

Case report

Sjögren's syndrome, vasculitis, and cryoglobulinaemia associated with a monoclonal IgM (kappa) paraprotein with rheumatoid factor activity

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SUMMARY A patient is described with primary Sjögren's syndrome with an infrequently reported complication—vasculitis and cryoglobulinaemia due to a monoclonal IgM (kappa) paraprotein with rheumatoid factor activity. The clinical and theoretical implications are discussed.

Sjögren's syndrome (SS) may occur in the absence (primary SS) or presence (secondary SS) of other autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, or primary biliary cirrhosis.¹ Clinically it is characterised by the presence of keratoconjunctivitis sicca, xerostomia, and, in 80% of patients, intermittent uni- or bilateral salivary gland enlargement. The numerous extraglandular features of SS, such as renal tubular acidosis, neuropathy, pancreatitis, and vasculitis, have been well reviewed.¹

Case history

A 67 year old woman presented to an ophthalmologist with malaise, feelings of depression, raised erythrocyte sedimentation rate (ESR) (70 mm/1st h) and diplopia due to sixth cranial nerve palsy. A provisional diagnosis of cranial arteritis was made and treatment with prednisolone (40 mg/day) instituted. Temporal artery biopsy was normal, however, and on further review by a neurologist the patient was found to have a symmetrical peripheral sensory neuropathy (stocking distribution) and symptoms of sicca syndrome. Electrophysiological studies showed an axonal neuropathy, and sural nerve biopsy showed that this was secondary to a necrotising vasculitis. Rose bengal staining showed the presence of keratitis. No further investigations were performed, and steroid therapy was continued

for the next three years in varying dosage up to 40 mg/day. The neuropathy remained stable and there were no further episodes of diplopia. The patient, however, reported episodes of non-palpable purpura affecting the lower limbs during hot weather. Further serological investigation showed the presence of cryoglobulinaemia, and she was referred to our unit for review.

On examination the patient had Cushingoid facies, a few splinter haemorrhages, fading purpuric lesions on the lower legs, and peripheral sensory loss in a stocking distribution. There was no evidence of inflammatory arthropathy, hepatosplenomegaly, or lymphadenopathy. The lacrimal and salivary glands were not enlarged, but the buccal mucosa was dry and glazed with sticky saliva. Schirmer's test was abnormal (at five minutes 0 mm/right eye, 5 mm/left eye; normal >15 mm).

The complete blood picture and plasma biochemistry were normal, ESR 60 mm/1st h, and antinuclear factor negative (titre 1/10; normal <1/40). Antibodies to extractable nuclear antigen, Ro(SS-A) and La(SS-B), were absent. Rheumatoid factor was detected by latex agglutination but not by the Rose-Waaler test. Cryoglobulins (3.3 g/l) were detected, which were shown by immunofixation to consist of polyclonal IgG and a monoclonal IgM kappa paraprotein (type II cryoglobulinaemia). After fractionation of the serum on a Sepharose 6B column (90 × 2.5 cm) the rheumatoid factor activity was found to coelute with the pentameric IgM peak. Rheumatoid factor activity in each fraction was detected by two methods: a nephelometric method

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employing human aggregated IgG as substrate and a latex agglutination method. A second peak of low molecular weight IgM was also noted, which did not contain rheumatoid factor activity. Fractionation of serum after removal of cryoprecipitate resulted in complete loss of rheumatoid factor activity from the IgM fraction. Blood viscosity was normal. Complement studies on warm serum showed C3=0.59 g/l (0.5–1.5), C4<0.01 g/l (0.2–0.5), and total haemolytic complement <40% (normal>90%). Lip biopsy showed generalised sialadenitis and lymphoid infiltrate consistent with Sjögren's syndrome. A bone marrow aspirate showed iron deficiency and increased T4/T8 lymphocyte subset ratio but no evidence of Waldenström's macroglobulinaemia. Urinary Bence-Jones protein was not detected.

On the basis of these features a diagnosis was made of primary SS associated with necrotising vasculitis, mixed cryoglobulinaemia, and IgM kappa paraproteinaemia. Subsequent management has been directed at symptomatic therapy of sicca symptoms and control of vasculitis with cyclophosphamide (100 mg/day) and prednisolone (7 mg/day). Plasmapheresis was considered but not used in this patient.

Discussion

The patient we describe has primary SS complicated by vasculitis and cryoglobulinaemia with an IgM kappa paraproteinaemia. The positive latex screening test for rheumatoid factor, the presence of monoclonal IgM with polyclonal IgG in the cryoglobulin, the coelution of rheumatoid factor activity with IgM on fractionation of serum, and loss of rheumatoid factor from serum after removal of the cryoprecipitate each provide evidence that the IgM paraprotein has rheumatoid factor specificity.

There is no consensus regarding optimal management of cryoglobulinaemia. Corticosteroids control the inflammatory effects of cryoglobulin deposition but have no effect on cryoglobulin levels.² Cytotoxic regimens have been used with success, but clearly their benefits must be balanced against potential iatrogenic risks such as malignancy. In our patient cyclophosphamide was introduced as a steroid sparing measure since the dose of prednisolone required to control vasculitis was unacceptably high (>15 mg/day). In patients with hyperviscosity syndromes, plasmapheresis is a valuable short term measure,³ but is probably of limited value in patients with longstanding disease.

Vasculitis due to mixed cryoglobulinaemia and an increased incidence of various forms of B cell neoplasia (including Waldenström's macroglobu-

linaemia) are both recognised features of Sjögren's syndrome.¹ Mixed cryoglobulins containing a monoclonal IgM (kappa) rheumatoid factor were first described in a patient with SS by Meltzer *et al* in 1966⁴; since then there have been further similar, but infrequent, case reports.^{1 5 6} Vasculitis may also occur in primary SS due to hypergammaglobulinaemia in the absence of cryoglobulins.⁷

The incidence of monoclonal protein production in SS, particularly in those patients with extraglandular features, may be much higher than has been appreciated. Moutsopoulos *et al* reported that 13 of a group of 17 patients with primary SS had free kappa or lambda light chains in the urine⁸; all 10 patients with extraglandular features had urinary monoclonal proteins and seven had detectable serum bands. In such patients the presence of an IgM paraprotein presumably reflects the expansion of an occult, neoplastic B cell clone of Waldenström's type; the subsequent appearance of frank clinical evidence of neoplasia is a function of time and the biological behaviour of the neoplastic clone.

The exact frequency of overt B cell neoplasia in SS is uncertain but may be as high as 5%.⁹ A similar association with B cell dyscrasias, including non-Hodgkin's lymphoma and chronic lymphatic leukaemia,¹⁰ and hairy cell leukaemia¹¹ has been reported in rheumatoid arthritis. Conversely, B cell neoplasia is frequently associated with the presence of paraproteins with rheumatoid factor or other autoimmune specificity; approximately 25% of patients with Waldenström's macroglobulinaemia or chronic lymphatic leukaemia have circulating paraproteins with rheumatoid factor specificity.^{12 13} Hairy cell leukaemia is also associated with vasculitis and autoantibody production.¹¹ The high frequency of paraproteins with autoimmune specificity suggests that autoimmune clones are more susceptible to malignant transformation.⁷

These observations of the close link between B cell neoplasia and autoimmune disease have led to the concept that primary SS and other autoimmune diseases may form part of a spectrum of lymphoproliferative diseases which share common origins with clonal neoplastic B cell proliferation.^{7 14} Our patient therefore represents an interesting example of this interface between autoimmunity and B cell neoplasia.

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