Levamisole-induced occlusive necrotising vasculitis in cocaine abusers: an unusual cause of skin necrosis and neutropenia

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Key words
Cocaine; Leukocytoclastic; Levamisole; p-ANCA; Vasculitis

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Abstract
We present three cases describing the various skin manifestations of presumed levamisole-contaminated cocaine use. Antibody-mediated vasculitis and neutropenia were consistent findings in these cases and repeat exposure resulted in distinct dermatologic complications. This phenomenon of levamisole-induced vasculitis and neutropenia is being increasingly described and has characteristic wound manifestations that must be recognised and treated early.

Case 1
A 45-year-old Caucasian female with a history of tobacco dependence was admitted with small necrotic skin lesions on her legs and thighs. Several days prior to the current admission she had presented to an outside hospital with neutropenia (absolute neutrophil count of 1000/μl) and lethargy. Infectious work up revealed negative serology for human immunodeficiency virus (HIV) and hepatitis B and C. She was treated with a single dose of granulocyte colony stimulating factor (filgrastim) 5 mcg/kg subcutaneously and discharged herself against medical advice. She presented 24 hours later with multiple ulcerative lesions affecting her legs, thighs, arms, face and ears (Figure 1A–C). A rheumatologic evaluation revealed a perinuclear antineutrophil cytoplasmic antibody (p-ANCA) of 1:640, with positive proteinase-3 (PR3) and myeloperoxidase (MPO). Although the patient had initially denied exposure to cocaine, urine toxicology was positive for exposure to cocaine and levamisole. The patient was treated with intravenous methylprednisolone 1 g per day for 3 days followed by prednisone 60 mg daily with slow taper. The patient also underwent 14 dives of hyperbaric oxygen, wound debridement and xenograft. Continued improvement in the ulcers was noted and the patient was discharged following a 28-day hospitalisation.

One month later, the patient was readmitted for new necrotic lesions, requiring debridement and antibiotics. Toxicology screen was again positive for cocaine and levamisole. Skin biopsy showed inconclusive necrotic tissue.

Key Messages
- we present three cases describing the various skin manifestations of presumed levamisole-contaminated cocaine use
- case 1: a 45-year-old Caucasian female with a history of tobacco dependence was admitted with small necrotic skin lesions on her legs and thighs
- infectious work up revealed negative serology for human immunodeficiency virus (HIV), hepatitis B and C
- although the patient had initially denied exposure to cocaine, urine toxicology was positive for exposure to cocaine and levamisole
- one month later, the patient was readmitted for new necrotic lesions requiring debridement and antibiotics
- toxicology screen was again positive for cocaine and levamisole
- six months after the original admission the patient was readmitted with blistering skin lesions, leucopenia and joint pain; toxicology was negative
- the symptoms responded to methylprednisolone 1 g per day for 2 days followed by 30 mg of prednisone and methotrexate
- the patient has now been followed for 24 months since the initial presentation and her wounds remain healed;
she remains abstinent from cocaine and has stopped smoking
• case 2: a 40-year-old African-American female was admitted for chest pain 2 hours after smoking ‘crack’ cocaine
• there was a discrete, hyperpigmented rash noted on her left arm, which rapidly expanded within 24 hours into ecchymotic lesions
• urine toxicology was negative. The symptoms responded to
• while some have implicated vasculitis as an aetiopathogenic mechanism emerging pharmacologic data suggests this may be a delayed hypersensitivity reaction to a reactive metabolite of the levamisole

A 40-year-old African-American female was admitted for chest pain 2 hours after smoking ‘crack’ cocaine. There was a discrete, hyperpigmented rash noted on her left arm (Figure 2A), which rapidly expanded within 24 hours (Figure 2B). Additional ecchymotic lesions developed on the right arm, right leg and left breast, and they evolved into blisters (Figure 2C). The lesions were exceptionally tender to the touch. Initial leukocyte count was 2900/μl. The absolute neutrophil count fell from 400/μl to zero within 48 hours of admission. Antinuclear antibody (ANA) was positive at a titre of 1:320, p-ANCA was also positive at a titre of 1:320; however, MPO and PR3 antibodies were both negative. Urine toxicology was positive for cocaine. However, levamisole and human neutrophil elastase (HNE) testing were not performed. Skin biopsy revealed leukocytoclastic vasculitis (Figure 2D). Bone marrow biopsy showed tri-lineage haematopoiesis. She was treated with granulocyte colony stimulating factor and was subsequently discharged following counselling for cocaine abstinence.

One week later, the patient was readmitted with recurrence of neutropenia and blistering, necrotic skin lesions on her upper and lower extremities (Figure 2E). Urine toxicology was again positive for cocaine. The patient admitted to using the ‘loveboat’ method for inhaling ‘crack’ cocaine, which involves the addition of embalming fluid. The neutropenia and rash improved with oral prednisone 60 mg daily. Four months later, after complete cocaine abstinence, her haematological indices were within normal limits and the rash had healed with residual scarring (Figure 2F).

A 43-year-old African-American female with a history of hypertension presented with a 3-day history of a painful erythematous, purpuric skin rash which started on the thighs and progressed to involve the arms, nose and ears
• case 3: a 43-year-old African-American female with a history of hypertension presented with a 3-day history of a painful erythematous, purpuric skin rash which started on the thighs and progressed to involve the arms, nose and ears
• she reported the use of ‘crack’ cocaine prior to the onset of the rash
• her neutropenia resolved within 3 days of oral prednisone therapy, with commencement of healing of the skin lesions
• the currently reported constellation of symptoms and signs with ischaemic skin lesions at unusual sites associated with neutropenia represents a new entity in the cocaine disease spectrum that is important for wound specialists to be aware of
• our patients exhibited rapid recurrence of symptoms upon rechallenge, thus supporting the recommendation that absolute abstinence from re-exposure to cocaine, levamisole or their metabolites is essential to prevent recurrence of this syndrome
• we have described three cases of levamisole adulterated cocaine-related skin necrosis associated with neutropenia, adding to the expanding literature of this entity
• it is important for wound care specialists to consider this in the differential diagnosis of unusual necrotic skin lesions to ensure that appropriate toxicology specimens are submitted
• while some have implicated vasculitis as an aetiopathogenic mechanism emerging pharmacologic data suggests this may be a delayed hypersensitivity reaction to a reactive metabolite of the levamisole

Six months after the original admission, the patient was readmitted with blistering skin lesions, leucopenia and joint pain. Toxicology was negative. The symptoms responded to methylprednisolone 1 g per day for 2 days followed by 30 mg of prednisone and methotrexate.

The patient has now been followed up for 24 months since the initial presentation and her wounds remain healed (Figure 1D). She is stable on methotrexate 15 mg per week as monotherapy. p-ANCA and MPO are now negative, but she has a persistently positive atypical p-ANCA at a titre of 1:640. She remains abstinent from cocaine and has stopped smoking.

Case 2

A 40-year-old African-American female was admitted for chest pain 2 hours after smoking ‘crack’ cocaine. There was a discrete, hyperpigmented rash noted on her left arm (Figure 2A), which rapidly expanded within 24 hours (Figure 2B). Additional ecchymotic lesions developed on the right arm, right leg and left breast, and they evolved into blisters (Figure 2C). The lesions were exceptionally tender to the touch. Initial leukocyte count was 2900/μl. The absolute neutrophil count fell from 400/μl to zero within 48 hours of admission. Antinuclear antibody (ANA) was positive at a titre of 1:320, p-ANCA was also positive at a titre of 1:320; however, MPO and PR3 antibodies were both negative. Urine toxicology was positive for cocaine. However, levamisole and human neutrophil elastase (HNE) testing were not performed. Skin biopsy revealed leukocytoclastic vasculitis (Figure 2D). Bone marrow biopsy showed tri-lineage haematopoiesis. She was treated with granulocyte colony stimulating factor and was subsequently discharged following counselling for cocaine abstinence.

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Case 3

A 43-year-old African-American female with a history of hypertension presented with a 3-day history of a painful erythematous, purpuric skin rash which started on the thighs and progressed to involve the arms, nose and ears. There was also swelling of the lips. The rash later crusted over and resulted in purple plaques (Figure 3A–C). She reported the use of ‘crack’ cocaine prior to the onset of the rash.

Laboratory assays revealed neutropenia of 1900/μl, with an absolute neutrophil count of 800/μl. Urine toxicology was positive for cocaine. The ANA was positive at 1:320 and the p-ANCA was 1:640, but both the PR3 and MPO antibodies were negative. Rheumatoid factor, c-ANCA, anti-Smith antibody, anti-RNP, HIV, RPR, hepatitis C antibody and anti-cardiolipin antibody were also negative. Skin biopsy of the thigh lesion revealed fibrin thrombi in small vessels with a
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Figure 1 Multiple purpuric and ecchymotic patches. (A) Dorsal aspect of both arms, (B) Anterior aspect of lower limbs, (C) Ulcer on left lower leg, (D) Leg ulcer after healing.

Figure 2 (A) Stellate violaceous patch with an erythematous border, (B) Rapid development of violaceous, ecchymotic patches on the left arm, (C) Tense bullae superimposed on a violaceous background, (D) Histological appearance of the skin biopsy showing thrombosed vessels with perivascular neutrophil infiltrate and vessel wall necrosis, (E) Epidermal necrosis with ruptured blisters on an ecchymotic background, (F) Scarring and depigmented patches with surrounding hyperpigmentation after healing.

demarcated epidermal layer, consistent with drug-induced vasculitis (Figure 3D). Her neutropenia resolved within 3 days of oral prednisone therapy, with commencement of healing of the skin lesions. The patient was referred to a substance abuse specialist.

The patient was admitted a few months later with a similar but more severe ischaemic lesion on the nose as well as neutropenia (Figure 3E). She again admitted to days of cocaine abuse. She received treatment with prednisone 60 mg daily and her symptoms again resolved.

Discussion

North America has the largest cocaine market, accounting for almost 40% of the global cocaine-using population (1). It is estimated that 2.1 million individuals in the USA use cocaine each month (2). As of July 2009, 69% of the cocaine seized at US borders was found to be contaminated with levamisole (3,4). Levamisole is an imidothiazole which is used as an anthelmintic agent in cattle and was developed as an immunomodulating adjunct in colon cancer therapy. It is no longer licensed by the US Federal Drug Administration for human use due to an association with agranulocytosis (5,6).

Cocaine-related mimics of medium- and small-sized vasculitides are well recognised (7–12). ANCA positive, midline granulomatous, perforating lesions of the oral and nasal cavities in chronic nasal cocaine users are known mimics of granulomatosis with polyangiitis (Wegener’s granulomatosis) but are differentiated on the basis of ANCA reactivity to HNE in patients with cocaine exposure (13–17). The currently reported constellation of symptoms and signs with ischaemic skin lesions at unusual sites associated with neutropenia represents a new entity in the cocaine disease
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Figure 3  (A) Purpuric and ecchymotic macules coalescing into large patches on the left forearm, (B) Stellate, ecchymotic patches on the anterior aspect of both legs, (C) Purpuric macules on the face and lips, (D) Histological appearance of the skin biopsy of the thigh showing fibrin thrombi, (E) Gangrenous appearance of the nose after re-exposure to cocaine.

Table 1  Demographics, clinical manifestations and serologies of three cases of levamisole-associated cocaine vasculitis

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
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<tbody>
<tr>
<td>Site of lesion</td>
<td>Lower limbs</td>
<td>Upper limbs</td>
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<tr>
<td>Histology</td>
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<td>Leukocytoclastic vasculitis</td>
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<tr>
<td>WBC/μl</td>
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<td>2900</td>
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<tr>
<td>p-ANCA</td>
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<td>1:320</td>
</tr>
<tr>
<td>c-ANCA</td>
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<td>Negative</td>
</tr>
<tr>
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<tr>
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</tr>
<tr>
<td>Hepatitis C</td>
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</table>

ANA, antinuclear antibody; ANC, absolute neutrophil count; ANCA, antineutrophil cytoplasmic antibody; HIV, human immunodeficiency virus; MPO, myeloperoxidase; PR3, positive proteinase-3.

spectrum (5–7,18–35) that is important for wound specialists to be aware of.

Skin lesions associated with levamisole-tainted cocaine exposure

Wounds associated with levamisole-tainted cocaine are typically asymmetric and may involve the pinnae, breasts and upper extremities, which are unusual sites for other forms of vasculitis or wounds of other aetiologies (18–22). Lesions range from superficial to full-thickness wounds but classically have a stellate, bright, erythematous border with central necrosis (23).

Pathologic features of levamisole-tainted cocaine-associated lesions

Histopathologic review of the patients reported here, along with reports of other cases from the literature, shows that both leukocytoclastic vasculitis and microvascular thrombosis may be seen histopathologically (Table 1).
Pathophysiology of skin necrosis associated with levamisole-tainted cocaine

In all cases of vasculopathy associated with levamisole-tainted cocaine, there is absence of internal organ involvement unlike in other mechanisms of systemic vasculitis. It is impossible to know at this time whether this is due to actions only of the levamisole, or whether there is a synergistic immune reaction between the levamisole and cocaine contributing to these lesions. Several possible aetiologic mechanisms for the skin necrosis have been suggested. Levamisole is an immunomodulator known to stimulate neutrophil chemotaxis (36), dendritic cell maturation (37) and Th1-mediated immunity (6,38). One of the metabolites of levamisole, 6-phenyl-2, 3-dihydroimidazo(2,1b)thiazole, is known to be a lymphocyte stimulator (6) and has been reported to be present in contaminated cocaine (39) and may be a contributor to the immunopathogenesis of these skin lesions.

Another possible aetiopathologic mechanism for the skin lesions with thrombotic vasculopathy is drug-induced antiphospholipid antibodies. Anti-cardiolipin antibodies were negative in all three cases reported here, but other groups have found transient positivity of antiphospholipid antibodies and have postulated that these antibodies may play a pathologic role in this disease (6,32,35,40,41).

Pathophysiology of agranulocytosis associated with levamisole-tainted cocaine

The association between levamisole and agranulocytosis is well recognised (5,42–51), with this side effect affecting 2.5–13% of individuals exposed clinically in a dose-dependent manner. Most case reports document WBC levels below 3000/μl, in some instances with absolute neutropenia. All the cases reported here showed an absolute neutropenia of below 2000/μl, and in two instances, bone marrow biopsies were performed to exclude malignancy. In these biopsies, tri-lineage haematopoiesis was described, in keeping with other case series (36,37,47) and suggesting that the mechanism of neutropenia in these cases may be related to peripheral neutrophil destruction rather than bone marrow suppression.

While human leukocyte antigen (HLA) typing was not performed on the three cases reported here, other case reports suggest an increased risk of levamisole-induced agranulocytosis in HLA-B27 positive patients (48–52). It has been hypothesised that these patients are more capable of metabolising levamisole into the thiazole derivative (6). Another possible mechanism for this association includes an immune-mediated delayed-type hypersensitivity in which levamisole or its metabolites form a hapten with self-antigens, inducing T-cell activation via the HLA-B27 genotype (5). This mechanism has been implicated in agranulocytosis caused by a number of other structurally diverse drugs and would seem to account for both the dose-dependent effect and the association with HLA-B27 genotype. Furthermore, one of the critical enzymes present in peripheral leukocytes and implicated in metabolising drugs to reactive metabolites capable of haptenisation is MPO (5,53). Development of autoantibodies to this molecule in a number of cases of levamisole-tainted cocaine exposure supports this molecule as possibly playing a pathogenic role.

Management of patients with suspected cutaneous lesions associated with levamisole-tainted cocaine exposure

It is critical to consider levamisole exposure early when evaluating a patient with unusual cutaneous lesions so that appropriate toxicology specimens may be submitted. Levamisole has a half-life of about 5 hours, and hence it may be undetectable 48 hours after ingestion. Therefore, early consideration of its use and measurement is necessary to confirm its presence. While all three patients reported here had documented cocaine exposure, levamisole contamination was only confirmed in the urine in one patient.

Resolution of cutaneous and haematologic manifestations with abstinence from exposure is typical. Resolution of neutropenia without corticosteroid or granulocyte colony stimulating factor has been reported, possibly because of the self-limiting effect of the thiazole derivatives of levamisole on neutrophils (5). In our series, neutropenia returned to normal range within 3 days in one patient; however, skin lesions typically took longer to resolve with a spectrum of clinical outcomes from complete wound healing to auto-amputation of skin lesions (particularly in poorly vascularised areas, such as the pinna), depending on the extent of tissue injury at presentation. Debridement may be indicated for subjects with gangrene and severe tissue necrosis.

Use of glucocorticoids by various routes, granulocyte colony stimulating factor, antibiotics, local and hyperbaric wound care, were employed at various time points in these and other reported cases but there is insufficient evidence to support firm recommendations on therapeutic use of these modalities and most cases are managed symptomatically with supportive therapy.

As with other reports of delayed hypersensitivity reactions, our patients exhibited rapid recurrence of symptoms upon rechallenge, thus supporting the recommendation that absolute abstinence from re-exposure to cocaine, levamisole or their metabolites (16) is essential to prevent recurrence of this syndrome.

Conclusions

We have described three cases of levamisole-adulterated cocaine-related skin necrosis associated with neutropenia, adding to the expanding literature of this entity. It is important for wound care specialists to consider this in the differential diagnosis of unusual necrotic skin lesions to ensure that appropriate toxicology specimens are submitted. While some have implicated vasculitis as an aetiopathogenic mechanism, emerging pharmacologic data suggests this may be a delayed hypersensitivity reaction to a reactive metabolite of the levamisole.

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