# Type I cryoglobulinaemia leading to bilateral above-the-knee amputations

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## DESCRIPTION

A man in his 50s with a 3-month history of progressive mucocutaneous lesions on his extremities, ears, tongue and hard palate (figure 1A–C) presented to the emergency department with severe ulcerations, sloughing and necrosis affecting the skin of his lower legs (figure 2). The wounds on his legs began about 2 months prior to presentation as painless lesions on his ankles that gave rise to necrotic bullae and arose in concert with retiform purpuric lesions affecting his upper extremities and ears. He also developed purpuric lesions on his tongue and hard palate around that time. These symptoms were accompanied by arthralgias primarily affecting his hands. His medical history was notable for a symmetrical, sensory peripheral neuropathy in a stocking-glove distribution that was diagnosed 2 years earlier as well as hyperlipidaemia and localised prostate cancer previously treated with radical prostatectomy. Recent outpatient therapy included a course of doxycycline followed by a course of amoxicillin/clavulanic acid, neither of which led to improvement in his skin lesions.

On presentation to the emergency department, the patient was initially started on empiric broad spectrum antibiotics. Punch biopsy of the right upper extremity on hospital day 2 demonstrated dermal capillary proliferation with periodic acid-Schiff-positive intraluminal thrombi and focal ischaemic necrosis. Laboratory evaluation showed an IgG kappa monoclonal protein of 0.3 g/dL, serum kappa free light chains (FLC) of 29.5 mg/dL and a kappa/lambda FLC ratio of 31. The cryocrit was 32% and cryoglobulin immunofixation confirmed a monoclonal IgG kappa cryoglobulin. Bone marrow biopsy demonstrated 3% kappa-restricted plasma cells and fluorescence in situ hybridisation showed amplification of chromosome 1q. A positron emission tomography (PET)/CT scan did not reveal any suspicious osseous lesions. Laboratory evaluation revealed a low serum complement C3 (42 mg/dL) and C4 levels (<8 mg/dL), elevated C reactive protein (211.9 mg/L) and normal creatinine (1.02 mg/dL). Urine studies demonstrated an elevated urine protein/creatinine ratio (1.34 mg/mg) and two red blood cells per high-powered field. Evaluations for the presence of rheumatoid factor, antinuclear antibodies, hepatitis C infection and HIV infection were all negative. The patient was diagnosed with type I cryoglobulinaemia with cryoglobulinaemic vasculitis in the setting of an underlying monoclonal gammopathy of uncertain significance (MGUS).

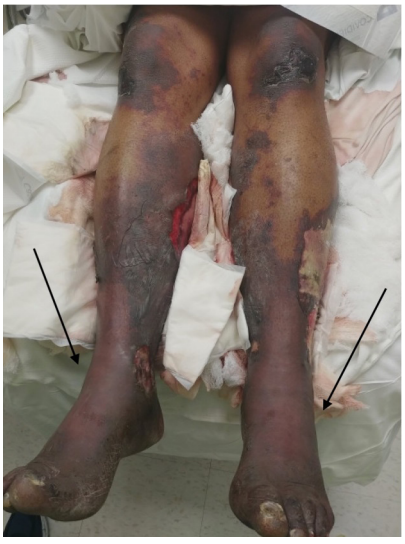

**Figure 2** Extensive ischaemic lesions involving the bilateral lower extremities.

On hospital day 5, the patient's lower extremities were noted to be cold and insensate, with doppler ultrasound revealing absent anterior and posterior tibial arterial flow bilaterally. The patient was treated with corticosteroids, heparin and plasma exchange followed by bortezomib, cyclophosphamide and dexamethasone in addition to bilateral above-the-knee amputations (AKA). Surgical pathology of the lower legs revealed early organising thromboses of the large arteries. The helices of both ears also autoamputated.

Because of an inadequate haematological response, therapy was subsequently transitioned to daratumumab, lenalidomide and dexamethasone. At 18 months follow-up, the patient had no recurrent symptoms attributable to cryoglobulinaemia and his cryocrit was negative.

We present here a case of severe MGUS-associated type I cryoglobulinaemia and cryoglobulinaemic vasculitis,[1] resulting in bilateral AKAs and autoamputation of bilateral auricular helices. Whereas

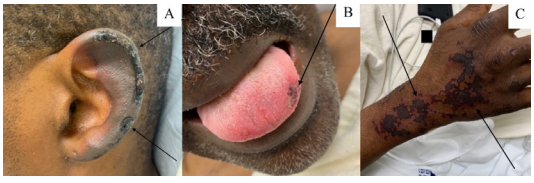


**Figure 1** (A) Ischaemic changes involving the helix, scapha and antihelix of the left ear. (B) Ischaemic lesion on the left lateral aspect of the tongue. (C) Ischaemic lesions involving the right hand and wrist.

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all types of cryoglobulinaemia involve immunoglobulins that precipitate at cold temperatures and are thus termed cryoglobulins, type I cryoglobulinaemia is characterised by monoclonal immunoglobulins as the source of the cryoglobulin, typically due to an underlying lymphoproliferative disorder. Type 1 cryoglobulin precipitation may occlude vessels and induce microthrombi formation, but large vessel occlusion and thrombosis is unusual.[2 3] While type I cryoglobulinaemia is known to occasionally result in ischaemia necessitating the amputation of digits,[4 5] or occasionally portions of distal extremities,[6 7] bilateral AKAs are highly unusual for this disease. Providers should be aware of the potential complications of type I cryoglobulinaemia that we illustrate here.

## Learning points

- Type I cryoglobulin precipitation may induce microthrombi and may be associated with focal ischaemia, sometimes resulting in amputation of digits.
- This case illustrates the potential of type I cryoglobulinaemia to result in large arterial thromboses and bilateral limb amputations.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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