

Hydralazine-Induced Dual ANCA-Positive Crescentic Glomerulonephritis

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ABSTRACT

An 80-year-old woman presented with rapidly progressive kidney failure following five months of hydralazine therapy at 100 mg daily. She reported dark urine, weight loss, and fatigue. Laboratory studies revealed dual anti-neutrophil cytoplasmic antibodies (ANCA) positivity (MPO 30 IU/mL, PR3 197 IU/mL), positive antinuclear antibodies (ANA), low complement C3, and active urinary sediment. Kidney biopsy demonstrated pauci-immune necrotising crescentic glomerulonephritis, consistent with ANCA-associated vasculitis (AAV). Hydralazine-induced vasculitis was suspected, and the drug was discontinued. She received high-dose intravenous methylprednisolone followed by rituximab, with partial recovery of kidney function at three weeks. Hydralazine-induced ANCA vasculitis is a rare but important cause of rapidly progressive glomerulonephritis that may closely mimic primary AAV. Dual ANCA positivity and ANA seropositivity are characteristic, although atypical serological patterns may occur. Recognition of this association and prompt discontinuation of hydralazine, alongside appropriate immunosuppression, are critical for improving kidney outcomes and preventing irreversible kidney injury.

Keywords: hydralazine; ANCA-associated vasculitis; drug-induced vasculitis; crescentic glomerulonephritis; dual ANCA; MPO; PR3; rapidly progressive renal failure; rituximab; drug-induced lupus

CASE PRESENTATION

An 80-year-old Caucasian woman was referred for rapidly progressive kidney failure. Over four months, she developed dark brown urine, lethargy, reduced appetite, and a 13-kg unintentional weight loss. Five months earlier, she had commenced hydralazine 100 mg daily for hypertension and later began multiple naturopathic supplements. She reported a persistent dry cough but denied dyspnoea, haemoptysis, rash, or arthralgia.

Her past medical history included chronic kidney disease (stage 3a), Graves' disease, hypertension, dyslipidaemia, anaemia, bronchitis, transient ischaemic attack, and migraines. Surgical history comprised coronary artery bypass graft, partial thyroidectomy, and hysterectomy. Current medications were hydralazine, metoprolol, aspirin, mirtazapine, darbepoetin alfa, levothyroxine, and famotidine. She was intolerant to several antihypertensives, and a first-degree relative had myasthenia gravis. She had received two AstraZeneca COVID-19 vaccines 2.5 years earlier and a Pfizer booster 1.5 years prior.

On examination, she was normotensive and afebrile, with no rash, oedema, or arthropathy. Laboratory investigations showed a serum creatinine of 600 $\mu\text{mol/L}$, an active urinary sediment with dysmorphic red cells ($>100 \times 10^6/\text{L}$) and proteinuria (albumin-creatinine ratio 8.5 mg/mmol). Five months earlier, her creatinine was 115 $\mu\text{mol/L}$, worsening progressively to 230 $\mu\text{mol/L}$ at 3 months, and 600 $\mu\text{mol/L}$ on admission. Findings were consistent with rapidly progressive glomerulonephritis (RPGN). Differential diagnoses included acute glomerulonephritis or drug-induced interstitial nephritis from her supplements.

Serology revealed dual ANCA positivity (MPO 30 IU/mL [cut-off: <6 IU/mL]; PR3 197 IU/mL [cut-off: <5 IU/mL]), positive ANA (1:320, homogenous), low complement C3 (0.6 g/L [reference range: 0.83–1.93 g/L]), and normal C4. Anti-double-stranded DNA (anti-dsDNA), anti-glomerular basement membrane (anti-GBM), anti-histone, and extractable nuclear antigen (ENA) antibodies were negative. All supplements were ceased. Given the progressive renal failure and dual ANCA positivity, she was empirically treated for ANCA-associated vasculitis with methylprednisolone 500 mg daily for three days, followed by rituximab (two fortnightly doses).

Kidney biopsy demonstrated necrotising and early crescentic glomerulonephritis with acute tubular injury. No extra-glomerular vasculitis was identified. Immunofluorescence was non-specific, and electron microscopy confirmed the absence of immune deposits, supporting a pauci-immune crescentic GN compatible with ANCA vasculitis.

Given the biopsy and serology findings, the diagnosis of hydralazine-induced ANCA-associated vasculitis was made. Hydralazine was discontinued.

At three-week follow-up, creatinine had decreased from 635 $\mu\text{mol/L}$ to 450 $\mu\text{mol/L}$ and estimated glomerular filtration rate (eGFR) improved from 5 to 8 mL/min/1.73 m^2 . She was maintained on six-monthly rituximab for remission. Her eGFR remained stable at 14 mL/min and ANCA titres normalised.

DISCUSSION

Antineutrophil cytoplasmic antibody-associated vasculitis (AAV) encompasses autoimmune small-vessel vasculitides characterised by necrotising inflammation affecting kidneys, lungs, and skin. ANCA binding to neutrophil antigens—myeloperoxidase (MPO) and proteinase 3 (PR3)—activates neutrophils, leading to endothelial injury and tissue necrosis. AAV may be primary (idiopathic) or secondary to infections, malignancy, or drugs.^{1,2}

Primary AAV typically demonstrates single ANCA positivity: MPO-ANCA with microscopic polyangiitis (MPA) or PR3-ANCA with granulomatosis with polyangiitis (GPA).³ In contrast, drug-induced vasculitis (DIV) often exhibits dual ANCA positivity, usually with accompanying autoantibodies such as ANA or anti-histone antibodies. Common culprits include hydralazine, propylthiouracil, levamisole-adulterated cocaine, and minocycline.⁴

Hydralazine, a vasodilator used for refractory hypertension, is known to cause both drug-induced lupus and vasculitis. It is hypothesised to promote autoimmunity by impairing immune tolerance and DNA methylation, enhancing MPO and PR3 expression in genetically susceptible individuals. Reported risk factors for hydralazine-induced vasculitis include female sex, thyroid disease, slow hepatic acetylation, prolonged use (>3 years), and doses >100 mg/day.^{4–6}

Our case was atypical: the patient developed vasculitis within five months of starting hydralazine, exhibited PR3-predominant dual ANCA positivity, and had normal anti-histone antibodies. While hydralazine-induced AAV is classically MPO-dominant with anti-histone antibody positivity, variable antigenic expression may explain the serological divergence.⁷ Furthermore, anti-histone antibodies, usually elevated in hydralazine-induced vasculitis,⁸ were within normal limits in this patient. While the PR3 predominance might relate to individual variation in hydralazine-induced epigenetic dysregulation favouring PR3 antigen expression, the reason for the normal anti-histone antibody level in this context is unclear and contributes to the unusual nature of this presentation.

Differentiating hydralazine-induced vasculitis from primary AAV is essential, as drug withdrawal is the cornerstone of treatment.⁹ Clinical clues include renal-limited disease, low complement, ANA positivity, and dual ANCA pattern—all present in this case. In contrast, primary AAV more often causes multi-organ involvement without serologic overlap (Table 1).

Table 1. Characteristics differentiating primary AAV from hydralazine-induced vasculitis.^{3,7,8}

Feature	Primary AAV	Hydralazine-induced vasculitis
Aetiology	Idiopathic – genetic/environmental triggers	Hydralazine exposure in genetically susceptible individuals
Serology	Single MPO- or PR3-ANCA positivity typical; dual positivity rare. MPO positivity with MPA/EGPA. PR3 positivity with GPA	High titre MPO or dual MPO/PR3 positivity common. ANA positivity. Anti-histone antibody positivity. Hypocomplementaemia
Clinical presentation	Multisystem – renal, pulmonary, ENT, skin	Rapidly progressive GN; extrarenal disease rare
Treatment	Immunosuppression (induction and maintenance)	Drug cessation and immunosuppression (induction potentially followed by maintenance depending on disease severity)

Abbreviations: AAV, ANCA-associated vasculitis; ANA, antinuclear antibody; ANCA, anti-neutrophil cytoplasmic antibody; EGPA, eosinophilic granulomatosis with polyangiitis; GN, glomerulonephritis; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; MPO, myeloperoxidase; PR3, proteinase 3.

The kidney biopsy findings of pauci-immune necrotising GN are indistinguishable between hydralazine-induced and primary AAV, reinforcing the need for thorough drug history.

Current management parallels primary AAV: high-dose corticosteroids combined with rituximab or cyclophosphamide for induction, followed by maintenance therapy (rituximab or azathioprine with low-dose steroids) for 18 months–4 years. In drug-induced cases, early discontinuation of the offending medication improves kidney outcomes and may allow tapering of immunosuppression sooner.¹⁰

Dual ANCA positivity is rare and may occur in other contexts including autoimmune diseases (e.g. systemic lupus erythematosus), infections (e.g. infective endocarditis), malignancies, and occasionally following COVID-19 mRNA vaccination, likely reflecting immune activation rather than direct causation.^{11,12}

This case underscores the diagnostic challenge posed by dual ANCA seropositivity and highlights the importance of correlating serological, clinical, and medication histories. Despite atypical serology and absence of anti-histone antibodies, hydralazine-induced vasculitis remained the most plausible diagnosis given recent drug exposure and renal-limited involvement. The partial recovery following hydralazine cessation and immunosuppression supports this conclusion.

CONCLUSION

Hydralazine-induced ANCA-associated vasculitis should be suspected in any patient presenting with rapidly progressive renal failure and dual MPO/PR3 positivity,

particularly when taking hydralazine at doses >100 mg/day. Although rare, this entity mimics primary AAV both clinically and histologically. Prompt recognition, discontinuation of hydralazine, and initiation of immunosuppressive therapy are crucial to improve renal recovery and prognosis.

DECLARATIONS

Conflict of Interest

Not applicable.

Funding

Not applicable.

Ethical Approval

Patient consent was obtained for publication of this case.

Data Availability

Not applicable.

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