Mod Rheumatol (2004) 14:61–65
DOI 10.1007/s10165-003-0267-0

CASE REPORT

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A case of lupus cystitis with a history of idiopathic thrombocytopenic purpura

Received: December 27, 2002 / Accepted: July 3, 2003

Abstract A 36-year-old Japanese woman who had been diagnosed as having systemic lupus erythematosus (SLE) at the age of 34 began to complain of severe bowel symptoms and developed severe hydroureteronephrosis. She had a history of idiopathic thrombocytopenic purpura. Biopsy specimens from her bladder showed interstitial cystitis. She was diagnosed as having lupus cystitis, and treated with intravenous methylprednisolone pulse therapy followed by oral prednisolone and ureter catheterization. Her urinary and bowel symptoms were alleviated and the level of hydroureteronephrosis improved. We note that cystitis could be a primary manifestation of SLE. Patients not only with SLE but also with some autoimmune diseases require careful urological evaluation when they complain of severe bowel symptoms.

Key words Idiopathic thrombocytopenic purpura (ITP) · Lupus cystitis · Systemic lupus erythematosus (SLE) · Urinary tract involvement

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease entity with multiorgan involvement. Although chronic involvement of the urinary tract is usually recognized in the form of glomerulonephritis, bladder injury is uncommon. In 1983, Orth et al.[1] first described six cases of SLE accompanied by chronic interstitial cystitis as "lupus cystitis," and several similar cases were subsequently reported from various countries.[1–29] As shown in these reports, the strong association between lupus cystitis and severe bowel symptoms is particularly interesting. However, the pathogenetic mechanism and backgrounds of the patients are still unidentified.

We report the case of a patient who had lupus cystitis with severe bowel symptoms for more than a year. She had no other systemic involvement, but had a history of idiopathic thrombocytopenic purpura. We also discuss the background of this disease for a distinct subgroup of SLE.

Case report

A 36-year-old woman was admitted to our hospital in July 2001 because of general fatigue, pollakiuria, and polyarthritis. In January 1999, she developed polyarthritis and visited her home doctor. She was diagnosed as having SLE on the basis of increased serum levels of antinuclear antibodies (ANA), anti-DNA antibodies, anti-Sm antibodies, and immune complex (anti-C1q), and prednisolone (PSL) at 7.5 mg daily was started. Her symptoms of arthralgia decreased after the administration of the medication, but she began to suffer from severe epigastralgia, nausea, vomiting, and diarrhea. These symptoms recurred frequently while she was taking 7.5 mg PSL daily, and she admitted to the local hospital for a few days whenever the symptoms appeared. From March 2001, the frequency of abdominal symptoms decreased, but she began to feel pollakiuria and mild suprapubic pain. In early summer 2001, severe hypertension, proteinuria, and hypocomplementemia were observed. The patient was thus referred to our hospital, and admitted for further examination and treatment on July 18, 2001. She had a history of idiopathic thrombocytopenic purpura (ITP), and she had a splenectomy at the age of 20. She also miscarried at the same age. Her platelet count was normalized by the splenectomy and had remained stable until January 1999.

On admission, she was found to have hypertension (180/88 mmHg). Her body temperature and pulse rate were 36.4°C and 70/min, respectively. Bilateral eyelids and lower

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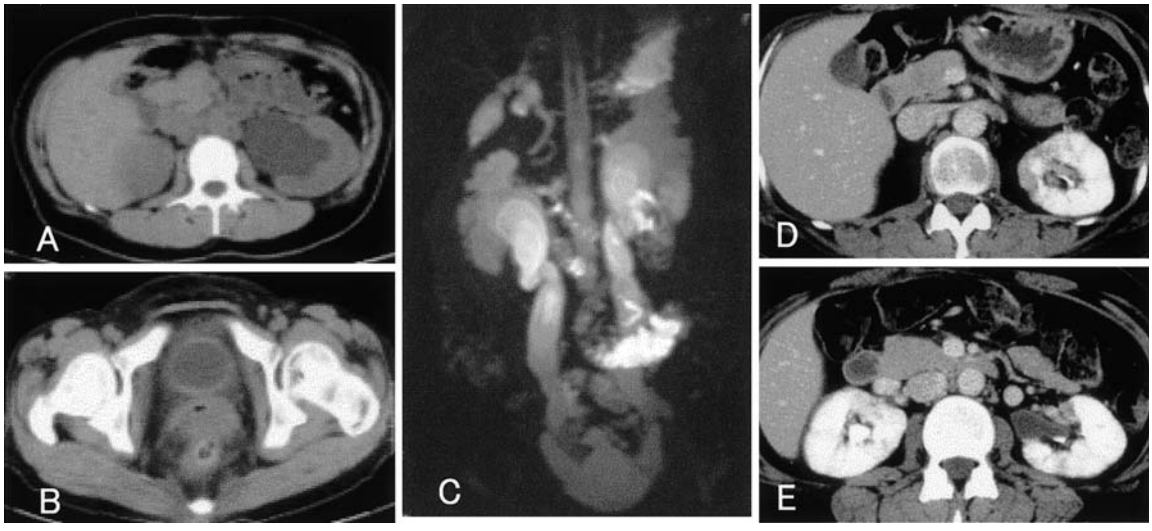

Fig. 1.A,B. Computed tomography (CT) of the abdomen on admission (July 25, 2001) showed marked bilateral hydroureteronephrosis and swelling of the bladder wall. **C** Magnetic resonance urography on admission (July 27, 2001) showed marked uniform dilatation from the renal pelvis to the entrance of the bladder. **D,E** Follow-up CT (December 4, 2001) showed an improvement in the hydroureteronephrosis

legs were slightly edematous. Her face and palpebral conjunctiva were anemic. Bilateral proximal intraphalanxial (PIP) joints, and wrist, knee, and ankle joints were swollen with mild tenderness. No characteristic signs of SLE, such as facial rash, ulcers of the oral cavity, or hair loss, were observed. The laboratory findings were as follows: urine protein unpronounced and urine occult blood negative; urine sediment and culture normal; erythrocyte sedimentation rate high (97 mm/h); white blood cell count 9000/mm^3; red blood cell count $306 \times 10^4/mm^3$; platelet count $57 \times 10^4/mm^3$; hemoglobin level 7.8 g/dl; hematocrit 36.2%. No evidence of hemolysis was found. On biochemical examination of the serum, mild hypoalbuminemia (total protein 6.7 g/dl, albumin 2.8 g/dl) was found; the level of blood urea nitrogen (BUN), creatinine, and uremic acid (UA) were slightly elevated (BUN 27 mg/dl, creatinine 1.4 mg/dl, UA 8.6 mg/dl); other findings were unremarkable. The immunological test results were as follows: level of C-reactive protein (CRP) 3.1 mg/dl; C3 67 mg/dl; C4 13 mg/dl; CH50 27; IgG 2198 mg/dl; IgA 434 mg/dl; IgM 157 mg/dl; ANA $\times$ 2560 (normal $<$ $\times$20); anti-DNA antibodies (radioimmunoassay) 13 IU/ml (normal $<$6); anti-double-stranded DNA antibodies 19 IU/ml; anti-single-stranded DNA antibodies 71 AU/ml; anti-Sm antibodies 66 C.I. (normal $<$15); anti-RNP antibodies 69 C.I. (normal $<$15); immune complex 14.7 μg/ml (anti-C1q, normal $<$2.9). Anticardiolipin β-2GPI antibodies were negative, but lupus anticoaglant was positive (dVRRT 1.5) and she had a history of miscarrige. Magnetic resonance imaging (MRI) findings of the brain showed multiple lacunar infarctions. All these findings led to her being diagnosed as having antiphospholipid syndrome. Moreover, her complaints of dry eyes and mouth, positive results for anti-SS-A/SS-B antibodies, and abnormalities in the gum test, Schirmer's test, and lip biopsy were consistent with Sjögren's syndrome (SS). Creatinine clearance had decreased (22 ml/min), but daily urine protein was 0.2 g with no cast. To determine the cause of renal dysfunction, several imaging studies were performed. Abdominal ultrasonography and computed tomography (CT) (Fig. 1A,B) showed significant bilateral hydronephroureter and swelling of the bladder wall. Ascites was not found. Magnetic resonance urography showed uniform dilatation from the renal pelvis to the entrance of the bladder (Fig. 1C). Cystoscopic examination showed atrophic mucosa and mild trabeculations, but neither ulceration nor hemorrhage was found. Biopsy specimens from the bladder wall showed edema of the submucosal layer and dilated vessels with mild inflammatory cell infiltration (Fig. 2), but fibrotic change was minor. Immunofluorescence staining was not performed. The patient was diagnosed as having lupus cystitis.

The clinical course of the patient is shown in Fig. 3. On admission, she was in a state of postrenal failure, and her renal function was deteriorating rapidly. Double-J-shaped ureter catheters were inserted in the bilateral ureter by a urologist on August 6, 2001. She was also given intravenous methylprednisolone (mPSL) pulse therapy (500 mg $\times$ 3 days) followed by 40 mg PSL daily from August 7. Unexpectedly, she rapidly developed a renal abscess by retrograde infection, and was in a state of septic shock and disseminated intravascular coagulation. Organism cultures from her urine and blood samples were positive for *Enterobacter faecalis*. Although several antibiotics were administrated and continuous hemodialysis/hemofiltration (CHDF) were performed, her condition did not improve. She eventually improved after abscess drainage. Even after the ureter catheters were removed, her bowel and urinary symptoms showed no relapse. At discharge on the 55th hospital day (October 23, 2001), she was free of any urinary or bowel symptoms. Immunological tests were normalized (Fig. 3). Follow-up CT (December 4, 2001) (Fig. 1D,E) and intravenous pyelography (February 5, 2002) in our

outpatient clinic showed an improvement in the hydroureteronephrosis.

Discussion

Several recent reports[1–29] have noted the occurrence of interstitial cystitis as a previously unrecognized manifestation of SLE. Interstitial cystitis leads to a contracted bladder and ureterovesical junction obstruction. The patient frequently develops hydroureteronephrosis and rapid renal failure due to obstructive uropathy.

The frequency of lupus cyctitis is reported to be 1%–2% of SLE patients.[27,30,31] Alarcon-Segovia et al.[32] reported that 11 of 35 necropsies from patients with SLE were found to have interstitial cystitis histologically, even though these patients had shown no obvious symptoms of cystitis while alive. This report suggests that subclinical interstitial cystitis is not rare in patients with SLE. On the other hand, it may be overlooked because patients with lupus cystitis often have concurrent systemic manifestations and respond well to low-dose medication in the earlier stage of the disease.[4,31]

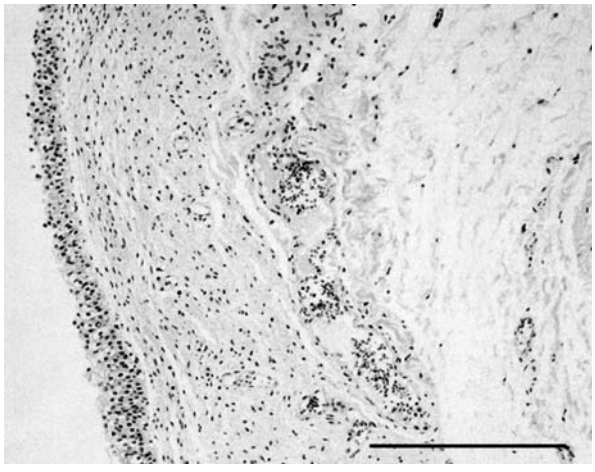

Fig. 2. Biopsy specimen of the bladder wall. Edema of the submucosal layer and mild inflammatory cell infiltration was found. H&E. *Bar* 250 μm

The pathogenesis of lupus cystitis is unknown, but it is believed to be due to immune complex deposition. In previous reports, immunohistological studies showed deposits of denatured DNA, IgG, IgM, IgA, and C3 in the bladder wall of patients with lupus cystitis.[5,20,22,33,34] Evidence of significant vasculitis was not shown, and the presense of immune complex deposition was not investigated in this case. However, elevation of the serum level of immune complex on admission, and the normalization after treatment, suggest that an autoimmune mechanism might have existed during the course of the disease when cystitis was prevalent.

It is particularly interesting that patients with lupus cystitis almost always complained of severe bowel symptoms such as vomiting, nausea, abdominal pain, diarrhea, malabsorption, paralytic ileus, and even ascites. The frequency of gastrointestinal manifestations in lupus cystitis was reported to be 78.4%–95%.[22,31] Although the reason for the association between interstitial cystitis and bowel involvement remains unclear, to date the autoimmune mechanism is the most widely proposed theory. The evidence of vasculitis within gastrointestinal walls was found in optical microscope examinations in several previous reports.[8,15] Weisman et al.[34] found the deposition of IgG and C3 in the blood-vessel walls of the small intestine, as well as in the bladder. It is thought that a common autoantigen of both the urinary bladder and the gastrointestinal tract might play an important pathological role in these patients.

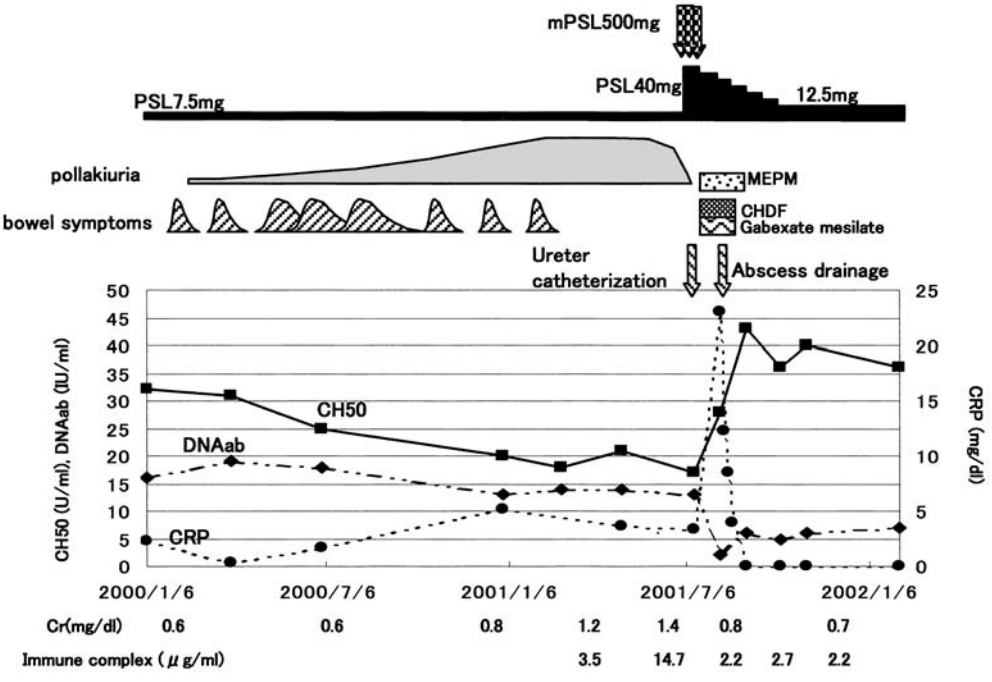

Fig. 3. Clinical course of the patient. *MEPM*, meropenem; *CHDF*, continuous hemodialysis/hemofiltration; *PSL*, prednisolone; *CRP*, c-reactive protein

In our case, the patient initially complained of severe bowel symptoms. No abnormalities were found on gastric endoscopic examination. The symptoms were explained as neuropsychiatric or psychosomatic. More than a year after the appearance of the bowel symptoms, she developed cystitis and obstructive renal failure without gastrointestinal involvement. Although the onset of lupus cystitis in this case remains unclear, it is reasonable that her cystitis should have concurred with the bowel symptoms, and that her disease activity had been progressively exacerbating when she was admitted on the basis of hypocomplementemia and elevation of her serum level of immune complex.

Systemic symptoms or signs which were characteristic of SLE were absent with the exception of arthritis, and the patient fulfilled the criteria for SLE (American College of Rheumatology, 1982) only if the history of ITP was interpreted as thrombocytopenia due to SLE. There are some reports of cases whose initial symptoms were limited to the lower urinary and gastrointestinal tract, and in which there was no other systemic involvement.[3,5,7,11,14,25,28,29] Furthermore, another case of spontaneous remission of hydroureteronephrosis with a systemic autoimmune phenomenon was reported previously.[16] Therefore, it tends to be overlooked, and explained away as a nonspecific complaint, psychosomatic disease, or pyelonephritis. Thus, the initiation of therapy can be delayed. As in our case, autoimmune hematological disorders such as hemolytic anemia or ITP preceded the onset of lupus cystitis by several years in 3 of 25 (12%) patients previously reported with lupus cystitis in Japan.[25,28,29] The frequency of lupus cystitis preceded by ITP was very similar to the frequncy of SLE preceded by ITP.[35] We subsequently had another patient with lupus enteritis who had a history of mPSL pulse therapy for Evans syndrome and SS (unpublished data). This patient also had not initially fulfilled the criteria for SLE. There are other reports of lupus cystitis or lupus enteritis in the course of Evans syndrome.[29,36] Hypocomplementemia was observed with the deteriorating condition of these patients who did not fulfill the SLE criteria. That might be diagnostic of the lupus cystitis or the enteritis.

Interestingly, our patient also had SS. Recently, Haarala et al.[37] reported that patients with SS and SLE complained of urinary symptoms more frequently than control patients. The most common symptoms in SS and SLE patients were pollakiuria and suprapubic pain. On the other hand, in the control group, the most common symptom was urinary incontinence. Haarala et al.[37] suggested that the similarities between SS and SLE support the concept of autoimmune diseases which have urinary involvement as autoimmune manifestations.

The prognosis of urinary bladder function in patients with lupus cystitis is closely related to the time-lag between the appearance of the symptoms and the initiation of steroid therapy.[4,5,31] Therefore, exact and early diagnosis is important. As mentioned above, some patients with lupus cystitis follow a very unconventional course, and do not fulfill the criteria for SLE. We should recognize the presence of this unique subgroup of SLE.

In summary, lupus cystitis is an uncommon complication of SLE. The pathogenesis is unclear, but it is reversible by early treatment. However, it may be easily overlooked because of the atypical course of SLE. Further studies are needed to identify a distinct subgroup of SLE as a new clinical entity by broadening our view to consider other autoimmune diseases.

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