Bladder involvement in systemic lupus erythematosus

Envolvimento vesical no lúpus eritematoso sistêmico

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ABSTRACT

Objective: To study bladder involvement in systemic lupus erythematosus patients through clinical and laboratorial evaluation, ultrasonography, radiological and endoscopic examination. **Methods:** Thirty-nine patients, either outpatients or inpatients at the Department of Rheumatology of Hospital das Clínicas da Faculdade de Medicina from Universidade de São Paulo were evaluated as to clinical and laboratorial data. All patients were submitted to ultrasonographic evaluation of the upper urinary tract, radiological and endoscopic examinations of the middle and lower urinary tracts. **Results:** Mean age of patients varied between 13 and 62 years (median = 29 years). Thirty-six were females and three were males. The disease varied from 6 months to 22 years (median three years and one month). Clinical and laboratory activity of the disease was present in 30 patients. Twenty-two patients had the diagnosis of lupus established for three years or more. Twenty-five patients were asymptomatic and all had received corticosteroids for treatment at least once. Twenty-three received antimalarial drugs; ten received cytostatics, and seven patients received non-steroid anti-inflammatory drugs. Upper urinary tract ultrasonography was normal in all cases but one with staghorn calculus associated with neurogenic bladder secondary to neurological involvement by the disease. Vesicoureteral reflux was observed in two cases. Other two patients had significant post-voiding residual urine, both with neurogenic bladder secondary to nervous system involvement by lupus. The average bladder maximum capacity in an awaken patient was 342 mL, and was decreased in 18.9% of cases. This subgroup of patients presented a greater frequency of urinary symptoms and greater use of cytostatic drugs ($Z > Z_{5\%}$). A pathognomonic cystoscopic pattern of bladder involvement in systemic lupus erythematosus could not be established. Cystoscopic aspects similar to those seen in the initial or minor forms of interstitial cystitis were present in 43.2% of patients. This finding was more frequent when cytostatic drugs were used for treating the disease. **Conclusions:** There was bladder involvement in systemic lupus erythematosus, even in asymptomatic patients, demonstrated by the occurrence of cystoscopic abnormalities or by reduced bladder maximum capacity associated with the presence of suprapubic pain, urinary irritation symptoms and the use of cytostatic drugs.

Keywords: Lupus erythematosus, systemic; Urinary bladder; Urinary tract; Ultrasonography; Cystitis, interstitial

RESUMO

Objetivo: Estudar o envolvimento vesical em pacientes com lúpus eritematoso sistêmico (LES) por meio de avaliações clínica, laboratorial, ultrassonográfica e de estudos radiológico e endoscópico. **Métodos:** Trinta e nove pacientes ambulatoriais ou internados no Serviço de Reumatologia do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo foram avaliados clínica e laboratorialmente. Todos foram submetidos à avaliação do trato urinário superior por meio da ultrassonografia, e a exames radiológicos e endoscópicos para a avaliação dos tratos médio e inferior. **Resultados:** A idade dos pacientes variou de 13 a 62 anos (mediana = 29 anos). Trinta e seis pacientes eram do sexo feminino e três do sexo masculino. O tempo de doença variou de seis meses a 22 anos (mediana = três anos e um mês). Trinta pacientes apresentavam atividade da doença na ocasião do estudo. O diagnóstico de lúpus havia sido estabelecido havia três anos ou mais em 22 pacientes. Vinte e cinco pacientes eram assintomáticos em relação às queixas urinárias e todos haviam feito uso de corticoides em alguma fase do tratamento. Vinte e três receberam antimaláricos; dez, citostáticos e sete anti-inflamatórios não-hormonais. A ultrassonografia do trato urinário superior foi normal em todos os casos, exceto um que apresentou cálculo coraliforme associado à bexiga neurogênica devido a envolvimento

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neurológico pelo lúpus. Refluxo vésico-ureteral foi demonstrado em dois pacientes e, em outros dois casos, observava-se grande resíduo pós-miccional secundário à lesão neurológica pela doença de base. A média da capacidade vesical máxima com paciente desperto foi de 342 ml e, em 18,9% dos casos este parâmetro estava diminuído. Este subgrupo apresentou maior incidência de manifestações urinárias e maior frequência de emprego de citostáticos ($Z > Z_{5\%}$). Não se caracterizou padrão diacrítico de participação vesical na doença. Em 43,2% dos pacientes, detectaram-se aspectos cistoscópicos semelhantes aos descritos para a forma precoce ou menor de cistite intersticial, guardando dependência apenas com o emprego de citostáticos no tratamento do lúpus eritematoso sistêmico. **Conclusões:** Demonstrou-se o envolvimento vesical no lúpus eritematoso sistêmico, mesmo em pacientes assintomáticos e que se manifestou pela ocorrência de alterações cistoscópicas e pela diminuição da capacidade vesical máxima em paciente desperto, estando esta associada à presença de dor suprapúbica à repleção vesical e manifestações irritativas urinárias, bem como ao uso de citostáticos.

Descritores: Lupus eritematoso sistêmico; Bexiga urinária; Trato urinário; Ultrassonografia; Cistite intersticial

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease of the connective tissue of unknown etiology. It is characterized by numerous immunological abnormalities and involvement of multiple organs[1-4]. The study of prevalence and incidence of SLE in the world is very complex. SLE has been considered as a rare disease; however, nowadays it seems to be relatively common in certain population groups. It is estimated that, in the United States, the prevalence of SLE is 500 cases per million inhabitants, and the annual incidence varies between 50 to 70 new cases per million inhabitants[5]. However, marked differences are found in the rates of different countries[6]. Some countries show higher prevalence than others and, in the same country, between populations of certain ethnic groups as compared to others[7]. As such, Afro-Americans, Afro-Caribbeans, Native Americans, Asian Indians, Polynesians and Chinese show higher rates of SLE than Caucasians[8]. Genetic factors are possibly responsible for the high risk of the disease in these groups; however, we cannot rule out that environmental, psychosocial, clinical, socioeconomic and demographic factors also play some decisive roles in the ethnic differences found[8-9]. Although SLE affects all age groups and both sexes, important variations are found according to sex and age[3,6-7]. SLE is 10-fold more frequent in females than in males[1]. Alamanos et al., in Greece, reported that the peak incidence is between 30 and 49 years old in both sexes[10]. In the UK, according to a study by Somers et al., the peak incidence in women was between 50 and 54 years old and, in men, between 70 and 74 years old[11].

Clinical manifestations of SLE may vary from transient symptoms to extremely severe events compromising patients' lives[12]. The most common clinical manifestations consist of, isolated or combined, fatigue, fever, anemia, leukopenia, skin eruptions, photosensitivity, alopecia, arthralgia, arthritis, pericarditis, pleuritis, peritonitis, vasculitis, nephritis, nervous system involvement and gastrointestinal disorders[3].

Although it seems evident that any organ can be affected in SLE, in general urinary bladder is considered unusual[1,3] with a reported incidence of 1 to 2% of SLE cases[1]. Alarcon-Segovia et al., in 1984, published the first histological study, performed in corpses, about the participation of the urinary bladder in SLE[13]. Histological abnormalities were observed in 16 of 35 necropsy specimen of patients with SLE, including 11 patients presenting interstitial cystitis[13].

It can be speculated that the rarity attributed to the bladder involvement was due to the fact that SLE is a multi-systemic disease in which more relevant and serious clinical manifestations are present, and the urinary symptoms would not be much valued. Additionally, bladder participation in SLE would not always be accompanied by clinical, radiological or endoscopic manifestations[3].

Therefore, the potential bladder involvement in patients with SLE, with or without urinary abnormalities, warrants a research with this purpose.

OBJECTIVES

To study involvement of the bladder in patients with SLE by means of clinical evaluation, ultrasonographic evaluation of the upper urinary tract and radiological and endoscopic study of the middle and lower urinary tract.

METHODS

Type of study: cohort, prospective.

Study site: Department of Rheumatology at Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HC-FMUSP).

Sample

Thirty-nine patients (outpatients or inpatients at the Department of Rheumatology of HC-FMUSP) diagnosed with SLE, according to criteria established

by the Arthritis Rheumatism Association, composed the sample[14]. Thirty-six of them were females and three were males.

All patients were informed about and agreed to be submitted to the department research protocol.

Procedures

A total of 39 patients underwent clinical, laboratory, ultrasonographic, radiological and endoscopic evaluation.

Clinical evaluation was performed by means of standard history including the patient's identification, sex, age, color and duration of disease. The urinary manifestations considered were the following: suprapubic pain upon bladder filling, macroscopic hematuria, irritative symptoms (when two or more abnormalities were present, including dysuria, pollakiuria, nycturia, and urinary urgency), urinary incontinence and a previous diagnosis of nephropathy.

Laboratory evaluation was performed with the following exams: complete blood count, albumin, alpha-2 globulin, gammaglobulin, erythrocyte sedimentation rate, mucoproteins, C reactive protein, LE cells (%), total complement, immunocomplexes, urinalysis, 24-hour proteinuria, urine culture and alcohol-and acid-fast bacilli (AAFB) culture.

We also took into account the clinical phase of the disease (activity or remission) evaluated according to the Disease Activity Index[15] and the drugs taken in any phase of the treatment (corticosteroids, antimalarial drugs, non-steroid anti-inflammatory drugs or cytostatic drugs).

Ultrasonographic evaluation of the upper urinary tract aimed at identifying potential bladder abnormalities caused by SLE. Radiological study by means of voiding urethrocystography was performed to evaluate vesicoureteral reflux, presence of diverticulum, failures of filling, measurement of post-voiding residue and determination of maximum bladder capacity in an awaken patient (MBCaw). The latter was considered decreased when the volume was ≤ 250 mL.

Endoscopic evaluation of the middle and lower urinary tracts was performed under anesthesia aiming at establishing the maximum bladder capacity in an anesthetized patient (MBCan), detection of final macroscopic hematuria and identification of petechial hemorrhages. Patients under anesthesia had their urethra and bladder inspected with instillation of irrigation fluid at a pressure of 70 cm H_2O. After reaching the maximum bladder capacity, the fluid was drained and the presence of final macroscopic hematuria was checked. A new bladder distension was performed under view and the fillings were compared to the initial bladder filling, as per standardization established by the Messing and Stamey technique[16]. If the mucosa was normal at the end of the first filling, but simultaneous macroscopic bleeding was present at the end of the infiltrated fluid drainage and emergence of hemorrhagic spots would appear, the clinical picture was denominated interstitial cystitis.

Statistical analysis

All statistical tests were performed with a significance level of 5% ($\alpha = 0.05$). Comparisons between two proportions were performed according to the classical procedure with continuity correction. For the statistical analysis of correlations between the events, such as decreased MBCaw, cystoscopy with interstitial pattern and unspecific chronic cystitis, the hypothesis of independence between the parameters was adopted and the Fisher's exact test was employed.

RESULTS

Table 1 shows the patients clinical features.

Table 1. General characteristics of patients

Characteristics	Values	
	n	%
Gender		
Male	3	7.7
Female	36	92.3
Age (years)		
Minimum	13	
Maximum	62	
Median	29	
Color		
White	24	61.5
Nonwhite	15	38.5
Length of disease		
Minimum (months)	6	
Maximum (years)	22	
Median	3a 1m	
$<$ 3 years	17	43.6
$\geq$ 3 years	22	56.4

With regard to the urinary symptoms, 29 patients (74.4%) had a previous diagnosis of nephropathy concurrently or not to urinary symptoms; 11 patients (28.2%) reported suprapubic pain upon bladder filling; 4 (10.3%) showed irritative urinary symptoms, of which 3 presented suprapubic pain simultaneously; 25 patients (64.1%) were asymptomatic at the time of the study. Two patients presented bladder dysfunction of neurological origin caused by SLE and, as a result, showed urinary retention, paradoxical incontinence and, at the same time, motor and sensory abnormalities.

Hematological evaluation was compatible with the diagnosis of SLE in all the patients. Laboratory urinary evaluation showed leukocyturia >10 leukocytes per field in 16 cases (41%); presence of erythrocytes >5/field in 12 cases (30.8%); presence of numerous epithelial cells in 17 cases (43.6%); 24-hour proteinuria higher than 0.05g/l in 36 cases (92.3%). Routine urine culture was negative in all cases, as well as the exam and culture of AAFB.

According to the Disease Activity Index[15], 30 patients (76.9%) were in activity and nine patients were in remission (23.1%). As to the prescribed drugs, all patients had received corticosteroids; 23 (59%) used antimalarial drugs; 10 (25.6%) had been treated with cytostatic drugs and 8 (20.5%) used non-steroid anti-inflammatory drugs.

Ultrasonographic evaluation of the upper urinary tract was normal in 34 patients (87.2%); four (10.2%) showed abnormalities of the renal echotexture pattern characterized by parenchymal hyperechogenicity and one (2.6%) showed staghorn lithiasis in the right kidney with hydronephrosis and partial secondary atrophy of renal parenchyma.

According to the radiological evaluation of middle and lower urinary tract, there was not cases of diverticula or failure of bladder filling. Post-voiding bladder residue was null or minimum in 37 patients (94.9%); two cases showed a large volume of residue (5.2%) with bladder dysfunction of neurological origin. Two other patients (5.2%) showed grade I right vesicoureteral reflux.

MBCaw was measured in 37 patients. In two patients, this data was not evaluated due to the presence of sensory abnormalities and urethral urinary loss. A variation of 100 to 500 mL was found with a mean MBCaw of 342 mL. Seven cases (18.9%) evidenced decreased MBCaw. Those patients were evaluated with analysis of clinical data (suprapubic pain, irritation symptoms), duration of disease, clinical period and use of drug treatments. It was statistically evidenced that the ratio of individuals with decreased MBCaw is higher in the setting of suprapubic pain and irritative symptoms ($Z = 2.222 > Z_{5\%} = 1.645$ and $Z = 2.356 > Z_{5\%} = 1.645$, respectively). There was also statistical evidence that the ratio of individuals with decreased MBCaw is higher when the patients are in clinical remission ($Z = 1.759 > Z_{5\%} = 1.645$). There were no statistical evidences concerning the association of decreased MBCaw and duration of disease. As to drug treatment, statistical evidences showed that the rate of patients with decreased MBCaw is higher in individuals treated with cytostatic drugs ($Z = 1.758 > Z_{5\%} = 1.645$) and there was no evidence with regard to the use of antimalarial and non-steroid anti-inflammatory drugs (Tables 2, 3 and 4).

Table 2. Proportion of reduced MBCaw as to presence of suprapubic pain and urinary irritation symptoms

Characteristics	Suprapubic pain		Urinary irritative symptons	
	Present	Absent	Presents	Absents
Reduced MBCaw	5/11 (45.4%)	2/26 (7.7%)	3/ 4 (75.0%)	4/33 (12.1%)
	$Z = 2.222 > Z_{5\%} = 1.645$		$Z = 2.356 > Z_{5\%} = 1.640$	

Table 3. Proportion of reduced MBCaw as to duration and clinical period of disease

Characteristics	Length of disease		Clinical phase of disease	
	≥ 3 years	< 3 years	Activity	Remission
Reduced MBCaw	3/21 (14.3%)	4/16 (25.0%)	3/ 28 (10.7%)	4/9 (44.4%)
	$Z = 0.400 < Z_{5\%} = 1.645$		$Z = 1.759 > Z_{5\%} = 1.640$	

Endoscopic evaluation of the middle and lower urinary tract showed a normal urethra in 37 patients (94.9%). One patient (2.6%) with neurological lesion secondary to SLE showed hypotonic urethra with increased diameter. Urethral caruncle was found in one case (2.6%).

Table 4. Proportion of reduced MBCaw as to use of therapeutic drugs

Characteristics	Antimalarial		Non-hormonal anti-inflammatory agents		Cytostatics	
	Yes	No	Yes	No	Yes	No
Reduced MBCaw	4/22 (18.2%)	3/15 (20.0%)	0/7 (0%)	7/30 (23.3%)	4/9 (44.4%)	3/28 (10.7%)
	$Z = 0.282 < Z_{5\%} = 1.645$		$Z = 0.888 < Z_{5\%} = 1.640$		$Z = 1.758 > Z_{5\%} = 1.640$	

Bladder trabeculation was observed in 13 patients (33.3%). One patient (2.6%) presented inflammatory polyps in the vesicle neck; another patient (2.6%) had a small diverticulum in the left lateral wall.

Cystoscopy was considered with interstitial pattern in 16/37 cases (43.2%). In two cases, this criterion was not applied due to urethral urinary loss.

MBCan was established in 37 patients and varied between 200 and 1,300 ml, with a mean value of 843.2 ml.

The subpopulation showing cystoscopy with an interstitial pattern (16 cases) was analyzed with regard to the presence of suprapubic pain, urinary irritation symptoms, duration of disease, clinical period and use of drug treatments. No statistical differences were found as to the presence of suprapubic pain, irritative urinary symptoms, duration of disease, clinical period. As to the drug use, statistical difference was found only in the use of cytostatic drugs ($Z = 2.017 > Z_{5\%} = 1.645$) (Tables 5, 6 and 7).

Table 5. Proportion of cystoscopies with interstitial pattern as to presence of suprapubic pain and irritative urinary symptoms

Characteristics	Suprapubic pain		Irritative urinary symptoms	
	Present	Absent	Present	Absent
Cytostatic with interstitial pattern	5/11 (45.4%)	11/26 (42.3%)	3 /4 (75.0%)	13/33 (39.4%)
	$Z = 0.186 < Z_{5\%} = 1.645$		$Z = 0.823 < Z_{5\%} = 1.654$	

Table 6. Proportion of cystoscopies with interstitial pattern as to duration and clinical period of disease

Characteristics	Length of disease		Clinical phase of disease	
	≥ 3 years	< 3 years	Activity	Remission
Cytostatic with interstitial pattern	8/21 (38.1%)	8/16 (50.0%)	12 /28 (42.9%)	4/9 (44.4%)
	$Z = 0.389 < Z_{5\%} = 1.645$		$Z = 0.300 < Z_{5\%} = 1.654$	

DISCUSSION

The interest on the participation of urinary tract in the so-called collagen diseases has been a routine with regard to the involvement of renal parenchyma[3,17-18]. However, publications on the involvement of the remaining urinary tract are becoming frequently available and bladder involvement in SLE, although considered rare, has been progressively recognized[1,3,19-21]. Several studies about bladder involvement in patients with SLE have especially focused the occurrence of interstitial cystitis in the disease. Orth et al., in 1983[19], named it "lupus cystitis", characterized for being accompanied by gastrointestinal and central nervous system symptoms. The precise mechanism involving lupus cystitis remains unclear. An immunocomplex-mediated vasculitis containing IgG may play a role[22].

In this current series, no gastrointestinal symptoms were identified, such as diarrhea or malabsorption syndrome. Patients who presented central nervous system involvement secondary to SLE had bladder dysfunction of neurological origin characterized by motor and sensory loss. Although most patients were asymptomatic, several symptoms occurring in interstitial cystitis were reported, such as suprapubic pain upon bladder filling with preserved bladder sensitivity and, in a low number of cases, two or more urinary symptoms were simultaneously identified, for example, dysuria, pollakiuria and urinary urgency. Investigation of a potential urinary infection was ruled out by negative urine cultures. The presence of macroscopic hematuria was also pointed out.

The great majority of patients was diagnosed with nephropathy, which was previously established by the presence of proteinuria, sterile leukocyturia, hematuria or increased serum levels of creatinine. However, the findings of sterile leukocyturia, hematuria and, eventually, minimum proteinuria, traditionally interpreted as an indication of glomerular inflammatory abnormalities must be carefully analyzed, for they may represent bladder involvement[3].

It is interesting to observe, in this present caseload, the predominance of patients showing clinical and laboratory activity, which was due to the fact that several patients with asymptomatic SLE have refused to participate in the study whereas the symptomatic patients agreed to participate.

Bladder inflammatory processes accompanied by wall thickening and decreased bladder capacity may cause injury to the upper urinary tract. Abnormalities of bladder anatomy allows the incarceration of ureters

Table 7. Proportion of cystoscopies with interstitial pattern as to use of therapeutical drugs

Characteristics	Antimalarial		Non-hormonal anti-inflammatory agents		Cytostatics	
	Yes	No	Yes	No	Yes	No
Cytostatic with interstitial pattern	10/22 (45.4%)	5/15 (40.0%)	3/7 (42.9%)	13/30 (43.3%)	7/9 (77.8%)	9/28 (32.1%)
	$Z = 0.009 < Z_{5\%} = 1.645$		$Z = 0.399 < Z_{5\%} = 1.640$		$Z = 2.017 > Z_{5\%} = 1.640$	

at the level of vesicoureteral junction and consequent ureterohydronephrosis[1,3,19,21]. In this paper, according to ultrasonographic evaluation, we did not observe any cases of ureterohydronephrosis secondary to ureteral incarceration at the level of vesicoureteral junction. However, another type of renal involvement was identified, an indirect function of the bladder involvement, whichever, the occurrence of staghorn lithiasis in the left kidney with hydronephrosis and secondary atrophy of the renal parenchyma. Bladder involvement was caused by transverse myelitis due to SLE with consequent bladder dysfunction entailing the use of an indwelling catheter for several months and urinary infection which led to calculus formation[23]. Among the cases with nephropathy, only a minority of patients showed abnormalities of renal echotexture during ultrasonographic evaluation, such as hyperechogenicity of the renal parenchyma.

The frequency of vericoureteral reflux diagnosed by urethrocystography in adults is not well established and may vary between 5 and 23% according to the series studied with a higher frequency in women[24-25]. In this paper, according to radiological evaluation of the middle and lower urinary tract, only a small number of patients showed vericoureteral reflux, a finding that is in accordance with data reported in literature.

The study of MBCaw showed reduced capacity due to the loss of resilience and elasticity of the bladder walls in approximately 20% of cases. In this subgroup of patients, suprapubic pain upon bladder filling, dysuria, pollakiuria and urgency were significantly more frequent. It is believed that urinary irritation symptoms in patients with SLE without urinary infection in a great majority of cases translates into an impairment of bladder capacity. Duration of disease does not seem to have influenced in a statistically significant manner the occurrence of decreased MBCaw, although patients with disease of shorter duration have shown higher rates of decreased MBCaw than those with disease duration longer than three years. The disease clinical activity has also influenced MBCaw with statistically significant evidence that the rate of individuals with SLE and decreased MBCaw is higher when the disease is in clinical remission. This fact allows the speculation that bladder capacity involvement is not caused by the pathogenic mechanisms of SLE, but rather it is the manifestation of some other associated phenomenon[3]. Analysis of the use of drug treatment for MBCaw showed that only the use of cytostatic drugs was associated to MBCaw decrease in a statistically significant way[1,26-27].

Endoscopic evaluation performed under anesthesia in patients with SLE showed some fortuitous results, such as the presence of uretheral caruncle, inflammatory polyps in the bladder neck and bladder diverticulum. The presence of interstitial cystitis corresponded to the early or minor type, as described in the literature[16] and it occurred in almost half of patients but, contrary to what one would suppose, there was no statistically significant association between the presence of urinary symptoms, duration of disease, and disease clinical period. As to the analysis of drug treatments, only the use of cytostatic drugs was significantly correlated with interstitial cystitis, supporting the evidence of a harmful action of these drugs on bladder resilience[3].

CONCLUSIONS

This paper demonstrated bladder involvement in patients with SLE. Lupus may directly or indirectly affect the bladder by means of central nervous system lesion and with secondary bladder involvement.

Bladder involvement in SLE was manifested by the isolated or associated occurrence of cystoscopic abnormalities and decreased MBCaw. The latter was associated with absence of disease clinical-laboratory activity, presence of suprapubic pain upon bladder filling and irritative urinary symptoms, as well as the use of cytostatic drugs.

Interstitial cystitis pattern found in cystoscopy was associated only with the use of cytostatic drugs.

Full understanding of the factors related to bladder involvement in SLE is fundamental to establish an effective treatment for this condition.

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