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Rare Case of Renal Limited Dual Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis: Double Trouble!

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ABSTRACT

Dual anti-neutrophil cytoplasmic antibody-associated vasculitis (AAV) characterized by the presence of both anti-proteinase-3 (PR3-ANCA) and anti-myeloperoxidase (MPO-ANCA) antibodies is a rare clinical entity. Only few cases have been reported previously, most of which were associated with infections, drugs, autoimmune diseases and malignancies. Herein, we describe a young woman who presented with rapidly progressive glomerulonephritis with hypocomplementemia and markedly elevated anti-PR3 and anti-MPO titres. Meticulous work-up ruled out all possible secondary causes. Renal biopsy showed the presence of focal fibrocellular crescents with focal mesangial hypercellularity. Immunofluorescence and electron microscopy showed pauci-immune deposits. The patient was treated with an induction regimen comprising oral prednisolone and cyclophosphamide. She attained both clinical and serological remission at 3 months and is currently on an azathioprine-based maintenance regimen. We have extensively reviewed all previous cases of dual AAV and have formulated an approach to diagnose and treat this rare entity.

KEYWORDS

ANCA-associated vasculitis, anti-proteinase-3, anti-myeloperoxidase, hypocomplementemia, crescents

LEARNING POINTS

- Dual anti-neutrophil cytoplasmic antibody-associated vasculitis characterized by both PR3-ANCA and MPO-ANCA antibodies is a rare clinical entity.
- Prior to treating with immunosuppression, we need to rule out secondary aetiologies such as drugs, certain infections, autoimmune diseases and haematological malignancies.
- Atypical presentations such as hypocomplementemia, other serological abnormalities like positive ANA, cryoglobulins, anti-histone antibody and histology showing mesangial hypercellularity, interstitial inflammation and lack of pauci-immunity, may create a diagnostic dilemma.

INTRODUCTION

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a small vessel vasculitis associated with either anti-proteinase-3 (PR3-ANCA) or anti-myeloperoxidase (MPO-ANCA) antibodies. PR3-ANCA is the predominant antibody seen in granulomatosis with polyangiitis (GPA), whereas MPO-ANCA is the dominant antibody in microscopic polyangiitis (MPA), eosinophilic granulomatosis with polyangiitis (EGPA) and renal limited AAV[1]. The presence of both PR3-ANCA and MPO-ANCA is unusual and has been previously reported

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with certain infections, drugs, autoimmune diseases and malignancies [2–5]. Herein, we report a rare case of idiopathic renal limited dual AAV which was treated successfully with immunosuppression.

CASE DESCRIPTION

A 30-year-old Indian woman presented with history of arthralgia of 2.5 years' duration, swelling of the feet for 1 month and oliguria of 7 days' duration. There was no history of any skin lesions, photosensitivity, hair loss, ear or nasal discharge, cough, haemoptysis, abdominal pain, melena, or wrist or foot drop. On examination, the patient was found to be hypertensive with elevated jugular venous pulsations and pitting pedal oedema. Coarse crepitations were heard on auscultation of basal lung fields.

Her initial laboratory parameters were as follows: haemoglobin 5.1 g/dl, total WBC count 11,100 cells/mm^3, platelet count 3.4×10^5 cells/mm^3, serum creatinine 6.87 mg/dl, and albumin 2.8 g/dl. Urine microscopy revealed protein 1+, RBC 47/HPF (dysmorphic RBC 60% with no RBC casts), WBC 11/HPF, and 24-hour urine protein was 1.6 g/day. Ultrasound of the abdomen showed normal sized kidneys and increased echogenicity with maintained corticomedullary differentiation. Autoimmune and serological work-up findings were as follows: ANA negative, dsDNA 12 U/ml, C3 29.7 (90–180 mg/dl), C4 9 (10–40 mg/dl), antiphospholipid antibody (APLA) panel negative, anti GBM antibody negative, anti U1-RNP antibody negative, anti histone antibody negative, viral serology (hepatitis B and C) negative, cryoglobulin negative, PR3-ANCA >200 U/ml and MPO-ANCA >200 U/ml.

The patient had no history of intake of any drugs known to cause ANCA vasculitis (*Table 1*). A thorough infective work-up did not isolate any pathogenic organisms. The findings included sterile blood and urine culture, normal procalcitonin levels, negative COVID-19 PCR and absence of vegetations on echocardiography. The patient underwent a kidney biopsy with three cores sent for light microscopy (LM), immunofluorescence microscopy (IF) and electron microscopy (EM). Of the 10 glomeruli available for evaluation on LM, four were globally sclerosed, two showed the presence of fibrocellular crescents (*Fig. 1A*) and the remaining viable glomeruli showed mild mesangial expansion with focal segmental mesangial hypercellularity (*Fig. 1B*). There was no evidence of fibrinoid necrosis, endocapillary hypercellularity or capillary wall reduplication. The tubulointerstitium showed diffuse acute tubular injury with moderate patchy interstitial fibrosis and tubular atrophy (40%) with mononuclear cell infiltration. On IF, there was granular mesangial staining for IgG (1+), C3 (2+), Kappa (1+) and Lambda (1+). Ultrastructural evaluation showed a few mesangial, sub-endothelial and sub-epithelial deposits (*Fig. 1C,D*).

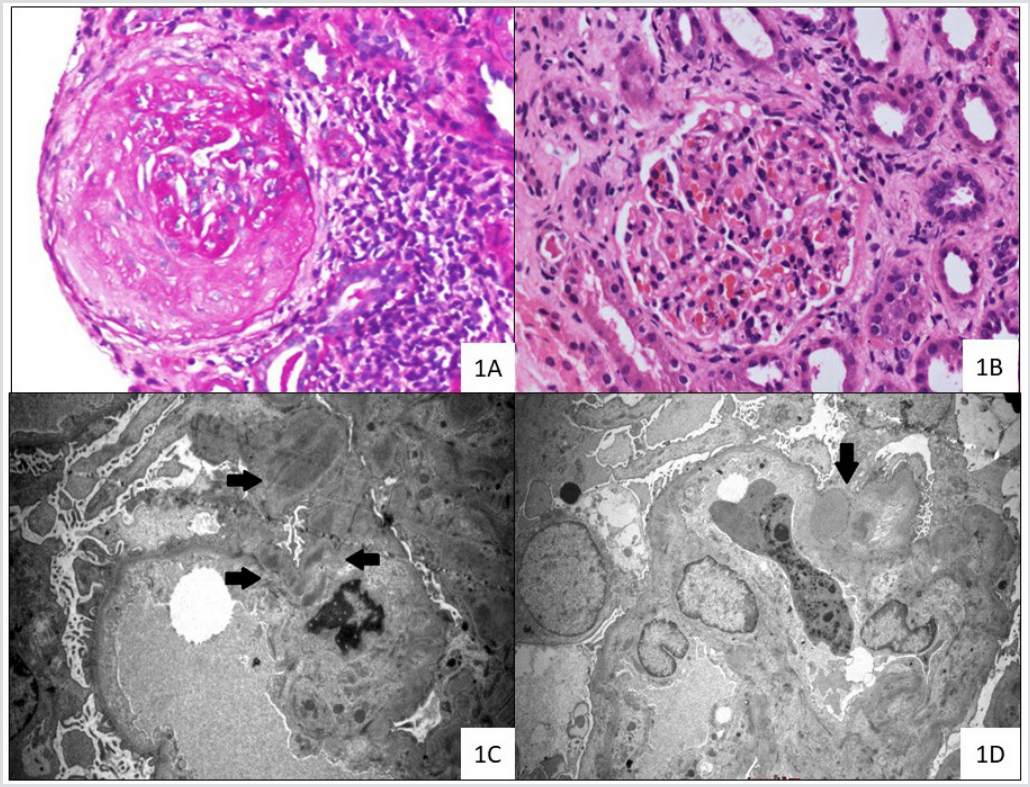

Figure 1. Renal biopsy findings of the current case of dual ANCA-associated vasculitis (1A) Fibrocellular crescent occluding capillary loop with interstitial mononuclear cell infiltration (haematoxylin and eosin stain; original magnification ×200). (1B) Glomerulus with congested loops and mild mesangial hypercellularity (periodic acid-Schiff stain; original magnification ×200). (1C) Glomeruli demonstrating mesangial ill-defined electron-dense deposits (bold black arrows) (transmission electron microscope; original magnification ×4200). (1D) Segment of glomeruli displaying a rare para-mesangial notch hump-like electron-dense deposit (marked with bold black arrow). Overlying podocytes showed marked foot process effacement. (transmission electron microscope; original magnification, ×4200)

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Aetiology	Prevalence of dual AAV (%)	Salient clinical features
Drugs		
Hydralazine	39	More than 1 year of drug intake, anti-MPO titres>anti-PR3 titres, anti-histone antibody (98%), ANA (89%), hypocomplementemia (58%), dsDNA (45%), mesangial hypercellularity (30%), Berden class: focal (50%), immune deposits on IF (20%), electron dense deposits (62%)
Cocaine adulterated with Levamisole	50	Necrotizing skin lesions, CIMDL, HLE ANCA, ANA (82%), hypocomplementemia (63%), LA (66%)
Propylthiouracil	10–11	Young females, less organ involvement, lower BVAS, less proteinuria, higher eGFR, histology: fewer crescents, interstitial inflammation and IFTA, good renal prognosis
Cimetidine	Case report	Severe interstitial mononuclear cell infiltration
Infections		
Sub-acute bacterial endocarditis Bacterial infections (*Staphylococcus aureus*, CoNS, *Streptococcus viridians*, Enterococcus, tuberculosis) *Viral infections* (hepatitis B, hepatitis C, COVID-19, parvovirus B19)	35	Younger age, hepatosplenomegaly, new heart murmurs (SABE), hypocomplementemia, anti-PR3 titres>anti-MPO titres, cryoglobulin (50%), lower relapse rates
Autoimmune diseases		
SLE	Case report	ANA, dsDNA, relapse
MCTD	Case report	ANA, anti U1-RNP antibody
HSP	Case report	Elevated serum IgA
Haematological malignancy	Case report	
Idiopathic dual AAV	Current case	Young age, hypocomplementemia, anti-PR3 titres=anti-MPO titres, mesangial hypercellularity

Table 1. Causes of dual anti-neutrophil cytoplasmic antibody-associated vasculitis

AAV, anti-neutrophil cytoplasmic antibody-associated vasculitis; ANA, anti-nuclear antibody; BVAS, Birmingham Vasculitis Activity score; CIMDL, cocaine-induced midline destructive lesions; CoNS, coagulase negative staphylococcus; dsDNA, double-stranded DNA; eGFR, estimated glomerular filtration rate; HLE, human leucocyte elastase; HSP, Henoch-Schonlein purpura; IF, immunofluorescence; IFTA, interstitial fibrosis and tubular atrophy; LA, lupus anticoagulant; MCTD, mixed connective tissue disease; MPO, myeloperoxidase; PR3, proteinase 3; SABE, sub-acute bacterial endocarditis; SLE, systemic lupus erythematosus.

The patient was treated with an induction regimen of oral prednisolone (1 mg/kg/day) and a renal adjusted dose of oral cyclophosphamide. Her symptoms improved within a month. Her parameters at a follow-up visit at 3 months were as follows: serum creatinine 0.8 mg/dl, Hb 10.5 g/dl; urine microscopy: protein negative, RBC 16/HPF, WBC 4/HPF, 24-hour protein 0.37 g/day, PR3-ANCA 61 U/ml, MPO-ANCA 133 U/ml, C3 115 mg/dl and C4 28.7 mg/dl. Steroid was tapered and azathioprine was initiated as maintenance agent. The patient was continuing to do well at her last visit (12 months) with normal renal function and negative ANCA titres.

DISCUSSION

The simultaneous occurrence of both PR3-ANCA and MPO-ANCA in patients with vasculitis is an uncommon phenomenon. In most cases, there seems to be a triggering factor such as drugs, infections, malignancy or autoimmunity (*Table 1*). Drug metabolites can bind to both MPO and PR3 antigens expressed by neutrophils and can induce an antigenic change predisposing to antibody production. An alternate hypothesis is drug-mediated neutrophil apoptosis with the formation of apoptotic blebs expressing MPO and PR3 antigens leading to ANCA production [3]. A unique form of neutrophil cell death is NETosis, wherein neutrophils release decondensed chromatin and granular contents into extracellular space forming a sticky mesh-like network containing MPO and PR3 antigens. Antigen-presenting cells will pick up these antigens from the neutrophil extracellular traps (NETs), thus activating autoreactive T and B cells [6]. Infections are known to trigger ANCA formation, predominantly PR3-ANCA. Stimulation of peripheral blood mononuclear cells isolated from patients with ANCA vasculitis with

unmethylated CpG oligonucleotide sequences found in bacterial and viral DNA resulted in increased production of ANCA (PR3>MPO-ANCA) [7]. The presence of dual ANCAs in autoimmune disease can be explained by the phenomenon of epitope spreading, wherein after the formation of an autoantibody, the antibody response may generalize to the rest of the auto antigens [6].

Table 2 lists previously reported cases of dual AAV [2,4,6,8–10]. In our case, we meticulously ruled out all possible secondary causes of dual AAV as given in *Table 1*. The clinical pointers which may enable an aetiological diagnosis to be narrowed down are the presence of extra-renal involvement, ANCA titres, associated serological abnormalities, complement levels, atypical histology like mesangial hypercellularity, immune deposits and interstitial inflammation. The presence of cutaneous gangrene and midline destructive lesions such as nasal septal perforation, palatal perforation or orbital erosive lesions, should lead to a strong suspicion of cocaine addiction [11]. Hepatosplenomegaly and new heart murmurs are pointers to sub-acute bacterial endocarditis (SABE) [5,9]. Drug-induced AAV is associated with markedly elevated anti-MPO antibody titres more than anti-PR3 titres [3,11], whereas in infections, PR3 titres are elevated more than MPO titres [5]. Dual AAV with marked elevation of both PR3 and MPO titres is seen in autoimmune [6] and idiopathic aetiologies, as in our case. Human leucocyte elastase (HLE) ANCA is specifically associated with cocaine-induced midline destructive lesions [11]. Associated serological abnormalities can predict underlying aetiology: anti-histone antibody (hydralazine-induced lupus nephritis) [3], anti U1-RNP antibody (mixed connective tissue disease) [10] and cryoglobulinemia (SABE, HCV infection or haematological malignancies) [5].

There is growing evidence of the involvement of an alternate complement pathway in the pathogenesis of AAV. Hypocomplementemia (low serum C3) is seen in 13–35% of patients with AAV. Patients with low C3 AAV are older, have higher mortality rates, have more severe tubulointerstitial injury on renal histology, and are more likely to progress to kidney failure [12]. Hypocomplementemia is a common feature seen in all aetiologies of dual AAV (*Table 1*), but whether this will translate to poor outcomes can be answered only after long follow-up studies. However, our patient achieved remission despite having hypocomplementemia, severe renal dysfunction and proteinuria at presentation and renal histology showing moderate to severe tubulointerstitial injury with C3 deposits on IF. Mesangial hypercellularity and prominent interstitial inflammation are pointers to drug-induced AAV [3,11], whereas immune deposits on IF are commonly seen with infections [5].

CONCLUSION

Dual AAV is a rare form of small vessel vasculitis which is associated with certain drugs, infections, autoimmune diseases and haematological malignancies. The majority of patients in published reports attained clinical and serological remission following immunosuppressive therapy. Future studies are needed to evaluate the underlying pathogenic mechanisms as well as long-term renal outcomes.

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Author	Meisels et al.[13]	Kim et al.[4]	Guardiola et al.[14]	Chou et al.[2]	Amaro et al.[15]	Ueda et al.[8]	Tiliakos et al.[9]		Sakalli et al.[16]	Murakami et al.[10]	Boyle et al.[6]	John et al. (current case)
Country	Boston	South Korea	Spain	Australia	Spain	Japan	Pennsylvania, USA		Turkey	Japan	Australia	India
Duration of study	1997	1997–2016	1999	2003–2013	2004	2005	2008		2011	2012	2020	2022
Total patients with dual AAV	1	8	1	15	1	1	2		1	1	1	1
Age (years)	50	68.5 (47–76) (median)	77	–	60	75	50	64	12	38	70	30
Sex	Male	1.6:1 (M:F)	Female	–	Male	Male	Male	Male	Female	Female	Female	Female
Organ involvement		(%)		(%)								
Constitutional symptoms	No	0	Yes	0	No	Yes	Yes	No	No	Yes	No	No
Upper respiratory tract	No	75	Yes	66	No	No	Yes	No	No	No	No	No
Lower respiratory tract	No	75	Yes	40	No	No	No	No	No	Yes	Yes	No
Kidney	Yes	100	Yes	26.6	Yes	Yes	Yes	No	No	No	Yes	Yes
CNS	No	62.5	Yes	13.3	No	No	Yes	Yes	Moyamoya	Yes	No	No
CVS	No	25	No	0	No	No	No	No	No	No	No	No
GIT	No	0	No	0	No	No	Yes	Yes	No	No	No	No
Skin	No	0	Yes	0	Yes	Yes	No	No	Yes	Yes	Yes	No
Joints	No	0	No	0	Yes	No	Yes	No	No	Yes	Yes	No
Eye	No	0	No	0	No	No	No	No	Retinal thrombosis	No	No	No
Aetiological diagnosis		(%)		(%)								
GPA	–	25	–	0	–	–	–	–	–	–	–	–
MPA	–	75	–	13.3	–	–	–	–	–	–	–	–
EGPA	–	0	EGPA+GCA	6.6	–	–	–	–	–	–	–	–
Renal limited vasculitis	–	0	–	6.6	–	–	–	–	–	–	–	Yes
Drug-induced AAV	–	0	–	6.6	–	Cimeti-dine	–	–	–	–	–	–
Infection-induced AAV	–	0	–	46.6	–	–	IE	IE	–	–	–	–
Autoimmune disease	–	0	–	20	–	–	–	–	Moyamoya	MCTD	SLE	–
Malignancy	–	0	–	0	–	–	–	–	–	–	–	–
Glomerulone-phritis	MN	0	–	0	HSP	–	–	–	–	–	–	–
Hypertension	–	–	–	–	No	Yes	Yes	Yes	–	No	No	Yes
Kidney function at presentation		Median (range)										
Creatinine (mg/dl)	6.9	4.3 (0.7–13.5)	1.24	–	Normal	2.9	–	–	–	0.5	2.91	6.87
eGFR (ml/min/1.73m^2)	-	16.5 (3.4–29)	32.57	_	Normal	44	_	_	110	–	–	7.3

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Urine microscopy (%)												
Proteinuria	Yes	100	Yes	–	Yes	No	Yes	No	No	Yes	Yes	Yes
Microhaematuria	Yes	100	Yes	_	Yes	No	Yes	No	No	Yes	Yes	Yes
24-hour urine protein (g/day)	–	–	0.8	–	3.14	–	–	–	–	–	–	1.6
Albumin (g/dl)	_	–	–	–	–	3.2	–	–	–	2.8	–	2.8
Haemoglobin (g/dl)	–	–	8.8	–	14.2	12.4	12	11.2	–	11.6	10.1	5.1
Total leucocyte count (cells/mm^2)	–	–	13,780	–	8400	4300	9300	8000	–	14,100	–	11,100
C-reactive protein	–	–	–	–	Elevated	–	–	–	Normal	Elevated	Elevated	Elevated
ANCA antibody titre (U/ml) at diagnosis												
PR3-ANCA	–	–	64	–	37	246	11	24	–	80.3	>100	>200
MPO-ANCA	–	–	34	–	40	318	17	16	–	31.3	>100	>200
Serological profile												
Hepatitis B	–	–	–	–	Negative	Negative	Negative		Negative	Negative	–	Negative
Hepatitis C	–	–	–	–	Negative	Negative	Negative		Negative	Negative	–	Negative
ANA	Negative	–	Positive	–	Negative	Negative	Negative		Positive	Positive	Positive	Negative
dsDNA	Negative	–	–	–	Negative	–	Negative		Negative	Negative	Positive	Negative
C3	–	–	–	–	Normal	Normal	–		Normal	Normal	Normal	Low
C4	–	–	–	–	Normal	Normal	–		Normal	Normal	Normal	Normal
Cryoglobulins	–	–	–	–	Negative	–	–		–	–	–	Negative
Anti cardiolipin Ab	–	–	Positive	–	–	–	–		Positive	–	–	Negative
Anti β2 glycoprotein Ab	–	–	–	–	–	–	–		–	–	–	Negative
Lupus anticoagulant	–	–	–	–	–	–	–		Negative	–	–	Negative
Anti histone antibody	–	–	–	–	–	–	–		–	–	–	Negative
Anti U1-RNP antibody	–	–	–	–	–	–	–		–	–	–	Negative
Anti GBM antibody	–	–	–	–	–	Negative	–		–	Positive	–	Negative
Renal histology												
Berden's classification	Crescent	ND	Focal	ND	Focal	Focal	ND		ND	ND	Mixed	Focal
Immunofluorescence	Linear IgG and granular IgA in capillary loops	ND	-	ND	IgA deposits in mesangial and capillary wall	Pauci-immune	ND		ND	ND	Pauci-immune	Pauci-immune
Electron microscopy	Sub-epithelial deposits	ND	-	ND	-	No deposits	ND		ND	ND	Focal deposits	Focal deposits

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Immunosuppression												
Induction therapy	Pred + oral CP + Plex	Pred			Pred	Nil	Pred	Pred	Pred + IV CP	Pred + Aza	Pred + IV CP	Pred + oral CP
Maintenance therapy	–	Pred			-	Nil	Nil	Nil	Pred	-	MMF, Ritux	Aza
Outcomes (%)												
Remission	Yes	50%	Yes	–	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Relapse	No	25%	No	–	No	No	No	No	No	No	No	No
Death	No	–	No	33.3%	No	No	No	No	No	No	No	No
ANCA titres at last visit	Negative	–	–	–	Negative	Negative	Neg	Neg	Negative	Persistent	Negative	Negative

Table 2. Comparison of previously reported cases of dual anti-neutrophil cytoplasmic antibody associated vasculitis with the current case

AAV, anti-neutrophil cytoplasmic antibody-associated vasculitis; Ab, Antibody; ANA, anti-nuclear antibody; Aza, azathioprine; CNS, central nervous system; CP, cyclophosphamide; CVS, cerebrovascular system; dsDNA, double-stranded DNA; EGPA, eosinophilic granulomatosis with polyangiitis; GBM, glomerular basement membrane; GCA, giant cell arteritis; GIT, gastrointestinal tract; HSP, Henoch-Schonlein purpura; IE, infective endocarditis; MCT, mixed connective tissue disease; MN, membranous nephropathy; MPO, myeloperoxidase; ND, not done; PR3, proteinase 3; Pre, prednisolone; Plex, plasmapheresis; Ritux, rituximab; RNP, ribonucleoprotein; SLE, systemic lupus erythematosus.

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