Teaching Point
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A 70-year-old man with weight loss, dry mouth and renal insufficiency

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Introduction

Kidney involvement is a frequent extraglandular manifestation of primary Sjögren’s syndrome (SS); however, a clinically significant renal impairment as a result of it is rare [1].

We report a patient with primary SS with renal failure, in whom we encountered diagnostic difficulties in ruling out renal lymphoma. Immunopathologic analysis of renal biopsy specimens from this patient showed polyclonal interstitial cell infiltration; and his renal failure, caused by severe tubulo-interstitial nephritis, responded favourably to oral prednisolone therapy.

Case

A 70-year-old Japanese man complained of bilateral cervical masses, dry mouth and weight loss starting in June 2000. His past medical history was unremarkable except for 20 years of well controlled hypertension. In May 2001, he was found to have renal dysfunction (serum creatinine = 2 mg/dl) and anaemia, and was therefore admitted to the internal medicine department for further work-up.

The patient had anorexia and a substantial weight loss (~17 kg, from 64 to 47 kg) over 1 year. His cervical masses had been present since the onset of the disease, but he had no history of local pain or fever. Enlarged submandibular salivary glands and a blood pressure of 100/60 mmHg were found on physical examination, which was otherwise unremarkable.

Laboratory tests revealed: serum creatinine 2.7 mg/dl; blood urea nitrogen 38.0 mg/dl; erythrocyte count 291–1044 µl; haemoglobin 9.7 mg/dl, with normocytic normochromic erythrocytes; leucocyte count 16.1–104/µl. Serum electrolytes were: sodium 138 mmol/l; potassium 4.9 mmol/l; calcium 8.8 mmol/l; and inorganic phosphorus 3.9 mg/dl. Serum uric acid was 7.7 mg/dl.

Urinalysis revealed a specific gravity of 1.015, a pH of 6, normal urinary sediments, and no sugar. Urinary protein excretion was 0.27 g/24 h and creatinine clearance was estimated to be 33 ml/min. Urine N-acetyl-b-D-glucosaminidase (NAG), and b2-microglobulin (beta 2MG) excretions were 2.8 IU/l (normal range 0.6–9.4 IU/l), and 13 200 ng/ml (normal range 13–301 ng/ml), respectively. Arterial blood gas analysis ruled out metabolic acidosis, and liver and pulmonary function tests were normal.

The patient’s total serum protein was 7.6 g/dl, and gammaglobulin was 31.3%. On immunoglobulin electrophoresis, the following values were found: immunoglobulin G (IgG) 2541 mg/l (normal range 870–1700 mg/dl), IgA 371 mg/dl (normal range 110–410 mg/dl), and IgM 53 mg/dl (normal range 65–135 mg/dl) without a monoclonal component. The C-reactive protein level was 0.2 mg/dl, and the erythrocyte sedimentation rate (ESR) 89 mm/h. The anti-nuclear antibody titre was 1:320; the following antibodies were absent: anti-DNA, anti-Sm, anti-RNP, anti-SCL-70, anti-Jo-1, anti-neutrophil cytoplasm, anti-hepatitis C and the anti-SSA and -SSB. The levels of C3, C4 and CH50 were 40.8 mg/dl (normal range 65–135 mg dl)
14.6 mg/dl (normal 13–35 mg/dl) and 27.8 U (normal range 28–53 U), respectively; the level of the soluble interleukin receptor (sIL-2R) antibody was elevated at 4590 U/ml (normal range 190–650 U/ml).

A precontrast computed tomography of his abdomen showed both kidneys to be of normal size. Magnetic resonance images (MRI) revealed loss of the renal cortico-medullary junction on T1-weighted images and multiple hypo-intense areas within the parenchyma on T2-weighted images (Figure 1). A Ga-67 scan showed prominent and diffuse accumulation of Ga-67 citrate in both kidneys.

At that time, the diagnosis of malignant lymphoma was entertained. Thoracic and abdominal scans failed to show lymph node enlargement. Bone marrow aspiration revealed a hypocellular bone marrow with a nuclear cell count of 2.7–10⁴/μl (megakaryocytic count 1+/μl), and the myeloid/erythrocytic ratio increased to 6.28 (normal range 2–3). Neither malignant cells nor an increase in the ratio of lymphocytes were found.

In September 2001, an open renal biopsy was performed. On light microscopy of the specimens, the most prominent feature discovered was massive interstitial infiltration with inflammatory cells, composed almost exclusively of mononuclear lymphocytes. Tubular degeneration and atrophy was marked, but tubulitis was mild. No proliferative glomerular changes were present, although 15 out of the 50 examined glomeruli were globally sclerosed. The glomerular basement membrane was wrinkled and thick. The Bowman’s capsule was also thick. The vessels were unremarkable except for mild arteriolar hyaline changes compatible with aging. An immunofluorescence study showed IgG, IgA and C3c deposits on the tubular basement membrane, and electron microscopy confirmed the presence of electron-dense deposits on it. Therefore, the renal biopsy was suggestive of severe tubulointerstitial nephritis. Still, lymphoma remained to be excluded. The immuno-histochemistry of the infiltrating mononuclear cells showed the majority of the inflammatory cells to be T lymphocytes (CD3, CD45RO positive), though some (<10%) were B lymphocytes (CD20, CD79 positive) without features of malignancy.

The diagnosis of tubulointerstitial nephritis with renal dysfunction was made based on clinical and histopathological findings. After excluding drug-induced interstitial nephritis, we suspected the diagnosis of SS. Schirmer’s test was positive. Technetium-99m pertechnetate (TC-99m) scintigraphy of the salivary glands revealed low uptake in the submandibular glands compared with the parotids. A submandibular gland biopsy showed distortion of the ductal pattern by diffuse inflammatory cells and a marked fibrosis. An immunohistochemical study revealed the slight predominance of T lymphocytes (CD45RO positive) over B lymphocytes (CD20 positive) among the cellular infiltrate.

Oral steroid therapy (40 mg/day prednisolone) was initiated in September 2001, because of progressive renal insufficiency and severe tubulointerstitial nephritis. Within 2 months of starting that treatment, the patient’s laboratory findings showed a dramatic improvement in concert with his subjective improvement. As for his renal function, serum creatinine decreased from 3.3 to 1.5 mg/dl and creatinine clearance improved from 15 to 47 ml/min. Proteinuria decreased from 0.34 to 0.09 g/day. His haemoglobin level increased markedly, from 9.1 to 13.7 g/dl, and the ESR returned to normal. Moreover, we succeeded in tapering the dose of oral prednisolone to 25 mg/day after 3 months and to 10 mg/day after 6 months. There have been no signs of a relapse so far. The patient was in good health on his last clinic visit, in July 2003, and his biochemical data were stable (serum creatinine 1.6 mg/dl, serum creatinine clearance 40 ml/min, haemoglobin 13.4 g/dl) on 7.5 mg/day prednisolone, with no adverse effects.

**Discussion**

The diagnosis of SS in this patient was made after excluding malignant lymphoma, and was based on the revised international classification criteria [2]: dry mouth and salivary glands enlargement, positive Schirmer’s test, decreased uptake of TC-99m on salivary gland scintigraphy, and lymphocytic sialoadenitis on salivary gland histopathology. The absence of anti-SSA or anti-SSB is not uncommon in SS. We found low levels of serum complements in our patient, notably of C3. Hypo-complementaemia is characteristic of systemic lupus erythematosus. It is also more prevalent in patients with hepatitis C virus-related SS compared with primary SS (60 vs 8%) [3]. Nonetheless, our patient did not show any other clinical or serological evidence of associated diseases.
We found a high level of sIL-2R in our patient, which is considered an index of disease activity in many rheumatic conditions, including SS. Spadaro et al. [4] found no relationship between sIL-2R serum levels and the extra-glandular manifestations of the disease in a group of patients with SS. The question remains, however: what serum levels of sIL-2R are associated with the development of lymphoma in patients with SS?

Various renal changes have been recognized in 20–30% of patients with SS. Tubulointerstitial nephritis may manifest as distal renal tubular acidosis (dRTA), which often is clinically silent [1,5]. Our patient showed progressive renal insufficiency because of severe tubulointerstitial nephritis. We assumed that dRTA did not occur in him, because measurements of his urinary pH were below 5.5; therefore, we did not perform a urine acidification test. Since his abdominal MRI (Figure 1) revealed multiple hypo-intense areas in the renal parenchyma on T2-weighted images, we performed open renal biopsies in order not to miss focal disease. Our histopathological findings on light microscopy, were compatible with those of severe tubulointerstitial nephritis. However, the diagnosis of lymphoma could not be ruled out because of the uniform appearance of infiltrating cells, composed almost exclusively of mononuclear lymphocytes (Figure 2). Typically, interstitial nephritis in patients with SS is characterized by the presence of lymphocytes, plasma cells and monocytes in the interstitium [5]. Immunopathologic studies in our patient failed to demonstrate a monotypic cell population. Although the majority of lymphocytes were T cells, B cells were also present. To verify the clonality of these cells, we wished to perform a gene rearrangement of the T-cell receptor and the heavy chain immunoglobulin; unfortunately, we could not elute enough DNA to perform the analysis because of the smallness of the frozen tissue sample. However, we believe that the immunohistochemical findings, as well as the favourable clinical course, made lymphoma an unlikely diagnosis. The distinction between renal involvement and malignant lymphoma in SS may not be straightforward; therefore, a thorough work-up is essential in a patient with tubulointerstitial nephritis. T cells have been described to be the prominent cell population invading the renal interstitium, whereas B cells detected by CD19 constituted a mean of 8.6% of the infiltrating cells in patients with tubulointerstitial nephritis associated with SS [6]. In our patient, the percentage of the sclerotic glomeruli (30%) was out of proportion with the vascular changes, suggesting that the tubulointerstitial lesion is the primary event, which secondarily affects glomeruli.

The renal pathology resembled that in the salivary glands; however, it was more active in the kidneys, as indicated by the rapid deterioration of renal function and the marked accumulation of Ga-67 in the kidneys, in comparison with the salivary glands (Figure 3). The absence of a temporal association between disease activities in glandular and extraglandular organs is not an uncommon feature of SS [1].

The pathogenesis of interstitial nephritis in SS is not well understood. In the interstitial nephritis associated with SS, most infiltrating cells are activated CD4+ T lymphocytes (1, 5). INFγ secreted by those lymphocytes can induce aberrant CD86 antigen expression by tubular epithelial cells, which in turn may activate T cells around the tubules [7]. The class-II type major histocompatibility antigen protein HLA-DR and the intracellular adhesion molecules ICAM-1 are also expressed by tubular epithelial cells in interstitial nephritis associated with SS, and they may have a role in the induction and progression of the inflammatory process [8]. Moreover, the enhanced expression of Fas on epithelial cells and the apoptosis induced by the Fas ligand on infiltrating lymphocytes could also be involved in the process [9]. On the other hand, other investigators have suggested a role for deposited immune complexes [10].

It is possible that in our patient interstitial infiltrates and immune complex deposits both contributed to the renal insufficiency, whose course was characterized by a good response to oral prednisolone, which had to be

Fig. 2. Light microscopy of renal biopsy specimen showing diffuse and uniform infiltration of the renal cortex with mononuclear lymphocytes (haematoxylin and eosin) (original magnification ×66).

Fig. 3. Ga-67 scan shows prominent and diffuse accumulation of Ga-67 citrate in both kidneys, in contrast to the salivary glands.
continued for prolonged period to maintain normal renal function.

Teaching points

1. Weight loss, dry mouth and renal insufficiency may be clinical signs of SS.
2. Absences of one or both of anti-SSA or -SSB-antibodies and of renal tubular acidosis do not exclude a renal involvement in this disease.
3. The secondary occurrence of a lymphoma has to be excluded in Sjögren’s disease.

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Conflict of interest statement. We declare that there are no conflicts of interest in this study.

References