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CASE REPORT

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A case of interstitial cystitis accompanying Sjögren's syndrome

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Abstract A 51-year-old woman with interstitial cystitis was referred for screening of autoimmune disease. She was positive for results of Schirmer and Saxon tests and for ss/A and ss/B antibodies. Autoantibodies to type 3 muscarinic acetylcholine receptor were detected in the patient's serum by Western blotting. We diagnosed her as having interstitial cystitis accompanying Sjögren's syndrome. To enable early treatment, interstitial cystitis should be considered when patients with Sjögren's syndrome complain of urinary symptoms.

Key words Anti type 3 muscarinic acetylcholine receptor antibody · Interstitial cystitis · Sjögren's syndrome

Introduction

Interstitial cystitis is a chronic inflammatory urologic condition mainly affecting women. The most widely accepted theories regarding the etiology of interstitial cystitis are (1) increased permeability of the bladder epithelium due to a deficient glycosaminoglycan layer allowing an unspecific toxic substance to cause inflammation[1] and (2) production of inflammation mediators as a result of activation of mast cells.[2–4] However, the etiology and pathogenesis of interstitial cystitis remain unclear. Although the cause of this disease has not been fully elucidated, it is known to accompany thyroid disease, systemic lupus erythematosus,[5,6] Sjögren's syndrome,[7] ulcerative colitis, and Crohn's disease.[8] Since infiltration of Th2 lymphocytes, eosinophils and mast cells is seen in the mucous membrane of the urinary bladder,[9] autoimmune mechanisms are believed to be at work.

Sjögren's syndrome is an autoimmune disease characterized by lymphocyte infiltration of the exocrine glands, particularly, the lacrimal and salivary glands. Recent studies suggest that autoantibody to type 3 muscarinic acetylcholine receptor (M3R) may contribute to sicca symptoms and may explain associated features of autonomic dysfunction in some patients.[10]

Interstitial cystitis accompanying Sjögren's syndrome was first reported by Van De Merwe and colleagues in 1993.[7] To the best of our knowledge, only three reports on interstitial cystitis accompanying Sjögren's syndrome have been published in Japan over the last 10 years.[11–13] In this report, we present a case of interstitial cystitis accompanying Sjögren's syndrome.

Case report

A 51-year-old woman with interstitial cystitis was referred to our department by the urology department of our institution in December 1998 to undergo screening for autoimmune disease. In 1983, the patient had been diagnosed with rheumatoid arthritis by another physician and was treated with unknown medication until 1988, when she stopped consulting the physician. From July 1998, the patient experienced dryness of the eyes and mouth, and in December of the same year, she consulted the urology department for examination of increased urinary frequency.

Urinalysis conducted in the urology department showed sterile hematuria, with 15–20 red cells and 1–3 white cells per high-power field. An intravenous urographic examination showed bilateral ureteral dilatation and hydronephrosis (Fig. 1). A cystogram showed an irregular bladder of small volume, only 70 ml (Fig. 2). Cystoscopy demonstrated redness, swelling, extensive ecchymosis, and petechial hemorrhage of the mucosal surface, and urothelial biopsy revealed infiltration of lymphocytes, plasmacytes, and mast

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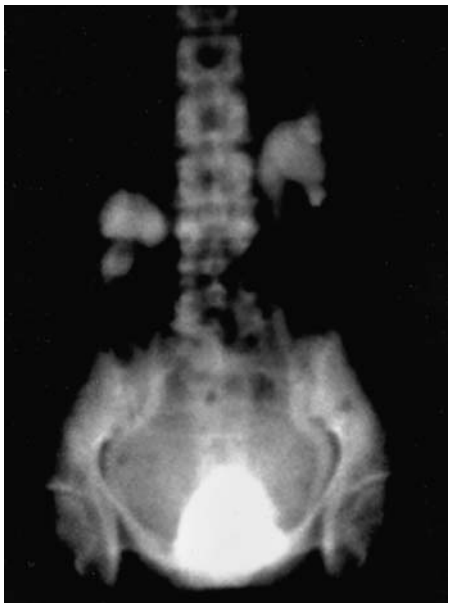

Fig. 1. Intravenous urographic examination revealed dilatation of the urinary tract and renal pelvis

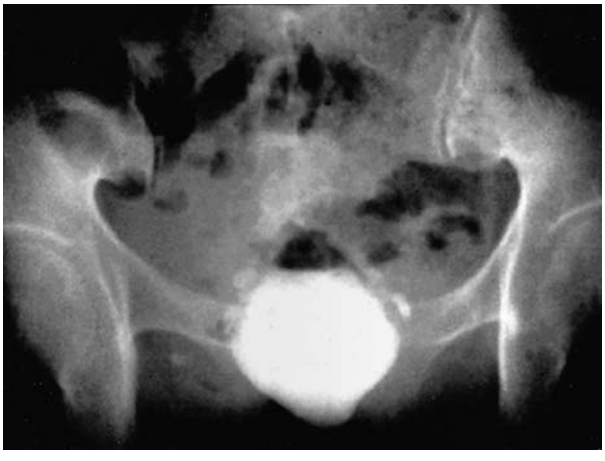

Fig. 2. Cystography confirmed poor bladder filling, and bladder volume was 70 ml

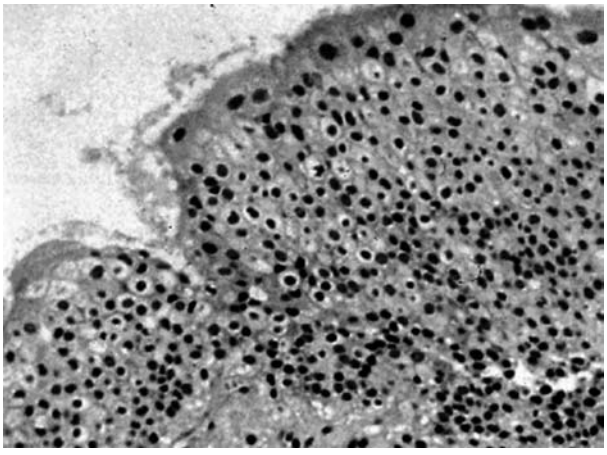

Fig. 3. Biopsy specimens of urinary bladder showed diffuse subepithelial edema and multiple foci of inflammatory infiltrates with lymphocytes, plasmacytes, and mastocytes (H&E stain)

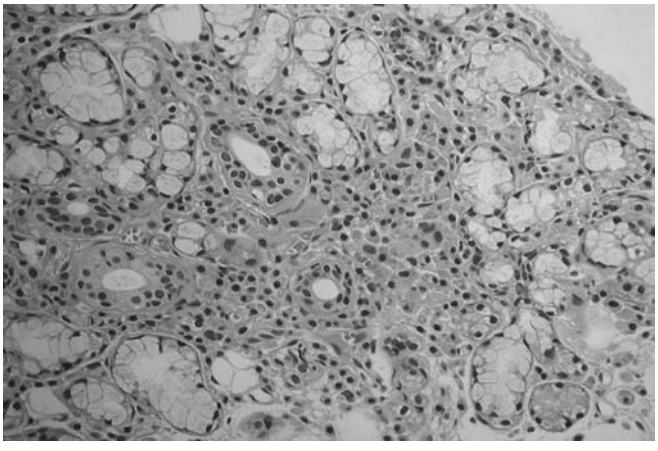

Fig. 4. Biopsy of labial salivary gland shows periductal infiltration of lymphocytes and plasmacytes (H&E stain)

cells accompanying submucosal edema (Fig. 3). Based on the above findings, the patient was diagnosed as having interstitial cystitis according to the diagnostic criteria established by the National Institutes of Health.[14] In addition, laboratory testing showed a positive reaction to antinuclear antibody, and the patient was consequently referred to our department to undergo screening for autoimmune disease.

On admission, mild pallor of the palpebral conjunctiva and bilateral deformation of the proximal and distal joints of the thumb were evident. The oral mucosa and tongue were dry. No other abnormality was seen.

Laboratory data at admission were as follows. Urinalysis: occult blood (+). Complete blood count: white blood cell count, 3000/μl; red blood cell count, 2810000/μl; Hb, 9.6 g/dl; platelet count, 209000/μl; erythrocyte sedimentation rate, 188 mm (60 min). Serum biochemistry: blood urea nitrogen, 8 mg/dl; creatinine, 0.7 mg/dl; IgG, 2180 mg/dl; IgM, 158 mg/dl; C3, 34 mg/dl; C4, 13 mg/dl; CH_{50}, 24.2 U/ml; IC-C1q, 9.9 μg/ml; IC-C3d, 26.6 μg/ml. Immunological tests: antinuclear antibody, 1280× (Ho, Sp); anti-DNA antibody, 8.3 IU/ml; anti-Sm antibody, 0.2 IU/ml; anti ss-A antibody, 157 IU/ml; anti ss-B antibody, 60.3 IU/ml; rheumatoid factor, 699 IU/ml. Ophthalmological examination: corneal erosion and positive results of Schirmer test (right: 2 mm; left: 2 mm). Saxon test: reduced salivary secretion (0.6 g/2 min). Biopsy of labial salivary gland: periductal infiltration of lymphocytes (Fig. 4).

Furthermore, blot reactivity to human M3R in the patient's serum was checked by Western blotting. We observed blot reactivity to M3R in patient's serum;

however, no blot reactivity was observed in serum of a healthy control (Fig. 5).

Based on the above findings and the history of dry eyes and mouth, the patient was diagnosed as having Sjögren's syndrome according to the European Sjögren's syndrome diagnosis criteria.[15] Because interstitial cystitis was thought be a complication of Sjögren's syndrome, administration of prednisolone was initiated at 30 mg/day. In response to this, urinary volume increased but urinary frequency did not improve. Hydraulic dilatation was additionally performed, and urinary frequency improved.

Discussion

Interstitial cystitis is a cryptogenic chronic inflammatory urologic condition. The incidence of this condition in Japan is 4.5 cases per 100000 women,[16] a lower frequency than those reported in other countries: 52–67 cases per 100000 women in America;[17] 18.1 per 100000 or 10.6 per 100000 women in Finland;[18] and 8–16 per 100000 women in the Netherlands.[19] This geographical variation in incidence might be due to racial factors or to diagnostic criteria. Furthermore, clinical symptoms and pathological findings are nonspecific, and diagnosis is based on various factors such as sterile urine and cystoscopic findings. Hence, interstitial cystitis may be misdiagnosed as simple bacterial cystitis, thus leading to unnecessary administration of antibiotics, or as neurogenic bladder.

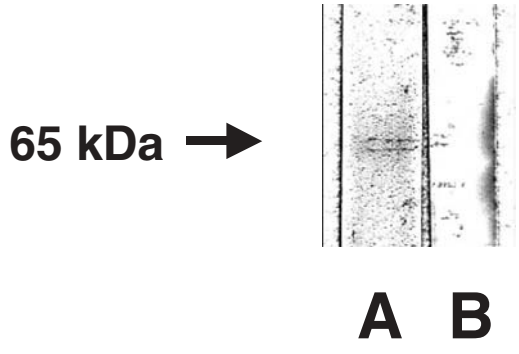

Fig. 5A,B. Western blot showing reactivity to human recombinant type 3 muscarinic acetylcholine receptor (M3R). M3R (2 μg/lane) was subjected to 10% sodium dodecyl sulfate–polyacrylamide gel electrophoresis, transferred onto polyvinylidene difluoride membrane, and probed with the patient's serum or serum of a healthy control (1/100 dilution). After washing, the membrane was incubated with alkaline phosphatase-conjugated anti-human IgG. **A** Autoantibody to M3R was detected as a band at *65 kDa* in serum of the patient. **B** No blot reactivity was observed in serum of a healthy control

The relationship between Sjögren's syndrome and interstitial cystitis has not been clarified. In both diseases it has been reported that the expression level of HLA-DR in the epithelia is high[20,21] and that the proportion of $CD4^+$ T-helper cells in infiltrating cells is high,[22,23] suggesting the existence of a common immunological abnormality. Van De Merwe and colleagues proposed the following onset mechanism: autoantibodies blocking muscarinic receptors, which are involved in contraction of smooth muscles, are produced in patients with Sjögren's syndrome, thus resulting in interstitial cystitis.[24]

We detected autoantibody to M3R in our patient's serum by Western blotting. Recent studies suggest that autoantibody to M3R may cause secretory dysfunction that leads to dry mouth in patients with Sjögren's syndrome.[10,25,26] Studies have also shown that sera from patients with Sjögren's syndrome inhibit smooth muscle contraction of isolated bladder strips in response to stimulation of M3R by a muscarinic receptor agonist. Autoantibody to M3R may explain manifestations of autonomic dysfunction, such as interstitial cystitis, in some patients with Sjögren's syndrome.

However, Gao and colleagues reported that autoantibodies to M3R were positive in a majority (9 of 11) of Sjögren's syndrome patients tested,[27] indicating that interstitial cystitis will not develop in all patients with Sjögren's syndrome who have autoantibodies to M3R. Further studies are needed to clarify the role of anti-M3R antibody in the development of interstitial cystitis in patients with Sjögren's syndrome.

Hydraulic dilatation, oral agents such as steroids, antidepressants, suplatast tosilate, and pentosan polysulfate, and intravesical injection of dimethyl sulfoxide are available as treatments;[12,28–33] however, there is no established treatment. In this case, we started treatment with steroids because we suspected autoimmune abnormalities could be involved in this case and because steroids were effective in combination with other therapies in the treatment of interstitial cystitis accompanying Sjögren's syndrome in all three reported cases in Japan (Table 1).

Interstitial cystitis can be easily confused with many different bladder diseases, and some patients with interstitial cystitis cannot get appropriate treatment because of misdiagnosis. To enable early treatment, it is necessary to consider interstitial cystitis when a patient with Sjögren's syndrome complains of urinary symptoms such as urinary frequency, urgency, nocturia, and suprapubic pain.

Table 1. Reported cases of interstitial cystitis with Sjögren's syndrome in Japan

Case	First author[Ref.]	Year	Age (years)/sex	Therapy	Outcome
1	Higuchi[11]	1998	53/F	Hydraulic dilatation → prednisolone	Improved
2	Nagaoka[12]	2003	77/F	Prednisolone + suplatast tosilate	Improved
3	Shibata[13]	2004	53/F	Prednisolone + cyclosporin	Improved
4	Present study		51/F	Prednisolone + hydraulic dilatation	Improved

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