Original Article

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Clinicopathological Outcome in Infection Related Glomerulonephritis

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Abstract

Background: The term infection-related glomerulonephritis (IRGN) was proposed as the streptococcal, staphylococcal and gram-negative organisms were being isolated among elderly and immunocompromised patients treated for glomerulonephritis. Previously these were called as Post-infectious glomerulonephritis (PIGN). Most of the reported patients were Caucasians and Asians with male predominance. Among the adult IRGN patients a kidney biopsy is recommended to confirm the diagnosis and to rule out other glomerulonephritis. The aim of the study is to study the clinical characteristics and pathological patterns of infection-related glomerulonephritis (IRGN) in adults and to assess the clinical and pathological differences of C3 dominant and codominant IRGN patients. **Subjects and Methods:** A hospital-based, analytical retrospective clinical study was conducted among seventy-three patients. Cases were included irrespective of gender with biopsy proven IRGN and aged equal to or greater than 18 years of age. The study was conducted for a period of 6 months from 1st June 2019 to 30th Nov 2019 at Sapthagiri Institute of Medical Sciences and Research Center, Bangalore. A prior permission from the institutional ethics committee and written consent from the patients and their family members were obtained. Data obtained was entered in Microsoft Excel-2013 and analyzed in SPSS version-22 trial. Appropriate statistical tests were applied and p-value less than 0.05 was considered as significant. **Results:** In the present study 73 patients were included based on the selection criteria. The mean age of the study population was 41.8 ± 14.5 years. Majority 51 p.c (37) of study population were males and 49 p.c (36) were females. Hypertension was the most common risk factor which was reported among 56 p.c (32) of the patients. Diabetes was reported among 17 p.c (10) of the patients. About 15 p.c (9) of the patients were alcoholics and 10 p.c (6) of the patients were smokers. **Conclusion:** Renal biopsy plays an important role in the assessment of prognosis and underlying glomerular nephritis (GN).

Keywords: Infection related glomerulonephritis (IRGN), Post-infectious glomerulonephritis (PIGN)

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Introduction

The term infection-related glomerulonephritis (IRGN) was proposed to the previously named PIGN (Post infectious glomerulonephritis) as the streptococcal, staphylococcal and gram negative organisms were increasingly being isolated among elderly and immunocompromised patients treated for glomerulonephritis.[1] The prognosis of PIGN was found to be good among children but biopsy confirmed adult PIGN showed progression to an end-stage renal disease (ESRD) in 2–34 p.c of the patients.[2,3] Sites of adult infection are more heterogeneous which include skin, upper respiratory tract, lung, heart, oral mucosa/teeth and urinary tract. Among these the most common predominant site among young adults is upper respiratory tract and skin is the most common predominant site among elderly population and diabetics.[4,5] Most of the reported patients were Caucasians and Asians with male predominance.[6–8] Diabetes, alcoholism, malignancy, severe malnutrition, synthetic heart valve, intravenous drug use, acquired immune deficiency syndrome (AIDS) and tuberculosis are the risk factors of IRGN.[6,7,9]

Kidney biopsy is recommended to confirm the diagnosis and to rule out other glomerulonephritis that have similar clinical presentations which may require a prompt aggressive immunosuppressive therapy. Biopsy tissue is sent for light microscopy, immunofluorescence and electron microscopy. The characteristics of kidney glomeruli, interstitium, vessels and tubules are seen in light microscopy. Immunofluorescence staining is done with IgG, IgM, IgA, C3, C1q, kappa, lambda, C4d. Glomerular basement membrane (GBM) thickness, foot process effacement, electron dense deposits, tubulo-reticular inclusions, tubules, extra glomerular deposits and arterioles are visualized in electron microscopy.

Various theories on pathogenesis of PIGN include

- Immune complex deposition.

- Localization of bacterial cationic antigen within subepithelium that forms the insitu immune complexes.[10]
- Molecular mimicry of bacterial antigen to glomerular antigen which causes complement activation.[11]
- Potential roles for cellular and autoimmunity were also proposed.[12]

Figure 1 shows the histology of IRGN:

A-LM: Diffuse mesangial and endocapillary hypercellularity, and a large number of polymorphonuclear neutrophils (hematoxylin and eosin stain).

B-LM: Endocapillary hypercellularity and many polymorphonuclear neutrophils (Jones silver stain).

C-LM: Crescent has ruptured the Bowman's capsule, and there is an intense lymphoplasmacytic interstitial inflammatory response (Jones silver stain).

D-IF: Irregular, coarse granular capillary loop and mesangial staining for immunoglobulin-G.

E-IF: Scattered, irregularly spaced capillary wall and mesangial coarse granular staining (starry-sky pattern).

F-EM: Subepithelial hump-like deposits, on top of the basement membrane with limited or no adjacent basement membrane reaction.

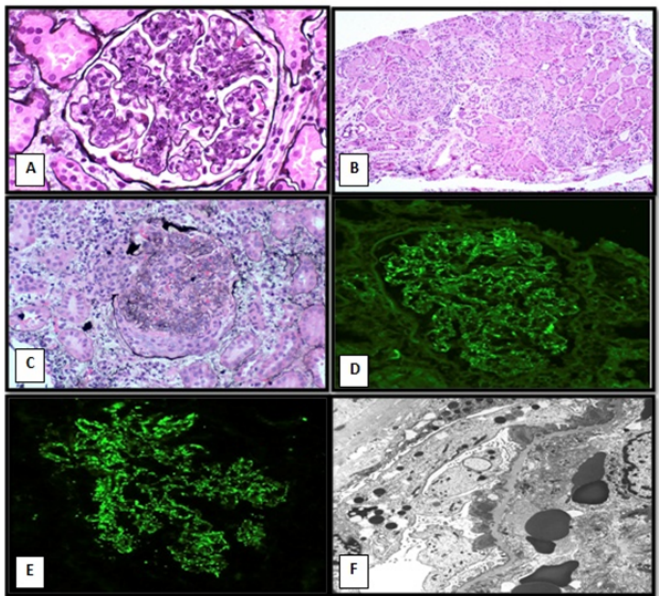

Figure 1: Histology of IRGN

Aims & Objectives

1. To study the clinical characteristics and pathological patterns of infection-related glomerulonephritis (IRGN in adults).
2. To assess the clinical and pathological differences of C3 dominant and codominant IRGN patients.

Subjects and Methods

A hospital-based, analytical retrospective clinical study was conducted among seventy three patients. Biopsy proven IRGN patients more than 18 years of age were included. Patients with other glomerular diseases like IgA nephropathy, lupus nephritis, C3 glomerulopathy; ANA, dsDNA, positive ANCA and with inadequate biopsy were excluded from the study. The study was conducted for a period of 6 months from 1st June 2019 to 30th Nov 2019 at Sapthagiri Institute of Medical Sciences and Research Center, Bangalore. A prior permission from the institutional ethics committee and written consent from the patients and their family members were obtained.

The records of all the patients who underwent biopsy during study period were obtained and those with diagnosis of IRGN were retrieved. All the relevant demographic, clinical, biochemical, pathology data was obtained. Written proformas were filled up during inclusion of patients which contained epidemiological information (age, sex, occupation, and place), questionnaires for risk factor evaluation (smoking, alcohol, HTN, Diabetes mellitus), information of clinical presentation (hematuria, oliguria, anasarca etc.) and clinical signs, investigations such as urinalysis, urine spot protein creatinine ratio, serum creatinine, complete blood count, complement (C3, C4), microbiological cultures and histopathology. All patients underwent a percutaneous renal biopsy after obtaining consent. The renal tissue has been processed for light microscopy, immunofluorescence and electron microscopy after appropriate staining. Data obtained was entered in Microsoft Excel-2013 and analyzed in SPSS version-22 trial. Appropriate statistical tests were applied and p-value less than 0.05 was considered significant.

Results

In the present study 73 patients were included based on the selection criteria. The mean age of the study population was 41.8 ± 14.5 years. Majority 51 p.c (37) of study population were males and 49 p.c (36) were females. Hypertension was the most common risk factor which was reported among 56 p.c (32) of the patients. Diabetes was reported among 17 p.c (10) of the patients. About 15 p.c (9) of the patients were alcoholics and 10 p.c (6) of the patients were smokers. Figure-2 reports the clinical presentation among the patients as follows- shortness of breath (44%), anasarca (38%), fever (36%), pedal edema (35%) and oliguria (31%). All the patients had hematuria (100%). Table-1 reports the renal histological findings.

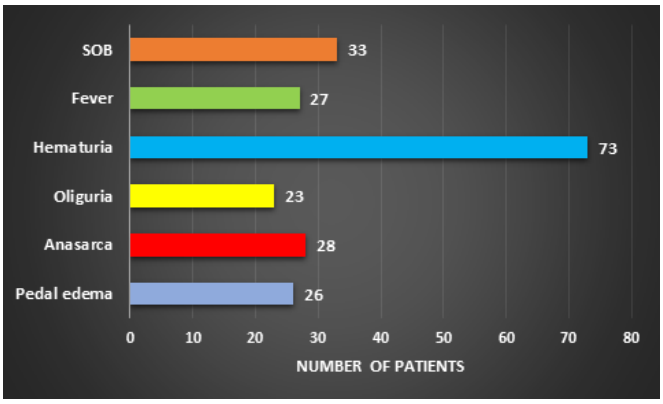

Figure 2: Showing Clinical Presentation

Table 1: Showing Renal Histological Findings (Light Microscopy Findings)

Biopsy Findings	Number of patients
Light Microscopy	
Diffuse proliferative glomerulonephritis	52 (70%)
Mesangioproliferative glomerulonephritis	2 (3%)
Crescents	12 (16%)
<30%	8
>30%	4
Diabetic Nephropathy	4 (5%)
IFTA (Interstitial fibrosis and tubular atrophy)	6 (8%)

Table 2: Showing Renal Histological Findings (Immunofluorescence Patterns)

Biopsy Findings	Number of patients
Immunofluorescence Patterns	
Full house	8 (10%)
IgA dominant	6 (8%)
IgG only	0
IgM+IgG	10 (13%)
C3 only	30 (40%)
IgG+C3	10 (13%)
IgG+C3+C1q	18(24%)
IgG+C3+K/L	6 (8%)
C3/C1q	3 (4%)

Table 3: Showing Renal Histological Findings (Electron Microscopy & Electron dense deposits)

Biopsy Findings	Number of patients
Electron Microscopy	
Diffuse effacement	13
Focal effacement	27
Tubuloreticular inclusion	1
Arteriolar hyalinization	8
Electron dense deposits	
Subepithelial humps	25
Mesangial	35
Subendothelial	22
PIG (Podocyte infolding glomerulopathy)	2

Table 4: Showing Comparision between C4D Negative, C3 Dominant & C4D Negative, C3 Codominant Groups

Variables	C4d negative, C3 dominant (n=15)	C4d negative, IgG/C1q+C3 (n=9)	p-value
Mean age	48.7±13.5 years	36.2±13.05 years	0.03
Symptoms			
Denovo HTN	5	1	
Pedal edema	6		
Oliguria	7	3	
Anasarca	5	5	
SOB	8		
Fever	3	6	
Risk Factors			
DM	3	2	
HTN	2	3	
Alcohol	2	1	
Smoker	2	0	

Discussion

IRGN is an immune mediated renal injury secondary to infectious causes. It is most commonly seen in the pediatric age groups following an episode of sore throat or pyoderma. The disease is also common in elderly patients especially the immune compromised ones.

Table 5: Showing Comparision between C4D Negative, C3 Dominant & C4D Negative, C3 Codominant Groups

Variables	C4d negative, C3 dominant (n=15)	C4d negative, IgG/C1q+C (n=9)	p-value
Infection Source			
UTI	3	2	
Pneumonia	1		
ASO titre>200	Nil	Nil	
Blood C/S	E.coli-1	Nil	
Urine C/S	E.coli-1	E.coli-1	
	Proteus-1	Proteus-1	
	Enterococcus-1	MP-1	
Serum creatinine (mg/dl)	4.1±2.6	3.3±2.5	0.8
Mean GFR at presentation	23.4±16.9	37.7± 36.3	0.2
Proteinuria	3.1±1.3gm	2.3±1.4gm	0.016
Spot PCR at presentation	3.3±0.8	2.3±0.8	0.007
Nephrotic range proteinuria	5	1	
Mean C3 at presentation	57.8±29.2	36.2±13.05	0.004
C3 at 3 months	106.8±13.6	102±11.3	0.3
Persistent C3	3	1	
C4 at presentation	32±7.14	22.5±13.4	0.003
Mean hsCRP	17.2±21	14.1±15.4	0.7
Procalcitonin	3.4±3.3	2.5±3.7	0.9

Table 6: Showing Comparision between C4D Negative, C3 Dominant & C4D Negative, C3 Codominant Groups

Variables	C4d negative, C3 dominant (n=15)	C4d negative, IgG/C1q+C3 (n=9)	p-value
Biopsy Findings			
LM			
Endocapillary proliferation	100%	100%	
Crescents			
Crescents<50'	3	2	
Crescents>50'	0	2	
IFTA (Interstitial fibrosis and tubular atrophy)			

Table 7: Showing Comparision between C4D Negative, C3 Dominant & C4D Negative, C3 Codominant Groups

Variables	C4d negative, C3 dominant (n=15)	C4d negative, IgG/C1q+C3 (n=9)	p-value
Immunofluorescence			
C3+	100%	100%	
IgG	0	7	
IgA	0	2	
IgM	0	2	
C1q	0	5	
Electron Microscopy	N=8	N=7	
GBM mean thickness	405.8±182	342.7±91.8	0.4
Effacement			
Diffuse	2 (25%)	2	
Focal	6	7	
Electron dense deposits			
Mesangial	5	5	
Subendothelia	4	7	
Subepithelial/	5	4	
Intramembran deposits	0	0	
Others	PIG-1		

Table 8: Showing Comparision between C4D Negative, C3 Dominant & C4D Negative, C3 Codominant Groups

Variables	C4d negative, C3 dominant (n=15)	C4d negative, IgG/C1q+C3 (n=9)	p-value
Treatment			
Plasmapheres	Nil	2	
Hemodialysis	5	2	
Immunosuppr	2	3	
Outcomes			
Recovered	8 (53%)	7 (77%)	
CKD	6 (25%)	2 (23%)	
RRT (HD/CAPD)	3 (13%)	1 (11%)	
Mortality	1 (7%)	Nil	
AT 1 year follow UP			
Persistent proteinuria	4(26%)	2 (28%)	
Spot PCR	0.54±0.72	0.34±0.39	0.47
Creatinine(mg	2.57±2.47	1.8±1.9	0.43
Mean GFR ml/min/1.73m	51.5±32.5	67±35.3	0.2

The most common light microscopic finding on renal biopsy was diffuse proliferative and exudative GN with abundant intracapillary neutrophils.[6] In a study conducted by Nasr SH et al in the year 2008 among 86 patients, this pattern was reported among 72 p.c of the patients, followed by focal endocapillary proliferative GN in 12 p.c and mesangial proliferative GN in 8 p.c of the patients respectively.[7] Another most common histological pattern of injury was endocapillary proliferation with neutrophils in mesangial tufts which was reported among 52 (70%)of the patients. Montseny et al in their study reported endocapillary GN in 58 p.c, crescentic GN in 34 p.c and membranoproliferative GN in 7 p.c of the patients. The focal endocapillary proliferative and mesangial patterns may represent milder disease or the disease in resolving phase. In our study, focal endocapillary proliferative pattern was observed among 5 (6%) of the patients. Crescentic glomerulonephritis with >50% crescents was rare and affected only 5 p.c of the cases in few studies, although focal crescents involving >20% of glomeruli encountered in up to a quarter of cases.[6,7] In the present study crescents were found in 17 p.c of the cases, where 8 p.c had crescents of more than 30% and rest had less than 30% crescents. Only 5 patients had crescents of >50%.

Immunofluorescence typically revealed C3-dominant or codominant glomerular staining. Most of the cases, had coarsely granular mesangial and glomerular wall staining, resembling the 'starry sky pattern'(54%), glomerular capillary wall positivity, the 'garland pattern'(32%) and predominantly mesangial staining, the 'mesangial pattern' (24%).[6,7,15] C3 can be the only immune-reactant detected which was observed in 27 p.c of patients.[6] But more often there was a co-deposition of one or more immune reactants (IgG, IgM, IgA, C1q).

Conclusion

Renal biopsy plays an important role in the assessment of prognosis and underlying glomerular nephritis (GN). There is no significant difference between the clinical presentation, electron microscopy findings and follow up between C4d negative, C3 dominant IRGN and Codominant IRGN.

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Table 9: Comparison between Different Studies

Variables	Present study	Jeyachandran et al, [13] 2 014	Trivedi et al, [14] 2 018
Number of patients	73	102	137
Mean age	43 years	32.7±15 years	22.7±15.8 years
M:F	1.02:1	1.21:1	1.07:1
Common infection source	UTI, Foot ulcer (33%)	URTI (25.4%)	Sore throat (41%)
Documented preceding infection	24%	32%	78.1%
Common isolated organism	E.coli (8%)	Streptococcus pyogenes (13.9%)	-
Common presentation	SOB	Edema, Oliguria	Oliguria
Common comorbid illness	HTN	DM, Alcohol related liver disease	HTN
Denovo hypertension	20%	74%	81.7%
Nephrotic range proteinuria	27%	60%	41.6%
Hematuria	100%	56%	79.5%
Low C3	91%	66%	89.7%
Low C3+C4	8%	4.9%	-

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