Multiple cutaneous and mucosal lesions in a patient with cocaine-levamisole–induced vasculopathy syndrome

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ABSTRACT

Levamisole is an adulterant found in nearly 70% of cocaine in the United States. The concomitant use of levamisole and cocaine leads to a distinct clinical syndrome that typically manifests as agranulocytosis, leukocytoclastic vasculitis, and elevated antineutrophil cytoplasmic antibody (ANCA) levels. Systemic involvement has also been rarely reported with this syndrome. This is a case of a 51-year-old woman with chronic cocaine use who initially presented with multiple cutaneous ulcerations and was later found to have pulmonary and renal involvement. Infectious workup was unrevealing and autoimmune workup revealed highly elevated levels of perinuclear ANCA. Due to continuous cocaine use despite counseling, the patient was readmitted with worsening pulmonary and renal manifestations requiring initiation of immunosuppressive therapy.

KEYWORDS ANCA antibody; cocaine-levamisole vasculitis; cocaine; levamisole

Cocaine-levamisole–induced vasculopathy syndrome (CLIVS) is characterized by cutaneous manifestations, neutropenia, positive antineutrophil cytoplasmic antibody (ANCA), and, rarely, systemic involvement. Levamisole, an anthelmintic agent, is often used as a cocaine adulterant due to its euphoric and stimulating properties. This case describes a unique presentation of CLIVS that involves the typical dermatologic lesions and hematologic manifestations as well as less frequently reported pulmonary and renal involvement.

CASE DESCRIPTION

A 51-year-old woman initially presented with a 5-day history of oral (*Figure 1a*), perianal, and lower extremity ulceration (*Figure 1b*), as well as purpuric stellate lesions on the toes and fingers (*Figure 1c*). She endorsed shortness of breath as well as frothy urine and admitted to chronic use of inhaled cocaine. Laboratory tests were remarkable for a white blood cell count of 1.54 K/uL, hemoglobin of 8.9 g/dL, absolute neutrophil count of 0.010, and creatinine of 2.29 mg/dL. Urinalysis showed proteinuria and hematuria. Urine drug screen was positive for cocaine, and her urine levamisole level was elevated to 0.16 mcg/mL (reference

range <0.10). The infectious workup was unremarkable, and the autoimmune workup was pertinent for elevated C-reactive protein at 173.2 mg/L, erythrocyte sedimentation rate >140 mm/h, perinuclear ANCA titer >1:640, microscopic polyangiitis >800, and rheumatoid factor 43 IU/mL. Computed tomography (CT) of the chest revealed diffuse ground-glass opacities in both lungs, and subsequent bronchoscopy with bronchoalveolar lavage was negative for hemorrhage. Bone marrow biopsy was normal. Skin biopsy showed superficial and deep perivascular dermatitis with scattered eosinophils, and oral ulcer biopsy demonstrated inflammatory exudates with necrosis and eosinophilia. The patient was managed supportively, and counseling was provided against cocaine use.

After several months, the patient was readmitted due to worsening shortness of breath. CT of the chest demonstrated an interval increase in multifocal opacities in all five lobes of the lungs with associated interlobular septal thickening and evidence of pulmonary edema (*Figure 2a*). Supportive management was provided with improvement in the CT (*Figure 2b*) and in symptoms prior to discharge. She presented again with worsening renal and respiratory failure and eventually required immunosuppression.

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Figure 1. (a) Soft palate ulcer. (b) Left shin ulceration. (c) Purpuric lesions in dorsum of right hand.

Figure 2. (a) Multifocal ground-glass opacities with associated interlobular septal thickening and bilateral moderate pleural effusions. (b) Improved changes of suspected vasculitis in both lungs with residual nodular airspace opacities and pleural effusions.

DISCUSSION

Levamisole was originally utilized as an anthelmintic agent during its initial production. It was later used in humans for treatment of rheumatoid arthritis and colon cancer; however, it was removed from the US market in early 2000 when it was found to cause neutropenia and agranulocytosis.¹ It continues to be used in certain countries for its therapeutic benefit in childhood nephrotic syndrome.² Despite Food and Drug Administration regulation, levamisole has continuously been used as a cocaine adulterant due to its synergistic effect with cocaine, leading to an increase in dopamine transmission, and its physical similarity to cocaine, making the sample appear purer.^{3,4}

CLIVS is identified by its cutaneous manifestations, neutropenia, and ANCA positivity.^{5,6} A conspicuous feature of CLIVS in early reports has been the paucity of organ involvement apart from dermatologic lesions and granulocytosis.⁷ Typical cutaneous manifestations include palpable purpura or petechiae with predilection for the external pinna.⁸ This is in contrast with cocaine-induced midline destructive lesions that have no coexisting lesions but present with destructive lesions of the nose, sinus, and palate.⁹ Systemic manifestations have rarely been reported. Those that have been previously documented include

thrombocytopenia, crescentic and necrotizing ANCA-associated pauci-immune glomerulonephritis, membranous nephropathy, pulmonary hemorrhage, and small vessel thrombosis.^{6,7,10}

Cocaine and levamisole induce an inflammatory reaction that leads to an immune response influenced by genetic susceptibility, such as the presence of the HLA B27 allele, which is associated with a higher risk of agranulocytosis, and environmental factors.^{6,7} Cocaine and levamisole also lead to the formation of neutrophil extracellular traps, which induce an adaptive immune response leading to production of ANCA.^{5,7} This leads to immune complex deposition with resultant vascular necrosis, inflammation, hemorrhage, and fibrin deposition.^{1,6,11}

Diagnosis requires the appropriate clinical history, classic cutaneous exam findings, leukopenia, ANCA positivity, and exclusion of infectious, idiopathic, or vasculitic entities.⁵ Among all forms of vasculitis, distinction from granulomatosis with polyangiitis is critical for the choice and duration of immunosuppressive therapy.¹ Laboratory findings include high titers of perinuclear ANCA, which are identified in 90% of cases, with cytoplasmic ANCA also being identified in 54% of cases.¹¹ Approximately 50% of patients are PR-3 antibody positive, and nearly all are MPO antibody positive (MPO-myeloperoxidase).¹² The elevated ANCA levels may

make it difficult to distinguish from other ANCA-associated vasculitides, but the presence of human neutrophil elastase may be helpful because it was found to be more specific in cocaine users.⁸ Lupus anticoagulant and anticardiolipin antibody titers can occasionally be elevated as well.⁸ Skin biopsy typically shows findings ranging from thrombotic vasculopathy to leukocytoclastic vasculitis with or without fibrinoid necrosis^{6,8} or eosinophilia from type II hypersensitivity Immunoglobulin M reaction, which is another presumed contributing factor.⁸

There are no specific guidelines for the treatment of CLIVS. Short courses of systemic corticosteroids and immunosuppressive medications were noted to be efficacious among patients who have evidence of systemic involvement or have severe skin lesions.^{1,7,8,13} Patients with pulmonary hemorrhage may benefit from plasmapheresis in addition to immunosuppression.⁷ With continued abstinence from cocaine use, neutropenia resolves within 5 to 10 days, skin lesions resolve within 2 to 3 weeks, and serologic markers resolve within 2 to 14 months.⁵ All manifestations reappear with each exposure and can be more severe than in the initial presentation; thus, the ultimate prevention and treatment is the cessation of levamisole-laced cocaine use.⁵

Among patients with known substance abuse who present with systemic symptoms, skin manifestations, and positive auto-immune testing, CLIVS should be considered as one of the possible causes. This case presents a rare manifestation of CLIVS with simultaneous renal and pulmonary involvement. Symptoms were noted to have resolved with a short course of steroids, conservative management, and discontinuation of cocaine use. This highlights the significance of early diagnosis, which may prevent unnecessary or prolonged use of immunosuppression. Patient education and psychosocial support are essential in preventing recurrence and disease progression.

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