

# Clinical Features of Lupus Cystitis Complicated with Hydroureteronephrosis in a Chinese Population

GUOJUAN ZHANG, HANG LI, WEN HUANG, XUEMEI LI, and XUEWANG LI

**ABSTRACT.** *Objective.* Lupus cystitis is a relatively rare complication of systemic lupus erythematosus (SLE). The clinical characterization of it remains obscure. We sought to provide insight for timely recognition and diagnosis of lupus cystitis, and for efficacious management of this disease entity. *Methods.* The clinical files of 18 patients with lupus cystitis treated at Peking Union Medical College Hospital were reviewed. Clinical manifestations, laboratory investigations, therapeutic measurements, and clinical outcomes were analyzed. *Results.* There were both male and female patients with a wide range of ages. The interval from onset of SLE to hydroureteronephrosis varied from 0 to 5 years. The most common clinical presentations were gastrointestinal (GI) symptoms, while urinary symptoms were less common and relatively mild. Lupus nephritis often presented concomitantly with lupus cystitis but was relatively less active pathologically. Laboratory findings showed a high rate of positive anti-SSA. Therapy of prednisone plus cyclophosphamide was effective for lupus cystitis. Delayed diagnosis and treatment may lead to irreversible obstructive uropathy and permanent loss of renal function. *Conclusion.* Lupus cystitis may not be so rare as has been thought. The diagnosis of lupus cystitis should be considered when patients with SLE present with GI symptoms, and therapy should begin as early as possible. (J Rheumatol First Release Jan 15 2011; doi:10.3899/jrheum.100617)

*Key Indexing Terms:*

SYSTEMIC LUPUS ERYTHEMATOSUS LUPUS CYSTITIS HYDROURETERONEPHROSIS

Systemic lupus erythematosus (SLE) is an autoimmune disease that may involve multiple organs. In the urinary system, aside from glomerulonephritis, the lower urinary system is also involved. The most common cause of lower urinary system involvement in patients with SLE is urinary tract infection. Other causes include cyclophosphamide-induced hemorrhagic cystitis, transverse myelopathy, inflammatory polyneuropathy, tuberculosis, and obstructive uropathy caused by nephrolithiasis. But another disease entity is not well reported, lupus cystitis. Lupus cystitis is a chronic interstitial cystitis first reported by Shipton in 1965<sup>1</sup>, and characterized by Orth, *et al* in 1983<sup>2</sup>. The typical symptoms include suprapubic pain, dysuria, urinary urgency and frequency, and nocturia. Urine culture is sterile. Widespread edema in submucosal tissue or chronic cystitis with perivascular infiltration of mononuclear cells is the pathological finding in bladder biopsies<sup>3,4</sup>. Ultrasound or computed tomographic (CT) scan may demonstrate a

markedly reduced bladder size with thickened bladder mucosa. Cystoscopy may show stellate scars and ulcers<sup>5</sup>. Hydroureter and hydronephrosis are common in lupus cystitis, probably due to edema or fibrosis of the ureterovesical junctions and spasm of the detrusor muscle. The etiology of lupus cystitis remains poorly defined, although an immune complex-mediated process was suggested by several authors<sup>3,6</sup>.

Lupus cystitis is a relatively rare complication of SLE. No more than 50 cases have been reported in the English language literature to date. Most cases were diagnosed in different medical centers and described in case reports<sup>5,7,8,9,10,11,12,13</sup>. The largest case series from a single medical center included only 6 patients<sup>14</sup>. However, autopsies of 35 SLE patients revealed 11 with pathologic evidence of interstitial cystitis<sup>15</sup>. The incidence of lupus cystitis might be underestimated, which may partly be because symptoms were relatively mild and often masked by other symptoms. Delayed diagnosis and treatment of lupus cystitis might lead to irreversible obstructive uropathy and renal function impairment. Recognizing the clinical characteristics of lupus cystitis is critical for timely diagnosis and management. Several reviews based on case reports from different clinical centers summarized some clinical features of lupus cystitis<sup>7</sup>. However, an analysis of this disease entity based on primary clinical information from a single center does not exist to date.

We analyzed 18 cases of lupus cystitis complicated with

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hydronephrosis admitted to Peking Union Medical College (PUMC) Hospital from January 1995 to April 2008. Our results may provide some insights for diagnosis and treatment of lupus cystitis.

## MATERIALS AND METHODS

The clinical files of patients with SLE admitted to PUMC Hospital from January 1995 to April 2008 were reviewed; in total there were 2947 patients with SLE. The diagnosis of SLE in this study was in accord with the American College of Rheumatology criteria for SLE modified in 1982<sup>16</sup>. We screened for patients who had hydronephrosis, then excluded cases caused by urinary tract infection, transverse myelopathy, inflammatory polyneuropathy, tuberculosis, cyclophosphamide-induced hemorrhagic cystitis, or obstructive uropathy caused by nephrolithiasis. In total there were 18 SLE patients having hydronephrosis caused by lupus cystitis. Clinical manifestations of the patients were reviewed and analyzed, including sex, age at SLE onset, age when hydronephrosis was diagnosed, the initial presentation of SLE, number of patients with urinary symptoms, gastrointestinal (GI) symptoms, central nervous system (CNS) symptoms, and number of patients with lupus nephritis. Laboratory investigations were carried out: complete blood cell count, blood urea nitrogen, serum creatinine, serum C3, antinuclear antibodies (ANA), anti-dsDNA, anti-ENA, and urinalysis. Ultrasound examinations of the urinary system were performed on all patients and intravenous pyelogram, enteroscopy, cystoscopy, or CT scan of abdomen was performed on a group of patients, and the results were analyzed. Finally, the therapeutic measurements and patients' outcomes were also analyzed.

## RESULTS

*Clinical manifestations and laboratory tests.* The frequency of lupus cystitis in our study was 0.6% (18 lupus cystitis patients out of 2947 SLE patients). The incidence of clinical features of the 18 patients is given in Table 1. There were 2 males and 16 females, a ratio of 1:8.0; median age at onset of SLE was 33.5 years (range 13–53 yrs) versus 34.5 years (range 15–53 yrs) at hydronephrosis diagnosed. The average interval from SLE onset to diagnosis of hydronephrosis was  $10.4 \pm 14.8$  months (range 0–60 mo).

The initial presentations of SLE varied among the 18 patients: GI complaints including nausea, anorexia, abdominal pain, vomiting, and diarrhea in 11 patients (61%); rash in 6 patients (33%); and fever and joint pain in 1 patient (6%). None presented with urinary symptoms initially. Nonetheless, 11 patients (61.1%) developed suprapubic pain, urinary urgency, frequency, or dysuria subsequently, which were relatively severe in 2 patients and very mild in another 9 patients. The remaining 7 patients (38.9%) had no urinary symptoms.

Of the 18 patients, 17 (94.4%) had GI symptoms, including intestinal pseudo-obstruction in 7 (38.9%) at some point during the disease course. Esophagogastroduodenoscopy was performed in 10 patients, which revealed chronic superficial gastritis in 8, reflux esophagitis in 2, and coarse gastric mucosa and destruction of submucosa in one patient. Colonoscopy was performed in 4 patients, with 2 showing normal colon and the other 2 showing mild inflammation or polyps. All of the 11 patients having urinary symptoms had GI symptoms; the urinary symptoms were much milder than

the GI symptoms in all of them but 2 patients. CNS symptoms were noted in 2 patients (11.1%), with headache in one and epilepsy in the other. Lupus nephritis was diagnosed in 14 patients (77.8%). All of them had proteinuria, ranging from 0.5 g/l to 5.0 g/l. Six patients had hematuria (42.8%). Three patients had elevated serum creatinine (21.4%); 2 accepted nephrostomy and the serum creatinine dropped to normal level (as detailed below). Among the 14 patients, 6 had renal biopsy (42.8%), with class II, class III, and class V lupus nephritis in 2 patients per class, respectively.

The reasons for hospitalization were severe GI symptoms in 14 patients (77.8%), urinary symptoms in 2 (11.1%), fever in 1 (5.6%), and edema in 1 (5.6%).

Laboratory tests revealed leukocytopenia in 2 patients, anemia in 13, and mild decreased platelets in 2. Three patients had elevated blood urea nitrogen and serum creatinine. All the patients had decreased serum C3 except one (94.4%). Nine patients (50%) had increased erythrocyte sedimentation rate. ANA was positive in 17 patients (94.4%), anti-dsDNA positive in 10 patients (55.6%), anti-SSA positive in 11 patients (61.1%), anti-SSB positive in 5 patients (27.8%), antiribonucleoprotein antibodies (RNP) positive in 7 patients (38.9%), rRNP positive in 3 patients (16.7%), and anti-Sm antibodies were positive in 7 patients (38.9%).

Hydronephrosis was unilateral in 2 patients and bilateral in the remaining 16 by ultrasound examination. Irregular thickening of urinary bladder wall was described in 12 patients. Of them, 6 had CT scans of the abdomen and pelvis and/or intravenous pyelogram, which confirmed the existence of hydronephrosis and hydronephrosis. Cystoscopy was performed in 4 patients: one showed diffuse hyperemia and edema of bladder wall; the second showed vesicoureteral junction obstruction and false diverticulum formation; the third showed a deformed bladder with reduced capacity and vesicoureteral reflux; and the last one showed diffuse edema of bladder wall and multiple trabeculation.

*Treatment and disease outcome.* All patients were treated with prednisone (0.8–1 mg/kg body weight per day) plus cyclophosphamide (200 mg every other day or 0.6–1.0 g every 3–4 weeks intravenously). Intravenous methylprednisolone pulse therapy (500–1000 mg/day for 3 days) was used in 6 patients (33.3%). Two patients were treated with Tripterygium glycosides (60 mg/day) and one with methotrexate (10 mg/week) additionally. With the above treatments, most patients achieved certain improvement of symptoms within 2–6 weeks. GI symptoms remitted in 15 patients (83.3%). Hydronephrosis remitted in 11 patients (61.1%) and remained unimproved in 7 patients (38.9%). Two of them (who had impaired renal function) had nephrostomy. Hydronephrosis resolved in both of them after procedures and their serum creatinine decreased from 244.0 and 203.3  $\mu\text{mol/l}$  to 96.4 and 97.2  $\mu\text{mol/l}$ , respectively. The third patient who had impaired renal function did not undergo nephrostomy due to severe

Table 1. Clinical characteristics of the 18 patients with lupus cystitis.

Pt	Sex	Age at SLE Onset, yrs	Interval*	Initial Presentation	Urinary Symptom	GI Symptom	CNS Symptom	LN	ANA	Anti-dsDNA	SSA	SSB	rRNP	Additional Treatment**	Urinary Outcome
1	F	17	60	Rash	Yes	Yes	No	Yes	-	-	-	-	-	-	Remission
2	F	31	0.75	Rash	Yes	Yes	Yes	Yes	+	+	+	+	+	-	Remission
3	F	42	4	Vomiting, abdominal pain, diarrhea	Yes	Yes	No	No	+	-	+	+	-	-	Remission
4	F	23	3	Fever and joint pain	No	Yes	Yes	No	+	+	+	-	-	-	Remission
5	F	35	12	Abdominal pain, diarrhea, nausea, vomiting	Yes	Yes	No	Yes	+	-	+	-	-	Pulse	No change
6	M	24	18	Nausea and vomiting	Yes	Yes	No	Yes	+	+	+	-	-	prednisolone Tripterygium glycosides	Remission
7	F	19	2	Nausea and vomiting	No	Yes	No	Yes	+	+	+	+	-	Pulse	Remission
8	F	13	24	Rash	Yes	Yes	No	Yes	+	+	-	-	-	prednisolone Pulse	Remission
9	M	38	1	Rash	No	No	No	Yes	+	+	-	-	-	prednisolone+ nephrostomy Pulse	No change
10	F	42	3	Rash	No	Yes	No	Yes	+	+	-	-	-	prednisolone	Remission
11	F	32	0	Abdominal pain, diarrhea, vomiting	Yes	Yes	No	Yes	+	-	+	+	-	Pulse prednisolone+ Methotrexate	Remission
12	F	38	16	Abdominal pain	No	Yes	No	No	+	-	-	-	-	-	Remission
13	F	22	12	Abdominal pain, diarrhea	Yes	Yes	No	Yes	+	-	+	-	+	Nephrostomy	Remission
14	F	44	5	Anorexia, vomiting, diarrhea	Yes	Yes	No	Yes	+	-	-	-	+	-	Remission
15	F	52	24	Rash	Yes	Yes	No	Yes	+	+	-	-	-	Tripterygium glycosides	Remission
16	F	53	1.75	Abdominal pain	No	Yes	No	Yes	+	-	+	+	-	-	No change
17	F	41	1	Abdominal pain, diarrhea, vomiting	Yes	Yes	No	No	+	+	+	-	-	Pulse	No change
18	F	16	0	Abdominal pain	No	Yes	No	Yes	+	+	+	-	-	prednisolone	Hemodialysis

\* Interval (months) between SLE onset and hydronephrosis. \*\* Treatment in addition to prednisone plus cyclophosphamide. SLE: systemic lupus erythematosus; GI: gastrointestinal; CNS: central nervous system; LN: lupus nephritis; ANA: antinuclear antibody.

pulmonary and GI tract hemorrhage. The remaining 4 patients with unimproved hydronephrosis but normal serum creatinine were discharged and were lost to followup.

## DISCUSSION

Of the 18 patients in our study, 12 had both hydronephrosis and irregular thickening of urinary bladder wall by ultrasound examination and/or CT scan. Another 6 patients showed only hydronephrosis, either with no obvious abnormality of bladder or without description of the bladder conditions. We found that the latter group had hydronephrosis in a relatively shorter period of time after SLE was diagnosed, ranging from 0 to 3 months (average  $1.75 \pm 1.20$  mo) compared to the patients with bladder abnormality ( $10.64 \pm 9.05$  mo). We speculated that this group of patients may have been at the early stage of lupus cystitis and the ultrasound examination was not sensitive enough to detect the abnormality. As we found no other causes to explain the existence of hydronephrosis, we included this group of patients as lupus cystitis in our analysis.

In our study, the youngest patient was 15 years old and the oldest 53 years old when hydronephrosis was diagnosed. In previous reports ages of patients with lupus cystitis ranged from 8 to 75 years<sup>13</sup>. This indicates that lupus cystitis can present over a wide range of ages. The interval from onset of SLE to hydronephrosis varied from 0 to 60 months in our patients, although the longest interval reported was 14 years<sup>17</sup>. Hydronephrosis may be caused by spasm of the detrusor muscle that induces vesicoureteral reflux, edema, or chronic fibrosis of vesicoureteral junctions or edema of ureter wall. Muscle spasm or edema may occur shortly after cystitis occurs and fibrosis of vesicoureteral junctions takes a longer period, which may explain why some patients presented hydronephrosis early in their disease course, while in others, hydronephrosis developed after several months or even years. Thus lower urinary tract involvement should be monitored in SLE patients throughout the disease course. In regard to gender, male to female ratio was 1:8, which is similar to that of general SLE patients, suggesting that male and female SLE patients may have similar risk to develop lupus cystitis.

The incidence of lupus cystitis in our study was 0.6%, but this may be lower than the real incidence. The patients we included all had hydroureteronephrosis rather than just bladder wall thickening, indicating that they were at the relatively severe end of the range of lupus cystitis. So the total incidence of lupus cystitis with or without hydroureteronephrosis must be higher than just 0.6%.

Urinary symptoms are not good indicators of lupus cystitis, because they are neither sensitive nor specific. Only 11 of 18 patients in our study had urinary symptoms, most of which were mild and not the chief complaint. No patient complained of urinary symptoms at their first visit to a doctor. Only 2 of them were hospitalized because of urinary symptoms, while most were hospitalized because of GI symptoms. Hydroureteronephrosis was often an unexpected finding of the ultrasound examination. Cases of lupus cystitis without bladder irritation symptoms were also reported by other authors<sup>18</sup>. Many patients with lupus cystitis are asymptomatic or the symptoms were unimpressive and easily overlooked. The prevalence of lupus cystitis might be underestimated. In contrast, GI symptoms were very common in patients with lupus cystitis and were often the initial presentations. Only one patient had no GI symptoms in our study. It had been hypothesized that smooth muscle in both the vesical wall and the intestinal wall were involved during the disease process. This might explain why lupus cystitis and GI tract involvement often coexist in patients with lupus<sup>18</sup>. Therefore, when a patient with SLE presents with GI symptoms, lupus cystitis should be considered.

Lupus nephritis is the most common complication of SLE and the leading cause of death. In our study, 14 patients had lupus nephritis. Pathological examination in 6 of them showed class II, class III, and class V changes in 2 patients each, respectively. None had the most active class IV. It is interesting that patients with lower urinary tract involvement have relatively mild glomerulus involvement. Another important cause of death in SLE patients is lupus encephalitis. It has been suggested that CNS involvement may present concomitantly with lupus cystitis. Of the 18 patients in our study, 2 had CNS symptoms. It may be not very common for patients with lupus cystitis to have lupus encephalitis at the same time.

A high rate of positive anti-SSA was another feature of lupus cystitis in our study. Of the 18 patients, 11 (61.1%) had positive anti-SSA. But it has been reported that the rate of positive anti-SSA in the general Chinese lupus population was around 60%<sup>19</sup>. We suspect the high positive rate of anti-SSA here was more likely due to an ethnic difference rather than a special characteristic of lupus cystitis.

Lupus cystitis usually responds well to combined prednisone and cyclophosphamide therapy. Most patients had ameliorated urinary symptoms, and hydroureteronephrosis disappeared or was alleviated with such therapy. This was the case in the current study and previous reports<sup>5,8,11</sup>. But

it should be noted that the patients in our study were all at the severe stage of lupus cystitis, and all had hydroureteronephrosis rather than just bladder involvement. So the therapy was relatively aggressive in our study. Those patients with milder lupus cystitis might not require such aggressive treatments. However, there were also patients that were refractory to corticosteroids and the immunosuppressants including cyclosporine, cyclophosphamide, azathioprine, and salazosulfapyridine. In this case, tacrolimus may provide an additional choice of therapy<sup>10</sup>. Unfortunately, some patients had to undergo nephrostomy or hemodialysis because of severely impaired renal function caused by hydroureteronephrosis. Early recognition and treatment of lupus is essential to prevent irreversible loss of renal function.

Due to the retrospective design of our study, there were a number of limitations. Cystoscopy and biopsy were performed in only 4 patients; thus the diagnosis of lupus cystitis in other patients may not have been as comprehensive. This reflected that lupus cystitis was often overlooked clinically. Only those with severe urinary symptoms were given sufficient examination and effective diagnosis.

In conclusion, lupus cystitis may not be as rare as we thought, especially in a Chinese patient population. It can affect both females and males in a wide range of ages. The urinary symptoms were often mild and easily overlooked. In contrast, GI symptoms were often significant. We should always keep in mind the possibility of lupus cystitis when patients with SLE present with GI symptoms, since delay of diagnosis can cause obstructive uropathy and impaired renal function. Timely diagnosis and effective treatment are essential to preserve kidney function and improve quality of life of these patients.

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