

LETTERS TO THE EDITOR

Raynaud's Phenomenon with Necrosis of the Extremities Induced by Cold Agglutinin Disease Secondary to a T-cell LymphomaClaude Bachmeyer¹, L. Blum², A. M. Chesneau³, J. Richecoeur⁴, F. Testard⁴, B. Benchaâ² and O. Danne²¹Department of Internal Medicine, Centre Hospitalier Laënnec, Boulevard Laënnec, B.P. 72, F-60109 Creil and ²General Medicine,³Anatomy and Pathology and ⁴Réanimation, Hôpital René Dubos, 6 Avenue de l'Ile-de-France, Pontoise, France. E-mail:

claude.bachmeyer@ch.creil-fr

Accepted March 28, 2003.

Sir,

Cold agglutinin disease is a disorder characterized by the production of antibodies directed against specific antigens on the red cell membrane, frequently causing haemolysis (1–3). Cutaneous lesions are unusual in the course of the condition. We report a case of Raynaud's phenomenon with necrosis of the extremities indicating cold agglutinin disease secondary to a T-cell lymphoma.

CASE REPORT

An 86-year-old woman was admitted to hospital in March 2000 as a result of fatigue and typical Raynaud's phenomenon of the hands and feet lasting for 4 weeks, and with some necrotic lesions of recent onset on the feet. She had no medical history and denied ingestion of any medication. She had lost 4 kg in weight during the month prior to admission and appeared fatigued. Physical examination was otherwise unremarkable. The white blood cell count was $6.6 \times 10^3/l$ leucocytes with 69% neutrophils and 16% lymphocytes; her haemoglobin level was 10.8 g/dl with mean corpuscular volume 97 fl (normal 84–98) and 15×10^3 reticulocytes; her platelet count was $225 \times 10^3/l$. The erythrocyte sedimentation rate was 56 mm/h. Serum liver tests and renal function were normal. Serum protein electrophoresis showed an albumin level of 32.6 g/l (36–55) and a polyclonal hypergammaglobulinaemia of 15.6 g/l (6.7–15.2). Serum lactate dehydrogenase was 253 IU/l (normal <280). Antinuclear antibodies were detected at 1/640 with a homogeneous pattern; the search for anti-double-stranded DNA, anti-extractable nuclear antigen and antiphospholipid antibodies was negative; serum C3 component of complement was 0.68 g/l (0.75–1.57); the C4 component was 0.18 g/l (0.24–0.46). No cryofibrinogenaemia or cryoglobulinaemia were detected. Direct Coombs' test was positive for IgG and C3d. A search for cold agglutinins at a temperature of 4°C was highly positive at a titre of 1/1024 with anti-I specificity. Coagulation studies showed normal fibrinogen level, prothrombin time. A search for lupus anticoagulant was negative, circulating anticoagulant plasma activity of protein C, protein S, antithrombin III and heparin cofactor II, and platelet aggregation tests were normal. Serologies for HIV, HCV and HBV, HTLV, Epstein-Barr virus, cytomegalovirus, syphilis and mycoplasma were

negative. Electrocardiogram (24 h) monitoring and transoesophageal echocardiography were normal. Doppler examination demonstrated distal narrowing of distal arteries. Histological examination of skin specimens from the necrotic lesions of legs showed small vessel thrombosis with eosinophilic thrombi of fibrin and erythrocytes but no vasculitis, and areas of ischaemic necrosis within the dermis and the subcutaneous tissue. Computed tomography scan of abdomen and thorax was normal. Bone marrow biopsy disclosed a massive infiltration by atypical small-sized lymphoid cells. Immunohistochemical studies showed that the neoplastic lymphocytes expressed CD3 and CD4 but did not express CD19, κ and λ light chain consistent with the diagnosis of T-cell lymphoma. No analyses of T-cell receptor gene rearrangement were performed. Progressively, the hands and feet became cyanotic and cool and turned to dry gangrene (Fig. 1) despite intravenous pulses of methylprednisolone and cyclophosphamide, then plasmapheresis and administration of etoposide. The patient died from septic shock one month after admission. No autopsy was allowed by the family.



Fig. 1. Necrosis of the extremities.

DISCUSSION

We report a case of Raynaud's phenomenon with necrosis of the extremities in a patient with cold agglutinin disease secondary to a T-cell lymphoma. Indeed, extensive investigations ruled out any underlying thromboembolic disease such as embolic heart disease, cholesterol embolism, connective tissue disease or a hyperviscosity state including antiphospholipid syndrome, cryoglobulinaemia and acral livedo due to vessel occlusion.

In cold agglutinin disease, the antibodies agglutinate erythrocytes with increasing affinity at decreasing body temperatures (1–3). Cold agglutinins are usually IgM antibodies, but also IgG and IgA, directed against I, i or Pr antigens of erythrocytes. A polyclonal form appears after mainly *Mycoplasma pneumoniae* infections and is usually benign, transient and with low titres. On the contrary, a monoclonal form is more chronic, with high titres of cold agglutinins. Cold agglutinins are produced by monoclonal B-cells and therefore can be observed in haematological malignancies such as chronic lymphocytic leukaemia, Waldenström disease and multiple myeloma (1–3). In a few cases, cold agglutinin disease is associated with a T-cell lymphoma and the antibodies are due to the stimulation of B-cell lymphocytes by the malignant clone of T-cells (4, 5).

Skin lesions as the presenting feature of cold agglutinin disease include acrocyanosis and Raynaud's phenomenon (1–3), livedo reticularis (3), cold-induced urticaria (6), petechiae and ecchymoses (7), but cutaneous necrosis is an exceptional complication (2, 6–10). They mainly involve acral areas exposed to lower temperatures such as distal extremities, earlobes and the tip of the nose. Histopathology demonstrates dilatation of dermal vessels with thinning of the vascular walls, eosinophilic thrombi of fibrin and erythrocytes but neither perivascular cell infiltrate nor vasculitis. A reactive angiendotheriomatosis with a glomeruloid pattern has been described (2).

Cold agglutinin disease is a difficult condition to treat. Avoidance of cold exposure is always required. Patients with cold agglutinin disease secondary to infections have a short course and require no treatment. When the condition is associated with malignancy,

treatment of the underlying lymphoma is mandated. Treatment for acute complications relies on plasmapheresis, cyclophosphamide and rituximab can be useful, systemic corticosteroids, intravenous immunoglobulins and splenectomy are often ineffective.

In conclusion, cutaneous lesions can be the presenting feature of cold agglutinin disease, and early recognition is mandatory allowing rapid institution of appropriate treatment.

REFERENCES

1. Crisp D, Pruzanski W. B-cell neoplasms with homogeneous cold-reacting antibodies (cold agglutinins). *Am J Med* 1982; 72: 915–922.
2. Porras-Luque JI, Fernandez-Herrera J, Dauden E, Fraga J, Fernandez-Villalta MJ, Garcia-Diez A. Cutaneous necrosis by cold agglutinins associated with glomeruloid reactive angiendotheriomatosis. *Br J Dermatol* 2000; 139: 1068–1072.
3. Lauchli S, Widmer L, Lautenschlager S. Cold agglutinin disease: the importance of cutaneous signs. *Dermatology* 2001; 202: 356–358.
4. Berth-Jones J, Homes J, Marks A. A case of mycosis fungoides (cutaneous T cell lymphoma) with cold agglutinins. *Br J Dermatol* 1988; 118: 854–855.
5. Takayanagi N, Sampi K. Immunoblastic lymphadenopathy-like T cell lymphoma with high levels of serum interleukin-6, cold agglutinin disease, and immune thrombocytopenia. *Rinsho Ketsueki* 2000; 39: 1109–1114.
6. Barth JH. Infectious mononucleosis (glandular fever) complicated by cold agglutinins, cold urticaria and leg ulceration. *Acta Derm Venereol* 1981; 61: 451–452.
7. Stone MS, Piette WW, Davey WP. Cutaneous necrosis at sites of transfusion: cold agglutinin disease. *J Am Acad Dermatol* 1988; 19: 356–367.
8. Kuenn JW, Weber R, Teague PO, Keitt AS. Cryopathic gangrene with an IgM lambda cryoprecipitating cold agglutinin. *Cancer* 1978; 42: 1826–1833.
9. Poldre P, Pruzansky W, Chiu HM, Dotten DA. Fulminant gangrene in transient cold agglutininemia associated with *Escherichia coli* infection. *Can Med Assoc J* 1985; 132: 261–263.
10. LeBoit PE, Solomon AR, Cruz DJS, Wick MR. Angiomatosis with luminal cryoprotein deposition. *J Am Acad Dermatol* 1992; 27: 969–973.
11. Berentsen S, Tjonnfjord GE, Brudevold R, Gjertsen BT, Langholm R, Lokkevik E, et al. Favourable response to therapy with the anti-CD20 monoclonal antibody rituximab in primary chronic cold agglutinin disease. *Br J Haematol* 2001; 115: 79–83.