Original Article

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Significance of Glomerular C1q Deposits in IgA Nephropathy

Pathology Section

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ABSTRACT

Introduction: Immunoglobulin A (IgA) nephropathy is the most common form of glomerulonephritis in young men, often presenting as gross or microscopic haematuria and accounts for approximately 10% of the patients with End-Stage Renal Disease (ESRD). The contribution of the complement system to amplify tissue injury in IgA nephropathy has been suggested but the precise pathways of complement activation especially the involvement of classical pathway remain largely unknown.

Aim: To determine the prevalence of glomerular C1q deposition in IgA nephropathy to delineate the relationship of glomerular C1q positivity and different histological variables indicating disease activity and disease progression and also to determine the relationship of glomerular C1q positivity and the Oxford scoring system in IgA nephropathy.

Materials and Methods: This was a prospective study conducted over a period of three years {January 2014-December 2016} in the Department of Pathology with the cooperation of the Department of Nephrology at Government Medical College, Kozhikode, Kerala, India. A total of 44 cases which were both biopsy and immunofluorescence proven as IgA nephropathy were included in the study. For light microscopy, the tissue received in buffered formalin was processed into paraffin blocks, stained with Haematoxylin and Eosin (H&E) and histopathological changes analysed. For immunofluorescence, tissue received in normal saline was frozen in cryostat and 3 µm sections were stained using the Dako polyclonal Fluorescein Isothiocyanate (FITC) conjugated antibodies IgG, IgM, IgA, C3, C1q and studied for pattern of glomerular staining. Chi-square test was used for statistical analysis.

Results: The prevalence of C1q deposits was 27.3%. Among histopathological variables, only fibrous crescent was found to have significant relationship with C1q positivity (p=0.04). On follow-up, 50% C1q positive patients and 11.76% C1q negative patients who were having normal renal functions at the start of the study went into renal insufficiency.

Conclusion: The study revealed that there was a fairly high prevalence of C1q deposits in IgA nephropathy patients. Also, significant association was found between C1q deposits and fibrous crescent. Most significantly the study concluded that there is an increased tendency for the C1q positive patients to go into renal failure.

Keywords: Complement, Crescent, Immunofluorescence, Mesangium

INTRODUCTION

Immunoglobulin A nephropathy was recognised as a distinct entity by Berger J and Hinglais N [1]. The initiating event in the pathogenesis of IgA nephropathy is the mesangial deposition of IgA. A widely stated hypothesis is that mucosal antigenic exposure in a genetically susceptible individual results in the generation of nephritogenic IgA antibodies that form complexes in the circulation and get deposited in glomeruli which is predominantly polymeric IgA of the IgA1 subclass (pIgA1) leading to glomerular injury. The prevalence, clinical course and outcomes are highly variable when compared between different regions of the world. Evidence obtained from research on immunogenetics as well as studies on racial differences in prevalence, and familial occurrence of IgA nephropathy strongly supports the role of genetic factors in the development and progression of the IgA nephropathy [2]. Mesangial deposition of IgA is the initiating event followed by complement activation [3]. IgA nephropathy is usually accompanied by C3 deposition [4].

The alternative pathway of the complement activation is implicated due to the absence of C1q and C4 [5,6]. In a study by Gunnarsson I et al., no correlations were observed between anti-C1q levels and renal function of IgA nephropathy patients [7]. Welch TR and McAdams J in their paper on childhood IgA nephropathy found that mesangial deposits of IgM or C1q which are seen frequently, probably due to heavy proteinuria at the time of biopsy, and do not contribute adversely to outcome [8]. An association between IgA nephropathy and the HLA Bw35 (Human Leucocyte Antigen) was initially reported in small Australian and French cohorts which was supported by several reports of twins with IgA nephropathy who shared the HLA-antigen Bw35 [9]. A higher prevalence has been noted in Asia including India and hence it can infer that environmental and genetic factor contribute to disease progression. Initially thought as benign, it is known to lead to ESRD [10,11]. A few studies have put forward the activation of the lectin pathway in IgA nephropathy cases [12,13]. Glomerular deposits of IgA are accompanied by C3 but rarely by C1q [8]. However, mesangial C1q deposition has been reported to be associated with a poor renal outcome in patients with IgA nephropathy [14]. Thus, there is no uniformity regarding the effect of C1q deposition in IgA nephropathy on outcome and renal histology. No similar studies have been done in Indian patients. So, the aim of the study was to look at the prevalence of C1q deposition in IgA nephropathy and its relation to various histological parameters and the Oxford scoring system [15].

MATERIALS AND METHODS

The present study was a prospective study conducted in the Department of Pathology with the cooperation of the Department of Nephrology at Government Medical College, Kozhikode, Kerala, India, over a period of three years {January 2014-December 2016}. A total of 44 cases were selected during January 2014 to March 2015 and followed-up for six months to two years. Ethical clearance for the study was obtained from Institutional Ethics Committee (IEC), Government Medical College, Koshikode. (Ref. No. GMCKKD/RP 2014/IEC/26/01 -22/1/2014). Informed consent was taken from all the participants.

Inclusion criteria: Cases of biopsy and immunofluorescence proven IgA nephropathy diagnosed were included in the study.

Exclusion criteria: Those with secondary causes of mesangial IgA deposits such as Henoch Schonlein Purpura (HSP) and Systemic Lupus Erythematous (SLE), patients with ESRD at the time of diagnostic biopsy, diseases other than IgA nephropathy, like Diabetes mellitus, cases in which immunofluorescence was not done and inadequate tissue were excluded.

Study Procedure

The medical records and the referral forms submitted at the time of biopsy from the Department of Nephrology were reviewed and the following information at the time of the renal biopsy recorded: patient age, sex, presence or absence of hypertension, Urine Protein Creatinine Ratio (PCR), Urine microscopy, Serum creatinine level, Serum complement and Haemoglobin levels {anaemia was defined as haemoglobin <13 g/dL in males and <12 g/dL in females [16]. Hypertension was defined as systolic blood pressure >120 mmHg and diastolic blood pressure >80 mmHg or taking antihypertensive [17]. Nephrotic range proteinuria was defined as Urine PCR >200 mg/mmol [18]. Glomerular Filtration Rate (GFR) was estimated in all the patients by the (Chronic Kidney Disease Epidemiology Collaboration) CKD-EPI formula. Normal Glomerular filtration rate (GFR) was defined ≥90 mL/min/1.73m^2. Renal insufficiency was defined as (estimated GFR) eGFR <60 mL/min/1.73 m^2. ESRD was defined as severe irreversible kidney damage and (estimated GFR) eGFR <15 mL/min/1.73 m^2 [18], Hypocomplimentemia was defined as serum C3 <80 mg/dL [19]}.

The patients were seen in the Nephrology OPD for follow-up assessment. They were followed-up for six months to two years.

Histological evaluation of renal lesions was done in each patient enrolled for this study. For light microscopy, the tissue submitted was fixed in buffered formalin and processed into paraffin blocks, sections were stained with H&E. Special stains (Periodic Acid Schiff) were done to identify necrosis and expansion in mesangial matrix and also help to distinguish mesangial hypercellularity associated with sclerosis from end capillary lesion. Initially, histopathological variables in Oxford classification were assessed [15] [Table/Fig-1].

Histopathological features	Definition	Score
Mesangial hypercellularity (M)	0-4 mesangial cells/mesangial area=0 4-5 mesangial cells/mesangial area=1 6-7 mesangial cells/mesangial area=2 >8 mesangial cells/mesangial area=3 The mesangial hypercellularity score is the mean score for all glomeruli	M0 <0.5 M1 >0.5
Segmental glomerulosclerosis (S)	Any amount of the tuft involved in sclerosis, but not involving the whole tuft or the presence of an adhesion	S0-absent S1-present
End capillary hypercellularity (E)	Hypercellularity due to increased number of cells within glomerular capillary lumina causing narrowing of the lumina.	E0-absent E1-present
Tubular atrophy/ interstitial fibrosis (T)	Percentage of cortical area involved by the tubular atrophy or interstitial fibrosis, whichever is greater	0-25% - T0 26-50% - T1 >50% - T2

[Table/Fig-1]: The four key pathological features that are recommended by the Oxford group to be included in the pathology reports for patients with IgA nephropathy [15].

Also, renal biopsy was arbitrarily divided the into three compartments as glomerulus, interstitium, and vascular. The histopathological changes in these compartments excluding those considered under the Oxford classification were separately analysed.

Glomeruli

- Mesangial matrix increase
- Capillary narrowing or disruption
- Cellular crescents
- Fibrous crescents
- Any crescent

Tubulointerstitial compartment

- Interstitial infiltrates
- Interstitial oedema
- Tubular dilation
- Vacuolisation

Vessels

- Intimal thickening (assessed by comparing thickness of intima relative to total medial thickness) [20].
- Medial hypertrophy (comparing thickness of the muscular wall relative to the vascular calibre) [21].

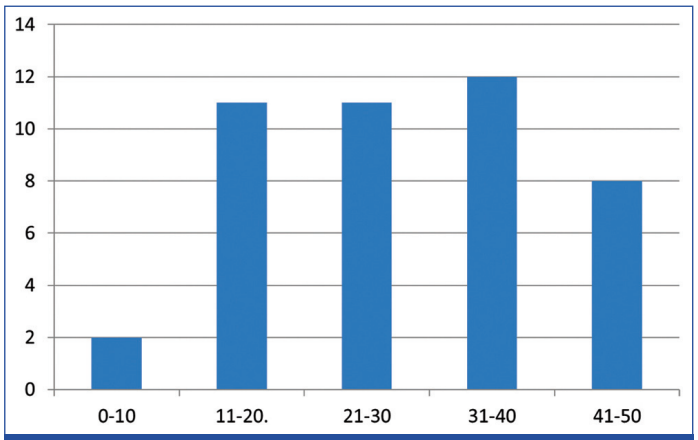
For immunofluorescence, tissue received in a separate bottle containing normal saline was frozen in the cryostat. The pattern of glomerular staining was studied using the Dako polyclonal FITC conjugated antibodies (IgG, IgM, IgA, C3, C1q). The immunofluorescence intensity in the mesangial area was graded on a 4-point scale: grade 0-absent; grade 1-weak; grade 2-moderate; grade 3-severe. (Visual grading based on the brightness of immunofluorescence). Mesangial deposits of immunoglobulin's and complement showing grade 1 to grade 3 fluorescence were considered positive [22].

STATISTICAL ANALYSIS

The data was entered in Microsoft excel 7 and the results were analysed using EPI INFO software, Chi-square test was applied and p-value was calculated. p<0.05 was considered significant.

RESULTS

A total of 44 cases were included in the study. Cases were serologically and clinically negative for SLE, 34 out of 44 cases belonged to the 11-40 age groups as shown in [Table/Fig-2]. The majority of the patients with IgA nephropathy were males constituting 27 (61.34%) of cases. Cases were divided into two groups according to the presence of C1q deposition: C1q positive (n=12) and C1q negative (n=32). Immunofluorescence findings are shown in [Table/Fig-3,4] and representative images are shown in [Table/Fig-5-7]. The relationship between various clinical parameters and renal morphological variables with C1q positivity was analysed [Table/Fig-8]. A total of 12 out of 44 cases (27.3%) showed C1q deposits in mesangium and C1q deposits were more commonly seen in females (7 out of 17 cases) but this did not show any statistical significance (p-value 0.09). The majority of patients diagnosed with IgA nephropathy were anaemic (28 out of 44 patients). However, anaemia was also not statistically significant since p-value >0.05. Among the 44 cases of IgA nephropathy, 18 cases had an initial presentation as haematuria of which only 4 cases were C1q positive. Two out of 44 cases of IgA nephropathy patients had complement levels less than 83 and they were C1q negative. Out of 44 cases studied, 23 patients had



[Table/Fig-2]: Age group (years) of the sample (x-axis), frequency (y-axis).

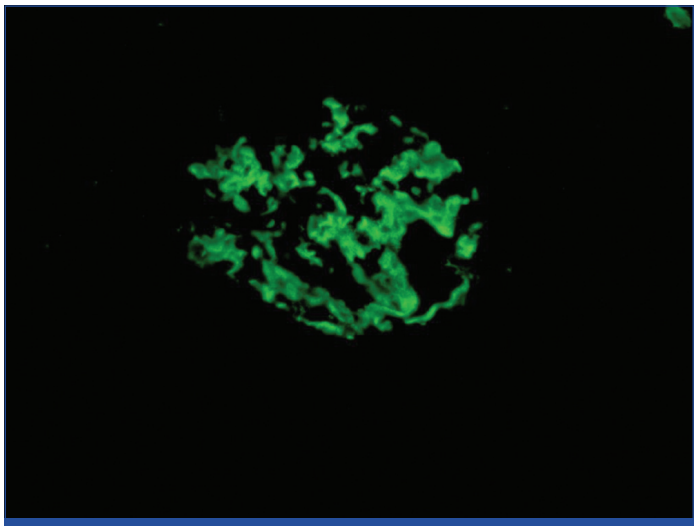
initial renal insufficiency and majority were C1q negative. None of the variables of oxford classification were statistically significant in comparison with C1q positivity [Table/Fig-9], (representative image of segmental glomerulosclerosis is shown in [Table/Fig-10]. The only histopathological variable which showed significant association with C1q positivity was fibrous crescent (p-value=0.04) [Table/Fig-11,12], (representative image of fibrous crescent is shown in [Table/Fig-13]. On follow-up, 2 out of 4 (50%) C1q positive patients and 2 out of 17 (11.76%) C1q negative patients who were having normal renal functions at the start of the study went into renal insufficiency.

Fluorescence pattern	C1q -	%	C1q+	%	All	%
IgA +C3	18	56.2	4	33.3	22	50.0
IgA +IgM+C3	8	25.0	5	41.7	13	29.5
IgA only	4	12.5	1	8.3	5	11.4
IgA + C3 +IgG	2	6.3	1	8.3	3	6.8
IgA + IgG	0	0	1	8.3	1	2.3
Total	32	100	12	100	44	100

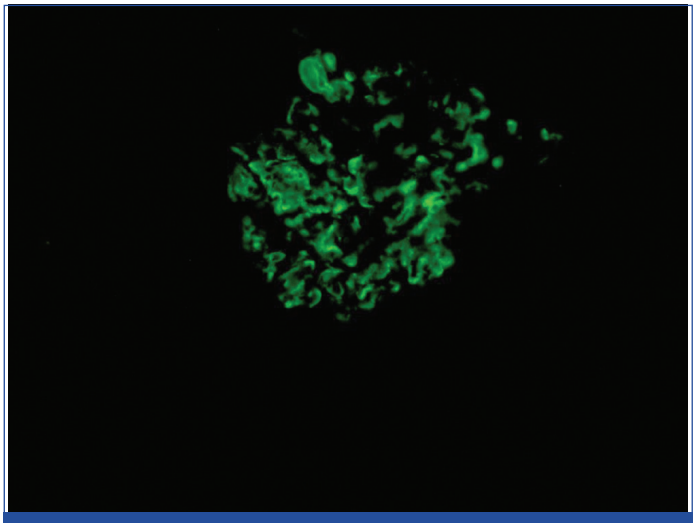
[Table/Fig-3]: Fluorescence pattern in C1q+ and C1q- cases.

Variables	C1q Negative	C1q positive	p-value
C3	28 (87.5%)	10 (83.3%)	0.5292
IgM	8 (25%)	6 (50%)	0.1120
IgG	2 (6.3%)	2 (16.7%)	0.2966

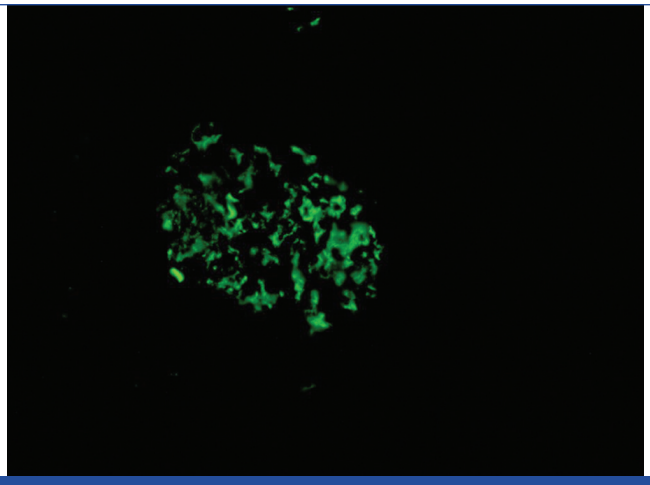
[Table/Fig-4]: Comparison of c1q positive and negative cases with complement c3 and antibodies IgM and IgG Chi-square.
test , p<0.05 considered significant



[Table/Fig-5]: Immunofluorescence showing 3+ diffuse granular mesangial deposits of IgA (FITC polyclonal rabbit anti-human IgA, × 400).



[Table/Fig-6]: Immunofluorescence showing 3+ diffuse granular mesangial deposits of C1q (FITC polyclonal rabbit anti-human C1q, × 400).



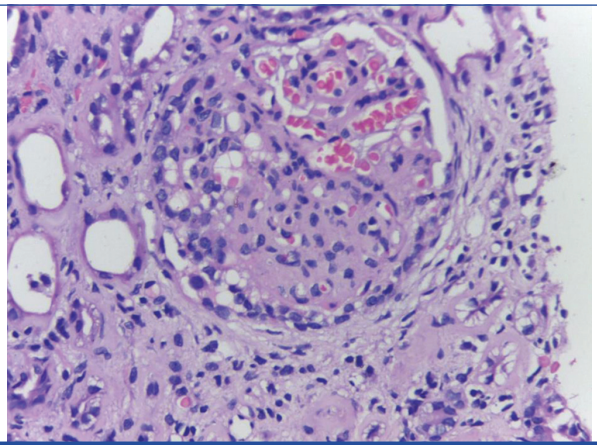
[Table/Fig-7]: Immunofluorescence showing 2+ diffuse granular mesangial deposits of IgM (FITC polyclonal rabbit anti-human IgM, × 400).

Variables	C1q negative n=32	C1q positive n=12	p-value
Mean age	28.50	31.2	0.51
Female sex	10 (31.3%)	7 (58.3%)	0.09
Anaemia	19 (59.4%)	9 (75.0%)	0.27
Macroscopic haematuria	14 (43.8%)	4 (33.0%)	0.39
Hypertension	14 (43.8%)	8 (66.7%)	0.15
Nephritic range proteinuria	6 (18.8%)	2 (16.7%)	0.62
Hypocomplementemia	2 (6.3%)	0	0.52
Renal insufficiency initial	15 (46.9%)	8 (66.7%)	0.20

[Table/Fig-8]: Clinical and demographic features (C1q+ Vs C1q- cases)
Chi-square test; p<0.05 considered significant

Variable	C1q negative n=32	C1q positive n=12	p-value
M	32 (100%)	11 (91.7%)	0.27
E	4 (12.5%)	2 (16.7%)	0.52
S	6 (18.8%)	3 (25.0%)	0.46
T1	14 (43.8%)	6 (50.0%)	0.93
T2	6 (18.8%)	2 (16.7%)	

[Table/Fig-9]: Oxford classification (C1q+ Vs C1q- cases).
M: Mesangial cellularity; E: End capillary hypercellularity; S: Segmental glomerulosclerosis; T: Tubular atrophy; Chi-square test, p<0.05 considered significant



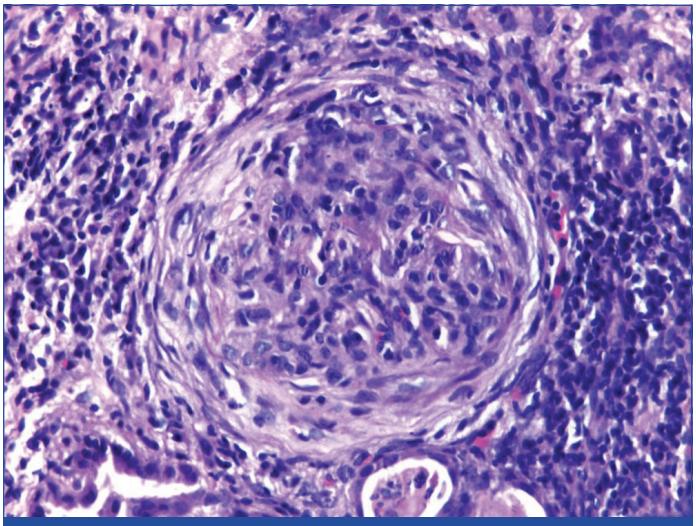
[Table/Fig-10]: Renal biopsy showing segmental sclerosis, H&E x 400.

Variables	C1q negative n=32	C1q positive n=12	p-value
Capillary narrowing	19 (59.3%)	8 (66.7%)	0.21
Mesangial matrix increase	29 (90.6%)	9 (75%)	0.18
Cellular crescent	4 (12.5%)	3 (25%)	0.28
Fibrous crescent	4 (12.5%)	5 (41.7%)	0.04*
Any crescent	7 (21.9%)	6 (50%)	0.07

[Table/Fig-11]: Histopathological changes of glomeruli (C1q+ Vs C1q- cases).
*Significant; Chi-square test; p<0.05 considered significant

Variables	C1q negative n=32	C1q positive n=12	p-value
Interstitial oedema	26 (81.2%)	10 (83.3%)	0.80
Interstitial infiltrate	25 (78.1%)	10 (83.3%)	0.29
Tubular dilatation	23 (71.9%)	9 (75%)	0.91
Tubular vacuolisation	2 (6.3%)	2 (16.7%)	0.29
Intimal thickening	3 (9.4%)	1 (8.3%)	0.52
Medial hypertrophy	12 (37.5%)	4 (33.3%)	0.92

[Table/Fig-12]: Histopathological changes of interstitial and vessels (C1q+ Vs C1q- cases).
Chi-square test; p<0.05 considered significant



[Table/Fig-13]: Renal biopsy showing mesangial cellularity and a fibrous crescent, H&E x 400.

DISCUSSION

In the present study, IgA nephropathy showed a predilection for the range of 31-40 years and most of the patients were in the age range of 11-40 years. Rajasekaran A et al., and Khairwa A, in their study found that IgA nephropathy peaks during first three decades of life [23,24]. Many studies have shown older age to be a predictor of a worse prognosis [25-29]. On the other hand, few studies have shown a worse prognosis in younger patient [30-32]. There was a male preponderance among IgA nephropathy cases in this study as in the previous studies [23,33]. This study did not show any significant association of age with C1q deposits. Among 44 patients who were diagnosed with IgA nephropathy, (27.3%) showed C1q deposits in mesangium. These cases were serologically and clinically negative for SLE. An Indian study demonstrated three cases of IgA nephropathy with C1q deposits and they were also serologically and clinically negative for SLE [11]. More research is warranted to determine whether the prevalence of C1q deposits is high in the IgA nephropathy cases among Indian population.

Glomerular deposits of IgA in IgA nephropathy are usually accompanied by C3 deposition [8]. A similar picture was obtained in this study too. Mesangial C3 deposition was not statistically significant when compared with C1q deposits since both C1q negative and positive cases showed almost equal percentages of C3 deposition with a p-value of 0.52. Welch TR and McAdams J stated in their paper that IgA nephropathy, in which mesangial C1q was detected, was accompanied by IgM and tends to occur in patients with significant proteinuria, suggesting possible non specific trapping rather than true activation of the classical pathway [8]. The study by Wada Y et al., concluded that mesangial IgG co-deposition with IgA is associated with a bad prognosis in IgA nephropathy [34]. In this study no significant association was obtained between C1q deposits and IgM deposition.

Among the 44 cases of IgA nephropathy, 18 cases had an initial presentation as haematuria. Of these, 4 cases were C1q positive and 14 cases were C1q negative. Generally, the degree of haematuria has apparent bearing on the severity or likelihood of progression of IgA nephropathy. However in the present study, there was no significance of haematuria with C1q deposit (p-value 0.39). Though hypertension was not statistically significant in this study, hypertension is an independent predictor of progression to ESRD by multivariate analysis in almost all studies in which such analysis was performed [29,35,36]. In a similar study, it was found that C1q patients had higher mean systolic pressure values than unmatched C1q negative patients [10,37-40]. The majority of patients diagnosed with IgA nephropathy were anaemic (28 out of 44 patients). As per the study 9 out of 12 (75%) C1q positive patients were anaemic compared to 19 out of 32 C1q negative patients. However, anaemia was also not statistically significant (p-value=0.27). Proteinuria at presentation is considered as a strong predictor of unfavourable outcome and patients with IgA nephropathy with mesangial C1q deposition had more proteinuria when compared with C1q negative group [28,29]. though present study did not show any significant association with C1q deposits (p-value 0.62). Two out of 44 cases of IgA nephropathy patients had complement levels less than 80 and these two cases were C1q negative. Out of 44 cases studied, 23 patients had initial renal insufficiency. Among these, eight cases were C1q positive and 15 cases C1q negative. Though it was not statistically significant (p-value=0.20). According to one study, the greater percentage of patients with renal insufficiency was C1q positive (66.7%) compared to C1q negative patients (46.9%). Baseline levels of serum keratinise, total cholesterol, 24-hour urine protein, low-density lipoprotein, β2 macroglobulin were found to be higher in C1q positive cases when compared with those in C1q negative group [41].

The Oxford classification of IgA nephropathy identified four histological features, which are independent predictors of clinical outcome [15]. However, in this study, no significant association was found between C1q deposits and variables of Oxford classification - M (p-value=0.27), E (p-value=0.52), S (p-value=0.46) and T (p-value=0.93). But, statistical analysis of histopathological variables revealed a significant association (p-value=0.04) between C1q deposits and fibrous crescent. Similarly, a fair correlation of crescents with serum creatinine was put forward by Mubarak M and Trimarchi H et al., in their research paper and this lesion was included in the revised version of the Oxford classification [42,43]. Tan L et al., in their study concluded that the risk factors which predicted poor renal survival in IgA nephropathy were serum creatinine, urinary protein and mesangial C1q deposition [44].

Interstitial infiltrates is associated with heavy proteinuria and decreased renal function in IgA nephropathy patients though in the present study no significance was found [45]. Tubular necrosis is associated with dilation of the lumen, desquamation of lining epithelial cells cytoplasmic degeneration and nuclear pyknosis. Tubular damage is associated with incomplete recovery of renal function though this factor was not significant in the present study [29]. Intimal thickening, medial hypertrophy and arteriolar hyalinosis of interlobar arteries has been reported in patient with IgA nephropathy and Prader Willi syndrome [46]. Intrarenal arterial lesions like arterial intimal thickening and arteriolar hyalinosis is associated with poorer renal outcomes [47], though found insignificant in the present study. Study by Dong L et al., concluded that intrarenal arterial and arteriolar lesions including intimal thickening was found in 40-45% of IgA nephropathy patients which can lead to chronic hypoxia and renal injury [48]. Another study by Wu J et al., also concluded that intensity of arterial-arteriolar lesions is associated with adverse outcomes [49]. However, in the original Oxford study, arterial and arteriolar lesions described as artery score is not related to renal outcome adversely [15].

On follow-up, 2 out of 4 (50%) C1q positive patients and 2 out of 17 (11.76%) C1q negative patients who were having normal renal functions at the start of the study went into renal insufficiency. Thus, it can be inferred that there is an increased tendency for C1q positive patients to go into renal failure. A similar study by Lee HJ et al.,

and Tan L et al., concluded that mesangial C1q deposition in the glomerulus is associated with a poor renal outcome and hence it could therefore serve as an indicator of poor renal prognosis [14,44]. Another study found that the C1q deposits found in 0-45% cases of IgA nephropathy and the absence of C1q deposition in the mesangial area in patients with IgA nephropathy is a novel positive predictive marker for the response to tonsillectomy plus steroid pulse therapy [50]. Mesangial C1q deposition may be triggering persistent inflammatory response which can lead to endothelial proliferation and cellular crescent formation. In the absence of therapy, these pathological lesions can transform into chronic renal fibrosis. Hence, mesangial C1q deposition in IgA nephropathy patients should be considered as an indication of aggressive disease, and thus requires treatment with corticosteroids or immunosuppression [41]. A retrospective study was carried out in Shanxi Medical University which also concluded that C1q deposits are an independent risk factor which greatly influenced the renal outcome in IgA nephropathy [41].

Activation of the complement system is the main culprit behind IgA nephropathy [6]. Classical complement pathway gets activated after binding of C1q to immune complexes. C1q deposition rates vary in IgA nephropathy patients and this variation among cases may be explained by the differences in race, age, gender ratio, urine protein and methods of analysis [14]. Since C1q deposits are not essential for the definitive diagnosis of IgAN, the clinical importance of C1q is not yet studied. Hence, further research is warranted to study the significance of C1q as a prognostic tool in IgAN.

Limitation(s)

The limitations of the study were small sample size and the short follow-up period.

CONCLUSION(S)

In this study prevalence of C1q deposits in IgA nephropathy patients was found to be 27.3%. Significant association was found between C1q deposits and fibrous crescent. 50% of C1q positive patients in this study went in to renal insufficiency thus it can be inferred that there is an increased tendency for C1q positive patients to go into renal failure. Hence C1q deposits can be considered as a novel prognostic indicator in IgA nephropathy patients. Thus, research to bring out the involvement of the classical pathway of complement activation is highly recommended in Indian scenario.

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