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CASE REPORT

Obstructive uropathy in two Chinese patients with lupus interstitial cystitis

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Abstract

We report herein two patients who presented with bilateral hydronephrosis attributed to lupus cystitis with two totally different clinical consequences. Both had systemic lupus erythematosus complicated with nephritis and nephrotic range of proteinuria. During the investigation of their proteinuria, they were noted to have a dilated collecting system. The site of obstruction was localized at the vesicoureteric obstruction by excretory urogram. The hydronephrosis resolved spontaneously in one patient before the commencement of any medical therapy, whereas in the other patient, there was no response to steroid therapy. Augmentation enterocystoplasty was thus performed. Reversible hydronephrosis caused by vesicoureteric junction obstruction in patients with systemic lupus erythematosus has been reported. Immune-mediated vasculitis involving the ureter and bladder mucosa was the postulated pathogenic mechanism. The condition usually showed good clinical response upon immunosuppressive therapy. We conclude that systemic lupus erythematosus-associated interstitial cystitis can have a spectrum of different prognoses.

Key words: Bladder/pathology, Cystitis/complications, Immunosuppressive agents/therapeutic use, Lupus erythematosus, Systemic/pathology

中文摘要

本文報道兩例因紅斑狼瘡而致雙側腎盂積水的患者出現兩種完全不同的臨床結果。兩例均為系統性紅斑狼瘡患者，併發腎炎和腎內蛋白尿。在檢查其蛋白尿時，發現集尿系統擴張。尿道排尿攝影顯示阻塞的部位位於膀胱輸尿管狹窄處。一例患者尚未開始採取任何治療方案，其腎盂積水即自行消失，而另一例以類固醇治療後無效，遂行腸道膀胱擴張整形術。既往已報道過系統性紅斑狼瘡患者因膀胱輸尿管接合處梗阻而引起可逆性腎盂積水。其發病機制可能是免疫介導的血管炎累及輸尿管和膀胱粘膜。這種病症採用免疫抑制療法通常能收到良好的臨床效果。我們的結論是：與系統性紅斑狼瘡相關的間質性膀胱炎可有多種預後。

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease entity with multiorgan involvement. The involvement of the genitourinary tract has been traditionally represented by glomerulonephritis. Extrarenal involvement of the genitourinary tract is not common. Bladder involvement in patients with SLE may have been underestimated based on autopsy studies (1). Idiopathic interstitial cystitis (IC) is a condition characterized by chronic inflammation of the bladder wall. This affects essentially middle-aged women. The patient usually presents with typical irritative symptoms including suprapubic discomfort, dysuria, and urine frequency (2). No infective organism can be isolated from the urine.

Interstitial cystitis in patients with SLE has been reported. Most of these were young Chinese women. Obstructive

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uropathy (OU) may or may not be the feature. The condition usually showed good clinical response to immunosuppressive therapy and was reversible. We report herein two patients who presented with bilateral hydronephrosis attributed to lupus cystitis with two totally different clinical consequences.

CASE REPORT

Case 1

A 39-year-old woman who was a known case of SLE had interstitial lung disease and was under the care of respiratory physicians. She was maintained on long-term oral prednisolone at a dose of 10 mg daily. She was referred to Queen Elizabeth Hospital because of persistent fever. Subsequent investigations revealed active lupus activity with antibody to double-strand DNA (anti-DNA) of 117 IU/mL (normal range, <60 IU/mL). Her serum C3 level was 0.83 g/L (normal range, 0.69-1.35 g/L) at that time. She was also noted to have a recent decrease in serum albumin level to 21g/L together with 5 g daily of proteinuria. Her liver and renal chemistries were otherwise normal. An ultrasonogram of the urinary system showed bilateral hydronephrosis and hydroureter. At that time, she began to experience urine frequency and fever. Empirical cefuroxime therapy was started after the urine was sent for culture. The urine culture revealed sterility with no mycobacterium. A urinalysis showed a small amount of red cells (+) and proteinuria (3+). A uroflowmetric study showed an unstable bladder with diminished bladder capacity to only 174 mL. An intravenous urogram confirmed the bilateral hydronephrosis and hydroureter, with the site of obstruction being located at vesical-ureteric junctions. The bladder was small and trabeculated. A cystoscopy was thus performed, which showed trabeculated bladder mucosa with bilateral edematous ureteric orifices. A bladder biopsy revealed IC.

The dosage of prednisolone was increased in consideration of her disease activity. A renal biopsy showed diffuse proliferative glomerulonephritis with early membranous changes (World Health Organization class IV and V). The disease remained active despite steroid therapy and thus cyclophosphamide was added later. The disease then went into remission gradual with improvement of the serum albumin level (31 g/L). The anti-DNA decreased to 19 IU/mL after 6 months of cyclophosphamide therapy. The cyclophosphamide was later replaced with azathioprine together with a maintenance dose of steroid.

However, the patient's urine symptoms persisted despite anticholinergic agents (oxybutynin) and immunosuppressive therapy. The bladder volume on follow-up uroflowmetry study when the disease remained in remission still showed a contracted bladder with a volume of 200 mL. Thus, augmentation enterocystoplasty was performed 2 years after her first presentation for symptomatic relief. Her renal function remained normal after the surgery with a serum creatinine of 59 μM (0.66 mg/dL) and a serum albumin of 37 g/L.

Case 2

A 51-year-old man, with previous good health, was referred for bilateral asymmetrical polyarthralgia associated with hotness and swelling of the involved joints, mainly the small hand joints, wrists, knees, and elbow joints for 1 year. There was no history of skin rash or oral mucosal lesions. He also was noted to have frothy urine. He was referred to us when he began to experience a fever of about 38°C. Laboratory investigations showed normochromic, normocytic anemia of 10 g/dL, and thrombocytopenia of 91×10^9 /L. The erythrocyte sedimentary rate was increased to 57 mm/hour. His renal chemistry was normal with a serum creatinine of 92 μM (1.05 mg/dL) and blood urea nitrogen of 5.5 mM (15.4 mg/dL). He passed 5 g of proteinuria per day with a creatinine clearance of 110 mL/min. His serum albumin was 25 g/dL. Immunologic studies revealed a positive antinuclear antibody (titer 1: 2560, homogenous pattern) and a weakly positive direct Coomb's test but a normal serum haptoglobulin level. There was high level of anti-DNA (926 IU/mL) with depressed C3 and C4 levels (0.25 and <0.1 g/L, respectively; normal range, 0.69-1.35 and 0.12-0.36 g/L, respectively). The activated partial thromboplastin time and thrombin time were prolonged (51.9 and 16.2 seconds, respectively). Anticardiolipin immunoglobulin (Ig) G was more than 80 GPL IU/mL. A Venereal Disease Research Laboratories test was nonreactive. An ultrasound showed bilateral hydronephrosis and hydroureter. No renal stone or mass was noted. A rectal examination did not reveal any enlargement of the prostate and the serum prostate specific antigen level was not increased.

The patient complained of frequency and dysuria at this time. He was treated with empirical cefuroxime therapy after urine was sent for a microbiological culture. Later, the urine specimen was found to be sterile. An excretory urogram showed bilateral hydronephrosis and hydroureter down to the vesicoureteric junction with the right side being more affected (Fig. 1). A cystoscopy performed 5 days later, however, revealed essentially normal findings. A cystoscopic biopsy was not performed. A renal isotope scan (DTPA scan) taken on the next day showed mildly impaired renal dynamic

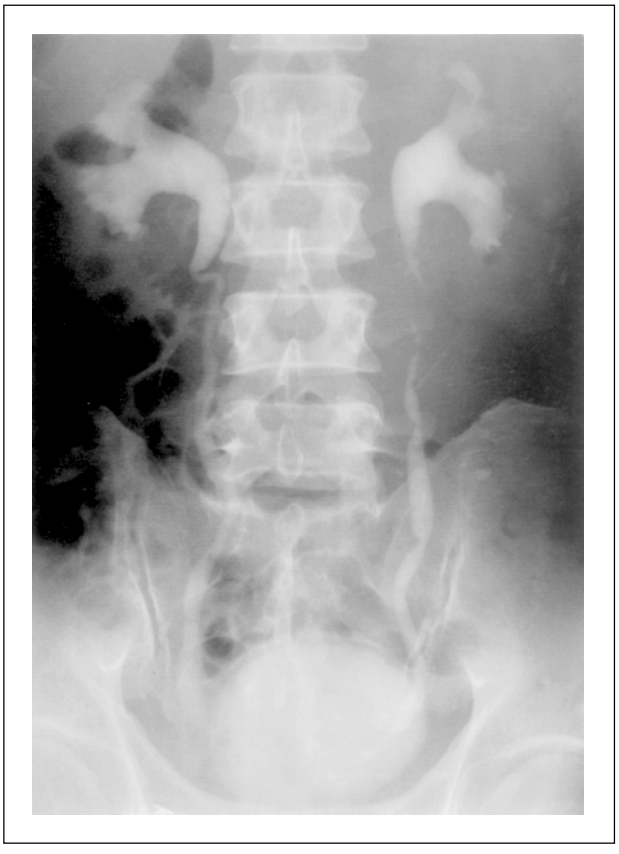

Figure 1. The excretory urogram of Case 2 shows bilateral hydronephrosis and hydroureter down to the vesicoureteric junction, with the right side being more affected. Partial holding up of contrast above both vesicoureteric junctions were demonstrated.

perfusion and glomerular function, but drainage was not obstructed. A renal biopsy was performed the next week under ultrasound guidance after the disappearance of dysuria. An ultrasound before the biopsy, however, showed complete resolution of hydronephrosis and hydroureter. This ultrasound was performed 2 weeks after the previous one. A renal biopsy later confirmed focal proliferative glomerulonephritis (World Health Organization class III). The patient was then started on steroid therapy (oral prednisolone 30 mg daily) to control the nephrosis and thrombocytopenia. His platelet count decreased to 49 x 10^9 /L before steroid therapy. Ankle edema and proteinuria gradually improved and the latest blood test showed that serum creatinine was 86 μM (0.97 mg/dL) and serum albumin was 38 g/L with daily proteinuria of 0.18 g and a creatinine clearance of 85.9 mL/min. The platelet count increased to 150 x 10^9 /L.

DISCUSSION

We report two Chinese patients with OU associated with SLE. The disease activity of Case 1 increased despite maintenance steroid therapy and her OU was attributed to IC. This failed to respond to more potent cytotoxic agents and surgical intervention was required. The obstruction in Case 2, however, went into remission even before commencement of medical therapy.

Interstitial cystitis in a patient with SLE was first reported by Shipton (3). Subsequently, many similar scattered reports followed and the condition was termed as lupus cystitis. Kataoka et al (4) was the first group to report a case of OU with bilateral hydronephrosis attributed to IC secondary to SLE. Kim et al (5) reviewed 19 cases of SLE complicated with OU. Most (84%) of these were Chinese women with a mean age of 32 years. Most of these patients had IC with bilateral hydronephrosis on radiologic imaging or ultrasonogram. No infective organisms could be isolated from the urine, as in the two cases reported here. On cystoscopy, the bladder was small with pale or hyperemic mucosa. Sometimes ulcers and stellate scars were present (6). As in Case 1, there was often a striking reduction of bladder capacity (7), and the mucosa typically bled when it was dilated during cystoscopy (8). Bladder biopsy revealed submucosal lesion with edema, hemorrhages, mononuclear cell infiltrates, and fibrosis (9). An intravenous pyelogram may show vesicoureteral reflux and bilateral hydronephrosis with an inverse relation to bladder capacity.

The presence of IC in SLE does not necessarily mean the development of OU. Development of this complication depends on the severity and chronicity of inflammatory activity during the course of IC secondary to SLE (5). However, the development of IC is usually associated with the disease activity and the presence of multisystem involvement. There is a strong association between IC and gastrointestinal manifestation of SLE (5). Gastrointestinal manifestations can range from trivial abdominal pain, vomiting, and diarrhea to life-threatening paralytic ileus and malabsorption. These are termed as lupus enteropathy. The association of IC and lupus enteropathy suggests that both complications share similar pathogenic mechanisms, although the exact relationship is yet to be defined.

The pathogenesis of IC in SLE is unknown. Various mechanisms including infection (10), small vessel or lymphatic blockage, transverse myelopathy (11), and immunosuppressive drug toxicity (12) have been suggested. The autoimmune mechanism is the most widely accepted pathogenic mechanism of IC. Deposition of denatured DNA, IgG, IgM, IgA, and C3 by immunofluorescent studies in the bladder was shown in SLE patients with IC (8). Immune complex-mediated vasculitis has been suggested (13). Unfortunately, the

results of immunofluorescence studies in the bladder biopsies of these wo cases were not available.

The natural history of bladder involvement in SLE is not known, and the role of specific therapy remains undefined. Most patients in various series responded rapidly to a high dose of corticosteroid therapy with improvement in urinary symptoms and bladder capacity (7). However, as mentioned above, because bladder manifestations usually occur in patients with active lupus, these manifestations together with other organ involvement such as lupus enteropathy can sometimes lead to mortality (14). The responsiveness of chronic IC to steroids seems to be higher in lupus-associated IC compared with idiopathic IC (9).

The clinical courses of the two cases in this report are not typical. The lupus activity of Case 1 increased despite maintenance steroid therapy. Her OU was attributed to IC as confirmed by bladder biopsy. However, this showed no response to heavy immunosuppressive therapy despite quiescent disease activity. Subsequently, surgery was needed to relieve her urine symptoms. Case 2, however, showed spontaneous resolution of his urine symptoms together with urological obstruction even before the commencement of medical therapy. We cannot find a similar case throughout our literature review. The site of his urological obstruction was located at the vesicoureteric junction, probably at the ureteric orifice, although a bladder biopsy was not performed. This suggests that the manifestation of bladder involvement in SLE is a spectrum, as enteropathy, with various severities and prognoses rather than a single entity.

In summary, bladder complications in systemic lupus are not common, but important. They range from spontaneous resolution to persistence and may require surgical intervention. Early recognition of bladder involvement is important, because it may be a partially reversible cause of renal failure in a patient with SLE. It is also possible that early identification and treatment of the inflammation phase may preserve bladder size and function, thus decreasing morbidity of patients with lupus.

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