ANCA-associated pauci-immune crescentic glomerulonephritis complicating Sjögren’s syndrome

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Introduction

Although ocular and oral dryness are the hallmarks of Sjögren’s syndrome (SS), SS patients can develop a variety of complications, affecting organs such as the liver, kidneys, lungs, muscles, and nervous system [1]. Renal involvement has been described in 25–30% of patients with SS, usually as a tubulointerstitial nephritis. However, glomerulonephritis (GN) is rare in primary SS and fewer than 25 cases have been reported. Most patients had membranous or membranoproliferative GN [2–7].

We report a patient with primary SS who developed a crescentic glomerulonephritis (CGN) associated with perinuclear antineutrophil cytoplasmic autoantibodies (ANCA). To our knowledge, this association has not been previously described in the literature.

Case report

A 74-year-old woman was admitted to the hospital because of malaise, progressive dyspnoea and bilateral lung infiltrates. Three years earlier the patient came to the hospital because of a transient ischaemic attack. On physical examination, cutis marmorata and an ejection murmur consistent with aortic stenosis were present. She had a rheumatoid factor of 147 U (normal, <22 U) and an antinuclear antibody titre of 1:1280 with a speckled pattern. A cranial CT scan showed an acute capsular infarction. Carotid Doppler ultrasonography was normal. Ticlopidine was added and she recovered without sequelae.

Seven months later, she was admitted to the hospital with a 2-week history of malaise, dry cough, and increasing dyspnoea. She then reported dryness of the mouth and eyes for over 4 years, as well as hand and feet paraesthesia.

On admission the patient’s temperature was 36.5°C, pulse 100, respirations 24, and blood pressure 150/100 mmHg. The jugular venous pressure was normal. She had a dry oral mucosa and cutis marmorata. A harsh systolic murmur was present along the left sternal border. Inspiratory crackles were heard over the lowest one-third of both lungs. The remainder of the examination was unremarkable.

The haematocrit was 26%, the haemoglobin was 8.8 g/dl (normocytic normochromic). The white cell count was 13.6 x 10⁹/l, with 92% neutrophils and 3% lymphocytes. The platelet count was 405 x 10⁹/l. The erythrocyte sedimentation rate was 116 mm/h. Blood urea was 13.4 mmol/l (81 mg/dl), plasma creatinine 229.8 µmol/l (2.6 mg/dl). The estimated creatinine clearance was 13 ml/min. Creatine kinase and thyroxin levels were normal. Other biochemical tests were also normal and microbiological studies were negative. Chest X-rays showed bilateral interstitial infiltrates. An echocardiogram revealed moderate aortic valve stenosis, with a normal ejection fraction.

The urinary sediment showed 2–3 white and 80–100 red blood cells per high-power field (40% dysmorphics) plus hyaline and granular casts. The 24-h protein excretion was 1.6 g. Rheumatoid factor was 50 U (normal, <22 U) and antinuclear antibodies were positive with a titre of 1:1280 and a speckled pattern. Anti-double-stranded DNA, anti-Sm, anti-RNP, antithyroid, anti-cardiolipin, and anti-glomerular basement membrane antibodies were negative. However,
tests for anti-SS-A and anti-SS-B were both positive. An ANCA test showed perinuclear staining (p-ANCA), and antinuclear peroxidase (MPO) antibodies were detected by EIA (59 U); normal, <10 U). The results were confirmed several times. C3, C4 and CH50 levels were all normal. Traces of cryoglobulins (IgG) were detected. A coagulation profile was normal and there was no evidence of lupus anticoagulant. Hepatitis B surface antigen and antibodies against hepatitis B and C viruses were negative.

Schirmer's and rose bengal tests were both positive. An electrophysiological study was consistent with a mixed distal asymmetric polyneuropathy. A minor salivary gland biopsy revealed two foci of more than 50 lymphocytes. A skin biopsy showed infiltration by lymphocytes and histiocytes around the dermal vessels.

Renal biopsy contained 18 glomeruli, two sclerosed and the remainder containing cellular crescents. There was moderate focal infiltration by lymphocyte and plasma cells around the glomeruli and some foci of interstitial fibrosis and tubular atrophy. Small arteries showed intimal fibrosis without inflammatory infiltration (Figure 1). No deposits were detected by immunofluorescence. A diagnosis of pauci-immune crescentic glomerulonephritis (CGN) and primary Sjögren's syndrome was made. The patient received three boluses of methylprednisolone (0.5 g daily), followed by oral prednisone (1 mg/kg per day). Two weeks later lung infiltrates had cleared and plasma creatinine was 141.4 μmol/l (1.6 mg/dl).

Discussion

Lymphocytic infiltration of kidney interstitium with tubular atrophy and fibrosis is a frequent extraglandular complication of SS [7]. However, glomerular disease is very uncommon. Previously published cases usually had morphological features of membranous or membranoproliferative glomerulonephritis [2-7].

The patient here reported had definite Sjögren's syndrome [8] without evidence of any other collagen vascular disease. The findings on renal biopsy were characteristics of a pauci-immune CGN. To our knowledge, only one case of CGN associated with primary Sjögren’s syndrome has been previously reported [9]. Similar to the present case, the patient reported by Dussol et al. had positive antinuclear and anti-SS-A antibodies. But unlike our patient, she had glomerular deposits of C3 and was ANCA-negative.

This patient had a multi-system disease affecting the exocrine glands, lungs, kidneys, and nervous system.

Fig. 1. A, Representative field with two glomeruli showing crescents. H&E ×25. B, Epithelial and fibrotic crescent in the urinary space of a glomerulus. H&E ×100.
ANCA-associated glomerulonephritis in Sjögren’s syndrome.

However, we did not find evidence of vasculitis in any of the three biopsies performed. Moreover, interstitial lung disease and peripheral neuropathy are common complications of SS [10,11]. Focal neurological deficits have also been described in patients with SS, particularly in the presence of anti-SS-A antibodies. Therefore we believe our patient had CGN associated with SS, without systemic necrotizing vasculitis. Nevertheless the distinction between microscopic polyarteritis and pauci-immune CGN is far from absolute, and in fact some authors consider idiopathic CGN as a renal-limited form of the former.

p-ANCA are very frequently detected in cases of pauci-immune CGN, commonly with anti-MPO specificity. Several in vitro studies favour the hypothesis of a pathophysiological role for these autoantibodies. Neutrophils primed by inflammatory cytokines express MPO and other target antigens for ANCA. Binding of the antibodies further activates the cells to release an array of reactive oxygen species and other inflammatory mediators. This leads in turn to damage of the endothelial cells, as neutrophils adhere to them following the upregulation of adhesion molecules [12]. Thus it is tempting to speculate that ANCA actually mediated renal injury in the present case. However, other mechanisms must be implicated. In fact, p-ANCA have been detected in up to one-quarter of patients with SS in some series [13], whereas glomerulonephritis is very uncommon.

The present case illustrates the multifaceted clinical spectrum of SS and the potential pathophysiological relationships between autoimmune disorders and ANCA-mediated renal disease. SS and some other collagen vascular diseases may have a subtle clinical expression, being difficult to recognize, particularly in fragile, elderly patients. However, since renal injury is potentially reversible with proper therapy, as happened in this case, these conditions should not be overlooked.

References


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