

# Hydralazine-Induced ANCA Vasculitis in the Setting of Acute Clostridium Difficile Infection

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## ABSTRACT

We report a rare case of Hydralazine-induced ANCA associated glomerulonephritis with alveolar hemorrhage in the setting of acute Clostridium Difficile Infection. A 71-year-old Caucasian woman with hypertension, who was being treated with hydralazine 25 mg twice a day for six years, presented to the hospital with diarrhea, nausea, vomiting and anemia. She had acute kidney injury and urinalysis showed proteinuria, dysmorphic RBCs, and rare RBC cast. She was found to have Clostridium difficile colitis which was successfully treated. She became hypoxemic; CT scan findings showed bilateral pulmonary infiltrates. Broncho-alveolar lavage was consistent with pulmonary hemorrhage. Kidney biopsy revealed focal segmental necrotizing and diffuse crescentic glomerulonephritis, pauci-immune type (ANCA-associated). Hydralazine was discontinued and the patient was treated with corticosteroids, intravenous cyclophosphamide and plasmapheresis. To our knowledge, hydralazine-associated low complement in the setting of C-diff infection has not been previously reported. This is considered a potentially life-threatening condition requiring immediate discontinuation of the offending medication and expedited lifesaving measures.

**KEYWORDS:** Hydralazine, ANCA Vasculitis, Clostridium Difficile

## INTRODUCTION

Drug-induced vasculitis (DIV) is known to be a form of inflammatory vasculitis in which a specific drug is the causal agent of disease and other forms of vasculitis are disregarded. Small-vessel vasculitis is the most commonly reported form of DIV.<sup>1</sup> Hydralazine-induced vasculitis fall under the category of drug-induced vasculitis, which includes other medications like antibiotics, antithyroid medication, and levamisole-adulterated cocaine. Hydralazine, being a direct vasodilator, is used as an adjuvant treatment for hypertension and heart failure.<sup>2</sup>

## CASE REPORT

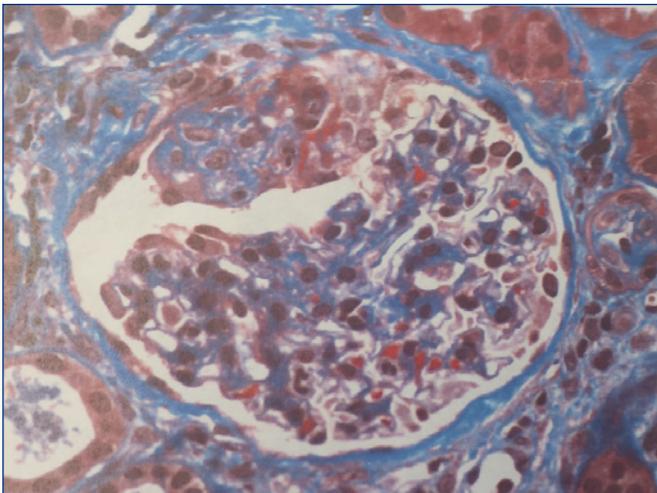
A 71-year-old Caucasian woman with a history of hypertension, gastrointestinal bleeding due to gastric peptic ulcer, anemia, remote history of hemorrhagic cerebrovascular accident, coronary artery disease, hyperlipidemia, and carotid stenosis presented to the hospital because of diarrhea, nausea, and vomiting that had been ongoing for 3 days. On examination her vital signs showed temperature 36.2 deg C, heart rate 110 bpm, respiratory rate 18 breaths/min, blood pressure 202 /98 mmHg, with oxygen saturation of 99% in room air. She was found to have bilateral equal air entry, abdominal tenderness and occult blood positive stools. Her laboratory work-up was remarkable for hemoglobin 7.4 g/dL, white blood cells 4.8 x10<sup>3</sup>/mcL, platelets 146 x10<sup>3</sup>/mcL, creatinine 5.35 mg/dL from baseline 1.27 mg/dL, blood urea nitrogen (BUN) 73 mg/dL. Her urine analysis showed RBC more than 182 /HPF, protein 100 mg/dL and negative for both leukocyte esterase and nitrates. On admission she was believed to have acute kidney injury and worsening of her baseline anemia due to dehydration and inability to have oral intake in the setting of gastrointestinal infection. Further work-up showed that she had clostridium difficile colitis for which she was started on oral Vancomycin. She was continued on her home medications including Doxazosin, Ecotrin, Hydralazine, Lopressor, Losartan and Zocor. Her renal function started to improve slowly to a creatinine of 4.68 mg/dL, while diarrhea subsided. She was

**Figure 1.** Chest CT scan without IV contrast



transfused with 4 packs of red blood cells over a 4-day course until she started to have progressive shortness of breath with hemoptysis on her fifth day of hospitalization. A chest X-ray showed right upper lobe and left lower lobe opacities suggesting newly developed pneumonia with probable left pleural effusion. She was started on Cefepime for hospital-acquired pneumonia; subsequently her kidney function started to get worse with gradual increase of her oxygen requirements. After 48 hours she was requiring BIPAP 100% FiO<sub>2</sub> with her creatinine reaching 6.93 mg/dL at the same time. She was transferred to the medical intensive care unit (MICU) given the rapid deterioration in her clinical status. On admission to the MICU, she had a CT scan of the chest without contrast (**Figure 1**), which showed right upper and middle lobe infiltrates with atelectasis in both lower lobes and the lingular associated with small pleural effusions. A few hours after the transfer to the MICU, she was intubated due to hypoxemic respiratory failure. Given her hemoptysis with worsening of her kidney function, the initial thoughts were that she has pulmonary-renal syndrome. Her Anti-Glomerular Basement Membrane Antibodies were negative < 0.2 unit. She was started on dialysis and autoimmune serology was ordered for suspicion of underlying vasculitis. Her total complement, C3, C4 were 41 unit/ml (normal), 53.8 mg/dl (low), 7.6 mg/dl (low) respectively. Her anti-neutrophilic antibodies were positive in 1:640 dilutions in a homogenous pattern suggesting strong positivity, while her dsDNA, anti-Smith, anti RNP were all negative. Drug-induced vasculitis was suspected and Hydralazine was stopped. Further confirmatory testing showed: P-ANCA positive at 1:80, positive MPO-ANCA 1.5 units, positive anti-histone 2.1 units. The patient had bronchoscopy with broncho-alveolar lavage which showed pulmonary hemorrhage with cytology negative for malignancy. Abundant fungal elements morphologically consistent with *Candida* were identified. A kidney biopsy was then done, which showed focal segmental necrotizing and diffuses crescentic glomerulonephritis (**Figure 2**),

**Figure 2.** Necrotizing crescent on kidney biopsy microscopic exam



pauci-immune type (ANCA-associated/clinical), with mild to moderate activity and moderate chronicity. By the previous results, the patient was confirmed to have drug-induced vasculitis.

The patient was started on pulse steroids with 250mg of methylprednisolone IV q24h on admission to the ICU; this was tapered down to prednisone 50mg oral dose daily which she continued on. She was given cyclophosphamide at 25mg orally twice a day (renal reduced dose), which she continued to take for a month, along with Trimethoprim/Sulfamethoxazole every other day for *Pneumocystis* prophylaxis. Given the renal biopsy results, the patient underwent 5 sessions of plasmapheresis and continued hemodialysis. The patient was successfully extubated with improvement in her respiratory function a few days after cyclophosphamide started. She was discharged to rehab on hemodialysis.

## DISCUSSION

This case presents combined complications of Hydralazine-induced vasculitis that affects both kidney and lung at the same time, precipitated by superimposed systemic infection. A high degree of suspicion is needed for quick intervention with life-saving measures.

The pathogenesis of Hydralazine-induced vasculitis remains unclear. One hypothesis posits that Hydralazine accumulates in neutrophils, binds to myeloperoxidase granules (MPO), and induces cytotoxic products formation that lead to neutrophil apoptosis. The cellular apoptosis in the absence of priming leads to the expression of ANCA antigen on the cellular surface, which can induce the production of antibodies. Binding of these antibodies to the cell membrane may propagate more neutrophils' activation.

The presence of multi-antigenicity in drug-induced vasculitis is explained by the alteration in molecular configuration of MPO granules by Hydralazine, ultimately, inducing the autoimmune response to other neutrophilic proteins (including lactoferrin, elastase, and nuclear antigen), thereby provoking their immunogenicity.<sup>3</sup>

Systemic manifestations include arthralgias, myalgias, hoarseness, and retinal vascular inflammation, with arthralgias and myalgias being the initial presenting symptoms. These symptoms have been reported to occur 6 months to 13 years after initiating treatment with Hydralazine.

Hydralazine-induced cutaneous vasculitic manifestations have included lower extremity palpable purpuric and maculopapular eruptions, and hemorrhagic blisters on the lower legs, arms, trunk, nasal septum, and uvula. Using various search terminologies (e.g., Churg-Strauss syndrome, Goodpasture's syndrome, Henoch-Schönlein purpura, various drugs suspected to induce vasculitis

Patients with pauci-immune GN usually show rapidly progressive glomerulonephritis with features of brown-colored urine, suggesting hematuria.

A 2009 review of the literature found 68 Hydralazine

vasculitis reports (mean duration of drug exposure 4.7 years; mean dose 142 mg/d); kidney disease was common on presentation. Combined pulmonary-renal syndrome with Hydralazine-associated ANCA vasculitis is rare, with only 15 suspected cases in the literature.<sup>5</sup>

Given the overlap in the clinical presentation of Hydralazine-associated SLE and ANCA associated vasculitis (AAV), both diagnoses should be considered.

There is no definitive criteria for the diagnosis of Hydralazine-induced vasculitis. History of exposure to Hydralazine for a long time is one of the strong positive features. Multiple serology work-up, including ANA, ANCA, MPO, with negative dsDNA, Anti GBM, can rule out other causes of renal-pulmonary syndromes.<sup>6</sup> The gold standard diagnostic procedure is kidney biopsy which shows either necrotizing glomerulonephritis with no immune complex deposition or immune complex mediated glomerulonephritis.<sup>7</sup>

Low C4 is usually associated with increased risk of AAV given the slow systemic clearance of the immune complexes. This may get worse with superimposed systemic infection like C-diff infection as was the case with our presenting patient.<sup>9</sup>

Stopping the offending agents is the cornerstone of treatments.

Treatment strategies consist of pulse dose steroids and, according to the severity of the disease, immunosuppressive agents including Cyclophosphamide, Mycophenolate, Methotrexate, Azathioprine or biological agents like Rituximab.<sup>3</sup> Plasma exchange is the last resort in treatment as it prevents progression to end-stage renal disease.<sup>8</sup>

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## Disclosures

None

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