Case Report

Crescentic glomerulonephritis associated with membranous nephropathy in a case with primary Sjögren’s syndrome

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Introduction

Sjögren’s syndrome is a connective tissue disorder affecting lacrimal and salivary glands, and other exocrine systems. Clinically, it causes xerophthalmia and xerostomia, and histologically, a destructive infiltration of chronic inflammatory cells is observed in those glands. This disorder is sometimes associated with such collagen diseases as rheumatoid arthritis, systemic lupus erythematosus and scleroderma, but it also develops without those underlying diseases. Renal involvement is seen in about 20–50% of patients with primary Sjögren’s syndrome [1–6]. Tubulointerstitial nephritis is the most frequent renal complication, but a little over 20 cases with glomerulonephritis have been reported [7]. Membranous nephropathy and membranoproliferative glomerulonephritis are the most common glomerular lesions in primary Sjögren’s syndrome, and crescentic glomerulonephritis is quite rare [7,8]. We report crescentic glomerulonephritis associated with membranous changes in a case with primary Sjögren’s syndrome. The patient’s renal insufficiency resolved after treatment with corticosteroids in combination with plasmapheresis.

Case

A 64-year-old woman with herpes zoster was referred to the Renal Unit of Kitasato University Hospital because of proteinuria and impaired renal function on 31 August 1995. She had a history of hypertension since 1988, and normal blood chemistry at that time. Since September 1994, she had suffered from xerostoma and mild proteinuria with microscopic hematuria, and her laboratory tests disclosed polyclonal hyper-γ-globulinemia, and a normal serum creatinine level.

On admission, her blood pressure was 124/70 mmHg, pulse 86 bpm, and body temperature 37.9°C. Her eyes, oral cavity and parotid glands were unremarkable. There was pretibial oedema. Painful vesicular eruptions were seen on the right shoulder and chest with a dermatomal distribution of T2 and T3. There were petechiae on her lower extremities. Urinalysis showed 0.3 g/day proteinuria, 3–5 red blood cells and 10–15 white blood cells per high-power field. Blood count disclosed mild normocytic anaemia (haemoglobin 10.4 g/dl), 5.5 × 10^9/l white blood cells, and 190 × 10^9/l platelets. The erythrocyte sedimentation rate was 137 mm/h. Blood chemistry showed total serum protein 111 g/l, albumin 30.4%, γ-globulin 57.7%, sodium 128 mmol/l, potassium 4.3 mmol/l, chloride 95 mmol/l, urea nitrogen 13.9 mmol/l and serum creatinine 176.8 μmol/l. Creatinine clearance was 37 ml/min. Serological tests were positive for rheumatoid factors, anti-nuclear antibodies (ANA) 1280 × with speckled pattern, positive for both anti-SS-A and anti-SS-B antibodies, and negative for antibodies against DNA, ribonucleoproteins (RNP) and Sm. The levels of C3, C4 and total haemolytic complement (CH50) were within normal limits. Cryoglobulin was examined three times, but it was not detected.

The cornea was intact, and fundoscopy revealed mild hypertensive retinæ (K-W II, S1, H1). Schirmer’s test was equivocal (right 9 mm/5 min, left 10 mm/5 min), and rose-Bengal and fluorescein tests were negative. Gom test was 3.5 ml/10 min, and sialography demonstrated a cavity pattern consistent with stage III according to the classification for sialography of Sjögren’s syndrome by Holt and Rubin. Lip biopsy revealed salivary ductal atrophy and infiltration of plasma cells and lymphocytes around the salivary gland. Renal ultrasound showed normal kidneys. Percutaneous renal biopsy was performed on 23 August and renal histology showed crescentic glomerulonephritis with membranous nephropathy and focal tubulointerstitial nephritis.
On 16 September, after the skin lesions of herpes zoster had improved, the patient was treated with plasmapheresis by the double-filtration membrane method using normal saline as a replacement solution, and was given oral steroid (prednisone 40 mg daily) following methylprednisolone pulse therapy based on the diagnosis of primary Sjögren’s syndrome associated with hyper-γ-globulinemia and crescentic glomerulonephritis. By October 1996, when the steroid therapy was discontinued, the xerostomia had disappeared. In February 1997, prednisone was administered again due to purpura on the lower extremities and hyper-γ-globulinemia. Her urinalysis showed proteinuria 0.2 g/day, serum creatinine 88.4 μmol/l, and serum protein 82 g/l with 24.5% of γ-globulin in August 1997.

Renal biopsy

Nineteen glomeruli were examined with four showing global sclerosis. Mild glomerular hypercellularity was observed diffusely. Three glomeruli showed cellular crescents. In one, the crescent was formed circumferentially with numerous infiltrates of polymorphonuclear leukocytes, and extravasation of fibrin deposits was evident in the urinary space (Figure 1). There were focal and segmental micro-thrombi in the glomerular capillary lumina. Periodic acid-methenamine silver staining appeared bubbly on the glomerular basement membrane in association with segmental small spikes. Mononuclear and plasma cell infiltration was prominent in the tubulointerstitial space along with focal interstitial fibrosis. Mild arterial sclerosis was seen at the level of the arcuate arteries.

Immunofluorescent microscopy revealed diffuse, finely granular deposition of IgM and C3 along the glomerular capillary walls (Figure 2). IgA and fibrinogen were equivocal, and IgG, C1q and C4 were negative. Electron microscopy showed subepithelial and intramembranous electron-dense deposits (Figure 3). No specific microtubular structures were observed in the endothelial cytoplasm.

Discussion

Although the case showed minor abnormality in ophthalmologic examination, except for equivocal Schirmer’s test, she had complained of xerostomia, her salivary excretion decreased, sialography demonstrated abnormal findings specific for Sjögren’s syndrome, and lip biopsy showed chronic inflammatory disease of the salivary gland. These findings were consistent with Sjögren’s syndrome according to the diagnostic criteria of the Sjögren’s Disease Research Committee of the Japanese Ministry of Health and Welfare [9]. Positive anti-SS-A and anti-SS-B antibodies, in addition to...
purpura on the lower extremities, probably due to the extremely high levels of serum immunoglobulins, further supported the diagnosis. Serology was positive for anti-nuclear antibody (ANA) and rheumatoid factor, but her clinical and laboratory findings did not indicate any other collagen disease.

Renal complications occur frequently in patients with primary Sjögren’s syndrome [5]. Tubular dysfunction has been detected even in patients without apparent clinical manifestations of renal disease [3]. Fujimoto and Dohi [6] described various degrees of histologic tubulointerstitial changes in 53% of 108 cases with primary Sjögren’s syndrome who underwent renal biopsy. However, glomerular disorders were uncommon. One case of mesangio proliferative glomerulonephritis among 65 cases with primary Sjögren’s syndrome was observed by Pokorny et al. [4]. Pavlides et al. [1] reported four cases with focal glomerulonephritis out of 47 patients. However, immunofluorescent or electron-microscopic findings were not described in the two reports, and the exact histological changes were not known. Two types of immune complex glomerulonephritis were prevalent, namely membranoproliferative glomerulonephritis and membranous nephropathy [2,10–12]. Dussol et al. [7] reviewed 21 cases of primary Sjögren’s syndrome with glomerulonephritis; 10 cases involved membranoproliferative glomerulonephritis, six had membranous nephropathy, and the type of glomerulonephritis was not specified in four. Among 13 cases for whom cryoglobulopha was tested, eight (62%) were positive for cryoglobulinaemia. This disorder is frequently associated with Sjögren’s syndrome, and is considered to be one of the major causes of glomerulonephritis in primary Sjögren’s syndrome. Fujimoto and Dohi [6] analyzed glomerular histologic changes in 109 patients with primary Sjögren’s syndrome. No glomerular changes were observed in 47 cases (43%), non-specific slight or irregular mesangial increase were noted in 55 (51%), and irregular thickening of the glomerular tuft in two (2%). There were three (3%) cases with membranous nephropathy and two (2%) with IgA nephropathy in their series. Recently, two cases of crescentic glomerulonephritis have been reported, one of which also showed membranous changes [7,8]. Both cases presented hyper-γ-globulinaemia, but serum cryoglobulin was not detected.

In our case, urinalysis showed mild proteinuria and haematuria associated with pyuria. Serum creatinine and creatinine clearance revealed moderate renal dysfunction. Renal ultrasound showed normal-sized kidneys. Light-microscopy of the kidney biopsy disclosed cellular crescents with underlying membranous nephropathy, mild interstitial nephritis with mild fibrotic lesions, and arterial sclerosis. Serum cryoglobulin was examined three times, but was negative. Segmental microthrombi in the glomerular capillary lumina might be caused by increased serum viscosity due to hyper-γ-globulinaemia. The decrease in renal function was considered to be mainly the consequence of the crescentic glomerulonephritis, and the tubulointerstitial nephritis, sclerotic arterial changes and diminished microcirculation due to serum hyperviscosity may also have contributed to it. Tubulo interstitial nephritis might develop following herpes zoster infection [13], but it has not been reported as a cause of glomerular disease. The crescentic glomerulonephritis in our case was thought to result from immunological disorders in Sjögren’s syndrome. The clinical and serological findings, the negative immunofluorescence studies for IgG and C1q deposition and the absence of microtubular structures on electron microscopy indicate that, in our case, glomerulonephritis was not caused by overlapping systemic lupus erythematosus.

Several reports have described the beneficial effects of corticosteroids, with or without cytotoxic agents, on glomerulonephritis in primary Sjögren’s syndrome [2,11–12,14]. Our case was treated with plasmapheresis for hyperviscosity syndrome in addition to methylprednisolone pulse therapy followed by conventional oral corticosteroids. Her renal function improved in response to the treatment.

In conclusion, tubular dysfunction due to tubulointerstitial nephritis is seen frequently in primary Sjögren’s syndrome, but glomerular disease is rare. There are two major types of glomerular complications, membranous nephropathy and membranoproliferative glomerulonephritis, both of which often develop in association with cryoglobulinaemia. Although crescentic glomerulonephritis is very rare in primary Sjögren’s syndrome, we must be alert to its possible involvement because prompt diagnosis and intensive therapy will be crucial for preventing renal failure in such cases.

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References
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