Isolated Hematuria and Sterile Pyuria May Indicate Systemic Lupus Erythematosus Activity

Jonathan Y.C. Ding, Dominique Ibañez, Dafna D. Gladman, and Murray B. Urowitz

ABSTRACT. ***Objective.*** To identify patients presenting with isolated hematuria and/or pyuria in the absence of other systemic lupus erythematosus (SLE) disease activity, describe their demographics, and determine whether they present with evidence of SLE flare in a period adjacent to the presentation.

Methods. We studied patients followed at the University of Toronto Lupus Clinic between 1970 and 2012. An episode of isolated hematuria (> 5 red blood cells per high power field) and/or pyuria (> 5 white blood cells per high power field) was defined as 2 consecutive visits with these findings in the absence of other concurrent SLE manifestations such as proteinuria, casts, or azotemia. We then excluded patients whose findings might be explained by urinary tract infections, menstruation, urolithiasis, and/or anticoagulation. Only patients presenting with no other SLE disease activity were included.

Results. Isolated hematuria and/or pyuria were identified in 49 patients, of whom 17 were excluded according to the criteria above, leaving 32. Twenty-four patients had another renal manifestation 1 year before and/or after the occurrence; 27 had a non-renal manifestation 1 year before and/or after the occurrence; 3 patients had a biopsy in the same time frame, all with evidence of active lupus nephritis. Therefore the majority of patients with an occurrence of isolated hematuria and/or pyuria had evidence of renal or other non-renal SLE disease activity at a time adjacent to this presentation.

Conclusion. Although not proven, our results suggest that these manifestations were associated with SLE activity, either before or after the episode, and therefore may represent a phase of active disease.
(First Release Jan 15 2015; J Rheumatol 2015;42:437–40; doi:10.3899/jrheum.140415)

Key Indexing Terms:
HEMATURIA PYURIA SYSTEMIC LUPUS ERYTHEMATOSUS LUPUS NEPHRITIS

Up to 60% of patients with systemic lupus erythematosus (SLE) present with renal involvement over their clinical course[1,2]. Clinical presentations are highly variable. Even in very severe or advanced cases, SLE renal manifestations may be asymptomatic[3,4,5,6]. Yet renal manifestations, and lupus nephritis in particular, carry a severe prognosis, increasing the risk of endstage renal disease, cardiovascular disease, and mortality, although outcomes may improve with appropriate management[7,8,9,10,11,12].

To detect silent involvement and to offer appropriate care, screening urinalysis has become a part of routine followup in SLE[13]. Given that most patients with SLE renal involvement present with protein in their urine, proteinuria in and of itself is considered a sign of disease activity; this often occurs in conjunction with hematuria and/or sterile pyuria, signs that could thus be confidently attributed to active SLE[14,15,16,17]. However, hematuria and pyuria may also occur in the absence of other renal findings (i.e., proteinuria, cellular casts, or azotemia) and other systemic involvement. In these cases, the significance of the findings and their relevance to SLE may be questioned.

Our aim was thus 2-fold: first, to describe the demographics of patients presenting with isolated hematuria and/or pyuria in the absence of other SLE activity; and second, to determine whether the presence of such presentations of hematuria and/or sterile pyuria were associated with prior and subsequent SLE.

MATERIALS AND METHODS

This is a descriptive study of patients enrolled in a large registry and followed longitudinally since 1970 at the University of Toronto Lupus Clinic. All patients enrolled in this clinic fulfilled the 1997 American College of Rheumatology (ACR) criteria for SLE[18]. Patients were reviewed at 2-month to 6-month intervals using a standard protocol. At each visit, clinic physicians obtained a complete history, conducted a full physical examination, and requested laboratory evaluations including serology. Routine renal investigations included microscopic urinalysis for red blood cells (RBC), white blood cells (WBC), and cellular casts; proteinuria by dipstick or a 24-h urinary assessment; and serum creatinine. Urine sediments were performed and reported within 24 h of the urine collection. Urine cultures may have been performed and results recorded if

From the University of Toronto Lupus Clinic, Centre for Prognosis Studies in the Rheumatic Diseases, Toronto Western Hospital, Toronto, Ontario, Canada.

Jonathan Y.C. Ding was the recipient of the Canadian Rheumatology Association Roche Summer Studentship.

J.Y.C. Ding, BSc, Medical Student, University of Toronto; D. Ibañez, MSc, Biostatistician, Centre for Prognosis Studies in the Rheumatic Diseases; D.D. Gladman, MD, FRCPC, Professor of Medicine, Senior Scientist, University of Toronto; M.B. Urowitz, MD, FRCPC, Professor of Medicine, Senior Scientist, University of Toronto.

Address correspondence to Dr. M.B. Urowitz, University of Toronto Lupus Clinic, Centre for Prognosis Studies in the Rheumatic Diseases, Toronto Western Hospital, 399 Bathurst St. 1E-410B, Toronto, Ontario M5T 2S8, Canada. E-mail: m.urowitz@utoronto.ca

Accepted for publication November 10, 2014.

a urinary tract infection (UTI) was suspected. Individuals assessing the urine specimens did not have any knowledge of the clinical status or dipstick testing of urine.

At each visit, the SLE Disease Activity Index 2000 (SLEDAI-2K) was calculated and reported[15]. Physicians also assessed damage (Systemic Lupus International Collaborating Clinics/ACR Damage Index) on an annual basis[19]. The full procedures and kits for the standard array of tests conducted at the clinic have been described[20].

Isolated hematuria and/or pyuria were defined as the presence of hematuria and/or pyuria in 2 or more consecutive visits in the absence of proteinuria, urinary casts, and azotemia. Only patients who presented with no other evidence of SLE (i.e., a SLEDAI-2K score of 0 excluding renal manifestations) were included. Hematuria was defined as having > 5 RBC per high power field (HPF); pyuria as > 5 WBC/HPF; proteinuria as > 0.5 g/24 h or > 3+ proteinuria prior to 1985 and thereafter in a semiquantitative urine analysis as > 500 mg; casts as heme-granular or RBC casts; and azotemia as serum creatinine > 140 μmol/l. Patients' charts were reviewed, and potential alternative causes for hematuria or pyuria were noted. Other exclusion criteria were urolithiasis 1 calendar year before or after clinical presentation (as suggested by clinical history or ultrasound), menstruation within 3 days of urine collection (as noted in our standard protocol), or potential UTI (as identified through clinical symptoms or a urine culture), and anticoagulation. Having ruled out such potential confounders, the hematuria and pyuria occurrences in our final cohort were thus highly likely attributable to SLE.

To determine disease activity adjacent to this presentation, we investigated the results of renal biopsies, urinalysis (for RBC, WBC, protein, and casts), serum creatinine, and non-renal SLEDAI-2K scores up to 1 year before or after the episode.

RESULTS

Of the 1621 patients being followed in the SLE clinic from 1970 to 2012, we identified 49 patients with isolated hematuria and/or sterile pyuria in the absence of other SLE manifestations; each patient presented with only 1 occurrence in their clinical history. Of the 49, 15 were noted to have a potential non-SLE cause for the findings, including urolithiasis, UTI, and/or menstruation within 3 days of urine collection, and there were 2 patients whose consecutive findings were spaced more than 12 months apart or who had visited the clinic 3 times or fewer. These were subsequently eliminated from our analysis. The final cohort included 32 patients (28 female) with a mean age of 42.3 years (SD 17.7), and occurrences lasting a mean of 8.0 months (SD 7.2; Table 1). Based on the history in 40% of the patients (13/32), in the opinion of the treating rheumatologist, there was no other underlying cause and as a result, no further investigations were performed to rule out other causes. In 19 of the 32 patients there was either a urology consult and cystoscopy or renal ultrasound or both. Twenty-eight patients were taking medication at the time of presentation: 23 were taking corticosteroids, 18 antimalarials, and 14 immunosuppressives. These patients were similar to the rest of the cohort in sex, age at SLE diagnosis, age at first visit to the clinic, and disease duration at first clinic visit.

Twenty-four of the 32 patients (75%) with isolated hematuria and/or pyuria in the absence of other concurrent SLE activity presented with at least 1 other renal manifestation (hematuria, pyuria, proteinuria, casts, or azotemia) 1 year before or 1 year after the episode. These included 38% pyuria, 58% hematuria, 25% casts, 13% azotemia, and 58% proteinuria. Table 2 gives a complete description of adjacent renal disease.

Twenty-seven (84%) had a positive non-renal SLEDAI-2K up to 1 year before or 1 year after the occurrences. Combined, 30 patients of the 32 in the cohort had a renal manifestation and/or systemic disease activity within 1 year of the occurrences.

Three patients had a renal biopsy within 12 months of the occurrences. None had normal glomeruli according to the World Health Organization (WHO) criteria[21]. Two of the patients were noted to have WHO class IIIa, and the third had class IV.

Table 1. Demographics of patients with isolated hematuria and/or pyuria in the absence of other systemic disease activity. Data are mean ± SD (median) or n (%).

Female	28 (88)
Age at presentation, yrs	42.3 ± 17.6 (40.1)
Disease duration at first episode, yrs	9.7 ± 9.0 (7.9)
Age at SLE diagnosis, yrs	32.6 ± 17.5 (27.6)
Mean length of followup, yrs	9.0 ± 10.9 (4.4)
Interval between the 2 consecutive visits with hematuria	4.3 ± 1.7 (3.4)
Duration of hematuria and/or pyuria (mos)	8.0 ± 7.2 (5.9)
Race	
White	18 (56)
Black	5 (16)
Asian	4 (13)
Others	5 (16)
Treatment at presentation	
Prednisone	23 (72)
Antimalarial	18 (56)
Immunosuppressants	14 (44)

SLE: systemic lupus erythematosus.

Table 2. Characteristics of adjacent renal disease. Data are n (%).

Urinary characteristics of prior renal disease within 1 year*	
Total no. patients	18 (100)
Proteinuria	11 (61)
Casts	3 (17)
Azotemia	3 (17)
Hematuria	11 (61)
Pyuria	7 (39)
Urinary characteristics of subsequent disease within 1 year	
Total no. patients	15 (100)
Proteinuria	5 (33)
Casts	4 (27)
Azotemia	0 (0)
Hematuria	11 (61)
Pyuria	4 (27)

*Patients often had more than 1 renal manifestation.

DISCUSSION

Lupus nephritis is a serious manifestation of SLE, with complex clinical presentations. Proteinuria and casts are strongly suggestive of glomerular or tubular involvement, and often are associated with hematuria and pyuria[22]. Although rare in the general population, isolated hematuria and pyuria are common in patients with SLE. Previous studies suggest that up to 23% of patients with SLE present with isolated pyuria during a calendar year, and more than one-third present with isolated hematuria during their clinical course[14,16,17].

Both are important indicators of disease. Pyuria often co-presents with more severe non-renal SLE disease activity and significant histological changes, and predicts future relapses[14,22,23,24]. Similarly, isolated hematuria often precedes other renal manifestations and is found to correlate significantly with concurrent non-renal disease activity, including serology and cytology[14,23,25,26,27]. Hematuria and pyuria are thus considered descriptors of SLE disease activity.

In about 20% of patients with these urinary findings, there is little or no evidence of concurrent SLE disease. In some cases, other causes for the abnormalities are found. However, in a portion of these patients, no other cause is found. Consequently, the significance of isolated hematuria and/or pyuria in the absence of other SLE activity has been the subject of much interest.

Our study suggests that the findings are probably attributable to lupus nephritis, even in the absence of other SLE signs. We base this premise on the following evidence from our present study: 24 patients (75%) in our cohort of 32 had at least 1 other renal manifestation 1 year before and/or after an occurrence of isolated hematuria and/or pyuria with no systemic involvement; 27 patients (84%) presented with non-renal SLEDAI-2K 1 year before and/or after the occurrences; altogether, 30 patients (94%) were found to have evidence of disease in the 1-year period adjacent to the occurrences. Further, 3 patients underwent biopsies in the same time frame, all showing significant glomerular changes consistent with the histopathological patterns of lupus nephritis[21]. Therefore, hematuria and pyuria are highly associated with renal and non-renal disease activity. The isolated occurrences likely represent a phase of active SLE, even in the absence of other systemic findings.

Potential alternative causes should be considered in cases of hematuria and pyuria[27,28]. In female patients, urinalysis may be contaminated by red and white blood cells from menstruation[29,30]. Urinary tract infections are among the most common infections in women, and can cause pyuria[31]. This may be a particular concern in SLE, a disease that in many patients is immunosuppressed therapeutically. Further, urolithiasis is a common cause of hematuria, particularly among older male patients[32]. We excluded patients with radiological findings indicative of urolithiasis or with bacterial urine culture samples indicative of UTI, women known to be menstruating within 3 days of urine data collection, and any clinical mention of suggestive symptoms. Clinically, it is also important to consider potential explanations before attributing isolated findings to SLE.

Our study has limitations. Because of the relatively small sample size, we were unable to investigate demographic factors that may affect renal manifestations, such as race[33]. Further studies should investigate how demographic variables interact with hematuria or pyuria in terms of clinical outcomes. Although causes for isolated hematuria and pyuria were investigated, based on the treating rheumatologist's opinion 40% of the patients did not undergo further urological investigations. Further, renal biopsies detect silent lupus nephritis, and determine the specific histological patterns of renal disease[5,21]. Clinical indications for renal biopsies vary. Only a small proportion of patients with occurrences of isolated hematuria or pyuria had biopsies in our study, each confirming the presence of SLE activity. Although it is unlikely that a non-SLE–related pattern of renal disease developed since the most recent episode of active SLE, only more biopsies during these episodes could definitively determine this. Further studies should investigate the value of using biopsies to determine the extent of kidney disease resulting in hematuria and pyuria.

Isolated hematuria and isolated sterile pyuria are associated with adjacent renal and non-renal disease activity and therefore could be interpreted as manifestations of active SLE and treated accordingly. Lastly, clinicians should thus monitor these patients closely for other signs of SLE flare.

REFERENCES

1. Cameron JS. Lupus nephritis. J Am Soc Nephrol 1999;10:413-24.
2. Christopher-Stine L, Siedner M, Lin J, Haas M, Parekh H, Petri M, et al. Renal biopsy in lupus patients with low levels of proteinuria. J Rheumatol 2007;34:332-5.
3. Wakasugi D, Gono T, Kawaguchi Y, Hara M, Koseki Y, Katsumata Y, et al. Frequency of class III and IV nephritis in systemic lupus erythematosus without clinical renal involvement: an analysis of predictive measures. J Rheumatol 2012;39:79-85.
4. Huong DL, Papo T, Beaufils H, Wechsler B, Blétry O, Baumelou A, et al. Renal involvement in systemic lupus erythematosus. A study of 180 patients from a single center. Medicine (Baltimore) 1999;78:148-66.
5. Gonzalez-Crespo MR, Lopez-Fernandez JI, Usera G, Poveda MJ, Gomez-Reino JJ. Outcome of silent lupus nephritis. Semin Arthritis Rheum 1996;26:468-76.
6. Nossent JC, Henzen-Logmans SC, Vroom TM, Huysen V, Berden JH, Swaak AJ. Relation between serological data at the time of biopsy and renal histology in lupus nephritis. Rheumatol Int 1991;11:77-82.
7. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002;39 Suppl 1:S1-266.
8. Reich HN, Gladman DD, Urowitz MB, Bargman JM, Hladunewich MA, Lou W, et al. Persistent proteinuria and dyslipidemia increase

the risk of progressive chronic kidney disease in lupus erythematosus. Kidney Int 2011;79:914-20.
9. Austin HA III, Klippel JH, Balow JE, le Riche NG, Steinberg AD, Plotz PH, et al. Therapy of lupus nephritis. Controlled trial of prednisone and cytotoxic drugs. N Engl J Med 1986;314:614-9.
10. Mok CC, Ho CT, Siu YP, Chan KW, Kwan TH, Lau CS, et al. Treatment of diffuse proliferative lupus glomerulonephritis: a comparison of two cyclophosphamide-containing regimens. Am J Kidney Dis 2001;38:256-64.
11. Steinberg AD, Steinberg SC. Long-term preservation of renal function in patients with lupus nephritis receiving treatment that includes cyclophosphamide versus those treated with prednisone only. Arthritis Rheum 1991;34:945-50.
12. Contreras G, Pardo V, Leclercq B, Lenz O, Tozman E, O'Nan P, et al. Sequential therapies for proliferative lupus nephritis. N Engl J Med 2004;350:971-80.
13. Houssiau FA. Management of lupus nephritis: an update. J Am Soc Nephrol 2004;15:2694-704.
14. Rahman P, Gladman DD, Ibanez D, Urowitz MB. Significance of isolated hematuria and isolated pyuria in systemic lupus erythematosus. Lupus 2001;10:418-23.
15. Gladman DD, Ibanez D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. J Rheumatol 2002;29:288-91.
16. Akbarian M, Soleymani H, Gharibdoost F, Nadji A, Jamshidi AR, Shahram F, et al. Isolated hematuria in SLE patients and its association with proteinuria, urinary cast and SLE disease activity. Acta Medica Iranica 2009;47:5-8.
17. Appenzeller S, Clark A, Pineau C, Vasilevsky M, Bernatsky S. Isolated pyuria in systemic lupus erythematosus. Lupus 2010;19:793-6.
18. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1997;40:1725.
19. Gladman DD, Urowitz MB, Goldsmith CH, Fortin P, Ginzler E, Gordon C, et al. The reliability of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index in patients with systemic lupus erythematosus. Arthritis Rheum 1997;40:809-13.
20. McLaughlin JR, Bombardier C, Farewell VT, Gladman DD, Urowitz MB. Kidney biopsy in systemic lupus erythematosus. III. Survival analysis controlling for clinical and laboratory variables. Arthritis Rheum 1994;37:559-67.
21. Weening JJ, D'Agati VD, Schwartz MM, Seshan SV, Alpers CE, Appel GB, et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited. J Am Soc Nephrol 2004;15:241-50.
22. Fairley KF, Birch DF. Microscopic urinalysis in glomerulonephritis. Kidney Int 1993;44:S9-12.
23. Chan RW, Lai FM, Li EK, Tam LS, Chung KY, Chow KM, et al. Urinary mononuclear cell and disease activity of systemic lupus erythematosus. Lupus 2006;15:262-7.
24. Roberti I, Dikman S, Spiera H, Reisman L, Eichenfield AH, Liberman KV. Comparative value of urinalysis, urine cytology and urine sIL2R in the assessment of renal disease in patients with systemic lupus erythematosus (SLE). Clin Nephrol 1996;46:176-82.
25. Hebert LA, Dillon JJ, Middendorf DF, Lewis EJ, Peter JB. Relationship between appearance of urinary red blood cell/white blood cell casts and the onset of renal relapse in systemic lupus erythematosus. Am J Kidney Dis 1995;26:432-8.
26. Balow JE. Clinical presentation and monitoring of lupus nephritis. Lupus 2005;14:25-30.
27. Dieter RS. Sterile pyuria: a differential diagnosis. Compr Ther 2000;26:150-2.
28. Mazhari R, Kimmel PL. Hematuria: an algorithmic approach to finding the cause. Clev Clin J Med 2002;69:870-84.
29. Cohen RA, Brown RS. Microscopic hematuria. N Engl J Med 2003;348:2330-8.
30. Morimoto M, Yanai H, Shukuya K, Chiba H, Kobayashi K, Matsuno K. Effects of midstream collection and the menstrual cycle on urine particles and dipstick urinalysis among healthy females. Clin Chem 2003;49:188-90.
31. Hooton TM. The epidemiology of urinary tract infection and the concept of significant bacteriuria. Infection 1990;18 Suppl 2:S40-3.
32. Li J, Kennedy D, Levine M, Kumer A, Mullen J. Absent hematuria and expensive computerized tomography: case characteristics of emergency urolithiasis. J Urol 2001;165:782-4.
33. Shimizu A, Tamura A, Tago O, Abe M, Nagai Y, Ishikawa O. Lupus cystitis: a case report and review of the literature. Lupus 2009;18:655-8.