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Original Article

The Spectrum of Glomerular Diseases as Studied by Immunofluorescence Microscopy: a Single Center Study in Iraq

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Abstract

Introduction: Immunofluorescence (IF) microscopy is an important tool for the diagnosis of glomerular diseases. In this study, we focused on using IF technique together with light microscopy (LM) and clinical features in the diagnosis of different types of glomerulonephritis (GN). We aimed to evaluate the spectrum of glomerular diseases in our center and compare it with other centers in Iraq as well as in other countries.

Methods: We studied a total of 58 kidney biopsies taken between June 2010 and June 2012. All biopsies were examined by LM and 56 of them were examined by IF technique. Clinical information was recorded in a pre-designed form before taking the biopsy.

Results: Nephrotic syndrome was the predominant clinical presentation in this study (75.9%). Focal segmental glomerulosclerosis (FSGS) was the commonest GN in this study (29.3%) followed by minimal change disease (20.7%) and membranous glomerulonephritis (13.8%). Immune deposition was observed in 37.5% of cases and the predominant deposit was immunoglobulin G (IgG). In all cases but one, deposition was granular and was found in the glomerular basement membrane (GBM) and/or in the mesangium. In one case, IF showed dominant positive staining (3+) for complement factor 1q (C1q) in the glomerular mesangium and slightly positive staining for complement factor 3 (C_3) in the same mesangeal areas. Two cases (3.4%) fulfilled the clinical, serological and histopathological criteria of lupus nephritis (LN).

Conclusion: Nephrotic syndrome was the predominant clinical presentation and FSGS was the most commonly diagnosed GN in this study. Using IF technique and correlating it with LM, clinical, biochemical and serological markers was very useful for the correct diagnosis of glomerular diseases.

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Introduction

Glomerular disorders constitute one of the major causes of morbidity and mortality [1]. Immune mechanisms are responsible for glomerular injury in most cases of primary glomerulonephritis (GN) and many of the secondary GN [2]. Accurate diagnosis of GN requires renal biopsy and histopathological examination by light microscopy (LM), immunofluorescence (IF) and electron microscopy (EM). In addition, it requires correlating clinical features and biochemical parameters with histopathology results [4]. 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. In addition, IF yields important correlations and prognostic features [3].

Facilities for EM studies are not readily available in many institutions. In most cases, LM and IF studies are satisfactory 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 [5]. 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 [5, 6]. Lupus nephritis (LN) patients of WHO class-V show immunohistological features of primary MGN similar to hepatitis B virus related nephropathy. At the time of biopsy, when systemic lupus erythematosus (SLE) is clinically suspected, the differentiation between hepatitis B virus related MGN

and LN may be difficult or impossible [7-9]. Although sub-endothelial and mesangial prominent IgA deposits are suggestive and only tubular basement membrane deposits are specific, correct diagnosis of LN can be made by correlating typical clinical features and serological markers [5]. Hepatitis B infection may be occult, serum transaminases may be normal and there may be no history of clinical hepatitis. The study of glomerular viral antigens and serological screening are important for the diagnosis of hepatitis B virus-related nephritis [9]. C1q is the first component of the classical pathway of complement activation. C1q nephropathy is a clinical condition characterized by onset in older children and young adults with severe proteinuria or nephrotic syndrome, with resistance to steroid treatment, frequent recurrence and a poor long-term prognosis. Asymptomatic hematuria and/or proteinuria are also seen in C1q nephropathy [10, 11]. Together with the deposition of C1q, deposition of immunoglobulin is often detected in glomeruli in C1q nephropathy.

In this study, different types of GN were diagnosed using LM and IF together with interpretation of clinical, biochemical and serological features. The spectrum of glomerular disease in our center was determined and compared with other studies in Iraq and in other countries.

Methods

This study was carried out at the Iraqi medical center in Karbala. A total of 58 cases of nephrotic syndrome, nephritic syndrome, kidney grafts, asymptomatic hematuria and proteinuria in various age groups were biopsied and included in this study. The study period was from June 2010 to June 2012. Clinical information was recorded in a pre-designed form before taking the biopsy. All kidney biopsies were performed by the first author after obtaining signed informed consent. At least two specimens of renal tissue measuring 12-20 mm in length were taken per biopsy. One specimen was kept in 10% formalin for LM study and another one in transport media of Zeus solution for IF study. Specimens were kept in an ice bag and sent to the laboratory where the formalin-fixed processed tissue sections were stained by hematoxylin-eosin, reticulin, silver methnamine, congo red and Periodic Acid Schiff (PAS) stains. The specimens were then examined by LM and IF and verified by at least two histopathologists.

The following criteria were used to define different terms and various patterns of GN; adequate for IF study: presence of at least one glomerulus under fluorescent microscope; adequate for light microscopic study: presence of at least five glomeruli under LM; mesangial proliferation: more than three mesangial cells embedded in matrix of one segment; endothelial proliferation: more than 2 nuclei per capillary loop; leukocyte infiltration: more than five leukocytes per glomerulus; crescentic GN: at least 50% of the glomeruli involved as crescents; MCD: no evidence of any change; FSGS: segmental (one or two lobules) sclerosis with hyalinosis involving portions of fewer than 50% of the glomeruli in a section; sclerosis: increase in amount of homogeneous non-fibrillary extracellular material of similar composition to GBM and mesangium; MGN: diffuse thickening of GBM due to sub-epithelial deposits of immune complex without evidence of inflammation or cellular proliferation; membrano-proliferative GN (MPGN): 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 LM; mesangio-proliferative GN (MesPGN): diffuse increase in glomerular cellularity predominantly due to mesangial cells often with concomitant increase in mesangial matrix. Systemic lupus erythematosus (SLE) was diagnosed according to the criteria of the American College of Rheumatology [12].

Photographs were taken for both LM and IF studies. Fluorescein dye conjugated anti-human antibodies (lgG, IgA, IgM, C1q, fibrin and C3) were fixed with the tissue section by ten times diluted anti-sera. Type (lgG, IgA, IgM ,C1q, fibrin and C3), pattern (granular or linear), site (GBM or mesangium) and intensity of deposition in the glomeruli were observed under IF. The intensity of fluorescein isothiocyanate staining was graded subjectively from 0 to +3. Clinical information regarding age, sex, duration of disease, presentation, urine analysis, biochemical, virological and serological parameters and past medical therapy were collected from data submitted along with biopsy.

Results

The study involved biopsies taken from 58 patients, including 30 males (51.7%) and 28 (48.3%) females. Their ages ranged from 6-50 years (mean=26 years). Table-1 shows the clinical presentation of GN in this study. The commonest presentation was nephrotic syndrome (75.9 %) followed by proteinuria (36.8 %) and systemic hypertension (29.3 %).

Definitive diagnosis was possible in all cases as all specimens were considered adequate. FSGS was the commonest GN in this study (29.3%) followed by MCD (20.7%) and MGN (13.8%) as shown in table-2.

Table-3 compares our findings to the reported spectrum of glomerular diseases in other Iraqi centers at different

Table 1: Clinical presentation of GN in this study

Mode of presentation	MesPGN (n=4)	HNS (n=2)	MGN (n=8)	LN (n=2)	IgAN (n=2)	GGS (n=5)	Am (N=3)	MCD (n=12)	FSGS (n=17)	TR (n=1)	IGN ANCA^{+ve} (n=2)	Total
AKF	0	0	0	1	0	1	0	0	1	0	0	5.2 %
Nephrotic syndrome	4	1	8	2	2	4	3	8	12	0	0	75.9 %
Proteinuria	2	0	8	1	0	3	3	8	12	0	0	62.1 %
Hematuria	2	1	0	1	2	0	0	0	0	0	0	10.3 %
SLE	0	0	0	1	0	0	0	0	1	0	0	3.4 %
Nephritic syndrome	2	1	0	1	0	1	0	0	0	0	0	10.3 %
Anemia	2	1	0	2	1	1	1	0	2	0	0	17.2 %
Hypertension	3	2	4	2	1	3	2	1	0	0	1	32.8 %
CKF	1	0	2	1	0	1	1	0	1	1	2	17.2 %

ARF: acute kidney failure; SLE: systemic lupus erythematosus; CKF:chronic kidney failure; MesPN: mesangio-proliferative glomerulonephritis; HNS: hypertensive nephrosclerosis; MGN: membranous glomerulonephritis; LN: lupus nephritis; IgAN: IgA nephropathy; GGS: global glomerulosclerosis; Am: amyloidosis; MCD: minimal change disease; FSGS: focal segmental glomerulosclerosis; TR: transplant rejection; IGN: immune glomerulonephritis; ANCA: antineutrophil cytoplasmic antibody.

Table 2: Histopathological diagnoses of the studied 58 renal biopsy specimens

Diagnosis	Number
Focal segmental glomerulosclerosis	17 (29.3 %)
Minimal change disease	12 (20.7 %)
Membranous GN	8 (13.8 %)
Global glomerulosclerosis	5 (8.6 %)
Mesangio-proliferative GN	4 (6.9 %)
Amyloidosis	3 (5.2 %)
Hypertensive nephrosclerosis	2 (3.5 %)
Lupus nephritis	2 (3.5 %)
IgA Nephropathy	2 (3.5 %)
Immune glomerulonephritis (ANCA $^{+ve}$)	2 (3.5 %)
Transplant rejection	2 (1.7 %)

GN: glomerulonephritis; ANCA: antineutrophil cytoplasmic antibody.

time. FSGS topped the list in all the studies except in Mahassin study where MesPGN was the commonest lesion. MCD and MesPGN were more frequent in the period 1986-1996, while FSGS was predominant during the period 1994-2012.

Table-4 compares our findings to the reported prevalence of glomerular lesions in different countries. MCD is more prevalent in north and south African countries except in Ghana where FSGS is predominant. In Saudi Arabia, India, Singapore, Hong Kong and the United Kingdom, MCD is predominant. In Iraq, FSGS is predominant.

Of the studied 58 cases, IF examination was done in 56 cases while in two cases no specimen was available for IF. Among those 56 cases, 21 biopsies (37.5%) were IF positive and 35 biopsies (62.5%) were negative. Table-5 shows the frequency of immune deposits in studied cases.

Among 12 cases of MCD, one showed mild increased cellularity and matrix in the mesangium by LM and mesangial deposits of C3 and C1q in IF. The remaining 11 cases were normal in IF and LM. MGN was diagnosed in 8 cases with IgG and C3 deposition in all and C1q deposition in two of them. In two cases (3.45%) specimens fulfilled clinical, morphological and immunofluorescent criteria for LN. The predominant deposits in IF of LN were C3 and IgG followed by C1q and fibrin in the crescents of one case (Figures 1-2). Deposits of IgG in a smooth, diffuse, linear pattern were found in a patient who had superimposition of anti-GBM disease on pre-existing MGN (Figure-3).One case of renal allograft specimen showed C4d deposits and was diagnosed as acute transplant rejection.

Table 3: Reported spectrum of glomerular diseases in different Iraqi studies [13]

Study period	Primary glomerular disease						Secondary glomerular disease						
	FSGS	MesPGN	MCD	MPN	MPGN	RPGN	LN	Am	DM	HGN	HNS	IgAN	TR
Present study* 2010-2012 (N = 58)	17 (29.31%)	4 (6.89%)	12 (20.6%)	0	8 13.8%)	2 (3.4%)	2 (3.4%)	3 (5.17%)	0	0	2 (3.4%)	2 (3.4%)	1 (1.7%)
Shakir *et al* 1994-2001 (N = 500)	117 (26.3%)	100 (22.5%)	76 (17.1%)	72 (16.2%)	65 (14.5%)	15 (3.4%)	25 (45.5%)	15 (27.3%)	8 (14.5%)	6 (10.9%)	1 (1.8%)	0	0
Abbas *et al* 1991-1994 (N = 136)	24 (17.6%)	23 (16.9%)	27 (19.7%)	19 (16.9%)	21 (15.4%)	0	0	0	0	0	0	0	0
Mahassin 1986-1996 (N = 369)	51 (13.8%)	98 (26.6%)	62 (16.8%)	48 (13%)	50 (13.5%)	0	27 (7.3%)	25 (6.8%)	0	0	0	0	0
Habal 1996-1998 (N = 42)	3 (7%)	0	8 (19%)	11 (26%)	9 (21%)	4 (9.5%)	3 (7%)	1 (2%)	1 (2%)	0	0	0	0

*Five patients with global glomerulosclerosis (GGS) were excluded in this table.

GN: glomerulonephritis; FSGS: focal segmental glomerulosclerosis; MesPGN: mesangio-proliferative GN; MCD: minimal change disease; MPGN: membrano-proliferative GN; MGN: membranous GN; RPGN: rapidly progressive GN; LN: lupus nephritis; Am: amyloidosis; DM: diabetes mellitus; HDN: hereditary GN; HNS: hypertensive nephrosclerosis; IgAN: IgA nephropathy; TR: transplant rejection.

Table 4: Reported prevalence of glomerular diseases among different countries [1, 2, 8, 9, 13, 14]

country	Number	MCD	FSGS	MPGN	MGN	PGN
Tunesia	304	49 (16%)	49 (16%)	51 (16.8%)	64 (21%)	91 (30%)
Sudan	40	7 (18%)	5 (13%)	0	13 (33%)	15 (38%)
Saudi Arabia	272	83 (31%)	30 (11%)	22 (8%)	16 (6%)	63 (23%)
United kingdom	272	83 (31%)	30 (11%)	47 (17.3%)	69 (25.4%)	43 (19.4%)
South Africa (black)	252	27 (10.7%)	9 (3.8%)	90 (35.7%)	54 (21.4%)	72 (28.6%)
South Africa (indian)	75	16 (21.3%)	3 (4.0%)	10 (13.3%)	16 (21.3%)	30 (40%)
India	98	28 (29%)	0	16 (16%)	16 (16%)	38 (39%)
Malaysia	866	42 (4.8%)	54 (6.5%)	24 (2.8%)	69 (8%)	306 (35.3%)
Singapore	607	190 (31.3%)	66 (10.9%)	14 (2.3%)	21 (3.5%)	316 (52%)
Hong Kong	271	75 (27.7%)	64 (23.6%)	29 (10.7%)	44 (16.2%)	59 (21.8)
Ghana	31	3 (10%)	11 (36%)	4 (13%)	5 (16%)	8 (25%)
Iraq (1986 -2001)	1047	173 (16.5%)	195 (18.6%)	150 (14.3%)	145 (13.8%)	240 (22.9%)
Iraq (2010-2012)*	58	12 (20.7%)	17 (29.31%)	0	8 (13.80%)	11 (18%)†

* Present study.

† 41 patients in our study had secondary GN and we excluded diabetic patients.

GN: glomerulonephritis; MCD: minimal change disease; FSGS: focal segmental glomerulosclerosis; MPGN: membrano-proliferative GN ; MGN: membranous GN; PGN: primary GN.

Table 5: Immunofluorescence findings in the studied 56 renal biopsy specimens

Disease	Fibrin	IgG	IgM	IgA	C1q	C3	Kappa LC	Lambda LC
MesPGN (n=4)	0	4	0	0	1	2	1	1
HNS (n=2)	0	0	0	0	0	0	0	0
MGN (n=8)	0	8	0	0	2	8	0	0
LN (n=2)	1	2	0	0	1	2	2	2
IgAN (n=2)	0	0	0	2	0	1	1	1
GGS (n=5)	0	0	0	0	0	0	0	0
Am (n=3)	0	0	0	0	0	0	0	0
MCD (n=12)	0	1	1	0	0	1	0	0
FSGS (n=17)	0	2	0	0	1	2	0	0
TR (n=1)	0	0	0	0	0	0*	0	0
IGN-ANCA^{+ve} (n=2)	0	2	0	0	1	2	2	2
Total	1	20	1	2	6	18	6	6

* C4d positive.

GN: glomerulonephritis; MesPGN: mesangio-proliferative GN; HNS: hypertensive nephrosclerosis; MGN: membranous GN; LN: lupus nephritis; IgAN: IgA Nephropathy; GGS: global glomerulosclerosis; Am: amyloidosis; MCD: minimal change disease; FSGS: focal segmental glomerulosclerosis; TR: transplant rejection; IGN: immune GN; ANCA: antineutrophil cytoplasmic antibody; LC: light chain.

Discussion

Since glomerulonephritidis are immunologically mediated, IF microscopy is helpful in the diagnosis of glomerular diseases. Yet, combined analysis of LM and IF findings together with correlation of clinical, biochemical and serological features are essential for accurate diagnosis.

In this study of 58 cases, FSGS (29.3 %) was the commonest pattern of glomerulonephritis followed by MCD. There is a great variation regarding the pattern of GN in different countries. Nevertheless, the present study has similarities with many other studies (Table-4) [1, 2, 8, 9, 13, 14]. This difference in the spectrum of gloemerular diseases may be attributed to the lack of IF examination of renal biopsies in some of these studies. Diagnosis of MCD is usually made by the absence of glomerular alteration in LM and lack of immune deposits in IF [15]. Minor degrees of mesangial matrix increment and/or hyper cellularity also form an integral part of MCD [15, 16]. When these feature are more marked, it becomes difficult to segregate MCD from MesPGN [16, 17].

Linear deposit of IG at the GBM and demonstration of anti-GBM antibody in the serum are the typical characters of anti-GBM disease [18, 19]. The reason for linear deposition of IgG and C3 along GBM and IgG deposition in the mesangium observed in one of our patient is due to superimposition of anti-GBM disease on pre-existing MGN. The predominant immune deposits in MesPGN were IgG and C3 in the mesangium and along the GBM; similar findings were also observed by other studies [7, 8, 19, 20].

In our study we found five patients with positive deposition of C1q complement component in the glomerular basement membrane in addition to IgG, kappa and lamda light chains and C3. One patient had mesangial deposition (3+) without glomerular basement membrane deposition; she was a 21 year old female with histopathological findings of FSGS in light microscopy and negative serology for SLE. Electron microscopy was not feasible for this patient and she was treated as primary C1q nephropathy with cyclosporine A and showed good clinical response. This is consistent with Jennette and Hipp who first proposed that C1q nephropathy was a distinct clinical entity that caused GN in the absence of SLE with deposition of C1q predominantly in the mesangial area [21, 22]. In these early reports, C1q nephropathy had specific histopathological patterns of mainly focal or diffuse mesPGN. Several patterns have subsequently been reported in renal biopsies, ranging from minor glomerular abnormalities or mesPGN to focal glomerulosclerosis. Most recent reports describe

Figure-1: MGN showing diffuse granular deposition of IgG and C3 along the glomerular basement membrane in a patient with positive serological markers of SLE (immunofluorescence micrograph).

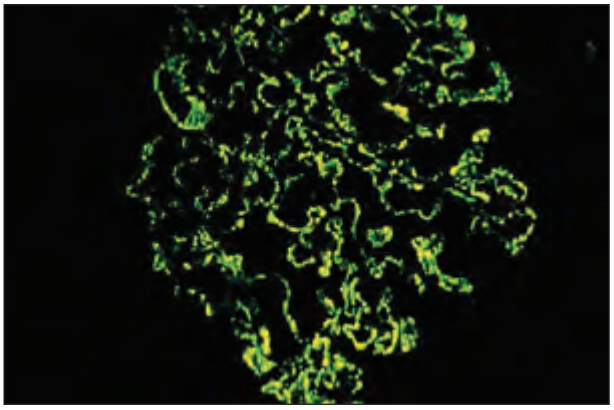


Figure-2: Deposits of fibrin in a patient with LN; the glomerular damage was so severe that fibrin leaked into Bowman's space leading to proliferation of the epithelial cells and formation of the bright crescent shown here (immunofluorescence micrograph).

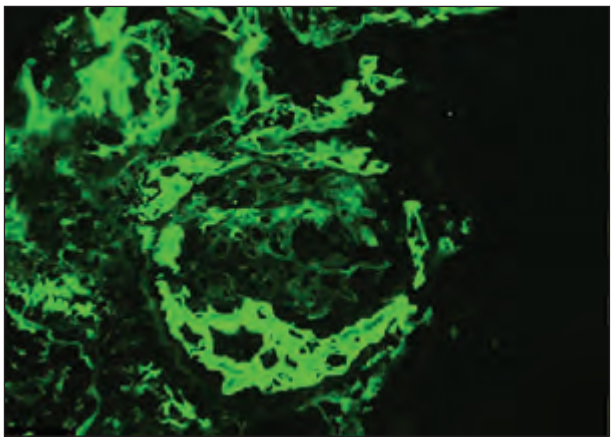
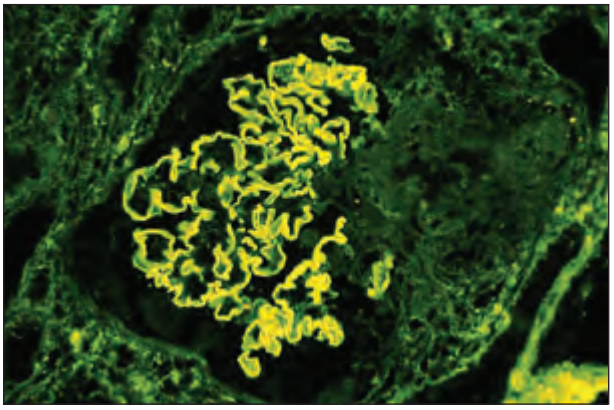


Figure-3: Deposits of IgG in a smooth, diffuse, linear pattern in a patient who had superimposition of anti-GBM disease on pre-existing MGN (immunofluorescence micrograph).



C1q nephropathy of the focal glomerulosclerosis type [22]. All other four patients with positive C1q had positive serological markers for SLE and three of them progressed to chronic kidney failure.

Using IF staining in all but two of our patients may explain the different spectrum of glomerular lesions seen in our study when compared with other Iraqi studies in which no IF staining was used. The use of IF also explains the difference in the prevalence of FSGS in our study when compared with other studies in different countries where MCD was predominant.

Conclusions

FSGS was the commonest GN in this cohort of adult patients and nephrotic syndrome was the predominant clinical presentation. Using IF technique and correlating it with LM together with clinical, biochemical and serological markers should be done on a regular basis for correct diagnosis of glomerular diseases.

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