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Levamisole-Induced Vasculopathy: A Report of 2 Cases and a Novel Histopathologic Finding

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Abstract: Although cocaine-induced pseudovasculitis and urticarial vasculitis have been reported in the past, levamisole-induced vasculopathy with ecchymosis and necrosis, termed here LIVEN, has only recently been described in association with cocaine use. Levamisole, a veterinary antihelminthic agent used previously as an immunomodulating agent, is present as a "cutting agent" in approximately two-thirds of the cocaine currently entering the United States. Levamisole is believed to potentiate the effects of cocaine and may also be used as a "signature" for tracing its market distribution. Herein, we report 2 cases of LIVEN in patients with histories of chronic cocaine use. In both the cases, a temporal association with neutropenia preceding the eruption was noted. A novel histopathologic finding present only in the second case was the presence of extensive interstitial and perivascular neovascularization. Our 2 cases reaffirm that neutropenia may precede the cutaneous eruption of LIVEN. Case 2 extends the spectrum of histopathologic findings to include the novel phenomenon of neovascularization—hitherto unreported in this entity.

Key Words: levamisole-induced vasculopathy, neovascularization

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INTRODUCTION

Levamisole, a veterinary antihelminthic agent used previously as an immunomodulating agent for treating steroid-resistant nephrotic syndrome, is present as a "cutting agent" in approximately two-thirds of the cocaine currently entering the United States.[1] Documented as a contaminant in cocaine by the US Drug Enforcement Agency since 2005, levamisole is believed to potentiate the effects of cocaine and may also be used as a "signature" for tracing its market distribution.[2] Cocaine-related cutaneous toxicities include necrosis,[3] ulcers,[4] acute generalized exanthematous pustulosis,[5] delusional parasitosis,[6,7] and a spectrum of small vessel vasculopathic conditions.[8–10] However, toxicities specific to levamisole include isolated leukopenia (1.1%),[11] agranulocytosis (2.3%), and necrotizing cutaneous vasculopathy (frequency unknown but likely rare). The agranulocytosis seems to be an IgM-mediated complement-dependent destruction of neutrophils[11] and is associated with positive anti-neutrophil cytoplasmic antibody (ANCA) serologies.[11,12] Neutropenia as low as 0 cells per microliter has been reported in levamisole-induced agranulocytosis.[13]

Levamisole-induced cutaneous vasculopathy presents clinically as tender purpuric plaques commonly seen on the ears, cheeks, nose, and digits, with additional retiform or stellate purpura occasionally present on the trunk or the extremities.[13–16] The purpuric eruption may progress to bullae, necrosis, crusting eschars, and ulcers before resolution, which typically occurs within several weeks to months.[13–16] Histopathologically, levamisole-induced cutaneous vasculopathy demonstrates microvascular thrombosis with or without leukocytoclastic vasculitis.[13–16] Levamisole-induced agranulocytosis may be asymptomatic or may present with fever and systemic infection, leading to death.[11] Bone marrow biopsies from patients with levamisole-induced agranulocytosis uniformly show severe myeloid hypoplasia.[11] In fact, the presence of circulating plasmacytoid lymphocytes, increased bone marrow plasma cells, and megakaryocytic hyperplasia are important discriminative parameters favoring cocaine-related over non–cocaine-related cases of agranulocytosis.[13] We report 2 cases of levamisole-induced vasculopathy (LIVEN) in patients with histories of chronic cocaine use presenting clinically with ecchymosis and necrosis and unexplained long-standing neutropenia preceding the cutaneous necrotizing vasculopathy. Additionally, histopathology from patient 2 showed extensive interstitial and perivascular neovascularization—a hitherto unreported histopathologic finding.

CASE REPORTS

Case 1

A 41-year-old white woman with a long-standing history of smoking cocaine presented to our inpatient service with a 5-day history of a painful purpuric eruption. The patient admitted to smoking cocaine 1 day before the onset of the eruption. The patient notably had a medical history of neutropenia of 700 cells per microliter persistent over the past 3 years; despite multiple bone marrow biopsies, the etiology of the neutropenia could not

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