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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.

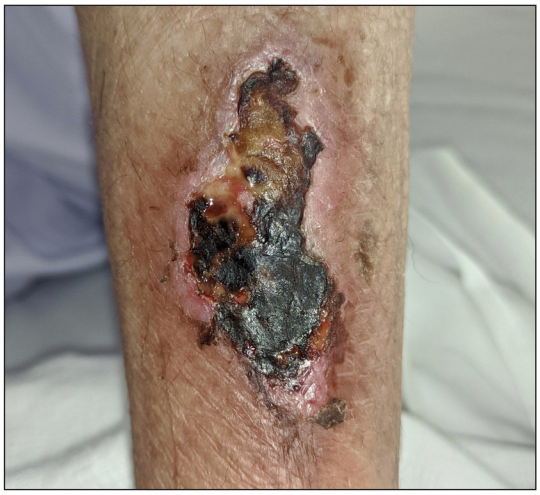

Figure 1: Retiform purpuric plaque with central necrosis on the left shin.

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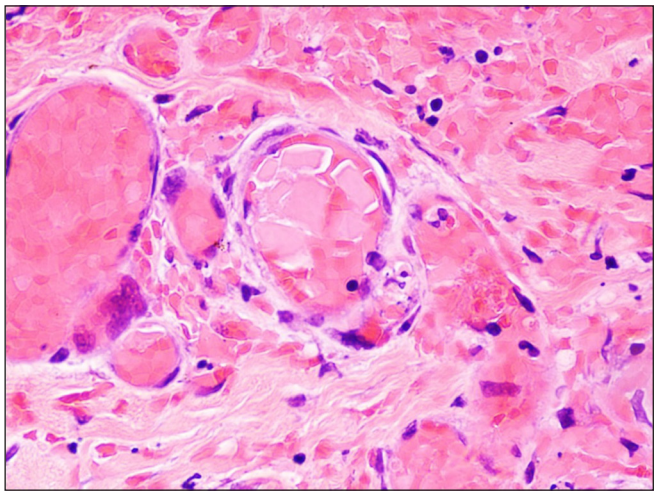

Figure 2: Punch biopsy of the skin showing oblong, crystalline eosinophilic pink deposits occluding the blood vessels in the superficial and deep dermis (Haematoxylin and eosin, 400×).

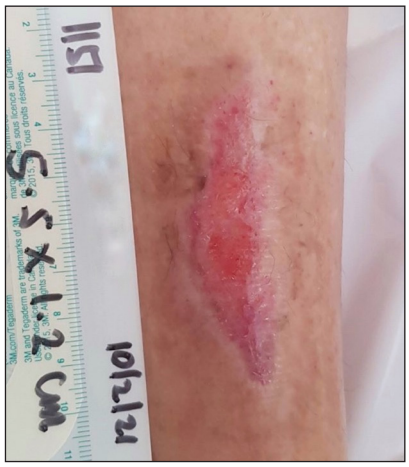

Figure 3: Improvement of the ulcer on the left shin after 3 months.

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 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.

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Acromegaloid facial appearance with generalised hypertrichosis: A novel phenotype of AFF4 mutation

Dear Editor,

Acromegaloid facial appearance (AFA) syndrome is a rare disorder characterised by coarse facies with a bulbous nose, thickened lips, and overgrowth of the oral mucosa. It has been described in association with hypertrichosis in the previous reports with no genetic loci identified so far.[1] Herein we describe a case presenting with the phenotype of AFA syndrome with previously undescribed distinct mutations in the AFF4 gene.

A 15 yr male child, born to parents unrelated by blood, presented with a history of generalised hypertrichosis since early childhood. Examination of the face revealed prominent metopic and supraorbital ridges with prominent brows, underdeveloped nasolabial folds, a short chin, coarse facies with heavy and rounded features, thickened skin, and prominent bulbous nose, thickened lips, gingival hyperplasia and generalised hypertrichosis [Figures 1 and 2]. Systemic examination was normal. He denied intake of any medications. There was no significant family history. He was born by a normal vaginal delivery without any complications. He was detected to have glucose-6-phosphate dehydrogenase (G6-PD) deficiency since birth. The child had normal developmental milestones with no intellectual disability. Keeping in mind the clinical picture, differentials of AFA syndrome, congenital generalised hypertrichosis terminalis, and CHOPS (cognitive impairment and coarse facies, heart defects, obesity, pulmonary involvement, short stature, and skeletal dysplasia) syndrome were considered and further evaluation was performed.

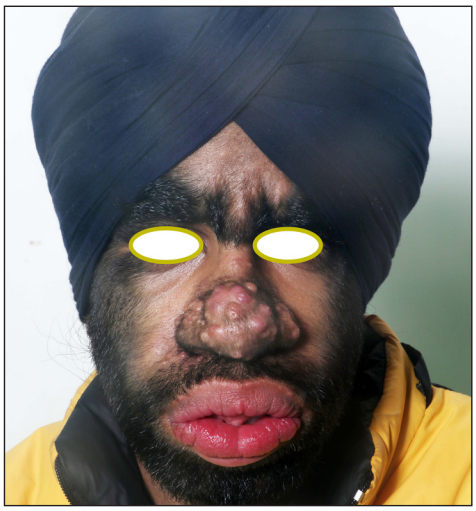

Figure 1: Prominent supraorbital ridges with prominent brows, underdeveloped nasolabial folds, short chin, coarse face with heavy and rounded features, thickened skin and prominent bulbous nose, thickened lips, gingival hyperplasia, and generalised hypertrichosis.

Contrast-enhanced computed tomography (CECT) of the chest to detect pulmonary involvement and a bone scan to evaluate skeletal deformities revealed no abnormalities. Echocardiography of the heart showed a small patent foramen

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