Received: 28 June 2021 | Revised: 13 January 2022 | Accepted: 18 January 2022

DOI: 10.1002/ccr3.5411

CASE REPORT

Clinical Case Reports Open Access WILEY

Rare complication of a commonly used antihypertensive agent: A case of hydralazine-induced ANCA-associated vasculitis presenting as rapidly progressive glomerulonephritis

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Funding information
None

Abstract

Hydralazine-induced ANCA-associated vasculitis is a rare clinical entity, with complications including rapidly progressive glomerulonephritis, pulmonary hemorrhage, and pulmonary-renal syndrome. We present this case to highlight the clinical features that support this challenging diagnosis and to emphasize the importance of prompt recognition and aggressive intervention given its significant morbidity and mortality.

KEYWORDS

drug-induced vasculitis, hydralazine, pulmonary hemorrhage, pulmonary-renal syndrome, rapidly progressive glomerulonephritis

1 | INTRODUCTION

Hydralazine is a direct-acting arterial vasodilator that emerged in 1951 and is regularly used for treatment-refractory hypertension, heart failure with reduced ejection fraction, and severe pregnancy-related hypertension.[1] Although it is a known causative agent of drug-induced lupus (DIL), emerging evidence supports its role in antineutrophilic cytoplasmic antibody (ANCA)-associated vasculitis as well.[2-6] Proposed mechanisms of hydralazine-induced ANCA-associated vasculitis (AAV) center on neutrophilic apoptosis with subsequent release of intracellular antigens, resulting in the production of pathogenic ANCAs.[7] Other hypotheses describe reversal of epigenetic silencing of MPO-ANCA and PR3-ANCA, formation and stabilization of neutrophilic extracellular traps (NETs), and disruption of central tolerance by metabolites of hydralazine.[7] We present this case to explore the diagnostic challenges of hydralazine-induced AAV and emphasize the importance of prompt identification and immediate discontinuation of the offending agent given its high rate of morbidity and mortality.

2 | CASE PRESENTATION

A 78-year-old Caucasian woman with a history of hypertension, atrial fibrillation, coronary artery disease, stage 3B/4 chronic kidney disease (CKD), gout, and depression presented to the emergency department following an isolated episode of hematemesis in the setting of chronic oral anticoagulation and antiplatelet therapy.

Review of systems was also significant for generalized weakness, malaise, unintentional ten-pound weight

This research was supported (in whole or in part) by HCA Healthcare and/or an HCA Healthcare affiliated entity. The views expressed in this publication represent those of the author(s) and do not necessarily represent the official views of HCA Healthcare or any of its affiliated entities.

loss over a three-month period, intermittent nausea with non-bilious, non-bloody emesis, and diarrhea. Reported surgical history was limited to coronary artery bypass grafting. Family history was significant for coronary artery disease (father) but otherwise noncontributory. The patient denied tobacco, alcohol, or illicit drug use. Her home medications included hydralazine 50 mg three times daily (treatment for upwards of three years) as well as apixaban, clopidogrel, isosorbide mononitrate, metoprolol succinate, simvastatin, valsartan, furosemide, famotidine, febuxostat, and fluoxetine. On admission, the patient's vital signs were significant for sinus tachycardia, but otherwise within normal limits. Physical examination revealed a chronically ill female appearing older than her stated age. Mild abdominal tenderness to palpation was noted. Basic laboratory studies showed acute-on-chronic microcytic anemia (Hgb 5.5 g/dl and MCV 74.1 fl; compared to baseline Hgb 10.5 g/dl MCV: 82.6 fl) and acute renal failure (ARF) in the setting of chronic kidney disease (serum BUN 78 mg/dl and serum creatinine 4.87 mg/dl; compared to baseline BUN 36–55 mg/dl and baseline creatinine 1.60–2.80 mg/dl). Urinalysis was significant for 30 mg/dl protein, 51-100/HPF red blood cells, 2-5/HPF white blood cells, and 2-5/LPF granular casts. Noncontrast computed tomography (CT) of the abdomen and pelvis demonstrated probable colitis involving the ascending and transverse segments of colon. Home anticoagulation and antiplatelet therapies were held, and the patient was transfused 2 units of packed red blood cells. The patient was subsequently admitted to the general medicine service for further evaluation and management.

With the assistance of gastroenterology, upper endoscopy was performed and demonstrated severe reflux esophagitis in the setting of a 35–40 cm hiatal hernia. Nephrology was also consulted for non-oliguric acute kidney injury on CKD stage 3B/4, which was initially presumed to be ischemia-mediated acute tubular necrosis versus progression of established CKD. However, serologic studies revealed positive titers for anti-nuclear antibody (1:80), positive cytoplasmic ANCA (c-ANCA) at 1.3 AI (reference range 0.0–0.9 AI), and positive anti-histone antibody at 5.5 units (reference range 0.0–0.9 units). Complement component C3 was within normal limits at 44 mg/dl (reference range 40–380 mg/dl) but complement component C4 was decreased at <8 mg/dl (reference range 14–44 mg/dl). Antibodies to double-stranded DNA and glomerular basement membrane (GBM) were negative. Workup for multiple myeloma was also unremarkable (Free kappa/lambda ratio was 1.09 and M-spike was not observed). A renal biopsy demonstrated acute-on-chronic renal disease with global sclerosis involving six of 13 glomeruli, severe arteriolar intimal fibrosis, and mild scattered lymphoplasmacytic inflammation with areas of prior scarring (Figure 1). Areas of segmental sclerosis with focal crescentic glomerulonephritis with mild, focal granular mesangial staining for IgM and C3 were noted as well (Figure 2). A Congo red stain showed neither amyloid nor extraglomerular staining. Given the patient's clinical presentation, longstanding exposure to high-dose hydralazine, rapidly progressive glomerulonephritis, serologic multiple antigenicity, and pathological findings on renal biopsy, the diagnosis of hydralazine-induced AAV was concluded.

Hydralazine was discontinued on admission. After an extensive risks versus benefits discussion, the patient was deemed to be a poor candidate for aggressive intervention via immunosuppressive therapy, thus, she and her family opted to pursue a time-limited trial of renal replacement therapy alone. The patient underwent three sessions of hemodialysis over course of hospitalization but, ultimately, transitioned to hospice as a result of poor tolerance of the abovementioned. Patient was discharged to home hospice after 31 days.

3 | DISCUSSION

AAV is a well-described clinical entity, with an annual incidence of approximately 10–20 cases per million.[8] The ANCA-associated vasculitides are characterized by severe, small-vessel necrotizing inflammation, with a predilection for the pulmonary and renal vasculature, predominantly manifesting as one of three clinical syndromes: microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA; formerly Wegener's granulomatosis), and eosinophilic granulomatosis with polyangiitis (EGPA; formerly Churg–Strauss syndrome).[9-11] AAV is hallmarked by pathogenic autoantibody production against myeloperoxidase (MPO) and proteinase 3 (PR3), classically distinguished by perinuclear and diffusely cytoplasmic immunofluorescence staining patterns, respectively.[10,12] Although idiopathic AAV is well-documented in the literature, drug-induced vasculitis is a subset of AAV that remains ill-defined; predominately related to key medication exposures, including hydralazine, allopurinol, propylthiouracil, minocycline, phenytoin, penicillamine, sulfasalazine, and levamisole-adulterated cocaine.[6,12-14] Per comprehensive literature review, it appears that the development of hydralazine-induced AAV is largely dose and duration dependent, as evidenced by an annual incidence of 5.4% and 10.4% in patients on 100 and 200 mg/day of hydralazine, respectively.[11] Additional epidemiological risk factors appear to include female gender, concurrent thyroid disease, slow hepatic-acetylation, human leukocyte antigen (HLA)-DR4 genotype, and the null-gene for C4.[14] The clinical presentation of hydralazine-induced

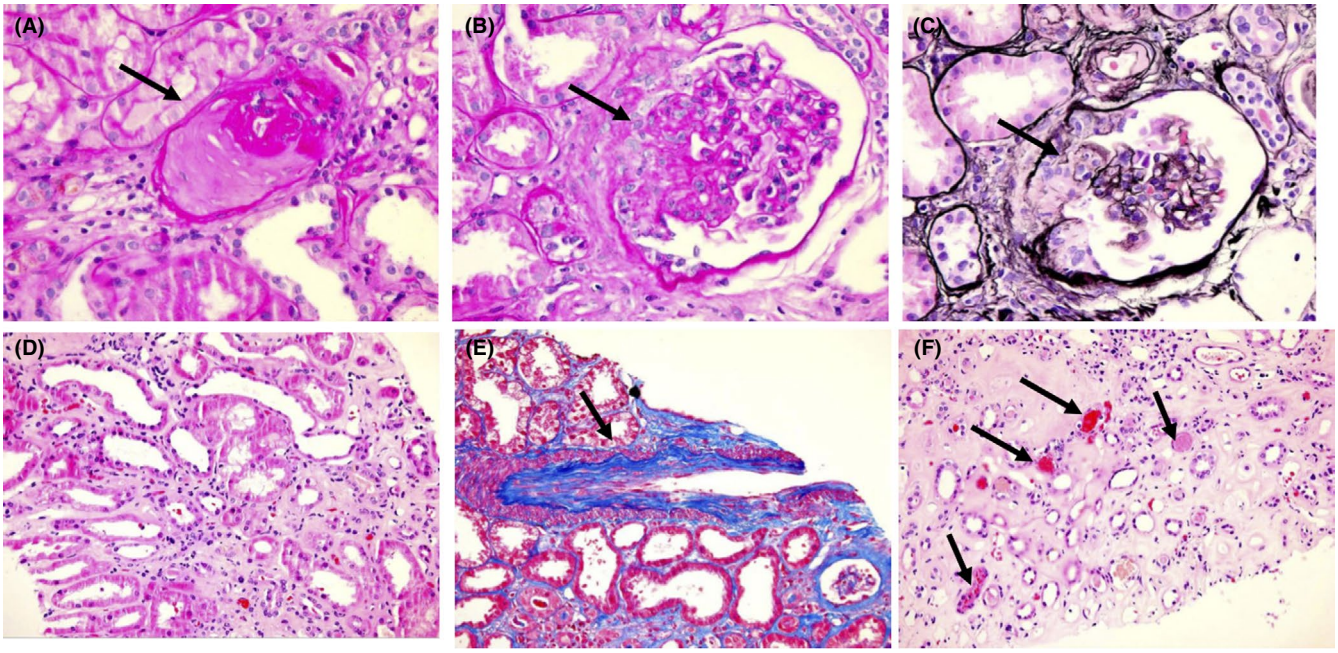
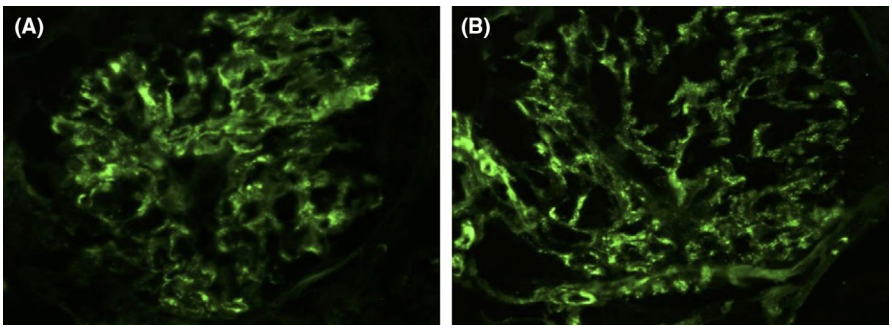


FIGURE 1 Renal biopsy demonstrating sclerotic glomeruli, a focally segmentally sclerosed glomerulus, patchy areas of tubular damage, and severe arteriole intimal fibrosis. A. Arrow identifying sclerotic glomeruli (PAS Stain). B. Arrow identifying a focally segmentally sclerosed glomerulus (PAS Stain). C. Arrow identifying a focally segmentally sclerosed glomerulus (Jones Silver Stain). D. Patchy areas of tubular damage (PAS Stain). E. Arrow identifying severe arteriole intimal fibrosis (Trichrome Stain). F. Arrows identifying occasional red blood cell casts in tubules

FIGURE 2 Renal biopsy with immunofluorescence staining demonstrating focal granular staining for IgM and C3. A. Focal granular staining for IgM. B. Focal granular staining for C3



AAV is comparable to that of idiopathic ANCA-associated vasculitis and is characterized by cutaneous, renal, and pulmonary involvement, with pulmonary hemorrhage representing the most significant predictor of death.[3] The combination of constitutional and organ-specific symptoms, chronic exposure to hydralazine, presence of multiple antigenicity (i.e., Antihistone antibody, perinuclear ANCA (p-ANCA), or cytoplasmic ANCA (c-ANCA)), and renal biopsy-proven pauci-immune glomerulonephritis with negligible immunofluorescence staining all support the diagnosis of hydralazine-induced AAV.[14-16]

Here, we present a patient with well-established risk factors for drug-induced AAV, including advanced age, female sex, and longstanding hydralazine use (i.e., total daily dose of 150 mg for upwards of 3 years).[4] The onset of acute and rapidly progressive renal failure in combination with characteristic serologic and histological findings, including c-ANCA positivity and focal crescentic glomerulonephritis with minimal immune complex deposition, ultimately, led to the diagnosis of hydralazine-induced AAV. Alternative causes of renal failure, including multiple myeloma, anti-GBM disease, and amyloidosis, were appropriately excluded as well.

The distinction between hydralazine-induced vasculitis and hydralazine-induced lupus presents a diagnostic challenge for the clinician. There is emerging evidence suggesting that hydralazine-induced autoimmunity exists on a spectrum of syndromes, including drug-induced vasculitis and drug-induced lupus (DIL), hallmarked by overlapping clinicopathological features.[3,7,16-18] For example, anti-nuclear antibodies and anti-histone antibodies have been identified in the setting of hydralazine use in 5–8% of cases, without supporting evidence of systemic lupus erythematosus.[7] Moreover, anti-histone antibody positivity is not independently diagnostic of DIL, particularly in the absence of other criteria supporting a diagnosis of

lupus.[3,4,7,13,19-22] Additionally, complement pathway activation and resulting hypocomplementemia have been described in both drug-induced vasculitis and drug-induced lupus.[7,23] In fact, recent studies have demonstrated the existence of complement pathway activation in AAV pathogenesis[24,25] and further connect it with more severe renal disease and poor survival outcomes.[23] This ultimately reinforces the idea that there is little utility in using serology alone to establish or refute a specific diagnosis.[7]

Patients with hydralazine-induced AAV have a comparably more severe clinical course requiring early and aggressive intervention and may present as a rapidly progressive glomerulonephritis, pulmonary hemorrhage, or pulmonary-renal syndrome.[7] One case series of hydralazine-induced vasculitis documented biopsy-proven pauci-immune crescentic glomerulonephritis as well as focal small artery and arteriolar fibrinoid necrosis suggesting that there may be a subacute to chronic component of the disease process, which may not respond to drug cessation alone.[7]

Management of drug-induced vasculitis remains largely individualized, requiring consideration of age, disease severity, presence of comorbidities, and renal function, given the absence of randomized controlled trials evaluating existing treatment strategies.[14] Immediate discontinuation of the offending agent is recommended and may facilitate resolution of mild cases of drug-induced AAV.[14] More aggressive intervention via initiation of immunosuppressive regimens, including corticosteroid therapy with cyclophosphamide or rituximab, should be considered in more severe cases, particularly in the event of pulmonary or renal involvement.[12,14,17,26] Ultimately, further research is necessary to establish optimal treatment strategies for drug-induced vasculitis.

4 | CONCLUSION

Hydralazine-induced AAV is a rare clinical entity characterized by constitutional and organ-specific symptoms, multiple antigenicity, and pauci-immune glomerulonephritis. Here, we highlight the diagnostic challenges of distinguishing hydralazine-induced AAV on the clinical spectrum of hydralazine-associated autoimmunity. It is clear that early identification, immediate drug discontinuation, and aggressive management are critical to improve clinical outcomes.

ACKNOWLEDGMENT

None.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

Dr. Kayle Warren and Dr. Khiem Vu involved in conceptualization, writing—original draft, writing—review and editing, and data curation. Dr. Karandeep Shergill, Dr. Brian Watson, and Dr. Mohamed Faris involved in writing—review and editing.

ETHICAL APPROVAL

This study was approved by the ethics committee.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

DATA AVAILABILITY STATEMENT

Not applicable.

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How to cite this article: Warren K, Vu K, Shergill K, Watson B, Faris M. Rare complication of a commonly used antihypertensive agent: A case of hydralazine-induced ANCA-associated vasculitis presenting as rapidly progressive glomerulonephritis. *Clin Case Rep*. 2022;10:e05411. doi:10.1002/ccr3.5411