Acute viral infection and Drug-induced vasculitis: a relationship that needs to be explored in the current pandemic

Hari Kandukuri MD, Anan Haija MD, Jay Shastri DO
Atlantic Regional Medical Center, 1925 Pacific Avenue, Atlantic City, New Jersey 08401

Introduction:
Numerous studies have shown a causal relationship between certain drugs and anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis. Of these, hydralazine is notorious for causing pauci-immune crescentic glomerulonephritis (PICG) presenting as rapidly progressive glomerulonephritis with hematuria, proteinuria, and renal insufficiency. Drug-induced vasculitis can also have other systemic manifestations including fever, palpable purpura, polyarthralgia, and pulmonary hemorrhage. It is hypothesized that hydralazine binds to intracellular myeloperoxidase granules leading to the synthesis of cytotoxic products and subsequent neutrophil apoptosis. During the apoptotic process, the antigen can be expressed on the cell surface leading to the formation of ANCA. Drug-induced vasculitis can be discriminated from idiopathic vasculitis with the presence of multi-antigenicity where antibodies are formed against other neutrophilic proteins including lactoferrin, nuclear antigen, and elastase. A very high myeloperoxidase (MPO)-ANCA titer is another important distinguishing feature. Infections such as Epstein Barr virus (EBV) have also been linked to ANCA associated vasculitis likely due to an interaction between EBV infected B cells and autoreactive T cells.

Case Presentation:
We report a case of a 66-year-old Caucasian male with a history of coronary artery disease, hypertension, chronic obstructive pulmonary disease, and non-insulin dependent diabetes mellitus type 2, who presented with generalized weakness with laboratory values evident for elevated creatinine, proteinuria, microscopic hematuria, and pancytopenia. The patient was being treated for hypertension with hydralazine for over three years which was discontinued outpatient before his admission. Laboratory evaluation revealed negative tests for hepatitis panel, HIV, but an elevated EBV IgM and IgG. This indicated an active EBV infection, despite no symptoms of infectious mononucleosis. Serum protein electrophoresis showed an M spike with a small band of restricted mobility and normal urine protein electrophoresis. Serum immunofixation revealed polyclonal gammopathy with IgM, but normal urine immunofixation. Autoimmune workup showed a positive anti-nuclear antibody (ANA) with a homogenous pattern, normal complements, elevated perinuclear-ANCA (p-ANCA), myeloperoxidase (MPO), and Proteinase 3(PR-3) antibodies. Other autoimmune diseases were excluded with negative cytoplasmic-ANCA (c-ANCA), rheumatoid factor, anti-double-stranded DNA, anti-glomerular basement membrane, anti-smooth muscle antibody, anti-smith, anti-SSA, anti-SSB, scleroderma, anti-cyclic citrullinated peptide, anti-chromatin, atypical p-ANCA antibodies. Ultrasound of the kidneys showed normal cortical thickness and echogenicity. The patient underwent kidney biopsy revealing segmental necrotizing glomerulonephritis with focal crescents consistent with pauci-immune ANCA vasculitis. The patient also had a bone marrow biopsy for pancytopenia which was negative for neoplasm or lymphoproliferative disorder. The patient’s glomerular filtration rate, p-ANCA, and MPO titers failed to improve despite completing treatment with pulse dose steroids in addition to rituximab and plasma exchange. He became dependent on hemodialysis and was continued on maintenance therapy with azathioprine outpatient.

Conclusion:
It is imperative to recognize the relationship between certain medications and ANCA vasculitis earlier in the presentation as withdrawing the offending agent typically shows an improved response. The elevated MPO antibody titers, kidney biopsy findings of PICG, and a known history of hydralazine exposure are highly suggestive of hydralazine associated ANCA vasculitis in this patient. However, the confounding factor was also an acute EBV
infection. There are few cases in the literature where an active viral infection has been associated with ANCA vasculitis. This case represents a very rare scenario where an active EBV infection can itself precipitate drug-induced vasculitis, a relationship that needs to be explored. This begs the question if we should refrain from medications such as hydralazine that are known to cause drug-induced vasculitis in the setting of acute viral infections in the current pandemic.