ISSN: 2581 – 3633
PubMed - National Library of Medicine - ID: 101745081

International Journal of Medical Science and Advanced Clinical Research (IJMACR)

Available Online at:www.ijmacr.com

Volume – 9, Issue – 3, May – 2026, Page No.: 171 – 177

Clinicopathological Features and Outcome of Antibody-Negative Anti-Glomerular Basement Membrane Disease

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How to citation this article: Dr. Manjuri Sharma, Dr. Bubu Gogoi, Dr. Prodip Kr Doley, Dr. Gayatri Pegu, Dr. Miranda Pegu, "Clinicopathological Features and Outcome of Antibody-Negative Anti-Glomerular Basement Membrane Disease", IJMACR – May – 2026, Volume – 9, Issue – 3, P. No. 171 – 177.

Type of Publication: Original Research Article

Conflicts of Interest: Nil

Abstract

Background: Anti-glomerular basement membrane disease is a rare autoimmune disorder targeting type IV collagen, causing rapidly progressive glomerulonephritis with or without pulmonary haemorrhage. While diagnosis typically relies on circulating anti-GBM antibodies and linear IgG staining, antibody-negative cases occur and may present atypically, posing diagnostic challenges and uncertain outcomes that warrant evaluation. We have collected 10 such cases to investigate the clinical & pathological features and outcomes of these patients.

Objective: To study the clinicopathological characteristics of patients with anti-GBM antibody-negative anti-GBM disease.

Methods: It was a hospital based retrospective observational study. Conducted in the Nephrology Department, Gauhati Medical College and Hospital from January 2020 to December 2024.

Results: Median age was 36 years (19–75) with female predominance (M: F = 4:6). Median illness duration was 37.5 days. Hypertension occurred in 70%, lung involvement in 10%, and hematuria in 9 patients. Mean proteinuria was 3.24 g/day and serum albumin 2.94±0.6 g/dL. 60% patients presented with RPGN. Median creatinine was 5.45 mg/dL. The median duration of follow-up was six months. During the follow-up, five (50%) patients progressed to ESRD. Two patients died due to pulmonary infection.

Conclusion: Like classical Anti-GBM disease, Antibody-negative anti-GBM disease carries poor renal

outcomes, highlighting the need for early detection and better therapeutic strategies.

Keywords: Anti Glomerular basement membrane disease, rapidly progressive glomerular disease, End stage renal disease.

Introduction

Anti-glomerular basement membrane (GBM) disease is a rare autoimmune disease mediated by antibodies with specificity for type IV collagen in basement membrane. The disease is characterized by the presence of circulating autoantibodies and rapidly progressive glomerulonephritis (GN), with or without alveolar hemorrhage [1]. Accompanying pulmonary hemorrhage occurs in over half the patients (termed Goodpasture's syndrome) [2].

The diagnosis is usually confirmed by the detection of circulating anti-GBM antibodies using commercially available enzyme-linked immunofluorescence assay (ELISA) and indirect immunofluorescence assay [2].

The pathological hallmark of this disease is bright linear staining of immunoglobulin along GBMs by immunofluorescence, and the renal histological lesions typically manifest as diffuse crescentic and/or necrotizing GN. The pathogenic immunoglobulins are usually of the IgG class, with predominate IgG1 and IgG3 subclass [1]. The occurrence of IgA or IgM class anti-GBM antibodies is also reported [6].

In recent years, there are increasing examples of atypical presentations of this disease published. These atypical cases often presented with lack of serum anti-GBM positivity or with atypical disease course. Often presents with less severe renal involvement. The pathological features of crescentic GN are usually absent. We have collected 10 such cases to investigate the clinical & pathological features and outcomes of these patients.

Materials and Methods

Study Design and Population

- Hospital based retrospective observational study.
- Conducted in the Nephrology Department, Gauhati Medical College and Hospital.
- Study period: From January 2020 to December 2024.
- Statistical analysis: SPSS Version 22 for windows.

Inclusion criteria

1. Patients with linear GBM IgG deposition on immunofluorescence (IF); and absence of serum anti-GBM antibodies by ELISA and indirect immunofluorescence assay.
2. Patients of either gender and varied age groups.

Exclusion criteria

1. The patients with a history of diabetes mellitus.
2. Post renal transplant patients
3. Patients who were lost to follow up.

All patients were subjected to-

- **Clinical studies and laboratory evaluation:**

Demographic, clinical and laboratory information was obtained on each patient at the time of renal biopsy. Follow-up and treatment information was obtained on all patients.

The following clinical definitions were used:

Nephrotic-range proteinuria: 24 hours' urinary protein excretion >3.5 g, serum albumin level ≥30 g/L.

Nephrotic syndrome: 24 hours' urinary protein excretion >3.5 g, serum albumin level 3.0 g/dL or less.

Hypertension: systolic BP >140 or diastolic BP >90 or the use of antihypertensive medications at the time of biopsy; and

End stage renal disease (ESRD): requirement of renal replacement therapy for more than 3 months.

- **Pathological studies:**

All patients had taken ultrasound-guided percutaneous renal biopsy. Kidney biopsy samples were processed for light microscopy (LM) and Immunofluorescence microscopy (IF).

On light microscopy:

Pattern of glomerular Injury

% of global and segmental sclerosis.

% of crescents and its type, acute tubular injury, tubular atrophy/interstitial fibrosis (IFTA).

Grading of IFTA:

None/minimal: <5% of cortical area

Mild: 5-25% of cortical area

Moderate: 26-50% of cortical area

Severe: >50% of cortical area

Immunofluorescence staining intensity was graded as-

0 (negative)

± (weak)

+(mild)

++(moderate) and

+++ (severe)

Results

Clinical characteristics of patients with antibody-negative anti-GBM disease (n=10):

Median age was 36 years (19–75) with female predominance (M: F = 4:6). Median illness duration was 37.5 days. Hypertension occurred in 70%, lung involvement in 10%, and hematuria in 9 patients. Mean proteinuria was 3.24 g/day and serum albumin 2.94±0.6 g/dL. 60% patients presented with RPGN. Median creatinine was 5.45 mg/dL.

Table 1: Clinical characteristics in patients with antibody-negative anti-glomerular basement membrane disease

Parameters	Values
Number of Patients	10
Median age (years)(Range)	36 (19-75)
Sex (Male/Female)	4/6
Duration of illness (Days)	37.5
Hypertension (n(%))	7(70%)
Lung involvement (n(%))	1(10%)
Urine protein (g/24 hours)	3.24
Hematuria (n)	9
Serum albumin (g/dL)	2.94±0.6
Rapidly progressive glomerulonephritis (RPGN) (n (%))	8(80%)
Serum Creatinine (mg/dL) (Range)	5.45(2.0-8.1)

Hemoglobin (g/dL)	11.2±2
Duration of follow-up (months)	6
ESRD (n(%))	5(50%)

Table 2: Microscopy findings in patients with antibody-negative anti-glomerular basement membrane disease

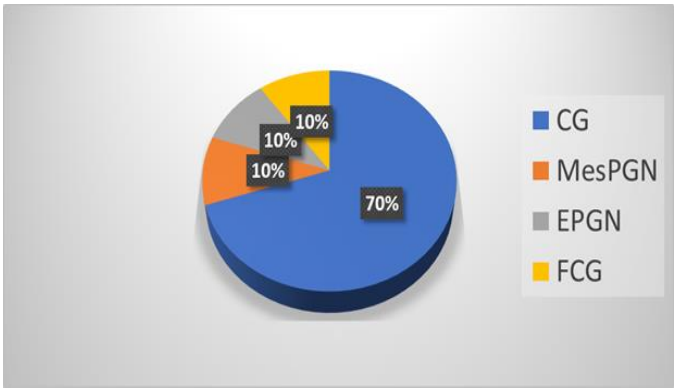
Patients	Glomerular pattern of injury	No of gloms/% global sclerosis/ % crescents/ % necrosis	IFTA	Immunoflorescence	IgG subclass staining by immunofluorescence
1	MPGN with diffuse crescents	15/20/66/7	Mild	Lin GBM and focal TBM IgG (2+), k (2+), and l (2+); neg IgA, IgM, C1q, and C3	2+ IgG4; neg IgG1
2	MesPGN with segmental scars and diffuse crescents/necrosis	13/0/61/15	Mild	Lin GBM and focal TBM IgG (3+), k (3+), l (3+), and IgA (+/-); þ/ gran mes IgM (+/-) and C3 (+/-); neg C1q	3+ IgG4; neg IgG1
3	EPGN	5/20/0/0	None	Lin GBM IgG (3+), k (3+), and l (3+); gran GBM C3 (1+) and IgM (+/-); neg IgA and C1q	2+ IgG1; 1+ IgG2; 1+ IgG4; neg IgG3
4	MesPGN with diffuse crescents and TMA features	16/19/100/0	Minimal	Lin GBM IgG (3+), k (3+), l (3+); gran mes IgA (+/-), IgM (+/-), and C3 (+/-); neg C1q	3+ IgG4; neg IgG1, IgG2, and IgG3
5	EPGN with focal crescents and TMA features	25/4/8/12	Moderate	Lin GBM IgG (3+), k (3+), and l (3+); gran C3 (1+); neg IgM, IgA, C1q	3+ IgG4; neg IgG1, IgG2, and IgG3
6	MesPGN with diffuse crescents	24/42/83/4	Moderate	Lin GBM IgG (2+), k (3+), l (3+); gran mes IgA (+/-), IgM (+/-), and C3 (+/-); neg C1q	2+ IgG1; 1+ IgG2; 1+ IgG4; neg IgG3
7	EPGN with diffuse crescents	10/20/ 60/0	Minimal	Lin GBM and focal TBM IgG (3+), k (3+), and l (3+); gran GBM C3 (1+) and IgM (+/-); neg IgA and C1q	3+ IgG1; 1+ IgG2; 1+ IgG4; neg IgG3
8	MesPGN with	15/0/0/0	Moderate	Lin GBM IgG (3+), k (3+), l	3+ IgG4; 1+ IgG2; 1+

	segmental scars			(3+), and IgA (+/-); þ/ gran mes IgM (+) and C3 (+); neg C1q	IgG1; neg IgG3
9	MesPGN with diffuse crescents	10/30/90/0	Moderate	Lin GBM IgG (3+), k (3+), l (3+); gran mes IgA (+/-), IgM (+/-), and C3 (+/-); neg C1q	3+ IgG4; 1+ IgG2; 1+ IgG1; neg IgG3
10	MesPGN with segmental scars and diffuse crescents	7/1/71/0	Severe	Lin GBM and focal TBM IgG (2+), k (3+), l (3+), and IgA (+/-); þ/ gran mes IgM (+) and C3 (+); neg C1q	2+ IgG4; 1+ IgG2; neg IgG1; neg IgG3

Light Microscopy findings (Glomerular injury pattern):

Crescentic glomerulonephritis (CG) was the predominant pattern, observed in 70% of patients. Mesangioproliferative glomerulonephritis (MesPGN), endocapillary proliferative glomerulonephritis (EPGN), and focal crescentic glomerulonephritis (FCG) were each seen in 10% of cases. CG was defined by >50% crescents, while FCG had <50% crescents.

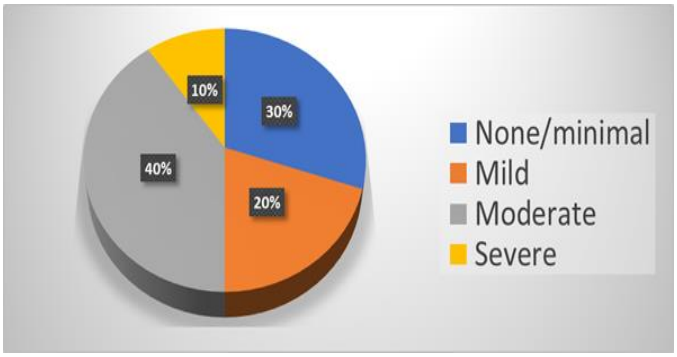
Figure 1: Glomerular injury pattern



Interstitial fibrosis and tubular atrophy (IFTA):

Moderate IFTA was the most common finding, seen in 40% of patients. None or minimal changes were observed in 30%, mild in 20%, and severe in 10% of cases, indicating that a substantial proportion had established chronic tubulointerstitial damage at presentation.

Figure 2: Interstitial fibrosis and tubular atrophy (IFTA):



Immunofluorescence

All patients showed at least 2+linear GBM IgG deposition and four patients had focal tubular deposition. There was trace to + staining for IgA and/or IgM in glomeruli in six patients. The GBM staining for kappa and lambda light chain were both positive in all patients. The IgG deposits were all polytypic with dominant subtype was IgG4 in seven patients and IgG1 in three patients.

Treatment and outcome

They received cyclophosphamide plus prednisone as per standard treatment guidelines. 5 patients also received Plasmapheresis along with above immunosuppressives. The median duration of follow-up was six months. During the follow-up, five (50%) patients progressed to ESRD. Two patients died due to pulmonary infection.

Table 3: Treatment outcome of the anti GBM disease

Outcome	No of patients
Complete renal recovery	0
CKD(ND)	3
ESRD	5
Death	2

Table 4: Comparisons with other studies

	Present study	Nasr et al	Liang et al
No of cases	10	20	19
Median Age (Years)(Range)	36(19-75)	58 (18-85)	36 (18-61)
Sex (M/F)	4/6	11/9	17/2
Urine protein (g/24 h)	3.24	3	2.1
Hematuria (n(%))	9(90%)	19(95%)	18(95%)
Nephrotic range proteinuria(n%)	3(30%)	10(50%)	8(42%)
Serum Creatinine (mg/dL)	5.45(2.0-8.5)	1.9(0.9-4.6)	1.8(0.84-9.6)
Pathological findings by LM -CG -FCG -MesPGN -EPGN	-7 -1 -1 -1	-0 -8 -6 -6	-1 -11 -4 -3
ESRD (n(%))	5(50%)	4(20%)	6(32%)
Death (n(%))	2(20%)	0(0%)	0(0%)

Discussion

In this study of antibody-negative anti-GBM disease, patients were younger than those reported by Nasr et al and similar to Liang et al, with a female predominance. Proteinuria and haematuria rates were comparable across studies, but serum creatinine was higher in our cohort, indicating more severe renal dysfunction at presentation. Crescentic glomerulonephritis was the dominant lesion, consistent with prior reports, though other proliferative patterns were also observed. The proportion progressing to ESRD (50%) was higher than in comparative studies, possibly reflecting delayed presentation, advanced disease, or limited resources. Mortality was low but present only in our cohort. Overall, antibody-negative anti-GBM disease demonstrates heterogeneous clinicopathological features and often poor renal

outcomes, underscoring the need for early recognition and aggressive management.

Conclusion

Like classical Anti-GBM disease, Antibody-negative anti-GBM disease is associated with severe renal involvement and unfavourable outcomes. Despite heterogeneous clinicopathological features, a high proportion progress to ESRD. These findings emphasize the importance of early diagnosis, prompt immunosuppressive therapy, and close follow-up to improve renal survival and overall prognosis.

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