Dual-Positive Anti-Neutrophil Cytoplasmic Antibodies in Renal-Limited Vasculitis: A Case Report from Pakistan

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ABSTRACT

The anti-neutrophil cytoplasmic antibodies (ANCAs) target different proteins of neutrophilic granules, mainly myeloperoxidase (MPO) and proteinase (PR3), and others. Dual-positive ANCA with both MPO and PR3 is an uncommon finding described in infections, autoimmune diseases, drugs, ANCA-associated vasculitis (AAV), COVID vaccination, and malignancies. An 18-year male patient presented with dyspnoea on exertion, weakness, and weight loss, without any systemic findings on examination. Baseline workup showed iron deficiency anaemia, proteinuria, and haematuria. After extensive investigations, serum ANCA was positive for both MPO and PR3, and the rest of the investigations, including bone marrow, radiological, autoimmune, biochemical, and microbial testing, were negative. He was treated as a case of AAV and started on steroids, which improved his symptoms. This case is an unusual presentation of dual- positive ANCA with renal-limited vasculitis. High vigilance is required for early diagnosis of AAV in unusual presentations.

Key Words: *Anti-neutrophil cytoplasmic antibodies, Anti-neutrophil cytoplasmic antibody-associated vasculitis, c-ANCA, p-ANCA*.

How to cite this article: Bibi M, Hussain M, Hassan MA, Mushtaq H, Alam M. Dual-Positive Anti-Neutrophil Cytoplasmic Antibodies in Renal-Limited Vasculitis: A Case Report from Pakistan. *JCPSP Case Rep* 2025; **3**:349-351.

INTRODUCTION

An 18-year man was referred to a tertiary care hospital with complaints of weakness, fatigue, and dyspnoea on exertion for two months. Initially, there was mild dyspnoea on exertion, but it increased to hamper routine tasks. He also had weight loss, pallor, and loss of appetite. There was no past history of any fever, diarrhoea, chest infection, any local or systemic illness, and no history of drug intake or recent vaccination.

General physical and systemic examinations were unremarkable, except for pallor. He was thoroughly investigated with complete blood count showing low haemoglobin (Hb), normal cell counts, and low serum iron levels (8 µmol/l) (Table I). The rest of the investigations were normal, with only abnormal findings in urine on routine examination, having 2+ proteins, red blood cells (RBCs) 3-7/HPF, and white blood cells (WBCs) 1-3/HPF. This was followed by 24-hour urine for protein levels, protein creatinine ratio, and albumin creatinine ratio, which were raised. Serum ANCAs showed an indiscernible pattern on ethanol-fixed slides, while on formalin-fixed slides, a cytoplasmic pattern was observed (3+ intensity and 1:80 titre) (Figure 1). Upon testing with the ELISA technique for antigen specificity, MPO and PR-3 were found to be positive, and results were confirmed using two different methods.

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Received: September 16, 2024; Revised: May 17, 2025; Accepted: July 09, 2025
DOI: https://doi.org/10.29271/jcpspcr.2025.349

Anti-glomerular basement membrane antibodies (anti-GBM) and other auto-immune profiles were negative. A thorough workup was performed to determine the cause of anaemia and ANCAs. Due to a lack of consent from the patient, renal biopsy was not performed. He was diagnosed as AAV and started on steroid therapy. He is under regular follow-up for monitoring of disease progression. Detailed laboratory results are shown in Table I.

DISCUSSION

ANCAs target various proteins of neutrophilic granules, primarily MPO and PR3, producing either perinuclear or cytoplasmic staining on IIF.[3] Dual-positive PR3-MPO ANCA is reported in a few cases with infections, drugs, autoimmune diseases, and malignancies.[5]

Dual-positive AAV is rare, and only a few case reports related to it are available. This patient presented with weakness and severe anaemia without having any systemic findings. Renal biopsy could not be performed in this case, which might have aided in reaching a conclusive diagnosis. Sarwal *et al*. reported a case of a 79-year-old female with similar symptoms who was diagnosed as dual-positive ANCA-associated glomerulonephritis.[6] John *et al*. described a case of a female patient with renal-limited vasculitis who presented with a sudden onset swelling of feet, oliguria, and chronic arthralgias. Her autoimmune profile, infectious aetiology, and drug intake were negative, having both MPO and PR3 ANCAs and a positive renal biopsy.[7] Kim *et al*. found eight cases of dual-positive ANCAs in 85 AAV patients having severe deranged kidney function and high respiratory involvement.[5]

Table I: Laboratory investigations of the patient.

Investigations	Results
Complete blood count	
Red blood cells	$3.3\times10^{12/1}$ (low)
Total leucocyte count	$11.2\times10^{9/1}$ (raised)
Haemoglobin	9.2 g/dl (low)
Platelets	$250\times10^{9/1}$ normal
Malarial parasite	Not detected
Liver function tests (LFTS)	Normal
Renal function tests (RFTs)	Normal
Bone marrow	Normal, preserved cell lines, and low iron stores
Inflammatory markers	
• C-reactive protein	28.1 mg/l (raised)
• Erythrocyte sedimentation rate	30 mm/1st hour (raised)
Auto-immune profiles	
• Coombs test (direct and indirect)	Negative
• Anti-nuclear antibodies (ANA)	Negative
• Anti-dsDNA antibodies	Negative
• Anti-extractable nuclear antigen antibodies (anti-ENA)	Negative
• RA factor	Negative
• Complement (C3, C4) levels	Normal
• CD55/59	Normal
Urine tests	
• Urine routine examination	RBC, proteins 2+, no cast
• Urine protein creatinine ratio	184.2mg/mmol (raised)
• 24-hour urine protein	344 mg/day (raised)
• Albumin: Creatinine ratio	160.1 (raised)
• Urine for dysmorphic RBCs	Not detected
Serology	
HBV/HCV/HIV serology	
Antibodies to legionella / mycoplasma pneumoniae	
Anti-tissue transglutaminase IgA antibodies (anti-TTG)	All negative
Microbiology workup	
• Culture and sensitivity for bacteria/fungus/MTB (EBW, blood)	Negative/ no MTB detected
• PCR for viral (COV-2/CMV/RSV/Parvo-B19) / MTB	Negative
• IGRA test	Negative
• Stool routine examination and occult blood	Normal/not detected
Anti-neutrophil cytoplasm antibodies (ANCA)	
• PR3 (c-ANCA)	125 AU/ml (positive)
• MPO (p-ANCA)	98 AU/ml (positive)
Histopathology	
• Antral/duodenal/colonic biopsies	Negative for infection/inflammation/malignancy mild active colitis, findings of early IBD
Tumour markers	
• Carcinoembryonic antigen (CEA)	
• Alpha foetoprotein	Negative
Radiological investigations	
• CECT abdomen and pelvis	Hepatosplenomegaly
• HRCT chest	Ground glass haze both lungs
• CT paranasal sinuses	No inflammation, infection

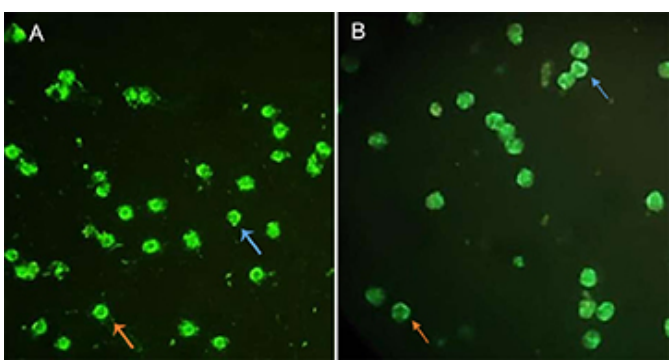

Figure 1: Indirect immunofluorescence (IIF) (40×): (A) Formalin fixed neutrophils. (B) Acetone fixed neutrophils showing perinuclear pattern as p-ANCA (blue arrows) and cytoplasmic pattern (orange arrows) as c-ANCA.

Despite thorough investigations, no infectious or auto-immune aetiology was identified in the present patient. Significant findings in this case were proteinuria, haematuria, anaemia, and weight loss. High-resolution CT (HRCT) of the chest revealed glassy haze, which may represent early vasculitic changes since infectious and malignant aetiologies were ruled out. However, the features of upper/lower airway, skin, joints or other systemic involvement were absent. Definite diagnosis is based on the clinical phenotype identification; specific serologic markers (ANCAs), tissue biopsy confirmation, exclusion of secondary/similar causes, and observation over time to increase the accuracy of diagnosis.[8] In this case, except for biopsy, other criteria fulfilled the diagnosis.

Aung and Tulsidas described a similar case of a 50-year female patient having non-specific symptoms of anaemia and weight loss without any systemic findings of infectious, auto-immune, or malignant aetiology. She was diagnosed as renal-limited vasculitis on renal biopsy and had raised MPO with normal PR3 levels.[9]

After thorough literature search, this is the first case of dual-positive ANCA with renal-limited vasculitis reported from Pakistan. Due to unusual presentation and various disease associations, a high index of suspicion should be kept in cases with dual-positive ANCAs for early diagnosis of AAV to prevent complications.

PATIENT'S CONSENT:
Informed consent was taken from the patient to publish the data concerning this case.

COMPETING INTEREST:
The authors declared no conflict of interest

AUTHORS' CONTRIBUTION:
MB: Conception of the study, data acquisition, interpretation, and writing.
MH: Critical revision.
MAH: Writing and literature review.
HM: Data collection.
MA: Critical review.
All authors approved the final version of the manuscript to be published.

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