

## 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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### 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-

tal pulp ulcers (3, 4).

In contrast, patients with pSS harbor a variety of serological traits which are associated with extraglandular involvements. Let us mention non organ-specific autoantibodies, monoclonal immunoglobulin (5), IgA-rheumatoid factor, IgA-containing immune complexes (6), and, above all, mixed cryoglobulinemia (7). The authors are right in assigning leg ulceration to the latest abnormality, and highlighting its predictive value in pSS for adverse outcomes, most notably non Hodgkin lymphoma (8).

To conclude, we might (should ?) indeed have quoted leg ulceration as a cutaneous manifestations in our review. We acknowledge the interesting contribution of Perry, Gordon and Porter, and agree that the occurrence of vasculitic ulceration should alert to a diagnostic of mixed cryoglobulin.

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Bilateral vertebral artery occlusion in giant cell arteritis

Sirs,  
Cerebrovascular accidents are one of the leading causes of GCA-related morbidity and mortality, and they are probably the most common cause of early death after diagnosis in GCA (1, 2). Involvement of the vertebrobasilar system results in strokes of the cerebellum, occipital lobe and brain stem. We report a case of bilateral vertebral artery occlusion (BVAO) due to GCA with acute bilateral cerebellar stroke without development of irreversible neurological complications.

A 78-year-old man was sent to our hospital because of dizziness. One year before, he had been diagnosed with polymyalgia rheumatica in another center. After that diagnosis he was started on treatment with prednisone 10 mg/day. However, to our surprise, the prednisone dosage had been maintained without progressive reduction since the time of diagnosis. Twenty-four hours before admission he began to complain of vertigo and headache. Twelve hours before admission he suffered an episode of right amaurosis fugax. Neurological examination showed gait unsteadiness and ataxia. Laboratory data, including coagulation tests, anticardiolipin antibodies, full blood cell count, and hepatic and renal function parameters, were negative or normal. The ESR was 84 mm/h, and CRP was 63 mg/L (normal: < 5 mg/L). Plain chest radiograph and electrocardiogram were normal. A T2-weighted and Flair MRI sequences showed several hyperintense foci at both cerebellar hemispheres. Angio-MRI showed BVAO (Fig. 1).

A biopsy of the right temporal artery performed 24 hours after admission showed interruption of the internal elastic laminae with infiltration of mononuclear cells into the arterial wall. Treatment with acetylsalicylic acid (300 mg/day) was started and prednisone dose was increased up to 60 mg/day. Dramatic improvement of symptoms was achieved. The patient was discharged from hospital two weeks later without neurological sequelae.

Atherosclerosis, GCA itself, and trauma are the main causes of BVAO. Headache and elevation of inflammatory laboratory markers may be of some help to consider a potential diagnosis of GCA in patients with BVAO (3). The much more accelerated BVAO related to GCA may contribute to the far higher mortality observed in GCA patients within the first month after the diagnosis of the disease (4).

The reason why our patient did not follow a catastrophic course is uncertain. Compensatory neovascularization phenomena, related to the persistence of a chronic and maintained inflammatory response over the

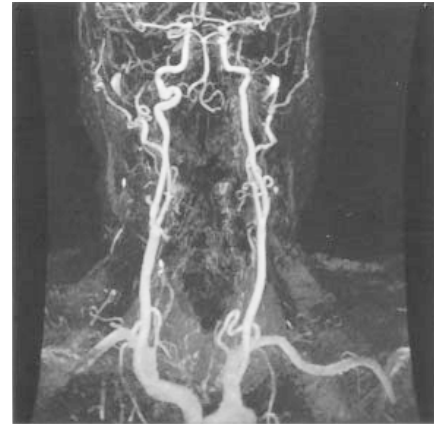


Fig. 1. Angio-MRI showing bilateral vertebral artery occlusion.

disease course due to the prolonged steroid therapy for a previous polymyalgia rheumatica diagnosis, might have been responsible for compensatory mechanism which prevented the patient from the development of irreversible neurological complications (5-7).

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