An intriguing case of anemia and renal failure

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ABSTRACT

Hydralazine-induced vasculitis is an established autoimmune entity but widely underdiagnosed despite its initial description in 1953. Hydralazine-induced lupus occurs in 5% to 10% of patients and is characterized by fever, arthralgias, rash, anemia, leukopenia, and positive antinuclear antibodies. Renal involvement is rare in drug-induced systemic lupus erythematosus but can occur. Hydralazine may also be associated with an antineutrophil cytoplasmic antibody to complicate the diagnostic evaluation. There are no definitive diagnostic criteria for hydralazine-induced lupus, and diagnosis relies on chronic exposure to high doses of hydralazine with positive antinuclear and antihistone antibodies and classical histopathological findings. We describe a 48-year-old man with fatigue, anemia, and renal failure from hydralazine-mediated lupus with concomitant antineutrophil cytoplasmic antibodies and highlight the importance of medication history and scrupulous interpretation of serologies and biopsy for diagnosis and management of this familiar yet underrecognized disease. Clinicians should analyze the risk of hydralazine-induced adverse effects before initiating therapy and continue clinical vigilance while patients are on hydralazine.

KEYWORDS ANCA vasculitis; anemia; hydralazine; lupus nephritis; renal failure

Hydralazine-induced lupus was first reported in 1953 and occurs in 5% to 10% of patients.¹ Though immune complex nephritis is the hallmark of systemic lupus erythematosus, it is uncommon in drug-instigated lupus. Hydralazine-associated autoimmunity can lead to both antinuclear antibody (ANA)–positive lupus and antineutrophil cytoplasmic antibody (ANCA) vasculitis, and clinical distinction can be daunting without renal biopsy. We present a rare case of crescentic immune complex trapping lupus nephritis from hydralazine with cutaneous myeloperoxidase and proteinase 3 antibodies.

CASE REPORT

A 48-year-old man presented with fatigue, dyspnea, and dizziness for 4 weeks and had a known history of hypertension, heart failure, and depression. Current medications included amlodipine 10 mg, carvedilol 50 mg, spironolactone 25 mg, citalopram 20 mg, and hydralazine 300 mg daily. He had hypertension, pallor, and pedal edema upon examination. Initial laboratory values included a hemoglobin of 3.4 g/dL; white blood cell count, $3 \times 10^9/L$; platelet count, $268 \times 10^9/L$; blood urea nitrogen, 77 mg/dL; and creatinine, 7.39 mg/dL, with

lymphopenia. Urine studies showed hematuria and 13 g proteinuria. Hemolytic markers, serum protein electrophoresis, hepatitis profile, urine drug screen, and thyroid tests were unrevealing.

A lupus anticoagulant test was positive with negative anticardiolipin and anti-beta-2 glycoprotein I antibodies. Serological evaluation divulged positive ANA 1:2560 with a homogenous pattern but negative anti-DS-DNA and extractable nuclear antigen antibody panels. Rheumatoid factor and complements were normal, but ANCA was positive at 1:640 with a perinuclear anti-neutrophil cytoplasmic antibodies pattern, and both myeloperoxidase and proteinase 3 antibodies were significantly elevated. The patient was appropriately treated with blood transfusions and initiated dialysis for uremia.

A renal biopsy for further evaluation of renal failure demonstrated diffuse proliferative immune complex trapping glomerulonephritis with crescent formation (35% of glomeruli show crescent formation) (*Figure 1*). The inflammatory lesion showed a striking “full house” immunofluorescence profile and abundant intracapillary electron dense deposits without vasculitis. Antihistone antibody eventually came back as significantly elevated at 5.4 (reference range, 0–0.9).

Our patient was diagnosed with hydralazine-induced lupus based on long-term use of hydralazine with positive

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Figure 1. Renal biopsy. (a) Light microscopy showing glomerulus with endocapillary proliferation with crescent formation. (b) Immunofluorescence showing "full house" pattern.

ANA, antihistone antibody, and biopsy consistent with lupus. Hydralazine was discontinued, and he was treated with steroids and cyclophosphamide for 12 weeks. Renal function initially improved but he relapsed with further deterioration and remained dialysis dependent.

DISCUSSION

Hydralazine-induced lupus is an unrecognized yet distinct autoimmune disease with a incidence of 5.4% with 100 mg daily and 10.4% with 200 mg daily.² Clinical manifestations include insidious onset of fever, rash, arthralgia, myalgia, fatigue, and weight loss. Renal involvement is uncommon but has been reported. A few subsets of patients can concurrently be ANCA positive, and some rarely have both myeloperoxidase and proteinase 3 antibodies.^{3,4}

The diagnosis of hydralazine-induced lupus nephritis can be challenging in the setting of associated comorbidities. Serologies and renal biopsy often aid the diagnosis in these complex situations. Risk factors include age, female sex, white race, slow acetylator phenotype, human leukocyte antigen DR4, and high doses and longer duration of hydralazine.⁵ However, acute low doses have also been reported to induce lupus.⁶ Antihistone antibodies are present in >90% of these patients. Hydralazine-induced apoptosis of neutrophils and resultant exposure of antigens as well as interference with neutrophils' self-tolerance and decreased T cell DNA methylation are some of the plausible clues to autoimmunity.⁷ Hydralazine is primarily metabolized in the liver by acetylation, and slow acetylators accumulate excessive reactive metabolites that can induce ANA in 50% to 60% of the patients.⁸ The mainstay of treatment is withdrawal of hydralazine; however, immunosuppression is often needed.

The presence of unexplained systemic manifestations with concomitant multiple antibodies is the hallmark for drug-induced enhanced autoimmunity. Exposure to hydralazine should be sought in patients presenting with autoimmune and vasculitis symptoms. Our case adds to the growing number of cases with hydralazine-induced lupus and associated ANCA

positivity. Careful clinical risk assessment should be done before initiating hydralazine, and efforts should be maintained to avoid high doses. Clinical surveillance for vasculitis and lupus is warranted for all patients taking hydralazine. Early recognition and cessation of the culprit drug is crucial, because renal prognosis can be inferior despite immunosuppressive therapy.⁹

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