Abstract

A 53-year-old woman presented with oliguria, urinary frequency, abdominal pain and severe edema of the lower extremities. Her serum creatinine was 8.1 mg/dl. Computed tomographic and ultrasonographic studies showed a severely dilated urinary bladder, and bilateral hydronephrosis. Examination of a urinary bladder biopsy specimen showed subepithelial edema and infiltration by lymphocytes and plasmacytes. However, the patient complained of dry mouth and dry eyes. Ophthalmologically, the Schirmer test was positive. A biopsy of the minor salivary glands in the lip showed chronic sialoadenitis. A diagnosis of Sjögren’s syndrome complicated by interstitial cystitis was made. Since she had been anuric, secondary to urinary obstruction, intermittent self-catheterization was started. Combination of corticosteroid and cyclosporin therapy was initiated. Spontaneous urination began, and gradually the patient’s symptoms remitted. After 8 months of therapy, bladder capacity increased from 140 ml to 350 ml, and she voided approximately 1,200 ml by herself and 600 ml by catheterization daily. This case suggests that when severe interstitial cystitis is associated with Sjögren’s syndrome, a therapeutic trial of corticosteroids and cyclosporin may be beneficial.

Key words: interstitial cystitis, Sjögren’s syndrome, corticosteroid, cyclosporin

Introduction

Interstitial cystitis is a syndrome of unknown etiology, characterized by bladder and/or pelvic pain, and irritable voiding symptoms (urgency, frequency, nocturia and dysuria) without evidence of overt infection. The prevalence is reported to be 52 to 67 cases per 100,000 women (1), approximately 90% of the patients overall being females (2).

Although its etiology is poorly understood, autoimmune mechanisms are implicated as one cause of interstitial cystitis. Several groups have reported a relationship between interstitial cystitis and systemic lupus erythematosus (SLE) (3). In addition to SLE, the coexistence of rheumatoid arthritis (RA), polyarteritis nodosa (PN), and scleroderma also have been observed (4–6). Cases with interstitial cystitis complicated by Sjögren’s syndrome have also been reported (7, 8).

The majority of severe cases of interstitial cystitis with obstructive uropathy involve SLE. This study discusses a rare reported case of severe interstitial cystitis associated with Sjögren’s syndrome.

For editorial comment, see p 174.

Case Report

A 53-year-old Japanese woman was admitted to our hospital on January 10, 2001, for the evaluation of oliguria and severe edema. In September 1999, urinary frequency and abdominal pain began. Oliguria and edema occurred on December 20, 2000, and were progressive.

On admission, the patient was 153 cm tall and weighed 57 kg. Her blood pressure was 220/110 mmHg, and she had severe edema mainly in the lower extremities. Although the patient complained of urinary frequency, urgency, dysuria, nocturia and suprapubic pain, she was oliguric with a urinary volume of less than 50 ml/day. There was no erythema, joint swelling, or Raynaud’s phenomenon. However the patient...
complained of dry mouth and dry eyes for more than 12 months.

Laboratory findings were as follows: erythrocyte count, \(3.35 \times 10^6/\mu l\); hematocrit, 30.1%; leukocyte count, 5,800/\(\mu l\); and thrombocyte count, \(23.8 \times 10^4/\mu l\). Total serum protein concentration was 7.5 g/dl; serum albumin, 3.1 g/dl; blood urea nitrogen, 55 mg/dl; serum creatinine, 8.1 mg/dl; and serum uric acid, 9.9 mg/dl. Serum sodium was 134 mmol/l; potassium, 3.5 mmol/l; and chloride, 102 mmol/l. The C-reactive protein concentration was 1.4 mg/dl, and erythrocyte sedimentation rate 80 mm/h. Serum immunoglobulin G (IgG) concentration was 1,620 mg/dl; IgA, 366 mg/dl; and IgM, 44.7 mg/dl. CH50 was 41 U; C3 concentration, 71 mg/dl; and C4, 21 mg/dl. LE cells, antinuclear antibody, anti-double strand DNA antibody and anti-RNP were negative. Antistreptolysin O concentration was 222 U/ml, anti-Ro antibody (SS-A) antibody (Ouchterlony double immuno-diffusion technique) was positive with 8 folds, and anti-Ro antibody (SS-B) was negative. Rheumatoid factor (ELISA) was negative. The urine pH was 5.5, negative for glucose, and 1+ for protein. Urine sediment contained 1 to 5 erythrocytes, and 1 to 5 leukocytes per high-power field (HPF). Urinary cultures yielded no growth.

Computed tomographic and ultrasonographic studies showed a severely dilated urinary bladder (10.5x9.4x13.0 cm), and bilateral hydroureteronephrosis (Fig. 1). The patient had acute renal failure due to obstructive uropathy, a urethral catheter was inserted. The patient discharged 4,500 ml of urine in the first 24 hours, and the serum creatinine level rapidly decreased and was within normal limits (0.8 mg/dl) on the 5th day of hospitalization. Her body weight returned to its premorbid value (50.5 kg), and her blood pressure decreased to a normal level (130/80 mmHg) on the 14th day of hospitalization. Drip infusion pyelography was performed on the 16th day of hospitalization (Fig. 2A). Bilateral hydroureteronephrosis and contracted bladder with irregular wall was apparent. A urodynamic study was performed on the 18th day of hospitalization. Although initial desire to void produced 56 ml of urine, the maximum effort to void produced 140 ml, and maximum intravesical pressure was 13 mmHg. Spontaneous urination was trivial.

Ophthalmologically, the Schirmer test was 1 mm on the right and 3 mm on the left in 5 minutes. Keratoconjunctivitis was observed. Salivary gland scintigraphy utilizing \(^{99m}\)TcO4 indicated decreased secretion of saliva (mainly in the submandibular and parotid glands).

On January 21, 2001, a biopsy of the minor salivary glands in the lip was performed, and a urinary bladder biopsy was performed cystoscopically on February 26, 2001.

**Salivary gland biopsy**

Moderate interstitial cellular infiltration by lymphocytes
Agglomeration of 2 foci of more than 50 mononuclear cells was confirmed in 4 mm² of glandular tissue. The acini were atrophic, with destruction of normal architecture; periductal fibrosis was observed. The final pathologic diagnosis was chronic sialoadenitis (Fig. 3A). Sjögren’s syndrome was diagnosed according to the latest European criteria (9).

Urinary bladder biopsy

Urinary mucosa contained petechiae and appeared edematous on cystoscopy, but no carcinoma in situ was found. Light microscopy of the biopsy specimens revealed diffuse epithelial and subepithelial edema with infiltration by lymphocytes and plasmacytes (Fig. 3B). Eosinophils were scarce. Immunofluorescent studies failed to reveal deposits of IgG, IgM, or complement C1q. Based on these results, the patient was diagnosed as having interstitial cystitis.

Clinical course

Our final diagnosis was serious interstitial cystitis associated with Sjögren’s syndrome. Since she had been anuric secondary to urinary obstruction on admission, a catheter was inserted into her bladder. Intermittent self-catheterization was started on January 31. Urinary volume (UV) value calculated by [(UV by herself/(UV by catheterization plus UV by herself daily)) × 100] was 4% at first. Suspecting that autoimmune mechanisms might be involved, treatment was started with prednisolone (40 mg/day) with concomitant methylprednisone pulse therapy (500 mg/day for 3 days) on March 4. Spontaneous urination began, though only in small amounts, around March 14, and continued to improve. On June 5, bladder capacity had increased from 140 ml to 250 ml. She was able to void approximately 40% of UV value, however this was a plateau. Since then, cyclosporin was given at a dose of 100 mg daily. Voiding by herself began to increase again until the 8th month of therapy, and she voided approximately 70% of UV value. Bladder capacity increased to 350 ml. The patient’s abdominal pain improved. UV value remained unchanged since then and greater improvement afterwards was not observed. Prednisolone was tapered gradually to 5 mg/day. Cyclosporin has been administered at a dose of 100 mg daily. On April 2003, ophthalmologically, her dry eyes improved, and the Schirmer test improved to 11 mm on the right and 13 mm on the left. Salivary gland scintigraphy also indicated improved secretion of saliva. Although renal function became normal, with serum creatinine of 1.0 mg/dl, she voids approximately 70% of UV value. On drip infusion pyelography, bilateral hydroureteronephrosis remains apparent, though with an increase of bladder capacity.
nephrosis remains apparent, though with an increase of bladder capacity (Fig. 2B).

**Discussion**

Interstitial cystitis is an inflammation of the bladder wall that primarily affects middle-aged women. Patients usually present with irritative symptoms, such as suprapubic pain, urinary frequency and nocturia. No infecting organism can be isolated from the urine. Histopathologic study of the bladder shows mucosal edema and mononuclear cell infiltration of the interstitium. Irritative bladder symptoms are the features of interstitial cystitis. In severe cases, bladder cavity may be markedly reduced, and an obstructive uropathy can develop (3).

Interstitial cystitis was first reported in 1915, when Hunner described it as “a rare type of bladder ulcer in women” (10). Despite its longstanding recognition, the etiology of interstitial cystitis remains uncharacterized. Fister reported a case of interstitial cystitis in a patient with SLE in 1938, linking interstitial cystitis with an autoimmune disease (11). Orth et al reported a series of 6 cases of interstitial cystitis associated with SLE in 1983 (3). They introduced the term, “lupus cystitis”, and noted that patients with lupus cystitis characteristically have concomitant disorders of the central nervous system and/or gastrointestinal tract. Histologically, immune deposits of IgG, IgA, IgM or complement C1q are found in the mucosa and perivascular regions of urinary bladder specimens. The coexistence of antibladder antibodies was also proposed in patients with idiopathic interstitial cystitis, and autoimmune mechanisms are implicated as one cause of interstitial cystitis (4, 12–15).

Sjögren’s syndrome is a common disease of unknown etiology with a prevalence of about 1% in the general population. Besides dry eyes and dry mouth, extraglandular manifestation, e.g., arthritis, interstitial pneumonitis, and interstitial nephropathy commonly are present in patients with primary Sjögren’s syndrome (16). Interstitial lesions characterized by lymphocytic infiltration may be the common factor in all these locations. However, an association between interstitial cystitis and Sjögren’s syndrome also has been reported. In 1993, Van de Merwe et al studied 10 patients with interstitial cystitis, 2 of whom were diagnosed as having Sjögren’s syndrome (7). Haarala et al showed the frequency of lower urinary tract problems in patient with Sjögren’s syndrome (8). Although the coexistence of interstitial cystitis and Sjögren’s syndrome may be relatively common, this condition may be underdiagnosed because of the paucity and subtlety of symptoms in Sjögren’s syndrome (8). In the present patient, severe visceral symptoms and a careful interview led us to the diagnosis.

While severe urgency and frequency are the hallmark of idiopathic interstitial cystitis, obstructive uropathy is uncommon. However, patients with interstitial cystitis associated with SLE frequently present with obstructive uropathy, and consequently are seriously ill (3, 17, 18). Severe cases with obstructive uropathy were not reported by Van de Merwe et al (7). This may be a rare report of Sjögren’s syndrome complicated by serious interstitial cystitis with obstructive uropathy. Interestingly, the present patient had no immune deposits in the urinary bladder. The histological findings may help to differentiate this condition from lupus cystitis. Interstitial lesions specific to Sjögren’s syndrome may occur with lymphocytic infiltration in the urinary bladder as well as pneumonitis and nephropathy.

Several oral therapies for idiopathic interstitial cystitis have been tried and essentially been discarded. Systemic steroids have also not been found to be useful (2). Recently,
Propert et al discussed the lack of any effective treatment for the majority of patients with interstitial cystitis (19). Since there have been several reports of patients with lupus cystitis who improved with immunosuppressant therapy, including corticosteroids (18, 20, 21), we administered combination therapy consisting of prednisolone and cyclosporin. Even though our patient required chronic intermittent self-catheterization, her bladder capacity increased from 140 ml to 350 ml, and oliguria continued to improve after therapy. Considering our experience and that of others, a therapeutic trial of immunosuppressants, including corticosteroids may be worthwhile in patients with severe interstitial cystitis, complicating an autoimmune disease such as SLE and/or Sjögren’s syndrome.

References