

Unexplained Chronic Skin Lesions in an Older Male! Consider The Iatrogenic Factor: Hydralazine Induced Cutaneous Lupus!

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Case Report

What could be the possible etiology for chronic discoid dermal lesions in an older adult with hypertension under one's care? A seventy-nine-year-old male with uncontrolled hypertension, coronary artery disease, hyperlipidemia and status / post radiotherapy for prostate cancer (now in remission) presented to the geriatrics clinic with skin lesions over the extremities and trunk. The lesions apparently persisted for months; they were annular, circumscribed, 1-2 inches in diameter and scaly. The patient was on multiple medications; a cardiologist whom he visited had prescribed hydralazine for hypertension, initially 25 mg thrice daily, increasing the dose to 100 mg thrice daily, a dose continued for 7 years. He was also on losartan for hypertension. Dermatology evaluation was requested; skin biopsy suggested nummular eczema, erythema annular centrifugum or purpuric spongiform dermatitis, with eosinophils. The patient did not manifest lung or pulmonary disease; he had chronic kidney disease, a consequence of severe hypertension and obstructive uropathy. The skin lesions did not improve with topical steroid creams prescribed by the dermatologist. The patient continued to use the cream intermittently, however, until the present.

In the absence of improvement, as a remote possibility, we requested testing for anti-nuclear antibodies; to our surprise, the test was positive at 1:160, homogenous pattern. Follow up tests included anti-double stranded DNA, positive at 13 (negative <4), histone antibody 1.4 (N: <1) and negative anti-Smith antibody. Testing for syphilis was negative. A diagnosis of cutaneous drug induced lupus (DIL) secondary to hydralazine became a consideration. Hydralazine was discontinued and the discoid skin lesions healed slowly but surely in about a year; the lesions continued to heal and were much better 2 years later; of relevance, no new lesions appeared (Figure 1).



Figure 1: Healed skin lesions, back and ankle, following discontinuation of hydralazine.

When hydralazine was discontinued, for control of hypertension, amlodipine was added. He was previously also on losartan and a thiazide; both drugs were continued.

A diagnosis of DIL requires a temporal relationship between drug administration and development of manifestations. Our patient was on high dose hydralazine for 7 years. To justify a diagnosis of cutaneous DIL, there should be no pre-existing lupus [1]. Follow up testing in our patient 2 years after diagnosis revealed the ANA titer to be lower at 1:80 and the histone antibody also lower at 1.0.

The case illustrates the need to consider an iatrogenic element as the etiology of unexplained medical disorders, even dermatological illness, which in this case manifested as chronic discoid lesions, bothersome to the patient. The fact that systemic lupus is rare in males undoubtedly played a role in lowering the initial consideration for DIL in our patient. In most cases of

DIL, ANA is positive [2-3]. Antibody to double stranded DNA is common in idiopathic lupus but rare in DIL; yet they were positive in our male patient. Although anti-histone antibodies are distinct for DIL, they are not necessarily always present; anti-histone antibodies occur in over 95% of those on hydralazine, procainamide, chlorpromazine and quinidine, resolving with drug discontinuation. Interestingly, the most commonly incriminated drugs for cutaneous lupus in a European study were proton pump inhibitors, thiazides, antifungals, chemotherapeutics, statins and antiepileptic agents [4]. Currently at least 118 drugs have been associated with DIL [5].

The mechanisms involved as to how drugs with heterogenous chemical structures and function lead to autoimmunity are only partially understood; they may relate to abnormal oxidative drug metabolism, innate immune responses, neutrophil responses, neutrophil extracellular trap formation and exposure of auto-antigens [6,7]. Clinical disease occurs in 5-10% of those on hydralazine; even doses of 100 mg daily may be causative, especially in slow acetylators. The dosage of hydralazine when lupus is induced ranges from 100 to 1600 mg. Risk factors for hydralazine induced lupus include white race, cumulative dose, female sex and the DR4 human leukocyte antigen [8]. Hydralazine induced DIL may be complicated by pericardial effusion, renal, pleural and lung disease [8].

A recent study of 2380 patients with cutaneous lupus demonstrated a female: male ratio of 4:1 [9]. As discussed earlier, this may be one reason DIL was not an early consideration by the dermatologist in our older male patient. DIL is a lupus variant with predominant skin involvement that resolves with drug discontinuation. The cutaneous features are widespread and distinctive in DIL compared to idiopathic cutaneous lupus erythematosus [3]. Dermatitis is in reality a less common manifestation of DIL, and typically involves the lower extremities, contrary to idiopathic lupus [8]. Nonspecific dermal lesions in DIL include erythema nodosum and purpura [8]. (Table 1) illustrates some of the features of DIL, in contrast to classic SLE.

Features of Drug Induced Lupus	
Disorder seen largely in older adults	
Although SLE is predominant in females, DIL must be a consideration regardless of sex	
More common in slow acetylators	
Arthralgias may be a manifestation	
Fever seen in fewer than half the cases	
Bullous lesions may be a feature	
ANA is positive in the majority	
Anti dsDNA is seldom positive	
Anti-histone antibodies are positive, suggesting the diagnosis	

DIL manifests 6 months or later following exposure to the offending agent
Lesions reverse upon withdrawal of offending agent
Procainamide, hydralazine, quinidine, TNF α inhibitors most commonly associated with DIL
Manifestations of DIL and SLE may overlap
For a diagnosis of DIL, there should be no pre-existing lupus

Table 1: Features of Drug Induced Lupus [1-6].

A patient on hydralazine with dermal lesions must receive consideration for DIL, as the adverse dermatological effects are reversible. Our case demonstrates that dermatological lesions of uncertain etiology in older adults require a meticulous review of all medications (and supplements) as possibly etiology for DIL. Vigilance is prudent in today's era of polypharmacy and related adverse drug effects. At times, deprescribing of medications may be the answer! [10].

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