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Clinicopathological Features and Treatment Outcomes of Double-Positive (ANCA and Anti-GBM) Glomerulonephritis: A Case Series from India

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Abstract

Background: Double-positive glomerulonephritis, defined by concurrent anti-glomerular basement membrane (GBM) and myeloperoxidase-antineutrophil cytoplasmic antibody (MPO-ANCA) positivity, represents a rare but severe form of small-vessel vasculitis. This case series examines the clinical characteristics, histopathological features, treatment strategies, and outcomes of patients with Double-positive Glomerulonephritis (GN) in a tertiary centre in India.

Materials and Methods: We retrospectively reviewed 48 patients diagnosed with anti-GBM disease from 2020 to 2024. Among them, 7 were double positive for ANCA and anti-GBM antibodies. Data on demographics, clinical presentation, laboratory findings, renal histopathology, treatment, and outcomes were collected and analysed.

Results: The median age was 33 years (range, 10–63), with a female predominance (n=5, 71.4%). All patients were anti-MPO positive and anti-GBM antibody positive. Renal involvement was universal, with 85.7% presenting with rapidly progressive renal failure. Pulmonary involvement was noted in 3 patients (42.8%), including diffuse alveolar haemorrhage, organizing pneumonia and interstitial lung disease. The median serum creatinine at presentation was 7.3 mg/dL (range, 6.1- 11.0mg/dL). Histologically, 6 patients had crescents in >50% of glomeruli. All patients received methylprednisolone pulses followed by oral prednisolone and cyclophosphamide; 3 underwent plasmapheresis. Despite immunosuppression and plasmapheresis, five patients (71.4%) remained dialysis dependent. Two patients showed partial renal recovery.

Conclusion: Double-positive glomerulonephritis represents a distinct, aggressive clinical phenotype with poor renal outcomes despite intensive immunosuppression. Early and aggressive immunosuppression with steroids, cyclophosphamide, and plasmapheresis may improve short-term outcomes, although many patients remain dialysis dependent.

KEYWORDS: Double-positive Glomerulonephritis, Anti-GBM disease, ANCA-associated vasculitis, rapidly progressive renal failure, Diffuse alveolar haemorrhage.

INTRODUCTION

Anti-GBM disease is characterized by autoantibodies targeting the glomerular basement membrane, leading to rapidly progressive glomerulonephritis and, occasionally, pulmonary haemorrhage. Coexistence with ANCA antibodies (termed "double-positive disease") has been increasingly recognized and poses diagnostic and therapeutic challenges. While ANCA vasculitis tends to respond well to immunosuppression, anti-GBM disease

is often more fulminant. Given the scarcity of Indian data on double-positive GN, this case series aims to characterize clinical features, histology, treatment, and outcomes from a single tertiary care centre.

METHODS

We conducted a retrospective analysis of patients diagnosed with anti-GBM disease between January 2021 and December 2024. Diagnosis was confirmed via serological detection of anti-GBM and ANCA antibodies. Patients with dual positivity were identified. Clinical and demographic data, laboratory values, renal biopsy findings, and treatment details were extracted from medical records. Outcomes were assessed based on dialysis dependence and renal function at last follow-up.

RESULTS

Patient Demographics and Presentation:

Seven patients were identified as double positive among 48 anti-GBM cases (14.58%). The most common presentation was rapidly progressive renal failure (6/7, 85.7%). Pulmonary symptoms were seen in 3 patients: one with diffuse alveolar haemorrhage, one with interstitial lung disease, and another with organising pneumonia. Fever (n=3), fatigue (n=2), and arthralgia (n=2) were common constitutional symptoms. One patient had Mononeuritis multiplex. Other laboratory and Serologic findings are mentioned in Table 1

Renal Histopathology:

All patients underwent biopsy. Five patients had >50% crescent formation. Glomerulosclerosis was variable, with a median of 72%. Fibrinoid necrosis was absent in all specimens. Interstitial fibrosis and tubular atrophy (IFTA) ranged from 15% to 90%. Immunofluorescence showed variable IgG, C3, and light chain staining. (Table 2)

Treatment outcomes:

All patients received methylprednisolone pulses followed by oral steroids and cyclophosphamide. Plasmapheresis was done in 3 patients (42.8%). Maintenance therapy included mycophenolate mofetil (n=1) and azathioprine (n=2); At last follow-up (median follow-up of 4 months), 5 of 7 (71.4%) remained dialysis dependent, and 2 had partial renal recovery. (Table 3)

DISCUSSION

Double-positive ANCA and anti-glomerular basement membrane (anti-GBM) disease is a rare autoimmune condition characterized by the concurrent presence of anti-neutrophil cytoplasmic antibodies (ANCA) and anti-GBM antibodies. This overlap syndrome presents with clinical and pathological features of both ANCA-associated vasculitis (AAV) and anti-GBM disease, complicating both diagnosis and management. The dual antibody positivity suggests a possible shared or sequential pathogenesis and necessitates a nuanced understanding of the disease spectrum.

Clinical Features

Demographic Characteristics

While previous studies suggest that double-positive glomerulonephritis mainly affects older adults, our cohort showed a younger median age of 33 years, ranging from 10 to 63 years, highlighting the bimodal age pattern typical of anti-GBM disease[1]. While Hu et al.[2] and Javed and Vohra[3] reported a higher prevalence of double-positive disease in older individuals, our findings highlight that this condition can also present aggressively in younger populations. The female predominance (71%) aligns with Zhao et al.[4], suggesting possible sex-linked immune factors. These differences may reflect underlying geographic or ethnic variations.

Renal Involvement

Renal involvement is typically the predominant and often most severe clinical manifestation in patients with dual positivity for anti–glomerular basement membrane (anti-GBM) antibodies and antineutrophil cytoplasmic antibodies (ANCAs)[5]. Clinically, our patients uniformly presented with aggressive renal involvement: 100%

had renal manifestations (hematuria, proteinuria, and rapidly progressive glomerulonephritis), and 86% presented with rapidly progressive renal failure requiring dialysis. This severity is consistent with prior reports of double-positive disease [2,6,7].

Extrarenal Manifestations

Pulmonary involvement was less common in our cohort (43% with pulmonary haemorrhage) than in many series. Published data vary: Hu et al. [2]found pulmonary "damage" in 75% of patients, and McAdoo et al.[8] reported pulmonary haemorrhage in roughly 70%. The systematic review by Philip et al[9]. estimated that about 51% of double-positive patients have alveolar haemorrhage. Our lower rate (43%) may be due to the small sample size or referral bias. Nevertheless, almost half had pulmonary-renal syndrome, underscoring the importance of evaluating lung involvement

All our patients had anaemia (median Hb 6.8 g/dL) and severe renal dysfunction (median creatinine 7.3 mg/dL), reflecting advanced disease. In comparison, published cohorts also report very high baseline creatinine; for instance, Philip et al. found a median creatinine of ~873 µmol/L (~9.9 mg/dL) among 538 cases. Overall, our clinical picture – severe, often dialysis-requiring GN with frequent lung haemorrhage – closely mirrors that of other double-positive cohorts. In addition to pulmonary disease, constitutional symptoms such as fever (43%), fatigue (29%), and arthralgia (29%) were frequently observed in our cohort. One patient (14%) had mononeuritis multiplex, reflecting peripheral nervous system involvement. [7]

Diagnostic Considerations

In terms of serology, all our patients had MPO-ANCA (per anti-MPO assay) in addition to anti-GBM antibodies. This predominance of anti-MPO is characteristic of double-positive disease: in the systematic review by Philip et al.,[9] 72% of ANCAs in double-positive cases were MPO-ANCA and only 20% PR3-ANCA. The reasons for MPO dominance (versus PR3) in this setting remain speculative, but they may relate to genetic or environmental factors predisposing to anti-MPO vasculitis. Notably, our cohort's "double positivity" was defined by serology (anti-GBM and ANCA antibodies); in some series, a few patients are classified as double-positive on biopsy grounds even with negative serology, but all our patients were seropositive for both markers.

Renal histology in double-positive disease typically shows features of both processes. In our biopsies, 6 of 7 patients had crescents involving >50% of glomeruli, and the median global glomerulosclerosis was 72%, indicating both active and chronic injury. This extent of crescent formation is in line with published data: Srivastava et al[6]. noted that the "majority of glomeruli" in their double-positive cases showed cellular crescents, and Clerte et al.[7] reported that double-positive patients had significantly more crescentic (vs sclerotic) lesions than severe ANCA cases. The high burden of crescents underscores the aggression of the disease and mirrors pure anti-GBM nephritis, where >70% crescents are typical.

By contrast, immunofluorescence findings can be more variable. In classic anti-GBM disease, one expects bright linear IgG staining of the GBM, whereas ANCA-associated GN is "pauci-immune." In our cases, the staining was heterogeneous: some biopsies showed linear IgG and C3 capillary deposition, while others had only weak or granular staining. This variability has been noted by others – double-positive patients may have either linear deposits or very scant immune complexes. Hu et al.[2] observed that IgA, IgG, and complement deposition tended to be higher in the double-positive group versus AAV, though not as intense as classic anti-GBM. Bowen's capsule rupture, a feature noted frequently in Hu's double-positive group, was also often seen (two of seven) in our biopsies, suggesting severe necrotising inflammation. Overall, the histopathology in our cohort was consistent with a superimposed vasculitic and anti-GBM process: widespread crescents and necrosis, marked chronic scarring, but variable immunofluorescence intensity.

Prognosis

The prognosis of double-positive disease is generally poor, and our findings reflect this grim outlook[10]. Most patients in our series remained dialysis-dependent at follow-up, consistent with the severity of presentation and extensive chronic damage on biopsy. Prior studies report similarly dismal outcomes. Srivastava et al.[6] found all nine patients progressed to ESRD by 1 year, and Clerte et al[7]. reported a 1-year renal survival of only 27%, significantly worse than in ANCA vasculitis. and Balderia et al[11]. documented 100% ESRD in both their double-

positive and anti-GBM cohorts. These findings reinforce that double-positive patients tend to follow a course more akin to anti-GBM disease than AAV.

Therapeutically, all patients in our study received aggressive immunosuppression (glucocorticoids plus cyclophosphamide) along with plasma exchange, per standard protocols for rapidly progressive GN. This mirrors other cohorts: for instance, Hu et al. report that 65% of double-positive patients received plasmapheresis (compared to ~78% of pure anti-GBM and only ~31% of MPO-ANCA cases[12] .Srivastava et al.[6] and McAdoo's[8] Group likewise emphasises combined immunosuppression and plasmapheresis in nearly all double-positive cases. The rationale is to suppress the ANCA-driven inflammation while removing anti-GBM antibodies via exchange. Despite such intensive therapy, renal outcomes often remain unfavourable. Some case reports describe adding rituximab or other agents for refractory disease, but the evidence is anecdotal. The dual nature of double-positive disease complicates management: it requires the aggressive early treatment typical of anti-GBM disease (to prevent further glomerular destruction) and, at the same time, vigilant long-term follow-up for relapsing vasculitis. Indeed, recent expert guidelines advise treating double-positive cases "as" anti-GBM disease for induction, but then considering maintenance regimens as in ANCA vasculitis[7]. In our cohort, the high degree of chronicity on biopsy suggests that even optimal therapy may have limited renal benefit; unfortunately, this was borne out in our outcomes.

Taken together, these data support the concept that double-positive patients exhibit a broader and more systemic disease spectrum than those with isolated anti-GBM or ANCA-associated vasculitis alone, necessitating a high index of suspicion for extrarenal involvement at presentation.

Limitation

The retrospective design and small sample size limit the generalizability of our findings. Additionally, follow-up duration was variable, and long-term relapse rates could not be assessed accurately."

CONCLUSION

Double-positive glomerulonephritis represents a severe, hybrid autoimmune phenotype with features of both ANCA-associated vasculitis and anti-GBM disease. In our cohort, patients were predominantly young and female, with nearly universal severe renal involvement and frequent pulmonary manifestations. Despite aggressive immunosuppression and plasmapheresis, renal outcomes were poor, with most patients remaining dialysis dependent. These findings underscore the need for early recognition, prompt combined immunosuppressive therapy, and further studies to optimise long-term management and improve outcomes in this rare but aggressive disease.

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Table 1: Demographic and Clinical Features of Double-Positive GN Patients

Characteristic	**Value (N = 7)**
Age, median (range), years	33 (10–63)
Female sex — no. (%)	5 (71)
Hypertension — no. (%)	5 (71)
Diabetes mellitus — no. (%)	1 (14)
Pulmonary involvement — no. (%)	3 (43)
Haemoptysis — no. (%)	2 (29)
Haematuria – no (%)	6 (85.7)
Renal involvement - no. (%)	7 (100)
Laboratory parameters	
Haemoglobin g/dL – median (IQR-25%-75%)	6.8 (6-10.6)
Serum creatinine at presentation, mg/dL - median (IQR-25%-75%)	7.3 (6.1- 11.0)
Proteinuria at presentation (Median)	2.55g
Anti-MPO positive — no. (%)	7 (100)
Anti-GBM titre, median (range)	108 units (27.2–200)
Anti MPO titre, median (range)	62 RU/ml (22-193)

Table 2 Renal Histopathological Findings

Patient	Light Microscopy			Immunofluorescence Microscopy			
	Glomerulosclerosis (%)	Cellular/Fibrocellular Crescents (%)	IFTA (%)	IgG	C3	Kappa	Lambda
1	75	90	60	2+	0	2+	2+
2	76	67	80	3+	0	4+	4+
3	45	100	90	3+	1+	4+	4+
4	72	20	15	4+	4+	4+	4+
5	23	40	80	4+	0	4+	4+
6	33	50	20	2+	2+	1+	1+
7	72	50	90	4+	2+	4+	3+

IFTA: Interstitial fibrosis and tubular atrophy; IgG: Immunoglobin G; C3: Complement component 3

Table 2 Treatment and Renal Outcomes

Pt	ANCA titres (RU/ml)	Anti-GBM titres (U)	Treatment	PLEX	FU (mo)	Cr (last)	GFR	Outcome
1	22	65.34	Steroids + CYC → MMF	10	4.0	4.76	12.6	Dialysis dependent
2	59	174	Steroids + CYC	6	3.5	11.37	3.39	Dialysis dependent
3	97	63.5	Steroids + CYC	0	4.0	10.7	4.77	Dialysis dependent
4	193	200	Steroids + CYC	8	3.0	6.0	3.3	Dialysis dependent
5	156	108	Steroids + CYC	0	3.0	7.0	7.59	Dialysis dependent
6	22.6	27.19	Steroids + CYC → AZA	0	60.0	2.39	26.24	CKD
7	62	94.2	Steroids + CYC → AZA	0	4.0	3.85	14.54	CKD

CYC: Cyclophosphamide; MMF: Mycophenolate mofetil; AZA: Azathioprine; PLEX: Plasmapheresis; FU: Follow-up in months; Cr: Creatinine (mg/dL); GFR: Glomerular Filtration Rate (mL/min/1.73m²)-CKD EPI GFR