Breaking-Out Bad: A Case of Levamisole-Induced Vasculitis

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About the Authors

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Summary

The addition of harmful adulterants to cocaine has become widespread in recent years and constitutes a novel etiological agent for disease. One agent in particular, the veterinary anthelmintic “levamisole,” has been increasingly used, owing to its potentiating effects of cocaine and its ability to pass crude methods of detection. Levamisole has been shown to cause a vasculitic syndrome of retiform purpura and skin necrosis, as well as leukopenia and autoantibody formation.

Résumé

L'ajout d'adultérants nocifs à la cocaïne s'est répandu dans les dernières années, à tel point que ces produits sont devenus de nouveaux agents étiologiques de maladies. L'un de ces agents en particulier, l'anthelminthique d'usage vétérinaire lévamisole, est de plus en plus utilisé pour son effet potentialisateur de celui de la cocaïne et parce qu'il n'est pas détecté par les méthodes de dépistage élémentaires.

Introduction

We present the case of a 56-year-old man with a history of “crack” cocaine with levamisole-induced vasculitis (LIV), confirmed by detection in the urine. He exhibited classic features of LIV, including purpuric rash over the ears, mild leukopenia, and significantly elevated cytoplasmic anti-neutrophil cytoplasmic antibodies (c-ANCA), with biopsy features of leukocytoclastic vasculitis. The patient was counselled to abstain from cocaine use and was treated with daily prednisone. Following a week, his symptoms rapidly improved.

This case highlights the clinical features, investigations, and management of a patient with LIV. It is important for health care practitioners to be able to recognize this disease phenomenon and gain familiarity with its diagnosis and treatment.

Background

Cocaine is the second most commonly used illicit substance in Canada. Its use has been linked to a variety of autoimmune syndromes that vary widely in clinical presentation and distribution.^{1,2} Moreover, the addition of harmful potentiating

substances to cocaine, such as levamisole, a veterinary anthelmintic agent banned for human use, has become increasingly widespread and constitutes a novel etiological agent for disease.³ We present a case of levamisole-induced vasculitis (LIV) and discuss its clinical features, diagnostic work-up, and management.

Case

A 56-year-old white man with a history of intravenous drug use⁴ (IVDU), chronic hepatitis C infection, type 2 diabetes mellitus, hypothyroidism, and major depressive disorder with a five-year history of increasing “crack” cocaine use presented to the emergency department with a two-month history of purpuric painful lesions. They were located preferentially on his inner thighs and knees, the posterior surfaces of his arms, and over his ears, the latter location being where they first appeared. He also endorsed a three-week history of a 10-pound unintentional weight loss, night sweats, chills, and diffuse arthralgia.

The patient's medications included metformin, gliclazide, ramipril, and citalopram. He had last smoked “crack”

cocaine four days prior. He had a known drug allergy to fluoroquinolones and hypersensitivity to alcohol. He denied any recent sick contacts, new sexual partners, or recent travel. Review of systems was negative.

On examination, the patient appeared well. He was afebrile. Examination of the skin revealed purpuric patches on the helices of the ears bilaterally, with regions of overlying frank necrosis and crusting eschars (Figure 1). The lesions were extremely tender on palpation. Large patches of retiform and stellate purpura were located symmetrically over the bilateral triceps, inner thighs, and knees (Figures 2 and 3). No other significant findings were present on physical examination.

On investigation, the leukocyte count was 3.4. The rest of the complete blood count, electrolytes, and liver and renal function tests were unremarkable. Urine dipstick was negative for proteinuria. ANA, RF, HIV screen, and hepatitis B serology were negative. c-ANCA was elevated at 4.3, and perinuclear antineutrophil cytoplasmic antibodies (p-ANCA) was normal. A urine toxicology screen confirmed ingestion of cocaine, levamisole, and citalopram.

A punch biopsy of a skin lesion over the back of the right arm was performed and the histology was in keeping with leukocytoclastic vasculitis. Specifically, fibrinoid necrosis of the blood vessel wall with perivascular neutrophilic infiltrate with occasional lymphocytes, eosinophils, and rare histiocytes, and nuclear dust secondary to karyorrhexis or leukocytoclastia was seen (Figure 4).

The patient was prescribed prednisone 20 mg daily and returned for follow-up in one week's time. During this time he had abstained from cocaine use. There was significant improvement in the appearance of his cutaneous lesions. The lesions had faded in colour and there was less overlying erythema. The patient endorsed pruritis at the sites of the lesions. The 2-x-2-cm necrosed lesion over the left ear helix remained unchanged.

Discussion

Ingestion of cocaine contaminated with levamisole is becoming increasingly recognized as a cause of vasculitis. A 2008 figure estimated that 11% of cocaine used in Canada is contaminated with levamisole, while the number is nearly seven-fold greater in the US.³ At the Hamilton General Hospital, 89% of urine samples (31 of 35) from January through April 2012 sent for confirmation of cocaine were also confirmed positive for levamisole.

Levamisole is currently used as an anthelmintic agent in veterinary medicine; previously, it has been a chemotherapy agent in humans for colon cancer and a treatment for recurrent pediatric nephrotic syndrome. Levamisole was banned in Canada in 2003 due to reports of agranulocytosis.⁴ Levamisole has become widely used as an additive or filler, because it

Figure 1. Patient's left and right ears with retiform purpura and necrotic eschars.

Figure 2. Patient's left and right medial aspect of legs with retiform pupura.

Figure 3. Patient's left and right back of arms.

Figure 4. Histopathological features of levamisole-induced vasculitis

potentiates the effects of cocaine and remains essentially undetectable to crude practices that test the purity of cocaine.

As an immune-modulating agent, levamisole has been shown to alter macrophage chemotaxis and T-cell lymphocyte function, enhance activation and maturation of human monocyte-derived dendritic cells, and inhibit the production of endogenous immunosuppressive factors.⁵ In the brain, levamisole augments dopaminergic and endogenous opioid effects via D1 dopamine receptor upregulation.⁵ Levamisole has been postulated to augment the effects of cocaine via inhibition of monoamine oxidase inhibitor (MAOI) and catechol-O-methyltransferase activity, thus prolonging the presence of catecholamine neurotransmitters in the neural synapses, adding to the reuptake-inhibition effect of cocaine.⁶

LIV is associated with several characteristic clinical, pathological, and serological findings. There is a 4:1 female predominance of clinical manifestations.³ The largest review to date, conducted by Larocque and Hoffman (2012),³ concluded that neutropenia and dermatologic manifestations were the most common findings consistent with LIV. In a recent review, leukopenia and neutropenia were reported among 63% of patients.⁷ With respect to cutaneous findings, lesions over the lower extremities, ears, and face have been reported in 60–80% of patients.⁸ In addition, the rash associated with LIV has typically been described as a retiform purpuric rash, with possible areas of central necrosis.^{3,7,8} On skin biopsy, common findings include leukocytoclastic vasculitis, as evidenced by perivascular inflammatory infiltrates with fibrinoid necrosis; thrombotic microangiopathy; and gross necrosis.^{3,7,8} Serologic findings of LIV include positive ANCA, with up to 90–100% of patients with positive p-ANCA and 50–60% of patients with positive c-ANCA.^{3,7} Other autoantibodies such as antiphospholipid antibody; antihuman neutrophil antibody; and anti-nuclear antibodies (ANAs), including anti-double-stranded DNA and lupus anticoagulant, have also been shown to be associated.^{9,10}

The pathogenesis of LIV is not fully known, although some hypothesize that levamisole may be directly cytotoxic to neutrophils or endothelial cells.¹¹ Other theories suggest it may be a nonspecific immune adjuvant in certain individuals predisposed to autoimmunity, or may induce loss of tolerance to specific autoantigens in a manner that initiates or perpetuates autoimmunity.¹¹ Some previous studies have suggested an underlying mechanism of immune complex-deposition involving Ig antibodies and complement.⁴

In terms of the natural progression of the disease, symptoms are typically self-resolving once exposure to the offending substance is stopped. Certain cases involving significant necrosis, neutropenia, continued cocaine use, or worsening disease despite treatment have been treated with steroids or

other immunosuppressive agents, as well as anticoagulation for thrombotic complications; however, there is no evidence to suggest this portends a better outcome.¹² In the case of severe cutaneous involvement, debridement, grafting, and appropriate management in a burn unit is generally advisable.

Unfortunately, LIV has been shown in studies to have a high recurrence rate.³ Integral to the management of the acute presentation is counselling for the underlying drug abuse. The importance of cessation of cocaine use must be emphasized, in order to ensure recovery. Patients desiring assistance for their drug abuse should be made aware of such resources as addictions counselling services, outpatient clinics, social work services, and support groups.

The case presented here describes a classic presentation of levamisole-induced vasculitis secondary to cocaine use. Cutaneous findings of retiform purpura overlying the helices of the ears, ANCA positivity, and leukocytoclastic vasculitis on skin biopsy are classic findings. A urine levamisole test by gas chromatography-mass spectrometry method confirmed our hypothesis.

The decision to treat with oral prednisone was largely based on the presence of small areas of necrosis, as well as the presence of mild leukopenia. To date, there are no evidence-based guidelines directing health care professionals to treatment options. As noted, although medications can provide short-term resolution in affected individuals, definitive cure and prevention of recurrence necessitates cessation of cocaine use.

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