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Pathology

PATHOLOGY AND RENAL OUTCOME OF THREE UNCOMMON FACES OF CRESCENTRIC GLOMERULONEPHRITIS

Dr Keya Basu*	Associate Professor, Department of Pathology Institute of Postgraduate Medical Education and Research, Kolkata.*Corresponding Author
Dr Dipankar Sircar	Associate Professor, Department of Nephrology, Institute of Postgraduate Medical Education and Research, Kolkata
Prof Manimoy Bandopadhyay	Director, Institute of Postgraduate Medical Education and Research, Health University, Kolkata, India

ABSTRACT **AIMS:** Rapidly progressive glomerulonephritis (RPGN) presents with rapidly deteriorating renal function (> 50% loss of glomerular filtration rate /GFR within 3 months) associated with nephritic urinary sediments and crescents in biopsy. Crescentric IgA Nephropathy, Anti-GBM (Glomerular basement membrane) disease and combined IgA Nephropathy with Anti-GBM disease are three uncommon reasons of RPGN. We have compared clinicopathological. Immunofluorescence (DIF) and renal outcome of three groups.

Setting and designs: Prospective, cross-sectional, single centre study.

METHODS AND MATERIALS : Ultrasonography guided core biopsies obtained, one stained with hematoxylin-eosin, periodic acid-Schiff, Masson's trichrome, and silver methenamine stain another one with immunofluorescence conjugated IgG, IgM, IgA, C3, C1q, kappa and lambda stain. Demographic, clinicopathological and therapeutic parameters with survival data were collected.

STATISTICAL ANALYSIS USED: Done using software (GraphPad PRISM 6).

RESULTS: We have included 9 cases of crescentric IgA Nephropathies, 6 cases of AntiGBM diseases and 2 cases of combined IgA Nephropathy and AntiGBM diseases. Significant difference seen in the incidences of hypertension, hemoptysis, serum creatinine, anti GBM antibody, total number of crescents and mesangial hypercellularity, fragmentation of GBM etc. IgG, IgA and kappa positivity in DIF show significant difference. Survival analysis and mortality versus dialysis dependence and complete and partial remission versus no remission showed no difference between these three groups.

CONCLUSIONS: Proper and early clinicopathological diagnosis is important since all are of poor renal outcome. Further renal outcome of the combined disease is same as that of individual ones.

KEYWORDS : Rapidly progressive glomerulonephritis; Anti-GBM disease; IgA Nephropathy; crescentric glomerulonephiritis; combined IgA Nephropathy with Anti-GBM disease

INTRODUCTION:

Rapidly progressive glomerulonephritis is very rare worldwide. The incidence in the United States of America is around 7 cases per 1 million person-years, while it is 2 cases per 1 million person-years reported in the United Kingdom. There are other reported clusters all over the world, suggesting a possible environmental influence on the pathogenesis[1]. It is more common among the White population, and some reported incidences in the Asian population as well. It is relatively uncommon in African Americans.

Anti-GBM disease is the cause of 10 to 20% of RPGN. When associated with pulmonary hemorrhage in nearly 50% of patients it is called Goodpasture`s syndrome. Genetically susceptible individuals develop anti-GBM IgG (rarely IgA and IgM) antibodies directed against specific epitopes located on the carboxy terminal or non-collagenous domain (NC1) of the alpha-3 chain of type IV collagen following a triggering event[2]. The specific organ injury reflects the predominant tissue distribution of the alpha-3 chain in glomerular and alveolar basement membranes[3]. The fenestrated endothelium of glomerular capillaries allows auto-antibody binding and development of glomerulonephritis. Therefore, hallmark of this disease is continuous linear deposition of immunoglobulin, usually immunoglobulin G (IgG) along GBMs, demonstrated by DIF microscopy[4-7]. Renal injury typically manifests as diffuse necrotizing and crescentic glomerulonephritis[4-6]. Similar linear staining of tubular basement membrane (TBM) correlates with anti-tubular BM antibodies and tubulo-interstitial disease[8]. Anti-GBM disease without major renal dysfunction is present in up to 30% of patients with anti-GBM auto-antibodies demonstrable in serum with conventional enzyme-linked immunosorbent assay (ELISA)[9]. The presence of anti-GBM antibodies is diagnostic, but the sensitivity is low. Thus, a negative auto-antibody test does not exclude anti-GBM antibody disease.

IgA nephropathy is the most common glomerulonephritis in adults[10]. The most typical presentation is macroscopic hematuria or rarely nephrotic syndrome shortly after a mucosal infection such as upper respiratory tract infection and bronchitis. Prognosis of the disease is highly variable with some patients showing a rapid progression causing of end stage renal disease (ESRD)[11]. Factors including male gender, persistent microscopic hematuria, increased serum creatinine, proteinuria more than 1 g/d, and hypertension at presentation are associated with a worse outcome. On biopsy, crescents, global or segmental sclerosis, tubular atrophy, interstitial fibrosis, interstitial cellular infiltrate, and peripheral capillary wall alterations such as deposits or endocapillary proliferation also indicate a poor prognosis[12].

IgA nephropathy can present with crescents in histology but simultaneous presentation of Anti-GBM disease with IgA nephropathy has been rarely described in the literature. In this study we are illustrating two cases of rare occurrence of anti-GBM glomerulonephritis with mesangial IgA deposition, suggesting IgA nephropathy. The association of these two pathogenetically unrelated glomerulonepritis may open up new windows and throw light in the pathogenesis and prognosis of both the diseases.

In this study we have also included the treatment history with a short followup. Hemodialysis and Plasmapheresis was also used when required in the patients of all the three groups. Response of the patient to all these as well as the survival was recorded and the prognosis were assessed in all the three.

AIMS AND OBJECTIVES:

1. To evaluate and compare the clinicopathological, histopathological and DIF microscopic features of cresentric IgA Nephropathy, Anti-GBM disease and combined IgA Nephropathy with Anti-GBM disease.
2. To evaluate and compare the renal outcome of cresentric IgA Nephropathy, Anti-GBM disease and combined IgA Nephropathy with Anti-GBM disease.
3. To compare the findings with the findings of the other researchers.

MATERIAL AND METHODS:

Patient and Public Involvement: Patients attending the Nephrology department and undergoing renal biopsy are included in this study after taking proper informed consent. Study was conducted in the nephropathology unit of department of Pathology.

STUDY DESIGN: Prospective, cross-sectional, single centre study in a tertiary care hospital.

Information on patients' demographics (age and sex), course of disease and co morbidities were collected. Ultrasonography guided percutaneous needle biopsies with two core of renal biopsies were obtained from each patient. The mean number of glomeruli in all 17 specimens was 17.94 ± 7.2, with a minimum no of 7 glomeruli and maximum 30 glomeruli.

Tissue for light microscopy was fixed in neutral buffered formalin, embedded in paraffin, and sectioned at 2-3 µm intervals. They were then stained with hematoxylin-eosin (HE), periodic acid-Schiff (PAS), Masson's trichrome, and silver methenamine stain. Frozen sections were examined for DIF after staining with fluorescein-conjugated (FITC) anti sera specific for human IgG, IgM, IgA, C3, C1q, kappa and lambda light chains (Dako, Denmark). They were then washed in phosphate-buffered saline, mounted in buffered glycerol, and examined in a fluorescent microscope. Fluorescence was graded as absent, trace, mild, moderate, bright or blazing intensity (0/0.5/1+/2+/3+), and the staining pattern was described as linear, granular, or lumpish deposition along glomerular capillary wall or in mesangium. The staining intensity was scored by two pathologists, and the average score was used.

Following laboratory tests were undertaken:

1. Urine protein quantification using a 24-hour collection.

2. Serum albumin, triglyceride, creatinine, complement 3 and 4 and effective glomerular filtration rate (eGFR).

3. AntiGBM antibody estimated by conventional ELISA method. Sera with low levels (<40%) of anti-GBM antibodies are further identified by Western-blot analysis using purified human α3 (IV)NC1 as solid-phase ligands[13].

4. Routine urine examination done for proteinuria, microscopic hematuria, pus cells and casts etc. The severity of proteinuria was graded 0 to 3+ with 0 representing the mildest and 3+ representing the most severe stage.

Outcome parameters. The following outcome and prognostic parameters were recorded and used for statistical analysis: development of ESRD, all-cause mortality, a permanent 50% reduction in eGFR compared with the baseline value/ no remission (NR), complete remission (CR), and partial remission (PR). CR was defined as urinary protein excretion <0.3 g/d (uPCR <300 mg/g or <30 mg/mmol) accompanied by a normal serum albumin concentration and a normal serum creatinine. PR was defined as urinary protein excretion <3.5 g/d (uPCR <3500mg/g or <350mg/mmol), a ≥50% reduction from peak values, an improvement or normalization of the serum albumin concentration, and stable serum creatinine[14,15]. ESRD was defined as a permanent drop in eGFR to 15mL/min/1.73m2 requiring dialysis or kidney transplantation. Poor renal outcome was indicated by NR, ESRD, hemodialysis dependence and death. Good renal outcome was indicated by PR or Cr[16].

Ethical issues: This study is approved by the Institutional Ethics Committee and Research Advisory Committee of the Institute. All the patients gave informed consent before participating in this study.

STATISTICALANALYSIS:

Mean value with two standard divisions were calculated for the serological parameters. We performed the oneway ANOVA(and nonparametric) test for comparisons between three groups, p-Value <0.05 was considered as significant. Survival analysis was done by Kaplan Meyer curve and comparison of survival curves were done by Log-rank (Mantel-Cox) test. p-Value <0.05 was considered as significant. We have used statistical software (GraphPad PRISM 6) for analysis.

RESULTS:

We have included 9 cases of IgA Nephropathy with crescents, 6 cases of AntiGBM disease and 2 cases of combined IgA Nephropathy and AntiGBM disease [Figure 1]. All the cases presented clinically with RPGN and histopathologically with crescentric glomerulopathy. Average age at presentation in three groups are 32.78± 12.04 years, 45.00± 11.38 years and 38.50± 13.44 years respectively. All the three groups showed male prepondarence with male female ratio being 1.25:1, 2:1 and 2:0 resepectively. More than half of the patients of IgA Nephropathy(55.5%) and AntiGBM disease (66.6%) presented with edema whereas it was not seen in the patients of combined disease. Diabetes was rarely seen in three groups. History of infection and hypertension were predominantly seen in patients of IgA Nephropathy and combined disease. Association of hypertension was statistically significant. Most prominant pulmonary symptom was hemoptysis which was predominantly seen among the patients of AntiGBM disease (83.3%) and combined disease (50%) and the association was statistically significant [Table 1].

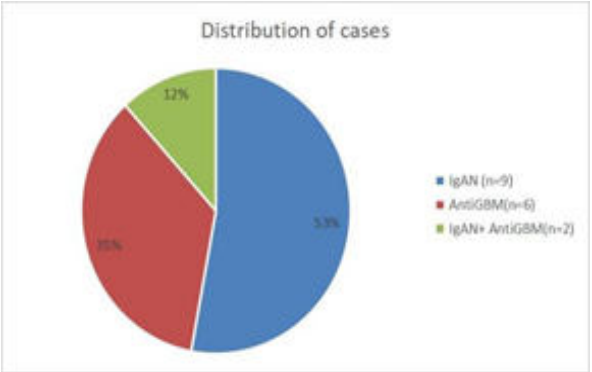

Figure 1: Distribution of the cases of Rapidly Progreesive Glomerulonephritis

In most patients serum albumin was reduced slightly and triglyceride was normal and none showed nephrotic syndrome. Anti GBM antibody was statistically significantly higher in AntiGBM disease (178.8± 140.6IU/mL) and combined disease (295.0± 190.9IU/mL). Both complement 3 and 4 levels were within normal limits in all the three groups. Among the renal function indicators serum creatinine was statistically significantly high in AntiGBM disease (10.8± 4.5 mg/dL) and combined disease (8.3± 1.7 mg/dL) than in IgA Nephropathy (4.6± 3.9 mg/dL). Quantitative protein estimation show 24 hour proteinuria in the range of 2.3± 0.84 gm, 2.4± 0.57 gm and 3.2± 0.56 gm respectively in three groups. Effective GFR was reduced in all the three groups. All the cases were ANCA (MPO ANCA and PR3 ANCA) negative. All the patients were tested for HIV serology along with HbsAg and HCV antibody which were negative [Table 1].

In routine urine examination red blood cell casts were statistically significantly associated with IgA Nephropathy (77.7%) rather than AntiGBM (0%) and combined (50%) disease. Other features like presence of RBC, pus cell and granular cast are comparable in all three groups. Urine protein excreation was 1+ to 2+ in dipstick examination in all the three groups [Table 1].

TABLE 1: Clinicopathological parameters and prognosis of three groups of patients

	CRESENTRIC IgANEPHROPATHY (n=9)	ANTI-GBM DISEASE (n= 6)	IgA AND ANTIGBM COMBINATION (n=2)	p VALUE
DEMOGRAPHICS				
Age (Years)	32.78± 12.04	45.00± 11.38	38.50± 13.44	0.1865
Men, n (%)	5 (55.5%)	4 (66.6%)	2 (100%)	0.5404
COMORBIDITIES, n (%)				
Edema	5 (55.5%)	4 (66.6%)	0 (0%)	0.2939
Hypertention	9 (100%)	2 (33.3%)	2 (100%)	**0.0030**
Diabetes	1 (11.1%)	1 (16.6%)	0 (0%)	0.8432
Infection	7 (77.7%)	1 (16.6%)	1 (50%)	0.0687
Pulmpnary disease	0 (0%)	5 (83.3%)	1 (50%)	**0.0006**
SEROLOGY				
Serum Albumin (g/dL)	2.6± 0.53	2.3±0.57	3.2± 0.56	0.2102
Serum Triglyceride (mg/dL)	158.4± 40.9	166.0± 54.1	217.0± 42.4	0.2971
AntiGBM antibody (IU/mL)	2.4± 2.5	178.8± 140.6	295.0± 190.9	**0.0018**
Complement 3 (g/dL)	111.4± 35.5	120.8± 13.7	159.5± 26.2	0.1411
Complement 4 (g/dL)	26.67± 6.4	25.50± 7.0	33.00± 5.6	0.3916
RENAL FUNCTION INDICATORS				
Serum Creatinine (mg/dL)	4.6± 3.9	10.8± 4.5	8.3± 1.7	**< 0.0001**

24 hour Proteinuria (gm)	2.3± 0.84	2.4± 0.57	3.2± 0.56	0.3490
eGFR (mL/min/ 1.73 m^2)	21.80± 14.5	18.63± 24.9	38.03± 14.4	0.4657
URINE ROUTINE EXAMINATION				
RBC (n/hpf)	16 ± 5.6	23± 28.1	7± 2.8	0.5126
Pus cell (n/hpf)	13.5 ± 7.3	5.8 ± 2.3	10.5 ± 6.4	0.0819
Red cell cast n, (%)	7 (77.7%)	0 (0%)	1 (50%)	**0.0063**
Granular cast n, (%(	3 (33.3%)	0 (0%)	0 (0%)	0.2278
Urine protein	2.1± 0.6	1.6 ± 0.8	1.5± 0.7	0.3645
CR n,%	3, 33.3%	1, 16.6%	0	0.5561
PR n, %	4, 44.4%	3, 50%	1, 50%	
NR n, %	2, 22.2%	2, 33.3%	1, 50%	
HD dependence n, %	4, 44.4%	2, 33.3%	1, 50%	0.7842
Death n, %	2, 22.2%	3, 50%	1, 50%	0.2558

Number of glomeruli detected in the kidney biopsy from all the three groups was comparable with the range of 7 to 30 glomeruli. Global sclerosis detected in all the three groups indicating chronicity. Segmental sclerosis seen in IgA Nephropathy [Figure 2] and combined disease [Figure 3] but not in AntiGBM disease [Figure 4]. Cresents are present in significantly higher number in AntiGBM (16.83± 7.6) and combined (16.00± 8.5) disease than in IgA Nephropathy (7.55± 3.2). Incidence of cellular and fibrocellular cresents are comparable in three groups whereas fibrous cresents are signicantly common in combined disease. Mesangial hypercellularity and matrix expansion were significantly more in IgA Nephropathy and combined disease. Endocapillary hypercellularity was present in IgA Nephropathy only whereas fragmentation of GBM was present in AntiGBM and combined diseases and this difference was statistically significant. Intraglomerular necrosis seen in IgA Nephropathy and AntiGBM disease. In the tubulointerstitial compartment proximal tubular epithelial injury in the form of vacuolar degenation, loss of brush border etc, tubular atrophy, presence of intratubular cast like granular cast, colloid cast and red cell cast, interstitial mononuclear inflammatory cell infiltration focally or diffusely and interstitial fibrosis are comparable in all the three groups. Different type of vascular changes identified. Commonest were hypertrophy of tunica media and arteriosclerosis. Others are mucoid intimal changes and leukocytoclastic vasculitis was comparable in all the three groups [Table 2].

In DIF microscopy IgG and kappa showed statistically significant expression along the GBM in linear fashion in Anti GBM and combined disease. Whereas IgA show significant mesangial positivity in IgA Nephropathy and combined disease. Lambda light chain and C3c showed comparable expression in all the three groups. IgM was segmentally positive in IgA Nephropathy whereas C1q was absolutely negative in all the three groups [Table 2].

TABLE 2: Histopathological and DIF microscopic finding in three groups

	CRESENTRIC IgA NEPHROPATHY (n=9)	ANTI-GBM DISEASE (n=6)	IgA AND ANTIGBM COMBINATION (n=2)	P Value
HISTOPATHOLOGICAL CHARACYERISTICS				
Number of Glomeruli	16.22± 7.4	19.50± 7.9	21.00± 4.2	0.5916
Global Sclerosis	3.78± 4.4	1.50± 2.5	1.00± 1.4	0.4180
Segmental sclerosis	0.89± 1.2	0	1.00± 1.4	0.2091
Total no of Crescents	7.55± 3.2	16.83± 7.6	16.00± 8.5	**0.0166**
Cellular Crescents	5.22± 3.7	15.50± 9.3	11.00± 15.5	0.0611
Fibrocellular Crescents	3.33± 4.9	1.33± 2.4	3.00± 4.2	0.6573
Fibrous Crescents	0.11± 0.3	0	2.00± 2.8	**0.0201**
Mesangial cell proliferation (present-1, absent-0)	0.78± 0.4	0	0.50± 0.7	**0.0063**
Mesangialmatrix expansion (present-1, absent-0))	1.00± 0.0	0.17± 0.4	1.00± 0.0	**< 0.0001**
Endocapillary hypercellularity (present-1, absent-0)	0.33± 0.5	0	0	0.2278
Fragmentation of GBM (present-1, absent-0)	0	0.83± 0.4	1.00± 0.0	**< 0.0001**
Necrosis (present-1, absent-0)	0.44± 0.5	0.33± 0.5	0	0.5404
Tubular injury (present-1, absent-0)	0.67± 0.5	0.33± 0.5	0.50± 0.7	0.4976
Intratubuler cast (present-1, absent-0)	0.78± 0.4	0.50± 0.5	1.00± 0.0	0.3645
Tubular atrophy (%)	18.89± 11.6	15.00± 13.4	30.00± 14.1	0.3457
Interstitial inflammation (diffuse-1,focal-0)	0.22± 0.4	0.50± 0.5	0.50± 0.7	0.5404
Interstitial fibrosis (%)	18.89± 11.6	15.00± 13.4	30.00± 14.1	0.3457
IFTA (%)	18.89± 11.6	15.00± 13.4	30.00± 14.1	0.3457
Vascularchanges (present-1, absent-0)	0.55± 0.5	0.17± 0.4	1.00± 0.0	0.1017
Arteriosclerosis (present-1, absent-0)	0.11± 0.3	0	0.50± 0.7	0.1871
DIF MICROSCOPY (INTENSITY SCORE)				
IgG	0.28± 0.26	2.83± 0.41	2.50± 0.71	**< 0.0001**
IgA	2.44± 0.53	0	2.00± 0.0	**< 0.0001**
IgM	0.22± 0.26	0	0	0.1068
C3c	1.00± 0.43	0.67± 0.82	0.50± 0.71	0.4538
C1q	0	0	0	
Kappa	0.55± 0.46	2.50± 0.84	2.50± 0.71	**< 0.0001**
Lambda	1.11± 0.93	2.17± 0.75	1.50± 0.71	0.0985

All patients were treated and followed up with a range of 8 months to 3 months. CR was seen in 33.3% and 16.6% of IgA Nephropathy and Anti GBM disease respectively but not in combined disease. On the other hand 22.2%, 33.3% and 50% of IgA Nephropathy, Anti GBM disease and combined disease respectively were totally nonresponsive to drugs and treated with hemodialysis among which 44.4% of IgA Nephropathy, 33.3% of Anti GBM disease and 50% of combined disease become dialysis dependent. 22.2% of IgA Nephropathy and 50% each of Anti GBM and combined disease died during follow up [Table 1,3,4 &5]. Kaplan Meyer survival analysis curve for all cause mortality versus dialysis dependence [Figure 2] and CR,PR versus NR [Figure 3] show no difference of survival between three groups as the comparisons are statistically insignificant in Log-rank test.

Different microscopic features of IgA Nephropathy [Figure 4], Anti GBM disease [Figure 5] and combined disease [Figure6] respectively.

TABLE 3: Followup of IgA Nephropathy cases

	DURATION (Months)	TYPE OF RESPONSE	DIALYSIS DEPENDANCE	DEATH
1	8	PR	Y	N
2	6	PR	N	Y
3	5	CR	N	N
4	6	NR	Y	N
5	7	CR	N	N

6	5	PR	N	Y
7	5	NR	Y	N
8	7	CR	N	N
9	6	PR	Y	N

TABLE 4: Followup of Anti-GBM disease

ANTI- GBM DISEASE	DURATION (Months)	TYPE OF RESPONSE	DIALYSIS DEPENDANCE	DEATH
1	5	NR	N	Y
2	7	PR	Y	N
3	3	NR	N	Y
4	6	PR	N	Y
5	7	CR	N	N
6	3	PR	Y	N

TABLE 5: Followup of Combined IgA Nephropathy and Anti-GBM disease

IgA NEPHROPATHY AND ANTI- GBM DISEASE	DURATION (Months)	TYPE OF RESPONSE	DIALYSIS DEPENDANCE	DEATH
1	5	NR	N	Y
2	7	PR	Y	N

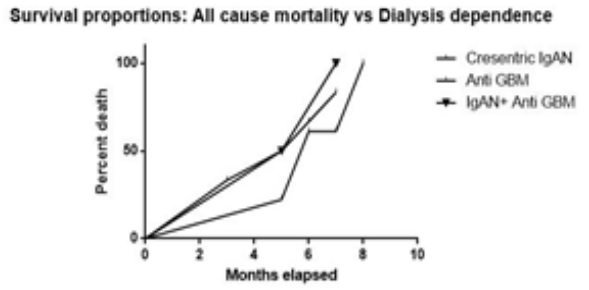

Figure 2: Percent survival of All cause mortality versus Dialysis dependance

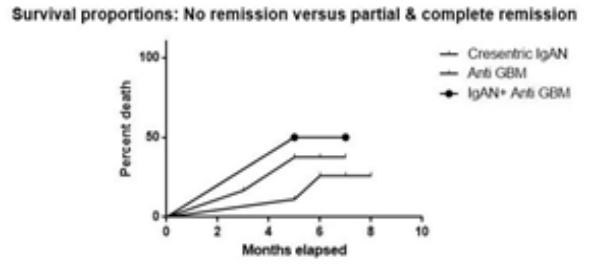

Figure 3: Percent survival of No remission versus Partial and Complete remission

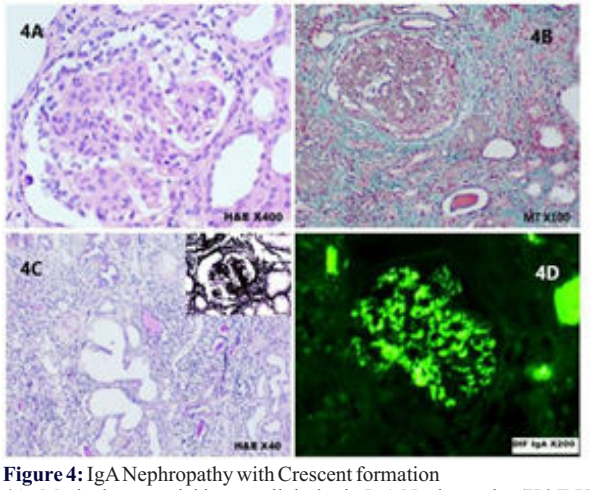

Figure 4: IgA Nephropathy with Crescent formation
4A: Marked mesangial hypercellularity in IgA Nephropathy (H&E X 400)
4B: Fibrocellular crescent in IgA Nephropathy (MT X 100)
4C: Interstitial fibrosis and tubular atrophy in IgA Nephropathy (H&E X 40)
Inset: Crescent in in IgA Nephropathy (JMS X 100)
4D: Mesangial granular IgA deposit in DIF (X200)

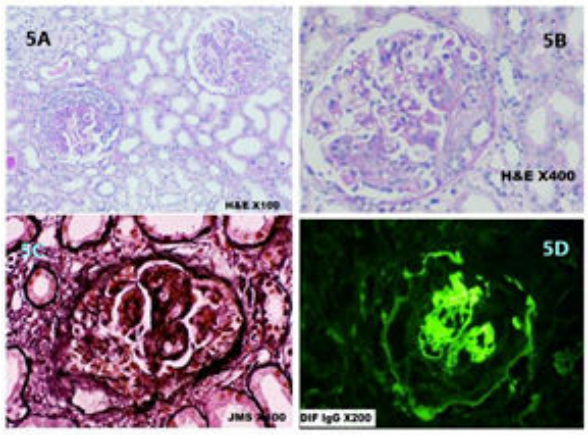

Figure 5: Anti-GBM Disease
5A: Cresents present in most glomeruli in Anti-GBM Disease (H&E X 100)
5B: Cellular crescent in Anti-GBM Disease (H&E X 400)
5C: Cellular crescent in Anti-GBM Disease (JMS X 400)
5D: Linear positivity of IgG along glomerular basement membrane (DIF X 200)

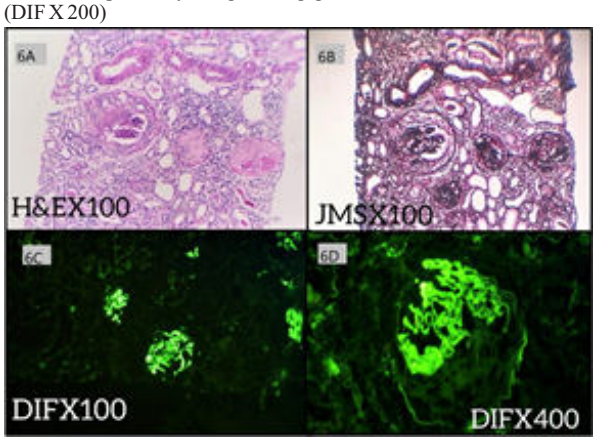

Figure 6: Combined IgA Nephropathy and Anti-GBM Disease
6A: Fibrocellular cresents in the glomeruli (H&E X 100)
6B: Fibrocellular cresents in the glomeruli (JMS X 100)
6C: Mesangial granular IgA deposits (DIF X 100)
6D: Linear positivity of IgG along glomerular basement membrane (DIF X 400)

DISCUSSION:

RPGN is suspected when there is a rapid decline in renal function (reduction of more than 50% of GFR within 3 months) along with nephritic urinary sediment and a normal or enlarged kidney size[17]. It is usually caused by one of the three following mechanisms: anti-GBM antibody disease with or without pulmonary hemorrhage, pauci-immune glomerulonephritis, and severe immune complex mediated glomerulonephritis[18]. Untreated patients with RPGN may rapidly progress to ESRD.

The main pathologic finding is extensive glomerular crescent formation. The percentage of glomeruli that exhibit crescents usually correlates with the severity of disease[18].The ubiquitous pathological feature of crescentic glomerulonephritis is a focal rupture of glomerular capillary walls that can be seen by light microscopy and electron microscopy.

In our study we have compared the clinical and serological parameters, renal function indicators, routine urine examination, renal biopsy findings by light and DIF microscopy in three different groups of patients presenting with RPGN- one group with IgA Nephropathy, one group with Anti-GBM disease and another with combined IgA Nephropathy with Anti-GBM disease. Small number of clinicopathological features show statistically significant difference between the three groups like incidence of hypertension, hemoptysis,

serum creatinine, anti GBM antibody, red cell casts in urine, total number of crescents including fibrous crescents and mesangial hypercellularity with matrix expansion, fragmentation of GBM etc. In DIF microscopy IgG, IgA and kappa light chain positivity show statistically significant difference between the three groups. After intense search of literature we have found that small number of previous studies have done similar type of comparison. Cui et al done comparison of clinical and laboratory data between the patients of Anti-GBM disease associated with immune complex deposition (10 cases) and and pure Anti-GBM disease (37 cases). Similar to our finding most of the features were comparable between the two groups without any significant difference[19]. Oliguria was less common in concurrent IgA Nephropathy and AntiGBM disease (10%) than Anti GBM disease with deposition of other immune complexes (40%). In our study both the patient presented with oliguria with eGFR in the range of 38.03± 14.4 mL/min/ 1.73 m^2. Percentage of crescent formation was less in concurrent IgA Nephropathy and AntiGBM disease (59%) than that in antiGBM disese with deposition of other immune complexes (93.8%). In our study incidence of crescents was 72% in concurrent IgA Nephropathy and AntiGBM disease.

All the diagnosed cases were treated and followed up. There was no significant difference between the response rate and poor renal outcome indicated by non response, ESRD, dialysis dependence and incidence of death within the three groups. Other researchers Cui et al found that concurrent IgA Nephropathy and Anti-GBM disease show better prognosis than AntiGBM disease alone[19], whereas Gupta et al found just the opposite[20]. Anti-GBM disease cases less commonly (10%) achieved dialysis indepence than concurrent IgA Nephropathy and AntiGBM disease (60%) . Similarly other researcher showed that that Anti-GBM disease wass the most aggressive form of crescentic glomerulonephritis, with the highest frequency of renal insufficiency followed by ANCA-associated vasculitis and then by immune complex-mediated crescentic glomerulonephritis[21]. Fifty percent of our patients with combined disease were dialysis dependent.

Prognosis depends not only on the number of crescents but also on the tubulointerstitial chronicity indicated by interstitial fibrosis and tubular atrophy (IFTA), number of sclerosed glomeruli and the presence of arteriosclerosis. When chronic changes are predominant in renal biopsy, intense immunosuppression protocol was not provided weighing the potential side effects of intense immunosuppression versus the low possibility of salvaging the renal function.

Anti-GBM disease occurs in all age group with a peak in third decade in male and sixth decade in both male and female[22]. Similarly our study show mean age group of fifth decade with slight male prepondarence.The diagnosis of Anti-GBM disease is made by demonstration of linear IgG positivity along the GBM in renal biopsy by DIF microscopy and is usually supported by the serological detection of circulating anti-GBM antibodies and presence of crescents in light microscopy of renal biopsy[23]. The sensitivity of ELISA in detecting anti-GBM antibodies is 87–90%, when combined with Western blot it increases to 95–99%. Early intervention of anti-GBM disease is crucial to preserve renal function and avoid severe pulmonary sequelae. Careful examination of renal biopsy along with clinical evaluation and serological evaluation of of anti-GBM antibody along with close follow-up are necessary in managing these patients.

Main aim of our study is to describe two unusual occurances of concurrent IgA Nephropathy and Anti-GBM disease. First report of anti-GBM disease and mesangial IgA deposits was described in 1998 in a 12 year postrenal transplant recipient from Canada[24]. After that several studies show similar type of dignosis with varied clinicopathological setup from different countries[25-29] [Table 6]. IgA Nephropathy may precede or follow Anti-GBM disease. When Anti-GBM disease superimpose on IgA Nephropathy possible mechanism may be IgA-related immune complex exposing the non-collagenous domain of the alpha-3 subunit, that are normally hidden by intrachain methionine cross-links[19,30,31]. Experimental models and in vivo studied on IgA nephropathy also prove the release of IL-1, TNF, IL-6, oxygen radicals, and eicosanoids by infiltrating glomerular and interstitial monocytes/macrophages and mesangial cells[23,32,]. Inflammatory mediators might initiate immunologic events causing conformational changes of GBM and exposure of antigens, thus facilitating anti-GBM antibody production. Altered IgA deposition in the mesangium characterised by defect in galactosylation of IgA1 occurs in IgA nephropathy[33]. Aberrant polysaccharide chain of IgA1 triggers anti-GBM IgG2 antibody production which gets deposited in the GBM[34]. Alternative hypothesis is given by Wang *et al*, highlighting the possibility of increased antigen synthesis or capping and shedding of antigen antibody complexes[35].

TABLE 6: Comparison of finding of Combined IgA Nephropathy and Anti-GBM disease of our study with other studies

	Yamaguchi et al[9] (2013)	Troxell et al[10] (2016)	Ge et al[11] (2015)	Xu et al[12] (2016)	Suh K-S et al[1] (2019)	Our study (2018-2019)
Country	Japan	USA	China	China	Korea	India
Number	1	1	1	1	1	2
Age	46	60	24	50	38	38.50± 13.44
Sex	M	F	M	F	F	M
Symptoms	Azotemia, fever	Fever, dysphagia, wt loss	Edema, heahache, nocturia	Gross hematuria	Fever	Hematuria & oliguria
Hypertension	134/83 mm Hg controlled	Negative	Positive 194/120	Negative	Negative	Positive in both (162/100 & 170/116)
Diabetes	Positive	Negative	Negative	Negative	Negative	Negative
Infection	Negative	Negative	Negative	Negative	Negative	Positive in 1
Hemoptysis	Negative	Negative	Negative	Negative	Negative	Positive in 1
Oliguria		Negative	Negative	Negative	Negative	Positive
Nephrotic syndrome	Negative	Negative	Positive	Negative	Negative	Negative
Hematuria	Positive	Negative	Negative	Positive	Positive	Positive
24 hour urine protein (gm) or in spot urine	2.9	0.4	7.04	0.41	1.4	3.2± 0.56
Creatinine (mg/dL)	5.2	0.73	3.7	2.6	5.4	8.3± 1.7
Anti GBM Ab	214 EU/mL	120-150%	Positive not described	258 EU/mL	187.2 U/mL	295.0± 190.9 IU/mL
Glomeruli ,n	16	12	31	18	16	21.00± 4.2
Global sclerosis	1	3	2	0	5	1.00± 1.4
Crescents,(%)	15 (94%)	1 (8%)	18 (58%)	16 (89%)	11 (63%)	32 (76%)
Type	Cellular (100%)	Cellular (100%)	Cellular (100%)	Cellular (75%), fibrocellular (25%)	Cellular (45.5%), fibrocellular (54.5%)	Cellular (68.7%), fibrocellular (18.7%), fibrous(12.5%)
Treatment	IV Metyl-PD+Oral-PD	IV Metyl-PD+ Oral-PD+ Methotrexate	IV Metyl-PD+ Oral-PD+IV cyclophsphamide	IV Metyl-PD+Oral PD+Mycophenolate mofetil	IV Metyl-PD+ Oral-PD +IV cyclophsphamide	IV Metyl-PD+Oral-PD
Plasmapheresis	Done , failed due to allergy	Not performed	Not performed	Not performed	Not performe d	Done in 1
Remission type	NR	CR	NR	CR	CR	PR in 1, NR in other
Hemodialysis	Dialysis dependant	Dialysis independent	Dialysis dependant	Dialysis independent	Dialysis independent	Dialysis dependant in 1
Death	No	No	No	No	No	Death in 1

When the AntiGBM disease preceds IgA Nephropathy, possible mechanism may be alteration of GBM permeability followed by the circulating immune complex deposition in the mesangium[19]. Mesangial IgA deposits are known to occur in association with bacterial and viral infection like HIV[36,37]. One of our patient also gave

history of upper respiratory tract infection.

CONCLUSION:

In our study we have analysed three relatively uncommon type of RPGN and found that crescentic IgA nephropathy, anti GBM disease and the combined one though have relative difference in presentation have similar therapeutic response and renal outcome. Proper and early clinicopathological diagnosis of these uncommon types of crescentric glomerulonephiritis is important since all are of poor renal outcome

LIMITATIONS:

More cases with an in-depth examination of underlying pathogenic relationships between anti-GBM disease and IgA nephropathy are needed to be analyzed.

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Ethics: This study is approved by the Institutional ethical committee. All the participants gave informed consent in writting at the begining of the study.

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Data sharing statement: No additional data available.

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ORCID iD : Dr Keya Basu(https://orcid.org/0000-0002-3960-2469)

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