

## Rapidly Progressing Skin Necrosis in a Woman after Travelling in Cold Weather: A Quiz

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A 57-year-old woman presented with a 4-day history of fever and rapidly progressing, large confluent purpura and necrosis, with blisters on her lower extremities, buttocks and face (Fig. 1A, B). She reported having travelled in cold weather before the abrupt development of the skin lesions. The patient had experienced worsening arthralgia and oedema in her lower legs during the past 2 years. Systemic low-dose glucocorticoids, methotrexate and topical steroids had been administered, with only partial response. During hospitalization, the patient underwent exacerbation of the rash, renal dysfunction and recurrent congestive heart failure, with transient confusion. Laboratory examination revealed severe anaemia (haemoglobin 59 g/l, normal range 115–150 g/l), elevated serum

creatinine (9 mg/dl, normal range 0.5–1.1 mg/dl), elevated serum IgG (18.5 g/l, normal range 5–15 g/l), and elevated serum lambda light chain (357.5 mg/l, normal range 5.7–26.3 mg/l). Serum immunofixation electrophoresis revealed monoclonal IgG lambda light-chain. Urine tests showed proteinuria (580 mg/24 h, normal range less than 150 mg/24 h) and haematuria (red blood cells 56.9/high power field (HPF), normal range 0–3/HPF). Autoantibodies, including antinuclear antibodies, anti-neutrophil cytoplasm antibodies, and lupus anti-coagulants were negative. Hepatitis A/B/C, cytomegalovirus, and HIV serologies were negative. A skin biopsy obtained from the purpura was performed (Fig. 1C).

*What is your diagnosis? See next page for answer.*



**Fig. 1. Clinical presentation and skin biopsy of the patient.** (A, B) Large confluent skin purpura and necrosis with blisters on the face and lower extremities. (C) Skin biopsy from the purpura, showing vascular dilatation with intravascular hyaline thrombi-filled small-sized vessels throughout the dermis (haematoxylin-eosin stain, original magnification  $\times 100$ ).

## ANSWERS TO QUIZ

**Rapidly Progressing Skin Necrosis in a Woman after Travelling in Cold Weather: A Commentary**

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**Diagnosis: Type I cryoglobulinaemia**

Skin biopsy revealed occlusive vasculopathy with eosinophilic hyaline thrombi filling the dilated blood vessels throughout the dermis. Renal biopsy showed intracapillary thrombi in renal glomeruli. Serum cryoglobulins were positive. Immunofixation electrophoresis on cryoglobulins confirmed monoclonal IgG lambda light-chain. Bone marrow biopsy revealed a lambda-restricted clonal plasma cell population, fulfilling the criteria of multiple myeloma (1). A diagnosis of type I cryoglobulinaemia associated with multiple myeloma was made. The skin purpura resolved markedly after 2 weeks of intensive plasmapheresis and systemic methylprednisolone. The patient was then treated with anti-myeloma chemotherapy with the BD (bortezomib and dexamethasone) regimen. However, she died one year later due to progression of the myeloma.

Cryoglobulins refer to immunoglobulins that precipitate at a cold temperature below 37°C (2). In 1974 Brout et al. (3) first classified cryoglobulinaemia according to the components of cryoprecipitate. Type I cryoglobulin is composed solely of monoclonal immunoglobulin and is usually secondary to a variety of lymphoproliferative disorders, including multiple myeloma, Waldenström's macroglobulinaemia, chronic lymphocytic leukaemia, and lymphocytic lymphoma (4), while type II and type III cryoglobulin (termed mixed cryoglobulins) consist of mixed polyclonal IgG with or without monoclonal IgM, and are associated with autoimmune disorders or HCV infection (5).

Type I cryoglobulinaemia accounts for 10–15% of cases, and the monoclonal cryoproteins are usually IgM paraproteins, less frequently IgG. These immunoglobulins precipitate upon cold exposure, and occlude blood vessels, leading to end-organ damage, including skin, kidney, heart, and nervous system (6). Skin manifestation is a frequent presenting sign for type I cryoglobulinaemia. Skin purpura or necrosis at acral sites of exposure is reported in 69–82% patients, which usually begins at lower extremities, but may extend to the trunk and upper extremities (7, 8). Acrocyanosis and Raynaud's phenomena are frequently seen. Extracutaneous diseases include peripheral neuropathy in 19–44% of patients, arthralgia in 28%, and renal disease in approximately 30% of cases (5). Life-threatening conditions, including large-confluent skin necrosis and acute renal failure, can develop in a small portion of patients, like the case in this patient. The histology was characterized by eosinophilic hyaline occlusion of small-sized blood vessels in multiple organs, especially in the dermis. For cryoglobulin occlusion, therapy is primarily directed at minimizing cold exposure and controlling the underlying plasma cell

dyscrasia or lymphoproliferative disorder in order to reduce the titre of monoclonal cryoglobulin. Plasmapheresis or plasma exchange is used to treat patients with severe hyperviscosity syndrome or life-threatening complications, and reduces circulating cryoglobulins and induces remission of the internal organ damage. Type I cryoglobulinaemia secondary to haematological malignancy is often associated with a poor prognosis.

Although overlap exists among the clinical features of types I, II and III cryoglobulinaemia, in general, mixed cryoglobulinaemia causes symptoms related to vasculitis, characterized by a typical clinical triad: purpura, weakness, and arthralgias. Skin purpura in mixed cryoglobulinaemia is typically intermittent. The face is generally spared, and bullous lesions are uncommon. Leukocytoclastic vasculitis of small-sized vessels with fibrinoid necrosis are characterized in histology (9). Different clinicoserological patterns help to differentiate among cryoglobulinaemias. Cryoglobulinaemia should also be differentiated from inflammatory vasculitis and thrombotic syndromes, including cutaneous leukocytoclastic vasculitis and thrombotic thrombocytopenic purpura, which may manifest as skin purpura with constitutional symptoms (10).

The key to the diagnosis of this patient was the rapidly deteriorating skin purpura after cold exposure, with characterized histological and serological results. However, the prognosis was determined by her underlying haematological disease, which resulted in an unfavourable clinical outcome. This case highlights the importance of recognizing the presenting signs of an underlying malignancy.

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