

Clinicopathological Study of Males with Lupus Nephritis: Pathologist's Experience at a Tertiary-Care Center

Abstract

Background: Systemic lupus erythematosus (SLE) is an autoimmune systemic disorder, more common in females of reproductive age-group as compared with males. There are very few studies regarding lupus nephritis (LN) in males. Hence, we decided to study the clinical and pathological findings of LN in males. **Materials and Methods:** We carried out a retrospective study over a period of 5 years (January 2014–December 2018) on indicated native renal biopsies from male patients with LN. We analyzed the clinical, laboratory, and histological findings of these patients. **Results:** Renal biopsies were performed on 228 patients with LN, of which 29 (12.72%) biopsies were in male patients. The mean age at presentation was 28.3 ± 12.98 years. Edema (65.5%) was the most common clinical feature followed by arthritis (27.58%), fever (27.58%), and skin rash (24.1%). The mean values for 24 hours urinary protein, serum double-stranded DNA, serum antinuclear antibody, and serum complement C3 were 4.98 ± 2.91 g, 137.7 ± 91.93 IU/mL, 2.96 ± 1.78 , and 65.07 ± 36.30 mg/dL, respectively. On histology, the most common class of LN was Class IV (34.48%) followed by Class V (20.68%), combined Class IV + V (20.68%), Classes II, III, and III + V. **Conclusion:** LN can affect males, although the prevalence is lower than in females. The incidence of LN in our study was 12.7% with the most common histological class being diffuse proliferative LN.

Keywords: Diffuse proliferative, hypocomplementemia, lupus nephritis, males

Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease, often called a “woman’s disease” because of the high prevalence of SLE in females.^[1,2] SLE can involve any organ, and when it affects the kidneys, it is known as “lupus nephritis” (LN). LN can manifest with minimal renal involvement in the form of mild proteinuria to severe end-stage renal disease (ESRD). Nearly 5% to 22% of these patients progress to ESRD.^[3,4] SLE is common during childbearing age in females, and males are usually affected in their adolescence.^[5,6] The main etiological factors considered are sex hormones and immunological factors. The criteria laid down by the American College of Rheumatology for SLE are used worldwide for diagnosis and disease activity.^[7,8] Renal biopsy is still the gold standard for diagnosis, and prognosis of LN and biopsy findings are reported according to the classification system by the International Society of Nephrology (ISN) and the Renal

Pathology Society (RPS).^[9] In this study, we analyzed the clinical, laboratory, and biopsy findings in male patients with LN.

Materials and Methods

This was an Institutional Review Board–approved, single-center, retrospective study of indicated renal biopsies performed on male patients with SLE between January 2014 and December 2018. The patient demography included age, sex, and clinical features. The laboratory parameters analyzed were 24 hours urinary protein (g), serum creatinine (SCr; mg/dL), serum anti-double-stranded deoxynucleotide antibody (anti-dsDNA; IU/mL), serum antinuclear antibody (S.ANA), and serum complement C3 (S.C3; mg/dL). Anti-dsDNA antibodies (titer <25 IU/mL: negative) were determined by immunometric enzyme immunoassay (AutoBind, Tosoh India Pvt. Ltd.), S. ANA (<1: negative; >1: positive) by immunometric enzyme immunoassay (AutoBind, Tosoh India Pvt. Ltd.), and S.C3 (normal range: 90–207 mg/dL) by quantitative, turbidimetric assay (Siemens, Germany).

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For light microscopy, formalin-fixed, paraffin-embedded sections of 3 to 4 μm thickness were stained with hematoxylin and eosin, periodic acid–Schiff, Jones’s methenamine silver, and Gomori’s trichrome stains. Immunofluorescence (IF) study was performed on 4 to 5 μm thick frozen sections cut on cryostat and stained with antihuman IgG, IgA, IgM, C3, C1q, and fibrinogen (polyclonal antihuman rabbit antisera; conjugated to fluorescein isothiocyanate, supplied by Dako, USA). The biopsies were studied for changes in the glomerulus, blood vessels, and tubulointerstitial compartment and were reported according to the histological classification as per the ISN/RPS 2003 classification of LN. The activity and chronicity scoring of LN was also calculated as per the ISN/RPS 2003 classification.^[9] Five pathologists independently reported, and the consensus diagnosis generated was finally reported.

Results

Of the 228 biopsy-proven LN patients, 29 (12.72%) were males (study group) and 199 (87.2%) were females (male: female = 1:14.5). The mean age at presentation was 28.3 ± 12.98 years. All patients (100%) had nephrotic–nephritic presentation. Other demographic details are shown in Table 1. Hematological investigation revealed anemia (100%) and thrombocytopenia and leukocytopenia (3.45%). The mean 24 hours urinary protein was 4.98 ± 2.91 g, and 13 (44.82%) patients presented with raised SCr (mean: 1.70 ± 1.30 mg/dL). The mean dsDNA was 137.7 ± 91.93 IU/mL and S. ANA was positive in 27 (93.1%) patients (mean: 2.96 ± 1.78). Hypocomplementemia was observed in 22 (75.86%) patients (mean: 65.07 ± 36.30 mg/dL). Table 2 presents the demographic characteristics with respect to histological class.

Light microscopy findings

Table 2 presents the demographic characteristics with respect to histological class. None of the biopsies

were reported to have histological changes of Class I/VI LN. Class II LN was reported on three (10.34%) biopsies [Figure 1]. Of these, 2 (66.66%) patients presented with nephrotic-range proteinuria (mean: 6.18 ± 2.04 g/day), and one (33.33%) had subnephrotic-range (1.71 g/day) proteinuria. Serum dsDNA (S. dsDNA) was high in all three cases, whereas S. ANA was positive only in 2 cases. The mean S.Cr was 0.89 ± 0.33 mg/dL.

Class III LN was reported in 2 biopsies with mild tubulointerstitial nephritis (TIN) and focal interstitial fibrosis in one biopsy [Figure 2]. Mean S. Cr was 0.73 ± 0.52 mg/dL. Ten (34.48%) biopsies revealed Class IV LN. This was the most commonly reported class. Histology revealed endocapillary proliferation (100%), neutrophilic infiltration (60%), wire loop lesions (60%), and hyaline thrombi (50%). Cellular crescents were noted in seven (70%), fibrous crescents in two (20%), and fibrinoid necrosis in one (10%) [Figure 3]. Class IV LN (G/A) was noted in 70% and Class IV (A/C) in 30% biopsies. Chronicity in the form of glomerular sclerosis, tubular atrophy with interstitial fibrosis, and chronic TIN was seen in three (30%), four (40%), and eight (80%) biopsies. Seven (70%) patients had a mean S. Cr of 2.53 ± 1.31 mg/dL with nephrotic-range (mean: 7.79 ± 2.59 g/day) and remaining three (30%) with subnephrotic-range (mean: 2.33 ± 0.45 g/day) proteinuria. All the patients revealed high S. dsDNA values. S. ANA was positive in all the patients of this class, and hypocomplementemia was seen in eight (80%) patients. Lupus vasculopathy was noted in one patient of this class.

Class V LN was reported in 6 (20.68%) cases with light microscopy changes of diffuse thickening of glomerular basement membranes with subepithelial spikes. Two (33.33%) revealed neutrophilic infiltration and wire loop lesions and 1 showed endocapillary proliferation.

Table 1: Clinical presentation of males with lupus nephritis along with comparison of other studies

Clinical Manifestation	Present study, n=29	Liu et al., ^[25] n=85	Wang et al., ^[24] n=45
Edema	19 (65.51%)	-	-
Hematuria	15 (51.72%)	57 (67.1%)	33 (73.3%)
Fever	8 (27.58%)	42 (49.4%)	17 (37.8%)
Arthritis	8 (27.58%)	31 (36.5%)	26 (57.8%)
Skin rash	7 (24.14%)	42 (49.4%)	26 (57.8%)
Serositis	4 (13.79%)	43 (50.6%)	7 (15.6%)
Oliguria	3 (10.34%)	-	-
Central Nervous system	1 (3.45%)	2 (2.4%)	2 (4.4%)
Leucopenia	1 (3.45%)	26 (30.6%)	25 (55.6%)
Thrombocytopenia	1 (3.45%)	27 (31.8%)	12 (27.3%)
Alopecia	-	18 (21.2%)	6 (13.3%)
Oral ulcer	-	15 (17.6%)	13 (28.9%)

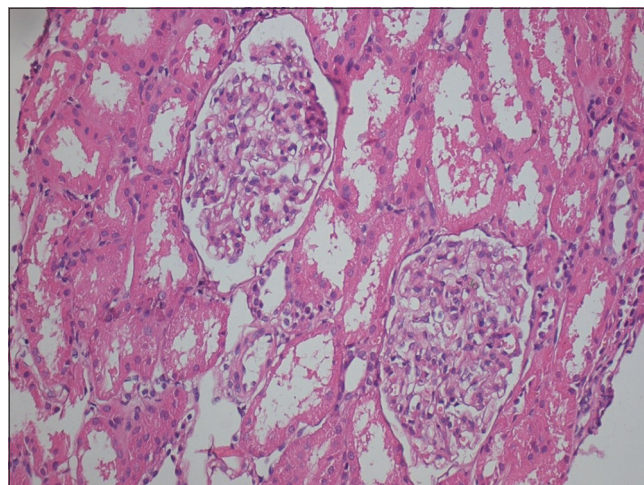


Figure 1: Light microscopy of a renal biopsy from a patient with Class II lupus nephritis. The glomerulus appears mildly enlarged with mild mesangial expansion and mild hypercellularity. Hematoxylin & eosin, magnification 200x

Table 2: Class-wise distribution of laboratory investigations of males with lupus nephritis

Total No., n=29	Class II, n=3 (10.34%)	Class III, n=2 (6.89%)	Class IV, n=10 (34.48%)	Class V, n=6 (20.68%)	Class IV + V, n=6 (20.68%)	Class III + V, n=2 (6.89%)
Low C3 (≤ 90 mg/dL)	2 (66.66)	2 (100)	8 (80)	3 (50)	5 (83.3)	2 (100)
S.dsDNA (≥ 25 IU/mL)	3 (100)	2 (100)	10 (100)	6 (100)	6 (100)	2 (100)
S.ANA titer (≥ 1)	2 (66.6)	2 (100)	10 (100)	5 (83.3)	6 (100)	2 (100)
S. Cr (≥ 1.4 mg/dL)	-	-	7 (70)	2 (40)	3 (50)	1 (50)
24 h urinary proteins (g) (>3.5)	2 (66.66)	-	7 (70)	4 (80)	5 (83.3)	1 (50)
24 h urinary proteins (g) (<3.5 but >1.5)	1 (33.3)	2 (100)	3 (30)	2 (40)	1 (16.66)	1 (50)

S. dsDNA=serum double-stranded deoxynucleotide antibody, S.ANA=Antinuclear antibody, S. Cr=serum creatinine

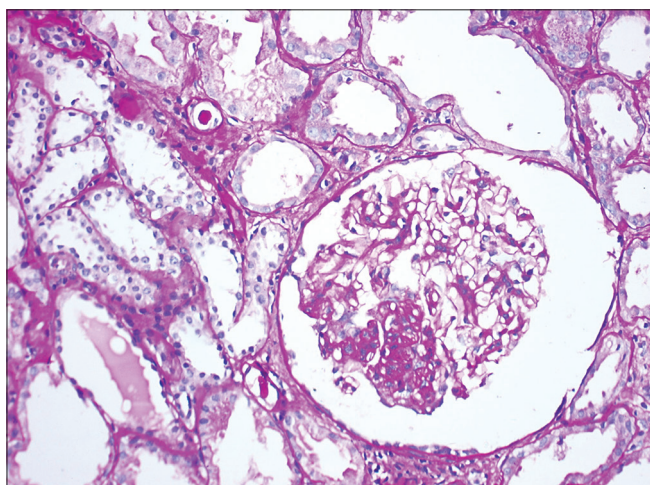


Figure 2: Light microscopy of a renal biopsy from a patient with Class III lupus nephritis. The glomerulus reveals focal sclerosing glomerulonephritis and focal hypercellularity. Periodic acid-Schiff, magnification 200 \times

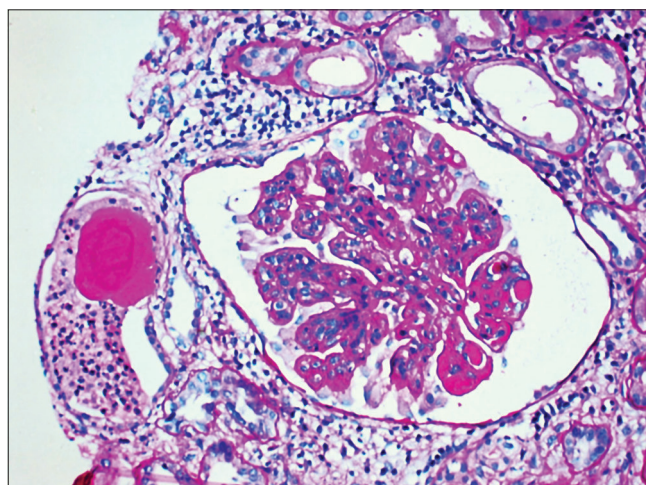


Figure 3: Light microscopy of a renal biopsy from a patient with Class IV lupus nephritis. The glomerulus showing hyaline thrombi, dilated capillary lumina, and mild mesangial hypercellularity. (a) Periodic acid-Schiff, magnification 400 \times

TIN was noted in 3 and interstitial fibrosis and tubular atrophy (IFTA) in 2 biopsies. Nephrotic-range (mean: 6.29 ± 1.53 g/day) proteinuria was noted in 4 and subnephrotic-range (mean: 2.38 ± 0.25 g/day) proteinuria in 2. All patients had high values for S. dsDNA of which positive S. ANA was observed in five (83.3%) cases. Three (50%) patients had low S. C3 and mean S. Cr was 1.10 ± 0.49 mg/dL.

Combined lesions

A mixed class (27.58% biopsies) was diagnosed when histological features of two classes were observed in the same biopsy core. The most common combined class was Class IV + V seen in 6 with 4 biopsies showing capillary lumina with neutrophils and hyaline thrombi. Cellular crescents were seen in 3 and fibrinoid necrosis in one biopsy. IFTA was seen in 3 and glomerulosclerosis in 2 biopsies [Figure 4]. Five (83.3%) patients presented with nephrotic-range proteinuria (mean: 5.74 ± 2.52 g/day). Raised S. dsDNA and positive S. ANA were noted in all the patients of this group. Hypocomplementemia was seen in five (83.3%) patients, and the mean S. Cr of patients with this class was 1.52 ± 0.67 mg/dL.

Of 2 biopsies of Class III + V, one showed hyaline thrombi with fibrinoid necrosis. Both the patients had high S.

dsDNA titer, positive S. ANA, and hypocomplementemia. One patient presented with nephrotic-range proteinuria and the other with subnephrotic-range proteinuria. Mean S. Cr was 1.14 ± 0.50 mg/dL.

Immunofluorescence microscopy findings

Seventeen (58.62%) biopsies revealed full-house positivity for immunoglobulins and complements on IF microscopy. IgG (intensity of +3 or +4 on the scale of 0 to +4) was noted in all the biopsies, followed by C1q (96.5%). Anti-IgA and anti-IgM were noted in 82.7% and C3 in 72.41% biopsies. IgA of +2 intensity was noted in 15 (51.72%) cases and of +3 in 14 (48.27%) cases. The intensity of IgM was variable, 10 (34.48%) biopsies revealed mesangial IgM deposit of +1 intensity, 11 (37.93%) of +2, and eight (27.58%) with +3 intensity.

Uniform presence of complements was seen in all the cases. C3 of +3 intensity was present in nine (31.03%) and of +4 intensity in 11 (37.93%) biopsies. An intensity of +3 for C1q was noted in 21 (72.41%) biopsies. Eight (27.58%) biopsies revealed the presence of C1q antibodies of +4 intensity [Figure 5]. The distribution of deposits was variable in each class. In Classes II, III, and IV, the deposits were mainly mesangial, whereas in Class V, the deposits

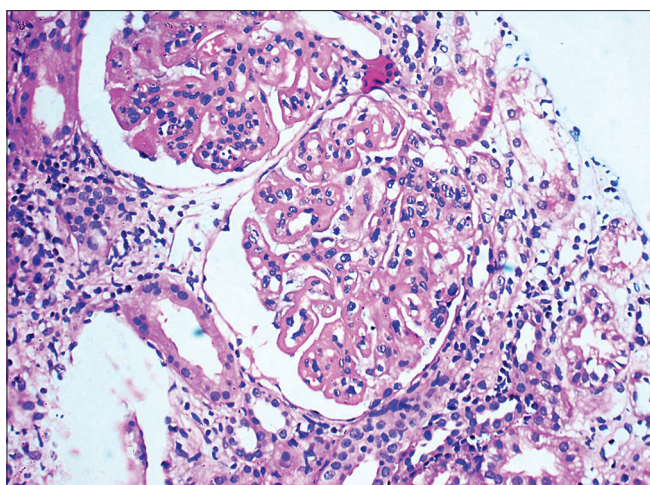


Figure 4: Light microscopy of a renal biopsy from a patient with Class IV + V lupus nephritis. The glomerulus showing lobular accentuation with capillary lumina lined by thickened membranes (wire loop lesion). (A) Periodic acid–Schiff, magnification 200×

were mainly along the glomerular capillary walls and also in the mesangium. IgG was noted along the tubular basement membrane in 26% of the biopsies and one case of lupus vasculopathy revealed the presence of IgG (+2) and fibrinogen (+2) in the vessel wall.

Discussion

LN can occur at any time during the course of SLE with implicated factors such as genetics, sex hormones, and autoimmunity. The relation between estrogen and autoimmune disease has been hypothesized for a high incidence of SLE in females. Dysregulation of T-cells, increased helper T-cell activity, and B-cell hyperactivity lead to the generation of autoantibodies.^[10-15] Shen *et al.*^[16] found a strong association of TLR7 with SLE in Eastern Asian males than in females. In males, the androgen hormone is responsible for renal injury.^[17]

Nearly 25% to 75% of SLE patients present with LN.^[1,3,18,19] The incidence of LN in males varies from 4% to 22% with an incidence of 12.7%.^[1,20] Basu *et al.*^[21] and de Carvalho *et al.*^[22] reported an incidence of male lupus of 9.67% and 13.6%, respectively. Patel *et al.*^[23] reported a high prevalence of male LN with increasing age. The mean age at presentation was 28.3 ± 12.98 years (range: 10–55 years) in our study, which was comparable with 42.6 years by Basu *et al.*,^[21] 32.67 ± 13.96 years by Wang *et al.*^[24] and 37.94 ± 16.96 years (10–87 years) by Liu *et al.*^[25] Male LN was common in the age-group of 20 to 40 years in the present study, Basu *et al.*^[21] (40–48 years), and Wang *et al.*^[24] (18–46 years).

The most common presenting symptom was edema 19 (65.5%) followed by hematuria 15 (51.72%) in the present study. Arthritis and fever were noted each in 8 (27.58%) patients. Skin rashes in 7 (24.14%), serositis in 4 (13.79%), and oliguria in 3 (10.34%) patients. Low

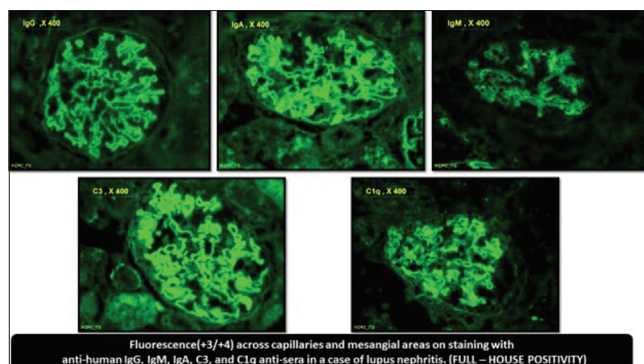


Figure 5: Immunofluorescence findings in an index case of lupus nephritis with immunoglobulins and complement

incidence of arthritis in males has also been reported by Faezi *et al.*^[26] Medina *et al.*,^[27] de Carvalho *et al.*,^[22] and Liu *et al.*^[25] reported a higher incidence of skin rash of 84%, 45.5%, 49.4%, respectively. We also reported a low incidence (13.79%) of serositis in our study, which was more common in the study by Voulgari *et al.*,^[28] Soto *et al.*,^[29] and Keskin *et al.*^[30] Some studies reported that male patients with LN have more of neurological involvement,^[29,31,32] vascular thrombosis,^[32,33] cardiovascular damage, and hypertension;^[34] however, we did not observe these.

Nephrotic-range proteinuria was observed in 19 (65.51%) patients (mean range: 4.98 ± 2.91 g), similar to the findings of Wang *et al.*,^[24] Hsu *et al.*,^[35] and Urrestarszú *et al.*^[5] who reported a mean 24 hours urinary protein (in g) of 5.26 (2.63–9.90), 5.0 (2.7–9.1), and 4.6 ± 3.5 , respectively. Nephrotic-range proteinuria was more common in Classes II, IV, V, and IV + V similar to the observation by Liu *et al.*^[25]

All the patients in our study revealed high anti-dsDNA titer. S. ANA was positive in 27 (93.1%) cases. Wang *et al.*^[24] reported high anti-dsDNA titer and positive S.ANA in 64.4% and 74% patients, respectively. The results obtained by Urrestarszú *et al.*^[5] were also similar. They also observed high serum anti-dsDNA and S.ANA in 96.0% and 97.8% patients, respectively.^[5]

The mean S.Cr in our study was 1.70 ± 1.30 mg/dL. High S.Cr (>1.4 mg/dL) was noted in 13 (44.82%) patients in our study, of which 7 (70%) were from Class IV, 2 from Class V, 3 from Class IV + V, and one from Class III + V. Mean S. Cr of patients with biopsy changes of Classes II and III was <1.4 mg/dL. High S. Cr levels were also reported in the study by Urrestarszú *et al.*^[5] and de Carvalho *et al.*^[22] (2.18 ± 1.47 and 3.16 ± 2.49 mg/dL, respectively). Proteinuria and S. Cr have been considered a significant overall prognostic parameter for the disease.^[36]

Very few authors have exclusively reviewed the histological parameters of LN in males. The results of our study are comparable with the studies by Wang *et al.*,^[24] Liu *et al.*,^[25]

Table 3: Comparison of results of our study with other studies

ISN/RPS CLASS	Present study, n=29	Wang <i>et al.</i> , ^[24] n=45	Liu <i>et al.</i> , ^[25] n=42	de Carvalho, ^[22] n=11
Class II	3 (10.3%)	3 (6.7%)	1 (2.7%)	-
Class III	2 (6.89%)	7 (15.6%)	5 (11.9%)	2 (18.2%)
Class IV	10 (34.48%)	26+1 (60%)	15 (35.7%)	4 (36.4%)
Class V	6 (20.68%)	8 (17.8%)	10 (23.8%)	5 (45.5%)
Class IV + V	6 (20.68%)	-	10 (23.8%)	-
Class III + V	2 (6.89%)	-	1 (2.4%)	-

ISN=International Society of Nephrology, RPS=Renal Pathology Society

and de Carvalho *et al.*^[22] Most of these studies show that Classes IV and V are the most common histological classes reported in male patients with LN. In our study also, we found that the most common class on histology was Class IV ($n = 10$; 34.48%). Class V and combined Class IV + V were next common to be reported in six (20.68%) patients. A high incidence of Class IV LN was also noted by Wang *et al.*^[24] (60%), Liu *et al.*^[25] (35.7%), and de Carvalho *et al.*^[22] (36.4%). However, de Carvalho *et al.*^[22] reported a higher incidence of Class V of 45.5%. The incidence of other classes in descending trend in our study was Class II (10.34%), Class III (6.89%), and Class III + V (6.89%), a comparison of which with other studies is summarized in Table 3.

We also analyzed the histological features seen on the biopsy, which was not done by any author previously. However, Hsu *et al.*^[35] did compare the activity and chronicity scores. The most common histological finding in our study was endocapillary proliferation, which was observed in 20 (68.96%) biopsies. The infiltration of glomeruli by neutrophils was seen in 12 (41.37%) cases and was the next common microscopic finding noted in our study. Hyaline thrombi were characteristically seen in 11 (37.93%), cellular crescents in 10 (34.48%), and wire loop lesions in eight (27.58%) biopsies. The least common finding in glomeruli was the presence of fibrinoid necrosis in three (8.7%) and the presence of fibrous crescents in two (6.89%) biopsies. Hsu *et al.*^[35] reported the presence of fibrinoid necrosis in 88.2% and the presence of cellular crescents on biopsy in 47.1% of cases of male LN. Tubular atrophy was noted in 10 (34.48%) biopsies and was more so noted in cases of Class IV LN. Similarly, interstitial fibrosis was more common in biopsies with changes of Class IV LN (4; 40%). Interstitial inflammation of variable degree was associated with all the classes; however, most of the cases of Class IV (8; 80%) revealed associated interstitial nephritis. Thus, renal involvement with nephrotic-nephritic presentation is also similarly noted in males with SLE.

Limitations of the study

Because of the unavailability of electron microscopy, the biopsies were not subjected to this modality. We did not follow up with the patients for change of class as we aimed at studying the histological and clinical profile of male patients with LN, hence it is not in the scope of this article.

Conclusion

SLE does affect the males, but with a lower incidence. The spectrum of histological changes are similar irrespective of sex.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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