Dermatologic Complications From Levamisole-Contaminated Cocaine: A Case Report and Review of the Literature

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Practice Points

- Exposure to levamisole-contaminated cocaine is an important public health issue that can be associated with a variety of cutaneous manifestations.
- Knowledge of the spectrum of clinical manifestations of levamisole exposure is important to allow for proper medical management.

Levamisole is a veterinary anthelmintic drug with immunomodulatory properties in humans. It has become increasingly common as a contaminant in cocaine and is now detected in the majority of cocaine seized in the United States. A variety of adverse reactions have been reported in association with levamisole, the most severe being agranulocytosis, vascular occlusive disease, and thrombotic vasculopathy, with or without vasculitis. The combination of rapidly progressive cutaneous ecchymosis and purpura leading to necrosis, often affecting the ears and cheeks; neutropenia or agranulocytosis; serologic autoantibodies; and thrombotic vasculopathy, with or without associated vasculitis, in a patient who has recently used cocaine is characteristic of exposure to contaminant levamisole. We report the case of a 54-year-old man who presented with the clinical findings of levamisole-contaminated cocaine use and review the literature regarding cutaneous reactions associated with levamisole. Our case highlights this important public health issue and represents a clinical course that is unusually severe.

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Levamisole is a synthetic anthelmintic drug used in veterinary medicine that has immunostimulatory and immunomodulatory properties in humans. Although today its use in humans is limited and infrequent, levamisole currently is approved by the US Food and Drug Administration as adjuvant chemotherapy for colon cancer. Previously, levamisole had been used in the treatment of a variety of conditions, including autoimmune diseases, pediatric kidney disease, and chronic infections, as well as in adjuvant chemotherapy for breast, lung, and colon cancers.[1-4] Levamisole has been reported to enhance cellular and humoral immunity (eg, T cell response, neutrophil activity, antibody production).[4,5] Although levamisole generally is well tolerated, cutaneous reactions including lichenoid drug eruptions, fixed drug eruptions, lichen planus, vasculitis, vascular occlusive disease, ulceration, nodules, erythema nodosum leprosum, and nonspecific maculopapular eruptions have been reported.[1-3,5-14] Cytopenia (eg, agranulocytosis, neutropenia, thrombocytopenia) also has been reported.[3,8,9]

The increasing prevalence of levamisole-contaminated cocaine has caused a reemergence of these clinical findings. In July 2009, 69% of the cocaine analyzed by the US Drug Enforcement Administration (DEA) was found to be contaminated with levamisole.[15] The most severe reactions include agranulocytosis, vascular occlusive disease, and thrombotic vasculopathy, with or without vasculitis. These adverse events are relatively uncommon in patients who are medically treated with

levamisole, but the incidence in individuals who are exposed to levamisole-contaminated cocaine is unclear, with few cases reported. Our case highlights this important public health issue and represents a clinical course that is unusually severe.

Case Report

A 54-year-old man presented with bilateral axillary adenopathy and fatigue of 2 weeks' duration. His medical history was unremarkable. He reported that he had been performing light construction work in a rural environment but denied insect bites or toxic exposure. He was started on broad-spectrum antibiotics trimethoprim-sulfamethoxazole followed by cephalexin without improvement. The enlarging axillary lymph nodes subsequently were lanced, and *Serratia marcescens* was cultured from the expressed material.

Within the next several days, the axillary lymph nodes became ulcerated and the patient developed fever, night sweats, oral ulcers, and dysphagia. He subsequently was admitted to the hospital. On admission, the patient was noted to have bilateral axillary adenopathy with lymph nodes measuring up to 2 cm as well as oral ulcers involving the proximal tongue and left maxillary gum. A chest radiograph was normal. Complete blood analysis showed leukopenia with severe neutropenia, with a white blood cell count of $2.4\times10^3/\mu L$ (reference range, $4.5–11.0\times10^3/\mu L$) and an absolute neutrophil count of $0.12\times10^3/\mu L$ (reference range, $1.5–7\times10^3/\mu L$). Hemoglobin (14.1 g/dL), hematocrit (43.2%), and platelet count ($419\times10^3/\mu L$) were within reference range, as well as serum electrolytes. The patient was started on granulocyte colony-stimulating factor and broad-spectrum antibiotics, and a bone marrow biopsy was performed to evaluate for hematopoietic malignancy.

Shortly after admission to the hospital, the patient developed rapid onset of progressive cutaneous violaceous ecchymosis, areas of purpura, and hemorrhagic bullae, most notably affecting the nasal tip, lips, and ears, which became ischemic and blackened. After several days, 40% of the skin surface was involved, including the extremities, trunk, and face, yielding second and third degree burnlike skin loss of approximately 30% and 10% of the skin surface area, respectively (Figure 1). Complete blood cell count noted the onset of thrombocytopenia, with the platelet count dropping to $98\times10^3/\mu L$. A skin biopsy revealed numerous intravascular thrombi involving superficial and deep dermal vessels without vasculitis that were consistent with vascular occlusive disease, excluding Stevens-Johnson syndrome secondary to antibiotic therapy (Figures 2 and 3). Special stains (ie, tissue Gram stain, Gomori methenamine-silver stain) for infectious organisms were negative. Laboratory data showed increased prothrombin time and partial thromboplastin time, decreased fibrinogen, decreased antithrombin III antigen, and decreased serum complement levels. All infectious serologies, including human immunodeficiency virus and *Rickettsia*, as well as blood smear review for parasites and multiple blood cultures were negative. A positive perinuclear antineutrophil cytoplasmic antibody (ANCA) and weakly positive IgM antiphospholipid autoantibody were present. Additional patient history obtained at this time revealed recent cocaine use that started prior to the onset of the initial symptoms of fatigue and adenopathy. The bone marrow was negative for a hematologic malignancy but showed reactive myeloid hyperplasia.

The possibility of purpura fulminans with disseminated intravascular coagulation secondary to

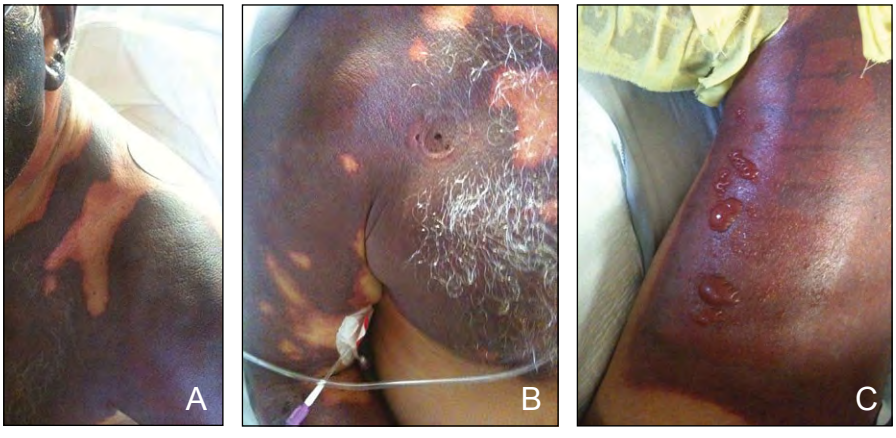

Figure 1. Extensive ischemic changes involving the face and trunk that developed shortly after hospital admission for treatment of enlarged ulcerated axillary lymph nodes, fever, night sweats, oral ulcers, and dysphagia (A). Purpura, ecchymosis, and ischemic changes involved the chest and upper arms (B). Palpable purpura, ecchymosis, and hemorrhagic bullae developed on the leg (C).

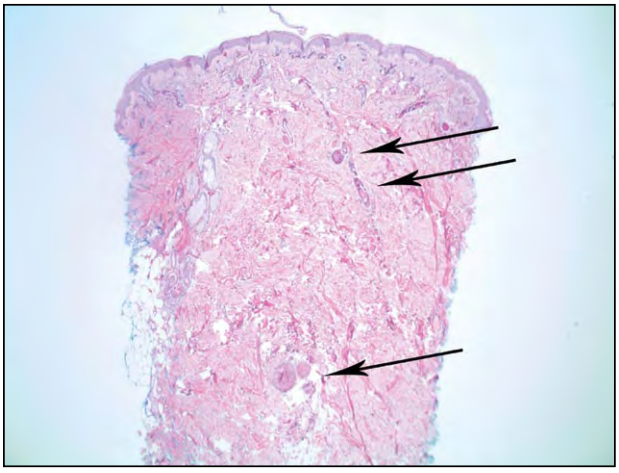

Figure 2. A skin biopsy on admission to the hospital showed scattered superficial and deep dermal intravascular thrombi without vasculitis (arrows). The overlying epidermis was intact (H&E, original magnification ×20).

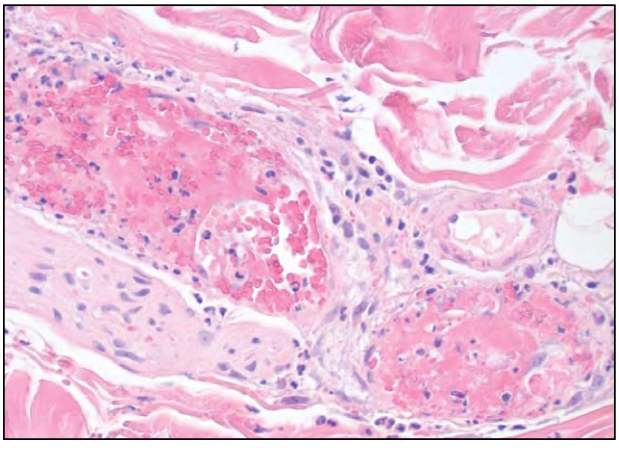

Figure 3. A skin biopsy on admission to the hospital showed dermal intravascular thrombi without vasculitis (H&E, original magnification ×400).

bacterial lymphadenitis was considered, but given its rarity in adults and the lack of systemic changes such as hypotension generally seen with this entity in addition to the patient's history and clinical findings (eg, facial involvement, neutropenia, positive autoimmune serologies), it was determined that the disease process was consistent with exposure to levamisole-contaminated cocaine. Given the short half-life of levamisole in vivo, confirmatory tests could not be performed. The patient was anticoagulated, with appropriate skin and wound care. A follow-up skin biopsy 3 days later revealed intravascular thrombi. The patient developed respiratory distress requiring transfer to the intensive care unit; he subsequently was transferred to a local burn unit. The patient continued to deteriorate, with development of renal and hepatic failure, and he lapsed into a transient coma. The cutaneous lesions also progressed, with complete necrosis of the nose; substantial skin and soft tissue loss in the chest and extremities, requiring extensive skin grafts; and focal necrosis of lower extremity muscles and bone. He remained hospitalized with ongoing therapy at the time of this report.

Comment

The recent reemergence of adverse reactions associated with levamisole is attributed to its prevalence as a contaminant in cocaine, which has been steadily increasing since it was first identified in the early 1990s.[11,15,16] From July 2008 to September 2008, 30% of the cocaine seized by the DEA was found to be contaminated with levamisole; in July 2009, this percentage increased to 69% with an average concentration of approximately 10%.[15] Levamisole-contaminated cocaine also has been reported in other countries, including Canada, England, Switzerland, Italy, and Australia.[16-18] Levamisole does not appear to be added to cocaine locally but at the point of manufacture in Columbia, which accounts for the widespread distribution of contaminated drugs.[19] Although the exact reason for use of levamisole is unclear, it is inexpensive, commonly available, and has a similar appearance and melting point to cocaine.[16] It also may enhance the biologic effects of cocaine.[11] Levamisole also has been reported as a contaminant in heroin but less commonly (ie, <3% of heroin seized by the DEA in 2009) and at a lower concentration.[15]

As highlighted in our case, the most serious complications associated with levamisole-contaminated cocaine include agranulocytosis, vascular occlusive disease, and thrombotic vasculopathy, with or without associated vasculitis. Approximately 2% to 20% of patients treated therapeutically with levamisole will develop reversible agranulocytosis.[2-4,15,20] The incidence in those exposed through contaminated cocaine is unknown. In 2009, levamisole-contaminated cocaine (both powder and crack forms) was identified as the causative agent in 21 cases of unexplained agranulocytosis, with 1 reported death.[15] Agranulocytosis usually is present in the peripheral blood and on bone marrow examination; it is reversible after discontinuing exposure to levamisole, with the neutrophil count generally recovering in 5 to 10 days.[2,17] Thrombocytopenia also has been reported but is less common.[2,21] There appears to be an increased incidence of levamisole-induced agranulocytosis in females, individuals with rheumatic disease, and patients who are HLA-B27 positive.[2,20]

Only a small minority of patients exposed to levamisole for medical therapy will develop vascular

occlusive disease or vasculitis, with approximately 15 cases (age range, 6 months to 65 years) reported in the English-language literature as of December 2011, according to a PubMed search of articles indexed for MEDLINE using the search terms *levamisole* and *levamisole and vasculitis/vascular occlusive disease/vasculopathy*.[1,2,5-7,22-25] In one series of patients, 5 of 160 (3%) children treated with levamisole for nephrotic syndrome developed levamisole-induced vasculitis or thrombotic vasculopathy.[6] As of December 2011, a PubMed search of articles indexed for MEDLINE using the search terms *levamisole*, *levamisole and cocaine*, and *levamisole and vasculitis/vascular occlusive disease/vasculopathy* yielded 5 cases that have been reported in association with cocaine contaminated with levamisole, with similar features to our case.[21,24,26] Affected patients generally present with ecchymosis and palpable purpura that progresses to necrosis, often involving the ears and cheeks and variably impacting other areas. In 2 reported cases, the legs were primarily affected.[26] A livedo pattern rash and retiform purpura also have been reported.[6,23,24,26]

Microscopically, affected areas typically show intravascular thrombi within the dermal blood vessels (superficial and variably deep) with or without accompanying leukocytoclastic vasculitis. Direct immunofluorescence has shown various antibodies (ie, IgM, IgA, IgG) and complement deposition in blood vessel walls in some but not all cases.[1,6,22] The majority of patients reported in the English-language literature had associated (often multiple) autoantibodies, including perinuclear ANCA, cytoplasmic ANCA, anticardiolipin antibody, lupus anticoagulant, antinuclear antibody, and anti–double-stranded DNA antibody, as well as a positive direct Coombs test. These autoantibodies were not known to exist prior to exposure to levamisole in the patients studied.[6] Antineutrophil cytoplasmic antibody reacting with human neutrophil elastase (HNE) has been reported to differentiate levamisole exposure from other etiologies of autoimmune vasculitis.[26,27] In one study, 84% of patients with cocaine-induced midline destructive lesions had detectable HNE by one assay (n=25), while patients with Wegener granulomatosis and microscopic polyangiitis were universally HNE ANCA negative.[27] Human neutrophil elastase and proteinase 3 ANCAs are related, and patients with cocaine-induced midline destructive lesions also can show positivity for proteinase 3 ANCA.[26,27] Concomitant agranulocytosis and neutropenia has been observed in patients with vasculitis or vasculopathy, including the majority of those cases secondary to levamisole-contaminated cocaine.[2,7,21,26,28] The serologic, pathologic, and clinical abnormalities typically resolve completely after cessation of levamisole exposure, with clinical symptoms resolving within 2 to 3 weeks, but serologic autoimmune antibodies can remain for up to 14 months.[6] The etiology of the vascular changes is unclear, though it is thought they may be related to vascular deposition of circulating antibodies to drug-related antigens, the direct toxic effect of levamisole on endothelial cells, or the immunomodulatory properties of levamisole. When present, ANCA antibodies also may contribute to neutropenia or agranulocytosis.

Conclusion

The combination of thrombotic vasculopathy with associated cutaneous purpura leading to necrosis, autoantibodies, and agranulocytosis or neutropenia in a patient with known, recent cocaine use was suggestive of exposure to levamisole in our patient. Levamisole has a short half-life of approximately 5 to 6 hours, and therefore blood and urine specimens should be obtained within 48 hours of suspected exposure.[15,16] Routine toxicology does not identify levamisole, which requires gas chromatography or mass spectrometry. Although testing for levamisole was not performed in our patient, the clinical and laboratory findings were consistent with exposure. Our case highlights this important public health issue and represents a clinical course that is unusually severe. Knowledge of this entity is vital to timely diagnosis and intervention. The possibility of illicit drug use must be considered in patients who have unexplained neutropenia or agranulocytosis and/or vascular occlusive disease, even in those patients with a low clinical suspicion of cocaine use.

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