Original Article

Burden of Seronegative Lupus Nephritis in a Tertiary Care Hospital

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ABSTRACT

Objective: The aim of our study was to determine the frequency of sero-negative lupus nephritis at a tertiary care Hospital at Karachi.

Study Design: Retrospective / cross sectional study

Place and Duration of Study: This study was conducted at the Department of Nephrology Liaquat National Hospital & Medical College, Karachi from January 2013 to December 2017.

Materials and Methods: This single center, non probability consecutive, cross sectional study was conducted from January2013toDecember 2017. After taking informed written consent, detailed history was taken, clinical examination was done and ANA and antids DNA were sent to check the outcome i-e seronegative lupus nephritis. All the collected information was entered in the prescribed Performa.

Results: Total of 20 patients with sign & symptoms of lupus nephritis were included. Four patients (20%) were males & 16 (80%) were females with the mean age was 31.800±10.471 years. Seronegative lupus nephritis was noted in 5 patients (25%).

Conclusion: In summary, seronegative lupus nephritis was observed in a quarter of patients (25%), thus balancing the absence of SLE-related serologies against a high probability of ANA-negative or seronegative LN pre-testing. When strongly suspected, the patient with close monitoring should be treated promptly.

Key Words: Systemic lupus erythematous, lupus nephritis, anti-nuclear antibody.

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INTRODUCTION

Involvement of renal system in systemic lupus erythematous (SLE), also known as lupus nephritis (LN), is a fairly common and fatal condition, approximately 90% of SLE patients developing pathological, often irreversible, impairment of renal function[1-3]. One-hundred and 400 per100, 000 Caucasian and African-American women, respectively, develop SLE annually with the recorded 10-152 women to men ratio. Around 23% and 60% of SLE patients can develop clinically diagnosed LN early in the course of the disease. Usually this complication occurs within the first 3 years of SLE diagnosis, depending on the duration of the follow-up and the patient's ethnicity.[2,4,5]. Lupus nephritis (LN) is a grievous and frequent complication of systemic lupus erythematous (SLE) predisposing to serious morbidity and death.[6]The prevalence of SLE and the chances of developing lupus nephritis (LN) vary considerably between different regions of the world and different races and ethnicities.[7,8]

Known classifications of LN and non-immune complex disease, including thrombotic microangiopathy, podocytopathy, and tubulointerstitial disease, are the two main types of renal injury identified in renal pathology. Immunofluorescence (IF) is characteristic of 3 groups of immunoglobulin (IgG, IgM, IgA) and 8-10 classic and alternative pathway of compliment deposits (C3, C4, C1q). Due to the widespread potential derangements, biopsy of kidney is important to the clinical diagnosis, as the pattern of LN injury that has been identified often dictates the course and prognosis of treatment.[2,9,10]

ANA-negative LN may be encountered in clinical practice. Therefore a high suspicion index should be present if the diagnosis is supported by clinical and pathological findings.

MATERIALS AND METHODS

This single center, Non probability consecutive, retrospective, cross sectional study was conducted at the Department of Nephrology Liaquat National Hospital & Medical College, Karachi from January 2013 to December 2017. Study population in the inclusion criteria was either gender, with 18 to 60 years

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Of age, who presented with sign & symptoms of lupus nephritis.

Patients who met the inclusion criteria attended department of nephrology, liaquat national hospital and medical college were enrolled in the study. Prior to inclusion patients were explained about benefits of the study written consent was taken. The approval from the institutional ethical committee was taken prior to commencement of study. Brief history regarding the sign and symptoms duration of disease and clinical examination was done. ANA and antids DNA was sent in all these patients to the institutional laboratory and renal biopsy was done, if renal biopsy was positive and ANA was negative with ACR criteria positive was labeled as seronegative lupus nephritis. Patients with sepsis (assessed by history, clinically and CT scan), malignancy (assessed by history, clinically and CT scan) and ` patients with any contraindication to renal biopsy were excluded.

Principal investigator recorded all clinical history demography on a Performa that was already designed, informed on paper consent was taken before enrollment. An exclusion criterion was firmly followed to avoid confounding variables**.**

RESULTS

A total of 20 patients with sign & symptoms of lupus nephritis were selected to conduct this study. The mean age was 31.800±10.471 years. The descriptive statistics of age is presented in Table-1. The frequency distribution of age is presented in graph-I. Four patients (20%) were males & 16 patients (80%) were females (as shown in Table-1).

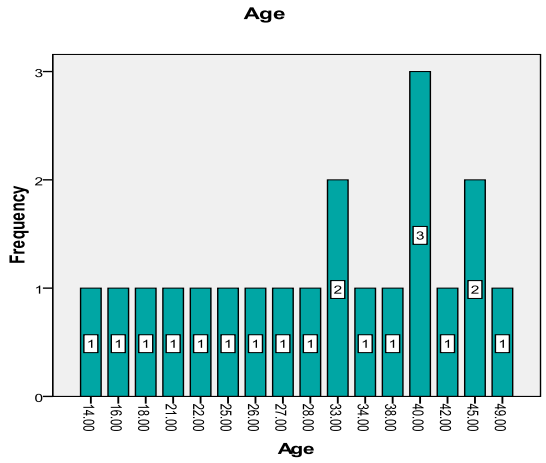

Figure No.1 Frequency distribution of Age (years)

The mean duration of sign & symptoms of SLE was 2.675±1.150 months. The descriptive statistics of duration of sign & symptoms of SLE is presented in Table-2. The frequency distribution of sign & symptoms of SLE is presented in graph-2.

Table No.1: Frequency Distribution of Age, Sex, Ana, Antidsdna, Lupus Nephritis on Renal Biopsy, Seronegative Lupus Nephritis, Protein urea, C3, C4, Haematuria, Dysmorphic Rbcs and Ana with Jo-1

	Characteristics	Frequency	Percentage
	14-20	3	15
	21-26	3	15
Age (years)	27-35	6	30
	36-49	40	40
Sex	Male	4	20
	Female	16	80
	Negative	6	30
ANA	Positive	14	70
AntidsDNA	Negative	12	60
	Positive	8	40
	I	1	5
	II	2	10
Lupus Nephritis on renal biopsy	III	3	15
	IV	12	60
	V	2	10
Seronegative lupus	No	15	75
nephritis	Yes	5	25
Proteinurea	Negative	17	85
	Positive	3	15
C3	Low Normal	9 11	45 55
	Low	8	40
C4	Normal	12	60
Ana With Jo-1	Negative	20	100
	Positive	0	0

The mean serum creatnine level was 2.290±0.865 mg/dl. The descriptive statistics of serum creatnine level is presented in Table-2.

ANA was negative in 6 patients (30%), while antids DNA was negative in 12 patients (60%), as shown in Table-1. The study outcome seronegative lupus nephritis was noted in 5 patients (25%), as shown in Table-1 The stage of lupus nephritis on renal biopsy was I in one patients (5%), II in 2 (10%), III in 3 (15%), IV in 12 (60%) & V in 2 (10%), as shown in Table-1

Table No.2: Descriptive statistics of Age, Sex, and Duration of sign & symptoms of SLE and Serum creatnine level

Variable	Min.	Max.	Mean	Standard Deviation
Age	14	49	31.800	10.471
Duration of sign & symptoms of SLE	1	5	2.675	1.150
Serum creatnine level	0.80	4.10	2.290	0.865

Table No. 3: Seronegative Lupus nephritis according to age, gender, Duration of sign & symptoms of SLE and Serum creatnine level (n=20)

Age Years	Seronegative lupus nephritis		Total	P-value
	No	Yes		
14-20	3(15%)	0	3(15%)	0.353
21-26	2(10%)	1(5%)	3(15%)	
27-35	3(15%)	1(5%)	4(20%)	
36-49	7(35%)	3(15%)	10(50%)	
Total	15(75%)	5(25%)	20(100%)	
Gender	**Seronegative lupus nephritis**		**Total**	**P-value**
	No	**Yes**		
Male	4(20%)	0	4(20%)	0.197
Female	11(55%)	5(25%)	16(80%)	
Total	15(75%)	5(25%)	20(100%)	
Duration of sign & symptoms of SLE	**Seronegative lupus nephritis**			**P-value**
	No	**Yes**		
1-2	8(40%)	1(5%)	9(45%)	0.125
3-5	7(35%)	4(20%)	11(55%)	
Total	15(75%)	5(25%)	20(100%)	
Serum creatnine level	**Seronegative lupus nephritis**			**P-value**
	No	**Yes**		
08-2.3	8(40%)	3(15%)	11(55%)	0.528
2.4-4.10	7(35%)	2(10%)	9(45%)	
Total	15(75%)	5(25%)	20(100%)	

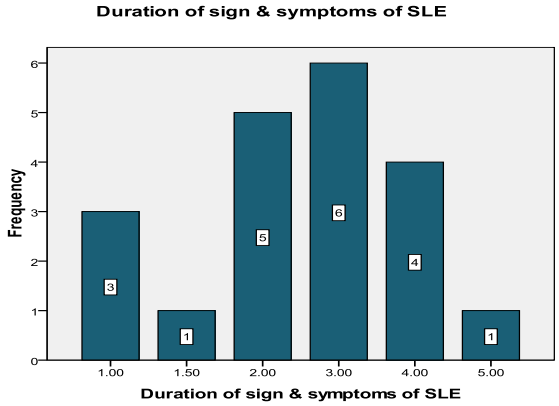

Figure No.2: Frequency distribution of duration of sign & symptoms of SLE (months)

ANA with Jo-1 was negative in all the patients, as shown in Table-1.

No significant association of seronegative lupus nephritis was noted with age, gender, duration of sign & symptoms of SLE with P-value of 0.353, 0.197, 0.125 & 0.528 respectively. As shown in Table-3

DISCUSSION

LN is a critical and common complication of SLE that, if left untreated, can cause major morbidity and mortality[2]. Seronegative and ANA-negative cases of LN pose a major challenge for rapid diagnosis and treatment[11]. Our review of the literature showed that LN could present without positive SLE serologies in the immediate follow-up period and could or could not convert to positive ones. In determining the diagnosis of LN, one must not depend on serologies or ACR or SLICC classification criteria. Recognizing the variable presentation of LN is important for prompt treatment, noting that some patients may develop serological manifestations of SLE years after the onset of LN.

LN is highly dependent on systemic autoimmunity development. A multitude of genetic variants and environmental triggers determine the degree of immunological dysregulation so that each LN patient may have a unique genetic predisposition that dictates the onset and clinical appearance of the disease.[12]

World Health Organization and the International Society of Nephrology / Renal Pathology Society (ISN / RPS) have classified LN's histopathological characteristics[13]. Immunofluorescence supports a diagnosis of LN by finding a "full-house" pattern of staining (IgG, IgA, IgM, C1q, and C3). Electron microscopy reveals a mixture of different types of mesangial, sub endothelial and/or sub epithelial deposits. TRIs typically occur in the cytoplasm of the endothelial cell.

Increased ANA and anti-dsDNA antibody levels and low serum compliments are the hallmark lupus laboratory tests that yield a combined SLE diagnostic sensitivity of more than 90 percent[13,14]. Autoantibodies usually occur many years before SLE is diagnosed, and the existence of autoantibodies in SLE patients usually follows a specific path with a gradual accumulation of common autoantibodies before the onset of SLE, whilst patients are asymptomatic.[14,15].

While identification of serum autoantibodies is regarded to be a hallmark of SLE clinical diagnosis, Autoantibodies to classic lupus antigens have been shown to be neither necessary nor sufficient for end-organ damage. It has been reported that patients with SLE and negative autoantibodies do not exclude SLE due to lack of positive serologies[16].

Certain possible explanations for negative serology may be related to laboratory techniques in full-house "lupus-like" nephritis. It may be a cause for ANA and/or autoantibodies levels too low to be detected through conventional laboratory testing. Some patients may need a longer follow-up period to detect lupus antibodies. Additional possibilities are the development of autoantibodies other than those often tested, or ANAs becoming trapped in circulating immune complexes.

In our study, the prevalence of seronegative lupus nephritis was 25 percent, relative to one previous cohort study of patients with existing clinical and pathological proof of LN with absence of serology, and 40 percent were in the pediatric population at last follow-up (age range 22 months-4 years). Others suggested that other disease mechanisms presenting as full-house nephropathy on renal biopsy should be considered in individuals with seronegative LN and absent extra-renal manifestations. These include IgA, post-infectious GN, idiopathic membranes, C1q and membranoproliferative GN[17]. Further diagnostic testing may be necessary for these patients to assist with clinical diagnosis. Finally, the only predictor of a diagnosis other than LN may be the response to treatment.

Baskin et al[18] noted a 10-year-old woman with decreasing kidney function and renal biopsy demonstrating "full-house" nephropathy with negative serologies (complement levels, autoantibodies, and ANCA) that also lacked clinical signs and symptoms of SLE.

Huerta et al[19] noted 4 female adult patients with renal biopsy showing highly suggestive IgG-dominant immune-complex-mediated GN with variable IgA, IgM, C3 andC1q co-deposits of LN, however without extra renal manifestations or SLE serologies at the time of biopsy or over 3 years of follow-up.

Caltik et al[7] recorded a 13-year-old boy who was revealed to have pretibial edema, arthritis, and petechia on bilateral ankles. The boy had high levels of creatinine (1.65 mg / dL), hypocomplementemia, proteinuria of the nephritic range, hematuria, and pleural effusion. There were negative ANA, autoantibodies, and ANCA serologies.

Only 3 patients with renal and extra-renal manifestations and missing serologies for SLE[10,20] were identified in the literature. One of them was a pediatric patient, the other two were adults.

With the advent of new clinical approaches to SLE treatment, 5-year survival rates have risen from 44% in the 1950s to at least 95% in the 2000s[21]. 17% of those diagnosed since Class IV LN were alive at the 5-year mark in the 1950s compared to 90-95% in the 2000s. However, the incidence of LN and subsequent ESRD has not changed significantly, and there has been no significant change in the degree of renal remission in current established treatment approaches. Considering that LN rehabilitation trials only recruited patients with clinical SLE diagnosis based on ACR guidelines, it is therefore extremely challenging to handle patients with LN and incomplete SLE diagnosis. For this reason, prompt detection of LN and maintaining a high level of suspicion for LN in patients without positive SLE serologies is of paramount importance to ensure early treatment and appropriate monitoring and follow-up**.**

CONCLUSION

In conclusion the seronegative lupus nephritis was found in quarter of patients (25%) so the absence of SLE-related serologies should be weighed against a high pre-test probability of ANA-negative or seronegative LN. If highly suspected, the patient should be treated promptly with close monitoring**.**

Author's Contribution:

Concept & Design of Study:	Farzana Adnan
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Revisiting Critically:	Farzana Adnan, Mehwish Qamar
Final Approval of version:	Farzana Adnan

Conflict of Interest: The study has no conflict of interest to declare by any author.

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