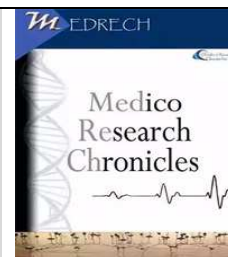




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ANTI-GLOMERULAR BASEMENT MEMBRANE ANTIBODY DISEASE AND ITS OUTCOME

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ARTICLE INFO	ABSTRACT	ORIGINAL RESEARCH ARTICLE
Article History Received: May' 2019 Accepted: June' 2019 Keywords: Anti GBM-anti glomerular basement membrane, GN-Glomerulonephritis, ESRD-End stage renal disease, HD-Hemodialysis.	Anti-glomerular basement membrane (anti-GBM) disease is an aggressive autoimmune disease which affects glomerular capillaries, characterized by glomerular fibrinoid necrosis and crescent formation with or without pulmonary hemorrhage. Patients presenting with dialysis-dependent renal failure have poor renal outcomes. There is limited data regarding the clinical presentation and outcomes of anti-GBM disease from India. Aim: To study the incidence, clinical, biochemical and pathological characteristics and outcome of patients with anti-glomerular basement membrane (anti-GBM) antibody disease. Methods and Material: This is a retrospective study conducted by screening renal biopsy reports of patients presented with rapidly progressing glomerulonephritis (RPGN) over a period of 45 months(JAN 2015-OCT 2018) Those patients who had histopathological features suggestive of ANTI GBM disease or those who had positive ANTI-GBM antibody titers were further analyzed. Their records were reviewed for the duration of symptoms before presentation, clinical features, and biochemical, pathology and serology reports. Follow up details were noted. Results: A total of 97 patients presented with RPGN during the period of 45 months (Jan 2015 to Oct 2018). Anti GBM disease (10/97) constituted 10.30% of rapidly progressive glomerular disease. Males and females were equally affected (M: F 5:5), males mean age; 43.6± 6.9 yrs and females mean age 28.8± 10.1 yrs. The presenting symptoms were pedal edema (80%), oliguria (60%), hematuria (40%) and hemoptysis (20%). Kidney biopsy was done after a mean period of 10.7± 7.2 days after first presentation. Mean sr. creatinine was 7.7± 3.3 mg/dl, Only 2 patients had a creatinine of <5 mg /dl. Eight patients screened for circulating anti-GBM antibodies were positive and one patient positive for p-ANCA. Mean crescents per biopsy specimen were 71 %, 3 had 100% crescents (30%). Conclusions: Anti GBM disease constituted 10.30% of rapidly progressive GN. Males and younger females were predominantly affected .All patients had >50% crescents and severe renal failure at presentation. Despite adequate immunosuppressive therapy all of them developed ESRD, due to delayed presentation.	
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INTRODUCTION:

Anti GBM antibody disease is a disorder in which circulating autoantibodies are directed against an intrinsic antigen to the glomerular basement membrane. The development of anti-GBM antibodies may precede the onset of clinical signs and symptoms by many months [3]. The principal target for the anti-GBM antibodies which are typically immunoglobulin G (IgG) 1 and 3 but sometimes IgA or IgM, is the NC1 domain of the alpha-3 chain of type IV collagen. ⁴ Experimental models and clinical studies suggest that autoreactive T cells may contribute to the development of anti-GBM antibody disease. [5-10] Most observations suggest that autoreactive T cells, in addition to enhancing B cell function and antibody production, may have a direct causative role in the glomerular and alveolar injury.

Patients presenting with dialysis-dependent renal failure have poor renal outcomes. There is limited data regarding the clinical presentation and outcomes of anti-GBM disease from India.

SUBJECTS AND METHODS:

To study the incidence, clinical, biochemical and pathological characteristics and outcome of patients with biopsy-proven anti-glomerular basement membrane antibody disease or those with isolated anti-GBM antibody positive.

Study design: a Retrospective observational study

Inclusion criteria:

We screened renal biopsies performed for those who presented with RPGN in the department of Nephrology, of our hospital over a period of 45 months (Jan 2015 to Oct 2018), of this biopsy, proven ANTI-GBM disease or isolated anti-GBM antibody-positive patients included in the study.

All biopsies were performed by nephrologists under ultrasound guidance and slides were examined by a single pathologist.

For light microscopy, 3 μ m thick paraffin sections were stained for hematoxylin and eosin, periodic acid–Schiff, Jones's methenamine silver, and trichrome stains.

Cryostat frozen sections were subjected to IF studies using anti-human IgG, IgA, IgM, C3, C1q, and fibrinogen antisera.

Exclusion criteria:

1. Patients with isolated ANCA positive.
2. Patients with other causes of linear IgG deposits like LUPUS/LCDD/DM.
3. Other causes of glomerulonephritis.
4. Other causes of vasculitis.

Clinical data were obtained from the patients' medical records. Their records were reviewed for clinical features, biochemical, pathology, and serology reports. Follow up details were noted. Institutional ethical committee approval obtained. During the study period, ten such biopsies were identified.

Statistical analysis was performed and Continuous variables were expressed as means $\pm$ standard deviation or medians (interquartile range), non-continuous data were expressed in percentage and numerical values.

RESULTS:

A total of 97 patients presented with RPGN during the period of 45 months (Jan 2015 to Oct 2018). Anti GBM disease (10/97) constituted 10.30% of rapidly progressive glomerular disease. Males and females were equally affected (M: F 5:5), males mean age; 43.6 ± 6.9 yrs and female's mean age 28.8 ± 10.1 yrs. The presenting symptoms were pedal edema (80%), oliguria (60%), hematuria (40%) and hemoptysis (20%). Mean SR creatinine was 7.7 ± 3.3 mg / dl, Only 2 patients had a creatinine of < 5 mg / dl. Eight patients screened for circulating anti-GBM antibodies were positive and one patient was positive for both including p-ANCA. Kidney biopsy was done after a mean of 10.7 ± 7.2 days after the first presentation. Mean crescent distribution per biopsy specimen was 71 %, of these 100% crescents in 3 (30%). One patient had IgA nephropathy and one had MPLA2R positive membranous nephropathy.

Renal biopsy was not done in one patient as she presented with bilateral contracted kidneys but Anti GBM antibody and P ANCA were positive. ^(Table 1)

TREATMENT AND OUTCOME:

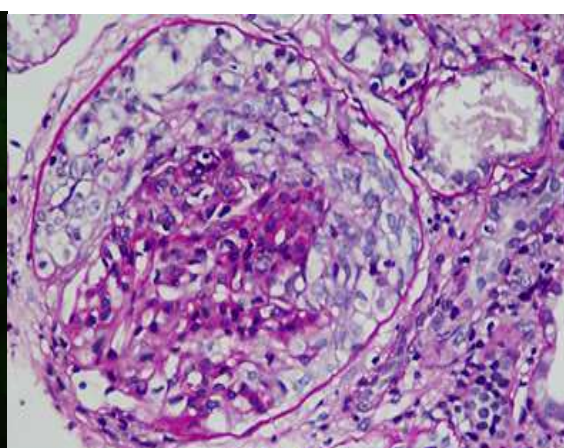
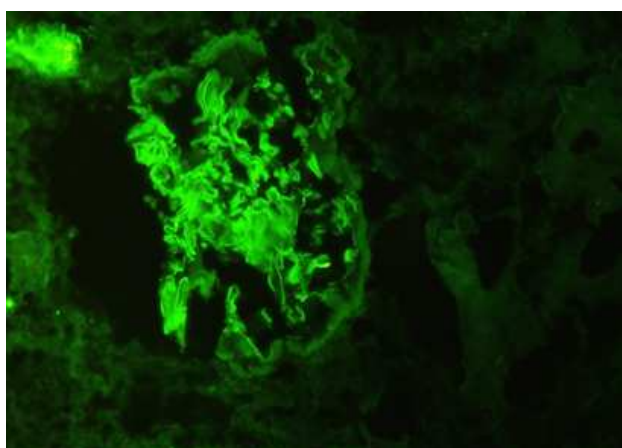
All patients received pulse methylprednisolone. Four received oral cyclophosphamide. Plasmapheresis was done in 5 patients

Two patients (20%) died after a mean duration of 3.8 ± 1.3 yrs after the biopsy.

Three patients lost to follow up after six months of therapy. One underwent live related renal transplantation. Two patients presented with mild renal failure did not respond to therapy and progressed to end-stage renal failure. Renal function did not recover in all the patients (0/10). (Table 1)

Table 1. Patients Characteristics

	1	2	3	4	5	6	7	8	9	10	Mean
Age/sex	43/M	31/F	45/F	19/F	22/F	52/M	39/M	35/M	49/M	27/F	36.2 $\pm$ 11.3 yrs.
Duration of Presentation (DAYS)	17	14	30	25	8	13	17	7	8	14	15.2 $\pm$ 7.5days
BP (mm/hg)	120/80	120/80	130/80	130/100	160/80	120/80	160/100	170/100	150/100	130/90	143 $\pm$ 19 / 95 $\pm$ 13 mm Hg
Sr.Cr (mg/dl)	6.9	6.7	6.4	13.1	2.0	19.8	7.2	12.0	3.6	10.1	7.7 $\pm$ 3.3
ANTI GBM AB/ANCA	+NA	+/-	NA/NA	++(P)	+/-	NA/NA	+/-	+/-	+/-	+/-	8/10 1/10
ASSOCIATION				Pul hge ANCA +VE	IgA N			Pul Hge	MN MPL A2R +		
Crescents	100%	70%	77%	----	100%	90%	82%	36% GS 64%	35% GS 60%	100%	71%
OUTCOME	HD	HD /3 MONTHS	HD	LRRT	HD /12 MONTHS	HD	HD	HD	HD /7DAYS	HD	10/10



Discussion:

In our study totally 97 patients presented with RPGN during the period of 45 months (Jan 2015 to Oct 2018) of which Anti GBM disease (10/97) constituted 10.30%.

A common observation from larger series of anti-GBM disease is that of bimodal age distribution, with peak incidences in the third decade, where a slight male preponderance and presentation with both kidney and lung disease are observed, and in the sixth to seventh decades, where presentation with isolated kidney disease is more common.^(11, 12, 13) A previous study from India had shown that the mean age of onset was 33.4 ± 13.2 years with male predominance (16:2).⁽¹⁴⁾ In our study, the mean age of presentation was 36.2 ± 11.3 years, and there was an equal gender distribution (male: female= 5:5) which is similar to the study by Fischer and Lager and Prabhakar et al which also showed a near equal gender representation.^(12, 15)

Co-existence of anti-GBM and ANCA has been reported in one-third to one-fourth patients of anti-GBM disease. We found MPO-ANCA in one of our patients.^(16,17) Although the presence of "double positivity" for ANCA and anti-GBM antibodies in anti-GBM disease does not alter the renal prognosis, it has been reported to be associated with an increased incidence of extrarenal symptoms in CrGN.⁽¹⁸⁾ However, our patient with double positivity had pulmonary hemorrhage but the initial presentation was ESRD.

Ahmad *et al.* reported hemoptysis in 33% patients and Prabhakar et al noted diffuse alveolar hemorrhage in 25% of patients, which is lower than the previous studies.^(14, 15) In our study 20 % had hemoptysis and they responded with plasmapheresis. Only four patients (40%) were smokers in our study, which may explain the low incidence of pulmonary hemorrhage. Fischer and Lager et al reported that their patients had crescents in more than 50% of glomeruli.¹² similarly our study kidney biopsy showed evidence of 100% crescents in 3 (30%) and mean distribution of crescents was 71 %.

On immunofluorescence, IgG is the most common immunoglobulin and C3, the most common complement with linear deposits along GBM. Tang *et al.* had reported IgG in 77.5% of patients and C3 in (21.1%) cases of anti-GBM nephritis.⁽¹⁹⁾ We found linear IgG in all (100%) and C3 deposition in 60% cases.

The first report of anti-GBM disease and mesangial IgA deposits was described in 1998 in renal transplant recipients after 12 years.^[20] Gao et al described a 38-year-old female with similar presentation.^[21] A rare form of anti-GBM glomerulonephritis mediated by IgA autoantibodies has also been described in the literature.⁽²²⁾ we also found one case of Anti-glomerular Basement Membrane Disease Superimposed on IgA Nephropathy. When compared to classical IgG-related anti-GBM disease, the prognosis of IgA-related anti-GBM disease is poor.⁽²³⁾

There have been very few case reports documenting the simultaneous appearance of anti-GBM disease and membranous nephropathy. It is possible that the intramembranous and epimembranous immune complexes found in membranous nephropathy alter the glomerular basement membrane, causing the release of normal or altered glomerular basement material with subsequent development of anti-GBM antibodies and crescentic glomerulonephritis.⁽²⁴⁾

In our study a middle-aged man initially presented with nephrotic syndrome and in oliguric renal failure, later progressing to anuric renal failure requiring dialysis, Biopsy showed features of membranous nephropathy superimposed on anti –GBM disease, the ti GBM titer was significantly positive, he was treated with plasmapheresis and oral cyclophosphamide, he did not recover renal function and remained dialysis dependent.

The renal prognosis in anti-GBM disease is usually poor with only less than one-third patients having maintained kidney function after 6 months of follow-up.⁽²⁵⁾ Our study and earlier reports from India suggest that these patients are diagnosed late resulting in a poor renal outcome.⁽²⁶⁾

Table 2. Comparison between previous Indian studies and the present study

	Ahamed et al ¹⁴	Prabhakar et al ¹⁵	OUR STUDY
Total No of Patients	18	17	10
Male : Female	16:2	9:8	5:5
Age (Mean)	33.4 $\pm$ 13.2 yrs	39.11 $\pm$ 16.58 yrs	36.2 $\pm$ 11.3 yrs
Hemoptysis	6	4	2
Dialysis requiring at presentation %	94.3	82.3	80%
Sr.Cr mg/dl	9.89 $\pm$ 3.49	8.64 $\pm$ 5.29	7.7 $\pm$ 3.3
Biopsy proven ANTI GBM	13	16	9
Pt who received PEX	7	14	5
Improved/Dialysis independant	4/22	4/17	0/10

Conclusion:

Anti GBM disease constituted 10.30% of rapidly progressive GN. Males and females were equally affected; younger females predominate in contrast to other studies. Most patients presented more than one or two weeks after the onset of symptom and those who presented with pulmonary hemorrhage were responded to plasmapheresis. All patients had >50% crescents and severe renal failure at presentation. Despite adequate immunosuppressive therapy, all of them developed ESRD, due to delayed presentation.

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