Relato de Caso / Case Report

Severe gangrene by cold agglutinemia
Gangrena grave causada por crioaglutinina

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*The cold agglutinin syndrome is a haemolytic disorder usually manifested by acrocyanosis and Raynaud's phenomenon. Gangrene is an uncommon complication, usually associated with infections or B-cell lymphoproliferative diseases. We present a case of fulminant gangrene of fingers, toes, and nose in a 77-year-old woman with atypical pneumonia and acute renal failure. The diagnosis of haemolytic anaemia with cold agglutinin syndrome was done and the treatment with antibiotics and corticosteroids was effective. However, amputation of all the toes on both feet could not be avoided. Clinical aspects of cold agglutinemia, transient or chronic, are briefly discussed. We conclude that, in the presence of cold agglutinin syndrome, the treatment should be promptly initiated in order to avoid complications such as extensive gangrene. Rev. bras. hematol. hemoter. 2004;**26**(1):46-48.*

Key words: *Cold agglutinemia; gangrene; cold agglutinin antibodies; haemolytic anaemia; atypical pneumonia.*

Introduction

The cold agglutinin syndrome is a haemolytic disorder characterised by the production of antibodies directed against specific antigens on the red blood cell membrane. These antibodies are commonly of IgM type and agglutinate erythrocytes usually below a temperature of 32º C.[1]

The most frequent manifestations are skin lesions, mainly on the acral areas, with acrocyanosis and Raynaud's phenomenon.[1,2] Livedo reticularis, urticaria, petechiae and ecchymosis have also been described.

Infectious diseases, such as those caused by *Mycoplasma pneumoniae* and *Epstein-Barr* virus, can present transient cold agglutinemia.[2-7] It usually causes reversible complications. Gangrene is an exceptional complication of cold agglutinemia, with isolated cases reported in the literature.[3,4,8,9,10] Only five well-documented cases complicating transient infection-related cold agglutinemia have been reported.[2,3,11,12,13] We describe one case of cold agglutinin mediated haemolytic anaemia complicated by gangrene and renal failure during the course of atypical pneumonia.

Case report

A 77-year-old female patient presented with a 5-day history of fever, dry cough, malaise, and acrocyanosis, without arthritis or Raynaud's phenomenon. At admission, she was afebrile, pale and with jaundice. Her blood pressure was 110 X 70 mmHg, pulse rate 120 beats per minute and respiratory rate 36 beats per minute. No lymphodenopathy was observed, and an abdominal examination revealed hepatomegaly without splenomegaly. Despite the fact that all peripheral pulses were palpable and symmetrical, she had gangrenous lesions on distal phalanges of her right hand, index finger of her left hand, all toes on both feet, and nose tip as well. (Figure 1 and 2)

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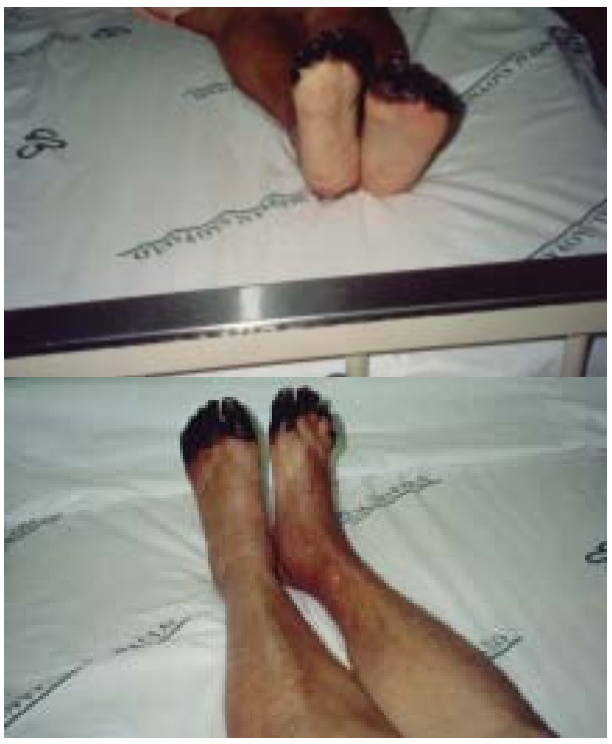

Fig. 1 – *Gangrenous lesions on all toes of both feet*

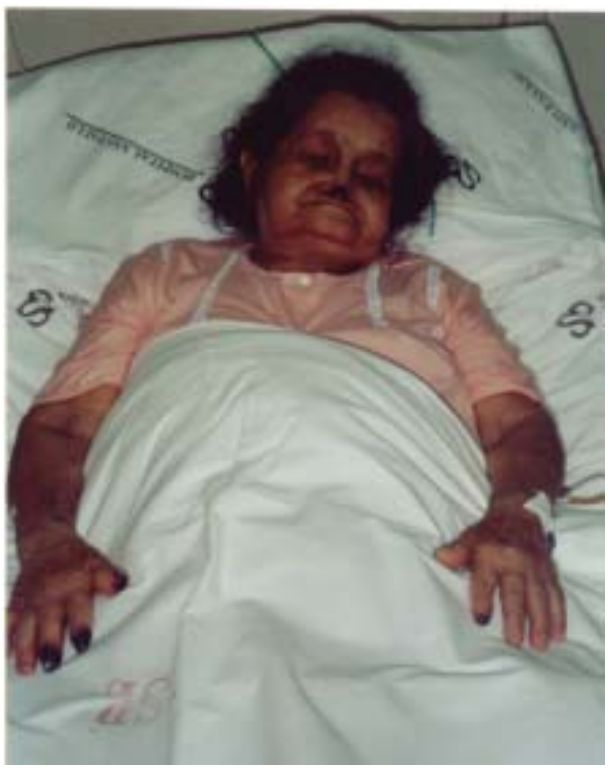

Fig. 2 – *Gangrenous lesions on the tip nose, distal phalanges of three fingers of right hand and index finger of the left hand*

Chest radiograph showed an extensive patchy infiltrate. Laboratory investigation showed haemoglobin level of 5.5 g/dL, red cells clumping, reticulocyte count of 8%, and white blood cell count of 26.7 X 10^9/L. Lactate dehydrogenase was 1918 U/L, creatinine level 3.4 mg/dL, and urea level 119 mg/dL. Direct and Indirect Coombs' tests were positive. The bone marrow aspirate demonstrated erythroid hyperplasia.

An elevated titre of cold agglutinin antibodies at a temperature of 4ºC was observed (1:1280), and the rheumatoid factor titre was 1:1280 IU/mL. Antinuclear antibodies, anti-DNA antibodies, anti-inheritable nuclear antibodies, cryoglobulins, anticardiolipin, and lupus anticoagulant were all negative with normal complement determination. Hepatitis B and C surface antigen and antibody were not found. Blood and urine cultures were negative.

The patient was treated with cefuroxime, azithromycin and prednisone (1.5 mg/kg/day). The gangrenous areas diminished in size, pain eased and her haemoglobin level and renal performance had significant improvement. However, three months after the onset of the symptoms, amputation of all toes was performed. Seven months after discharge, her general condition was excellent with no need for corticosteroids.

Discussion

Cold agglutinin disorders are subdivided into primary or idiopathic and secondary. This last form is usually associated with infections (*Mycoplasma spp, Epstein-Barr virus, Cytomegalovirus, Legionella spp* and *Adenovirus*), or with lymphoproliferative B-cell diseases.[2,14,15]

Clinical manifestations of cold agglutinemia depend on the thermal amplitude of the cold agglutination and the degree of complement activation. The classical clinical syndrome consists of hemolysis and Raynaud's phenomenon. As agglutination is rapidly reversible on warming, almost never leading to permanent obstruction of blood vessels, gangrene is an exceptional manifestation of the cold agglutinin gangrene.[2,7,16]

Up to 20% of community acquired pneumonia is caused by *Mycoplasma pneumoniae* and it is considered a major cause in cold agglutinin-positive pneumonic patients.[17,18,19] Secretion of peroxides by *M. pneumoniae* alters red cell antigens, which become immunogenic leading to the formation of immunoglobulin (Ig) M cold agglutinins.[20]

Cold agglutinin mediated haemolytic anaemia is relatively common complication associated with *M. pneumoniae* infection but the sensitivity of serological methods for the diagnosis of such pathogen in acute stage is only 28%.[18] Therefore, the presence of cold agglutinins in the appropriate clinical setting permits a presumptive

diagnosis of *M. pneumoniae* infection. In this report, we observed cold agglutinins and atypical pneumoniae with clinical response to treatment with azithromycin, supporting the presumptive diagnosis of *M. pneumoniae* infection.

Despite the fact that gangrene is a rare complication of transient cold agglutinemia, the precise treatment could prevent it. Corticosteroid treatment probably has value in decreasing the severity of haemolytic anaemia due to transient cold agglutinin.[21] So, in presence of auto cold-agglutinin activity and haemolytic anaemia, the hypothesis of infection should be considered and an empirical course of antibiotic and corticosteroids should be promptly initiated.

Resumo

*Doença da aglutinina a frio é uma patologia caracterizada pela produção de anticorpos contra antígenos específicos da membrana eritrocitária, geralmente de classe IgM, que aglutinam hemácias em temperaturas abaixo de 32° C. Relatamos um caso de gangrena e insuficiência renal em uma mulher de 77 anos com pneumonia atípica. Anemia hemolítica secundária a crioaglutininas foi observada. O tratamento com antibióticos e corticóides foi eficaz com regressão do quadro, porém foi necessária a amputação de todos os dedos do pé (falanges) bilateralmente, preservando o restante dos pés (tarsos e metatarsos). Anemia hemolítica secundária a crioaglutininas manifesta-se freqüentemente por acrocianose e fenômeno de Raynaud. Gangrena é uma complicação incomum dessa doença, principalmente quando secundária a etiologia infecciosa, sendo observada apenas em pacientes com altos títulos persistentes. Está correlacionada freqüentemente com causa infecciosa (Mycoplasma spp, vírus Epstein-Barr, citomegalovírus, vírus Influenza A, adenovírus, Legionella spp), linfoproliferativas B e idiopáticas. Suspeita clínica de crioaglutininemia deve ser confirmada e tratada prontamente em função da risco de possíveis complicações graves. Rev. bras. hematol. hemoter. 2004;**26**(1):46-48.*

Pavavras-chave: *Anemia hemolítica; crioaglutinina; gangrena seca.*

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