Histopathological Spectrum of Renal Lesions in Adults with Proteinuria

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Abstracts: Background and Objectives: Proteinuria of more than 2.0 g in 24 hours is indicative of renal disease and a value of more than 3.5 g is a component of Nephrotic syndrome. The pathology resulting in proteinuria can be glomerular, tubular and others. Renal biopsy is gold standard in evaluation and management of patients with proteinuria especially Nephrotic syndrome. **Methods:** A retrospective analysis of all renal biopsies from adult patients with significant proteinuria over a period of 4 years was performed to study the pattern of renal pathology. The morphological findings were correlated with Clinical findings, laboratory findings &Immunofluorescence profile as per availability. **Results:** It was observed that clinical diagnosis matched the final pathological diagnosis in 79 (58.09%) cases. Further, Light Microscopy findings corresponded with Immunofluorescence in 142 out of 158 cases, while the diagnosis was changed in 16 (10.13%) cases after IF. **Conclusions:** The results thus indicate that renal biopsy along with IF plays an important role in diagnosis of cases with significant proteinuria a fact highlighted by low concordance % between the clinical and the pathological diagnosis. An accurate diagnosis is not only essential to initiate appropriate therapy but also in prognostication of renal lesions. [Selhi P NJIRM 2014; 5(5):90-95]

Key Words: Renal Biopsy, Proteinuria, Immunoflourescence

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Introduction: Renal biopsy continues to be a pivotal tool and indispensable diagnostic procedure in the clinical assessment of proteinuria, microscopichaematuria and /or unexplained renal disease [1]. It is a cornerstone in management of patients presenting with nephrotic range proteinuria, unexplained renal failure & renal involvement in systemic diseases[2].

Normally up to 150mg of protein is excreted in urine per 24 hrs. [3] Detection of an abnormal amount of protein in urine is an important indicator of renaldisease. Based on pathophysiologic mechanisms, proteinuria can be classified as – glomerular, tubular and overflow proteinuria. [22] Among these, glomerular disease is the most common cause of pathologic proteinuria[4].

Nephrotic syndrome is a clinical complex characterized by heavy proteinuria (>3.5 g per 24 hours), hypoalbuminemia, edema, hyperlipidemia, lipiduria and hypercoagubility[5] and is the most important indication for renal biopsy. Accurate interpretation of glomerular pathology is essential for prognostication, and is a guide to appropriate therapy. The goals for therapy and disease specific protocols have evolved over the past years, making the rationale for an initial biopsy more compelling.

This study is a retrospective study planned to analyze all renal biopsies from adult patients with significant proteinuria received in the Department of Pathology, DMCH, over a period of four years and provide a pattern of renal pathology. Correlation of the light microscopic findings and histological diagnosis with the clinical profile and immunoflourescence findings was done wherever possible.

Materials and Methods: This was a retrospective study done on all kidney biopsies of adult patients presenting with significant proteinuria received in the Department of Pathology over a period of 4 year with reference to light microscopy and immunoflourescence wherever possible and correlated with the clinical profile i.e. clinical presentation, diagnosis and laboratory parameters. The patient charts (Files) in the medical records department were accessed to record thepatientdetails, clinical profile and immunofluorescence findingsthe study included kidney biopsies from patients with age > 18 years presenting with significant proteinuria with or without hematuria.

Therenal biopsy slides were reviewed and histologically typed based on light microscopic findings using routine (H & E) & special stains.

Correlation with immunoflourescence findings was done wherever possible. For light microscopy, 2-3 μm thick even sections, stained with H &E and special stains like PAS, Masson's trichrome, silver stain and Congo red were analyzedand findings recorded.

Changes in glomeruli, tubules, interstitium and blood vessels were recorded. In the glomerulus, glomerular proliferation (mesangial, endocapillary, extracapillary), influx of leucocytes, foci of necrosis, crescents, scarring and basement membrane changes etc were noted. Tubular and interstitial atrophy/ inflammation/fibrosis were recorded.In the blood vessels a note of arteriosclerosis, sub inflammatory necrotizing vasculopathy, thrombotic microangiopathy and necrotizing vasculitis etc was made.

Renal lesions were grouped asPrimary Glomerulopathy and Secondary glomerulopathies as per the standard protocol. The histological lesions were correlated with the immunoflourescence findings, degree of proteinuria and clinical presentation, which was then statistically, analyzed using z-test. A p-value of <0.05 indicated statistical significance.

Observations: A total of 228 biopsiesreceived over a period of 4 years formed the study group. Cases presenting with nephrotic range proteinuria constituted the bulk (76.5%) as compared to those presenting with Subnephrotic range proteinuria (23.5%).7 were inadequate for opinion (composed of medullary tissue only) and were not included in statistical analysis of cases.

The age ranged from 18-80 years with a mean age of 38.57 ± 14.74 years with the highest number of cases i.e. 109 (49.32%) in 18-35 year age group.Male predominance (62.44%) was seen as compared to females (37.56%) with a male: female ratio of 1.7:1. Edema (63.9%) was seen in majority of patients followed by fever and generalized weakness (9.7%), decreased urine output (6.2%), and macroscopic haematuria (4.4%). 7.9% of patients were known cases of Systemic lupus erythematosis (SLE) who were biopsied for classification of lupus nephritis with 1 case each of Wegener's granulomatosis and Sjogren's syndrome, accounting for 0.4% of total biopsies. 22.6% of total cases had hypertension and 5.0% had diabetes mellitus at the time of presentation. Laboratory analysis showed presence of microscopic haematuriawith proteinuria in 37.56% cases with 73/128 cases (57.03%) exhibiting raised serum creatinine levels (>1.2 mg/dl).

Amongst the pathological categories, Primary glomerulopathies formed the major group constituting 65.2% of all renal biopsies, secondary glomerulopathies constituted 20.8%, tubulointerstitial diseases 3.6% and chronic renal disease 10.4% cases.

MPGN was the most common primary glomerulopathy and Lupus nephritis was the most common secondary glomerulopathy in our study.

Table 1: Distribution of Cases According To Pathological Diagnosis

DIAGNOSIS	No.	%age
MPGN	44	19.9
FSGS	31	14.0
MN	28	12.7
CKD	23	10.4
Lupus nephritis	21	9.5
MCD	16	7.2
Cresc. GN	16	7.2
Amyloidosis	15	6.8
IgA nephropathy	9	4.1
CIN	7	3.2
DM nephropathy	5	2.3
Cast nephropathy	2	0.9
Anti-GBM disease	1	0.5
Wegner's granulomatosis	1	0.5
Microscopic PAN	1	0.5
AIN	1	0.5
Total	221	100.0

FSGS was the most common histopathological lesion diagnosed in young adults (18-35 years) presenting with nephrotic range proteinuria while Lupus nephritis was the most common pathology in sub nephrotics. Highest incidence of lupus nephritis and Ig A nephropathy was noted in this group.

Table 2: Distribution of lesions in 18-35 year age group

Diagnosis	18-35 years age group					
	Nephrotic		Sub nephrotic		Total	
	No.	%	No.	%	No.	%
MPGN	13	16.46	5	16.67	18	16.51
FSGS	17	21.52	4	13.33	21	19.27
MN	7	8.86	0	0.00	7	6.42
CKD	12	15.19	3	10.00	15	13.76
Lupus nephritis	8	10.13	7	23.33	15	13.76
MCD	9	11.39	1	3.33	10	9.17
Cresc. GN	4	5.06	5	16.67	9	8.26
Amyloidosis	3	3.80	0	0.00	3	2.75
Ig A nephropathy	4	5.06	2	6.67	6	5.50
CIN	0	0.00	3	10.00	3	2.75
DM nephropathy	2	2.53	0	0.00	2	1.83
Total	79	100.00	30	100.00	109	100.00

The common primary renal pathologies diagnosed in older adults (36-65 years) in nephrotic group was MPGN and in the sub nephrotic group was Crescentic glomerulonephritis.

Table 3: Distribution of Cases in 36-65 Year Age Group

Diagnosis	36-65 years age group					
	Nephrotic		Sub nephrotic		Total	
	No.	%	No.	%	No.	%
MPGN	**22**	**27.16**	0.00	0.00	22	21.78
FSGS	6	7.41	1.00	5.00	7	6.93
MN	19	23.46	1.00	5.00	20	19.80
CKD	8	9.88	0.00	0.00	8	7.92
Lupus nephritis	5	6.17	1.00	5.00	6	5.94
MCD	6	7.41	0.00	0.00	6	5.94
Cresc. GN	2	2.47	**5.00**	**25.00**	7	6.93
Amyloidosis	10	12.35	1.00	5.00	11	10.89
Ig A nephropathy	2	2.47	1.00	5.00	3	2.97
CIN	0	0.00	4.00	20.00	4	3.96
DM nephropathy	1	1.23	1.00	5.00	2	1.98
Cast nephropathy	0	0.00	1.00	5.00	1	0.99
Anti- GBM disease	0	0.00	1.00	5.00	1	0.99
Wegner's granulomatosis	0	0.00	1.00	5.00	1	0.99
Microscopic PAN	0	0.00	1.00	5.00	1	0.99
AIN	0	0.00	1.00	5.00	1	0.99
Total	81	100.00	20.00	100.00	101	100.00

The most common pathology in elderly age (more than 65 years) was MPGN followed by FSGS. The incidence of MPGN, FSGS, Diabetic nephropathy and cast nephropathy (myeloma kidney) was highest in individuals >65 years.

Table 4: Distribution of Cases in >65 Year Age Group

Diagnosis	>65 years age group					
	Nephrotic		Sub nephrotic		Total	
	No.	%	No.	%	No.	%
MPGN	4	44.44	0	0.00	4	36.36
FSGS	2	22.22	1	50.00	3	27.27
MN	1	11.11	0	0.00	1	9.09
Amyloidosis	1	11.11	0	0.00	1	9.09
DM nephropathy	1	11.11	0	0.00	1	9.09
Cast nephropathy	1	11.11	1	50.00	1	9.09
Total	9	100.00	2	100.00	11	100.00

Male predominance was seen in all the major glomerulopathies except lupus nephritis where females predominated.

Table 5: Distribution of Cases According To Pathological Diagnosis in Nephrotic and Sub Nephrotic Categories

	Nephrotic		**Sub-Nephrotic**	
	No.	**%age**	**No.**	**%age**
MPGN	**39**	**23.1**	5	9.6
FSGS	25	14.8	6	11.5
MN	27	16.0	1	1.9
CKD	20	11.8	3	5.8
Lupus nephritis	13	7.7	8	15.4

MCD	15	8.9	1	1.9
Cresc. GN	6	3.6	**10**	**19.2**
Amyloidosis	14	8.3	1	1.9
IgA nephropathy	6	3.6	3	5.8
CIN	0	0.0	7	13.5
DM nephropathy	4	2.4	1	1.9
Cast nephropathy	0	0.0	2	3.8
Anti-GBM disease	0	0.0	1	1.9
Wegner's granulomatosis	0	0.0	1	1.9
Microscopic PAN	0	0.0	1	1.9
AIN	0	0.0	1	1.9
Total	169	100.00	52	100.00

Correlation of degree of proteinuria andhistopathological findings revealed that majority of cases in nephrotic group were constituted by MPGN (23.1%), followed by Membranous nephropathy (16.0%). In the sub-nephrotic group, Crescentic GN (19.2%) was the most common entity

Tubulointerstitial diseases constituted the least common group with only 8(3.6%) cases presenting with sub nephrotic range proteinuria. Chronic interstitial nephritisaccounted for majority of these (7 cases -3.1%) with one being a known case of Sjogren's syndrome. Sex distribution revealed a slight female preponderance in CIN cases, M: F ratio of 1:1.3. Only a single case of acute interstitial nephritis (drug induced) was noted in our study.

Chronic kidney disease (CKD) was seen in 23(10.41%) cases with majority being in 18-35 year age group (65.22%) with male dominance accounting for 15 out of 23 cases (M:F=1.9:1). 20(86.96%) cases presented with nephrotic range proteinuria while only 3 cases (13.04%) with clinical diagnosis of RPGN presented with sub nephrotic proteinuria.

In 85 out of 221 cases (38.46%), the clinician suggested no specific diagnosisand the pathologist gave the final morphological diagnosis. In the remaining 136 cases, 78 were concordant with the clinical diagnosis;concordant ratebeing 57.35%. This difference between the clinical diagnosis and the pathological diagnosis was found to be statistically significant (p value < 0.05).Hence, implying that renal biopsy plays a significant role in diagnosis of renal lesions in adults presenting with proteinuria.

In the present study, immunoflourescence was available and adequate in 158 cases out of 221 and morphological diagnosis correlated with immunoflourescence diagnosis in 142 cases with a concordance rate of 89.87%. In 16 cases (10.13%), a definite diagnosis was made only with help of immunoflourescence as light microscopy was either inconclusive or was corrected by IF findings. 9 of the cases after IF were given a specific label of IgA nephropathy which were earlier reported as Proliferative lesion based on LM. This further re-affirms the fact that Ig A nephropathy is a diagnosis based on IF.

1 case each of MPGN & lupus nephritis were labeled as proliferative lesion on LM, and the diagnosis was revised based on full house positivity in SLE and normal ASO titer and granular positivity in MPGN. In another case diagnosed as Crescentic GN on light microscopy, a definite diagnosis of Anti-GBM disease was made based on linear IgG deposits on IF. Three cases of FSGS were diagnosed on immunoflourescence, 2 of which were inconclusive on LM and one was diagnosed as minimal change disease.Finally one case was misdiagnosed as membranous nephropathy on LM and later to MCD as IF was negative. After the IF was done, thinner sections were asked for which showed a normal BM. This error is thus attributed to the thickness of the section. Hence, immunoflourescence is significant not only in diagnosis but also confirmation of light microscopic findings in specific renal histopathological lesions. Also the role of immunoflourescence in specific diagnosis of proliferative glomerular lesions is being stressed with the above findings.

Discussion: The most common clinical presentation in our study was nephrotic range proteinuria -169 (76.5%) cases, which is comparable to the study by Balakrishnan et al [10] and Narasimhan et al [8]. Males outnumbered females with anM: F ratio of 1.7:1 in all major glomerulopathies except lupus nephritis where a high female preponderance was seen (M: F ratio -1:9.5). Rivera et al[6]Rychlik et al [12] and Choi et al[7] also reported a similar pattern in their

analysis of renal biopsies.Edema, a manifestation of protein loss in urine is the commonest presenting symptom in nephrotics was seen in majority of patients (63.9%).

Primary glomerulopathies formed a major group constituting 65.2% of all cases which was comparable to Rychlik et al[12,] Narasimhan et al[8] and Mitwalli et al[9] who reported a higher incidence of primary glomerular disease constituting 60%, 71% and 79% of all renal biopsy specimens, respectively, thecause of a higher biopsy rate may be due tothe infrequency with which renal biopsy is performed in patients having a known secondary cause of renal disease.

Overall, the predominant primary glomerular pathology in our study was MPGN which accounted for 19.9% cases. Second most common primary glomerular disease was FSGS (14.0%) followed by membranous nephropathy (12.7%). The pattern of renal diseases is not uniform in all countries as reported by various authors from different parts of the world. Al-Khader et al[14] (Saudi Arabia) found in their series of patients with nephrotic syndrome that MPGN was the most common cause (25%) followed by FSGS. Similar results were also obtained by Huraib et al[15] and Chen et al[16] with incidence of MPGN being 26.4% and 40.4% in their respective studies on renal biopsies. However, studies by Schena [11] and Briganti et al [17], however, indicated Ig A nephropathy to be the most prevalent pathology in their countries.

The most common secondary glomerulopathy in our study was Lupus nephritis constituting 9.5% of the total and 45.6% of secondary glomerulonephritis cases. Similarly, studies by Huraib et al [15], Mitwalli et al [9] showed highest prevalence of Lupus nephritis cases (57% and 48.5% respectively) among the secondary glomerulopathies.

On correlating with degree of proteinuria, it was found that the most common glomerulopathy in the nephrotic group was MPGN (23.1%) in the young age group.In the age group 18-35 years, FSGS (19.27%) was the predominant lesion while in 36-65 years and >65 years age group, MPGN, was the most common (21.78% and 36.36%, respectively).The frequency of MPGN increased with age, being the highest in the elderly population (36.36%).

All primary glomerulopathies except Crescentic GN presented mainly as nephrotic range proteinuria.Higher percentage of cases presenting with sub nephrotic proteinuria were noted in Crescentic GN (62.5%) and most of these cases presented with rapidly progressive renal failure clinically.

Clinical diagnosis matched the final pathological diagnosis in 79 (58.09%) cases. Renal biopsy not only confirmed but also changed the diagnosis in many cases. Richards et al[13] in their study noted that management was altered in 42% cases with an overall concordance of 58%. This also corresponded with other case studies, by Turner et al[18], Cohen et al [19]andPfister et al[20].

Of 158 cases where Immunoflourescence was done, LM findings corresponded with IF in 142 cases, while the diagnosis was changed in 16 (10.13%) cases after IF. Similar findings were observed by Date et al[113] in their study to determine the additional information obtained by IF over that given by LM alone.

Of the above mentioned 16 cases, 9 were Ig A nephropathy which could be diagnosed only on IF. Remaining cases were of MPGN (1), FSGS (3), MCD (1), Anti-GBM disease (1) and lupus nephritis (1). Two cases reported as proliferative could also be categorized as MPGN and Lupus nephritis. IF also helps to differentiate MCD from FSGS especially if the LM does not show foci of sclerosis (3 cases in our study). Usefulness of IF is well accepted in sub classification of Crescentic GN a fact highlighted in our study where we could give a specific label of Anti-GBM disease. Therefore, IF is an important diagnostic tool especially in cases of proliferative glomerulopathies.

Conclusion: The above results thus indicate that renal biopsy along with IF plays an important role in diagnosis of cases with significant proteinuria a fact highlighted by low concordance % between the clinical and the pathological diagnosis. An

accurate diagnosis is not only essential to initiate appropriate therapy but also in prognostication of renal lesions. A review of renal biopsy data provides insight into the spectrum of clinically significant renal diseases and basic epidemiological data on renal disease in community. Our study can provide as a basis for further studies.

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