ont été identifiés lors de la recherche d'anticorps réagissant à froid au cours des épreuves de compatibilité croisée. L'un était une patiente enceinte de 30 ans souffrant d'anémie falciforme, qui a été suivie pendant 9 ans. L'autre était un patient âgé de 76 ans souffrant d'un cancer du côlon, qui a été géré avec succès et suivi pendant 3 ans.

RÉSULTATS

La patiente souffrant d'anémie falciforme a été transfusée avec succès avec du sang réchauffé, mais a présenté neuf ans plus tard une acrocyanose et des ulcères des mains et des pieds. Le patient souffrant de cancer du côlon a également été transfusé avec succès, et a reçu une chimiothérapie après la chirurgie. La rémission de la tumeur maligne a été obtenue et par la suite, les anticorps froids ont disparu sur une période de trois ans de suivi.

CONCLUSION

Meticulous crossmatching by standard techniques, of blood for transfusion, and a high index of suspicion and resourcefulness are required to detect and manage anomalous factors in blood transfusion practice in resource-constrained developing countries.

CONCLUSION

Un cross-match minutieux du sang destiné à la transfusion à l'aide de techniques standards, un indice de suspicion élevé et de l'ingéniosité sont nécessaires pour détecter et gérer les facteurs anormaux dans la pratique de la transfusion sanguine dans les pays en développement à ressources limitées.

INTRODUCTION

Cold-reacting antibodies, or cold agglutinins, are mainly IgM antibodies with thermal optimum at 0°C, which, if they bind to erythrocytes at sub-normal temperature in-vivo, can cause red cell haemolysis.^{1,2} Cold antibodies are usually harmless as they do not react beyond 30°C. The exact cause of cold antibodies is not known, but most of them are thought to be auto-antibodies directed against the I, i H and Pr blood group antigens.³ The auto-antibodies, which are monoclonal, produce a chronic autoimmune haemolytic anaemia, (AIHA), and manifest as a clinical syndrome called chronic haemagglutinin disease (CHAD or CAD). Other cold antibodies are associated with some infections, such as mycoplasma, or with some lympho-proliferative disorders. These latter types of cold antibodies are polyclonal, and usually transient.¹ When cold agglutinin activity occurs in parts of the body exposed to cold weather, not only intravascular agglutination and/or lysis, but also vasoconstriction of peripheral blood vessels may occur. The resultant acrocyanosis and pain, particularly in the extremities, constitute what is called the Raynaud's phenomenon.⁴ Recurrent Raynaud's episodes may cause ulceration and digital deformity.⁴ Cold agglutinin-induced intravascular haemolysis may produce haemoglobinuria and haemoglobinuria, with potential for renal failure.

Detection of most cold agglutinins is best at low temperature as agglutination is lost when the test is incubated at temperatures above 30°C. The presence of a cold antibody is therefore to be suspected when, during a routine crossmatch, agglutination is observed only in the tube incubated at room temperature of 25°C or below, and not in the tubes incubated at 37°C. This observation can sometimes initially constitute a diagnostic puzzle. Agglutination due to cold-reacting antibodies is also lost when the serum is treated with mercaptoethanol (IgM antibodies), or neuraminidase (Pr antibodies).^{1,5} Individuals with cold antibodies, who require blood transfusion, may be transfused safely with blood above the thermal threshold for agglutination. This usually involves pre-warming banked blood before transfusion, and, or, nursing the patient in a surrounding of forced air surface warming.⁶

METHODS

Blood was requested for two patients and a routine crossmatch was set up for each one. At our centre, routine crossmatch involves the reaction of one volume of patient's serum with one volume of 2% donor red cell suspension in saline. Crossmatch is done by four techniques, namely, incubation in saline at room temperature (usually 20 - 25°C), incubation in saline at 37°C, incubation in saline with albumin enhancement at 37°C, and the indirect antiglobulin technique with initial incubation for one hour at 37°C.

CASE PRESENTATION

Case 1

CN a 30 year old health worker, and a known sickle cell anaemia patient, presented in the 31st week of her third pregnancy with sickle cell crisis and severe anaemia. Her routine management had been with anti-malarial prophylaxis, folic acid and analgesics and antibiotics when required. Blood was requested to carry out a partial exchange transfusion, in order to reduce the concentration of circulating haemoglobin-S- containing erythrocytes. At routine crossmatch, with group identical donor red cells, agglutination was observed in the room temperature tube, but not in the tubes incubated at 37°C. The room temperature test was repeated with incubation at blood bank refrigerator temperature of 4°C, and lysis was observed. In the absence of facilities to identify and further characterise the antibody, it was concluded that the patient had cold-reacting antibodies in her blood. The crossmatched units of blood were warmed in a 38°C incubator for 45 minutes, and later transfused uneventfully. The patient's serum was retested periodically by incubation with group identical red cells, and the cold antibodies were persistently present. Subsequent occasional transfusions were given in the same way. Then nine years after the initial presentation, during a particularly cold harmattan season, when average ambient temperature was about 16°C, the patient was referred to the haematology clinic with maroon coloured, pruritic, macular lesions over the dorsa of both feet and hands, and the extensor surfaces of the arms. The intensive itching and scratching had resulted in ulcers on the hands. Antifungal and anti-scabies treatment had been given at the general clinic without any relief. Tests for LE cells and anti-nuclear antibodies were negative, but the cold antibody test was persistently positive. Management consisted of warm dressings, antibiotics and antihistamines along with her routine sickle cell anaemia therapy. There was marked improvement in the clinical condition.

Case 2

AA was a 76 year old community leader on whom a provisional diagnosis of colonic carcinoma had been made, and blood was requested to correct anaemia from rectal haemorrhage, and to prepare for surgery. At routine crossmatch with group-identical donor red cells, lysis was observed in the room temperature tube but not in the tubes incubated at 37°C. Incubation at 4°C also produced lysis. It was concluded that these reactions indicated the presence of a cold-reacting antibody. Blood for transfusion was immersed in warm water (37°C) for 30 minutes, and transfusion proceeded without adverse reaction. Jaundice was not observed, and serial haemoglobin concentration determinations, post-surgery, did not reveal significant fall. Thereafter chemotherapy was commenced, with follow-up tests for the cold antibodies. Upon achievement of clinical remission of the primary malignancy, the cold antibody test gradually became less strongly positive, and disappeared over a 3-year follow-up period.

DISCUSSION

Sickle cell anaemia is the most common haemoglobin disorder in Nigeria, affecting some 2% of the adult population⁷. The periodic haemolytic crisis and vaso-occlusive events make the sickle cell anaemia patient a potential recipient of repeated red cell transfusions with an annual transfusion demand estimated at 0.5 units per patient per annum in the least complicated cases⁸. Repeated transfusions, especially from diverse donors, make the patient susceptible to development of allo-antibodies. Kuliya Gwarzo et al, reported an allo-antibody prevalence of 8.8% among multi-transfused patients with sickle cell anaemia⁹. The antibodies identified by Gwarzo included anti-D, anti-E, anti-Kp^a, anti-Js, anti-Wr^a, anti-Mg, anti-Vw, and anti-Goa in various combinations⁹.

Besides allo-antibody formation, chronic slow-healing ulcers of the lower extremities are common in sickle cell anaemia patients.⁷ The exact pathogenesis of the ulcers is not clear, but vascular insufficiency, peripheral nerve damage, immune deficiency and some mineral deficiencies have been variously implicated¹⁰.

The first case, a sickle cell anaemia patient, was found to have cold antibodies, which could be auto-immune in origin, or due to allo-immunisation from previous red cell transfusions. The persistence of the antibodies with clinical presentation 9 years after first detection in the absence of overt malignancy makes an infectious cause unlikely. On the other hand, presentation during an unusually cold harmattan season, with ambient temperature of about 16°C suggests that the acrocyanosis and ulcers on the hands and feet may be due to Raynaud's phenomenon, and not just the ulcers of sickle cell anaemia. Synergy between the two phenomena of agglutinin-induced, and sickle cell, ulceration can however not be ruled out. The second case was a patient with colonic carcinoma whose cold antibodies were first detected at crossmatch for peri-operative blood transfusion. The disappearance of the antibodies with remission of the primary malignancy suggests that the antibodies were associated with the malignancy. If the histological diagnosis of colonic carcinoma was correct, this association is unusual, since lymphoproliferative malignancies are more commonly implicated.¹

CONCLUSION

The paucity of reports of development of cold antibodies in the course of sickle cell anaemia, and failure to find other cases in a 9 year follow-up at our centre, confirm the rarity of the condition. The detection of cold antibodies in our two cases during routine crossmatch, underscores the need for meticulous crossmatching of blood for transfusion by multiple standard techniques.

The inability to identify or characterise the antibodies further, and the non-standard method of warming blood, are challenges for blood transfusion practice in developing countries.

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