

Immune Deposits in Glomerular Diseases and Their Clinical, Histopathological and Immunopathological Correlation

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Abstract

Glomerulonephritis (GN) is a common renal disease and common cause of chronic renal failure (CRF) accounts for more than one-third of patients of end stage renal disease (ESRD) requiring either dialysis or transplantation. In our country, early diagnosis and treatment of GN depends on routine urine and blood examination and using light and immunofluorescent microscopic study of renal biopsy. The purpose of this study was to demonstrate the frequency, type, intensity, pattern and site of deposition of immunoglobulin IgG, IgA, IgM and C3 by direct immunofluorescence microscopic technique (DIF) in various pattern of GN and to correlate with clinical and histopathological findings.

Among 120 cases of renal biopsy, 110 cases (91.67%; n=120) were adequate for histopathologic study only and 98 cases (81.67%; n=120) were adequate for both histopathologic and direct immunofluorescence microscopic study. In this series, maximum numbers of cases were found in 21-30 age group (27.27%). Most frequent clinical presentation and pattern of glomerulonephritis were nephrotic syndrome (61.22%; n=98) and mesangioproliferative GN (40.81%) respectively. Among 98 cases of study group, 49 cases (50%; n=98) were DIF positive. The most frequent type of depositions were C3 (type) in various combinations (98%; n=49) followed by IgG (67.35%) and IgA (40%). Mesangium followed by glomerular basement membrane were the most frequent site and granular pattern was the most frequent pattern of deposition. The frequent combination of depositions in various pattern of GN were C3 + IgG (36.73%; n=49) followed by C3 + IgA (20.41%). There was a correlation between histopathologic pattern of GN and type-site-pattern of deposition in the glomeruli. Immune-depositions were cent percent in IgA nephropathy, membranous GN (MGN), diffuse proliferative GN and membranoproliferative GN. Among 15 cases of IgA nephropathy (15.31%; n=98), most frequent pattern and clinical presentation of GN was mesangioproliferative GN (60%; n=15) and haematuria (46.67; n=15) respectively.

In this study, DIF was proved to be essential, sensitive and specific diagnostic tool in the evaluation of glomerular diseases. However, DIF study is no substitute of light microscopy but both provide information which when taken as a whole contributes to better understanding of GN.

Key words : DIF, GN, CRF, ESRD

Introduction

Glomerulonephritis is the common renal disease and also common cause of chronic renal failure in both developed and developing countries¹. Renal biopsy remains the "gold standard" for the diagnosis of glomerular diseases. To evaluate kidney biopsy, one should correlate complete clinical and laboratory information with light, immunofluorescence and electron microscopic findings. Most of the glomerulopathies are still classified and named according to their morphologic features. A given clinical syndrome can be associated with several histopathologic patterns. Focal as well as diffuse proliferative GN, crescentic and mesangial GN usually present with nephritic syndrome. Classic

pathologic correlate of the nephritic syndrome is proliferative GN². The morphologic pattern affecting the glomerular filtration barrier for protein, namely the glomerular basement membrane (GBM) and visceral epithelial cells are membranous GN, minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS)-typically present with nephrotic range proteinuria². Membranoproliferative GN is a hybrid lesion that presents a combination of nephritic-nephrotic features. Glomerular deposition diseases can also trigger nephrotic type, nephritic type response or combination of both and thus show marked clinical and morphologic overlap². The site of the antibody deposition within the glomerulus is a critical determinant of clinico-pathologic presentation.

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Relatively anionic antigens are repelled by the GBM and trapped in the sub-endothelial and mesangial location usually causing proliferative GN². Relatively cationic antigens tend to permeate GBM and deposits within sub-epithelial aspects of GBM and visceral epithelial cells causing nephrotic type response. Acute sub-endothelial deposits are responsible for leukocyte infiltration, vasoconstriction and thrombotic microangiopathy causing nephritic syndrome. But sub-epithelial, intramembranous immune-deposits usually cause nephrotic range proteinuria².

Direct immunofluorescence microscopic (DIF) study has resulted in a considerable expansion in the understanding of human glomerular diseases³. It seems that there is a need to further study of the pattern of GN after applying the usual histopathologic technique. By DIF technique, it can correlate sometimes significantly with light microscopic diagnosis and clinical syndromes but impossible to group patients into any specific categories³. Immune-deposits of IgG-IgA/C3 were found higher frequency in patients of haematuria due to secondary cause and patients with immune-deposits of IgA/C3 had recurring respiratory infection⁴. Since the treatment of glomerulonephritis is often determined by the histopathologic findings, any technique that identifies the particular lesion quickly, easily and definitely may be of clinical assistance. It is the combination of great sensitivity and specificity together with the use of histologic technique that makes immunofluorescence technique so useful. Therefore, an attempt to correlate the findings of this technique with the clinical and histological diagnosis will further enhance its reliability.

In the light of above context, renal biopsies were analyzed to detect and correlate the findings of DIF with the various pattern of glomerulonephritis and clinical syndromes.

Material and Methods

Renal biopsy (needle biopsy) specimens were obtained from the clinically suspected and biopsy indicated patients of glomerulonephritis (GN) after proper willen and vecbul consent and studied in the Department of Pathology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka and in the Histopathology Department of Armed Forces Institute of Pathology (AFIP), Dhaka during the period from January/1999-December/1999.

Patients were selected from the Department of Nephrology, Bangabandhu Sheikh Mujib Medical

University (BSMMU), Dhaka, Dhaka Medical College Hospital, Combined Military Hospital (CMH) and few other referral hospitals of Dhaka city.

One hundred and twenty (120) clinically diagnosed cases of nephrotic syndrome, nephritic syndrome, asymptomatic hematuria or proteinuria etc of various age groups were biopsied and preliminary included in this study. Clinical information was recorded in a pre-designed proforma before doing histopathology and DIF study. Renal biopsies were performed by Nephrologist. At least two specimens of 12-20 mm in length renal tissues, one in 10% formalin for histopathology (light microscopic study) and another one in normal saline for DIF study were taken. Cryostat machine (for frozen section), fluorescent microscope (NIKON; Labophot-2, model-661012, Japan), micropipette, phosphate buffer saline (PBS) and commercially prepared fluorescein isothiocyanate (FITC) conjugated goat antihuman IgG, IgA, IgM, and C3 reagent (Sanofi Diagnostics Pasteur, Inc. 1000 lake Hazeltine Drive, Chaska, USA, MN 55318. Cat-800-666-5111) were used for DIF study. Formalin-fixed processed tissue section were stained by both haematoxylin-eosin (H & E) and Periodic Acid Schiff (PAS) stain for histopathologic study. GBM thickness was observed under light microscope with PAS stain.

Histopathology of the biopsied specimens were performed by the author himself and thoroughly verified by at least two Histopathologists-the Head of the Department of Pathology and the Professor of Pathology, BSMMU, Dhaka. The DIF study was performed by the Head of the Department of Histopathology of Armed Forces Institute of Pathology (AFIP), Dhaka and the author himself along with verification by the Head of the Department of Pathology, BSMMU, Dhaka.

Following were the criteria to define different terms and various patterns of GN.

Adequate for DIF study: Presence of at least one glomerulus under fluorescent microscope. Adequate for light microscopic study: Presence of at least 5 glomeruli under light microscope⁵. Mesangial proliferation: More than 3 mesangial cells embedded in matrix of one segment. Endothelial proliferation: More than 2 nuclei per capillary loops and leukocyte infiltration: More than 5 leukocytes per glomerulus⁶. Crescentic GN: When at least 50% of the glomeruli involved as crescents and minimal change disease (MCD) when no evidence of any change or presence of minimal mesangial proliferation of less than 50% of the glomeruli in a section⁷. Lesions are classified as focal or diffuse proliferative when they

involve the minority (< 50%) or majority (?50%) of glomeruli respectively². IgA nephropathy: Predominant mesangial deposition of IgA along with C3 detected by immunofluorescence microscopy⁸. Clinical presentation and patterns of 15 cases of IgA nephropathy in this study were evaluated separately. Focal segmental glomerulosclerosis (FSGS): Segmental (one or two lobules) sclerosis with hyalinosis involving portions of fewer than 50% of the glomeruli in a section. Sclerosis was defined as increase in amount of homogeneous non-fibrillar extracellular material of similar composition to GBM and mesangium.

Membranous GN: Diffuse thickening of GBM due to sub-epithelial deposits of immune complex without evidence of inflammation or cellular proliferation.
Membranoproliferative GN: Diffuse thickening of GBM with predominant proliferation of mesangial cells and extension of matrix often with interposition in between the endothelial cells and GBM causing tram-track appearance under light microscope².
Mesangioproliferative GN: Diffuse increase in glomerular cellularity predominantly due to mesangial cells often with concomitant increase in mesangial matrix⁹.

Photographs were taken in both cases of light microscopic and DIF study.

Fluorescein dye conjugated antihuman antibodies (IgG, IgA, IgM and C3) were fixed with the tissue section by ten times diluted anti-sera. Then fall of ultraviolet light into the stained tissue section become excited and emit light of higher wave length to be visible (apple green colour) under fluorescent microscope if there is any antigen in the tissue section. Here antibodies and complement lies within the tissue section (if any) act as antigen and artificially prepared antihuman antibodies and complement act as antibody.

Total number of glomeruli, GBM, mesangial, endothelial and epithelial cells and infiltration of inflammatory infiltrates, tubules, interstitium and blood vessels were observed under light microscope^{6,7}.

Type (IgG, IgA, IgM and C3), pattern (granular or linear), site (GBM or mesangium) and intensity of deposition in the glomeruli were observed under fluorescent microscope. The intensity of FITC staining was graded subjectively from 0 to +3: 0 being negative and +3 maximum intensity (mild +1; moderate ++2; marked +++3)^{6,7}.

The clinical information were recorded, then histopathological diagnosis of formalin-fixed

processed renal tissue were made based on H&E and PAS stain followed by saline-fixed tissue frozen section under -25 degree centigrade temperature, DIF staining and immunofluorescence microscopic study. These three findings were then correlated and evaluated.

Results

Out of 120 renal biopsies, 10 cases were labeled as inadequate for histopathologic study and 12 cases showed no glomeruli and inadequate for DIF study. Clinical, histopathological and DIF study were done among remaining 98 cases. Among 98 study cases, 56 were male (57%) and 42 (43%) were female. The age ranged from 8-70 years and mean age of 30.67 years. Mesangioproliferative GN (40.81%; n=98) was the most frequent pattern of GN followed by focal segmental proliferative GN (20.41%), IgA nephropathy (15.31%), MCD (10.21%) and membranoproliferative GN (10.21%) of all age group. The most frequent clinical presentation of the study group was the nephrotic syndrome (61.22%) followed by haematuria (11.22%) and nephritic syndrome (11.22%) (Table-1). Among fifteen cases (15.31%; n=98) of IgA nephropathy, there were 60% mesangioproliferative GN, 26.75% CGN, 6.7% MPGN and 6.75% focal segmental proliferative GN of histopathologic pattern in this study group. Sixty cases (61.22%; n=98) presented with nephrotic syndrome showed as pattern of mesangioproliferative GN (25.51%), focal segmental proliferative GN (11.22%), MCD (10.21%), MPGN (6.13%), membranous GN (4.08%), crescentic GN (2.04%) and lupus nephritis (2.04%). On the other hand, 40 (40.81%) cases of mesangioproliferative GN of this study clinically presented with nephrotic syndrome (25.51%), haematuria (7.15%), nephritic syndrome (1.02%), CRF (1.02%), proteinuria (5.10%) and RPGN (1.02%). Twenty (20.41%) cases of focal segmental proliferative GN were clinically presented with nephrotic syndrome (11.21%), haematuria (3.06%), nephritic syndrome (4.08%) and proteinuria (2.04%) (Table-1). Hundred percent of MCD, membranous GN and lupus nephritis, 66.67% of crescentic GN (n=3), 62.51% of mesangioproliferative GN (n=40), 55% of focal segmental proliferative GN (n=20) and 60% of membranoproliferative GN (n=10) were presented with nephrotic syndrome. Sixty-seven percent (66.67%; n=3) of FSGS, 20% of focal segmental proliferative GN (n=20), 100% of diffuse proliferative GN (n=2) and 30% of membranoproliferative GN (n=10) were presented with nephritic syndrome. Forty-seven percent of IgA nephropathy (n=15),

17.5% of mesangioproliferative GN (n=40), and 10% of membranoproliferative GN (n=10) were presented with haematuria. Among 110 histopathologically adequate cases, 12 cases were left out from DIF study because of 'no glomeruli' under fluorescent microscope. DIF study was done in the rest 98 cases of which 49 cases (50%) were DIF positive and another 49 cases (50%) DIF negative (Table-11). The sites of deposition were predominantly in the mesangium in case of IgA nephropathy, mesangioproliferative GN, FSGS and focal segmental proliferative GN and in the GBM in case of membranous and membranoproliferative GN. All of the glomerular depositions were granular in pattern. The most frequent type of single immune-deposits in various combination was C3 (98%, n=49) followed by IgG (67.35%, 33 out of 49 cases) and IgA (40%). The most frequent combination of deposits were IgG+C3 found in 18 cases (36.73%, n=49) followed by IgA+C3 in (20.41%) cases (Table-111). Most frequent presentation in IgA nephropathy was haematuria (46.7%; n=15) followed by nephrotic syndrome (26.7%). The most frequent pattern of GN in IgA nephropathy was mesangioproliferative GN (60%; n=15). In IgA nephropathy, depositions were mesangial, granular and mostly IgA along with mild deposition of C3 combination. DIF positivity of IgA nephropathy, MGN, MPGN and diffuse proliferative GN and lupus nephritis of the present study were cent percent but positivity of mesangioproliferative GN, MCD and crescentic GN were 36.67, 18.18 and 33.33 percent respectively (Table-1V).

Table-1

Correlation of clinical presentation and histopathologic pattern (n=98)

Clinical features	Pattern of Glomerulonephritis										
	Mesangioproliferative GN	Focal segmental GN	MCD	MPGN	MGN	FSGS	Crescentic	DPGN	CGN	Lupus	Total
Nephrotic	25 (25.51)	11 (11.22)	10 (10.21)	06 (6.13)	04 (4.06)	00	02 (2.04)	00	00	02 (2.04)	06 (6.12)
Haematuria	07 (7.15)	03 (3.06)	00	01 (1.02)	00	00	00	00	00	00	11 (11.22)
Nephritic	01 (1.02)	04 (4.08)	00	03 (3.06)	00	02 (2.04)	00	01 (1.02)	00	00	11 (11.22)
CRF	01 (1.02)	00	00	00	00	01 (1.02)	00	01 (1.02)	03 (3.06)	00	06 (6.13)
Proteinuria	05 (5.10)	02 (2.04)	00	00	00	00	00	00	00	00	07 (7.15)
CRF	01 (1.02)	00	00	00	00	00	01 (1.02)	00	01 (1.02)	00	03 (3.06)
RPGN	40 (40.81)	20 (20.41)	10 (10.21)	10 (10.21)	04 (4.06)	03 (3.06)	03 (3.06)	02 (2.04)	04 (4.06)	02 (2.04)	98 (100)

Table-II

Histopathologic pattern and DIF findings in 98 study cases

Pattern	Cases	DIF positive	DIF negative
Mesangioproliferative GN	30	11	36.67
Focal segmental proliferative GN	18	03	16.67
IgA nephropathy	15	15	100
Minimal change disease	11	02	18.18
Membranoproliferative GN	08	08	100
Membranous GN	04	04	100
FSGS	03	00	000
Crescentic GN	03	01	33.33
Diffuse proliferative GN	02	02	100
Chronic glomerulonephritis	01	00	000
Lupus nephritis	02	02	100
Total	98	49	50

Table-III

Distribution of immunoglobulin IgG, IgA, IgM and C3 of 49 DIF positive cases in various pattern of GN

Immunoglobulin and C3	No. of cases (n=49)	Percentage
IgG+C3	18	36.73
IgA+C3	10	20.41
IgG+IgM+C3	06	12.24
IgA+IgG+C3	05	10.20
IgG+IgA+IgM+C3	04	8.16
IgM+C3	03	6.12
IgA+IgM+C3	01	2.04
C3 alone	01	2.04
IgM alone	01	2.04
Total	49	100

Table-1V

Comparative study of DIF positive cases by different authors

Pattern of GN	DIF positive findings in percentage						
	Moroi-Marogor, 1972	Larsen, 1978	Mehta et al, 1983	Tabasum, 1988	Sharmin, 1984	Nabir, 1996	Present study
Mesangioproliferative	53.33	85	45	80	70	60	36.67
Focal proliferative	74.58	90.67	65	60	50	40	52.48
MCD	00	60	57.1	00	00	00	18.18
Membranous GN	100	100	100	100	100	100	100
MPGN	100	100	100	100	100	100	100
IgA nephropathy	100	100	100	100	100	100	100
Diffuse proliferative	83.88	77.7	100	100	100	100	100
CGN	00	00	00	00	50	00	00
Crescentic GN	76	65	33	100	100	00	33.33
FSGS	76.32	40	60	33.33	10	00	66.67
Lupus nephritis	100	100	100	100	100	100	100

Discussion

In the present study, the maximum number of cases occurred in the 21-30 age group followed by 11-20 and 31-40 age groups. Nephrotic syndrome was the most frequent clinical presentation shown by Cameron, 1980 (57.77%)¹⁰, Ziauddin et al, 1993 (56.6%)¹¹ and Rahman et al, 1984 (94%)¹² similar to our study (61.22%). There was a wide variation regarding the commonest pattern of glomerulonephritis yet done in home and abroad.

In the study of Rahman et al in 1984, Ziauddin et al in 1993 and Nabir et al in 1996 showed that MCD, diffuse proliferative GN and focal segmental proliferative GN were the most frequent pattern of GN respectively¹³. But the study of Tabassum, 1988 and Sharmin, 1994 along with our study reveal mesangioproliferative GN is the most frequent pattern of GN^{14,15}. Diffuse proliferative GN is the commonest pattern of GN in western world^{16,17, 18}. It needs serial sections and examination of more glomeruli during microscopic study to differentiate MCD from focal segmental proliferative GN. In fact, mesangial cellularity of MCD is an intermediate step in the evolution of MCD to FSGS¹⁹. By light microscopy, evidence of segmental proliferations may be missed if the biopsy specimen contains an insufficient number of glomeruli. Clinico-pathologic correlation of different patterns of GN in this study group was more or less similar to other studies².

In this study, DIF was positive in 49 cases (50%) and negative in another 49 cases (50%). Similar results were obtained by other two investigators done in Bangladesh^{14,15}. Our study also reveals predominantly generalized distribution of deposits either in the mesangium or GBM (93.88%) rather than focal (6-12%) which signifies usual generalized involvement of immune-deposits in glomerular diseases. More or less similar findings were reported by other authors^{14, 15, 20, 21}.

Conventionally, apparently normal glomeruli in light microscope and no deposition in DIF study regarded as MCD. But our study reveals DIF positivity of 18.18% in MCD cases similar with a few other studies^{4, 21}. Brenner and Rector in 2004 explained about DIF positivity due to differentiation between mild prominences of mesangial cells as observed in MCD and definite mesangial proliferation is subjective and highly susceptible to artifacts of sectioning and specimen preparation⁵.

The most frequent type of single immune-deposits in various combinations was IgG followed by C3 and IgA in the study of Tabassum, 1988 and Nabir, 1996-dissimilar to our study (C3 followed by IgG and IgA). Regarding most frequent presentation (haematuria), pattern and combination of deposition (IgA+C3) of present study in IgA nephropathy also showed very similar result reported by Sharmin, 1994 and Khan et al, 1990^{15, 23}. It was also observed that the type, site, pattern and intensity of immune-depositions greatly modify the clinical presentation and course of GN². There is a variation of DIF positivity by different authors done in home and abroad^{24, 4, 13, 14,15} (Table-1V).

Conclusion

Our study revealed that many of the glomerulonephritis were immune-deposit mediated causing different patterns of GN and clinical syndromes. IgA nephropathy showed mesangioproliferative, membranoproliferative, chronic glomerulonephritis and focal segmental proliferative phenotypes of GN. In this study, most of the patterns of GN were diagnosed by light microscopy; a few of them such as IgA nephropathy-DIF study was essential. The extent of focal lesion might misjudge in a small biopsy specimen and sections through glomeruli might miss segmental lesions. It needs large samples as well as serial sections with more glomeruli to diagnose MCD, FSGS and focal segmental proliferative GN properly. Though somewhat expensive, DIF was proved to be simple, rapid, sensitive and highly specific diagnostic procedure. The site, type, pattern and intensity of immune-deposits was identified by fluorescent microscope but to identify the exact location of the site (sub-endothelial or sub-epithelial or intramembranous) of immune deposits, electron microscope is needed. It was observed that proper diagnosis and treatment of glomerular diseases depend on correlation of clinical, light and fluorescent as well as electron microscopic study.

We can conclude with an expectation of introducing immunofluorescence technique as an essential diagnostic tool for the evaluation of renal biopsy in Bangladesh.

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