

## BRIEF ARTICLES

## Painful Retiform Purpura with Cutaneous Necrosis

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## ABSTRACT

Levamisole-induced vasculitis is characterized by a painful, purpuric rash in a retiform or stellate pattern with or without central necrosis that commonly involves the trunk, extremities, digits, distal nose, cheeks, and ear helices. This clinical syndrome is associated with the use of levamisole-adulterated cocaine. Histologic findings for levamisole-induced vasculitis are not disease specific but may include leukocytoclastic vasculitis, microvascular thrombosis, and panniculitis. Laboratory findings of levamisole-induced toxicity include agranulocytosis, neutropenia, hepatotoxicity, glomerulonephritis, pulmonary hemorrhage, and positive p-ANCA, c-ANCA tests, ANA, or lupus anticoagulant. The differential diagnosis for levamisole-induced vasculitis includes leukocytoclastic vasculitis, drug reaction, cryoglobulinemia, idiopathic thrombocytopenic purpura, granulomatosis with polyangiitis, Churg-Strauss syndrome, and polyarteritis nodosa. Levamisole-induced vasculitis typically resolves spontaneously with cessation of cocaine use however; recurrence is common following re-exposure.

## INTRODUCTION

Levamisole is an antihelminthic veterinary medication that was previously used as an immunomodulator in humans to treat malignancies, autoimmune disorders, and pediatric nephrotic syndrome.<sup>1</sup> The drug was removed from American and Canadian markets in 2000 and 2003, respectively, due to adverse effects of agranulocytosis, leukopenia, thrombocytopenia, and skin vasculitis.<sup>1-3</sup> Since 2003, levamisole has been detected as a cocaine contaminant.<sup>2</sup> Levamisole is an attractive diluent of cocaine because it passes the “bleach test,” a street test for cocaine purity.<sup>3</sup> Additionally, levamisole may amplify the euphoric high of cocaine through inhibition of monoamine

oxidase and catechol-O-methyltransferase,<sup>1,3</sup> and potentiation of nicotinic acetylcholinergic signals.<sup>2</sup>

In 2009, 71% of the cocaine samples in the United States,<sup>4</sup> and 50% of samples in the United Kingdom tested positive for levamisole.<sup>5</sup> The concentration of levamisole in cocaine has also been increasing,<sup>2</sup> causing cases of levamisole-induced toxicity to be more common. We herein report a case of a 46-year-old Caucasian male who developed Levamisole-Induced Vasculitis from crack cocaine use.

## CASE PRESENTATION

A 46-year-old Caucasian male with a past medical history significant for hepatitis C

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virus (HCV) infection, metastatic melanoma, and years of crack cocaine use presented to the emergency department with a one-week history of painful lesions involving the nose, limbs, and mouth.

Skin exam showed painful purpura of the ears and right nasal ala (Figure 1A), retiform purpura with necrosis of all four extremities (Figure 1B), and an ulcer of the left buccal mucosa (Figure 1C). He denied any personal history or family history of vasculitis, but reported an increase in crack cocaine use shortly before the onset of his skin lesions and a similar episode following cocaine use 5 years ago.

His initial laboratory values were significant for microcytic anemia, decreased complement levels, and a positive drug screen for cocaine. HCV viral load was undetectable and serum cryoglobulins were negative. Autoimmune workup was positive for anti-myeloperoxidase anti-neutrophil cytoplasmic antibodies (p-ANCA) and anti-PR3 anti-neutrophil cytoplasmic antibodies (c-ANCA), and negative for anti-nuclear antibodies, anti-double-stranded DNA antibodies, and anti-Smith antibodies.

Given the temporal relationship of cocaine use to the onset of the purpura, characteristic ear involvement, and positive p-ANCA and c-ANCA tests, the patient was diagnosed with levamisole-induced vasculitis. He agreed to cease cocaine use and was treated with high-dose corticosteroids and debridement of necrotic tissue. He later developed secondary methicillin resistant *Staphylococcus aureus* infection of his right lower extremity, which was successfully treated with trimethoprim-sulfamethoxazole and amoxicillin clavulanate.

## DISCUSSION

Characteristic findings of levamisole-induced toxicity include purpura, agranulocytosis, neutropenia, and hepatotoxicity, along with infrequent findings of glomerulonephritis and pulmonary hemorrhage. Approximately 90% of patients have cutaneous manifestations, most frequently purpura of the ear helices and cheeks and retiform purpura of the extremities. The purpura often become necrotic and may develop bullae and abscesses.<sup>1,4</sup> Fever, oral sores, fatigue, and dyspnea are also common manifestations.<sup>6</sup>

The differential diagnosis for levamisole-induced vasculitis includes leukocytoclastic vasculitis, drug reaction, cryoglobulinemia, idiopathic thrombocytopenic purpura, granulomatosis with polyangiitis, Churg-Strauss syndrome, and polyarteritis nodosa.<sup>2,6</sup> Histologic findings for levamisole-induced vasculitis are not disease specific but may include leukocytoclastic vasculitis, thrombosis, and panniculitis.<sup>2,6</sup> Diagnosis is therefore made through laboratory values and clinical history. Useful tests include complete blood cell count with differential, comprehensive metabolic panel, coagulation studies, antineutrophil cytoplasmic antibodies, antiphospholipid antibodies, cryoglobulins, and lupus anticoagulants.<sup>2,6</sup> The majority of patients with levamisole-induced vasculitis are positive for p-ANCA, while c-ANCA positivity has been reported in about 50% of patients.<sup>3,4,7</sup> Anti-double-stranded DNA and lupus anticoagulant studies may also be positive.<sup>2</sup> The anti-human elastase antibody is a sensitive and specific test to cocaine-induced lesions<sup>8</sup> which can be helpful to distinguish levamisole-induced vasculitis from ANCA-associated vasculitis.<sup>2</sup> In a study examining available case reports, anti-human elastase antibody was the only antibody found to be positive in all patients with levamisole-

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**Figure 1** Levamisole-induced Vasculitis in a 46-year-Old Male. (A) Purpura of Right Ear. (B) Purpura with Necrosis of Left Lower Extremity. (C) Ulcer of Left Buccal Mucosa.



induced vasculitis, and this antibody positivity was more indicative of levamisole-induced vasculitis than other autoimmune vasculitis.<sup>9</sup> Testing urine for levamisole is not recommended as it has a short half-life of 5.6 hours, and only 2% to 5% of the parent drug is present within 48 hours of use. Additionally, levamisole testing is expensive and limited in availability.<sup>3,6</sup> The propensity for levamisole-induced vasculitis to affect the ears and zygomatic area also helps distinguish it from other ANCA-associated vasculitides.<sup>1</sup>

Levamisole-induced vasculitis typically resolves spontaneously with cessation of cocaine use. Adjuvant care can include systemic corticosteroids, surgical debridement, antibiotics, and plasmapheresis.<sup>6,10</sup> It is important to note, however, that levamisole-induced vasculitis frequently recurs following re-exposure to contaminated cocaine and therefore, complete abstinence must be counseled.<sup>11</sup>

## CONCLUSION

The use of levamisole as a cocaine diluent has become increasingly popular, making awareness of levamisole-induced vasculitis imperative for clinicians. To distinguish levamisole-induced vasculitis from other forms of vasculitis, anti-human elastase antibody has been shown to be a useful tool, as it is negative in other types of autoimmune vasculitis.

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