

Cocaine-Induced Cutaneous Necrosis: More Histologic and Clinical Evidence to Indicate Levamisole as the Culprit



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INTRODUCTION & METHODS

- Levamisole is a veterinary anthelmintic that has been previously used as an immunomodulating agent and cancer adjuvant.
- Cutaneous necrotizing vasculitis from levamisole was first reported in 1978 when it was used in a patient with breast cancer¹.
- Neutropenia from levamisole appears to be due to autoimmune and complement-dependent granulocytotoxic antibodies².
- Purpura of the ears has been described as a vasculopathy in children being treated with levamisole for nephrotic syndrome³.
- Cocaine contamination with levamisole has been detected since 2003 and rapidly increasing as of 2008. Approximately 70% of the US cocaine supply is contaminated with levamisole and it is believed to be used as a cutting agent to potentiate cocaine's euphoric effects.
- We searched PubMed for literature dated from 1970 to 2012 using MeSH terms *cocaine, levamisole, neutropenia, purpura and vasculitis*.
- We describe 3 patients who were found to have purpura of the ears, leukopenia and/or neutropenia, p-ANCA positivity and thrombotic and/or vasculitic histopathology in the setting of cocaine use.

CASE 1

34-year-old female presented with purpura involving bilateral ears, arms and the left thigh. Hemorrhagic bullae were present.

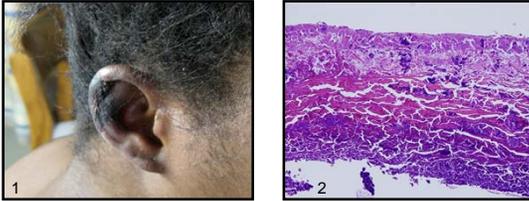


Figure 1. Purpuric necrotic plaque with hemorrhagic crust and black eschar on the helix and anthelix.
 Figure 2. H&E stained section revealing necrotic epidermis and collections of fibrinopurulent exudate (200x).

CASE 2

48-year-old female presented with diffuse tender retiform purpura involving bilateral ears, cheeks, nose, trunk and all extremities.

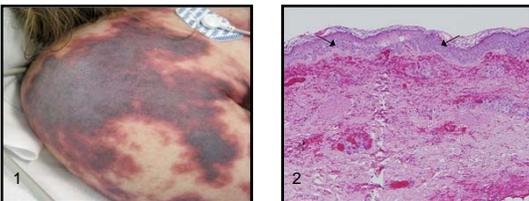


Figure 1. Reticulated purpura with central necrosis on the left shoulder.
 Figure 2. H&E stained section showing microthrombi (arrows) within superficial and deep vessels(100x).

TABLE

	Case 1	Case 2	Case 3 Admission #1	Case 3 Admission #2
Admit to cocaine use	Yes	Yes	No	No
Urine drug screen for cocaine	Positive	Positive	N/A	Positive
Purpura of the ears	Yes	Yes	Yes	Yes
White blood cell count (cell/L)	Admission: 2.9 x 10 ⁹ HD #2: 2.7 x 10 ⁹	Admission: 1.7 x 10 ⁹ HD #2: 1.8 x 10 ⁹	Admission: 2.8 x 10 ⁹ HD #2: 1.9 x 10 ⁹	Admission: 6.8 x 10 ⁹ HD #19: 3.7 x 10 ⁹
Absolute neutrophil count (cell/mm ³)	N/A	Admission: 1,275 HD #2: 918	Admission: 812 HD #2: 551	Admission: 3,773 HD #19: 1,776
p-ANCA titer	<1:20	<1:20	<1:20 Positive upon transfer to KU	N/A
Atypical p-ANCA titer	1:640	1:640	<1:20	N/A
Rheumatological workup	Lupus anticoagulant + Anticardiolipin IgM >100 ANA titer 1:160	Anticardiolipin IgM 11 ANA titer 1:80 Smith Ab + PR3 Ab >100 MPO Ab >100	ANA titer 1:80 C-ANCA 1:160 Smooth muscle Ab weak +	N/A
Histopathological findings	Occlusive vasculopathy with epidermal necrosis and fibrinopurulent exudate	Occlusive vasculopathy with intravascular microthrombi formation and leukocytoclastic vasculitis	N/A	1. Leukocytoclastic vasculitis, panniculitis 2. Dermal vascular thrombosis, perivascular inflammation
Immunofluorescence	Positive for C3 and C1q in dermal blood vessel walls	Negative	N/A	Negative

ANA, Antineutrophil antibody; C-ANCA, cytoplasmic antineutrophil cytoplasmic antibody; MPO, antilysozyme antibodies; P-ANCA, perinuclear antineutrophil cytoplasmic antibody; PR3, anti-proteinase-3 antibodies

CASE 3

46-year-old female with a known history of cocaine abuse presented on two occasions with a purpuric eruption including the arms, legs, buttocks, nose and bilateral ears.



Figure 1. Purpura and bullae formation on helix and anthelix.

Figure 2. Dry black necrotic eschar with erythematous border on nose.

CONCLUSION

- Our patients displayed findings suggestive of levamisole exposure:
 - Retiform purpura of the ears
 - Leukopenia and/or neutropenia
 - p-ANCA positivity
 - Histopathological features of occlusive vasculopathy with or without vasculitis
 - Temporal association with cocaine use
- Cocaine-levamisole-associated cutaneous necrosis is a diagnosis of exclusion made only after other etiologies of vasculitis are ruled out.
- Clinicians suspecting levamisole-induced toxicity may consider a urine toxicology screen, urinalysis, liver and renal function tests, a complete blood cell count with differential, ANCA, antiphospholipid antibodies, lupus anticoagulant and coagulation studies.
- This case series is limited by a lack of testing for levamisole in the blood or urine to prove it as the causative agent.
- Urine testing for levamisole requires gas chromatography/mass spectrometry. Detection is complicated by a short half-life of 5.6 hours.
- With increasing reports of this phenomenon, physicians need to be aware of this emerging public health problem. They should be able to identify the characteristic skin lesions and be mindful of potential complications including agranulocytosis.
- A more detailed understanding of the pathogenesis and patient-specific susceptibilities to cocaine-levamisole-related cutaneous necrosis is warranted.

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