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

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Abstract

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

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

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.)

Keywords

agranulocytosis; cocaine; drug reaction; levamisole; neutropenia; purpura; vasculitis

This brief case series follows up on the letter¹ 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 [ANCA], 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 literature² 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.

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 hypothesized⁴ 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 agranulocytosis⁵ associated with cocaine use and in some patients with cocaine-associated purpura.

Both smoking and snorting contaminated cocaine has been associated with the described toxicities. Both men and women can be affected. The half-life of levamisole is 5.6 hours and only 2% to 5% of the parent drug can be found in the urine. Gas chromatography and mass spectrometry are required for detection.⁴ Because of these difficulties in testing and because other treatable causes of vasculitis may be present, levamisole-induced toxicity must remain a diagnosis of exclusion. Checking the urine or serum for levamisole must be performed within 48 hours and because the sensitivity is not known for this methodology, testing may not necessarily be indicated for routine clinical management. Despite the striking clinical presentation, most cases resolve without long-term sequelae. Elevated serologic markers tend to resolve after 2 to 10 months. Interventions have included broad-spectrum antibiotics for patients with fever and agranulocytosis to systemic steroids for patients with more prominent vasculitis. Although many of our patients were treated systemically, once the offending agents (cocaine and levamisole) have been discontinued, it is not known if systemic steroids are required for resolution.

Published case reports have described patients with medical histories that involve both chronic and acute infections along with signs of chronic autoimmune disease. Other patients have had absolutely no medical history. Because neutropenia is a common presenting sign of this toxicity, systemic bacterial or fungal infections caused by immunosuppression may be presenting features of levamisole-induced toxicity. These infections should be carefully

considered and appropriately treated in patients who have already been given a diagnosis of levamisole-induced toxicity.

The differential diagnosis for levamisole-contaminated cocaine toxicity includes many of the same diagnoses as LCV or drug toxicities and is outlined in more detail in the prior letter by Waller et al.¹ Secondary causes of LCV such as bacterial or viral infections, medication reactions, neoplasms, and autoimmune connective tissue disorders should be considered. Cryoglobulinemia, polyarteritis no-dosa, Wegener granulomatosis, and idiopathic thrombocytopenic purpura may also have similar presentations. Sometimes nonvasculitic purpura on the lower extremities may be palpable such as those seen in excessive anticoagulation with warfarin or heparin or disseminated intravascular coagulation.

A skin biopsy specimen may be helpful to rule out other diseases, but will not implicate cocaine or levamisole directly. Although skin lesions appear “vasculitic” and fibrin thrombi are commonly seen in the vessels, not all histologic features of LCV have been present in all reported cases. In the two patients at Harbor-UCLA Medical Center who had direct immunofluorescence studies performed on the skin biopsy specimens, the results supported an immune complex-mediated process (Fig 1 and Table I). Clinicians suspecting levamisole-induced toxicity should consider a urine toxicology screen to detect cocaine use, liver function tests, a complete blood cell count with differential, a routine urinalysis, renal function tests, ANCAs, antiphospholipid antibodies, lupus anticoagulants, and coagulation studies. A lumbar puncture or imaging studies can be ordered to rule out other causes of vasculitis or altered mental status if localizing symptoms are present. Consultations may be needed with critical care, infectious disease, or rheumatology. Depending on the level of cocaine abuse or the use of other addictive drugs, psychiatry may need to be consulted during withdrawal.

Although very suggestive, the use of cocaine before a characteristic purpuric eruption does not necessarily prove causation. Indeed, prior reports of cocaine-induced vasculitis may suggest cocaine itself can cause this dangerous side effect.⁷ Alternatively, prior reports may not have considered contamination with levamisole. Because many patients may not report cocaine use and the dose of levamisole required to induce vasculitis or agranulocytosis is not known, it is very difficult to determine the true rate of levamisole-induced toxicity in the general public at this time. It is important to identify other treatable causes of vasculitis such as infection or autoimmune disease. Because many of these patients do have positive ANCA serologies and positive lupus anticoagulant,^{4,6} distinguishing these conditions may require consultation with a rheumatologist. Possibly even more important is to consider levamisole-induced toxicity in the differential diagnosis in patients undergoing evaluation for presumptive autoimmune disease.

In summary, we believe our case series of 6 remarkably similar recent patients with purpuric eruptions, necrosis, and eschars of the ears after cocaine use in New York and California supports the theory posed by the University of California, San Francisco group¹ that their patients’ skin problems could have been caused by levamisole-contaminated cocaine. The astute dermatologist or primary care physician should be aware of this new public health

problem. They should be able to recognize the characteristic skin lesions and be wary of the potential development of agranulocytosis.

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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.



Fig 1.

A, Ear, cheek, and thigh of 46-year-old woman. **B**, Ear, left cheek, and right cheek of 57-year-old woman. **C**, Ear, neck, and thigh of 46-year-old woman. **D**, Cheek, nose, and thigh of 22-year-old woman. **E**, Ear (*left*) and trunk (*middle*) of 37-year-old man on admission, and same ear resolving 1 week later (*right*). **F**, Ear, abdomen, and arm of 50-year-old man. **G**, Representative histopathology from ear of patient (*E*) showing leukocytoclastic vasculitis at 32.5 (*left*), $\times 20$ (*middle*), and $\times 40$ (*right*) magnification. **H**, Representative direct immuno-fluorescence of ear biopsy specimen demonstrating positive IgM (*left*) and positive fibrin (*right*) in vascular and perivascular spaces.

Table 1

Patient characteristics

Patient	Medical history	Presentation, Tx, and outcome	Laboratory results	Urine toxicology	Skin biopsy specimen results
A 46 y Caucasian Female	Substance abuse	1-mo History of purpura and necrosis on bilateral ears, cheeks, and upper and lower extremities Tx: steroids Initial improvement, lost to f/u	Neutropenia: no P-ANCA >2500 --Positive MPO and PR3 Anticardiolipin IgM positive ANA, hepatitis, HIV negative Cryoglobulins negative	Not performed on admission, but previously positive for cocaine and THC	Small vessel vasculitis with intravascular thrombi
B 57 y African American Female	Substance abuse, depression, anxiety, hypertension, and recurrent <i>Staphylococcus aureus</i> skin infections	1-wk History of purpura and necrosis of bilateral ears and cheeks Tx: IV antibiotics, gradual improvement; neutropenia treated with filgrastim Relapse 6 mo later with same presentation, laboratory results, and positive cocaine urine test result	Neutropenia: yes P-ANCA >2500 --Positive MPO and PR3 Anticardiolipin IgM positive ANA, SSA, SSB, dsDNA, C3, C4 negative Hepatitis, HIV negative Cryoglobulins negative	Positive for cocaine	Intravascular thrombi
C 46 y Hispanic Female	Substance abuse, hepatitis C, hypothyroidism	Bilateral ear necrosis, diffuse retiform purpura with necrosis on neck, trunk, and extremities Tx: IV methylprednisolone Gradual improvement initially, lost to f/u	Neutropenia: yes P-ANCA 640, C-ANCA, 1280 Anticardiolipin IgM positive ANA, SSA, SSB, dsDNA, C3, C4 negative Cryoglobulins negative	Positive for cocaine and opiates	Multiple intravascular thrombi
D 22 y Hispanic Female	Substance abuse	3-wk History of purpura and necrosis of bilateral ears, cheeks, nasal tip, buttocks, and thighs Tx: IV methylprednisolone Skin and neutropenia improved rapidly	Neutropenia: yes P-ANCA 2560 --Negative MPO and PR3 Anticardiolipin IgM positive ANA, SSA, SSB, dsDNA negative Cryoglobulins negative	Positive for cocaine and opiates	Small vessel vasculitis with multiple intravascular thrombi
E 37 y Hispanic Male	Substance abuse	Tender bilateral ear purpura and necrosis, diffuse retiform purpura on trunk and extremities Tx: supportive Rapid improvement of skin	Neutropenia: no P-ANCA 640 CRP 16.2 mg/L, ESR 41 mm/h, D-dimer elevated at 3260, LDH 390 IU/L, PTT 37.7 sec, INR 1.3 ANA 1:40 HIV negative	Positive for cocaine	Leukocytoclastic vasculitis IF: vascular deposits of IgM, with weak staining for C3, IgG, and IgA; vascular and perivascular staining for fibrin
F 50 y African American Male	Substance abuse	Altered mental status; 3-wk history of tender purpura and necrosis of bilateral ears; purpura and bullae	Neutropenia: no P-ANCA 640 CRP 5.67 mg/L, ESR 32 mm/hr, D-dimer elevated at 548, PTT	Positive for cocaine	Leukocytoclastic vasculitis and focal panniculitis IF: vascular deposits of IgM, IgA, C3, and weakly IgG;

Patient	Medical history	Presentation, Tx, and outcome	Laboratory results	Urine toxicology	Skin biopsy specimen results
		over trunk and extremities Tx: antibiotics Mental status and skin improved rapidly	39.6 sec ANA 1:40 HIV negative		interstitial and vascular positive staining for fibrin

ANA, Antinuclear antibody; C-ANCA, cytoplasmic antineutrophil cytoplasmic antibody; CRP, c-reactive protein; dsDNA, double-stranded DNA; ESR, erythrocyte sedimentation rate; *f/u*, follow-up; IF, immunofluorescence; INR, international normalized ratio; IV, intravenous; LDH, lactate dehydrogenase; MPO, antimyeloperoxidase antibodies; P-ANCA, perinuclear antineutrophil cytoplasmic antibody; PR3, anti-proteinase-3 antibodies; PTT, partial thromboplastin time; SSA, Sjogren Syndrome A (anti-Ro); SSB, Sjogren Syndrome B (anti-La); THC, tetrahydrocannabinol (marijuana component); Tx, treatment.