

## Letters to the Editor

### Vasculitic leg ulceration in Sjögren's syndrome should alert to cryoglobulinemia

Sirs,

We note with interest the review article by Roguedas *et al.* (1) and agree that vasculitis is by far the most severe cutaneous complication. Ulceration, however, ought to alert to dual pathology, as outlined below.

We present a 60-year-old lady with primary Sjögren's syndrome (SS) diagnosed three years ago on the basis of history and immunology. She presented on this occasion with a very painful leg ulcer. The ulcer had been present for 8 months but recently had increased in size. She also had a 2-year history of intermittent rash on both legs, bilateral paraesthesia in her lower limbs and recent pain in the same distribution. Past history included thyrotoxicosis, depression, endometrial carcinoma and L5/S1 vertebral collapse. She was a smoker with no significant family history.

Medication at time of presentation included azathioprine 150 mg/day, prednisolone 10 mg/day and alendronate 70 mg weekly.

On examination, there was a 5 x 3 cm superficial leg ulcer located on the anterior surface of the left leg, with a dusky discoloration, induration and a small area of central necrosis. There was no surrounding cellulitis, but a bilateral vasculitic rash was present in a stocking distribution. Neurologically, there was reduced sensation to fine touch in a stocking distribution in both lower limbs, but with preserved motor function and reflexes. Upper limb examination was normal. There was no lymphadenopathy or synovitis.

Initial investigations showed normal biochemical profile, with the exception of an elevated fasting glucose of 9.9. There was an acute phase response with C-reactive protein (CRP) of 14 g/dl, erythrocyte sedimentation rate (ESR) of 45 mm/hr, elevated total white cell count of 36 (4.00-11.00), predominantly a neutrophilia. Serologically, rheumatoid factor was positive at 220 IU/ml (0-22), antinuclear factor and ANCA were negative at this point (extractable nuclear antigens were not detected, including Ro/La/Sm/RNP/Jo-1/Sci-70) and immunoelectrophoresis demonstrated polyclonal IgG and an IgM kappa paraprotein. Hepatitis B/C serology was negative. Further investigations including X-rays of knees and pelvis, CT of the chest, abdomen and pelvis were normal. Bone marrow aspirate was normal with no evidence of myeloma. Nerve conduction studies demonstrated findings which were consistent with distal axonal neuropathy or confluent mononeuritis multiplex bilaterally. Cryoglobulin assay returned positive with IgG 8.53 g/l, IgA 2.43 g/l, IgM 14.3 g/l and she was diagnosed as having Type 2 mixed cryoglobu-

linemia with vasculitis. The new diagnosis of Non Insulin Dependent Diabetes Mellitus (NIDDM) was noted.

She was treated with high dose oral corticosteroids and subsequent intravenous methylprednisolone with intravenous pulse cyclophosphamide 750 mg/month. The ulcer continued to grow in size, with tendons exposed, and eventual tendon rupture. She required plasma exchange, and had a good initial response. Complications developed with concurrent ulcer infection by methicillin resistant staphylococcus aureus (MRSA). Once cleared of infection she underwent skin grafting, with good results. Currently she is maintained on a reducing dose of prednisolone with pulse cyclophosphamide. There is now a well established link between Sjögren's syndrome (SS) (primary and secondary) and type 2 cryoglobulinemia (MC) (2). Hypergammaglobulinaemia is the most common serological finding in SS, and includes a spectrum of organ specific autoantibodies, as well as rheumatoid factor. Cryoglobulins can also be produced with variable reports in the literature with prevalence between 5-20% (3). Moreover, both conditions are associated with lymphoproliferative disease such as B-cell non-Hodgkins lymphoma (NHL) (4). Indeed, it has been suggested that MC can be regarded as "benign" B-cell neoplasm, and there is a continuum between some autoimmune disorders, MC and B-cell neoplasms (4).

The pathogenesis has been postulated as follows: contact with an environmental agent such as Hepatitis C Virus (HCV), initiates a polyclonal B cell activation which may evolve to oligoclonal/monoclonal B-cell selection, and thereafter frank monocyte B cell proliferation (2). The mechanism of change from polyclonal to monoclonal expansion remains poorly understood in SS. It has been suggested that Fas and Fas-1 germline mutations are responsible for many lymphoproliferative syndromes in patients with SS and type 2 MC. One study suggested that qualification of cryoglobulin could be used as a laboratory predictive factor for lymphoma development in primary SS. Higher levels of cryoglobulin correlated with lymphoma development, as did three specific immunoglobulin idiotypes (5).

The presentation of vasculitic ulceration in SS should alert to a diagnosis of cryoglobulinaemia, which is estimated to occur in up to 10% of patients. Aggressive treatment is required, including plasma exchange, intravenous immunoglobulin or methylprednisolone as corticosteroids are unlikely to adequately immunosuppress on their own (3). The anti Cd20 chimeric monoclonal antibody, rituximab has shown promise in the treatment of cryoglobulinaemia. Two small studies have shown good initial clinical response to once weekly administration of the drug for a period of 4 weeks, although

hepatitis B virus RNA multiplied twofold in one of the studies (6, 7). This treatment remains an option for our patient.

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### References

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### REPLY. Cryoglobulin-induced leg ulceration in primary Sjögren's syndrome

Sirs,

We appreciate the interest of Perry and colleagues in our recent review article (1), as well as this opportunity to respond to their comments. They agree with our statement that vasculitis is by far the most severe cutaneous complication of primary Sjögren's syndrome (pSS). They are also concerned about the development of a leg ulceration, as a long-run complication of mixed cryoglobulin.

Their case presentation is reminiscent of the severe chronic cutaneous neutrophilic vasculitis described, a few years ago, in a patient with pSS (2). This is seemingly in conflict with previous evidence. What needs, indeed, to be disclosed is that this complication is relatively uncommon in such setting. There, Raynaud's phenomenon does not lead to localized sequelae, including digital ulcers, gangrene and digi-