A simultaneous presentation of drug-induced lupus with drug-induced ANCA vasculitis secondary to hydralazine use in a patient with sarcoidosis

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ABSTRACT

Frequently used in the management of hypertension and heart failure, hydralazine is associated with the development of adverse rheumatologic side effects. The authors highlight a unique case of drug-induced lupus and drug-induced anti-neutrophil cytoplasmic antibody (ANCA) vasculitis from hydralazine use in a 50-year-old man with sarcoidosis and hypertension.

KEYWORDS Drug-induced anti-neutrophil cytoplasmic antibody vasculitis; drug-induced lupus; hydralazine; leukocytoclastic vasculitis

Drug-induced lupus (DIL) is a recognized rheumatologic adverse effect of hydralazine. DIL typically manifests with fever, polyarthralgias, pleurisy, and/or pericarditis. Various skin findings have been reported, including nonspecific erythematous or urticarial lesions, acrocyanosis, discoid lupus, and malar rash.^{1,2} In contrast to systemic lupus erythematosus, DIL has a less severe disease course and resolves with cessation of the offending drug.³ Hydralazine-induced anti-neutrophil cytoplasmic antibody (ANCA) vasculitis may present with leukocytoclastic vasculitis, pulmonary interstitial infiltrates, pauci-immune glomerulonephritis, and elevated ANCA titers.² Due to the diverse clinical presentations, varying duration of hydralazine use prior to disease onset, infrequent cases, and limited understanding of these drug-induced disorders, the diagnosis of DIL or ANCA drug-induced vasculitis (ANCA DIV) can be challenging. We report a case of a patient with sarcoidosis who developed DIL with concomitant ANCA DIV secondary to hydralazine.

CASE STUDY

A 50-year-old man with pulmonary sarcoidosis, sarcoid parotitis, and a history of end-stage renal disease secondary to uncontrolled diabetes mellitus and hypertension presented with 2 days of oral ulcers and vesiculobullous necrotic lesions

on his fingertips, forearms, posterior neck, and lateral nasal bridge, which ruptured into shallow ulcers (*Figure 1*). He had been taking hydralazine 50 mg twice daily for 1 year. He had no alopecia, malar rash, photosensitivity, joint pain, epistaxis, history of sinus disease, asthma, dyspnea, cough, hemoptysis, new paresthesia, or wrist or foot drop. He had no history of substance abuse and no family history of rheumatologic disease. A transthoracic echocardiogram showed no valvular vegetations suggestive of endocarditis. All blood cultures were negative. Viral studies including Cocksackie B1–2, types 2, 4, 7, 9, 10, 16, adenovirus, and human immunodeficiency virus were negative. Skin biopsy with the specimen sent for bacterial and fungal organisms, acid-fast bacilli, and herpes viruses was also unrevealing. Biopsy of the neck lesion revealed leukocytoclastic vasculitis (*Figure 2*). Rheumatologic laboratory findings are included in *Table 1*. The patient's oral ulcers, positive antinuclear antibody (ANA), anti-histone antibody, thrombocytopenia and hypocomplementemia, absence of prior diagnosis of systemic lupus erythematosus, and clinical improvement upon hydralazine cessation were all consistent with DIL. Furthermore, his extensive cutaneous leukocytoclastic vasculitis and positive serology for ANCA and anti-proteinase-3 were features consistent with ANCA DIV. In addition to discontinuation of hydralazine, the patient received

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Received October 1, 2018; Revised January 4, 2019; Accepted January 10, 2019.

Figure 1. (a, b) Bilateral ulcerations lateral to nasal bridge that were vesiculobullous on initial presentation. (c) Multiple ulcerations and erythema on the palate (circled) and posterior oropharynx (not pictured). (d, e) Vesiculobullous and necrotic lesions on palmar and dorsal fingertips bilaterally. (f) Vesiculobullous lesions on the back of the patient's neck after skin biopsy. These images may not reflect the severity at initial presentation, because they were taken 1 week after cessation of hydralazine and initiation of steroid treatment.

Figure 2. Hematoxylin and eosin–stained sections show vessel wall infiltration by lymphocytes and neutrophils and necrosis with surrounding inflammation and edema (20× original objective magnification).

intravenous dexamethasone and transitioned to a 3-month prednisone taper with resolution of symptoms. The patient remained asymptomatic at 1-year follow-up.

DISCUSSION

DIL and ANCA DIV caused by hydralazine have been reported in the medical literature. This case is distinct in that our patient with sarcoidosis had a simultaneous presentation of DIL with ANCA DIV, adding complexity to an already diagnostically challenging case.

There is no consensus on definitive diagnostic criteria for ANCA DIV. Clinical manifestations may also include non-specific constitutional symptoms, arthralgias, pulmonary-renal syndrome, mucosal ulcerations of the aerodigestive tract, and a wide spectrum of skin lesions (*Table 2*).^{1,4–11} Similarities between skin eruptions caused by hydralazine-induced ANCA vasculitis and *Streptococcus pyogenes* have been reported, making it difficult to discern between an autoimmune and an infectious etiology of cutaneous findings.⁸ Acute viral infections can also cause mucosal ulcerations. However, our patient underwent an extensive infectious workup that was unrevealing. It is important to note that major end-organ involvement in ANCA DIV, such as pulmonary-renal syndrome, can carry significant morbidity and mortality despite immunosuppressive therapy.¹²

Table 1. Patient's laboratory findings

Variables	Results	Reference value
ANA	1:320 homogenous	<1:20
C3 (mg/L)	105	79–152
C4 (mg/L)	10.6	19.6–55.9
CRP (mg/L)	1.2	<0.7
ESR (mm/hour)	7.0	0–20
CK (IU/L)	156.0	60–174
ANCA	cANCA <1:20 pANCA 1:320	<1:20 <1:20
Anti-MPO (U)	9.0	0.0–9.0
Cryoglobulin	Positive repeated negative	Negative
Anti-dsDNA (IU/ml)	2.0	Negative
Anti-RNP (U)	0.3	<20
Anti-SS-A (U)	<0.2	<1
Anti-histone (U)	2.9	<1
Anti-proteinase-3 (U)	>100.0	0.0–3.5
Anti-cardiolipin IgM	21	0–12 normal 15–20 indeterminate >20–80 low–medium positive

ANA indicates antinuclear antibody; ANCA, anti-neutrophil cytoplasmic antibody; anti-dsDNA, anti-double stranded DNA; anti-MPO, anti-myeloperoxidase; anti-RNP, anti-ribonucleoprotein; anti-SS-A, anti-Sjögren's syndrome-related antigen A; C3, complement component 3; C4, complement component 4; CK, creatinine kinase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

Similar to the lack of consensus on the diagnosis of ANCA DIV, the diagnostic criteria for DIL have also been debated. DIL, which often does not fulfill the classic diagnostic criteria for idiopathic systemic lupus erythematosus, has a less severe disease course typically without major end-organ involvement.

The pathogenesis of hydralazine-induced ANCA vasculitis and DIL is not fully understood. It has been postulated that hydralazine accumulates within neutrophils binding with myeloperoxidase, leading to formation of cytotoxic products and neutrophil cell death. As a result, antigens typically sequestered are released and recognized by antigen-presenting cells. These antigens subsequently activate T and B cells, leading to the formation of antibodies such as ANCA and ANA. Additionally, it has been reported that hydralazine affects neutrophil extracellular traps, also causing exposure of sequestered antigens, triggering an autoimmune response.^{2,9,13,14}

Given similar features, it has been reported that DIL and ANCA DIV may represent one disease spectrum.² Our patient demonstrated overlapping features of both drug-induced rheumatologic disorders. ANCA DIV was evidenced by extensive cutaneous leukocytoclastic vasculitis, positive ANCA, and anti-proteinase-3 antibody. DIL was manifested by oral ulcers, positive ANA and anti-histone antibody, thrombocytopenia, and hypocomplementemia. It has been reported that overlapping presentations of DIL with ANCA DIV have been characterized by the presence of high ANCA and ANA titers, positive anti-histone antibody, and positive anti-phospholipid antibodies, as seen in our patient. It has

Table 2. Case reports that demonstrated cutaneous involvement and skin biopsy results in patients with hydralazine-induced ANCA vasculitis

Source	Total daily hydralazine dosage × duration in years	Positive serology	Cutaneous involvement	Skin biopsy
Bernstein et al ¹⁰	250 mg × 1	ANA 1/2560, ESR 33 mm/h	Ulcerating cutaneous vasculitis in extremities	Vasculitis, fibrinoid necrosis IgM, fibrin and C3 deposits
	100 mg × 2	ANA 1/640, ESR 69 mm/h	Superficial ulcerating blisters to extremities	Vasculitis, fibrinoid necrosis of dermal capillaries
Peacock and Weatherall ¹¹	75 mg × 7	ANA 1/160, ESR 130 mm/h, low C3/C4	Mucosal and cutaneous hemorrhagic blisters	Acute hemorrhagic vasculitis
Weiser et al ⁷	200 mg × 0.5	ANA 1/256, AHA, anti-dsDNA	Ulcerated lesions in epiglottis, arytenoepiglottic folds	Necrotizing vasculitis
Cameron and Ramsay ¹	200 mg × 1.3	ESR 93 mm/h, anti-dsDNA	Widespread acrocyanosis, urticarial lesions	N/A
Novikov et al ⁶	300 mg × 2	N/A	Vesiculobullous rash, ulcerations in oral cavity	Necrotizing neutrophil-rich venulitis, pseudomelanosis
Magro et al ⁹	N/A	Anti-PR3, anti-MPO	Acral vesiculopustular in the larynx	ANCA-positive cutaneous vasculitis
Keasberry et al ⁸	150 mg × 3	ANA >2560, AHA, anti-dsDNA, anti-MPO	Cutaneous rash to arms, mouth, and throat ulcers	Neutrophil infiltrate to full thickness of dermis

AHA indicates anti-histone antibodies; ANA, antinuclear antibody; ANCA, anti-neutrophil cytoplasmic antibody; anti-dsDNA, anti-double stranded DNA; anti-MPO, anti-myeloperoxidase; anti-PR3, anti-proteinase 3; C3, complement component 3; C4, complement component 4; ESR, erythrocyte sedimentation rate; IgG, immunoglobulin G; IgM, immunoglobulin M.

also been reported that such development of multiple antibodies may indicate a drug-induced autoimmune process. Hypocomplementemia has also been described, which was present in our case. Clinically these patients may present with small vessel vasculitis of the skin, as in our patient. Weight loss, cough, lung disease, and kidney disease have also been described.²

Despite the poorly understood pathogenesis and variable clinical presentations of ANCA DIV and DIL, medication cessation remains the mainstay therapy. Some patients may benefit from a short steroid course, as in the case of our patient. Additional immunosuppressive therapy may be required depending on disease severity.² As highlighted in this case, both DIL and ANCA DIV can manifest simultaneously. To our knowledge, this is the first case where both conditions were observed in a patient with pulmonary sarcoid and sarcoid parotitis. Increased recognition and a high index of suspicion are key to proper diagnosis and prompt withdrawal of the offending drug. Awareness of these drug-induced disorders can play a vital role in preventing long-term and protracted immunosuppressive therapies where the mainstay of treatment is drug cessation.

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