Fatal Case of Levamisole-Induced Vasculopathy in a Cocaine User

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PRACTICE **POINTS**

- Levamisole-induced vasculopathy usually resolves upon cessation of cocaine use without long-term sequelae.
- Presentation of a purpuric vasculitis, with or without associated neutropenia and positive autoantibodies, should prompt the consideration of levamisole-contaminated cocaine use in the clinician's differential. Early recognition and discontinuation of the offending agent could be lifesaving.

To the Editor:

Levamisole is a veterinary anthelmintic drug with immunomodulating properties that was once approved by the US Food and Drug Administration for the treatment of various conditions, including autoimmune diseases, cancer, pediatric kidney disease, and chronic infections.[1-4] Levamisole was banned in 2000 after reports of associated agranulocytosis and a characteristic painful purpuric vasculitis.[4,5] Despite the ban, its use persists due to its increasing incorporation as an adulterant in cocaine, presumably for its dopaminergic properties that potentiate psychotropic effects.[6] In 2009, the Drug Enforcement Administration reported that 69% of seized cocaine in the United States contains this chemical, with an average concentration of 10%.[5] Levamisole-induced vasculopathy (LIV) typically resolves following the cessation of cocaine without further treatment necessary. We present a fatal case of LIV to emphasize that early recognition and discontinuation of the offending agent could be lifesaving.

A 40-year-old woman with a history of cocaine abuse was admitted with tender, reticular, purpuric, and erythematous patches and plaques on the lower extremities with areas of necrosis (Figure 1). The lesions had been present intermittently for 6 months. She tried topical mupirocin and oral amoxicillin clavulanate without improvement. She also described polyarthralgia in the hands, but the remainder of the review of symptoms and physical examination was negative.

Coagulation studies and white blood cell counts were within reference range. A urine toxicology screen was positive for cocaine; however, urine testing for levamisole was not performed given the short half-life of levamisole in vivo. A biopsy of one of the skin lesions on the right thigh showed pauci-inflammatory superficial and deep vein thrombosis with recanalization (Figure 2). A rheumatology workup revealed an elevated C-reactive protein level, low C3, positive antinuclear antibody, positive anti–double-stranded DNA, positive anticardiolipin antibody, positive lupus anticoagulant, and positive perinuclear antineutrophil cytoplasmic antibody (ANCA). Tests for HIV, hepatitis B and C, cryoglobulinemia, and cytomegalovirus were negative. Given the clinical picture and laboratory findings, levamisole-induced vasculitis was deemed likely. The patient was treated with appropriate skin and wound care. She was discharged with a

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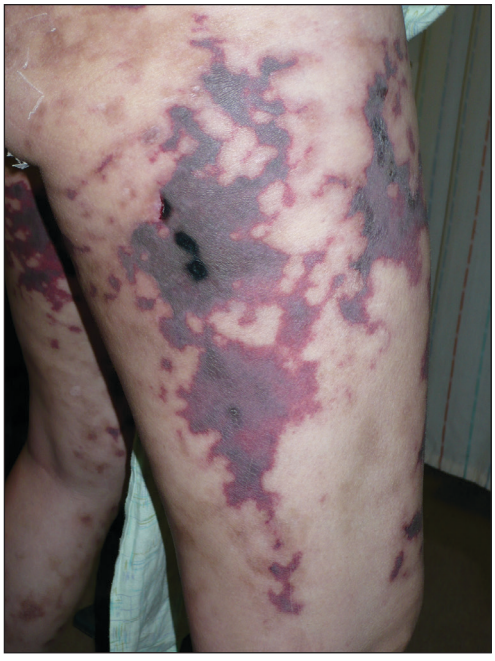

FIGURE 1. Levamisole-induced vasculopathy with retiform and stellate purpuric patches and plaques with some areas of central necrosis on the legs.

prednisone taper and oral cephalexin and was counseled on cocaine cessation.

Five months later, the patient was readmitted for lower extremity edema and worsening painful lesions that had progressed to involve the legs, thighs, buttocks, flanks, and the tip of her nose. A deep vein thrombosis workup was negative. She admitted to ongoing cocaine use that was confirmed with urine toxicology. Coagulation studies and white blood cell counts remained within reference range. Repeat skin biopsy was consistent with prior findings, demonstrating thrombosis of superficial and deep vessels with recanalization. In addition, it showed focal epidermal necrosis and a perivascular infiltrate of lymphocytes, histiocytes, and rare neutrophils. She was placed on high-dose methylprednisolone. Over the course of the next month, her urine continued to test positive for cocaine, and she developed necrotizing fasciitis necessitating lower extremity amputation, abdominal washout, and debridement. She quickly deteriorated, developing multiorgan failure with sepsis, leading to death. Of note, the patient was never found to have neutropenia or agranulocytosis throughout the disease course.

Because levamisole is no longer in clinical use, reports of its adverse effects come exclusively from users of cocaine, whether via smoking or snorting. Levamisole-induced vasculopathy typically is painful and purpuric, with or without necrosis, in a retiform or stellate pattern and commonly involves the extremities, trunk, face, and external ears.[7] The average age of presentation is 43 years and it more commonly is seen in women.[8]

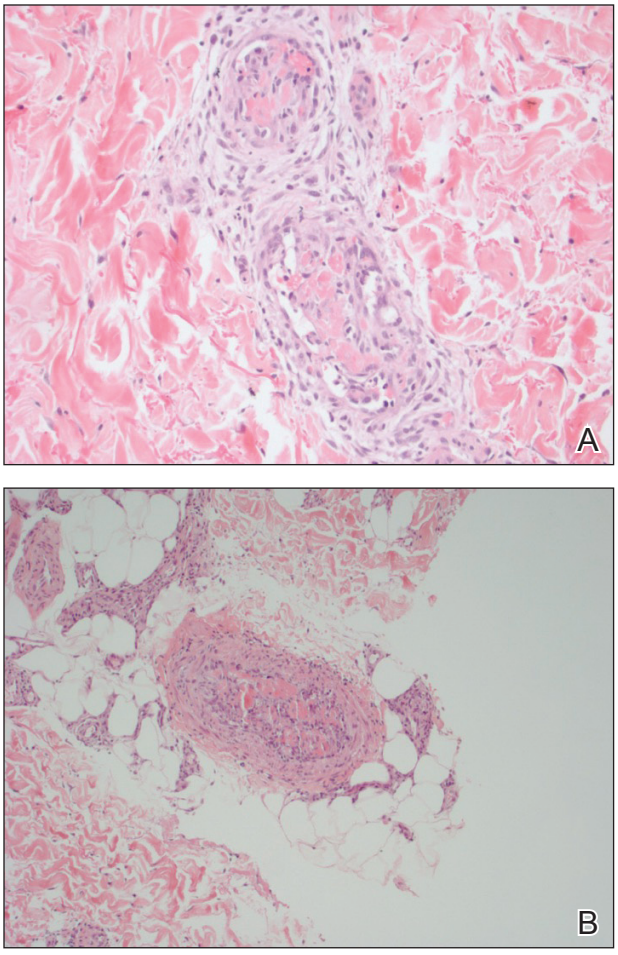

FIGURE 2. A and B, Histopathology revealed intravascular fibrin thrombi of the mid to deep dermal vessels, consistent with levamisole-induced occlusive vasculopathy (H&E, original magnifications ×20 and ×10).

Levamisole-induced vasculopathy remains a diagnosis of exclusion, so it is important to rule out other treatable causes. The differential diagnosis for purpura associated with vasculitis also includes other antineutrophilic cytoplasmic–associated vasculitides (eg, granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis), infectious purpura fulminans, antiphospholipid syndrome, cryoglobulinemia, and disseminated intravascular coagulation.[9] In LIV patients, perinuclear ANCAs are present in up to 90% of cases, and cytoplasmic ANCAs in 19% to 59% of cases.[10,11] Although leukopenia and neutropenia complicate approximately 60% of LIV cases, they are not required to make the diagnosis.[11,12] Elevated erythrocyte sedimentation rate, normal coagulation studies, and positive antineutrophil antibodies and lupus anticoagulant further aid in the diagnosis.[8] Urine should be tested for cocaine in suspected patients. Urine also can be tested for levamisole, which is challenging because of the short half-life of 5.6 hours. Only 2% to 5% of levamisole is excreted unchanged in the urine, and testing requires gas chromatography and mass

spectrometry that was not readily available to perform on our patient.[7] In addition to laboratory and urine studies, hair strand testing,[10] skin biopsy, and histologic findings also can be used to support the diagnosis.

The pathogenesis of LIV is not completely understood, but it is thought to be an immune complex–mediated process based on immunofluorescence studies in the skin.[13,14] Classic pathologic findings include multiple fibrin thrombi within small vessels in the superficial and deep dermis, leukocytoclastic vasculitis of small vessels consisting of fibrinoid necrosis of the vessel wall, extravasated erythrocytes, karyorrhectic debris, and angiocentric inflammation.[14] Direct immunofluorescence is not routinely performed but most commonly demonstrates deposition of IgA, IgM, and C3.[14,15]

Levamisole-induced vasculopathy usually resolves upon cessation of cocaine use without long-term sequelae. Steroids have been used as treatment of prominent vasculitis with variable success; however, immunosuppressive effects should be closely monitored, especially with inpatients with concurrent granulocytopenia. Broad-spectrum antibiotics have been used in cases with fever and agranulocytosis. Cutaneous lesions typically disappear within 2 to 3 weeks, and serologic markers resolve within 2 to 10 months. Recurrent use of cocaine generally results in recurrent neutropenia and skin eruptions, supporting the causal role. Our patient's recurrent prolonged cocaine use with vasculopathy was assumed to be the source of the necrotizing fasciitis that led to a cascade of sepsis, rapidly progressing multiorgan failure, and ultimate demise.

Presentation of a purpuric vasculopathy, with or without associated neutropenia and positive autoantibodies, should prompt the consideration of levamisole-contaminated cocaine use in the clinician's differential. Although the patient may initially deny cocaine use, it is important to keep this diagnosis in mind when the clinical picture fits, and urine toxicology screen should be ordered when there is question. Physicians and patients should be wary of potential complications, even death. Early recognition and discontinuation of the offending agent could be lifesaving.

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