JOURNAL Of Medical Science And Clinical Research
IGM Publication   An Official Publication Of IGM Publication

Morphological pattern of glomerular diseases and its correlation with immunofluorescence findings and clinical presentation

Authors
Nur-E-Jannatul Ferdous[1*], Md. Golam Mostofa[2], Dabashis Patowary[3],
SK. Md. Jaynul Islam[4], Tania Gaffar[5], Sabina Yeasmin[6], Md. Nasimul Islum[7],
Enamul Kabir[8], Harunur Rashid Khan[9]
[1]Associate Professor, Department Of Pathology, Ashiyan Medical College, Dhaka
[2]Department of Medicine Combined Military Hospital (CMH), Jalalabad Cantonment, Sylhet
[3]Associate Professor, Department of Oncology, North East Medical College, Sylhet
[4]Histopathologist, Armed Forces Institute of Pathology, Bangladesh
[5]Assistant Professor, Department Of Pathology, Uttara Adhunic Medical College, Uttara, Dhaka
[6]Lecturer, Department of Pathology, Mugda Medical college, Dhaka.
[7]Professor and Head of the Department of Pathology Anwar Khan Modern Medical College, Dhaka
[8]Professor and Head of the Department of Pathology, Popular Medical College, Dhaka
[9]Professor and Head of the Department of Pathology, Sir Salimullah Medical College
*Corresponding Author
Dr Nur-E-Jannatul Ferdous

Abstract
Introduction: *The renal biopsy is a very important tool for the evaluation of patients with medical and surgical renal diseases.*
Materials & Methods: *A prospective, cross-sectional and descriptive study was conducted in the Department of Pathology, Sir Salimullah Medical College, Dhaka, Bangladesh and Histopathology Department of Armed Forces Institute of Pathology (AFIP), Dhaka, Bangladesh over a period of 2 years from July 2015 to June 2017. Patients of different age group and both sex were selected for this study according to inclusion and exclusion criteria. Inclusion criteria was histologicaly proven glomerular disease. The exclusion criteria were, HIV infection, Nephrectomy. Solitary kidney, Intravenous drug abuse.*
Results: *Present study included 119 cases of histologically proven glomerular disease, the age range of the patients was 3-67 years, 65 were male and 54 were female. Minimal change disease was found to be the most common diagnosis followed by membranoproliferative and IgM nephropathy. Nephrotic syndrome was the most common clinical presentation. Most common immune deposition was IgG Among 119 cases 11.76% was diffuse proliferative glomerulonephritis, 3.36% crescentic glomerulonephritis, 10.93% membranous glomerulonephritis, 13.44% minimal change disease, 7.56% focal segmental glomerulsclerosis, 12.60% membranoproliferative glomerulonephritis, 10.08% IgA nephropathy, 1.68% C1q nephropathy, 5.04% C3 glomerulopathy, 12.61%IgM nephropathy and 10.93% lupus nephritis).*
Conclusion: *In this study we addressed IgM nephropathy, C3 glomerulopathy, C1q nephropathy as well as IgA nephropathy mostly based on Immunofluorescence findings. As now various type of immunotherapy are introduced in the therapeutic world and glomerular diseases are mostly immune mediated. It's a new hope for renal disease. The recent availability of an anti-complement agent (eculizumab) has allowed to consider therapeutic options for C3 glomerulopathy.*
Keyword: *IgA nephropathy, IgM nephropathy, C1q nephropathy, C3 glomerulopathy.*

Introduction

The renal biopsy is a very important tool for the evaluation of patients with medical and surgical renal diseases. By this procedure, it is possible to establish an accurate diagnosis as well as to obtain critical information on the evolution and prognosis of the disease process and develop a rational approach to the treatment of a renal disorder. Even a biopsy can provide clues regarding the possibility of recurrence of the disease following transplantation. The renal biopsy is also useful in the management of the transplant recipient.[1] Glomerular disorders constitute one of the major causes of morbidity and mortality.[2] Immune mechanisms are responsible for glomerular injury in most cases of primary glomerulonephritis (GN) and many of the secondary GN.[3] Accurate diagnosis of GN requires renal biopsy and histopathological examination by light microscopy (LM), immunofluorescence (IF) and sometime electron microscopy (EM). In addition, it requires correlating clinical features and biochemical parameters with histopathology results. IF microscopy provides insight into the pathogenesis of glomerular diseases and it is very useful in diagnosing primary renal diseases and assessing the nature and severity of renal involvement in various systemic disorders.[4] In addition, IF yields important correlations and prognostic features.[5] Facilities for EM studies are not available in our country. In most cases, LM and IF studies are adequate for the definitive diagnosis of GN.[4] For instance, in stage-1 of membranous GN (MGN) there is no thickening of the glomerular basement (GBM) and no spikes on silver stain, and so it may not be distinguished from minimal change disease (MCD) by LM.[6] IF reveals the fine granular deposition of immunoglobulin and complement and confirms the diagnosis of MGN, at the same time distinguishing it from anti-GBM nephritis where liner deposits in IF and anti-GBM antibodies in serum are seen.[6,7] Correct diagnosis of lupus nephritis (LN) can be made by correlating typical clinical features and serological markers.[6]

Material and Methods

A prospective, descriptive cross-sectional study was conducted in the the Department of Pathology, Sir Salimullah Medical College, Dhaka, Bangladesh and Histopathology Department of Armed Forces Institute of Pathology (AFIP), Dhaka, Bangladesh over a period of 2 years from July 2015 to June 2017. Patients of different age group and both sex were selected for this study according to inclusion and exclusion criteria. Inclusion criteria was Patients of all ages and both sexes with histologicaly proven of glomerular disease. The exclusion criteria were HIV infection, Nephrectomy, Solitary kidney and Intravenous drug abuse A total of 119 cases who met the enrolment criteria were included in this study.

Renal biopsy was performed in all the 119 patients with informed written consent who met the inclusion criteria of the study. Tru-cut per-cutaneous needle biopsy was performed without any image guidance by trained nephrologists. The preferred site was the center of the lower pole of the left kidney. The bony landmarks were the tips of the dorsal processes of lumbar spine and lower border of the 12th rib. Local anesthesia was given in skin and subcutaneous tissues. Two needle core biopsy samples were taken.

Specimen for light microscopic examination was preserved in 10% formalin. Tissue for immunofluorescent microscopy was carried in normal saline. Both the samples were immediately transferred to the department of pathology in the Armed Forces Institute of Pathology (AFIP). Tissue with 10% formalin was kept at room temperature for routine processing and the tissue with normal saline was preserved in a refrigerator for immunofluorescent processing at -20 degree centigrade.

Tissue was fixed in 10% nutral buffered formalin and was embedded in paraffin block and processed routinely. The tissue sections were cut

at 4-5 micrometer thickness and were stained with H&E and PAS staining.

The tissue for immunofluorescence microscopy was stored in a freezer in normal saline and was transferred to a cabinet, placed on a block holder, embedded in O.C.T (Optimum cutting temperature) compound (Leica CM 1860, USA) and quickly frozen at -40 C. Sections were cut at -20 C cooled chamber a thickness of 4-5 micrometer and were picked up on a specially designed ring slides. The sections were air dried and was stained with FITC- conjugated rabbit anti-sera against human IgG, IgM, IgA, and Complement3 (DAKO). C1q staining was done on selective cases (66 cases) only.

The degree of fluorescence was graded in an arbitrary scale from (+) to (+++). Control slides were stained with the same procedure.

Data were collected on variables of interest. All the data were recorded in the predesigned data collection form. Data processing and analysis were done using SPSS (statistical package for social sciences), version 20.0. The test statistics used to analyze the data were descriptive statistics.

Results

Total 119 renal biopsies (needle biopsy) with histologically proven glomerular diseases were obtained in present study through convenience sampling technique.

In the present study mean age of patient was 30.29 ± 14.65 years. The age range was 3 to 67 years. Among the total recruited patients 31 were children ($\leq$ 18yrs) and 88 were adults (>18yrs).

Over half (54.67%) of the patients were male giving a male to female ratio of roughly 1:1.

The most frequent clinical presentation of the study group was nephrotic syndrome (54.62%) followed by nephrito-nephrotic presentation (25.22%) and nephritic syndrome (10.08%) and systemic lupus erythematosus (10.08%)

Minimal change disease was the most frequent disease pattern (16 cases & 13.44%) in study group followed by membranous glomerulonephritis and IgM nephropathy (15 cases; 12.61%, each).

In the present study all the patients with minimal change disease and most of the patients with membranous nephropathy and IgM nephropathy clinically presented as nephrotic syndrome. On the other hand most of the patients with membranoproliferative glomerulonephritis had nephrito-nephrotic presentation. Maximum number of patients with diffuse proliferative glomerulonephritis presented clinically as nephritic syndrome

Regarding diffuse proliferative glomerulonephritis, maximum number of patients presented with nephritic syndrome followed by nephrite-nephrotic presentation. Mean age of patient was 34.21 years . The most frequent immunoglobulin deposition was IgG which occurred in 14 cases followed by IgM in10 cases. All were granular deposits and distributed in mesangium and along the GBM

Regarding crescentic glomerulonephritis, predominant pattern of presentation was with nephrito-nephrotic features followed by nephrotic syndrome. Mean age of patients was 40 years. The most frequent immune deposition was IgG and C3 which occurred in all 4 cases followed by IgM in 2 cases. All were linear deposits and distributed in mesangium and along the GBM

Of the total 13 cases of membranous nephropathy, 11 cases presented with nephrotic syndrome the rest (2 cases) had nephrito-nephrotic presentation. Mean age of patients was 32.38 years. The most frequent immune deposition was IgG which occurred in all 13 cases followed by C1q in 6 cases. All were granular deposits and distributed along the GBM

Of the total 16 cases of minimal change disease, all presented with nephrotic syndrome. Eight cases were children and 8 cases were adults. Mean age of patients was 24.13 years. Nine were male and 7 were female. Ten cases show mild focal deposition of IgM

Regarding focal segmental glomerulosclerosis, all of the patients came with nephrotic syndrome. Six

were male and three were female. Mean age of patients was 35.59 years. The most frequent immune deposition was IgG which occurred in all six cases followed by IgM in 3 cases. All were granular deposits and were focal and segmental in distribution.

Of the total 15 cases of membranoproliferative glomerulonephritis, 12 patients came with nephrito-nephrotic presentation followed by 3 patients with nephrotic syndrome. Mean age of the patients was 37.93 years. The most frequent immune deposition was IgG which occurred in all 15 cases followed by IgM and C3 in 13 cases each. All were granular deposits and distributed in both mesangium and along the GBM

Twelve patients were morphologically diagnosed as IgA nephropathy. Of them 8 patients presented with nephrotic syndrome followed by 2 cases with nephritic syndrome and 2 cases with nephrito-nephrotic presentation. Mean age of the patients was 29.3 years. The most frequent immune deposition was IgA which occurred in all 12 cases followed by IgM in 6 cases. All were granular deposits and distributed in the mesangium

Among 119 cases, only 2 cases (3.57%) were diagnosed as C1q nephropathy. Both of them were female, one of which presented with nephrotic syndrome while another one had nephrito-nephrotic presentation. Mean age of the patients was 34 years. Regarding immune depositions IgM, C1q and C3 were present in the glomeruli of

both cases. IgG deposition is present in one of the case only. All were granular deposit and distributed in mesangium

C3 glomerulopathy was diagnosed in 6 cases. Most of these patients had nephrotic syndrome (4 cases). Other two patients had nephrito-nephrotic presentation. Mean age of the patients was 23.83 years. The most frequent immune deposition was C3 which occurred in all 6 cases followed byIgG and IgM each in 4 cases. All were granular deposits and distributed both in mesangium and along the GBM

Maximum number of patients with IgM nephropathy came with nephrotic syndrome followed by nephritic syndrome. Mean age of the patients was 24.23 years. The most frequent immune deposition was IgM which occurred in all 15 cases followed by IgG in 7 cases. All had granular deposits and distributed in mesangium

Of the total 13 patients with lupus nephritis, 12 patients presented with the systemic manifestations of SLE. In a single case nephrotic syndrome was the presentation. Mean age of patient was 25.9 years. The most frequent immunoglobulin deposition was IgG which occurred in all 13 cases followed by IgM and IgA in 12 cases, C3 and C1q were present in 11 and 2 cases respectively. All were granular deposits and distributed in both mesangium and along the GBM
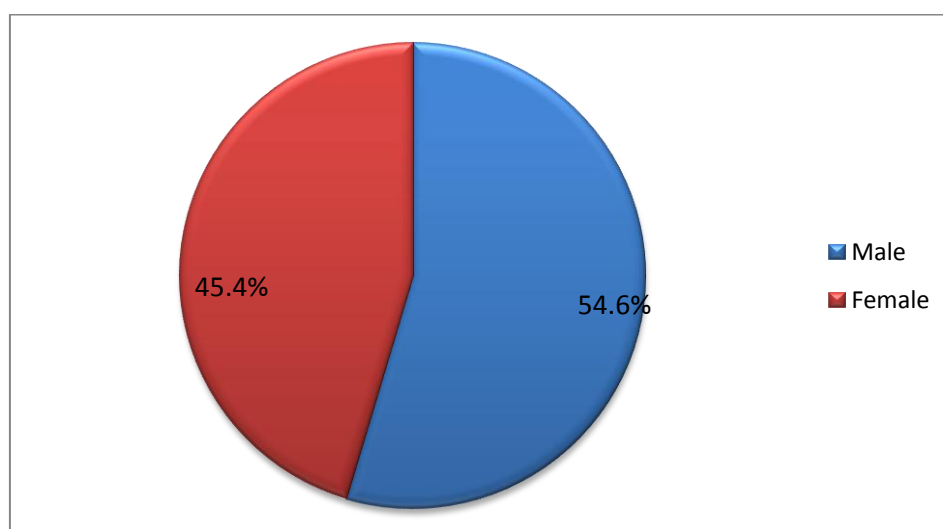

Fig-1: Pie chart showing distribution of patients by sex (n =119).

Table 1: Clinical presentations of present study (n= 119).

Clinical presentation	Frequency (Percentage)	Male	Female
Nephrotic syndrome	65(54.62%)	40	25
Nephritic syndrome	12(10.08%)	5	7
Nephrito-nephrotic presentation	30(25.22%)	20	10
Systemic lupus erythematosus	12(10.08%)	0	12
Total	119(100%)	65	54

Table 2 Morphological pattern of diseases in the study group (n=119).

Morphological type	Frequency		
	Children(≤ 18yrs)	Adult	Total
Diffuse proliferative glomerulonephritis	3	11	14 (11.7%)
Crescentic glomerulonephritis	1	3	4 (3.3%)
Membranous glomerulonephritis	2	11	13 (10.93%)
Minimal change disease	8	8	16 (13.44%)
Focal segmental glomerulosclerosis	1	8	9 (7.56%)
Membranoproliferative glomerulonephritis	1	14	15 (12.61%)
IgA Nephropathy	3	9	12 (10.08%)
C1q nephropathy	0	2	2 (1.68%)
C3 glomerulopathy	2	4	6 (5.05%)
IgM Nephropathy	6	9	15 (12.61%)
Lupus nephritis	4	9	13 (10.93%)
Total	31	88	119 (100%)

Table 3 Correlation of morphological pattern and clinical presentation of the study group

Morphological type	Nephrotic presentation	Nephritic presentation	Nephrito-nephrotic presentation	SLE	Total
Diffuse proliferative glomerulonephritis	1	8	5	0	14
Crescentic glomerulonephritis	1	0	3	0	4
Membranous glomerulonephritis	11	0	2	0	13
Minimal change disease	16	0	0	0	16
Focal segmental glomerulosclerosis	9	0	0	0	9
Membranoproliferative glomerulonephritis	3	0	12	0	15
IgA Nephropathy	8	2	2	0	12
C1q nephropathy	1	0	1	0	2
C3 glomerulopathy	4	0	2	0	6
IgM Nephropathy	11	2	2	0	15
Lupus nephritis	0	0	1	12	13
Total	65	12	30	12	119

Table 4-1: Clinical presentation of diffuse proliferative glomerulonephritis

Total case	Clinical presentation	Frequency	Male	Female	Mean age
14	Nephrotic	1	1	0	24
	Nephritic	8	3	5	34.5
	Nephrito-nephrotic	5	2	3	35.8
	Systemic lupus erythematosus	0	0	0	0
Total		14	6	8	34.21

Table 4-2: Immunofluorescence findings of diffuse proliferative glomerulonephritis

DIF	Frequency	Negative	Positive				Pattern	Distribution
			Mild	Mod	Strong	Total		
IgG	14	0	6	8	0	14	Granular	Mesangial and along the GBM
IgM	14	4	7	3	0	10	Granular	Mesangial and along the GBM
IgA	14	0	2	0	0	2	Granular	Along the GBM
C3	14	7	2	3	0	5	Granular	Mesangial and along the GBM
C1q	7	4	1	2	0	3	Granular	Mesangial and along the GBM

Table 5-1: Clinical presentation of crescentic glomerulonephritis

Total case	Clinical presentation	Frequency	Male	Female	Mean age in years
4	Nephrotic	1	1	0	50
	Nephritic	0	0	0	0
	Nephrito-nephrotic	3	3	0	36.67
	Systemic lupus erythematosus	0	0	0	0
Total		4	4	0	40

Table 5-2: Immunofluorescence findings of crescentic glomerulonephritis

DIF	Frequency	Negative	Positive				Pattern	Distribution
			Mild	Mod	Strong	Total		
IgG	4	0	1	2	1	4	Linear	Mesangial and along the GBM
IgM	4	2	0	2	0	2	Linear	Mesangial and along the GBM
IgA	4	4	0	0	0	0	0	
C3	4	0	1	3	0	4	Linar	Mesangial and along the GBM
C1q	2	1	0	1	0	1	Linear	Mesangial and along the GBM

Table 6-1: Clinical presentation of membranous glomerulonephritis

Total case	Clinical presentation	Frequency	Male	Female	Mean age
13	Nephrotic	11	5	6	34.36
	Nephritic	0	0	0	0
	Nephrito-nephrotic	2	1	1	21.5
	Systemic lupus erythematosus	0	0	0	0
Total		13	6	7	32.38

Table 6-2 : Immunofluorescence findings of membranous glomerulonephritis

DIF	Frequency	Negative	Positive				Pattern	Distribution
			Mild	Mod	Strong	Total		
IgG	13	0	5	8	0	13	Granular	Along the GBM
IgM	13	8	3	2	0	5	Granular	Along the GBM
IgA	13	0	0	0	0	0		
C3	13	11	0	2	0	2	Granular	Along the GBM
C1q	8	2	5	1	0	6	Granular	Along the GBM

Table 7-1: Clinical presentation of minimal change disease.

Total case	Clinical presentation	Frequency	Male	Female	Mean age
16	Nephrotic	16	9	7	24.13
	Nephritic	0	0	0	0
	Nephrito-nephrotic	0	0	0	0
	Systemic lupus erythematosus	0	0	0	0
Total		16	9	7	24.13

Table 7-2: Immunofluorescence findings of minimal change disease

DIF	Frequency	Negative	Positive				Pattern	Distribution
			Mild	Mod	Strong	Total		
IgG	16	11	5	0	0	5		Focal
IgM	16	6	10	0	0	10		Focal
IgA	16	16	0	0	0	0		
C3	16	16	0	0	0	0		
C1q	6	6	0	0	0	0		

Table 8-1: Clinical presentation of focal segmental glomerulosclrosis.

Total case	Clinical presentation	Frequency	Male	Female	Mean age
9	Nephrotic	9	6	3	35.59
	Nephritic	0	0	0	0
	Nephrito-nephrotic	0	0	0	0
	Systemic lupus erythematosus	0	0	0	0
Total		9	6	3	35.59

Table 8-2: Immunofluorescence findings of focal segmental glomeruloscerosis.

DIF	Frequency	Negative	Positive				Pattern	Distribution
			Mild	Mod	Strong	Total		
IgG	9	3	6	0	0	6	Granular	Focal, Segmental
IgM	9	6	3	0	0	3	Granular	Focal, Segmental
IgA	9	9	0	0	0	0	Granular	Focal, Segmental
C3	9	7	2	0	0	2	Granular	Focal, Segmental
C1q	4	3	1	0	0	1	Granular	Focal, Segmental

Table 9-1: Clinical presentation ofmembranoproliferative glomerulonephritis

Total case	Clinical presentation	Frequency	Male	Female	Mean age
15	Nephrotic	3	3	0	42.33
	Nephritic	0	0	0	0
	Nephrito-nephrotic	12	9	3	31.54
	Systemic lupus erythematosus	0	0	0	0
Total		15	12	3	37.93

Table 9-2: Immunofluorescence findings of membranoproliferative glomerulonephritis

DIF	Frequency	Negative	Positive				Pattern	Distribution
			Mild	Mod	Strong	Total		
IgG	15	0	0	9	6	15	Granular	Mesangial and along the GBM
IgM	15	2	8	4	1	13	Granular	Mesangial and along the GBM
IgA	15	15	0	0	0	0	Granular	Mesangial and along the GBM
C3	15	2	9	4	0	13	Granular	Mesangial and along the GBM
C1q	9	2	3	2	2	7	Granular	Mesangial and along the GBM

Table 10-1: Clinical presentation of IgA nephropathy

Total case	Clinical presentation	Frequency	Male	Female	Mean age
	Nephrotic	8	7	1	29.8
	Nephritic	2	1	1	21
	Nephrito-nephrotic	2	2		34
	Systemic lupus erythematosus	0	0	0	0
Total		12	10	2	29.3

Table 10-2: Immunofluorescence findings of IgA nephropathy

DIF	Frequency	Negative	Positive				Pattern	Distribution
			Mild	Mod	Strong	Total		
IgG	12	7	4	1	0	5	Granular	Mesangial
IgM	12	6	5	1	0	6	Granular	Mesangial
IgA	12	0	0	11	1	12	Granular	Mesangial
C3	12	10	2	0	0	2	Granular	Mesangial
C1q	6	6	0	0	0	0	0	0

Table 11-1: Clinical presentation of C1q nephropathy

Total case	Clinical presentation	Frequency	Male	Female	Mean age
	Nephrotic	1	0	1	30
	Nephritic	0	0	0	0
	Nephrito-nephrotic	1	0	1	38
2	Systemic lupus erythematosus	0	0	0	0
Total		2	0	2	34

Table 11-2: Immunofluorescence findings of C1q nephropathy

DIF	Frequency	Negative	Positive				Pattern	Distribution
			Mild	Mod	Strong	Total		
IgG	2	1	1	0	0	1	Granular	Mesangial
IgM	2	0	2	0	0	2	Granular	Mesangial
IgA	2	2	0	0	0	0		
C3	2	0	2	0	0	2	Granular	Mesangial
C1q	2	0	0	2	0	2	Granular	Mesangial

Table 12-1: Clinical presentation of C3 glomerulopathy

Total case	Clinical presentation	Frequency	Male	Female	Mean age
	Nephrotic	4	2	2	24.5
	Nephritic	0	0	0	0
	Nephrito-nephrotic	2	2		22.5
6	Systemic lupus erythematosus	0	0	0	0
Total		6	4	2	23.83

Table 12-2: Immunofluorescence findings of C3 glomerulopathy

DIF	Frequency	Negative	Positive				Pattern	Distribution
			Mild	Mod	Strong	Total		
IgG	6	2	4	0	0	4	Granular	Mesangial and along the GBM
IgM	6	2	4		0	4	Granular	Mesangial and along the GBM
IgA	6	6	0	0	0	0	Granular	Mesangial and along the GBM
C3	6	0	0	5	1	6	Granular	Mesangial and along the GBM
C1q	6	6	0	0	0	0	0	0

Table 13-1: Clinical presentation of IgM nephropathy

Total case	Clinical presentation	Frequency	Male	Female	Mean age
15	Nephrotic	11	6	5	24.56
	Nephritic	2	1	1	23.23
	Nephrito-nephrotic	2	1	1	26.37
	Systemic lupus erythematosus	0	0	0	0
Total		15	8	7	24.23

Table 13-2: Immunofluorescence findings of IgM nephropahy

DIF	Frequency	Negative	Positive				Pattern	Distribution
			Mild	Mod	Strong	Total		
IgG	15	8	6	1	0	7	Granular	Mesangial
IgM	15	0	0	14	1	15	Granular	Mesangial
IgA	15	15	0	0	0	0	Granular	Mesangial
C3	15	10	5	0	0	5	Granular	Mesangial
C1q	6	6	0	0	0	0	0	0

Table1 4-1: Clinical presentation of lupus nephritis

Total case	Clinical presentation	Frequency	Type and its frequency	Male	Female	Mean age
13	Nephrotic	1	IV(1)	0	1	
	Nephritic	0		0	0	
	Nephrito-nephrotic	0		0	0	
	Systemic lupus erythematosus	12	I(1) 11(1) III(3) IV(3) V (4)	0	12	25.69
Total		13		0	13	25.9

Table 14-2: Immunofluorescence findings of lupus nephritis

DIF	Frequency	Negative	Positive				Pattern	Distribution
			Mild	Mod	Strong	Total		
IgG	13	0	0	10	3	13	Granular	Mesangial and along the GBM
IgM	13	1	10	2	0	12	Granular	Mesangial and along the GBM
IgA	13	1	5	6	1	12	Granular	Mesangial and along the GBM
C3	13	2	5	6	0	11	Granular	Mesangial and along the GBM
C1q	13	10	1	2	0	3	Granular	Mesangial and along the GBM
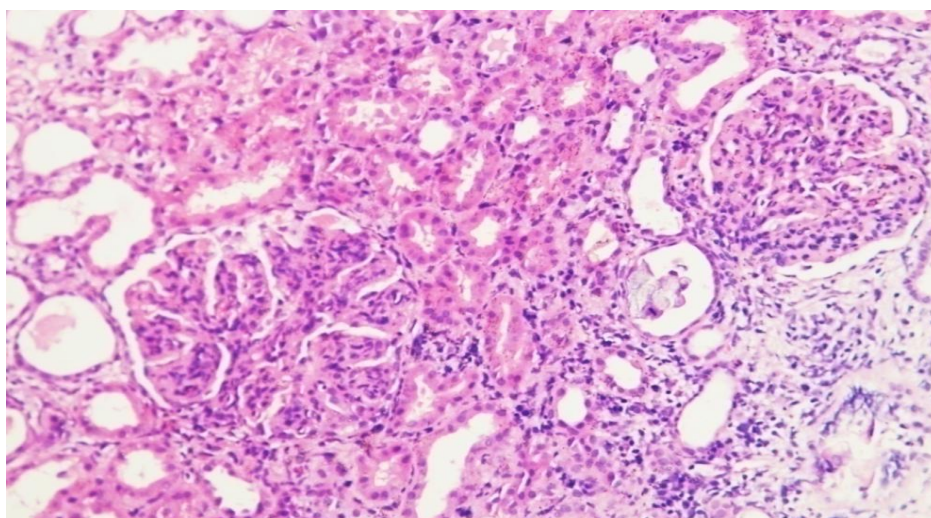
Figure- 1: C3 glomerulopathy showing glomerular hypercellularity and thickened GBM. (Case no. 10, H&E stain, 400X)
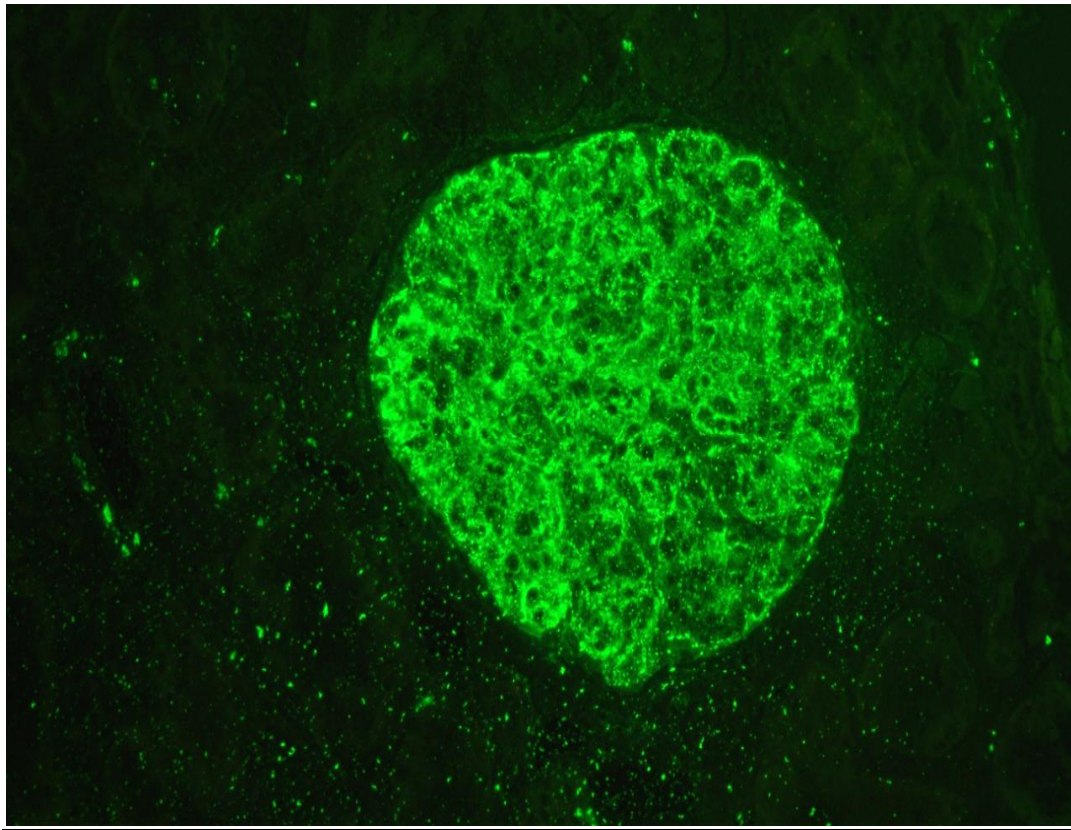
Figure-2 Strong, granular deposition of C3 along basement membrane and mesangium. (Case no 10, DIF)

Discussion

Renal glomerular diseases, both primary and secondary are initially diagnosed by histopathology (including special stains) followed by immunofluorescence study. Electron microscope is required in selected cases. In the present study, 119 cases of glomerular diseases were categorized. The clinical and immunofluorescence characteristics were correlated with various types of morphological pattern of glomerular disease.

Devasahayam et al., Markowitz et al., Said et al., Hisano et al.,Vzjak et al. and some others worked on pathology, clinical presentation and outcomes of C1q nephropathy.[8-12] Moreover, Pescoviz et al. first stated one C1qN to be treated successfully with rituximab, a chimeric anti-human CD20 antibody, Sinha et al. also described role of rituximab on C1q nephropathy.[13,14]

Including a consensus report there are many publication on C3 glomurulopathy and role of eculizumab, an anti-compliment agent (C5 antibody) on C3 glomerulopathy.[15-21]

IgM nephropathy is also relatively recently described entity defined by immunologic feature.[22-24]

So far known there is no publication in Bangladesh about these recently introduced glomerular diseases. In his study these issues were addressed and parameters were clinicopathologically correlated.

In the present study, the mean age of patients was 30.29 ± 14.65 years. The age range was 3 to 67 years. Among the total recruited patients 31 were children ($\leq$ 18yrs) and 88 were adult ((>18yrs) . Al-Saegh et al. showed the age range 6-50 years. The present study, the affected pediatric patients were a little bit younger and adult patient were a little bit older compared to study by Al-Saegh et al.[25]

In present study, regarding the sex distribution of recruited 119 patients, 65(54.5%) were male and 54(45.5%) were female The male to female ratio is roughly 1:1 which is almost similar to the study done by Al-Saegh et al. and slightly lower to the study (58.18% male) described by Hossain et al.[25,3]

Regarding the clinical presentations, the most frequent clinical presentation of the study group was the nephrotic syndrome (54.62%) followed by nephrito-nephrotic presentation (25.22%), nephritic syndrome and systemic lupus erythematosus (10.08%, each). Mean age of nephrotic syndrome was 28.98 years (Table 4-2). Cameron (1980) in his study of 746 cases, found nephrotic syndrome as the presenting symptom in 431cases(57.77%).In a study on Bangladeshi population, by Ziauddin et al. showed 56.6% cases as nephrotic syndrome. Hossain et al. and Al-Saeghet al. also found nephrotic syndrome as a predominant clinical presentation. All are similar with the findings of present study.[26.3.25]

In present study, regarding histological diagnosis minimal change disease was the most frequent disease pattern (16 cases & 13.44%) followed by membranoproloferative and IgM nephropathy (15cases each &12.61% each). The next frequent group is lupus nephritis (13 cases, 10.93%) followed by IgA nephropathy (12 cases, 10.08%)(Table. In a study by Goddard et al. IgA nephropathy was the most frequent glomerular disease but Neves et al. showed membranous nephropathy as most common(49.7%) glomerulopathy followed by minimal change disease (25.2%), Shakir et al. showed focal segmental glomerulosclerosis (26.3%)was most frequent in their study followed by mesangio-proliferative GN(22.5%) and minimal change disease(17.1%). Al-Saegh et al. found focal segmental glomerulosclerosis (29.31) as most frequent diagnosed glomerular disease followed by minimal change disease(20.6%). In Bangladesh Sharmin et al. Showed 5 IgA nephropathy out of 42 biopsies(11.90%).But Hossain et al. found mesangio-proliferative GN (32.73%) was the most frequent glomerulonephritis. Banu et al. conducted a retrospective study on 786 cases of renal biopsy reported over five years, from January 2009 to December 2013, published in January 2017 and found mesangial proliferative glomerulonephritis (32.4%) was the commonest diagnosis followed by membranoproliferative

glomerulonephritis (29.42%). Above mentioned studies found different types of findings in their study.[3,25,27-30]

Pound et al. 1987 addressed mesangial proliferative glomerulonephritis and diffuse endocapilary proliferative glomerulonephritis together as diffuse proliferative glomerulonephritis.[31] In present study, we also lumped together mesangial proliferative glomerulonephritis and diffuse endocapilary proliferative glomerulonephritis as diffuse proliferative glomerulonephritis. Regarding diffuse proliferative glomerulonephritis the most frequent immunoglobulin deposition was IgG which occurred in 14 cases followed by IgM in10 cases. All were granular deposits and distributed in mesangium and along the GBM. Banu et al. found Ig M as the most frequent mesangial immune deposit which is not similar to this study.[30]

Regarding crescentic glomerulonephritis, present study found 4 cases (3.36%) out of 119 cases. Mean age of patients was 40 years. The most frequent immune deposition was IgG and C3 which occurred in all 4 cases followed by IgM in 2 cases. All were linear deposits and distributed in mesangium and along the GBM. Hossain et al.[3] found crescentic glomerulonephritis 2.73% which is slightly lower than present study. They also found mean age 57.67 years of the patient of crescentic glomerulonephritis, which is higher than present study. Regarding immune deposition he found IgG and C3 immune deposition in mesangium and along the GBM which is similar to present study.

Regarding membranous glomerulonephritis, in present study out of 119 cases, 13 cases (10.93%) were diagnosed as membranous glomerulonephritis. The most frequent immune deposition was IgG which occurred in all 13 cases followed by C1q in 6 cases. All were granular deposits and distributed along the GBM. Das et al. found membranous glomerulonephritis 10.7 % and most frequent immune deposition Ig G which is similar to present study.[32]

In present study, minimal change disease was the most frequent morphological pattern of glomerular disease (16 cases and 13.44%), all presented with nephrotic syndrome. Eight cases were children and 8 cases were adults. Ten cases show mild focal deposition of IgM. Khakurel et al. found minimal change disease as the most frequent morphological pattern of glomerular disease and most of them presented with nephrotic syndrome.[33]

Regarding focal segmental glomerulosclerosis, in the present study 6 patients were male and 3 patients were female. The male female ratio was 2:1. All patients presented as nephrotic syndrome. Immunofluorescence findings showed mostly granular, focal, segmental staining for IgG followed by IgM. D'Agati et al.2011 showed total 65 of focal segmental glomerulosclerosis, 46 were male and 19 were female.[34] The male, female ratio was 2.4:1. All patients had nephrotic syndrome and most of the immunofluorescence findings were granular deposition of IgG. All of these were similar to present study.

Regarding membranoproliferative glomerulonephritis, Banu et al. conducted a retrospective study on 786 cases of renal biopsy reported over five years, from January 2009 to December 2013, found membranoproliferative glomerulonephritis (29.42%) as second most frequent morphological pattern of glomerulonephritis which is similar to present study but the percentage was higher than present study.[31]

In present study 12 patients (10.08%) were morphologically diagnosed as IgA nephropathy. Of them, 8 patients presented with nephrotic syndrome followed by 2 cases with nephritic syndrome and 2 cases with nephrito-nephrotic presentation. Mean age of the patients was 29.3 years. The most frequent immune deposition was IgA which occurred in all 12 cases followed by IgM in 6 cases. All were granular deposits and distributed in the mesangium. Sharmin et al 1997 found IgA nephropathy 11.91% which is almost same to present study.[30]

Medjeral et al. reviewed 4554 biopsies, among them 61 were C3 glomerulopathy representing an incidence (1.34%) of biopsy-proven C3 glomerulopathy.[16] The incidence was higher in present study. They also found male predominance and median age 25 years which were similar to present study.

The reported frequency of IgM nephropathy in literature has varied widely from 2% to 18.5%.[35-37] In fact, the frequency indicated a rising trend during the early period of its recognition. The studies by Cohen et al. and Bhasin et al. were the first two pioneering studies reported incidence of 2% and 6.1% respectively in their biopsies.[35,36] These reports were soon followed by a study of 23 patients from England by Lawler et al.[38] showing an incidence of 11.7% of IgM nephropathy. Hsu et al. from Taiwan found a frequency of 10% of IgM nephropathy in all biopsies with primary glomerular disease.[39] More recently, Mubarak et al. found a frequency of 18.5% of IgM nephropathy.[37] The present study showed 12.61% of IgM nephropathy which is similar to study of Lawler et al.[38]

Devasahayam et al. and Mallehappa et al. stated the prevalence of C1q nephropathy in renal biopsies varied from 0.2% to 16%, the present study also found similar result.[8,40] Vizjak et at showed 1.9% prevalence of C1q nephropathy which is also similar with present study (1.68%).[12] Markowitz et al. showed female predominance (78.9%) and nephritic presentation which is also similar to present study.[41]

The complement C3 is activated by both classical and alternate pathway. But in classical pathway IgG and IgM are involved. When C3 is activated without help of IgG and IgM that indicates activation of C3 by alternate pathway. So C3 glomerulopathy indicates the activation of alternate pathway. IgA is also involve the alternate pathway. Thomas et al. stated about recent insights into pathogenetic links between C3 glomerulopathy and much more common forms of GN including IgA nephropathy underline the expanding importance of complement

dysregulation in the pathophysiology of GN.[18] As both of the glomerular disease (C3 glomerulopathy and IgA nephropathy) involve alternate pathway and have pathogenitic link.

Regarding lupus nephritis, mean age of patients with lupus nephritis of present study was 25.69 years. All patients were female; Most of the patient presented with systemic manifestation of SLE, in a single case nephrotic syndrome was the presentation. The most frequent immunoglobulin deposition was IgG which occurred in all 13 cases followed by IgM and IgA in 12 cases. All were granular deposits and distributed in both mesangium and along the GBM. Baqui et al. showed mean age of the patient of lupus nephritis 26 years, male female ratio was 1:10, all patients were presented with systemic manifestations, and most frequent immunoglobulin deposition was IgG. All are almost same to present study.[42]

Conclusion

In this study we addressed IgM nephropathy (15 case, 12.61%), C3 glomerulopathy (6 cases, 5.04%), C1q nephropathy (2 cases, 1.68%) first time in Bangladesh as well as IgA nephropathy (12 cases, 10.08) mostly based on Immunofluorescence findings. As now various type of immunotherapy are introduced in the therapeutic world and glomerular diseases are mostly immune mediated. It's a new hope for renal disease. The recent availability of an anti-complement agent (eculizumab) has allowed to consider therapeutic options for C3 glomerulopathy.

Authors Contribution
Data gathering and idea owner of this study: Nur-E-Jannatul Ferdous & Md. Golam Mostofa.
Study design: Nur-E-Jannatul Ferdous & Enamul Kabir
Data gathering:. Nur-E-Jannatul Ferdous & SK. Md. Jaynul Islam

Writing and submitting manuscript: Nur-E-Jannatul Ferdous, Dabashis Patowary, Tania Gaffar & Sabina Yeasmin
Editing and approval of final draft: Md. Nasimul Islum & Rashid Khan

Reference

1. Nelson G. Ordonez and Juan Rosai: Urinary tract: Kidney, renal pelvis, and ureter; Bladder' In: Rosai and Ackerman's Surgical Pathology, 10th ed., Mosby Elsevier .London, 2011: 17: pp 1101-72

2. Khalid, Jamal Ahmad, MuhammadAzmat Khan: Histopathological pattern of glomerular lesions on percutaneous renal biopsy in protenuric patient: Pak Arme Forces Med J 2017; 67 (2): 211-15.

3. Hossain T, Begum M, Rahman A, Kamal M. Immune Deposits in glomerular diseases and their clinical, histopathological and immuunopathological correlation, Bangladesh Journal of Pathology. 2011; 26(1): 14-9.

4. Pasquariello A, Innocenti M, Batini V, Rindi S, Moriconi L. Routine immunofluorescence and light microscopy processing with a single renal biopsy specimen: 18 years' experience in a single centre. J Nephrol. 2000 Mar-Apr;13(2):116-9.

5. Schena FP, Gesualdo L. Renal biopsy--beyond histology and immunofluorescence. Nephrol Dial Transplant. 1994;9(11):1541-4.

6. Wasserstein AG. Membranous glomerulonephritis. J Am Soc Nephrol. 1997 Apr; 8(4): 664-74.

7. Larsen S, Brun C. Immune deposits in human glomerulopathy. Fluorescent microscopy findings in 366 kidney biopsies correlated to symptoms, clinical course and immunosuppressive therapy. Acta Pathol Microbiol Scand A. 1979 Sep;87A(5):321-33.

8. Devasahayam, Gowrishankar Erode-Singeravelu, Zeenat Bhat, Tony Oliver, Arul Chandran, XuZeng 2016; Clq Nephropathy: The Unique Underrecognized Pathological Entity, European Renal Association – European Dialysis and Transplant Assoc, Oxford JournalsOxford University 1753-0784.,

9. Markowitz, J. A. Schwimmer, M. B. Stokes et al., "Clq nephropathy: a variant of focal segmental glomerulosclerosis," Kidney International, 2003 vol. 64, no. 4, pp. 1232-1240.

10. Said, M L. D. Comell, A. M. Valeri et al., "Clq deposition in the renal allograft: a report of 24 cases," Modern Pathology, 2010: vol. 23, no. 8, pp. 1080-1088.

11. Hisano S, Fukuma Y, Segawa Y, et al.: Clinicopathologic correlation and outcome of Clq nephropathy. Clin J Am SocNephrol 2008; 3: 1637-1643.

12. Vizjak A, Ferluga D, Rozic M, et al. Pathology, clinical presentations, and outcomes of Clq nephropathy. J Am SocNephrol 2008; 19: 2237-2244.

13. Pescovitz MD. Rituximab, an anti-cd20 monoclonal antibody: history and mechanism of action. Am J Transplant 2006;6:859-866.

14. Sinha A, Bagga A, Moudgil A. Rituximab in patients with the steroid-resistant nephrotic syndrome. N Engl J Med 2007;356:2751-2752.

15. Pickering MC, D'Agati VD, Nester CM, et al. C3 glomerulopathy: consensus report. *Kidney Int*2013;*84: 1079-1089.*

16. Medjeral-Thomas NR, O'Shaughnessy MM, O'Regan JA, Traynor C, Flanagan M, Wong L, et al. C3 glomerulopathy: Clinicopathologic features and predictors of outcome. Clin J AM Soc Nephrol. 2014; 9: 46-53.

17. Barbour TD, Pickering MC, Cook HT*:* Recent insights into C3 glomerulopathy.*Nephrol Dial* Transplant: *2013: 28: 1685–1693.*

18. Thomas N, Morgan BP, Nast CC, Noel L-H, Peters DK, Rodríguez de Córdoba S, Servais A et al.C3 glomerulopathy: consensus report. Kidney Inter 2013 Oct 30 ; 84:1079-89.

19. Bomback AS, Smith RJH, Barile GR, Zhang y, Heher EC, Herlitz L et al: Eculizumab for Dense Deposit Disease and C3 Glomerulonephritis. Clin J Am Soc Nephrol 2012 Mar: 8; 7(5): 748-56.

20. Donia AF, Sobh MA, Moustafa FE, Bakr MA, Foda MA: Clinical significance and long-term evolution of minimal change histopathologic variants and of IGM nephropathy among Egyptians. J Nephrol. 2000; 13(4): 275-81.

21. Sethi S, Fervenza FC, Zhang Y, Zand L, Vrana JA, Nasr SH, Theis JD, Dogan A, Smith RJH. C3 Glomerulonephritis: clinicopathologic findings, complement abnormalities, glomerular proteomic profile, treatment and follow-up. Kidney Inter 2012 Jun 6 [Epub ahead of print]; 82:465-73, 2012.

22. Kopolovic J, Shvil Y, Pomeranz A, Ron N, Rubinger D, Oren R. (1987). IgM nephropathy: morphological study related to clinical findings. Am J Nephrol, V0l. 7, No. pp, 275-80.

23. Helin H, Mustonen J, Pasternack A, Antonen J: IgM-associated glomerulonephritis. 1982; 31(1): 11-6.

24. Hamed RM: Clinical significance and long-term evolution of mesangial proliferative IgM nephropathy among Jordanian children. Ann Saudi Med. 2003; 23(5): 323-7.

25. Al-Saegh Riyadh Muhi and LinaWagih Assad, The Spectrum of Glomerular Diseases as Studied by Immunofluorescence Microscopy: a Single Center Study in Iraq Arab Journal of Nephrology and Transplantation. 2013 Sep;6(3):161-7

26. Ziauddin A and Hossain, A clinicopathologic analysis of glomerulonephritis, Bangladesh Armed Forces Medical JounalVol-XVII 1993, 51-54.

27. Goddard.J. and A.N.2014 Turner,Kidey and urinary tract disease, Brian R. Waiker, Nicki R. Colledge, Stuart H. Ralston and Ian D. Penmen, Davidson's Principles & Practice of Medicine, 22 th edition, 17; 461-524

28. Shakir IK, Al-Saedi AJ, Al-Salam S, Saleem MS, Al-ShammaIA.Spectrum of glomerular disease in Iraqi patients from a single center. Saudi J Kidney Dis Transpl.2002 October-December; 13(4): 515-9.

29. Sharmin F, Khan BR, Rahman M, Rashid HU, Islam B, Kamal M, Borua AR, Chowdhury MA, Mohsin AU, Ahmed S: IgA Nephropathy in Teaching Hospital of Dhaka.Bangladesh Med Res Counc Bull, . Apr 1997, 23 (1),25-9

30. Banu SG, Ruhini Kumar Das, Mohammed Kamal: Distribution of immune Deposits in the glomerular mesangiumin mesangial proliferative and mesangiocapillary glomerulonephritis; Bangladesh J Pathol 22 (2); 13-15.

31. Pound SE, Macdonald M, Thomson Detal: Diffuse proliferative glomerulonephritis: How many types ? Histopathology, 1987: 11(3)227-43.

32. Das RK, Saleh AF, Kabir AN, Talukder SI, Kamal M: Immunofluorescence studies of renal biopsies: Dinajpur Med Col J: 2008: 1(1): 8-13.

33. Khakurel, R.K. Agrawal, R.Haa: Pattern of glomerular disease in Nepal: A single centre experience: Saudi J Kidney Dis Transpl: 2015: 26 (4): 833-838.

34. D'Agati VD, Kaskel FJ, Falk RJ Focal Segmental glomerulosclerosis.N.Engl.J.Med. 365,2011, 2398-2411

35. Cohen AH, Border WA, Glassock RJ: Nehprotic syndrome with glomerular mesangial IgM deposits. Lab Invest. 1978; 38(5): 610-9.

36. Bhasin HK, Abuelo JG, Nayak R, Esparza AR: Mesangial proliferative glomerulonephritis. Lab Invest. 1978; 39(1): 21-9.

37. Mubarak M, Kazi JI, Shakeel S, Lanewala A, Hashmi S, Akhter F. Clinicopathologic characteristics and steroid response of IgM nephropathy in children presenting with idiopathic nephrotic syndrome. APMIS. 2011; 119(3): 180-6.

38. Lawer W, Williams G, Tarpey P, Mallick NP. (1980). IgM associated primary diffuse mesangial proliferative glomerulonephritis. J ClinPathol, Vol. 33, No. 11, pp. 1029-38.

39. Hsu HC, Chen WY, Lin GJ, Chen L, Kao SL, Huang CC, et al: Clinical and immunopathologic study of mesangial IgM nephropathy: report of 41 cases. Histopathology. 1984; 8(3): 435-46.

40. Malleshappa R. Ranganath, A. P. Chaudhari, A. Ayiangar, and S. Lohitaksha, "Clq nephropathy presenting as acute renal failure," Saudi Journal of Kidney Diseases and Transplantation, 2011, vol. 22, no. 2, pp. 324-326.

41. Markowitz, J. A. Schwimmer, M. B. Stokes et al., "Clq nephropathy: a variant of focal segmental glomerulosclerosis," Kidney International, 2003 vol. 64, no. 4, pp. 1232-1240.

42. Baqui M.N, ShabnamAkhter, Enamul Kabir, Mohammad Shamiul Islam: A clinicopathologicalsudy on lupas nephritis; experience of 34 cases from Bangladesh: J Nephropharmacol. 2016: 5(2): 19-23.