Case Report

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IgA Nephropathy with ANCA Vasculitis: A Case with Diagnostic and Therapeutic Challenges

Internal Medicine Section

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ABSTRACT

The co-existence of IgA nephropathy (IgAN) and Anti-Neutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis (AAV) is rare but presents a distinct diagnostic and therapeutic challenge. IgAN is the common glomerulonephritis characterised by mesangial IgA deposition, while AAV typically involves small-vessel vasculitis associated with Myeloperoxidase (MPO)-ANCA or PR3-ANCA positivity. Although these are classically considered separate entities, emerging evidence suggests that ANCA positivity can be seen in a subset of IgAN patients, often associated with more aggressive renal involvement and a broader systemic inflammatory response. We describe three cases of biopsy-proven IgA nephropathy with AAV. All patients had histological features consistent with both mesangial IgA deposition and crescentic glomerulonephritis, along with elevated ANCA titers. Presentations varied from constitutional symptoms to a severe pulmonary-renal syndrome. All patients received immunosuppressive therapy including corticosteroids and cyclophosphamide, followed by maintenance with mycophenolate mofetil. Two patients showed improvement in renal function, while one progressed to end-stage kidney disease requiring dialysis. This case series underscores the importance of considering ANCA testing in IgA nephropathy with atypical or rapidly progressive features and supports a combined immunosuppressive treatment approach in such overlapping pathologies.

Keywords: Crescentic glomerulonephritis, Glomerular diseases, Haematuria, Proteinuria

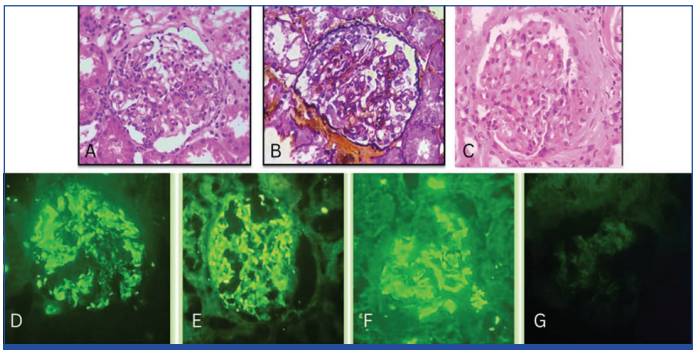
INTRODUCTION

The AAV involves small vessels and is associated with autoantibodies against the neutrophil proteins leukocyte proteinase 3 (PR3-ANCA) or myeloperoxidase (MPO-ANCA). It encompasses granulomatosis with polyangiitis, microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis, marked by necrotising inflammation of small vessels and the presence of ANCAs [1]. Immunoglobulin A nephropathy (IgAN) is characterised by the deposition of immunoglobulin A (IgA) in the glomerular mesangium. It presents with varying degrees of haematuria, proteinuria, and progressive renal dysfunction [2]. IgAN and AAV are distinct renal pathologies, but their coexistence, though rare, presents a complex clinical scenario, and their significance is not properly defined [3,4].

CASE SERIES

Case 1

A 47-year-old male with an eight-year history of hypertension on amlodipine 5 mg once daily presented with generalised weakness, loss of weight of around 4 kg over a month, and low-grade fever for one month. On presentation, BP was 160/90 mmHg. Investigations revealed serum creatinine of 1.8 mg/dL and haemoglobin 10.1 g/dL. Urine analysis showed 2+ proteinuria, Urine Protein Creatinine Ratio (UPCR) was 1.5 g/g, and haematuria (264 RBC/hpf). ESR was 46 mm/hr and CRP was 22 mg/dL. C3 was 100 mg/dL and C4 was 25 mg/dL, both were within normal limits. The patient's serum creatinine one month back was 1.1 mg/dL. In view of the above presenting features, ANCA titres were sent on admission and showed MPO-ANCA of 142 RU/mL, while PR3-ANCA was negative. Renal biopsy was done which revealed mesangial matrix expansion with some showing mesangial hypercellularity, 2 out of 15 glomeruli showed cellular crescents. There was 10% interstitial fibrosis and tubular atrophy. Blood vessels showed endothelial cell prominence, hyalinosis, and medial wall hypertrophy. Immunofluorescence showed mesangial positivity for IgA; other conjugates were negative [Table/Fig-1].



[Table/Fig-1]: Renal biopsy Case 1: a) Haematoxyline and Eosin (H&E) stained sections showing glomerulus with mesangial hypercellularity and segmental endocapillary hypercellularity x400; b,c) H&E and silver stain highlighting a crescent x400; d-f) Immunofluorescence (IF) showed mesangial positivity for IgA, kappa and Lambda x100; g) IF for IgG was negative x100.

The final diagnosis was IgA nephropathy with AAV. Pulse methylprednisolone 500 mg for three days followed by oral steroids 60 mg once daily. Intravenous cyclophosphamide 1g was given every two weeks for three doses, followed by every three weeks for the next three doses. On follow-up after one month, renal function improved, creatinine was 1.3 mg/dL, and haematuria and proteinuria resolved. ANCA titres were negative after three months. Patient was started on maintenance therapy with mycophenolate mofetil 1g twice daily. Patient continued to be on follow-up, oral steroids were reduced to 5 mg once daily, and after six months, his creatinine was 0.9 mg/dL and urine routine did not show any active urinary sediments, maintenance immunosuppression was continued.

Case 2

A 44-year-old female with no known co-morbidities presented with history of low-grade fever for 10 days. On examination, she was afebrile, with a pulse rate of 98/min and a BP of 150/90 mmHg. She was found to have increased serum creatinine (1.4 mg/dL), haemoglobin 11.6 g/dL, proteinuria (UPCR 0.4 g/g) and microscopic haematuria. MPO-ANCA was >200 RU/mL. Complement C3 and C4 were within normal limits (C3-98 mg/dL, C4-22 mg/dL), ESR was

42 mm/hr and CRP was 20 mg/dL. ANA was negative. Renal biopsy showed 31 glomeruli with four showing cellular crescents, many glomeruli showed mild mesangial hypercellularity. A 10% interstitial fibrosis and tubular atrophy. Blood vessels showed presence of medial wall hypertrophy with endothelial cell prominence, along with few foci of perivascular inflammatory cells. Immunofluorescence showed mesangial positivity for IgA, other conjugates were negative. The final diagnosis was IgA nephropathy with AAV. She was treated with intravenous pulse steroids 500 mg for three days followed by oral steroid 60 mg once daily and tapered gradually. Following this, i.v. cyclophosphamide 1g was given every two weeks for three doses followed by every three weeks for next three doses. Induction was followed by maintenance immunosuppression with tablet mycophenolate mofetil 1g twice daily. On follow up after three months, there was improvement in renal function, creatinine was 1.0 mg/dL, urine analysis showed UPCR of 0.07 g/g and 60 RBC/hpf. Following, which patient was on low dose oral steroid (5 mg). On follow-up after three years, patient presented with fever and dyspnoea for one week; CT chest did not show any features suggestive of diffuse alveolar haemorrhage. Throat swab was positive for influenza A, and she was treated with oseltamavir. Investigations showed serum creatinine of 1.3 mg/dL, MPO-ANCA was >200 RU/mL, urine analysis showed 1+ proteinuria, 155 RBC/hpf, UPCR was 0.67 g/g. Steroid dose was increased to 60 mg once daily and restarted on mycophenolate mofetil 1g twice daily.

Case 3

A 54-year-old male patient presented to the emergency department with dyspnoea of MMRC grade III and haemoptysis in the form of blood tinged sputum for two days. Investigations revealed creatinine of 21 mg/dL, haemoglobin was 6.6 g/dL, total counts were 7740 cells/ microliter, platelets were 3.24 x 10^5 /microliter. C3 and C4 were within normal range (C3-105 mg/dL, C4-29 mg/dL). ESR was 32 mm/hr and CRP was 26 mg/dL. Urine routine showed urine protein 2+ (UPCR 1.2 g/g), RBC-150/hpf. PR3-ANCA was 70.90 RU/mL and MPO-ANCA was 6.14 RU/mL. CT chest was done which showed features suggestive of diffuse alveolar haemorrhage. Renal biopsy was done revealed 13 glomeruli out of which four showed fibrous crescents, mesangial matrix expansion and hypercellularity. There was 60% interstitial fibrosis and tubular atrophy. Blood vessels showed endothelial cell prominence, concentric intimal reduplication, mucoid degeneration, and medial wall hypertrophy. Immunofluorescence showed granular mesangial positivity for IgA other conjugates were negative. Thus, overall features were suggestive of combined IgA nephropathy and AAV. He was started on pulse methylprednisolone 500 mg for three days followed by oral steroids 60 mg once daily and intravenous cyclophosphamide 1g. Diffuse alveolar haemorrhage resolved as patient did not require oxygen supplementation and chest X-ray demonstrated clearing of infiltrates but there was no improvement in renal function. One week after first dose of cyclophosphamide, he presented with fever (102° F), was diagnosed with UTI and was started on piperacillin-tazobactam in renal modified dose 2.25 g thrice daily for seven days. Hence, further treatment with cyclophosphamide was deferred. Currently, the patient is on maintenance haemodialysis and is planned for a renal transplant.

Clinical, laboratory, and renal biopsy findings of the three cases are summarised in [Table/Fig-2].

Feature	Case 1	Case 2	Case 3
Age/sex	47-year-old male	44-year-old female	54-year-old male
Height/weight	168 cm/72 kg	164 cm/75 kg	176 cm/80 kg
Comorbidities	Hypertension (8 years)	None	None
Presenting symptoms	Generalised weakness, weight loss, fever (1 month)	Low-grade fever (10 days)	Dyspnea, haemoptysis
Initial creatinine	1.8 mg/dL (was 1.1 mg/dL one month ago)	1.4 mg/dL	21 mg/dL
ANCA	MPO-ANCA: 142 RU/mL	MPO-ANCA: >200 RU/mL	PR3-ANCA: 70.90 RU/mL
Renal biopsy	15 glomeruli: mesangial matrix expansion, 2 crescents.	31 glomeruli: 4 crescents, mild mesangial hypercellularity	13 glomeruli: 4 fibrous crescents, mesangial hypercellularity
IF findings	Mesangial IgA positivity	Mesangial IgA positivity	Granular mesangial IgA positivity
IFTA	10%	10%	60%
Treatment	Methylprednisolone pulse + oral steroids IV cyclophosphamide → Mycophenolate mofetil	Methylprednisolone pulse + oral steroids + IV cyclophosphamide → Mycophenolate mofetil	Methylprednisolone + oral steroids + IV cyclophosphamide → Mycophenolate mofetil

[Table/Fig-2]: Comparative summary of clinical and renal biopsy findings of the three cases.

DISCUSSION

The prevalence of ANCA positive IgAN is about 0.2-2% according to literature [3-5]. In this case series, the first two patients had MPO-ANCA positive AAV overlapping with IgAN while the third patient presented with PR3-AAV and IgAN. All had features of crescentic glomerulonephritis with mesangial hypercellularity on biopsy. While the latter case presented with severe renal failure as well as Diffuse Alveolar Haemorrhage (DAH), the other two patients presented with milder degree of renal injury with no extrarenal organ manifestations. All had constitutional symptoms. In this case series, all three patients received pulse methylprednisolone followed by cyclophosphamide. While the patients with MPO-ANCA positivity responded well and went into remission, the patient with PR3-ANCA positivity had persistent renal dysfunction and continued haemodialysis. One patient had a relapse following a viral infection, which required reinitiation of immunosuppression.

In the retrospective study by Yang YZ et al., out of 1,729 IgAN patients tested for ANCA, 20 were ANCA-positive. These were compared with 40 ANCA-negative IgAN patients, matched for the proportion of crescents, and 40 patients with AAV with renal involvement. Within the ANCA-positive IgAN group, nine patients had crescentic IgAN (>50% crescents) and were specifically analysed against 22 patients with crescentic ANCA-negative IgAN and 40 patients with crescentic AAV. This study highlighted that although ANCA-positive IgAN patients had more severe presentations and more fibrinoid necrosis on biopsy, they showed a better short-term renal response to aggressive immunosuppressive therapy compared to ANCA-negative crescentic IgAN [5]. The management of ANCA-positive IgAN is based on guidelines for AAV; no specific guidelines exist for managing such cases. Studies have shown that compared with ANCA-negative IgAN patients, ANCA-positive IgAN patients showed a more severe clinical picture, but a better response to aggressive immunosuppressive therapy and better renal outcomes in the short-term [5,6].

In the study by Agraz I et al., (2022), 17 adults with biopsy-proven crescentic IgAN were retrospectively analysed, of whom five patients (29.4%) were ANCA-positive. Compared with ANCA-

negative patients, the ANCA-positive group had a higher proportion of crescents (>25% in all cases) and a greater frequency of fibrinoid necrosis (80% vs 20%). All patients received intensive immunosuppressive therapy following AAV protocols, including high-dose corticosteroids combined with cyclophosphamide. At 6-12 months follow-up both groups showed improvement in renal function, with mean creatinine declining to 1.57 mg/dL at one year. Although four patients (23.5%) required renal replacement therapy and four patients died during follow-up; the authors concluded that the presence of ANCA did not independently worsen renal prognosis when patients received timely and aggressive treatment [7].

In the case series by Bantis C et al., (2010), eight patients with crescentic IgAN and ANCA positivity (MPO n=5, PR3 n=3) were described. All were treated with a combination of high-dose corticosteroids and cyclophosphamide according to AAV treatment protocols. Renal function improved in every patient, with mean serum creatinine decreasing from approximately 4.2 mg/dL at presentation to 1.7 mg/dL during follow-up. Notably, their response to therapy was significantly better than that observed in ANCA-negative crescentic IgAN patients in the same cohort, highlighting the potential for reversibility when intensive immunosuppression is initiated promptly [8].

The pathophysiology of ANCA-positive IgAN involves a complex interplay between the immune mechanisms underlying IgAN and AAV. Exact pathophysiology is not known, some authors suggested that presence of IgA deposits may be initial stage of typical ANCA vasculitis and these immune complexes are suspected to initiate an inflammatory reaction augmented with ANCA and later cleared by enzymes [6]. On follow biopsies at six months by Bantis C et al., found that IgA deposits were still present [8]. ANCA positive IgAN may be a coincidence of two condition or one condition acting as a trigger for another. Further studies are necessary for further understanding of underlying pathophysiology and developing targeted therapies.

CONCLUSION(S)

ANCA-positive IgAN, though rare, is a significant clinical entity. The presence of crescents on renal biopsy, along with mesangial IgA deposition and elevated ANCA titers, should prompt consideration of this overlap syndrome. Early and aggressive immunosuppressive therapy is crucial to prevent irreversible renal damage and improve outcomes. However, relapses can occur, particularly in the setting of infections. This highlights the need for long-term monitoring and maintenance therapy. Further research is needed to better understand the pathogenesis of this overlap and to optimise therapeutic strategies.

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