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Hydralazine-Induced Anca Vasculitis in a Patient with Congenital Afibrinogenemia

Antonio Gabriel Corona and Harold Michael Szerlip*

Department of Palliative Care, University of Michigan, USA

Introduction

A 62-year-old Caucasian male with an established history of congenital afibrinogenemia presented to the emergency department with blood-tinged sputum. This started five days prior and was associated with progressive shortness of breath. Since the patient had multiple hospitalizations with recurrent hemorrhagic episodes, including frequent hemoptysis which required cryoprecipitate transfusions, his presentation did not raise any suspicions for a new underlying process. He had a history of long-standing hypertension for which he had been taking lisinopril and hydralazine. Review of systems revealed subjective fevers and chills, ankle swelling, and rashes over his lower extremities. Pertinent physical examination findings included harsh breath sounds with diffuse crackles, and a popular rash over his ankles. CT chest showed multifocal regions of alveolar ground glass opacities representing pulmonary hemorrhage. Initial workup included at chest CT scan which revealed multifocal regions of alveolar ground glass opacities representing pulmonary hemorrhage. Laboratory studies showed: hemoglobin 9.0, platelets 165, prothrombin time 15.3, INR 1.3, activated partial thromboplastin time 39.3, and fibrinogen 59. On his metabolic panel, however, he was found to have an elevated serum creatinine of 2.16. He was admitted to the hospital under the care of the medical team, and was managed with oxygen supplementation via nasal cannula and intravenous fluids.

The patient remained hemodynamically stable throughout the subsequent hospital days, but his oxygen requirement did not improve. Additionally, daily laboratory studies were obtained to monitor his renal function, but his creatinine did not improve with volume resuscitation. A repeat chest X-ray did not show any improvement of his patchy, homogenous opacities, bilaterally. A bronchoalveolar lavage the medical team decided to consult Nephrology for further evaluation and management.

Urine studies were ordered, including a urinalysis which revealed 2+ protein, 3+ blood, and 50-100 RBC's/HPF. Spot urine protein: creatinine was 1.1 gms/gm. A renal biopsy was planned, but due to the patient's tendency to bleed, this was delayed after some careful planning. Additional serologic workup was ordered and was positive for: ANA 1:640, dsDNA 1:40, Histone antibodies 4.7 units, pANCA 1:2560, MPO and PR3 antibodies. C3 and C4 were normal. Anti-GBM was negative. Eventually, a renal biopsy was performed after the patient's fibrinogen levels were corrected with cryoprecipitate infusions.

What is the interpretation of the autoimmune panel?

Drug-induced ANCA vasculitis has been shown to induce circulating antibodies against Myeloperoxidase (MPO), proteinase 3 (PR3), elastase, lactoferrin, histone, double-stranded DNA, and against cellular nuclear components [1] [2]. The co-expression of MPO and PR3 antibodies, while uncommon, has been reported in drug-induced ANCA vasculitis. Combined positivity is rarely associated with other etiologies [3]. Hydralazine is a commonly implicated medication which causes drug-induced ANCA vasculitis [4]. Other medications include: propylthiouracil, minocycline, phenytoin, penicillamine, allopurinol and sulfasalazine.

Hydralazine- induced ANCA Vasculitis (HAAV) is a rare disease entity [5]. The pathogenesis of HAAV is thought to be from drug accumulation inside neutrophils, inducing cellular apoptosis and formation of cytotoxic products. This subsequently stimulates the formation of circulating antibodies which are present in HAAV [1]. These antibodies are hypothesized to contribute to the disease by itself or by an interaction with an infectious agent. Identified risk factors include: (HLA)-DR4 genotype, slow hepatic acetylators, and the null gene for C4 [5].

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Correspondence:
Antonio Gabriel Corona, Department of Palliative Care, University of Michigan, American Board of Medical Specialties, USA,
E-mail: coronaa@med.umich.edu

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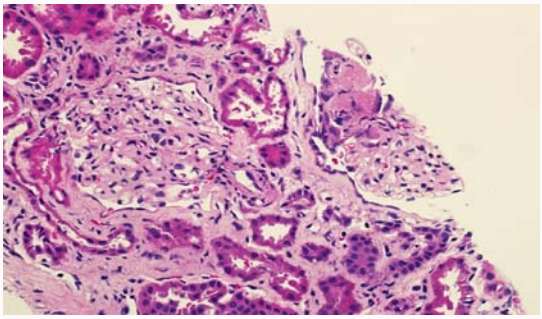

Figure 1: What is the interpretation of the autoimmune panel?

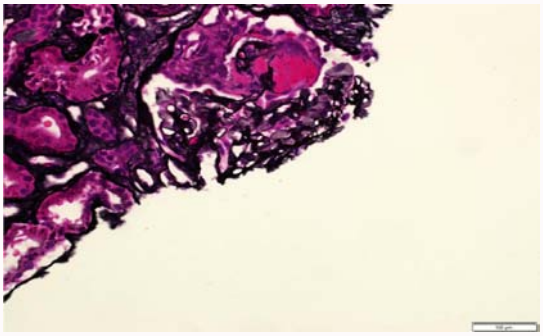

Figure 2: What does the kidney biopsy show?

What does the kidney biopsy show?

The kidney biopsy shows focal fibrinoid necrosis with crescent formation. The unaffected segments show patent glomerular capillary without endocapillary hypercellularity. The mesangial regions have segmental widening, also without hypercellularity (Figure 1). On silver stain, the glomerular basement membrane does not seem thickened, and is without spikes or pinhole deposits (Figure 2). Electron microscopy shows no electron-dense deposits. Immunofluorescence microscopy (not shown) was negative for all immunoreactants, including antibodies IgG, IgA, IgM, C1q, C3, albumin, fibrinogen, and both kappa and lambda immunoglobulin light chains. In summary, the findings of pauci-immune glomerulonephritis with early crescent formation are consistent with ANCA vasculitis (Figure 3).

What is the ideal management of this patient?

The early withdrawal of the offending drug is the first step in management. Immunosuppression is generally recommended for HAAV due to afulminant disease course which affects the lung and kidneys [6]. 13 reported cases of HAAV resenting as pulmonary-renal syndrome were described in a review in 2014, wherein only 7 of the 13 patients survived. Pulmonary hemorrhage was the most powerful predictor of death [1]. There is no established, optimal course of treatment, but some case reports have reported amelioration of the disease with glucocorticoids and cyclophosphamide [6]. Another case report details good response with glucocorticoids and rituximab [7].

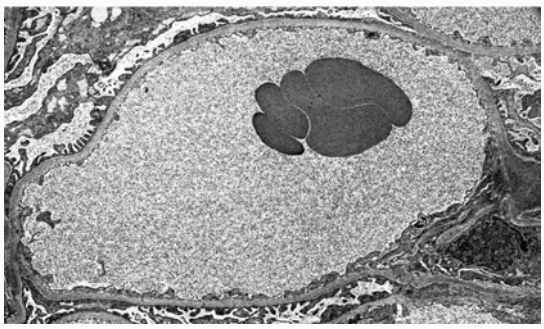

Figure 3: What is the ideal management of this patient?

In our case, due to our patient's active bleeding and low fibrinogen levels, plasma exchange was deferred. He 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 improved and stable pulmonary and renal function.

Final Diagnosis

Pulmonary-renal syndrome secondary to hydralazine-induced ANCA vasculitis, managed with hydralazine withdrawal and immunosuppressive therapy with corticosteroid and rituximab.

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