A CASE OF PRIMARY SJÖGREN'S SYNDROME, COMPROMISED BY CRYOglobulinaemic glomerulonephritis, PERICARDIAL AND PLEURAL EFFUSIONS

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SUMMARY

Primary Sjögren's syndrome (SS1) complicated by glomerulonephritis is rare and is usually associated with the presence of cryoglobulins. Cryoglobulinaemic glomerulonephritis as described in type II essential mixed cryoglobulinaemia, characterized by the presence of deposits of cryoglobulins within the glomerular capillary lumen, occurring in SS1 has previously been reported only once in the literature. Our case was also complicated by pleural and pericardial effusions. We discuss the treatment options available for the renal lesion.

KEY WORDS: Sjögren's syndrome, Cryoglobulinaemic glomerulonephritis, Pleural effusion, Pericardial effusion.

Sjögren's syndrome (SS) is a systemic autoimmune disorder characterized by lymphocyte proliferation and infiltration of exocrine glands, giving dry eyes (keratoconjunctivitis sicca) and dry mouth (xerostomia) as well as affecting other organs. It may exist as a primary condition, primary Sjögren's syndrome (SS1), or in association with rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) or other autoimmune disorders, when it is known as secondary Sjögren's syndrome (SS2).

Cryoglobulinaemia is found in up to a third of patients with SS1 [1]. The cryoglobulin is frequently characterized as a type II mixed cryoglobulin. Type I cryoglobulin is monoclonal. Types II and III cryoglobulins are mixed, containing at least two immunoglobulins. In both a polyclonal IgG is bound to another immunoglobulin, which is an antiglobulin. However, in type II the antiglobulin is monoclonal, whereas in type III, seen in SLE and RA, it is polyclonal [2].

We report a case of SS1 with type II mixed cryoglobulinaemia and multi-organ involvement, including cryoglobulinaemic glomerulonephritis (CGN), pleural effusion and pericardial effusion.

CASE REPORT

A 53-yr-old Caucasian woman with known SS1 and type II cryoglobulinaemia with monoclonal IgM kappa (IgMk) component presented with a 2-week history of periorbital oedema. A week prior to admission she had suffered from left parotitis which was treated with ciprofloxacin. A previous sialogram (Fig. 1) had shown typical changes of SS. She had a 2-day history of a dry cough but no other respiratory symptoms. For a year she had suffered from mild sensory peripheral neuropathy, more noticeable in the cold and predominantly affecting her lower limbs. This was confirmed by nerve conduction studies. Symptoms of Raynaud's phenomenon, keratoconjunctivitis sicca and xerostomia were a constant feature.

On examination she was pyrexial and the left parotid gland was swollen and tender. Dental caries and gingivitis were noted and she had a dry oral mucosa. There was a widespread petechial rash below the knees. No significant lymphadenopathy or hepatosplenomegaly were noted. She had a tachycardia with a blood pressure of 170/100 mmHg. There were signs of mild congestive cardiac failure and a left-sided pleural effusion. Schirmer's test revealed both strips recording only 1 mm at 5 min. Rose Bengal conjunctival staining was positive. Fundoscopy was normal. Other investigations were as follows. Mid-stream urine specimen revealed red cells, granular casts and pus cells but no growth. Twenty-four-hour urine excretion of protein was 2 g. Peripheral blood count showed a normochromic, normocytic anaemia, lymphopenia and thrombocytopenia. Bone marrow examination was normal. Urea was 14.3 mmol/l (normal range 2–7) and creatinine 253 μmol (≤112). Creatinine clearance determined by ethylenediamine tetra-acetic acid (CrEDTA) showed a glomerular filtration rate of 15.2 ml/min (>70). Liver function tests were normal, including a serum albumin of 38 g/l.

Erythrocyte sedimentation rate and plasma viscosity at prevailing room temperature (20°C) were 34 mm/h (Westergren) and 1.49 cP (1.4–1.7), respectively. C-reactive protein was 11 mg/l. Coagulation screen was normal. Total immunoglobulins were 21 g/l; IgA 1.07 g/l (0.8–4), IgG 6.25 g/l (5.4–16.1), IgM 5.23 g/l (0.5–2). Serum electrophoresis showed a monoclonal band characterized as kappa light chains. Complement levels were reduced: C3 0.25 g/l (0.75–1.65) and C4 <0.08 g/l (0.2–0.65). The cryoglobulin level was 1.747 g/l, comprising monoclonal IgMk and polyclonal IgG. Blood samples for cryoglobulins were always maintained at 37°C until cryoprecipitation, which was performed at 4°C for 4 days before estimation. A radiological skeletal survey was negative. Antinuclear antibodies were positive at a titre of 1:160. Antibodies to double-stranded DNA, Sm and RNP were negative, but antibodies to Ro (SSA) and La (SSB) were positive. Rheumatoid factor (RF) (Beckman, nephelometric assay) was 603 IU/ml (0–30). Subsequent analysis of another serum sample showed that the RF in the supernatant after cryoprecipitation was 995 IU/l and the level in the redissolved cryoprecipitate was 217 IU/l.
IgM anticardiolipin antibody was positive at 7.3 units (<5). Blood cultures, hepatitis B serology and hepatitis C ribonucleic acid (RNA) were negative. Chest X-ray showed pulmonary oedema and a left pleural effusion. A diagnostic thoracocentesis was undertaken and revealed a clear, sterile exudate (protein level 31 g/l). Echocardiography showed mild mitral regurgitation and a small pericardial effusion but no vegetations. A computerized tomography scan of the head, thorax and abdomen showed no abnormality, in particular there was no lymphadenopathy. Renal biopsy (Fig. 2) showed a membranoproliferative, glomerulonephritis with splitting of the basement membrane, but more significantly virtually all the glomeruli showed the presence of numerous intraluminal 'thrombi' with mild mononuclear cell infiltration. Epithelial crescents and vasculitis were absent. Immunofixation showed IgG and IgM within the glomerular capillary walls corresponding to the intraluminal 'thrombi'. C3 was present in small quantities and Clq was negative. Unfortunately, electron microscopy was unsatisfactory for technical reasons.

The patient was given 1 g of intravenous methylprednisolone and 750 mg of intravenous cyclophosphamide, immediately followed by two daily pulses of 1 g of intravenous methylprednisolone. In view of the renal biopsy findings plasma exchange (PE) was undertaken with five consecutive daily exchanges of 31 of plasma for 21 of 4.5% human albumin solution and 11 of normal saline. There was an immediate subjective and objective improvement in the patient's well-being and a dramatic improvement in her renal function (Fig. 3). Oral cyclophosphamide 100 mg daily was started with a daily maintenance dose of 15 mg of prednisolone. The cryoglobulin level post PE was 0.4 g/l but complement levels remained low. Haematocrit and proteinuria persisted. Twenty-four-hour urinary protein excretion 1 month after admission was 2.3 g and CrEDTA recovered to 55 ml/min. Repeat nerve conduction studies 1 month after the initial treatment remained unchanged and still showed evidence of peripheral neuropathy. Intolerance to oral cyclophosphamide prompted the use of azathioprine 50 mg thrice daily in its place. The patient responded to further PE. The patient remains well 2 yr after presentation but still requires weekly PE and monthly pulses of intravenous cyclophosphamide 350 mg. Her renal function is stable (CrEDTA 70 ml/min) but her peripheral neuropathy continues to trouble her, particularly in the cold.

**DISCUSSION**

Our patient has the features consistent with a diagnosis of SS1. She possessed the serological markers Ro (SSA) and La (SSB) but was persistently negative for antibodies to double-stranded DNA and antibodies to Sm, making SLE an unlikely diagnosis in the presence of glomerulonephritis. Joint symptoms were never a prominent feature and not associated with any signs of synovial proliferation, and the RF in our patient can be explained by the presence of the monoclonal IgMk, which almost always possesses RF activity [2].

Pleural and pericardial effusions are rare manifestations of SS1. In a study of 40 patients with SS1, 26 with SS2 and 40 with RA without SS2, only patients with RA with or without SS had pleural effusions [3]. Although our patient was in congestive cardiac failure, analysis of the pleural fluid suggested it was a sterile, inflammatory exudate. It is possible that immune complex deposition occurred in the pleura and the pericardium, resulting in an inflammatory response and effusion. It is also interesting to note that the pleural effusion disappeared rapidly following treatment with intravenous steroids, cyclophosphamide and PE. A similar observation was made by De Vecchi et al., where the pleural effusion responded rapidly to intravenous methylprednisolone in patients with CGN [4].

Renal involvement in SS1 is well recognized. In contrast to amino aciduria and interstitial nephritis, which are well documented, glomerulonephritis is much less common [5–7]. Glomerulonephritis in type II essential mixed cryoglobulinaemia (EMC), however, is well documented, especially where IgMk is the monoclonal component and in these patients hypocomplementaemia is present [8]. Mazzuco et al. [9] described 'cryoglobulinaemic glomerulonephritis' characterized by: (a) endocapillary proliferation due to an infiltration by mainly monocytes, frequently in large numbers; (b) the presence of intraluminal 'thrombi' which represents deposition of circulating cryoglobulins; and (c) thickening of the glomerular basement membrane with a double-contoured appearance. The renal biopsy in our patient displayed all the above features and in addition was shown to have circulating IgMk and a low C3 and C4, consistent with a picture of CGN.

To our knowledge only one other such case [7] with SS1 and type II cryoglobulinaemia has been described with renal lesions as described in this case report—which is distinct from glomerulonephritis described in other cases of SS1 with cryoglobulins [5, 6]. The co-existence of CGN with SS1, albeit very rare, is not a completely unpredictable situation since in EMC type II cryoglobulins are the cause of the renal pathology; it would not be unreasonable for the same renal lesion...
to occur in SSI in the presence of the same type of cryoglobulins. Several treatment modalities had been used in patients with CGN but such is the rarity of the disease that a large randomized trial has not yet been performed to evaluate their efficacy. The current treatments available include intravenous pulsed methylprednisolone, which produced a beneficial outcome in patients with CGN [4]. PE alone, or in combination with steroids and immunosuppression, was shown to be beneficial in patients with rapidly deteriorating renal function but not in patients with established chronic renal insufficiency [10–12].

In the case reported here the rapidity of the recovery of the renal failure and the sense of well-being suggest that the PE was mainly responsible—although concurrent administration of methylprednisolone and cyclophosphamide was used in the initial treatment, PE was the sole treatment used for the relapse and supports this view. The mechanism by which PE improves the clinical condition of EMC is not clear, but it may be due to the restoration of the defective reticuloendothelial system clearance of immune complexes from the peripheral circulation [13]. More recently, α-interferon, which has been used in the treatment of haematological malignancies, has been used with success in patients with EMC [14, 15], whether such treatment would be of benefit to patient such as ours is unknown.

In conclusion, we report a case of SSI complicated by pleural and pericardial effusions and CGN. The patient responded to intensive PE and immunosuppression with pulsed intravenous methylprednisolone and cyclophosphamide. The response to PE alone during relapse is evidence that PE is an important therapeutic measure in patients presenting acutely with CGN.
ACKNOWLEDGEMENTS

We gratefully acknowledge the clinical support of Dr G. R. V. Hughes, consultant rheumatologist at St Thomas’ Hospital, London and Dr A. G. Prentice, consultant haematologist at Derriford Hospital, Plymouth.

REFERENCES


