Small Vessel Vasculitis Associated With Cocaine Use

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We report a case of cocaine-induced small vessel vasculitis in a 51-year-old woman. We postulate that levamisole, an adulterant of cocaine, likely is the cause of this increase in cocaine-induced vasculitis. Based on a literature review, we suggest some helpful tests to differentiate cocaine-induced vasculitis from true autoimmune vasculitis in the setting of midline destructive nasal lesions.
Cutis. 2013;91:21-24.

Cocaine use has been reported in association with vasculitis, retiform purpura, and antineutrophil cytoplasmic antibodies (ANCAs).[1-3] We report a case of cocaine-induced small vessel vasculitis in a 51-year-old woman. This case serves as an example of an emerging and dangerous complication of cocaine use.

Case Report

A 51-year-old woman presented to the emergency department with a 2-month history of joint pain and extensive retiform purpura. She denied trauma, foreign travel, wilderness trips, and exposure to ticks. The patient currently was not taking prescription or over-the-counter medications; however, she did admit to intermittent intranasal cocaine use for the last 15 years. Physical examination revealed multiple purpuric plaques on the breasts, cheeks, thighs, and left leg that were several centimeters in diameter, as well as bogginess and erythema of the nasal cavity and a small erosion on the right nasal septum (Figure 1). The plaques were associated with central necrosis and bulla formation. Biopsy of a representative lesion showed fibrinoid necrosis and thrombosis of small- to medium-sized blood vessels, neutrophilic infiltration in and around blood vessel walls, and karyorrhexis (Figure 2). Laboratory investigation showed cocaine and barbiturate metabolites in the urine. Other positive findings included

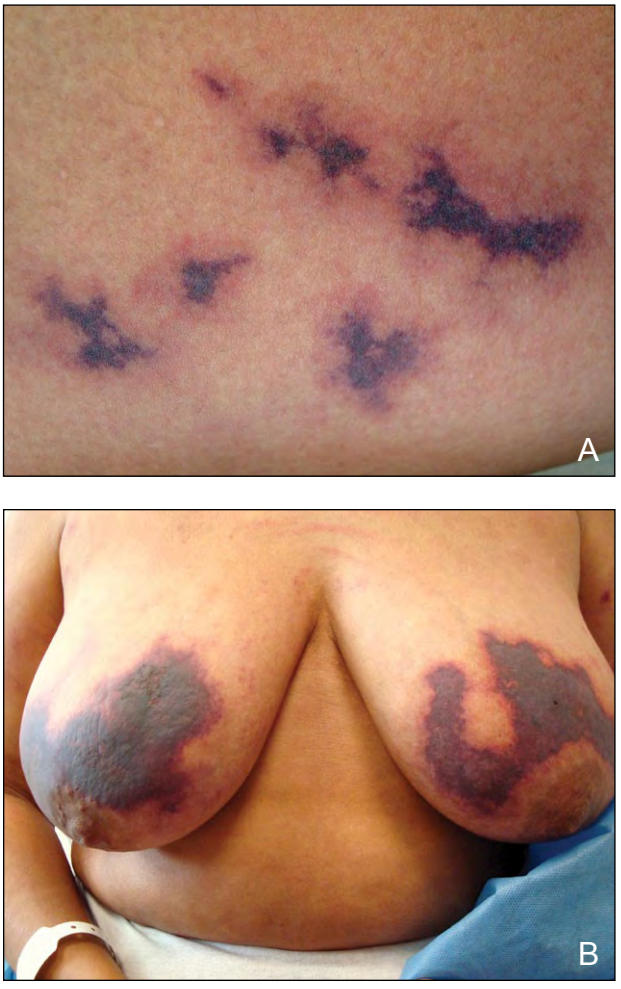

Figure 1. Retiform lesions on the right thigh (A) and breasts (B).

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The authors report no conflict of interest.
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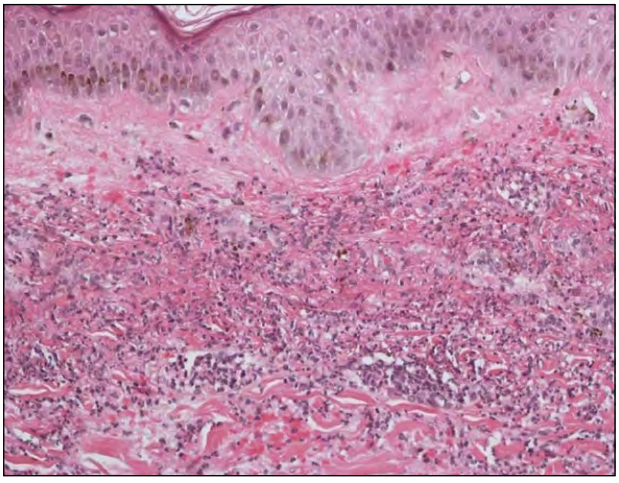

Figure 2. Histologic section of a representative lesion showing neutrophils, abundant karyorrhexis, and perivascular fibrin around superficial blood vessels (H&E, original magnification ×40).

the presence of perinuclear ANCA, anticardiolipin antibody, and heparin-induced thrombocytopenia antibody. The patient was admitted as an inpatient and was administered morphine for pain control. Lesions were debrided and covered with hydrocolloid dressings. The lesions healed within 4 weeks with residual scarring and postinflammatory hypopigmentation. The patient again presented to the emergency department 3 months after the initial episode with retiform purpura of both thighs. Laboratory investigation showed cocaine metabolites in the urine and the presence of perinuclear ANCA and anticardiolipin antibody in the serum. She left the hospital against medical advice and has been lost to follow-up.

Comment

Retiform purpura with associated small vessel vasculitis is a serious complication of cocaine use that is increasing in incidence throughout the United States. Awareness of this complication by physicians can lead to earlier diagnosis and institution of therapy. Although cocaine has been used for decades and cocaine itself has been reported to cause vasculitis, there has been a dramatic increase in the number of reports of cocaine-induced vasculitis in recent years,[1-3] perhaps because at least 35% of the cocaine imported from South America to the United States and Canada is adulterated with levamisole.[4-8]

Levamisole is an anthelmintic medication commonly used in veterinary practice. Because of its immunomodulatory effects, the drug also has been used in humans as an adjuvant treatment of breast and colon cancers and for the treatment of childhood glomerulonephritis.[9,10] Levamisole's immunomodulatory effects are thought to be related to its ability to alter activation and maturation of monocytes and T cells.[11] In addition to its immunologic effects, levamisole also affects the central nervous system. It has the ability to increase dopamine levels in euphoric centers of the brain and alter catecholamine levels in synapses.[5,7,12] Both of these pharmacologic actions are thought to enhance the action of cocaine.

Levamisole is a known cause of neutropenia, agranulocytosis, and vasculitis.[3,6,7,13] Levamisole-associated vasculitis was first reported by Macfarlane and Bacon[14] and Scheinberg et al[15] in 1978. Macfarlane and Bacon[14] reported a case of a 65-year-old woman with rheumatoid arthritis who developed a widespread rash with livedo pattern, predominantly on her arms and legs after 2 months of treatment with levamisole. A biopsy of a typical lesion showed leukocytoclastic vasculitis.[14] Similarly, Scheinberg et al[15] reported a case of a 58-year-old woman with breast cancer who developed a rash and a fever after 3 months of treatment with levamisole. Her rash was clinically consistent with necrotizing vasculitis, and a biopsy of a representative lesion showed leukocytoclastic vasculitis.[15] Laux-End et al[16] reported a case of an 11-year-old girl with nephrotic syndrome who developed a nonpalpable purpuric rash with a livedo pattern on the face, arms, and breasts after more than 3 years of intermittent use of levamisole. A biopsy was not performed; however, ANCA levels were elevated and the rash subsided after discontinuation of levamisole.[16] Menni et al[17] reported a case of a 10-year-old child with nephrotic syndrome who developed bullous hemorrhagic lesions on both earlobes after 1.5 years of treatment with levamisole. A biopsy of one lesion was consistent with small-, medium-, and large-vessel vasculitis. Rongioletti et al[18] reported 5 cases of purpura of the ears and associated vasculitis in children undergoing treatment with levamisole.

Numerous articles have presented cases of retiform purpura, purpuric rashes with a livedo pattern, or necrotizing purpuric lesions in patients who used cocaine that was contaminated with levamisole.[1,6,8,19] It is important to note that the cocaine-abusing patients who presented to Bradford et al[20] and Buchanan et al[8] with purpuric necrotic earlobe lesions showed virtually identical clinical and histologic features as the medical patients reported by Menni et al[17] and Rongioletti et al.[18]

Cocaine snorting is a known cause of midline destructive lesions of the nose and nasal structures and also is associated with the development of ANCAs.[1-3,21] If a patient presents with midline destructive nasal lesions, the physician must consider natural killer cell lymphoma; advanced basal cell or squamous cell carcinomas; an infectious process such

as tertiary syphilis, leishmaniasis, rhinoscleroma, or lupus vulgaris; and Wegener granulomatosis (WG) in the differential diagnosis.

The presence of ANCAs is suggestive but by no means pathognomonic of a diagnosis of WG or any other form of vasculitis. The criteria for a diagnosis of WG include biopsy-proven necrotizing as well as granulomatous vasculitis of the upper or lower respiratory tracts, kidneys, or skin.[22] Typically, WG is associated with elevated cytoplasmic ANCAs with antiproteinase 3 specificity, whereas cocaine use often is associated with elevated human neutrophil elastase (HNE).[1,2] Patients with WG usually are negative for HNE.[2] The presence of ANCAs in cocaine users may be a secondary phenomenon resulting from ischemic damage to nasal mucosa and proliferation of *Staphylococcus aureus*.[23] Damage may not necessarily be grossly visible, but it may be enough to trigger development of ANCAs.

In the presence of midline destructive lesions and positive ANCAs, urine should be tested for cocaine metabolites because patients often do not admit to cocaine use. In addition, ANCAs binding to HNE frequently are found in cocaine-induced midline destructive nasal lesions but not in WG,[2,3] which may serve as a diagnostic marker separating the 2 conditions.[3] Human neutrophil elastase ANCAs do not appear to be pathogenic.[24]

Conclusion

Vasculitis associated with cocaine use is a growing problem. Duflou et al[25] reported a fatal outcome from use of cocaine that was contaminated with levamisole. The paucity of reports of vasculitis in cocaine users as well as the substantial number of prior reports of levamisole-induced vasculitis complicating its medical use suggest that levamisole and not cocaine is the cause of this phenomenon. The presence of ANCAs in vasculitis and destructive nasal lesions does not necessarily indicate WG. Often, ANCAs can be secondary effects of cocaine use and are not necessarily pathogenic. Furthermore, the presence of HNE ANCAs, which are common in cocaine users, may help differentiate the 2 conditions.

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