Extensive Skin Necrosis From Suspected Levamisole-Contaminated Cocaine

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To the Editor:

A 52-year-old man presented to the emergency department with skin pain. Although he felt well overall, he reported that he had developed skin sores 3 weeks prior to presentation that were progressively causing skin pain and sleep loss. He acknowledged smoking cigarettes and snorting cocaine but denied intravenous use of cocaine or using any other drugs. His usual medications were lisinopril and tramadol, and he had no known drug allergies. His history was remarkable for methicillin-resistant *Staphylococcus aureus* (MRSA) septic arthritis of the shoulder and MRSA prepatellar bursitis within the last 2 years. During examination in the emergency department he was alert, afebrile, nontoxic, generally healthy, and in no acute distress. Extensive necrotic skin lesions were present on the trunk, extremities, and both ears. The lesions were large necrotic patches with irregular, sharply angulated borders with thin or ulcerated epidermis surrounded by a bright halo of erythema (Figure 1). Ulcers were noted on the tongue (Figure 2).

The clinical diagnosis was probable thrombosis of skin vessels with skin necrosis due to cocaine that was likely contaminated with levamisole. Pertinent laboratory results included the following: mild anemia and mild leukopenia; values within reference range for liver function, serum protein electrophoresis, hepatitis profile, human immunodeficiency virus 1 and 2, rapid plasma reagin, and antinuclear antibody; normal thrombotic studies for antithrombin III, protein C, protein S, factor V Leiden, prothrombin mutation G20210A, anticardiolipin IgG, IgM, and IgA; erythrocyte sedimentation rate of 26 mm/h (reference range, 0–15 mm/h); perinuclear antineutrophil cytoplasmic antibody greater than 1:320 (reference range, <1:20) with normal proteinase 3 and myeloperoxidase antibodies; urine positive for cocaine but blood negative for cocaine; normal chest radiograph; and normal electrocardiogram.

The patient was stable with good family support and was discharged from the emergency department to be followed in our dermatology office. The following day his skin biopsies were interpreted as neutrophilic vasculitis with extensive intravascular early and organizing thrombi involving all small- and medium-sized blood vessels consistent with levamisole-induced necrosis or septic vasculitis (Figure 3). With his history of MRSA septic arthritis and bursitis, he was hospitalized for treatment with intravenous vancomycin pending further studies. Skin biopsy for direct immunofluorescence revealed granular deposits of IgM and linear deposits of C3 at the dermoepidermal junction and in blood vessel walls. Two tissue cultures for bacteria and fungi were negative and 2 blood cultures were negative. An echocardiogram was normal and without evidence of emboli. The patient remained stable and antibiotics were discontinued. He was released from the hospital and his skin lesions healed satisfactorily with showering and mupirocin ointment.

Cocaine is a white powder that is primarily derived from the leaves of the coca plant in South America. It is ingested orally; injected intravenously; snorted intranasally; chewed; eaten; used as a suppository; or dissolved in water and baking soda then heated to crystallization for smoking, which is the most addictive method and known as freebasing. When smoked, crack cocaine produces a crackling sound. Cocaine stimulates the central nervous system similar to amphetamine but may harm any body organ through vasoconstriction/vasospasm and cause skin necrosis without any additive. Perhaps less known is its ability to produce smooth muscle hyperplasia of small vessels and premature atherosclerosis.[1]

Levamisole has been used to treat worms, cancer, and stimulation of the immune system but currently

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The authors report no conflict of interest.

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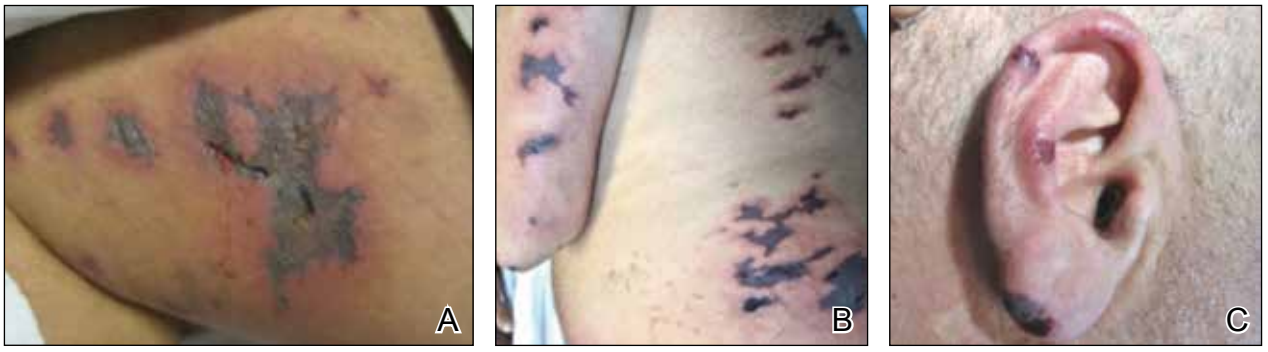

Figure 1. Extensive skin necrosis on the leg from levamisole-contaminated cocaine (A). Necrotic skin lesions also were present on the trunk, arm (B), and ear (C).

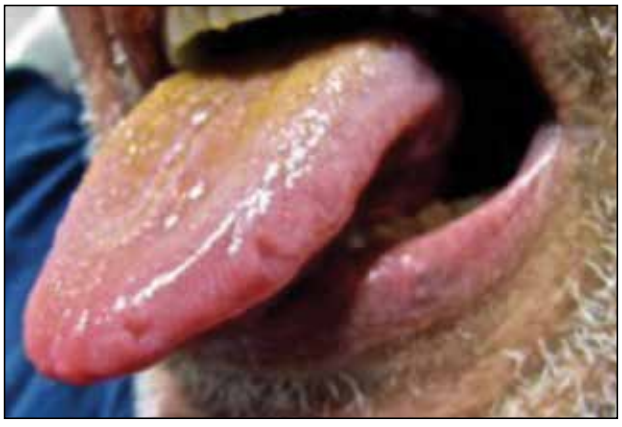

Figure 2. Ulcers were noted on the tongue.

is used only by veterinarians because of agranulocytosis and vasculitis in humans. As of July 2009, the Drug Enforcement Agency reported that 69% of seized cocaine lots coming into the United States contained levamisole.[2] By January 2010, 73.2% of seized cocaine exhibits contained levamisole according to the California Poison Control System, with reports of contamination rates from across the country ranging from 40% to 90%.[3] Levamisole is an inexpensive additive to cocaine and may increase the release of brain dopamine.[4] It is difficult to detect levamisole in urine due to its short half-life of 5.6 hours and only 2% to 5% of the parent compound being found in the urine.[5]

Skin necrosis due to cocaine-contaminated levamisole usually occurs in younger individuals who have characteristic skin lesions and a history of cocaine use. Skin lesions usually are multiple, purpuric or necrotic with irregular angulated edges and a halo of erythema. Ear involvement is common but not invariable.[6] Descriptive adjectives include branched, netlike, retiform, and stellate, all revealing the compromised underlying dermal and subcutaneous vascular anatomy. Supportive evidence includes a decreased white blood cell count (neutropenia in up to 50%),[5] positive antineutrophilic cytoplasmic antibodies,[5,7] and/or positive drug screen. Skin biopsy may reveal thrombosis,[4] fibrin thrombi without vasculitis,[8] or leukocytoclastic vasculitis,[4,5] or may suggest septic vasculitis.[9] Direct immunofluorescence may suggest an immune complex-mediated vasculitis.[5]

The differential diagnosis for a patient with purpuric/necrotic skin lesions should be broad and include vasculitis (eg, inflammatory, antineutrophil cytoplasmic antibody positive, septic), hypercoagulopathy (eg, antiphospholipid syndrome, antithrombin III, prothrombin mutation G20210A, factor V Leiden, protein C, protein S), drugs (eg, heparin, warfarin, cocaine with or without levamisole, intravenous drug use, hydroxyurea, ergotamine, propylthiouracil[10]), calciphylaxis, cold-induced thrombosis, emboli (eg, atheroma, cholesterol, endocarditis, myxoma, aortic angiosarcoma, marantic), febrile ulceronecrotic Mucha-Habermann disease, infection especially if immunosuppressed (eg, disseminated *Acanthamoeba*/*Candida*/histoplasmosis/strongyloides/varicella-zoster virus, *S aureus*, streptococcus, ecthyma gangrenosum, gas gangrene, hemorrhagic smallpox, lues maligna with human immunodeficiency virus, Meleney ulcer, Rocky Mountain spotted fever, *Vibrio vulnificus*), idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, thrombocythemia, Waldenström hyperglobulinemic purpura, pyoderma gangrenosum, cancer (eg, paraneoplastic arterial thrombi), oxalosis, paraproteinemia (eg, multiple myeloma), and lupus with generalized coagulopathy. Less likely diagnoses might include Degos disease, factitial dermatitis, foreign bodies, multiple spider bites, paroxysmal nocturnal hemoglobinuria, sickle

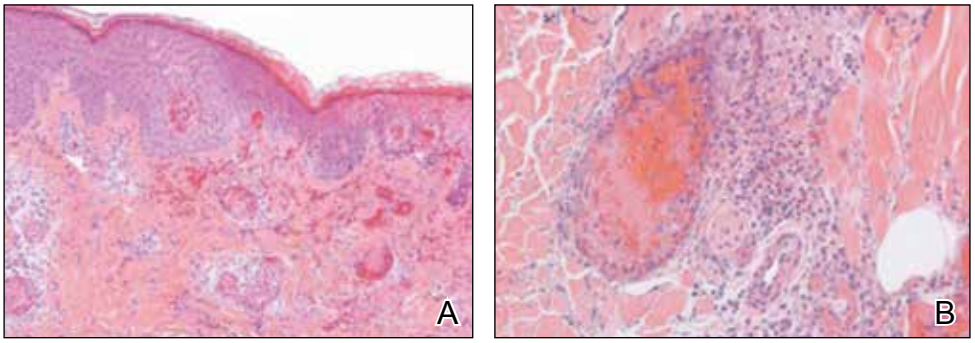

Figure 3. Thrombotic occlusion of blood vessels was seen on histopathology (A and B)(H&E, original magnifications ×100 and ×400).

cell anemia, Buruli ulcer, or thromboangiitis obliterans. Branched, angulated, retiform lesions are an important finding, and some of these diagnostic possibilities are not classically retiform. However, clinical findings are not always classical, and astute physicians want to be circumspect. Had more ominous findings been present in our patient (eg, fever, hemodynamic instability, progressive skin lesions, systemic organ involvement), prompt hospitalization and additional considerations would have been necessary, such as septicemia (eg, meningococcemia, bubonic plague [Black Death], necrotizing fasciitis, purpura fulminans), catastrophic antiphospholipid syndrome, or disseminated intravascular coagulation.

The prognosis for skin necrosis caused by levamisole-contaminated cocaine generally is good without long-term sequelae.[5] Autoantibody serologies normalize within weeks to months after stopping levamisole.[5,8] Our patient recovered with conservative measures.

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