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CASE REPORT

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Abacterial prostatitis and primary biliary cirrhosis with Sjögren's syndrome

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Abstract In patients with Sjögren's syndrome (SS), the salivary and lacrimal glands are often affected, although other epithelial tissues can become inflamed. Here, we report the first case of abacterial prostatitis in a patient with SS complicated by primary biliary cirrhosis. Histologically, the distribution and subpopulation of infiltrating lymphocytes were similar in the salivary gland, liver, and prostate. Treatment with steroid was successful. We speculate that the prostate may be one of the target organs in SS.

Key words Primary biliary cirrhosis (PBC) · Propstatitis · Sjögren's syndrome (SS) · Steroid · T cell

Introduction

In patients with Sjögren's syndrome (SS), the exocrine glands, including the lacrimal and salivary glands, are mainly affected, although "extra glandular" manifestations such as thyroiditis, tubulo-interstitial nephritis, interstitial pneumonitis, primary biliary cirrhosis, or mono-neuritis multiplex have also been described. Many of these manifestations are referred to as "autoimmune exocrinopathy"[1] or "autoimmune epithelitis",[2] primarily because of their histopathological presentation, in which affected exocrine glands are infiltrated with mononuclear cells, resulting in the destruction and dysfunction of the glands. Here, we present a case of abacterial prostatitis associated with SS where the histopathological findings of the prostate, minor salivary glands, and liver were similar, and oral corticosteroid therapy was effective. Although the pathophysiology and appropriate treatment are yet to be clarified, this is the first case report describing abacterial prostatitis as one of the glandular symptoms of SS.

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Case report

The patient was a 56-year-old Japanese man who presented with a 1-month history of recurrent swelling of the parotid and lacrimal glands, as well as dysuria and nocturia. He was found to have swollen salivary and lacrimal glands, hyper-γ-globulinemia, and mild liver dysfunction. Sjögren's syndrome (SS) was suspected. He was admitted to the Department of Rheumatology of our hospital in June, 1999, for further evaluation. On physical examination, bilateral submandibular glands, the left parotid gland, and bilateral lacrimal glands were swollen but nontender. Fever, joint swelling, dry eyes, dry mouth, and superficial lymph node swelling were not present. Cardiopulmonary, vascular, and abdominal examinations were normal. Complete blood cell count, urinalysis, and stool analysis revealed no abnormalities. Serum C-reactive protein level was slightly elevated at 1.0 mg/dl, and erythrocyte sedimentation rate was elevated at 44 mm/h. Polyclonal hyper-γ-globulinemia up to 3.73 g/dl was noted. Liver dysfunction was evident as follows: aspartate aminotransferase 62 IU/l, alanine aminotransferase 74 IU/l, alkaline phosphatase 744 IU/l, lactate dehydrogenase 167 IU/l, γ-glutamyl transpeptidase 432 IU/l. Serum C_3 level normal, and C_4 and CH_{50} levels low at 4 mg/dl and 21.5 U/ml, respectively. Antinuclear antibody was positive at 1:40 with a cytoplasmic pattern, and antimitochondrial M2 antibody was strongly positive (820.0 U/ml), whereas antismooth muscle antibody was negative. Anti-SSA/Ro, anti-SSB/La, anti-DNA, anti-Sm, anti-RNP, anti-Jo-1, anti-centromere, and myeloperoxidase–antineutrophil cytoplasmic antibodies were negative, as were immune complexes measured by C1q-binding assay, anti-C3d assay, and mono-

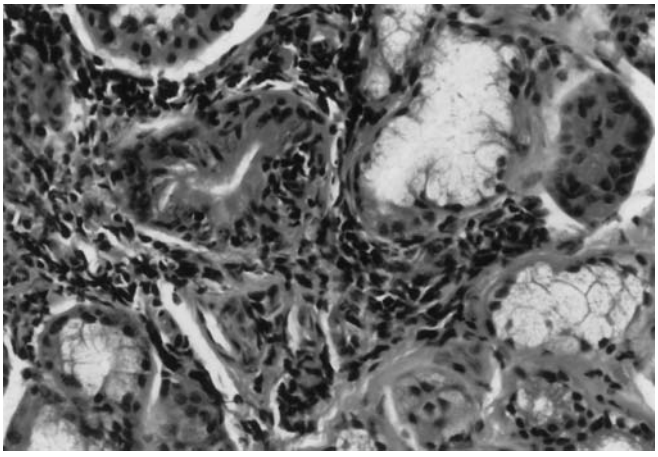

Fig. 1. Histology of the salivary gland, showing lymphocyte infiltration around the acinar epithelium and the interstitial tissues (H&E staining)

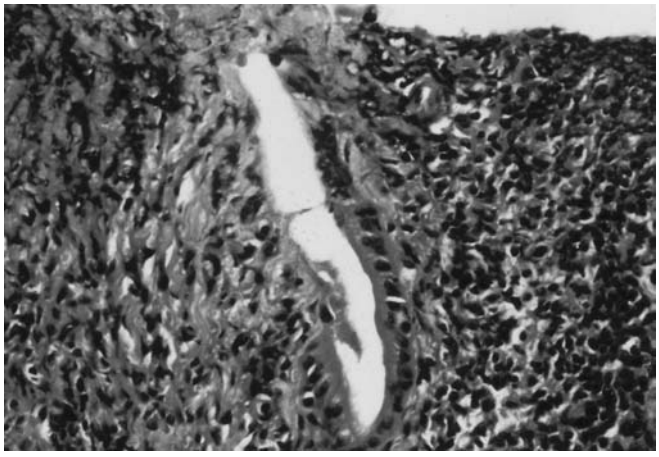

Fig. 2. Histology of the liver, showing nonsuppurative cholangitis, which is compatible with primary biliary cirrhosis (H&E staining)

clonal rheumatoid factor assay. Ophthalmologically, keratoconjunctivitis was not evident, although the Schirmer test revealed decreased lacrimal secretion, which was less than 5 mm/5 min. Although no abnormalities were found in the sialography, a salivary gland biopsy revealed chronic sialoadenitis with lobulus destruction and a strong accumulation of mononuclear cells. A needle biopsy of the liver revealed nonsuppurative cholangitis with mononuclear cell infiltration, mild fibrosis in Glisson's capsule, and focal bridging. These findings were compatible with primary biliary cirrhosis (PBC). Because of the positive findings for oral symptoms, ocular signs, and histopathology, the patient was classified as having SS associated with PBC, based on the European Epidemiology Center Criteria.[3]

Oral administration of ursodeoxycholic acid (600 mg/day) was followed by a gradual improvement in liver function, although the lacrimal and salivary glands remained swollen. Scintigraphy showed galium uptake in the salivary glands and lacrimal glands bilaterally, as well as in the prostate. Because of continued genitourinary tract symptoms, urological examinations were performed. A rectal examination and MRI revealed prostate enlargement. Needle biopsy specimens of the prostate showed severe abacterial prostatitis, with lymphocytic infiltration around the acinar epithelium and the interstitial tissues. No destruction of glands or malignancy were evident. Cultures of semen showed no evidence of bacterial infection. Immunostaining of salivary gland, liver, and prostate specimens was performed using anti-CD4 and anti-CD8 monoclonal antibodies. Infiltrating lymphocytes were predominantly CD4+ cells and were located in the periductal area, whereas a small number of CD8+ cells were found attached to the ductal epithelial cells (Figs. 1–4). Based on the concordance observed in these three organs, we concluded that the abacterial prostatitis found in this patient was a manifestation of active SS, as were the sialoadenitis and PBC. Oral prednisolone was administered, with an initial dose of 40 mg/day. The swelling of the lacrimal and salivary glands, as well as the dysuria, improved rapidly. After 2 weeks, prednisolone was gradually tapered to 5 mg/day without recurrence of the symptoms. A histological improvement in the prostatitis was also shown by another biopsy of the prostate.

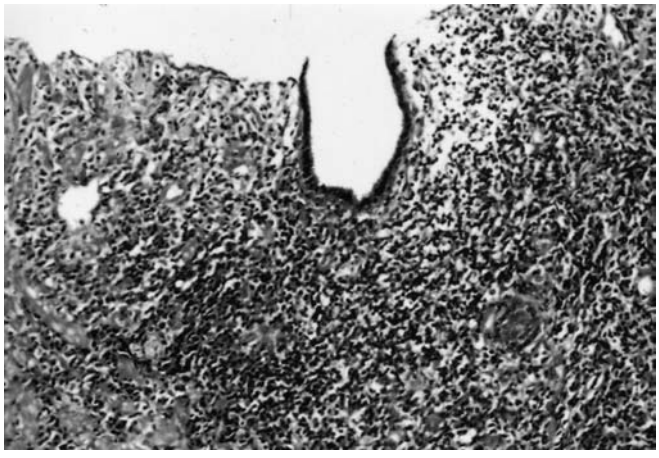

Fig. 3. Histology of the prostate, showing severe abacterial prostatitis with lymphocyte infiltration (H&E staining)

Discussion

In SS, the T lymphocytes that infiltrate the exocrine glands cause dysfunction of the affected glands via apoptosis of the epithelial glandular cells.[4] The majority of the infiltrating cells are CD4+ T cells, although a small number of CD8+ T cells are also observed in the inflammatory lesions. Fujihara et al.[5] reported that such infiltrating CD8+ T cells are located around the acinar epithelial cells and express integrin $\alpha_E\beta_7$. The interaction between $\alpha_E\beta_7$ and E-cadherin,[6] which is expressed on the acinar epithelial cells, plays a key role in inducing the apoptosis of epithelial cells. The liver involvement in SS is similar to that in PBC in pathology in that circulating anti-mitochondrial antibodies are found in patients' sera. In PBC, the infiltrating lymphocytes are mainly CD4+ T cells, but the precise mechanisms of bile duct destruction and the role of infiltrating T cells are

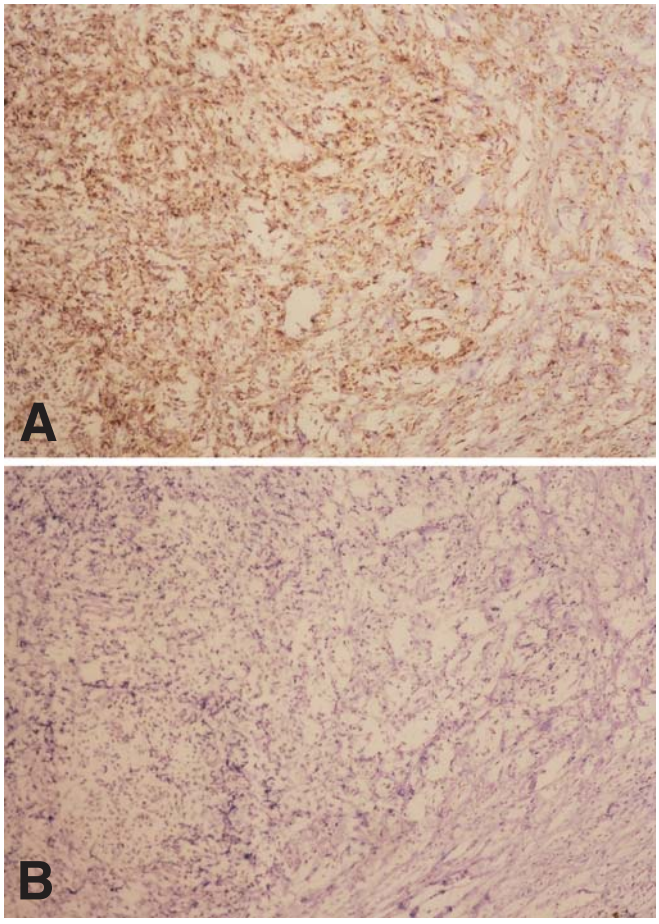

Fig. 4. Prostate stained with anti-CD4 antibody (**A**) and anti-CD8 antibody (**B**). Infiltrating lymphocytes were predominantly CD4+ cells, but a small number of CD8+ cells were found. The infiltrated lymphocytes observed in the salivary gland (Fig. 1) and the liver (Fig. 2) were also predominantly CD4+ cells. This was confirmed by immunostaining with anti-CD4 and anti-CD8 antibody

not clear. Inada et al.[7] investigated the T cell repertoire in the liver of PBC patients, and the results suggested that CD4+ T cells with V-β-4 and J-β-2.7 might play an important role in the pathogenesis of PBC, whereas CD8+ T cells with V-β-17 and J-β-2.1 appeared to be important in antigen recognition in some patients. Thus, CD4+ T cells and CD8+ T cells both play a role in patients with SS or PBC.

Chronic abacterial prostatitis/chronic pelvic pain syndrome (CAP/CPPS) is a common clinical syndrome characterized by lower genitourinary tract symptoms in the absence of uropathogens in the urine or prostatic secretions.[8] The etiology, pathophysiology, and appropreate treatment for this syndrome are still unknown. One histological study of a series of patients with CAP/CPPS showed that the inflammatory cells are predominantly mononuclear, but that the severity of inflammation and the distribution of infiltrating cells differ greatly among patients,[9] suggesting variability in the underlying pathogenesis of this clinical entity and difficulty in choosing treatment. Nevertheless, there are a few reports suggesting an autoimmune basis for CAP/CPPS. Bates and Talbot[10] used a short course of prednisolone in the successful treatment of three of four patients whose diseases had been resistant to conventional therapies such as antibiotics and/or non-steroidal anti-inflammatory drugs. In addition, the reactivity of CD4+ T cells against prostatic proteins was reported in patients with CAP, suggesting an autoimmune mechanism.[11]

In our case, prednisolone was effective in reducing the swelling of the prostate, salivary, and lacrimal glands. Because the patient had no sign of infection, such as fever or lymph node swelling, and because remission was obtained without using antibiotics, it is unlikely that viral or bacterial infection played a major role in the current episode. In SS, "extraglandular" involvement is directed against other epithelial tissues, such as renal tubular, bronchial, and cholangial epithelia.[2] Here, we suggest that inflammation of the prostate in which cadherins, including E-cadherin, are expressed[12] can be associated with, and may be a manifestation, of SS. We speculate that SS may have been overlooked in CAP/CPPS patients, and vice versa. Further large-scale studies are necessary to establish a definite association between SS and CAP/CPPS and determine its etiology and appropriate treatment.

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