Isolated Hematuria in SLE Patients and Its Association with Proteinuria, Urinary Cast and SLE Disease Activity

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Abstract: Isolated hematuria and its association with proteinuria, and urinary cast and systemic lupus erythematosus (SLE) disease activity, and decision for renal biopsy is a dilemma for physician in SLE patients. The aim of this study was to investigate 1. whether isolated hematuria is associated with active SLE, 2. to determine duration between hematuria and proteinuria and urinary cast, and 3. to determine renal histological type in SLE patients with isolated hematuria**.** All episodes of isolated hematuria between 1981 and 1997 were identified from Lupus Unit, Rheumatology Research Center database. Isolated hematuria was defined as >5 RBC/hpf in the absence of urinary infection and other renal manifestations. Relation of hematuria was assessed with proteinuria and urinary cast and SLE disease activity. Needle renal biopsy was done in 19 SLE patents with isolated hematuria. 4.42% (31/700) of our cohort had at least one episode of isolated hematuria. Out of 31 patients in whom the isolated hematuria was the first documented renal manifestation, 11 patients (35.48%) developed another renal manifestation (25.8% proteinuria and 9.67% casts). 54.54% (6/11) of patients developed proteinuria and urinary cast within 3 months. The mean time for development of a second renal manifestation for the patients with isolated hematuria was 19.9 months. Renal needle biopsy was performed for 19 patients (5.78% type IV, 63.15% type III and 21.50% type II). The results of the present study indicate that isolated hematuria is not rare in SLE patients. Also, there was no significant relationship between isolated hematuria and anti ds-DNA, C3, C4 and major organ involvement in patients with SLE. Our study suggests that SLE patients who have isolated hematuria should undergo renal biopsy and that isolated hematuria should be considered a manifestation of active renal SLE.

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Key words: Isolated hematuria, systemic lupus erythematosus, SLE disease activity

Introduction

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease of unknown etiology, which involves different organs systems to a variable degree. Of the various manifestations of SLE, lupus nephritis and CNS involvement, are the most serious. Microscopic hematuria is a common diagnostic problem in general practice. The appearance of hematuria in the presence of proteinuria, suggests glomerular disease. In the absence of proteinuria, non-glomerular diseases are suspected and patients are often subjected to extensive urological investigations.

For a number of reasons, there are different approaches to isolated hematuria in SLE patients; first, lupus patients with isolated hematuria, frequently have histological evidence of renal pathology (1); second, lupus patients may have significant histological changes in renal biopsies in the absence of clinical features of renal disease (active urine sediment), the so-called 'silent lupus nephritis' (2). The appearance of an active urinary sediment (hematuria, sterile pyuria and casts) has been shown to be predictive of significant renal disease (proteinuria and azotemia) (3) and the presence of hematuria has been demonstrated to be an independent predictor of mortality in SLE (4). Hematuria was the

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only renal manifestation incorporated into the Lupus Activity Criteria Count (LACC), as it was among the seven clinical and laboratory measures noted to be highly associated with active SLE (5).

Hematuria has also been included as an independent descriptor in the SLE disease activity index (SLEDAI) (6). This is a validated index for the measurement of disease activity in SLE based on statistical modeling of the judgment of a panel of experienced rheumatologists with an expertise in SLE. It has been the practice of our lupus clinic to consider hematuria as a manifestation of active nephritis, regardless of the presence or absence of other renal manifestations. However, an ongoing debate has emerged among lupologists and nephrologists regarding the significance of isolated hematuria. To our knowledge, the relationship between isolated hematuria and lupus disease activity has not been formally studied. Thus, our objective was to determine if the presence of isolated hematuria was associated with active renal and non-renal disease and to determine duration between hematuria with proteinuria and urinary cast.

Patients and Methods

This is a descriptive study of a large SLE cohort followed retrospectively since 1981 at the Rheumatology Research Center, Tehran University of Medical sciences. Every SLE patients who refer to Lupus Clinic, has a computerized file since 1975. All patients enrolled in this clinic fulfill the American College of Rheumatology (ACR) criteria for SLE. Each assessment includes a complete history, physical examination, and laboratory investigations. Routine renal investigations include microscopic urinary sediment performed by hospital laboratories for red blood cells (RBCs), white blood cells (WBCs) and cellular casts, proteinuria by dipstick and/or a 24 hours urinary assessments, and serum creatinine. Isolated hematuria was defined as having >5 urinary RBCs per high power field (HPF), in the absence of sterile pyuria (>5 WBCs/HPF), any cellular casts, proteinuria (urine protein >0.5 g/24 h or >3 plus proteinuria on dipstick)**,** each of which have been demonstrated in our studies to represent more than 500 mg/24 h for hematuria to be recorded in our databank. Urine samples had to be obtained a week after the menses, so that it was unlikely that the isolated hematuria was due to menstrual blood loss. Moreover, infection had to be ruled out by a urine culture and repeat urinalysis.

All episodes of isolated hematuria were identified from our database between 1981 and 1997 and followed for 5 years. To evaluate the presence of disease activity at the time of isolated hematuria, SLEDAI score was calculated for each patient at their first clinic visit with isolated hematuria. DNA antibodies were measured by ELIZA, and complement levels by nephelometry. Urine sediments were performed and reported within 24 h of the urine collection. The individuals assessing the urine specimens did not have any knowledge of the clinical status or dipstick testing of the urine.

To assess the relationship between isolated hematuria and renal disease involvement in renal biopsy, all patients with renal biopsies were performed at the time of detecting isolated hematuria. The renal biopsies were assessed using the WHO classification.

Results

Of a total of 1700 SLE patients from 1981 and 1997 were identified in our database, 700 patients (41.16%) had hematuria. Episodes of isolated hematuria were identified in 31patients (4.42%).

Out of the 31 patients in whom the isolated hematuria was the first documented renal manifestation, 11 patients (35.48%) went on to develop another renal manifestation (3 patients (9.67%) with urinary cast and 8 patients (25.8%) with proteinuria). 54.54% (6/11) of patients developed a different renal manifestation within 3 months of the detection of hematuria. The mean time for development of a second renal manifestation for the 11 patients with isolated hematuria was 19.9 months.

Low serum complement levels were noted in 58.06% (18/31) and high level double-stranded DNA antibodies were noted in 67.74% (21/31) of patients with isolated hematuria. We assessed the frequency of non-renal disease activity (defined as non-renal SLEDAI>0) in all patients with isolated hematuria during the first three months of presentation. Of 31 patients, 6 (19.3%) had non-renal SLEDAI=0 and 25 (80.6%) had non-renal SLEDAI>0. 9.6% (3/31) of patients had non-renal manifestations as SLEDAI>12. Nineteen patients with isolated hematuria had a renal biopsy on detection of hematuria. None had normal glomeruli according to the WHO criteria. 4 of the 19 patients (21.50%) who had renal biopsies were noted to have WHO class II, 12 patients (63.15%) had WHO class III, and 3 patients (15.78%) had WHO class IV renal biopsy.

Discussion

Isolated hematuria found in a routine clinical assessment often presents a clinical dilemma for the treating physician. Urinary casts, proteinuria and renal tubular cells

strongly suggest glomerular or tubular involvement. However, even in the absence of such features, our study suggests that isolated hematuria is probably attributable to lupus nephritis. This premise is based on the following evidence derived from the previous (7) and present studies: (i) Isolated hematuria occurs frequently in the SLE population and is associated with a high likelihood of another renal manifestation at some point in the patient's course; (ii) Isolated hematuria should be considered a manifestation of active renal SLE, and (iii) Histological evidence of lupus involvement is seen in renal biopsy performed on detecting isolated hematuria.

4.42% (31/700) of patients in our cohort had at least one episode of isolated hematuria. This is substantially higher than the normal population where only up to 3% have microscopic hematuria (defined by >3 RBC per HPF) (1, 8).

Thus, the acquisition of a second renal manifestation after the development of isolated hematuria or the manifestation of a renal abnormality in the visit just prior to the isolated hematuria suggests that these isolated manifestations were probably the result of active renal disease. 54.54% of patients with isolated hematuria developed a second renal manifestation within 3 months (next clinic visit) of the onset of hematuria. Furthermore, within 1 year of the onset of isolated hematuria, the percentage of patients with a second renal manifestation was the same (54.54%). Thus, a substantial proportion of patients with an isolated renal manifestation developed a second renal manifestation in a reasonably short duration.

For those patients who presented with the isolated hematuria as their first renal manifestation, another renal feature occurred within a mean of 19.9 months. However, in some patients, the second renal manifestation was delayed. For this subset of patients we cannot necessarily infer that the ongoing renal inflammation at the time of the isolated hematuria resulted in a second renal manifestation. Thus, our findings need to be interpreted in conjunction with other relevant data presented in this study (renal biopsy changes at the time of isolated hematuria in order to support the proposed hypothesis). Concurrent serological abnormality in either the double-stranded DNA antibody or serum complement levels was noted in over 54.83% (17/31) of the patients with isolated hematuria; however, in this study there was not significant correlation between isolated hematuria and C3, C4 or anti-dsDNA. Both of these findings support our clinical impression that isolated hematuria is associated with active lupus nephritis and elevated double-stranded DNA, and low serum complements have been shown to be associated with active lupus nephritis (9, 10).

Indication for the renal biopsies varies in different centers. It has been a practice of Lupus Clinic of the University of Tehran to perform a renal biopsy in patients with active urine sediment (proteinuria>500 mg/24 hours, urinary cast). In this study, 19 of the 31 (61.29%) patients with isolated hematuria were biopsied as part of their initial assessment of lupus. Thus, biopsies were performed irrespective of the status of severe renal manifestations and were not based on more severe non-renal disease activity or on previous history of renal involvement. In patients with isolated hematuria, attention should also be given to non-immune related causes of glomerular diseases such as renal hemangiomas, benign familial thin basement membrane disease, as well as lower urinary tract etiologies such as malignancy or asymptomatic stones. The presence of glomerular hematuria does not preclude the presence of a concomitant urological malignancy, especially in the setting of cyclophosphamide use. Furthermore, hematuria in older patients or those with a family history of renal failure should prompt a thorough investigation. The enumeration of dysmorphic red blood cells, particularly acanthocytes, has been shown to be more specific for hematuria of renal etiology; however, this was not examined in all patients in our study.

Out of all the patients who had renal biopsies on detection of isolated hematuria, 15.78% had important renal involvement (WHO class IV), being the same as Rahman et al. study (7) (Table 1)

In summary, the appearance of isolated hematuria is associated with active renal disease. The results of this study suggest that isolated hematuria is a manifestation of active lupus and, thus, the inclusion of hematuria as an independent feature of the disease activity the SLEDAI appears to be justified.

Table 1. Comparison of renal biopsies in SLE patients with isolated hematuria

	RRC study (Iran)	P Rahman (Canada)
Total number of biopsies	19	22
Class I	0	1 (4.5%)
Class II	4(21.5%)	12(56%)
Class III	12(63.15%)	4(18%)
Class IV	3(15.78%)	4(18%)
Class V	0	1(4.5%)

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However, if the significance of the isolated hematuria is in doubt given the context of the patient's overall disease status, a search for a non-renal etiology for this abnormality is justified. If this fails to resolve the issue, then a renal biopsy is warranted.

Persistent isolated hematuria should not be ignored as a 'benign' urinary finding in patients with SLE until the possibility of renal involvement has been ruled out with a renal biopsy.

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