



CASE REPORT

Hydralazine Induced Lupus-Like Syndrome

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INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disorder with multiorgan involvement and variable manifestations. The etiology of SLE remains unknown. However, a different presentation of lupus erythematosus due to certain drugs such as hydralazine¹, procainamide¹, and minocycline² has long been recognized. The first reported case of hydralazine leading to Drug-induced Lupus Erythematosus (DILE) was published in 1953.³ Since then, this association has been well established in the medical literature. However, as hydralazine is used less frequently, the incidence of DILE due to hydralazine and the recognition of this association among clinicians have diminished. This case report and review revisits this association and reminds the clinicians to consider DILE when evaluating patients with unusual manifestations mimicking a connective tissue disease.

CASE REPORT

A 68-year-old Caucasian male with a past medical history significant for gastroesophageal reflux disease, hypertension, obstructive sleep apnea, obesity, chronic obstructive pulmonary disease (COPD), and hypothyroidism had developed bilateral hand arthralgia intermittently for several years. He presented with myalgia and fatigue in late 2013 and by late January 2014, his symptoms progressed with diffuse myalgia, polyarthralgia, fatigue, poor appetite, nocturnal low grade fevers, as well as unintentional weight loss of about 30 pounds.

Subsequently, he developed pruritic dermatitis and dyspnea out of proportion to his baseline COPD. His wife also noticed onset of poor memory. He experienced two episodes of asymptomatic hematuria without any known history of nephrolithiasis. He was admitted to an outside hospital for progressive dyspnea, fatigue, myalgia, polyarthralgia, hematuria, and the dermatitis on his upper back. Physical examination revealed a

matology, neurology, infectious disease, and rheumatology. Basic labs revealed leukopenia and anemia. He had an elevated erythrocyte sedimentation rate of 97 and C-reactive protein of 212 mg/L with normal creatinine kinase and aldolase. Infectious disease work-up included negative Epstein-Barr virus, Lyme disease, human herpesvirus 6, cytomegalovirus, and human immunodeficiency virus. Cerebrospinal fluid analysis was negative including for cryptococcus, toxoplasma, and viral studies.

Computed tomography scan (CT) of the chest, abdomen, and pelvis was negative except for splenomegaly. Bone marrow biopsy was unrevealing with normal cytogenetics. The right upper back skin biopsy was non-diagnostic as it did not identify eosinophils or other specific features of connective tissue disease but the findings were thought to be compatible with a "drug eruption or viral exanthem".

Since a clear diagnosis was not made, he established care at our tertiary institution. He was seen in the outpatient hematology and general internal medicine clinics after which he was referred to the rheumatology clinic. His medication list included hydralazine that was started about four years prior for treatment of hypertension. Prior to being seen by the physicians at University of Kansas Hospital, he developed a new symmetrical erythematous, macular, small, and round dermatitis of hands and anterior thighs bilaterally. His laboratory evaluation was significant for a persistent leukopenia (white blood cells of $2.03 \times 10^9/L$) and anemia (hemoglobin of 9.8 mg/dL). The renal and liver functions, creatine kinase, and lactate dehydrogenase were normal. The antinuclear antibody (ANA) was elevated at 1:640 in a homogenous pattern. The histone antibody was elevated. The anti-phospholipid antibodies were abnormal including elevated hexagonal lupus, Dilute Russell Viper Venom Test, IgM anti-cardiolipin antibody, and IgM Beta 2-glycoprotein 1. His ds-DNA, Anti-Smith, Anti-SSA, Anti-SSB, Anti-RNP, Rheumatoid Factor, Anti-Centromere, Anti-SCL-70, Anti-CCP IgG, Anti-Jo-1 were normal. His Complement C3 and C4 were within normal limits.

A chest x-ray showed a small left pleural effusion. Joint survey x-rays showed degenerative changes of the cervical spine, right knee, and bilateral hands. A repeat CT showed splenic auto-infarction. He was diagnosed with Drug-induced Lupus Erythematosus (DILE). At that time, he was prescribed a prednisone taper and hydralazine was discontinued. Two months after discontinuation of hydralazine, he had a negative ANA and a decreasing anti-histone antibody. The anti-phospholipid antibody panel was negative.

DISCUSSION

This 68-year-old male patient's symptoms and clinical findings including laboratory abnormalities began several years after he first took hydralazine and resolved following its discontinuation. DILE is a diagnosis of exclusion that is confirmed when the patient improves once the culprit drug is discontinued. A unique aspect of this case was the length of time after which the patient developed DILE while on a low dose of hydralazine. Usually, DILE develops on higher doses of hydralazine (greater than 200 mg/day) and sooner than was seen on our case.⁴

The incidence of the lupus syndrome induced by hydralazine was determined in a longitudinal study of 281 patients starting hydralazine for hypertension over a 51-month period.⁴ After three years of treatment with hydralazine, the incidence of the lupus syndrome was 6.7% (95% confidence limits 3.2-10.2%). The incidence was dose dependent, with no cases recorded in patients taking 50 mg daily and incidences of 5.4% with 100 mg daily and of 10.4% with 200 mg daily. Our patient had been prescribed hydralazine 75 mg for hypertension before presenting with lupus-like symptoms. To our knowledge, there have been no published case reports of DILE due to hydralazine at a dose of 75 mg daily.

Risk factors for development of hydralazine DILE include doses greater than 200 mg/day, female gender, slow hepatic acetylation, and immunogenetic factors.^{4,7} Clinical manifestations of DILE include fever, fatigue, myalgia, dermatitis, arthralgia, and serositis.⁸ DILE is generally less severe without significant systemic involvement, such as nephritis. Both idiopathic systemic lupus erythematosus (SLE) and DILE develop elevated ANA; but anti-Smith antibody (SM), ds-DNA, and hypocomplementemia rarely are observed in DILE as compared to SLE.

Anti-histone antibodies are present in more than 95 percent of patients with DILE.⁹ Anti-histone antibodies can also be seen in up to 80% of patients with idiopathic SLE, however, patients with idiopathic SLE also form a variety of other autoantibodies, including anti-Smith antibody or ds-DNA antibody, which are less common in drug-induced lupus. Management of DILE consists of discontinuation of the offending agent along with supportive care and short term therapy of any specific manifestations with medications such as oral prednisone until symptomatic and clinical resolution.

CONCLUSION

Prompt recognition of DILE is important in evaluation of patients with lupus like syndrome while on medications such as hydralazine. Distinguishing idiopathic SLE from DILE is very important as the intensity and duration of therapy and prognosis is different between the two. Hence, patients should be monitored closely when initiating hydralazine.

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