Steroid Pulse Therapy in Lupus Cystitis
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A middle-aged woman with lupus cystitis showed no other symptoms of lupus vasculitis. Cystoscopic findings revealed mucosal hemorrhage and hyperemia. Histological studies of the bladder showed mucosal edema, inflammatory cellular infiltration and the deposition of immune complexes along the vessels. She was treated with a combination of intravenous methylprednisolone pulse therapy and oral prednisolone. Cystoscopy and histological findings showed appreciable improvement. Elevated urinary levels of chemokines such as interleukin-8 (IL-8) and monocyte chemotactic and activating factor (MCAF) decreased during convalescence. These results suggest that the early diagnosis and treatment with steroid pulse therapy achieves improvement of an unusual vasculitis symptom, lupus cystitis.

Key words: systemic lupus erythematosus (SLE), interleukin-8 (IL-8), monocyte chemotactic and activating factor (MCAF), chemokine, methylprednisolone pulse therapy

Introduction

Bladder injury is a rare complication in systemic lupus erythematosus (SLE) (1-4). The incidence of lupus cystitis, caused by immune complex-mediated vasculitis, is reported to be 1-2% of SLE (1). Lupus cystitis is frequently accompanied by lupus enteritis and/or central nervous system (CNS) lupus and shows poor prognosis in spite of various immune suppressive therapies. We describe here a patient with lupus cystitis who showed no other systemic involvement of vasculitis; she was efficiently treated with a combination of methylprednisolone pulse therapy and oral prednisolone therapy. This suggests that high-dose steroid therapy is effective in such lupus cystitis patients.

Case Report

In July 1989, a 45-year-old woman was admitted to Kanazawa University Hospital because of pollakisuria, dry mouth, dry eye, arthralgia and Raynaud’s phenomenon. From March 1985, she had suffered from pollakisuria which is resistant to various types of antibiotics. Physical examination revealed the swelling of bilateral parotid glands and sausage-like fingers.

Urine analysis showed proteinuria of 0.70 g/day and no microscopic hematuria. The urine sediment showed some granular casts. Urine culture and cytology were negative. Hematological laboratory test results were hematocrit 26.2%, red blood count 308,000/mm³ and hemoglobin 8.7 g/dl. Renal function was normal. Serological testing was positive for direct Coombs’ test. Erythrocyte sedimentation rate (ESR) was 157 mm/h. Antinuclear antibody (ANA) titer was ×10,240 (homogeneous, speckled pattern) and antibody to double-stranded DNA (ds-DNA Ab) was 542 U/ml. Lupus erythematosus (LE) test and anti SS-A antibody were positive, however, anti ribonucleoprotein (RNP) antibody was negative. CH50 and components of complement were decreased (CH50 25 U/ml, C3c 33 mg/dl, C4 12 mg/dl). There was remarkable hypergamma globulinemia (IgG 6,638 mg/dl, IgA 477 mg/dl, IgM 187 mg/dl). Amylase was increased to 673 U/l and salivary component was dominant.

SLE was diagnosed on the 1982 criteria of the American Rheumatoid Association. A renal biopsy showed pure mesangial alteration (World Health Organization, WHO class II). There were no findings of CNS lupus and lupus enteritis. In addition, a diagnosis of Sjögren’s syndrome (SjS) was made with conjunctivitis with positive Schirmer and rose bengal tests, and defects in salivary glands on ⁹⁹mTcO₄⁻ scan. Moreover, progressive systemic sclerosis (PSS) was diagnosed from sausage-like fingers and histological findings of arm skin biopsy. Taken

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together, the diagnosis of overlap syndrome was made. The cystoscopic examination revealed hyperemia and patches of hemorrhages in the mucosa of the bladder. A bladder biopsy showed edema of the mucosa, predominant infiltration of plasma cells and mononuclear lymphocytes in the interstitium, and deposition of acidophilic substance along the blood vessel walls with lymphocyte infiltration (Fig. 1a, b). The immunofluorescence microscopic findings revealed granular deposition of immune complex containing IgG, C3, C1q, C5 and C9 along the blood vessel walls (Fig. 1c). Accordingly, we made the diagnosis of lupus cystitis due to immune complex-mediated vasculitis.

Methylprednisolone pulse therapy (1,000 mg/day, 3 days) was performed five times accompanied by oral daily prednisolone 20 mg (Fig. 2). These treatments provided both the improvement of serological data and clinical symptoms. After the therapy, cystoscopic examination and bladder biopsy showed excellent improvement. We measured the urinary levels of chemokines, interleukin-8 (IL-8) and monocyte chemotactic and activating factor (MCAF) by ELISA, which are involved in both the recruitment and activation of neutrophils and monocytes respectively (5). Elevated urinary IL-8 level (29.7 pg/ml, detection limit in this ELISA, <16 pg/ml) and MCAF level (178.0 pg/ml, detection limit in this ELISA, <40 pg/ml) decreased during steroid pulse therapy-induced convalescence (<16 pg/ml, 84.0 pg/ml, respectively). She had received daily prednisolone 10 mg for maintenance, but again suffered from pollakisuria concomitant with elevation of the titer of ds-DNA Ab three years later. Steroid pulse therapy was performed three more times, and her symptoms were improved (Fig. 2). She has been receiving daily prednisolone 20 mg for maintenance and her symptoms have never recurred.

**Discussion**

In 1938, Fister first reported a patient of SLE accompanied with interstitial cystitis (6). The exact etiology of lupus cystitis is unknown. Bladder biopsies of lupus cystitis show granular deposits of immune complex (IgG, IgA, IgM and C3, C1q) with mononuclear and polymorphonuclear leukocytes along blood vessel walls, as was also shown in our patient (7–9). These findings suggest that immune complex-mediated vasculitis is one of the attributable causes of lupus cystitis (5, 7). Anti-bladder antibody and anti-intermediate filament antibody have been detected and these antibodies might cause lupus cystitis in some cases (8). On the other hand, both SjS and PSS have never been reported to be accompanied by immune complex-mediated vasculitis; and in the present case, these complications showed only subclinical symptoms. Lupus cystitis is often accompanied with lupus enteritis and/or CNS lupus, but the exact mechanisms remain unclear (1–4, 7, 10–14). Bowel involvement of SLE is generally thought to be due to either mesenteric arteritis or sterile serotitis and the deposition of immune complex or the infiltration of lymphocytes around blood vessel walls have been observed in some cases (1, 3, 11). The mechanism of CNS lupus is varied and difficult to confirm.
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because of rare autopsy chance, but vasculitis is considered as
one of the most important causes based on brain scan findings
on magnetic resonance imaging (15). Taken altogether, lupus
cystitis, including our case, can be regarded as a sign of a
widespread vasculitis (10, 11, 16).

The onset of lupus cystitis in the present case remains
unclear. There are some reports about cases whose cystitis
preceded other symptoms of SLE by several years as in the
present case (1, 4). In addition, our case had neither lupus
enteropathy nor CNS lupus and showed good responses to
therapy. Moreover, lupus cystitis patients with other vasculitic
symptoms show poor responses to therapy (1, 3, 4, 10). These
results suggested that a precise and early diagnosis of lupus
cystitis should be made when seeing patients with symptoms
like cystitis. As for the treatment of lupus cystitis, corticosteroids
and immunosuppressive drugs are used and improve the prog-
nosis of lupus cystitis by daily oral 40 to 120 mg of prednisolone
(1, 7, 9, 11, 13). In previous reports, patients with earlier diagnoses achieved improvement of symp-
toms of lupus cystitis by daily oral 40 to 120 mg of prednisolone
(1, 7, 9, 11, 13). In the present case, we administered intravenous methylprednisolone pulse therapy 5 times (1,000 mg daily
for three days) as well as daily prednisolone 20 mg and achieved
good response from cystitis symptoms. Four lupus cystitis
patients treated with methylprednisolone pulse therapy have
been previously reported (1, 4, 10, 11). The patient with fewer
complications of vasculitis showed a better response to meth-
ylprednisolone pulse therapy (11). In our case, multiple meth-
ylprednisolone pulse therapies were necessary to treat cystic
vasculitis, because the cystitis symptoms could not be im-
proved by the typical oral prednisolone therapy and there was
partial relapse after each methylprednisolone pulse therapy.
These results suggested that early and appropriate treatment, as
well as an exact and early diagnosis, in addition to methylpred-
nisolone pulse therapy may be important in achieving an
improvement of lupus cystitis.

Clinical improvement of lupus cystitis by high doses of
intravenous methylprednisolone was noted in patients without
other systemic involvement of vasculitis (11). However, the
precise mechanism of the effects of corticosteroid remains
unclear. In lupus nephritis, the aberrant expression of HLA-DQ
antigen in glomeruli and various cytokines, such as γ-IFN are
related to the activity of lupus nephritis (18). Moreover, the
abnormal cytokine production and intraglomerular cellular
activation could be improved by methylprednisolone pulse
therapy (5). The involvement of various cytokines in lupus

cystitis is not clear. However, we observed cellular infiltration
around the vessels and pathological resolution of infiltrated
cells concomitant with disease activities associated with the
resolution of elevated levels of urinary chemokines, IL-8 and
MCAF. These results suggested that similar mechanisms of
abnormal cytokine production and cellular activation in the
bladder might play an important role in immune-mediated
lupus cystitis and that the pulse therapy may induce clinical and
pathological resolution by suppressing the excess cytokine
production from activated T lymphocytes and monocytes and
activated cells in the bladder.
Some cases improved with treatment of a combination of steroid and immunosuppressive drugs (4, 8, 10, 17). It is impossible to determine the best therapy for lupus cystitis based on only a few reports, thus further study is necessary.

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References