Acute Kidney Injury and Proteinuria in a Man With Hemoptysis
Marco Bonilla and Antonio D. Corona

Clinical Presentation
A 62-year-old man was transferred to our hospital for evaluation and management of hemoptysis and dyspnea that had started 5 days earlier. Review of systems revealed subjective fevers and chills, ankle swelling, and a rash on his feet. His home medications included lisinopril, hydralazine, metoprolol, and levothyroxine. Blood pressure was 142/80 mm Hg, heart rate 87 beats per minute, respiratory rate of 14 per minute, and he was afebrile. Physical examination findings included harsh breath sounds with diffuse crackles, and a papular rash over his ankles.

Initial laboratory data revealed hemoglobin 9.0 g/dL, platelet count of 165 × 10^3/μL, and serum creatinine 2.16 mg/dL (unknown baseline), with normal coagulation studies. Urinalysis was positive for 300 mg/dL protein and blood by dipstick with 50-100 red blood cells per high-power field with about 25% dysmorphic red blood cells. A spot urinary protein-creatinine ratio was 1.1 g/g. Serological workup was positive for 300 mg/dL protein and blood by dipstick with 50-100 red blood cells per high-power field with about 25% dysmorphic red blood cells. A spot urinary protein-creatinine ratio was 1.1 g/g. Serological workup was positive for antinuclear antibody (titer of 1:640), double-stranded DNA antibody (titer of 1:40), antihistone antibodies (4.7 U), perinuclear antineutrophil cytoplasmic antibody (pANCA; titer of 1:2,560), and myeloperoxidase (MPO) and proteinase 3 (PR3) ANCA (104 and 80 U, respectively; reference range for both, ≤20 U). Complement levels were normal. Computed tomography scan of the chest showed multifocal regions of alveolar ground-glass opacities representing pulmonary hemorrhage. A kidney biopsy was performed (Fig 1).

Discussion

What is the differential diagnosis of this patient’s presentation?
Our patient presented with pulmonary-renal syndrome (PRS). The approach to the underlying cause of a PRS relies on a combination of clinical findings, serological results, and histopathology. The differential diagnosis can be classified as (1) anti–glomerular basement membrane (GBM) disease, (2) immune complex–induced disease, (3) ANCA-associated vasculitis (AAV), (4) non-ANCA-associated vasculitis, and (5) idiopathic. A summary of associations is shown in Box 1.

What is the interpretation of the autoimmune panel?
The ANCA serotypes differ in their disease associations. In about three-quarters of cases, granulomatosis with polyangiitis is associated with PR3-ANCA, while microscopic polyangiitis and renal-limited vasculitis are more commonly associated with MPO-ANCA (in about 60% and 80% of patients, respectively). PR3- or MPO-ANCA have been also found in association with chronic infections (endocarditis, hepatitis C, bartonellosis, HIV, tuberculosis). Drug-induced ANCA vasculitis has been shown to induce circulating antibodies against MPO, PR3, elastase, lactoferrin, histone, double-stranded DNA, and cellular nuclear components. The co-expression of MPO and PR3 antibodies, while uncommon, has been reported in drug-induced ANCA vasculitis.

What does the kidney biopsy show?
The kidney biopsy shows fibrinoid necrosis and epithelial hyperplasia and hypertrophy, suggesting early crescent formation. The unaffected segments show glomerular capillary tufts were open without

Figure 1. Kidney biopsy. (A) Hematoxylin-eosin stain. (B) Silver stain. (C) Electron microscopy. Images courtesy of D.A. Savino.
endocapillary hypercellularity. The mesangial regions have segmental widening without hypercellularity (Fig 1A). On silver stain, the GBM does not seem thickened, and is without spikes or pinhole deposits (Fig 1B). Electron microscopy shows no electron-dense deposits (Fig 1C). Immunofluorescence microscopy (not shown) was negative for all immunoreactants, including IgG, IgA, IgM, C1q, C3, albumin, fibrinogen, and both κ and λ immunoglobulin light chains. In summary, the findings of pauci-immune glomerulonephritis with early crescent formation are consistent with AAV.

**What is the cause of this patient’s presentation?**

Hydralazine has been implicated as a rare cause of AAV. Other implicated medications include propylthiouracil, minocycline, phenytoin, penicillamine, allopurinol, and sulfasalazine.

Hydralazine-induced AAV (HAAV) is a rare disease entity and PRS is the most severe clinical presentation. There are several hypothesized pathogenetic mechanisms for HAAV, including apoptosis of the neutrophils in response to hydralazine-MPO binding and formation of autoantibodies. Another theory is that there is an increased expression of neutrophil autoantigens through a reversal of epigenetic silencing of MPO and PR3 and a disruption in tolerance in slow versus fast hepatic acetylators of hydralazine. Identified risk factors include (HLA)-DR4 genotype, slow hepatic acetylators, and the null gene for C4.

**How should this patient be managed?**

HAAV presenting as a PRS is rare, with about 16 suspected cases reported. Pulmonary hemorrhage was the most powerful predictor of death. There is no established, optimal course of treatment; in severe cases like PRS, aggressive immunosuppressive regimens should be considered, including cyclophosphamide with corticosteroids, or rituximab and plasma exchange. Choi et al described one of the largest analyses of drug-associated AAV, with a study of 30 patients. The patients were 12% of 250 new patients with ANCA-positive vasculitis tested during the study period. All 30 patients had MPO antibodies as high as 12 times the median titer of the 250 individuals tested. Ten of the 30 patients had been previously exposed to hydralazine, 9 of whom had evidence of glomerulonephritis. Kidney biopsy in 5 patients revealed pauci-immune necrotizing and crescentic glomerulonephritis. All 10 patients were managed with glucocorticoids and discontinuation of hydralazine; 8 were also treated with cyclophosphamide. Two of the 10 patients died and 3 required hemodialysis (2 of whom had kidney recovery). Seven of the 8 surviving patients had a 6-month follow-up and were found to be in remission.

Our patient was started on induction therapy with corticosteroids and rituximab at a dose of 375 mg per square meter of body surface area on days 1 and 14. He has since been seen in the outpatient setting with stable pulmonary and kidney function. All patients with HAAV should receive education about future drug avoidance and have this noted in their medical record.

**Final Diagnosis**

Pulmonary-renal syndrome secondary to hydralazine-induced ANCA vasculitis.

**Box 1. Differential Diagnosis for Pulmonary-Renal Syndrome**

1) Anti–glomerular basement membrane disease
2) Immune complex disease
   - Systemic lupus erythematosus
   - Systemic sclerosis
   - Rheumatoid arthritis
3) ANCA-associated vasculitis
   - Granulomatosis with polyangiitis
   - Microscopic polyangiitis
   - Eosinophilic granulomatosis with polyangiitis
   - Drug-induced vasculitis
   - Renal–limited vasculitis
4) Non-ANCA-associated vasculitis
   - Henoch-Schönlein purpura
   - Cryoglobulinemia
   - Behçet disease
   - IgA nephropathy
5) Idiopathic

**Quiz**

**Differential Diagnosis for Pulmonary-Renal Syndrome**

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**Patient Protections:** The authors declare that they have obtained consent from the patient reported in this article for publication of the information about him that appears within this Quiz.
References


