HISTOPATHOLOGICAL CORRELATION OF LUPUS NEPHRITIS WITH EXTRA-RENAL MANIFESTATION AND LABORATORY FINDINGS

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ABSTRACT

Background

Lupus nephritis is one of the most serious manifestations of Systemic lupus erythematosis and it is a major cause of morbidity and mortality.

Objectives

To find out the relation between Histopathologyical classes of Lupus nephritis with renal, extra renal clinical manifestation and laboratory data.

Patients and Methods

A cross-sectional study performed on 45 patients with biopsy proven lupus nephritis, which they were collected from April 2012 to April 2013.

Results

The current study shows female predominance 32 (71.1%) compared with 13 (28.9%) male. Class IV 15 (33.3%) was the most common type followed by class III 9 (20.9%). The new onset hypertension was the commonest clinical renal presentation 32 (71.1%) and the musculoskeletal manifestation 37 (82.2%) was the most common extra renal manifestation. The correlation between classes of Lupus nephritis with clinical and laboratory data were significant for hypertension, 24 hrs urinary protein excretion, S. Creatinine, S. Albumin, Anti-Sm and Anti-dsDNA positivity and low complement levels (C3, C4).

Conclusion

Class IV is the commonest class of Lupus nephritis. Female preponderance becomes less pronounce in lupus nephritis compared to prevalence SLE.

Keywords: *Systemic lupus erythematosis, Lupus nephritis, Histopathological classification.*

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INTRODUCTION

Systemic lupus erythematosis (SLE) is a multi-systemic autoimmune disease of unknown etiology. In all series of SLE worldwide, women constitute more than 90% of all patients. This female preponderance becomes less pronounced before puberty and after menopause, which suggests that estrogen metabolism and its link with the immune system may play roles in the pathogenesis of the disease [(1)].

Lupus nephritis (LN) is one of the common manifestations of SLE, occurring in about 50–70% of patients, and is a major cause of morbidity and mortality in the SLE population [(2)].

The clinical course of LN is heterogeneous and varies from mild subclinical disease to an aggressive course that may rapidly progress to end-stage renal disease (ESRD) [(2)].

The clinical diagnosis of lupus nephritis is by measuring 24-hour urinary protein excretion , although universally practiced, variable results may occur over a short period of time, probably due to changes in physical activity or collection errors and the latter problem can be remedied by quantifying total creatinine in the same 24-hour urine collection. Alternatively the urinary protein excretion rate can be estimated by assaying the protein/creatinine ratio in a random daytime urinary sample, and this ratio approximates the total number of grams per day of proteinuria [(3)]. The urinary sediment is also useful for characterizing renal disease activity [(4)].

A rising anti-DNA antibody titer and hypo-complementemia, especially with low C3, are strong indicators of active lupus renal disease, although serology cannot be used in isolation to diagnose or monitor renal disease, The hypo-albuminemia accompanied by significant proteinuria is a component of the nephrotic syndrome that may accompany active lupus renal disease, the hypercholesterolemia is another marker and also a clinical complication of the nephrotic syndrome that can accompany active LN [(3)].

The histological diagnosis of lupus nephritis is by renal biopsy which is the mainstay for the diagnosis of LN and nephritis can be the first clinical manifestation of SLE in up to 15 to 20% of patients [(3)] and the renal biopsy also helps to establish the extent of histopathological chronicity and activity, disease prognosis, and also serves as a guide for therapy [(3)].

ISN/RPS histological classification of lupus nephritis:

Class I (minimal mesangial LN), class II (mesangial proliferative LN), class III (focal LN), class IV (diffuse LN), and this class further is divided into diffuse segmental (IV-S) and diffuse global (IV-G) LN, class V (membranous LN), class VI (advanced sclerotic LN) [(5)].

PATIENTS AND METHODS

A cross sectional, descriptive study performed on 45 patients with systemic lupus erythematosis (SLE) who attended the Rheumatology Department In Slemani city from April 2012 to April 2013. Patients had been diagnosed according to the American College of Rheumatology (ACR)1997 revised criteria for classification of SLE, and their renal biopsy proved to have lupus nephritis. The patients selected on the bases of clinical and laboratory evidence of renal disease which was defined as varying combinations of the following:

1. Active sediments in general urine examination (hematuria , granular casts and dipstick proteins).
2. Urinary protein excretion >0.5 g/24 hours .
3. Edema requiring diuretic therapy.
4. Diastolic blood pressure >90 mm Hg .
5. Serum creatinine more than (1.5 mg/dl) without compelling alternative causes (such as sepsis , hypovolemia, or medication).

The renal biopsies were done for all patients and classified according to international society of nephrology/renal pathology society (ISN/RPS 2003). The patient with clinical and laboratory evidence of renal involvement who didn't agree doing renal biopsy or the result of their biopsies were not consistent with any classes of lupus nephritis have been excluded from the study.

Statistical analysis: Different statistical analyses were carried out using statistical package for social science (SPSS) version 16.0 windows.

Statistical analysis included both descriptive and inferential statistic for analyzing the data obtained from the study to explain the results, both Chi Square and Fischer exact test used for categorical data, and ANOVA test used for continuous data to determine the level of significance (P-value).

RESULTS

Among the 45 lupus nephritis patients enrolled in the study, 32 (71.1%) patients were female and 13 (28.9%) were male, with a male to female ratio of 1:2.4.The mean age for SLE diagnosis was 27.2±11, ranging from (11–67 yr), and for LN diagnosis was 29.3±11.1 ranging from (12–67 yr) respectively. The time interval between the two conditions was 2.1±2.4 ranging from (0–12 yr) as shown in the table (1).

The prevalence of renal histopathological classes from the commonest to the least common were as following: class IV 15(33.3%), 10(22.2%) as class IV segmental(IV-S) and 5 (11.11%) as IV- global(IV-G), class III 9(20%), class II 8(17.8 %), class V+III 4(8.9%). Both class V and class I had the same frequency which was 3(6.7%), class V+IV-S 2 (4 .4%), class V+II found in 1 (2.2%) of patients as shown in table (2).

Class III and IV were further subdivided into active (A), active/chronic (A/C) and chronic (C) groups. Within Class III, the number of class III (A) was four, III (A/C) was three and III (C) was two. Within Class IV-S, the number of IV-S (A) was zero, IV-S (A/C) was nine and IV-S (C) was one. Within Class IV-G, the number of IV-G (A) was one, IV-G (A/C) was four and IV-G (C) was zero. Within class V+III, the number of V+III(A) was one, V+III(A/C) was two, V+III(C) was one. Within class V+IV-S the number of V+IV-S(A) was zero, V+IV-S(A/C) was two, V+IV-S(C) was zero as shown in table (3).

The most common renal clinical presentation was new onset hypertension found in 32(71.1%) followed by edema in 10(22.2%) of cases, and oliguria in 6(13.33%) of cases, as shown in table (4).

Table 1. Demographic data.

Demographic data M±SD (range)	Total (45 cases)
Age at SLE diagnosis	27.2±11 (11 – 67)
Age of nephritis diagnosis	29.3±11.1 (12 – 67)
Time interval between two in years	2.1±2.4 (0 – 12)

Table 2. Prevalence of classes of LN.

Class	No. (%)
Class I	3 (6.7)
Class II	8 (17.8)
Class III	9 (20)
Class IV	15 (33.3)
Class IV-S	10 (22.2)
Class IV-G	5 (11.11)
Class V	3 (6.7)
Class VI	0 (0)
Class (V + II)	1 (2.2)
Class (V + III)	4 (8.9)
Class (V+ IV-S)	2 (4.4)
Total	45 (100)

Table 3. Activity and chronicity feature in proliferative LN.

Activity and chronicity (n %)	Class III (n=9)	Class IV-S (n=10)	Class IV-G (n=5)	Class V+III (n=4)	Class V+IV-S (n=2)	Total (n=30)
Active (A)	4(44)	0(0)	1(20)	1(25)	0(0)	6(20)
Active/chronic(A/C)	3(33)	9(90)	4(80)	2(50)	2(100)	20(66.7)
Chronic (C)	2(22)	1(10)	0(0)	1(25)	0(0)	4(13.3)

Table 4.Common renal clinical presentation in both genders.

Symptom and sign (n %)	Total (n=45)
Hypertension	32 (71.1)
Edema	10 (22.2)
Oliguria	6 (13.33)

The main extra-renal clinical manifestations were musculoskeletal 37(82.2%) followed by mucocutaneous 35(77.8%), hematological in 30 (66.67%), pulmonary 15(33.3%), CNS 8(17.78%), cardiovascular 7(15.56%) and GIT 2(4.44%) as shown in table (5).

The Common immunological profile in different classes of LN including ANA, Anti-dsDNA, Anti-Sm, complements (C3,C4) are shown in the table (8).

Table 5. Prevalence of extra-renal clinical manifestation among patients with LN.

Extra-renal manifestation (n %)	Total (n=45)
Musculoskeletal	37 (82.2)
Mucocutaneous	35 (77.8)
Hematological	30 (66.7)
pulmonary system	15 (33.3)
CNS	8 (17.78)
CVS	7 (15.56)
GIT	2 (4.44)

Table 6. show urine sediment and 24 hrs protein excretion according to the classes of lupus nephritis.

Variables	Class I,II (n=11)	Class III (n=9)	Class IV (n=15)	Class V and combinations (n=10)	Total (n=45)	P-value
Microscopic Hematuria	6(54.5)	7(77.8)	12(80)	8(80)	33(73.3)	0.5
Dipstick protein	11(100)	9(100)	15(100)	10(100)	45(100)	NA
Granular cast	7(63.6)	7(77.8)	11(73.3)	10(100)	35(77.8)	0.2
24 hrs protein(g)M±SD	1.5±0.85	1.8±1.1	2.5±0.6	2.7±0.9	2.7±0.96	0.005
24 hrs protein < 3 g/day	10(91)	7(77.8)	11(73.3)	4(40)	32(71.1)	0.09
24 hrs protein ≥ 3 g/day	1(9.1)	2(22.2)	4(26.7)	6(60)	13(28.9)	0.09

NA: not applicable because of inadequate number of patients. For categorical data values are represented as a number and percentage (n %) and P- value calculated by Chi-Square test. For continuous data P- value calculated by ANOVA test.

Table 7. Show clinical and laboratory parameter in different classes of lupus nephritis.

Variable	Class I, II (n=11)	Class III (n=9)	Class IV (n=15)	Class V and combinations (n=10)	Total (n=45)	P -value
Hypertension (n %)	4(36.4%)	7(77.8%)	12(80%)	9(90%)	32(71.1%)	0.04
Bl.urea (mg/dl)	27±7.4	50±45.1	54±17.4	58.9±47.1	47.7±32.9	0.1
S.creatinin (mg/dl)	0.6 ±0.23	1.3±1.4	1.6±0.5	1.7±1.4	1.3±1	0.03
S.albumin (gram/dl)	3.7± 0.8	3.3±0.5	2.9±0.7	2.6±0.9	3.1±0.8	0.008
S.cholesterol(mg/dl)	204.6±84.7	218.1±85.5	285.6±57.3	310±169.4	257±108.7	0.06
S.triglyceride(mg/dl)	196±123.9	190±75.9	262.1±63.7	231.3±88.8	224.8±91.5	0.1
ESR (mm/hr)	49.8±28.9	64.4±29.5	53.9±20.5	57.7±25.9	55.8±25.4	0.6

NB: for continuous data values are represented as mean and standard deviations. For continuous data P- value calculated by ANOVA test. For categorical data P- value calculated by Chi-Square test.

Table 8. Common immunological profile in different classes of LN (number & %).

Immunological Profile (n %)	Class I,II (n=11)	Class III (n=9)	Class IV (n=15)	Class V and combinations (n=10)	Total (n=45)	P-value
+ve ANA	10(91)	6(66.7)	8(53.3)	6(60)	30(66.7)	0.2
+veAnti-dsDNA	7(63.6)	9(100)	10(66.7)	10(100)	36(80)	0.03
+ve Anti-Sm	3(27.3)	5(55.6)	1(6.7)	4(40)	13(28.9)	0.05
Low C3	3(27.3)	9(100)	12(80)	7(70)	31(68.9)	0.002
Low C4	4(36.4)	9(100)	12(80)	8(80)	33(73.3)	0.01

For ANA rodent tissues used instead of (HEp-2). P-value calculated by Chi-Square test.

DISCUSSION

SLE is a complex autoimmune disease that can involve multiple organs and kidneys are the most common visceral organs affected [6,7]. Nephropathy occurs in about half or more of the patients with SLE and it is a presenting feature in 30%-50% of patients [8,9]. Progression of the nephropathy to chronic renal insufficiency or end stage renal disease occurs in 45% and 12% respectively [8], and it is well known that renal disease is a major cause of death and is responsible for about half of the SLE related mortality[10,11].

The role of renal biopsy remains somewhat controversial; some investigators believe that all patients with SLE should have renal biopsy to detect those rare patients who have a major renal pathology without clinical signs and to determine the histopathologic types for diagnostic and therapeutic reasons [12].

In the current study there was a female preponderance by a ratio of 2.4:1 which was close to the result found by Zahra Mirfeizi *et al* [13], lower to the figure of Khader N. Mustafa et *al* [14] and Luo Ping Lu Shan *et al* [15] this difference might be explained on the bases of ethnicity, race and/or could be age related, although SLE is female predominance, in LN the female predominance is less prominent [16] .

The mean ages for the SLE and LN diagnosis were 27.2 years and 29.3 years respectively which were differ from the result found by Ana Karla *et al* [17]. The mean time interval between them was 2.1 years which was close to that of Ana Karla *et al* [17].

In the classification of LN; class IV was predominant followed by class III. A similar results were found by Huong DLT *et al* in (France) [18], Derksen RH *et al* in (Netherlands)[19], Seedat YK *et al* in (South Africa)[20], Shayakul C *et al* in (Thailand) [21] and Chu SJ *et al* in (Taiwan)[22] where class IV was more common followed by class III. Unlike the results found by Al-Jarallah K *et al* in (Kuwait) [23], Al-Attia HM *et al* in (UAE) [24], and Hamdy Sliem *et al* in (Egypt) [25] in which class III was more common followed by class IV.

The onset of nephritis associated with edema present in 22.2% of cases which was close to the study of *Niang A et al* [26] and with oliguria which was present in 13.33% of cases which was close to the result of Varun Dhir *et al* [27] and lower than that of Preetha A. *et al* [28] this might be explained by the fact that clinical symptoms and signs suggestive of renal disease have been found to have very low sensitivity to predict renal disease in SLE as patients are largely asymptomatic [28].

The new onset of hypertension was found in 71.1% of cases which was close to that of Carlos F *et al* [29] and differ from the result found by Niang A *et al* [26] and that of Varun Dhir *et al* [27] and lower as compared to studies of Preetha A *et al* [28] . The frequency of hypertension was more common in class V and combination compared to other classes of LN, the same result found by Indiran P Naiker *et al* [30] and Carlos F *et al* [29] .

The musculoskeletal manifestations was the most common extra renal manifestation in this study followed by mucocutaneous and hematological which are similar to the results of Ana karla *et al* [17] and differ from the results found by Niang A *et al* [26] in which the most common extra renal manifestations were hematological followed by mucocutaneous and musculoskeletal. These variations may be due to different sample sizes, different patients' ages, variable disease durations, unreported recent or mild cases, and seasonal, regional or racial variations [20].

The current study showed that dipstick proteinuria present in all patients, the same results is concluded by Stewart J. Cameron [31],and is also close to the results of Preetha A *et al* [28]. The granular cast was present in 77.78% of cases in our study which was differs from the results of by Simin et *al* [32], the highest percent of granular cast found in class V and combinations, this was close to that found by Preetha A *et al* [28] who found that highest percent of granular cast present in class V also.

The microscopic hematuria found in 73.3% of our cases this figure is close to the results of Simin *et al* [32] and it was most commonly present in class IV, V and combinations. Similar results were found by Simin *et al* [32] who found that microscopic hematuria most commonly present in class IV.

The mean 24 hrs urinary protein excretion was 2.7±0.96 g,which is close to the result found by Hitoshi Y. *et al* [33] and the highest level of 24 hrs urinary protein excretion found in class V and combinations this result was comparable to the study of Simin *et al* [32].

The nephrotic rang proteinuria found in 28.9% of our cases and non-nephrotic range proteinuria found in 71.1%, this was differ from the result found by Jim LC Yong *et al* [34] and also differ from that of Surya V. Seshan *et al* [35].

The highest percentage of nephrotic range proteinuria was found in class V and combinations,a similar result concluded by P Parichatikanond P *et al* [36]. The highest percentage of non nephrotic range proteinuria was found in class I and II similar result was reported by Surya V. Seshan *et al* [35].

The mean serum creatinine was 1.3 mg/dl,which is close to the result of Ana Karla *et al* [17]. The mean blood urea was 47.7 mg/dl, differ from the result of Simin *et al* [32]. The highest level of mean blood urea and serum creatinine were observed in class V and combinations, these differ from the results of Preetha A *et al* [28] and Simin *et al* [32] who found the highest level of blood urea and serum creatinine in class IV.

The mean serum albumin was low in current study 3.1 g/dl, it was also low in the study of Wang Guo-bao *et al* [37]. The lowest level of serum albumin recorded in classes V and combinations, unlike the result of Hiramatsu N. *et al* [38] who recorded the lowest level of S.albumin in class IV followed by V .

The mean serum cholesterol was 257±108.7,the figure is close to that of which Laena OngaJyooth *et al* [39]. The highest level found in class V and combinations. The mean S.triglyceride was 224.8±91.5, differs from that of Laena OngaJyooth *et al* [39]and the highest level recorded in class IV.

The mean ESR was 55.8±25.4 and its highest level detected in class III, it was comparable to the result of Carlos F *et al* [29].

The immunological profile shows that ANA positivity found in 66.7% of cases, the figure than those of Zahra Mirfeizi *et al* [13] and Habib Emre *et al* [40], one explanation for the ANA negative finding is technical inaccuracy [41-43] , the laboratory used rat liver substrate instead of human epithelial (Hep-2) substrate has decreased the sensitivity of ANA[41] and the labs. in Slemani still using this old technique.

The positive Anti-dsDNA found in 80% of patients, similar to the result found by Uthman IW *et al* in Lebanon[44] and it's also close to the result of G Moroni *et al* [45] but differ from the result of Zahra Mirfeizi *et al* [13] and Al-Attia HM *et al* in (UAE)[24].

The highest percentage of positive anti-dsDNA found in class III, V and combinations, similar result concluded by Drakoulogkona Ourania *et al* [46] who found the highest percentage of anti-dsDNA positivity in class III.

The percentage of positive Anti-Sm was 28.9%, it was higher than that found by Drakoulogkona Ourania *et al* [46] and P Alba *et al* [47], this high percentage may be due to various ethnicity which more commonly positive in Asian than Caucasian [48] and the highest percentage of Anti-Sm positivity were observed in class III, in contrast to the study of Drakoulogkona Ourania *et al* [46] who found their highest percentage of anti-Sm positivity was in class V.

The low complement levels were 68.9% for C3 and 73.3% for C4, this was close to the result of Varun Dhir *et al* [27] and differ from that found by G Moroni *et al* [45]. The highest percentage of low C3 and C4 levels were found in class III, similar to that concluded by Carlos F. *et al* [29].

We concluded that class IV was the most frequent type of LN. The new onset hypertension is the most frequent renal clinical presentation. The musculoskeletal manifestation is the most frequent extra renal manifestation followed by mucocutaneous and hematological, there is meaningful correlation between new onset hypertension, increased serum creatinine, low serum albumin and increasing 24 hr urinary protein excretion, low level complements in LN classes. Based on clinical features, the degree of urine protein, abnormal urinary sediments, presence or absence of hypertension, it is not possible to predict the histopathological classes.

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