Characteristic purpura of the ears, vasculitis, and neutropenia—a potential public health epidemic associated with levamisole-adulterated cocaine

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Background: Dermatologists at the University of California, San Francisco recently reported two patients in the online *Journal of the American Academy of Dermatology* with purpura presumably induced by levamisole in contaminated cocaine. Levamisole-induced vasculitis and neutropenia has been reported elsewhere in the United States and Canada. Up to 70% of cocaine in the United States could be contaminated.

Objective: We sought to describe similar cases of vasculitis associated with cocaine use.

Methods: This is a retrospective case series.

Results: We report 6 remarkably similar patients seen over just the past few months with retiform purpura on the body and tender purpuric eruptions, necrosis, and eschars of the ears after cocaine use in New York and California. All of these patients had positive perinuclear antineutrophil cytoplasmic antibody values and 3 of the 6 also had an associated neutropenia. Direct immunofluorescence studies suggested an immune complex–mediated vasculitis.

Limitations: This case series is descriptive in nature and, because testing is not easily performed, we did not test for levamisole in the serum or blood to prove this is the causative agent.

Conclusion: It appears the use of cocaine is associated with the peculiar clinical findings of ear purpura, retiform purpura of the trunk, and neutropenia. We believe this case series may represent the tip of the iceberg as a looming public health problem caused by levamisole. Although the direct causal relationship may be difficult to establish, the astute dermatologist or primary care physician should be able to recognize the characteristic skin lesions and should be wary of the potential development of agranulocytosis. (J Am Acad Dermatol 2011;65:722-5.)

Key words: agranulocytosis; cocaine; drug reaction; levamisole; neutropenia; purpura; vasculitis.

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Funding sources: None.

Conflicts of interest: None declared.

Two of the 6 patients were discussed in one of the referenced articles. None of the images of these patients was published.

Accepted for publication August 21, 2010.

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Published online June 9, 2011.

0190-9622/$36.00

doi:10.1016/j.jaad.2010.08.024

This brief case series follows up on the letter[1] published online in March 2010 in the *Journal of the American Academy of Dermatology* by dermatologists at the University of California, San Francisco describing two patients with probable levamisole-induced toxicities. In that letter, they describe two complicated medical patients with recent cocaine use, ensuing neutropenia, and retiform purpura. Because these patients had various positive serologic tests (eg, antineutrophil cytoplasmic antibodies [ANCAs], lupus anticoagulants) and confounding medical problems (hepatitis C and methicillin-resistant *Staphylococcus aureus* infection), the team at the University of California,

San Francisco thoroughly reviewed the differential diagnosis for these patients and then astutely posed the question: could these symptoms and signs be caused by levamisole-contaminated cocaine?

Here, we describe 6 strikingly similar patients within the last few months at two institutions in New York and California, one private and one public. All 6 patients presented with remarkably similar purpuric eruptions involving the ears, nose, cheeks, and various other anatomic locations after cocaine use (Fig 1 and Table I; available online at http://www.eblue.org). This purpura progressed to necrosis and eschar over the course of several weeks and resolved without complications. In half of the patients there was an associated neutropenia. At Harbor-UCLA Medical Center in Torrance, CA, two healthy male patients presented to the emergency department with rapidly progressive purpura of the ears after admitting to cocaine use the day prior. Both had skin biopsy specimens demonstrating leukocytoclastic vasculitis (LCV) with positive direct immunofluorescence staining suggestive of an immune complex–mediated process. At Strong Memorial Hospital at the University of Rochester Medical School, in Rochester, NY, 4 recent similar cases have been documented. Two of these patients were recently discussed in the internal medicine literature[2] and we describe two additional patients from Rochester, NY, here with similar clinical findings (Table I). Although somewhat variable in clinical presentation, the features common to all patients are a characteristic tender ear purpura and a positive perinuclear ANCA serology after recent cocaine use.

This letter will serve to alert the dermatology and broader medical community of a potential epidemic of levamisole-contaminated cocaine-induced toxicities. Because of ethical standards of research and the unreliable nature of levamisole testing, it may not be possible to establish a direct causal relationship between these symptoms and the cocaine use that preceded them. However, we believe the striking similarities of these clinical presentations and associated agranulocytosis warrants a louder national alert and additional discussion of this potential public health epidemic.

CAPSULE SUMMARY

- We describe a case series of 6 similar patients within the last few months in New York and California.
- These patients presented with remarkably similar purpuric eruptions involving the ears and retiform purpura on the body after cocaine use.
- All patients also had a positive perinuclear antineutrophil cytoplasmic antibody serology and half were neutropenic.
- We believe these complications are caused by adulteration of cocaine with levamisole and warn clinicians to consider this diagnosis in a patient with purpura.

Usually, side effects of medications are anecdotal, coincidental, and observational. Such reports commonly suffer from recall bias and other types of cognitive and analytical errors. However, because of the potential harm caused by prescribed medications, the standards for reporting "assumed" causative relationships in clinical medicine must be somewhat lower than experimental science. The relationship between the symptoms described here and levamisole presents a similar conundrum as with reporting any medication-induced side effect, and warrants a justifiably cautionary response.

Cocaine contaminated with levamisole has been detected since 2003 and the incidence of toxicity caused by this contamination has been increasing rapidly since 2008.[3] The reason for adulteration of cocaine is not known. Levamisole is a veterinary antihelminthic and has been used previously as an immunomodulator and cancer adjuvant. Others have hypothesized[4] that because both cocaine and levamisole are known to increase dopamine in the euphoric centers of the brain, perhaps levamisole is added to enhance or prolong the psychoactive effects of cocaine. The US Department of Justice estimates that approximately 70% of cocaine in the United States may be contaminated with levamisole.[5] Use of cocaine that has been adulterated with levamisole can lead to a constellation of signs and symptoms including agranulocytosis, neutropenia, and a tender, vasculitis-like purpuric skin eruption. The most common site of purpura is on the external ears and cheeks. These characteristic signs and symptoms of levamisole toxicity were first described in children being treated with levamisole.[6] The purpura may progress to bullae and is generally followed by necrosis, resolving several weeks after cessation of cocaine use. Recurrent use of contaminated cocaine generally results in recurrent neutropenia and skin eruptions supporting a causal role. Concomitant symptoms of arthralgias, fever, mouth pain (gums and pharynx), mouth sores, fatigue, and dyspnea have been commonly reported in patients with agranulocytosis[5] associated with cocaine use and in some patients with cocaine-associated purpura.