Case Series

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Pathology Section

Combined Anti-glomerular Basement Membrane and Anti-Nuclear Cytoplasmic Antibody (ANCA) associated Crescentic Glomerulonephritis: A Series of 6 Cases

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ABSTRACT

Anti-GBM and ANCA-mediated glomerulonephritis are common causes of crescentic glomerulonephritis. Dual or double-positive glomerulonephritis is rare, with few cases reported in the literature and a worse prognosis. This case series of six patients describes the clinico-pathological features of anti-glomerular basement membrane glomerulonephritis (anti-GBM GN) with concomitant ANCA vasculitis and assesses the specific histopathological injury pattern in this combined presentation. The patients had a mean age of 42 years, with a female predominance. Almost all presented with haematuria and features of RPGN. One patient presented with pulmonary-renal syndrome, and another with systemic vasculitis. Approximately 66% of cases showed mixed lesions, and other features such as small vessel necrotising vasculitis were noted. All cases showed moderate to intense (2-4+) linear IgG staining, along with serum positivity for P-ANCA (MPO) or C-ANCA (PR3). These features aided in categorising concomitant anti-GBM and ANCA cases. In conclusion, anti-GBM antibodies and ANCAs (double-positive patients) rarely co-exist and are associated with poor renal survival. Intense linear glomerular staining suggests concurrent anti-GBM, as these patients may have small vessel vasculitis, which is not a feature of anti-GBM alone. This mandates ANCA antibody testing in all cases of rapidly progressive renal failure, even if clinically and pathologically consistent with anti-GBM GN, enabling prompt and aggressive immunosuppressive management.

Keywords: Anti-GBM, ANCA, Crescentic

INTRODUCTION

Crescentic glomerulonephritis is a common cause of Rapidly Progressive Glomerulonephritis (RPGN), morphologically defined by crescents in >50% of glomeruli. Three categories exist: anti-GBM glomerulonephritis (I), pauci-immune crescentic glomerulonephritis (II), and immune complex CGN (III) [1].

Anti-GBM disease is characterised by serum autoantibodies against the α3 chain of type IV collagen. It has an incidence of 1 in 1,000,000 and a bimodal age distribution (30 and 60 years) [1,2]. Goodpasture syndrome, isolated pulmonary haemorrhage, and isolated anti-GBM GN represent varied expressions of this disease [1,3]. Pulmonary involvement, with haemoptysis, dyspnoea, rales, and rhonchi, occurs with variable frequency [2].

Pauci-immune glomerulonephritis may present as isolated renal disease or part of systemic vasculitis (*microscopic polyangiitis* and *granulomatosis* with *polyangiitis*), defined by elevated serum ANCA levels [1]. Anti-GBM GN and ANCA GN are associated with higher frequency and more destructive crescent formation; severity is attributed to the proximity and exposure of subendothelial immune complexes to immune mediators in the circulatory system [1]. These are distinguished from immune complex GN by uninvolved glomerular capillaries exhibiting normal thickness and minimal or absent hypercellularity [1].

The pathognomonic feature of anti-GBM GN is diffuse, glomerulocentric crescentic glomerulonephritis. Crescents are poorly demarcated due to frequent capsular rupture [1,3] and are often at a similar stage of pathological injury. Linear immunoglobulin staining on immunofluorescence microscopy confirms the diagnosis.

ANCA crescentic GN shows glomerular crescents, with a mixture of active necrotising (cellular crescent) and chronic sclerosing lesions (fibrous and fibrocellular crescents), along with necrotising small vessel vasculitis (arteritis and arteriolitis) of extraglomerular renal vessels [1]. Immunofluorescence shows little or no antibody expression [1,3].

Anti-GBM GN has an aggressive course with poor renal and patient survival, rarely relapsing or remitting, with antibodies becoming undetectable after therapy. It requires rapid institution of immunosuppressive therapy, including high-dose corticosteroids, cytotoxic drugs, and plasma exchange [1,4,5]. ANCA GN (pauci-immune GN), conversely, often relapses and remits, warranting phased aggressive immunosuppression (remission induction, maintenance, and relapse treatment). Double positivity for both anti-GBM and ANCA is rare, lifethreatening, and its histopathological significance is poorly understood, with limited reporting in short case series [6]. It is reported more frequently in the elderly [6]. Histologically, mixed lesions (active and chronic) with varying degrees of injury and concomitant linear immunoglobulin staining on immunofluorescence microscopy are observed [1,6,7]. Periglomerular granulomatous inflammation is common [1,6,8]. Extraglomerular vasculitis in otherwise typical anti-GBM GN should raise suspicion of co-existing ANCA disease [4,6].

Renal survival in patients with concurrent disease (anti-GBM with ANCA GN) is comparable to, or worse than, isolated anti-GBM GN [1,7-9]. This highlights that mixed lesions (active and chronic) and extraglomerular vessel involvement with necrotising vasculitis mandate serum ANCA testing to exclude concurrent disease. This facilitates life-long maintenance immunosuppressive therapy with corticosteroids to improve renal and patient survival.

Six cases of anti-GBM GN with concomitant ANCA GN diagnosed between January 2018 and December 2022 were retrieved from the archives. Patients were identified using the Department of General Pathology's electronic database; relevant clinical details and follow-up were gathered from hospital records. Slides were reviewed by four pathologists.

CASE SERIES

Six cases of concomitant anti-GBM and ANCA GN were recorded among all crescentic GN cases (January 2018-December 2022). All were clinically diagnosed with RPGN, and renal biopsies were sent for histopathological evaluation.

Demography: The mean age at presentation was 42 years (range 14-67 years), with a female predominance (M:F=1:5).

Clinical presentation [Table/Fig-1]: All six cases presented with acute kidney injury, haematuria, and oliguria, with an average duration of 15 days to one month [Table/Fig-1]. Extrarenal manifestations were noted in two cases: Case 3 presented with pulmonary-renal syndrome and severe haemoptysis (but no evidence of diffuse alveolar haemorrhage or vasculitis), while Case 6 had systemic vasculitis with a skin biopsy suggestive of leukocytoclastic vasculitis [Table/Fig-1].

Serological investigations: At diagnosis, all patients had elevated serum creatinine levels (5.4-9.35 mg/dL). Five patients had significantly elevated serum MPO titres, and three had concomitant elevated anti-GBM levels [Table/Fig-1].

Histopathology [Table/Fig-2]: Detailed descriptions of the histopathological findings for each case (Cases 1-6) would follow here, including images ([Table/Fig-2-8] as referenced in the original text).

Case 1

Diagnosis: Focal necrotising and diffuse sclerosing glomerulonephritis. A 67-year-old female with significantly elevated anti-MPO titres displayed predominantly global scarring in 10 of 17 glomeruli [Table/Fig-3a]. Active lesions with tuft necrosis and cellular crescents were observed. Immunofluorescence showed 2-3+ linear capillary wall staining for IgG [Table/Fig-3b].

Case 2

Diagnosis: Diffuse necrotising and crescentic glomerulonephritis with fibrinoid necrotising vasculitis. A 56-year-old male had elevated anti-GBM (92.56) and anti-MPO (46 Ru/ml), predominantly active lesions with tuft necrosis in all 11 glomeruli [Table/Fig-4a], two of which also showed cellular crescents [Table/Fig-4b]. IgG (2-3+) with linear capillary wall staining was observed.

Case 3

Diagnosis: Focally active necrotising, crescentic, and focal sclerosing glomerulonephritis. A 47-year-old female with anti-MPO (113 Ru/ml) showed mixed (chronic and active; [Table/Fig-5a] lesions. Of 25 glomeruli, active lesions such as glomerular tuft necrosis were seen in 16, with crescentic GN (cellular crescents (2), and fibrocellular crescents (2)). Chronic lesions included fibrous crescents and glomerular scarring. Strong (3+) linear capillary wall staining for IgG was observed [Table/Fig-5b].

Case 4

Diagnosis: Diffuse sclerosing and focally active necrotising crescentic glomerulonephritis. A 30-year-old female with elevated anti-GBM (50.70) and anti-MPO (129) showed mixed (chronic and active) lesions [Table/Fig-6a], predominantly fibrous crescents (9) and one glomerulus with tuft necrosis. Linear capillary wall staining for IgG (3+) was observed in immunofluorescence [Table/Fig-6b].

Case 5

Diagnosis: Chronic diffuse sclerosing glomerulonephritis with diffuse global glomerulosclerosis. A 39-year-old female with elevated anti-PR3 (154 Ru/ml) displayed only chronic lesions with global and segmental scarring of glomeruli [Table/Fig-7a]. Immunofluorescence showed strong (4+) linear capillary wall staining for IgG [Table/Fig-7b].

Case 6

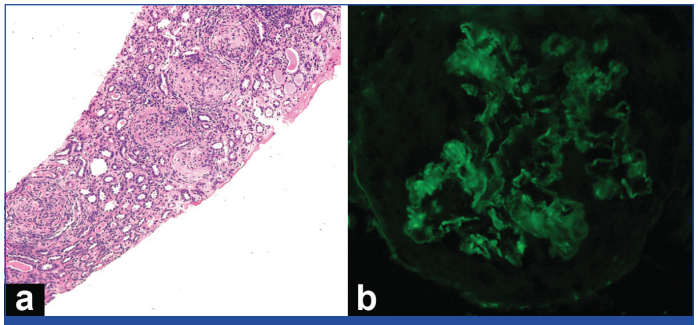
Diagnosis: Pauci-immune focal sclerosing and active glomerulonephritis. A 14-year-old female with elevated anti-MPO (22.8) and anti-GBM (65.34) showed mixed lesions (active and chronic) with glomerular scarring and one cellular crescent

Case no	Age/ Sex	Renal involvement			Serum creatinine (mg/dL) Normal M: 0.7-1.4 F: 0.5-1.1	UP/UC ratio Adults and children >2 years (<0.21)	Anti PR^3 (Ru/mL)	Anti MPO (Ru/mL)	Anti GBM (Units)	Pulmonary involvement		Multisystemic disease
		Haematuria (>/=5/hpf)	Oliguria	Proteinuria**						Haemoptysis	Diffuse Alveolar Haemorrhage (DAH)	
1	67/F	+	_	++	5.45	1.26	3	172	NA	_	_	_
2	56/M	+	+	+	6.09	NA	5.5	46	92.56	_	_	-
3	47/F	+	_	+	6.41	3.72	<2	113	1.11	+ *	_	_
4	30/F	+	+	+++	9.35	43.7	20	129	50.70	_	_	_
5	39/F	+	_	+	5.86	2.37	154	<2	NA	_	_	_
6***	14/F	+	_	+	0.57	5.99	2	22.8	65.34	_	_	+ Skin involvement

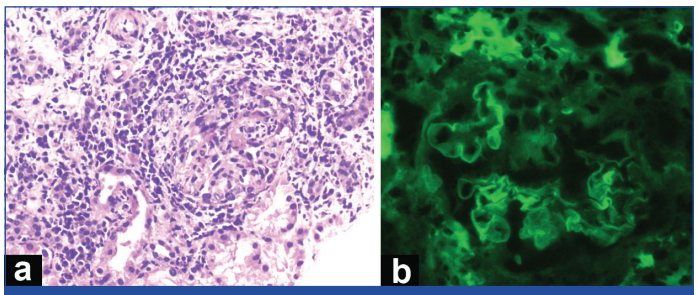
[Table/Fig-1]: The clinical features and biochemical parameters.
UP/UC: Urine protein to urine creatinine ratio; *Patient 3 presented with Haemoptysis on and off but no documented DAH was seen; **Proteinuria based on dipstick Urinalysis (mg/dL): Negative; Trace (15), + (30), ++ (100), +++ (400); ***Patient six had co-existing leukocytoclastic vasculitis involving skin

Case no	Total glomeruli	Glomerular scarring n (%)		Glomeruli with crescents n (%)			Isolated Glomerular tuft necrosis	Number of periglomerular granulomatous inflammation	IFTA (%)	Vessels arteriosclerosis	Linear IgG staining (0 to 4+)
		Global	Segmental	Cellular	Fibro-cellular	Fibrous					
1	17	10 (58)	0	2 (11)	0	0	2 (focal)	4	80-90	Moderate	2-3+
2	11	0	0	2 (18)	0	0	11 (Diffuse)	2	40	Moderate*	2-3+
3	25	9 (36)	1 (4)	2 (8)	2 (8)	2 (8)	16 (focal)	0	20-30	Moderate	3+
4	13	1 (7)	0	2 (15.38)	1 (7.69)	9 (69.23)	1 (focal)	0	15	Unremarkable	3+
5	10	9 (90)	1 (10)	0	0	0	0	0	30	Mild	4+
6	10	2(20)	4(40)	1(10)	0	0	0	0	5	Unremarkable	2+

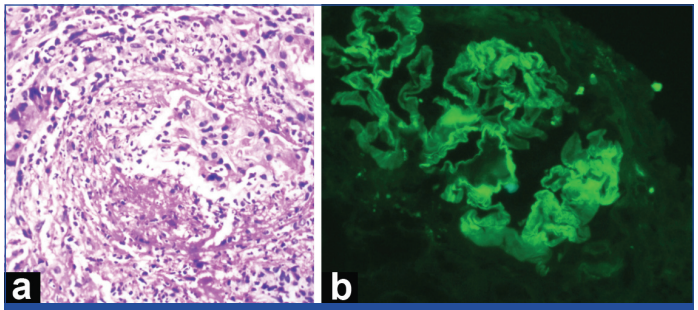
[Table/Fig-2]: Renal biopsy findings and IgG Immunofluorescence pattern.
*Patient 2 with concomitant necrotising small vessel vasculitis on immunofluorescence; **Immunofluorescence pattern- linear capillary loop staining unless indicated



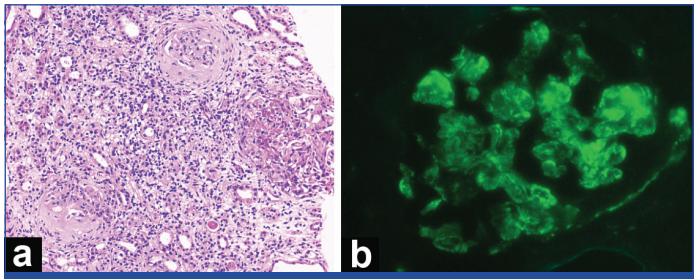
[Table/Fig-3]: a) Sclerosing lesion with circumferential fibro-cellular crescent (H&E stain, 4x); b) Immunofluorescence- Strong linear capillary wall staining for IgG (3+) (4x).



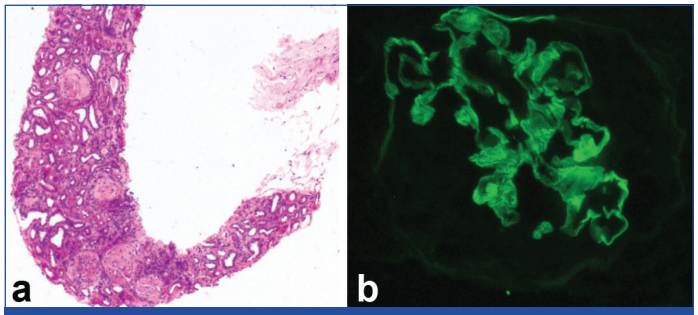
[Table/Fig-4]: a) Active fibrinoid necrosis with near total destruction of capillary tuft, inflammatory mononuclear and neutrophilic infiltration, rupture of Bowman's capsule and circumferential cellular crescent formation (H&E stain 4x); b) Immunofluorescence: Linear capillary wall staining for IgG (2-3+) (10x).



[Table/Fig-5]: a) Glomeruli displaying extensive tuft necrosis (H&E stain, 10x); b) Glomeruli displaying extensive tuft necrosis (10x).



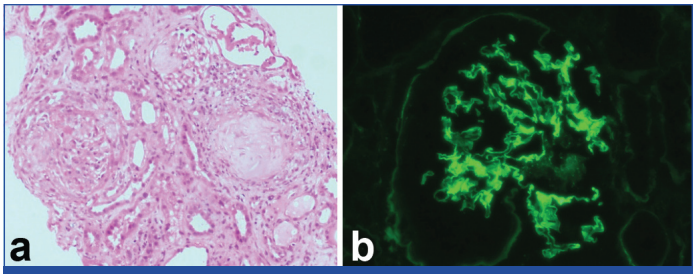
[Table/Fig-6]: a) Three glomeruli. One Glomerulus displaying Focal segmental fibrinoid necrosis. The other two glomeruli displaying Segmental tuft scarring and fibro-cellular crescent (H&E stain 4x); b) Immunofluorescence: capillary wall staining for IgG (3+), (4x).



[Table/Fig-7]: a) Tissue section displaying globally scarred Glomeruli (H&E stain 4x); b) Immunofluorescence: Strong linear capillary wall staining for IgG (4+) (4x).

[Table/Fig-8a]. Immunofluorescence showed strong linear capillary wall staining for IgG (3-4+) [Table/Fig-8b].

Four of six cases were predominantly sclerosing (Cases 1 and 5) and in a minimally active phase, with focal/diffuse glomerulosclerosis



[Table/Fig-8]: a) Tissue section with 3 glomeruli each at different stages of lesion; one with focal scarring, another with fibrous crescent and a fibrocellular crescent (H&E stain, 4x); b) Immunofluorescence: Strong linear capillary wall staining for IgG (3-4+).

(36-90%)/fibrous crescents (8% and 69%) or diffuse tubulointerstitial scarring (30-90%). One patient had mixed active and sclerosing changes, and one had predominantly active changes. Active changes comprised glomerular tuft fibrinoid necrosis or cellular/fibrocellular crescents (Cases 2 and 3). All cases exhibited linear staining for IgG (2+ to 4+). Antibody staining in immunofluorescence microscopy was graded from 0-4+ intensity.

Treatment and follow-up [Table/Fig-9]: All patients received corticosteroids and cyclophosphamide. Only one patient (predominantly active lesions) received additional plasma exchange therapy. Renal function (serum creatinine) did not improve in five of six patients, one becoming dialysis-dependent. One patient (patient 6) maintained normal glomerular filtration and fully recovered, possibly due to less severe glomerular and tubulointerstitial injury.

DISCUSSION

Anti-GBM GN is caused by circulating anti-GBM antibodies targeting the alpha-3 chain of type IV collagen, present in glomeruli and alveoli. Patients have a bimodal age distribution, present with RPGN, and show characteristically similar degrees of injury on histology [1,3,9]. Injury patterns may be active/necrotising or diffuse sclerotic.

ANCA-mediated glomerulonephritis usually has a waxing and waning course. According to the ANCA classification [1], injury patterns are active, mixed (active + chronic), or chronic/sclerosing, with mixed lesions being predominant [10].

The double/Dual-Positive Phenotype (DPP) is unclear regarding which component initiates the disease {anti-GBM or ANCA). Hypotheses include: (I) aberrant Myeloperoxidase (MPO) expression (a component of Neutrophil Extracellular Traps (NETs)} causing anti-MPO antibody expression. This explains why anti-GBM may cause AAV when neutrophils are recruited, and why anti-MPO (PR3) (around 73.5%) is the most common cooccurrence in DPP cases [10]; (II) chronic, long-standing AAV damaging the GBM, resulting in anti-GBM antibodies.

It has been reported that >60%, and some report 32%, of anti-GBM cases have concomitant ANCA [6,11]. The first large South Asian series on crescentic GN showed 32.3% DPP cases associated with type I GN [9].

This short case series, along with other short series or case reports, emphasises the importance of pathological diagnosis and clinical implications of DPP (anti-GBM+ANCA) associated crescentic glomerulonephritis.

This series showed a bimodal age distribution (14-67 years), with a mean age of 42 years and female predominance, similar to literature reports [12,13]. At biopsy, all presented with RPGN, with a mean serum creatinine of 5.62 mg/dL and a UP/UC ratio of 11.48 [4,6,9]. Compared to other literature, one case showed reno-pulmonary involvement [13], while others showed leukocytoclastic vasculitis of the skin [10,13], indicating extrarenal manifestations are more common in DPP. Serum anti-MPO was the most commonly associated ANCA antibody [6,11,14].

Renal biopsy findings showed a characteristic mixed picture of variable active (cellular and fibrocellular crescents) and chronic

Case no.	Renal biopsy diagnosis	Therapy				F/up months	F/up Sr. Creatinine (mg/dL) Normal M: 0.7-1.4 F: 0.5-1.1	F/up UP/UC ratio Adults and children >2 years (<0.21)
		Corticosteroids	Immunosuppressant's	TPE	MHD			
1	Focal necrotising and diffuse sclerosing glomerulonephritis	T. Wysolone	T. Endoxan T. Azathioprine	_	_*	19	8.67	0.89
2	Diffuse necrotising and crescentic glomerulonephritis with fibrinoid necrotising vasculitis	T. Wysolone	T. Endoxan	_	_*	1	4.44	NA
3	Focally active necrotising, crescentic and focal sclerosing glomerulonephritis	T. Wysolone	T. Endoxan	_	_*	1	8.06	NA
4	Diffuse sclerosing and focally active necrotising crescentic glomerulonephritis	T. Wysolone	T. Endoxan	_	+	1	8.92	NA
5	Chronic diffuse sclerosing glomerulonephritis with diffuse global glomerulosclerosis	T. Wysolone	T. Endoxan	_	+***	18	9.10	NA
6	Pauci-immune focal sclerosing and active glomerulonephritis	T Wysolone	T Mycophenolate Mofetil T Endoxan	+	-	7	0.56	1.00

[Table/Fig-9]: Biopsy diagnosis, therapy and follow-up details.
#TPE: Therapeutic plasma exchange; MHD: Maintenance haemodialysis; UP/UC: Urine Protein to urine Creatinine ratio; *Patients 1-3 were given corticosteroids and Immunosuppressant for period of three months and started on Low dose corticosteroid and were given the option of MHD; Patient 1 was not willful for MHD and discontinued treatment at our hospital; Patient 2,3,4 lost follow-up the following month after diagnosis; ***Patient 5 was considered for renal allograft

lesions (fibrous and sclerosing lesions). Almost all cases had significant chronic lesions [6,8,9]. All cases showed strong global linear capillary loop staining for IgG on immunofluorescence.

Our results show that DPP patients predominantly have mixed chronic and active lesions, aiding diagnosis. Therefore, in patients presenting with RPGN and crescentic GN suggestive of anti-GBM or ANCA, serum anti-GBM and serum MPO/PR3 titres should be evaluated, rather than making a single diagnosis (anti-GBM or ANCA glomerulonephritis).

All cases required dialysis at presentation and corticosteroids and immunosuppressants (azathioprine, cyclophosphamide, and mycophenolate mofetil). Patients with follow-up data showed persistent increases in serum creatinine, suggesting poor renal survival, as documented in other series [6,9,12]. One patient received therapeutic plasma exchange, improving renal function (normalised serum creatinine 0.56 mg/dL).

CONCLUSION(S)

DPP presents with RPGN and has a poor renal and overall survival prognosis. These lesions show destructive lesions (as in GBM disease) and frequent relapses (as in AAV). Timely diagnosis of DPP enables prompt immunosuppression and maintenance therapy to preserve renal function and improve patient survival. Furthermore, identifying these rare diseases mandates close long-term follow-up to exclude recurrence.

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