Case Letter

Successful treatment of skin-limited crystalglobulinemia with oral corticosteroids: A report and review of the literature

Dear Editor,

Crystalglobulinemia (CG) is characterised by the crystallisation of paraproteins in the vasculature, resulting in systemic thrombotic vasculopathy. It can be associated with multiple myeloma (MM) and monoclonal gammopathy of undetermined significance (MGUS). Prompt aggressive treatment has been recommended in patients with CG due to the potential life-threatening complications. We describe a unique case of a patient with MGUS with skin-limited CG, which responded to corticosteroid therapy alone.

A 56-year-old Chinese woman presented with a painful ulcer on left shin for 3 weeks. She had a history of mixed connective tissue disease complicated by end-stage renal disease, Immunoglobulin (Ig)-Gκ MGUS, hypertension and non-ischemic cardiomyopathy. On examination, she was afebrile and there was a retiform purpuric plaque measuring 5 × 3 cm with central necrosis on her left shin [Figure 1].

Histological examination of a biopsy of the ulcer showed oblong, crystalline eosinophilic pink deposits occluding the blood vessels in the superficial and deep dermis with no evidence of vasculitis [Figure 2]. The crystals stained positively for periodic-acid-schiff (PAS)-diastase. There was a superficial and deep infiltrate of lymphocytes, neutrophils and plasma cells. A prothrombotic screen including factor V Leiden, lupus anticoagulant, antithrombin III, protein C, protein S and cryoglobulin were negative. Serum protein electrophoresis showed IgG 4.1 g/L (8.5–18.0), IgA 1.7 g/L (1.2–4.4), IgM <0.3 g/L (0.4–2.4) and total protein 44 g/L (65–82). On immunofixation, a monoclonal IgG kappa band was seen. Her bone marrow biopsy demonstrated 1% plasma cells with normal cytogenetics and a skeletal survey showed no lytic lesions.

She was diagnosed with skin-limited CG associated with IgGκ MGUS and started on oral prednisolone 45 mg daily (1 mg/kg/day), which was gradually tapered. After three

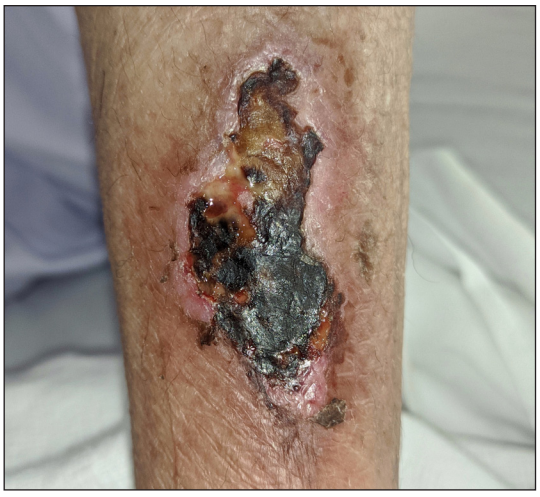

Figure 1: Retiform purpuric plaque with central necrosis on the left shin.

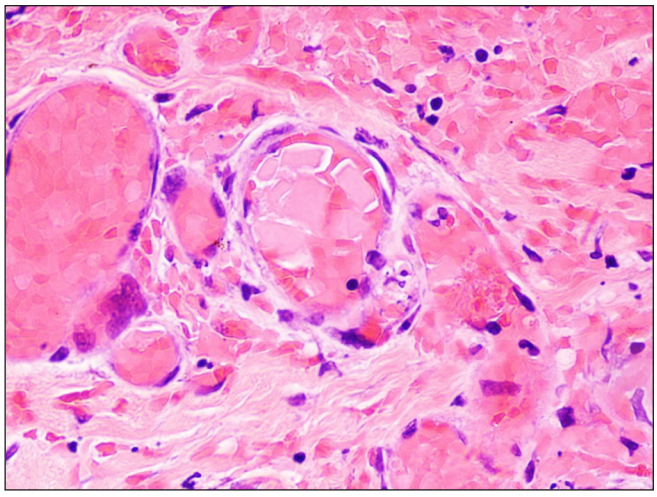

Figure 2: Punch biopsy of the skin showing oblong, crystalline eosinophilic pink deposits occluding the blood vessels in the superficial and deep dermis (haematoxylin and eosin, 400×).

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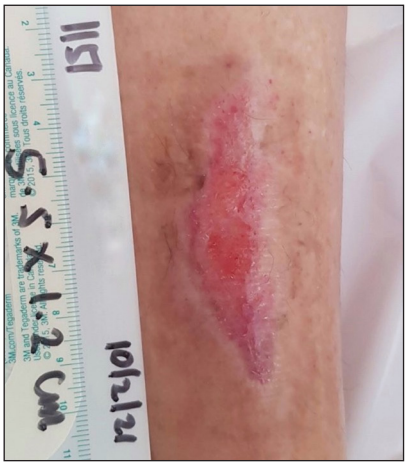

Figure 3: Improvement of the ulcer on the left shin after 3 months.

months, her ulcer improved and there was no progression of her disease [Figure 3].

In 1938, von Bonsdorf reported spontaneous crystallisation of a paraprotein in a patient with MM and described this as "cryo crystal globulinemia." Subsequently, cases of crystal-forming paraproteins without cryoprecipitate were reported and termed "crystalglobulinemia".[1] CG is characterised by the deposition of crystallised paraproteins in systemic vasculature, resulting in cell injury, thrombosis and ischemia. This may manifest as purpura, ulceration, polyarthralgia and renal failure.[1]

It is postulated that Fc–Fc interactions of IgG-type monoclonal protein and abnormal N-glycosylation of kappa light chains of IgG result in protein misfolding, decreased solubility and spontaneous crystallisation of the paraproteins. The process of cryoprecipitation does not appear to necessitate the presence of globulin crystallisation, as many reported cases, including ours, revealed negative serum cryoglobulins. The diagnosis is primarily established by detecting characteristic crystalline paraproteins in blood smears or tissue biopsies.[1]

The presence of a paraprotein band defines MGUS without evidence of terminal organ involvement and bone marrow disease. Although largely benign, the concept of monoclonal gammopathy of cutaneous significance (MGCS) was described by Lipsker in 2016 as cutaneous sequelae otherwise unaccounted for in the disease classification may be seen.[2] Apart from CG, this includes scleromyxedema, Schnitzler syndrome polyneuropathy, organomegaly, endocrinopathy, M spike and skin changes syndrome (POEMS).[3]

Treatment is typically not initiated in patients with MGUS without progression to MM. However, should they develop an associated M-protein-related disease, particularly with renal involvement, fulminant end-organ damage may occur. Thus, chemotherapeutic treatment (typically with cyclophosphamide, dexamethasone and bortezomib) and plasmapheresis, similar to that used in MM, have been recommended to decrease the production of monoclonal components and to eliminate deposited immunoglobulins.[4] Owing to the significant morbidity associated with CG, early initiation of aggressive treatment is recommended to improve outcomes. However, should the end-organ involvement be restricted to the skin, the clinician must weigh the costs and benefits of such therapies, given their high likelihood of toxicity.

We reviewed the literature for reported cases of CG/CCG and found only 11 previous reports of CG/CCG associated with MGUS. This is the second case with skin-limited symptoms and the first case that responded to corticosteroids alone. Grossman *et al*. described a case of MGCS, which responded well to oral prednisolone and plasmapheresis.[5] For our patient, in consult with the haematologist, systemic corticosteroid treatment was started in line with expert recommendations extrapolated from treating Type 1 cryoglobulinemia,[6] with marked clinical improvement.

We surmised that MGCS without systemic involvement, particularly renal involvement, may confer a better prognosis. It may be prudent for such patients to utilise non-chemotherapeutic treatments at the outset. Corticosteroid therapy is effective and can circumvent the risk of chemotherapy and plasmapheresis-related complications, supplemented by close monitoring for disease progression.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript, and no images were manipulated using AI.

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