Pattern of Light Microscopic Changes on Kidney Biopsy in Lupus Nephritis Patients an Experience at Rajshahi Medical College Hospital

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Lupus nephritis is one of the most common and serious manifestations of systemic lupus erythematosus. It is regarded as both a strong predictor and a leading cause for morbidity and mortality amongst who suffer from the disease. The World Health Organization (WHO) and the International Society of Nephrology/ Renal Pathology Society (ISN/RPS 2003) classifications of lupus nephritis is the most widely accepted classification at present. Treatment decisions depend largely on histological type of the disease. For this reason, a good number of studies have been done in different parts of the world and the pattern of involvement varied greatly among these studies. The purpose of the present study was to look on our context in this northern part of Bangladesh that which patterns of histological changes are predominant in our lupus patients. This is a hospital based cross sectional observational type study conducted in the Department of Nephrology in Rajshahi Medical College Hospital from 1st March, 2013 to 31st August, 2013. Consecutive 30 SLE patients (fulfilled at least four of the American College of Rheumatology Revised Classification criteria for SLE), having proteinuria (>0.5 g/d or 3+) or cellular cast (red cell, granular or tubular) or haematuria were enrolled for the study and were undergone kidney biopsy and histopathological examination. Patients who had contraindications to kidney biopsy were excluded from the study. The mean age of the study patients was 25.26 years (SD=±5.92). 90% of the study patients were female whereas only 3 (10%) patients were male among the 30 subjects. Class-IV lupus nephritis (43.3%) was the most common class in our community. Second most common class was class-III (30%). It was also revealed that class-I and class-VI lupus nephritis were the least happened class among the study subjects (3.3% each).

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Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease primarily occurring in young women and is characterized by variable clinical and laboratory manifestations.[1,2] The overall incidence of SLE ranges from 1.8 to 7.6 cases per 100,000 with a prevalence of from 4 to 250 cases per 100,000.[3,4] Renal involvement is common in SLE. Abnormal urinalysis with or without an elevated plasma creatinine concentration is present in a large proportion of patients at the time of diagnosis and may eventually develop in up to 75% of the cases. The most frequently observed abnormality is proteinuria.[5] There are a number of types of renal disease in SLE, usually differentiated by a renal biopsy, with immune

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complex-mediated glomerular diseases being the most common. In addition, non-lupus renal diseases may be observed.[6] The introduction of renal biopsy in the 1950s, the application of immunofluorescence and electron microscopic techniques in the 1960s and increasing knowledge about mechanisms of immune mediated glomerular injury derived from experimental studies on serum sickness formed the basis of the recognition and classification of the various patterns of renal injury in SLE. Since then different classifications have been proposed by different authority.[7,8] In order to accommodate the clinicopathologic and pathogenetic insights that have accumulated since 1982 and 1995 modifications of the original 1974 WHO classification and to eliminate inconsistencies and ambiguities, a new classification system of Lupus Nephritis was developed by a group of renal pathologists, nephrologists and rheumatologists which was published in 2004.[8] This World Health Organization (WHO) and the International Society of Nephrology/ Renal Pathology Society (ISN/RPS 2003) classifications of lupus nephritis is the most widely accepted classification at present. Treatment decisions depend largely on histological type of the disease. For this reason a good number of studies have been done in different parts of the world and the pattern of involvement varied greatly among these studies. The purpose of the present study is to look on our context in this northern part of Bangladesh that which patterns of histological changes are predominant in our lupus patients. Lupus nephritis have varied clinical presentations. Almost half of the patients present with asymptomatic urine abnormalities such as hematuria and proteinuria. Nephrotic or nephritic syndrome or both can be observed in 30% of patients. Rarely patients may present with chronic renal insufficiency, rapidly progressive glomerulonephritis or a pulmonary-renal vasculitis syndrome.[7] Systemic lupus erythematosus is a chronic multisystem autoimmune disease[8]. The American College of Rheumatology (ACR) classification criteria were developed to operationalize the definition of systemic lupus erythematosus and to allow comparison of clinical research from different centers, but also serve to facilitate education and to guide clinical practice.[9]

Table I: The 1982 Revised Criteria for Classification of Systemic Lupus Erythematosus

1. Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2. Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3. Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by physician
5. Arthritis	Nonerosive arthritis involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion
6. Serositis	a) Pleuritis--convincing history of pleuritic pain or rubbing heard by a physician or evidence of pleural effusion *OR* b) Pericarditis--documented by ECG or rub or evidence of pericardial effusion
7. Renal disorder	a) Persistent proteinuria greater than 0.5 grams per day or greater than 3+ if quantitation not performed *OR* b) Cellular casts--may be red cell, hemoglobin, granular, tubular, or mixed
8. Neurologic disorder	a) Seizures--in the absence of offending drugs or known metabolic derangements; e.g., uremia, ketoacidosis, or electrolyte imbalance *OR*

	b) Psychosis--in the absence of offending drugs or known metabolic derangements, e.g., uremia, ketoacidosis, or electrolyte imbalance
9. Hematologic disorder	a) Hemolytic anemia--with reticulocytosis *OR* b) Leukopenia--less than 4,000/mm<>3<> total on 2 or more occasions *OR* c) Lyphopenia--less than 1,500/mm<>3<> on 2 or more occasions *OR* d) Thrombocytopenia--less than 100,000/mm<>3<> in the absence of offending drugs
10. Immunologic disorder	a) Positive LE cell preparation *OR* b) Anti-DNA: antibody to native DNA in abnormal titer *OR* c) Anti-Sm: presence of antibody to Sm nuclear antigen *OR* d) False positive serologic test for syphilis known to be positive for at least 6 months and confirmed by *Treponema pallidum* immobilization or fluorescent treponemal antibody absorption test
11. Antinuclear antibody	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with "drug-induced lupus" syndrome

* The proposed classification is based on 11 criteria. For the purpose of identifying patients in clinical studies, a person shall be said to have systemic lupus erythematosus if any 4 or more of the 11 criteria are present, serially or simultaneously, during any interval of observation. In this study each biopsy will be classified according to WHO and ISN/RPS 2003 classification system.[10]

Table II: International Society of nephrology/ Renal pathology society (INS/RPS) 2003 classification of lupus nephritis

Class I	**Minimal mesangial lupus nephritis** Normal glomeruli by light microscopy, but mesangial immune deposits by immunofluorescence
Class II	**Mesangial proliferative lupus nephritis** Purely mesangial hypercellularity of any degree or mesangial matrix expansion by light microscopy, with mesangial immune deposits May be a few isolated subepithelial or subendothelial deposits visible by immunofluorescence or electron microscopy, but not by light microscopy
Class III	**Focal lupus nephritis**[a] Active or inactive focal, segmental or global endo- or extracapillary glomerulonephritis involving <50% of all glomeruli, typically with focal subendothelial immune deposits, with or without mesangial alterations
Class III (A)	Active lesions: focal proliferative lupus nephritis
Class III (A/C)	Active and chronic lesions: focal proliferative and sclerosing lupus nephritis
Class III (C)	Chronic inactive lesions with glomerular scars: focal sclerosing lupus nephritis
Class IV	**Diffuse lupus nephritis**[b] Active or inactive diffuse, segmental or global endo- or extracapillary glomerulonephritis involving ≥50% of all glomeruli, typically with diffuse subendothelial immune deposits, with or without mesangial alterations. This class is divided into diffuse segmental (IV-S) lupus nephritis when ≥50% of the involved glomeruli have segmental lesions, and diffuse global (IV-G) lupus nephritis when ≥50% of the involved glomeruli have global lesions. Segmental is defined as a glomerular lesion that

		involves less than half of the glomerular tuft. This class includes cases with diffuse wire loop deposits but with little or no glomerular proliferation
Class (A)	IV-S	Active lesions: diffuse segmental proliferative lupus nephritis
Class (A)	IV-G	Active lesions: diffuse global proliferative lupus nephritis
Class (A/C)	IV-S	Active and chronic lesions: diffuse segmental proliferative and sclerosing lupus nephritis
		Active and chronic lesions: diffuse global proliferative and sclerosing lupus nephritis
Class (C)	IV-S	Chronic inactive lesions with scars: diffuse segmental sclerosing lupus nephritis
Class (C)	IV-G	Chronic inactive lesions with scars: diffuse global sclerosing lupus nephritis
Class V		**Membranous lupus nephritis**
		Global or segmental subepithelial immune deposits or their morphologic sequelae by light microscopy and by immunofluorescence or electron microscopy, with or without mesangial alterations
		Class V lupus nephritis may occur in combination with class III or IV in which case both will be diagnosed
		Class V lupus nephritis show advanced sclerosis
Class VI		**Advanced sclerosis lupus nephritis**
		≥90% of glomeruli globally sclerosed without residual activity

[a] Indicate the proportion of glomeruli with active and with sclerotic lesions.

[b] Indicate the proportion of glomeruli with fibrinoid necrosis and/or cellular crescents.

Methods

This is a cross sectional observational type study which was carried out in the department of Nephrology of Rajshahi Medical College Hospital for six months duration among the systemic lupus erythematosus patients (fulfilling ACR revised classification criteria) having proteinuria. Diagnosed cases of Lupus nephritis on the basis of ACR criteria, irrespective of age and sex were studied with subsequent renal biopsy and histopathology. SLE patients who did not agree to be included in the study and Patients who had contraindication of renal biopsy (e.g. uncorrectable bleeding diathesis, uncontrollable severe hypertension, active renal infection, skin infection at biopsy site, solitary kidney) were excluded from the study. After taking informed written consent from the patient, data was collected with the help of a predetermined questionnaire and data collection form. The patients were undergone percutaneous renal biopsy with all aseptic precaution. After proper labeling one core of tissue was collected in a normal saline containing pot for DIF and another core was collected in formalin containing pot for histopathological examination. Then both of the pots were preserved in refrigerator at 4˚ c before taking into a parcel service for sending the specimen to a reference laboratory in Dhaka. During transport an ice box was be used to maintain appropriate preservation of the sample. Histopathology reports were collected and analyzed. After renal biopsy, each patient was observed for at least 24 hours in the hospital.

Results

A total of 30 cases of clinically diagnosed lupus nephritis were included in the present study. The mean age of the study patients was 25.26 years (SD=±5.92).

Table III: Age distribution of study patients

Age group	Frequency (n/%)
11-20 years	10(33.3%)
21-30 years	15(50%)
31-40 years	4(13.3%)
41-50 years	1(3.3%)

From the above observation it can be stated that younger people (<30 years of age) were more affected (cumulative percentage is 83%) in lupus nephritis than relatively older individual (> 30 years of age).

Table IV: Sex distribution of study patients

Sex	Frequency(n/%)
Male	3(10%)
Female	27(90%)

90% of the study patients were female whereas only 3 (10%) patients were male among the 30 subjects. Percutaneous renal biopsy followed by histopathological examination including immunofluorescence was done in all study patients. When findings are classified according to WHO and ISN/RPS 2003 classification system the following results are found: Class I: 1 (3.3%) patients, class II: 3 (10%) patients, class III: 10 (30%) patients, class IV: 13 (43.3%) patients, class V: 3 (10%) patients, and class VI: 1 (3.3%) patient.

It can be inferred that class-IV lupus nephritis (43.3%) was the most common class among the studied patients. Second most common class was class-III (30%). It was also revealed that class-I and class-VI lupus nephritis were the least happened class among the study subjects (3.3% each).

Table V: Frequency of histopathological class of lupus nephritis patients

Histopathological Class	Frequency (n/%)
Class-I	1(3.3%)
Class-II	3(10%)
Class-III	10(30%)
Class-IV	13(43.3%)
Class-V	3(10%)
Class-VI	1(3.3%)

Discussion

Renal involvement is common in systemic lupus erythematosus and often determines the course of the disease.[11] The glomerular lesions that frequently accompany systemic lupus erythematosus have been the subject of intense investigation by clinicians and pathologists for nearly a half of century. These efforts have generated numerous attempts to classify and categorize the pathological features of lupus nephritis. After several revisions of WHO classification of lupus nephritis, the WHO and ISN/RPS 2003 classification aims to enhance the quality of communication among renal pathologists and clinical nephrologists regarding pathologic findings in lupus nephritis.[6,12] In this study, the mean age of the study patients was 25.26 years (SD=±5.92) which was similar to most other studies.[6,13,14] 90% of the study patients were female whereas only 3 (10%) patients were male among the 30 subjects. This distribution is also similar to other studies.[13] This study clearly documents that class-IV lupus nephritis (43.3%) was the most common class according to WHO and ISN/RPS 2003 classification in patients at Rajshahi Medical College Hospital. Second most common class was class-III (30%). It was also revealed that class-I and class-VI lupus nephritis were the least happened class among the study subjects (3.3% each). This finding is consistent with findings of Nezhad

and Sepaskhah[15] where they found Class I: 2 (1.15%) patients, class II: 27 (15.6%) patients, class III: 22 (12.7%) patients, class IV: 97 (56%) patients, class V: 24 (13.8%) patients, and class VI: 1 (0.57%) patient. Williams[16] in Jamaica and Yacoyama[17] in Japan also reported similar findings as depicted in most of the other studies.[18,19,20] Parichatikanond et al[21] also found Class-IV lupus nephritis as the most predominant lesion which was 58.6% among their study patients. Al-Zahranit and Qayyume[22] also showed Class-IV lupus nephritis as the most predominant class in their study. Qario[23] also found class-IV disease in 72.4% cases. You et al[24] reported the number of patient group by pathologic classification was 4 cases for class II, 15 cases for class III, 30 cases for class IV and 15 cases for class V among the 67 cases they studied. Okpechi et al[25] commented on their paper that in South African community the ISN/RPS class III and IV LN occurred more frequently than other classes of LN and were seen in 20.7% respectively. Nevertheless, Apple[26] in Baltimore and Cameron[27] reported the class II & III were more frequent than other classes. So findings in the present study regarding the pattern of histopathological changes followed the global trend.

Conclusion

The present study was done on a small number of samples so it is difficult to reach a definite conclusion. Still the study revealed that class IV lupus nephritis are the most common pattern in our patients that follow the same global trend as in other parts of the world.

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