ORIGINAL RESEARCH PAPER

Volume-9 | Issue-5 | May-2020 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

# CLINICOPATHOLOGICAL CORRELATION OF INTRARENAL VASCULAR LESIONS IN PATIENTS WITH SEVERE LUPUS NEPHRITIS - SINGLE CENTRE EXPERIENCE

Nephrology

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## ABSTRACT

**Aim :** To study the clinicopathological correlation and outcome of intra renal vascular lesions in severe lupus nephritis **Methods :** A Prospective observational study was done in a tertiary care centre in South India over 15 months with biopsy proven severe lupus nephritis patients. **Results:** 55 patients are included in the study, of which class 3(20%), class 4(50.9%), class 5(5.5%), class 3+5(5.4%),and class 4+5(18.2%).Vascular lesions are found in 45% cases. Most common vascular lesions are arteriosclerosis & arteriolosclerosis (28%) , Lupus vasculitis (28%).Vascular lesions are common in ISN class 4 patients(isolated-64%, class 4+5-24%). Poor outcome was seen with TMA (100%) followed by lupus vasculitis (66.6%). Good outcome was seen with arteriosclerosis andarteriolosclerosis(100%). **Conclusion :** Vascular lesions are more commonly associated with class 4 lupus nephritis. Renal vascular lesions are associated with renal outcomes and prognosis in severe lupus nephritis.

## KEYWORDS

Renal vascular lesions, Systemic lupus eryhtematosus, ISN-RPS(International society of nephrology-Renal pathology society), TMA (Thrombotic microangiopathy).

## INTRODUCTION :

Lupus nephritis is an immune complex glomerulonephritis that is a common and serious feature of SLE. Lupus patients with LN have worse outcomes than those with no kidney involvement(1,2,3).In adult SLE patients, 60% will have renal involvement. The reported incidence of clinically important kidney disease in systemic lupus is about 38%(4).The incidence of kidney involvement differs with ethnicity. Caucasians (European, European Americans; 12–33%) are less likely to have LN than black (African American, Afro-Caribbean; 40–69%), Hispanic (36–61%), or Asian (Indian, Chinese; 47–53%) patients(5). Based on the United States Renal Data Service database, between 1996 and 2004 the incidence of ESRD attributed to LN in adults was 4.5 cases per million in the general population, but was greater in blacks (17–20/million) and Hispanics (6/million) than Caucasians (2.5/million).(6)The classification of lupus nephritis is based on glomerular involvement. The currently used classification is ISN-RPS(international society of nephrology – Renal pathology society)(7)

**Fig 1 :ISN RPS Classification**

| | |
|---|---|
| **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 IV-S (A) | Active lesions: diffuse segmental proliferative lupus nephritis |
| Class IV-G (A) | Active lesions: diffuse global proliferative lupus nephritis |
| Class IV-S (A/C) | Active and chronic lesions: diffuse segmental proliferative and sclerosing lupus nephritis |
| | Active and chronic lesions: diffuse global proliferative and sclerosing lupus nephritis |
| Class IV-S (C) | Chronic inactive lesions with scars: diffuse segmental sclerosing lupus nephritis |
| Class IV-G (C) | 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 |

## Vasular lesions in Lupus Nephritis :

Vascular lesions are commonly encountered in renal biopsy specimens from patients with SLE and may assume a variety of morphologic forms.

These include:

1. Arteriosclerosis and arteriolosclerosis
2. Uncomplicated vascular immune deposits
3. Noninflammatory necrotizing vasculopathy (so-called lupus vasculopathy)
4. Thrombotic microangiopathy
5. Necrotizing vasculitis (PAN type)

To accurately classify renal vascular lesions, vessels must be systematically examined by light, fluorescence, and electron microscopy.

Because the glomerular pathology is primary importance in the classification of lupus nephritis, the presence and significance of these vascular lesions are often overlooked. Although associations between RVLs and renal outcomes have been proposed , the literature is hampered by its largely retrospective nature, and it has been argued that, because no clear definitions exist for many of the described lesions, their prognostic significance is not well understood. The purpose of this study is to obtain histologic description of intra renal vascular lesions and study the clinicopathological correlation and outcomes in severe lupus nephritis patients.

**Materials And Methods :** It is prospective observational study done for period of 15 months. Patients with biopsy proven severe lupus nephritis were included in the study. Routine blood investigations, CUE , 24hr urine protein, urine c/s, GFR estimation, ANA, Anti ds DNA were done for this patients.

## RESULTS

A total of 55 patients are included in the study .Female to male ratio is 8.17:1.Female patients constituted almost 90% of total cases.

**Table 1-General descriptions of clinical and laboratory variables**

| Patient variable | Mean | Standard deviation |
|---|---|---|
| Age (yrs) | 27.25 | 10.27 |
| Systolic BP(mm of Hg) | 139.82 | 14.59 |
| Diastolic BP(mm of Hg) | 90.91 | 6.16 |
| Hemoglobin (gm/dl) | 8.6 | 1.3 |
| ESR (mm 1 st hour) | 66.44 | 33.05 |
| B .urea (mg/dl) | 40.36 | 24.17 |
| S.creatinine(mg/dl) | 1.6 | 1.1 |
| e GFR | 63.89 | 35.84 |
| 24 hr urinary protein(gm/day) | 2.5 | 1.7 |
| S albumin(gm/dl) | 2.6 | 0.7 |
| S.cholesterol(mg/dl) | 206.8 | 56.03 |

Mean age of presentation is 27.25+/- 10.27 with peak incidence in 2nd

and 3 rd decade. Mean systolic and diastolic BP were 139 and 90 respectively. Mean hemoglobin at the time of presentation was 8.6+/-1.3. Mean ESR was 66.44.Mean blood urea and creatinine were 40.36 and 1.6 respectively. Mean 24 hr urinary protein is 2.5 gm/day .Mean blood urea and creatinine were 40.36 and 1.6 mg/dl respectively.Mean e GFR was 63.89ml/min/1.73m2 at the time of presentation. Means of albumin and s.cholesterol were 2.6 mg/dl and 206.8

**Table 2 -ISN-RPS Classification**

| | Frequency | Percent |
|---|---|---|
| Class 3 | 11 | 20 |
| **Class 4** | **28** | **50.9** |
| Class 5 | 3 | 5.5 |
| Class 3+5 | 3 | 5.4 |
| Class 4+5 | 10 | 18.2 |
| Total | 55 | 100 |

Most common ISN/RPS type lesion is class 4 (50.9%) followed by class 3(20%).

**Table 3 - Renal dysfunction**

| e GFR | Frequency | Percentage |
|---|---|---|
| <60 | 30 | 54.54 |
| >60 | 25 | 45.45 |

About 54.54 % of patients presented with baseline e GFR below 60 ml/min/1.73 m2.

Renal dysfunction(e GFR<60) more commonly associated with class 4 ISN/RPS either isolated or in combination

**Table 4 -Distribution of study subjects based on Systolic blood pressure**

| Systolic Bp | Frequency | Percent |
|---|---|---|
| <140 | 32 | 58.2 |
| >140 | 23 | 41.8 |
| | 55 | 100 |

Around 42% patients presented with systolic blood pressure more than 140. Hypertension (systolic) more common among patients with class 4 lesion.

**Table 5 - Nephrotic syndrome presentation**

| 24 hr urinary protein | N | Percentage |
|---|---|---|
| <3.5 gm | 41 | 76.3 |
| >3.5 gm | 14 | 23.6 |
| | 55 | 100 |

Nephrotic range of proteinuria was presenting feature in 23.6% of patients.

**Table 6 - Clinical response**

| | Frequency | Percent |
|---|---|---|
| Complete response | 26 | 47.3 |
| Partial response | 17 | 30.9 |
| Death | 5 | 9.1 |
| No response | 7 | 12.7 |
| Total | 55 | 100 |

Of total 55 cases , 26 patients showed complete response, 17 showed partial response,5 patients died and 7 patients showed no response(dialysis dependence and dialysis non dependence) at the end of 8 months of followup. Clinical response were categorized into good response(complete and partial response) and bad response(no response and death).

**Table 7 - Variables and their correlation with clinical response**

| Variable | Good response | Bad response | P value |
|---|---|---|---|
| Systolic BP>140 | 14 | 9 | **<0.05** |
| Systolic BP<140 | 29 | 3 | |
| Diastolic BP>90 | 6 | 7 | **<0.05** |
| Diastolic BP <90 | 37 | 5 | |
| e GFR<60 | 19 | 11 | **<0.05** |
| e GFR >60 | 24 | 1 | |
| Anti dsDNA positive | 36 | 12 | >0.05 |
| Anti dsDNA negative | 7 | 0 | |
| ANA positive | 41 | 12 | >0.05 |
| ANA negative | 2 | 0 | |
| Low c3 | 32 | 11 | >0.05 |
| Normal c3 | 11 | 1 | |
| Low c4 | 35 | 12 | >0.05 |
| Normal c4 | 8 | 0 | |
| Activity index>7 | 2 | 11 | **<0.05** |
| Activity index <7 | 41 | 1 | |
| Chronicity index >3 | 0 | 1 | ---- |
| Chronicity index <3 | 30 | 24 | |
| 24 hr proteinuria>3.5 gm | 12 | 1 | >0.05 |
| 24 hr proteinuria<3.5 gm | 31 | 11 | |

Systolic blood pressure and diastolic blood pressure in the hypertensive range at the time of presentation is significantly correlated with clinical outcome.54.54% of patients presented with renal dysfunction at the time of admission .Patient presenting with renal dysfunction with e GFR <60 were significantly correlated with poor clinical outcome. Positivity of anti dsDNA and ANA positivity were not significantly correlated with clinical outcome. Low c3 and low c4 levels at the time of presentation has no effect on clinical outcome. Activity index more than 7 on renal biopsy is correlated with poor clinical outcome. Correlation of chronicity index could not be found out because of low sample size. Nephrotic range of proteinuria is not significantly correlated with clinical outcome.

**Table 8 - Clinical response (good v/s bad) in relation to vascular lesions**

| Clinical response | Vascular lesions absent | Vascular lesion present | P value |
|---|---|---|---|
| Bad response (no response/death) | 0 | 12 | <0.05(fisher's exact) |
| Good response(complete /partial response) | 30 | 13 | |
| Total | 30 | 25 | |

Presence of vascular lesion significantly correlated with clinical response at the end of followup.

**Table 9 - VASCULAR LESIONS**

| | Frequency | Percent |
|---|---|---|
| Arteriosclerosis and arteriolosclerosis | 7 | 12.7% |
| Lupus vasculitis | 6 | 10.9% |
| Lupus vasculitis +TMA | 1 | 1.8% |
| Lupus vasculopathy (LV) | 3 | 5.4% |
| TMA | 6 | 10.9% |
| Uncomplicated vascular immune deposits (UVID) | 2 | 3.6% |
| No lesions | 30 | 54.5% |
| Total | 55 | 100 |

Vascular lesions were found in 25 patients of which most common lesion being arterial sclerosis and arteriolar hyalinosis.(28%) and lupus vasculitis(either isolated or in combination) (28%).

**Table 10 - Vascular lesions and their correlation with clinical and laboratory variables**

| | Categorization | vascular lesions absent | Vascular lesions present | P value |
|---|---|---|---|---|
| Systolic BP | <140 | 21 | 11 | **<0.05*** |
| | >140 | 9 | 14 | |
| e GFR | <60 | 7 | 23 | **<0.05*** |
| | >60 | 23 | 2 | |
| C3 | Low | 23 | 20 | >0.05 |
| | Normal | 7 | 5 | |
| C4 | Low | 23 | 24 | >0.05 |
| | Normal | 7 | 1 | |
| ANA | Negative | 1 | 1 | >0.05 |
| | Positive | 29 | 24 | |
| Anti ds DNA | Negative | 7 | 0 | >0.05 |
| | Positive | 23 | 25 | |
| Urinary protein | <3.5 | 21 | 21 | >0.05 |
| | >3.5 | 9 | 4 | |
| Activity index | <7 | 30 | 12 | **<0.05** |
| | >7 | 0 | 13 | |

| | | | | |
|---|---|---|---|---|
| Chronicity index | <3 | 30 | 24 | – |
| | >3 | 0 | 1 | |

* Significant

After applying univariate analysis Systolic BP , e GFR and activity index were found to correlated with vascular lesions which is statistically significant .Low c3 ,low c4 ,ANA positivity ,Anti Ds DNA positivity and nephrotic range of proteinuria were not significantly correlated with intrarenal vascular lesions.significance of chronicity index with vascular lesions could not be ascertained.

**Table 11 - Vascular lesion distribution among ISN class**

| ISN Class | Vascular lesion present N | Percentage |
|---|---|---|
| Class 3 | 3 | 12 |
| Class 4 | 16 | 64 |
| Class 4+5 | 6 | 24 |
| | 25 | 100 |

Vascular lesions are more common among patients with ISN class 4 histology.16 out of 25 total cases are belongs to class IV category. Isolated cases of class V category are not associated with vascular lesions.

**Table 12 - Vascular lesions and their outcomes**

| | Clinical response | | | |
|---|---|---|---|---|
| Lesions | Complete response | Partial response | No response | Death |
| ARTERIOSCLEROSIS AND ARTERIOLOSCLEROSIS | 3 | 4 | 0 | 0 |
| LUPUS VASCULITIS | 0 | 2 | 3 | 1 |
| LUPUS VASCULITIS+TMA | 0 | 1 | 0 | 0 |
| LV | 0 | 1 | 2 | 0 |
| TMA | 0 | 0 | 2 | 4 |
| UVID | 0 | 1 | 0 | 0 |

Poor response (no response and death) was correlated with TMA i.e. (100%) followed by LUPUS VASCULITIS (66.6%). Whereas good response (either complete response or partial response) were correlated with Arteriosclerosis and Arteriolosclerosis (100%).Most of the deaths occurred due to TMA. Category of no response included those who have not achieved complete or partial response as well as those entered into stage of dialysis dependence.

## CONCLUSION :

CLASS IV is the most common lesion. Systolic hypertension ,renal dysfunction, and microscopic hematuria commonly associated with class 4 lupus nephritis.

- Systolic and diastolic hypertension ,renal dysfunction and high activity index at the time admission are significantly correlated with clinical outcome at end of the follow up.
- Vascular lesions are common in lupus nephritis and most common lesion is Arteriosclerosis and arteriolosclerosis.
- Systolic blood pressure and e GFR significantly correlated with vascular lesions.
- Vascular lesions more commonly associated with class 4 lupus nephritis.
- Arteriosclerosis and arteriolosclerosis are associated with good outcome.
- TMA is associated with poor prognosis.

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