ISSN 2394–806X (Print), ISSN 2454-5139 (Electronic)
IJHRMLP, Vol: 06 No: 01, January, 2020
Printed in India

ORIGINAL RESEARCH PAPER

Clinicopathological presentation of treatment naive crescentic v/s non-crescentic lupus nephritis patients

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Received on October 31, 2019; editorial approval on December 15, 2019

ABSTRACT

Introduction*: Renal biopsies play an important role in the diagnosis, management and prognosis of patients with lupus nephritis (LN). This paucity of knowledge in this particular area prompted us to undertake this retrospective analysis of clinicopathological presentation of biopsy-proven LN.* ***Materials and methods****: Biopsy proven (n=120) treatment naive LN class IV patients from March 2007 to August 2018 were included. Out of these, 85 were class IV non-crescentic and 35 were class IV crescentic lupus nephritis patients. Clinical and histopathological data were studied retrospectively.* ***Results****: Patients with crescentic LN presented with significantly more severe disease (anemia, renal failure, higher serum creatinine level and hypertension and hematuria) as compared to the non-crescentic group ($p < 0.05$). Mean scores of activity index and chronicity index in crescentic LN patients were significantly higher ($p < 0.001$ and 0.014 respectively), and not crescent but near about all parameters (except glomerular sclerosis, $p = 0.61$ and subendothelial immune deposition, $p = 0.52$) of these scores were significantly higher in the crescentic group. The average intensity of IgG, IgA, IgM, and C3 was lower and average intensity of C1q was higher in the crescentic group. But only the difference in IgA reached statistical significance.* ***Conclusion****: In our study, crescentic LN patients had lower hemoglobin levels, with more hematuria and hypertensive patients and also had higher Activity Index and Chronicity Index compared to non-crescentic LN. Not only crescent but, near about all parameters of these scores were significantly higher in crescentic group. The average intensity of IgA was significantly higher in non- crescentic group in IF study.*

Keywords*: Activity index; histopathology; chronicity index; glomerulonephritis.*

INTRODUCTION

Crescentic Glomerulonephritis (GN) is a light microscopic feature of severe injury of glomeruli, that can be caused by many different etiologies, and is not a disease per se. However, different crescentic glomerular diseases have different clinical presentation and outcome. Crescentic Post-streptococcal Glomerulonephritis (PSGN) has a relatively better prognosis than Lupus Nephritis (LN).

Initially, the term 'Lupus' was first used by the Romans for ulcerative lesions of skin in patients of Systemic lupus erythematosus (SLE), with a resemblance to wolf bite.

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Cite this article as: *Doley PK, Alam Shahzad, Sharma Manjuri, Mahanta PJ, Awasthi Shahtakshi, Jain Priyanka. Clinicopathological presentation of treatment naive crescentic v/s non- crescentic lupus nephritis patients. Int J Health Res Medico Leg Prae 2020 January;6(1):14-18. DOI 10.31741/ijhrmlp.v6.i1.2020.3*

(Lupus, a Latin term, means wolf). William Osler has first mentioned nephritis as a part of SLE disease activity.[1] Systemic lupus erythematosus (SLE) is an autoimmune disease.[2] In the SLE population, 40 to 70% of the patients develop lupus nephritis (LN) in their clinical course.[3]

Notwithstanding the advancement in therapy for lupus, conversion rate to end stage renal disease has remained 10% in 5 to 10 years, that has unfortunately remained unchanged over the last 3 decades.[4,5]

The prevalence rate of lupus nephritis in SLE patients was 5 to 10 times higher in Indo-Asians (Asians of Indian subcontinent) in comparison with the rate in the white population,[6] although long standing prognosis are similar in both the population.[7] So, race is also an important factor to predict severity and outcome in LN.

Presently, only few studies are available which throw light on the exact effect of presence of crescents on clinicopathological spectrum in lupus nephritis patients in Indian population.

This is a retrospective observational study done with aims to understand the nature and behavior of this non-conquered disease from Roman era, in Indian population, in terms of presence versus absence of crescents.

The study aims to determine the relative clinicopathological spectrum of crescentic v/s non-crescentic treatment naive Lupus Nephritis patient.

Materials and Methods

Inclusion Criteria: 1. Informed consent 2. ≥18 years of age. 3. Not taken any conventional disease (SLE/LN) specific immunosuppressive therapy in past. 4. Diagnosis of ISN/RPS Class IV lupus nephritis (LN). 5. >10 glomeruli in renal biopsy and biopsy was done with in 1st week of admission

Exclusion Criteria: 1. Significant or uncontrolled medical disease in any organ system not related to SLE or LN. 2. Concomitant chronic conditions, excluding SLE (eg, Asthma, Crohn's disease) that require immunosuppressives 3. History of renal transplant. 4. Known HIV, Hep B or C infection.

The clinico-pathological archives of 120 adult patients with renal biopsy-proven International Society of Nephrology (ISN/RPS) class IV-G, treatment naive LN, diagnosed between March 2007 to August 2018 in department of Nephrology, Gauhati Medical College, Assam were reviewed.

Clinical and histopathological data at the time of presentation were studied retrospectively and divided into two groups: Group a - Crescentic lupus nephritis group, n=35 (≥50% crescents) and Group b - Non crescentic lupus nephritis group, n=85 (<50% crescents).

Pathologist, with knowledge of patient's clinical course, reported the pathological features. A crescent is defined as either proliferating extracapillary lesions occupying >25% of the Bowman's capsular circumference.[8] Diffuse global lupus nephritis (class IV-G) was defined as more than 50% of glomeruli display endocapillary or extracapillary glomerulonephritis. In this class, patients with crescentic glomerulonephritis, defined as more than 50% of glomeruli, had crescent formation on light microscopy, and always presented with rapidly progressive glomerulonephritis clinically. Crescents should be composed of more than 2 cell layers in order to distinguish them from apposition of the single layers of hypertrophied visceral and parietal cells.[9]

The renal biopsy specimens were examined under light microscopy, direct immunofluorescence techniques. Renal biopsy specimens were fixed in 4.5% buffered formaldehyde for light microscopy. Consecutive 3-mm serial sections were used for histological staining. Stains employed included hematoxylin and eosin, silver methenamine, periodic acid-Schiff and Masson's trichrome. Pathological parameters such as activity indexes and CI were approached by renal pathologists using a modification of an earlier reported system involving semi-quantitative scoring of specific biopsy findings.[8,10]

Direct immunofluorescence examination- The immunofluorescence for deposition of immunoglobulin IgG, IgA, IgM, C3 and C1q, was semi-quantitatively graded from 0 to 4+ according to the intensity of fluorescence. Intensity of staining was scored as negative (0), mild (1+), moderate (2+), strong (3+), or very strong (4+).

The patients fulfilled the American College of Rheumatology revised criteria for SLE,1997.[11] The disease activity was assessed by the SLE Disease Activity Index (SLEDAI).[12]

The detailed clinical data of patients were retrospectively analyzed. Informed consent was obtained for blood sampling and renal biopsy from each patient. Baseline clinical examination included serum anti-dsDNA antibodies, hemoglobin, white blood cell count, red blood cell count, platelet count, serum albumin, serum creatinine (SCr), C3, and C4, urine routine microscopy and 24-h urine protein.

Statistical Analysis

Quantitative data were expressed as mean ± SD, and median (interquartile range). Differences of numerical data with normal distribution were tested by Student t test. Categorical data were interpreted in the form of constituent ratio and percentage, and compared by chi-square test. Statistical significance was considered as $p<0.05$.

RESULTS

Among the 340 patients diagnosed with lupus nephritis during March 2007 to August 2018 in Department of Nephrology, GMC, Guwahati, Assam, 120 cases were reclassified as class IV treatment naive patients. In total, 35 of this 120 patients (29.17%) also fulfilled the diagnosis of

crescentic glomerulonephritis. In patients with crescentic glomerulonephritis, 26 (74.29%) were female and 9 (25.71%) were male with an average age of 22.42 ± 4.3 years at presentation. The mean value of serum creatinine was 3.74 ± 2.68 mg/dl (range 1.7–11.4 mg/dl) on diagnosis. In non-crescentic glomerulonephritis group, 69(81.18%) were female and 16(18.82%) were male with an average age of 21.97 ± 4.74 years at presentation ,and mean value of serum creatinine was 2.33 ± 0.753 mg/dl) on diagnosis (**Table 1**).

Table 1 Comparisons of baseline clinical and laboratory variable

Clinical Parameter	CGN	NCGN	p-value
No. of patients	35	85	
Gender (M/F)	9/26	16/69	
Age (in years, mean±SD)	22.42 ± 4.3	21.97 ± 4.74	0.812
Anemia(n, %)	35 (100)	67 (78.82)	0.001
Renal Dysfunction (n, %)	27 (81.1)	41 (48.23)	0.001
Hb(gm%)	8.5 ± 1.287	11.14 ± 1.728	0.002
S.Creatinine (mg/dl)	3.74 ± 0..594	2.33 ± 0.753	0.017
24 Hrs Urine protein (gm/day)	3.0 ± 0.594	2.58 ± 0.822	0.006
Hypertention (n, %)	32 (91)	39 (45.88)	<0.001
SBP (in mm Hg,mean)	163.26 ± 13.565	140.54 ± 16.378	0.003
DBP(in mm Hg, mean)	94.51 ± 7.660	85.34 ± 7.530	<0.001
Microscopic Hematuria(n, %)	26 (74)	48 (56.47)	0.006
Serum albumin (gm/dl)	2.20 ± 0.390	2.29 ± 0.618	0.417
Nephrotic syndrome (n, %)	27 (77.14)	62 (72.9)	0.4
Positive ANA	35 (100)	82 (97)	0.35
Positive anti ds DNA	34 (97)	76 (90)	0.16

There was a significantly higher proportion of hypertension (p = 0.002) in the crescentic group. The patients with crescentic LN had significantly higher mean systolic and diastolic blood pressure when compared to patients with non-crescentic LN (163 vs 140 mmHg; p = 0.003 and 94 vs 85 mmHg; p = 0.001 respectively respectively). The proportion of patients showing hypertension (91% vs 45.88%; p = 0.002), haematuria (n = 26, 74% vs n = 48, 56.47%; p = 0.006), renal dysfunction (81.1% vs 48.23%; p = 0.001), and anemia (100% vs 78.82%; p = 0.001) was significantly higher in crescentic LN group that non-crescentic LN group. Significantly decreased mean Hb levels (8.5 ± 1.287 vs 11.14 ± 1.728 g/dL; p = 0.001) and significantly increased mean urine protein (3.1 vs 2.57 g/day; p = 0.006) and mean serum creatinine (3.74 vs 2.33 mg/dL; p = 0.003) levels were observed in patients with crescentic LN than non-crescentic LN (**Table 1**).

Percentage of nephrotic syndrome (77.14% vs 72.9%; p=0.4) were comparable between patients of crescentic LN and non-crescentic LN groups. No significant difference was seen in the mean serum albumin levels between patients of both the groups (2.2 vs 2.29 g/dL; p = 0.428) The difference in presence of ANA (100% vs 97%; p = 0.76) and Anti dsDNA (97% vs 90%; p = 0.87) in serum were not clinically significant (**Table 1**).

In light microscopy study, mean scores of activity index and chronicity index in crescentic LN patients were significantly higher (p < 0.001 and 0.014 respectively), and not only crescent but near about all parameters (except glomerular sclerosis, p = 0.61 and subendothelial immune deposition, p = 0.052) of these scores were significantly higher in crescentic group (**Table 2**).

Table 2 Light microscopy and Immunofluorescence parameters

Light Microscopy	CGN	NCGN	p-value
No. of biopsies	**35**	**85**	
No. of glomeruli	19 ± 2.81	18.88 ± 2.826	
% of sub-class A	18	21	
% of sub-class A/C	56	62	
% of sub-class C	26	17	
AI score	12.37 ± 0.94	6.82 ± 1.356	0.001
Cellular crescents	6 ± 0	1.2 ± 0.986	0.001
Karyorrhexis/fibrinoid necrosis	1.54 ± 0.67	1.21 ± 0.411	0.0013
Interstitial inflammation	1.61 ± 0.47	1.39 ± 0.49	0.038
Glomerular leukocyte	1.77 ± 0.426	1.61 ± 0.49	0.04
Endocapillary hypercellularity	1.8 ± 0.40	1.39 ± 0.49	0.01
Subendothelial hyaline deposits	1.64 ± 0.44	1.41 ± 0.495	0.052
CI score	4.4 ± 1.16	3.98 ± 0.899	0.014
Fibrous crescents	2.45 ± 0.64	0.6 ± 0.49	0.001
Tubular atrophy	1.31 ± 0.42	1.1 ± 0.34	0.038
Interstitial fibrosis	1.0 ± 0.68	0.78 ± 0.49	0.041
Glomerular sclerosis	1.31 ± 0.47	1.38 ± 0.85	0.61
Immunofluorescence parameters			
Number of biopsies	**35**	**85**	
Ig G	1.26 ± 0.41	1.38 ± 0.41	0.81
Ig M	1.3 ± 0.49	1.43 ± 0.36	0.63
Ig A	1.13 ± 0.63	1.54 ± 0.49	0.013
C1 q	1.17 ± 0.38	1.16 ± 0.43	0.77
C3	1.92 ± 0.79	2.1 ± 0.68	0.36

In light microscopy, the average activity index were 12.37

± 0.94 vs 6.82 ± 1.356 ($p < 0.001$), and average chronicity index was 4.4 ± 1.16 vs 3.98 ± 0.899 ($p < 0.014$). In semi-quantitative scale average cellular crescent score was 6±0 vs 1.2 ± 0.986 ($p < 0.001$); average karyorrhexis/ fibrinoid necrosis score was 1. 54 ± 0.67 vs 1.21 ± 0.21 ($p = 0.0013$); average interstitial inflammation score was 1.61 ± 0.47 vs1.39 ± 0.49 ($p= 0.038$); glomerular leukocytosis score was 1.77 ± 0.426 vs 1.61 ± 0.49 ($p = 0.04$); average endocapillary hypercellularity score was 1.8 ± 0.40 vs 1.39±0.49 ($p=0.01$) and average subendothelial immune deposition score was 1.64 ± 0.4 vs 1.41 ± 0.495 ($p = 0.052$) (**Table 2**).

In chronicity index: In semi-quantitative scale average fibrous crescent score was 2.45 ± 0.64 vs 0.6 ± 0.49 ($p<0.001$); and average tubular atrophy score was 1.31 ± 0.42 vs 1.1 ± 0.34 ($p=0.038$); average interstitial fibrosis score was 1.0 ± 0.68 vs 0.78 ± 0.49, ($p = 0.04$) and average glomerular sclerosis score was 1.31 ± 0.47 vs 1.38 ± 0.85 ($p=0.61$) in crescentic verses non-crescentic group respectively (**Table 2**).

On evaluation of immunofluorescence parameters, there was no significant difference in the locations of immunoglobulin deposition between the two groups. However, the average intensity of IgG, IgA, IgM, and C3 and was lower in patients with crescentic glomerulonephritis in immunofluorescence study and average intensity of C1q was higher in crescentic group. The difference in IgA was onlyreached statistical significance in these finding (**Table 2**).

DISCUSSION

Renal involvement is not very uncommon in SLE and there are a number of different pathological phenotypes of lupus nephritis. Although crescent formation is common in lupus nephritis especially in the background of proliferative glomerular lesions, the ratio of 'true' crescentic glomerulonephritis in lupus nephritis is not clear and the pathogenesis remains inconclusive.

In the literature, Sumethkul V et al. showed that lupus nephritis with crescentic glomerulonephritis accounted for 51.6% of all patients with biopsy-proven various crescentic glomerulonephritis.[13]

Therefore, lupus nephritis with crescentic glomerulonephritis should be paid more attention. In our study, comparison with lupus nephritis class IV-G without crescentic glomerulonephritis, crescentic group had more severe disease with higher creatinine levels and lower hemoglobin levels, with more hematuria and with more hypertensive patients.

In histopathological analysis of our study, crescentic group had higher mean Activity Index and mean Chronicity Index compare to non-crescentic LN. Not only crescent but, near about all parameters (except glomerular sclerosis and subendothelial immune deposition) of these scores were significantly higher on semi quantitative scale in crescentic group compare to non-crescentic LN. In Zhang W et al[14]. study 51.5% patients demonstrating crescents at biopsy, and had more severe baseline status: more proteinuria, more severe microscopic hematuria, lower estimated eGFR, and higher pathological scores for both activity index (AI) and chronicity index (CIn) (all $p < 0.001$, respectively).

It was not surprising that patients with crescentic glomerulonephritis had a significantly higher more severe disease with higher creatinine levels and lower hemoglobin levels, more hematuria and with more hypertensive patients, because of the presence of rapidly progressive glomerulonephritis clinically in our study.

More interestingly, we found that the average intensity of IgG, IgA, IgM, and C3 and was lower in patients with crescentic glomerulonephritis in immunofluorescence study and average intensity of C1q was higher in crescentic group. The difference in IgA only reached statistical significance.

These results suggested that both acute and chronic lesions in renal biopsy were more prominent in patients with crescentic glomerulonephritis.

A study by Fung et al[15]. showed significantly increased AI and CI scores in patients of crescentic LN group. Fung et al[15]. also reported significantly lower intensity of IgA and higher score for interstitial inflammation, which corroborates with the present study findings. However, the insignificantly lower score of karyorrhexis/fibrinoid necrosis, glomerular leukocyte and endocapillary hypercellularity in crescentic LN patients in their study contradicts with the present study results. They also reported significantly lower average intensity of IgA, IgM and C1 q in patients with crescentic LN.

The main limitations of the present study were retrospective approach and single center study design. The time of presentation to renal biopsy was not considered. Further, effect of treatment and long term follow up was not considered.

CONCLUSION

In North-East Indian population, crescentic LN patients had more severe disease with higher creatinine levels, more nephrotic syndrome and lower hemoglobin levels, with more hematuria and hypertension. In histopathological study this group had higher Activity Index and Chronicity Index compare to non-crescentic LN. Not only crescent but, near about all parameters (except glomerular sclerosis and subendothelial immune deposition) of these scores were significantly higher in crescentic group compare to non-crescentic LN. The average intensity of IgA was significantly

higher in non-crescentic group in IF study.

Disclosure: This work has not been published elsewhere. The paper has been read and approved by all the authors. All the authors declared no competing interest

REFERENCES

1. Golbus J, McCune WJ. Lupus nephritis. Classification, prognosis, immunopathogenesis, and treatment. Rheumatic diseases clinics of North America 1994 Feb;20(1):213-42.
2. Lorenz G, Desai J, Anders HJ. Lupus nephritis: update on mechanisms of systemic autoimmunity and kidney immunopathology. Current opinion in nephrology and hypertension 2014 May 1;23(3):211-7.
3. Coplon NS, Diskin CJ, Petersen J, Swenson RS. The long-term clinical course of systemic lupus erythematosus in end-stage renal disease. New England Journal of Medicine 1983 Jan 27;308(4):186-90.
4. Croca SC, Rodrigues T, Isenberg DA. Assessment of a lupus nephritis cohort over a 30-year period. Rheumatology 2011 Mar 16;50(8):1424-30.
5. Ward MM. Changes in the incidence of end-stage renal disease due to lupus nephritis, 1982-1995. Archives of internal medicine 2000 Nov 13;160(20):3136-40.
6. Seligman VA, Lum RF, Olson JL, Li H, Criswell LA. Demographic differences in the development of lupus nephritis: a retrospective analysis. The American J of medicine 2002 Jun 15;112(9):726-9.
7. Chan TM, Tse KC, Tang CS, Lai KN, Li FK. Long-term outcome of patients with diffuse proliferative lupus nephritis treated with prednisolone and oral cyclophosphamide followed by azathioprine. Lupus 2005 Apr;14(4):265-72.
8. Austin III HA, Muenz LR, Joyce KM, Antonovych TT, Balow JE. Diffuse proliferative lupus nephritis: identification of specific pathologic features affecting renal outcome. Kidney international 1984 Apr 1;25(4):689-95.
9. Bajema IM, Wilhelmus S, Alpers CE, Bruijn JA, Colvin RB, Cook HTet al. Revision of the International Society of Nephrology/Renal Pathology Society classification for lupus nephritis: clarification of definitions, and modified National Institutes of Health activity and chronicity indices. Kidney international 2018 Apr 1;93(4):789-96.
10. Austin III HA, Boumpas DT, Vaughan EM, Balow JE. Predicting renal outcomes in severe lupus nephritis: contributions of clinical and histologic data. Kidney international 1994 Feb 1;45(2):544-50.
11. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis & Rheumatism: Official J of the American College of Rheumatology 1997 Sep;40(9):1725.
12. Bombardier C, Gladman DD, Urowitz MB, Caron D, Chang CH, Austin A et al. Derivation of the SLEDAI. A disease activity index for lupus patients. Arthritis & Rheumatism: Official J of the American College of Rheumatology 1992 Jun;35(6):630-40.
13. Sumethkul V, Chalermsanyakorn P, Changsirikulchai S, Radinahamed P. Lupus nephritis: a challenging cause of rapidly progressive crescentic glomerulonephritis. Lupus 2000 Jul;9(6):424-8.
14. Zhang W, Yuan M, Hong L, Zhou Q, Chen W, Yang S et al. Clinical outcomes of lupus nephritis patients with different proportions of crescents. Lupus 2016 Dec;25(14):1532-41.
15. Yu F, Tan Y, Liu G, Wang SX, Zou WZ, Zhao MH. Clinicopathological characteristics and outcomes of patients with crescentic lupus nephritis. Kidney international 2009 Aug 1;76(3):307-17.