Levamisole-induced vasculitis

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Levamisole-contaminated cocaine is an increasingly reported cause of a syndrome characterized by vasculitic skin lesions and immunologic abnormalities. With approximately 70% of cocaine in the United States now contaminated with levamisole, the incidence of this syndrome is likely to increase. We report two cases of this syndrome and review its clinical presentation, course, and prognosis.

DESCRIPTION

The first patient, an African American woman, presented with recurrent necrotizing vasculitis of her ears (*Figure 1*) and was found to have positive serology for cytoplasmic antineutrophil cytoplasmic antibody, human neutrophil elastase antibody, and anticardiolipin antibody. The second patient was an African American woman with widespread necrotizing vasculitis of her ears, nose, cheeks, and about 30% of her body surface area (*Figure 2*). She also had necrotizing pneumonia. Serologic findings were similar to those of the first case. She did not improve despite maximum supportive management and died. The *Table* shows the major laboratory and clinical features of the cases.

DISCUSSION

Levamisole-induced vasculitis was first described in the 1970s. This syndrome produces a characteristic clinical presentation of vasculitis in association with a variable pattern of immunologic disturbances. In a case series of five children treated with levamisole for nephrotic syndrome, all five developed necrosis of their ears, with variable involvement of their cheeks and extremities (1). Levamisole was originally marketed as an anthelmintic agent but was also found to have major immunomodulatory properties. It induced interferon synthesis and synergized the effect of steroids and other immunosuppressants. It was used in cancer therapy, to treat various immunological renal diseases, and to treat a number of skin diseases, including Behçet's disease. However, the drug was withdrawn from the

human market in 1999 because of serious side effects including leukopenia, agranulocytosis, and skin vasculitis (2). It is still available as a veterinarian deworming drug.

Relevant to this manuscript, levamisole has also been recognized as an adulterant in illicit cocaine since 2003 (3). A 2009 national survey found that approximately 70% of cocaine in the USA is contaminated with levamisole (2, 3). Levamisole is added to cocaine because it potentiates its stimulant effects by inhibiting both monoamine oxidase and catechol-*O*-methyltransferase activity, thereby prolonging the action of catecholamines in the neuronal synapse and increasing the reuptake-inhibition

Figure 1. Case 1: (a) leg ulcer, (b) nasal skin necrosis, and (c) ear skin necrosis.

Figure 2. Case 2: (a) ear necrosis, (b) facial scar, and (c) leg scars and bullae formation.

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Table. Characteristics of the two cases of levamisole-induced vasculitis

Variable	Case 1	Case 2
Age (years)	40	50
Race	African American	African American
Urine cocaine screen	Positive	Positive
ESR (mm/hr)	52	40
CRP (mg/dL)	4.5	13.8
Serum levamisole	Negative	Not checked
Antinuclear antibody titer	1:12,560	1:640
Antineutrophil cytoplasmic antibody (indirect immunofluorescence)	p-ANCA, 1:2,560 c-ANCA, negative	p-ANCA, 1:10,240 c-ANCA, 1:320
Antibodies against neutrophil cytoplasmic antigens (ELISA capture)	Anti-HNE, positive Anti-PR3, positive Anti-MPO, negative	Anti-HNE, positive Anti-PR3, positive Anti-MPO, positive
IgM anticardiolipin antibody (normal 0.0–12.4 U/mL)	21.4	14.4
Skin findings	Markedly tender, black discoloration and necrosis of the helices and antihelices of both ears; a large, necrotic, indurated, inflammatory plaque on her nose; a 5.0-cm-diameter punched-out ulcer on her left lateral shin; an indurated livedoid plaque on her left upper arm; nailfold infarcts	Extensive black discoloration and necrosis of the ears, eyelashes, forehead, and bilateral cheeks; digital necrosis of both hands and feet; rapidly progressive areas of epidermal detachment, necrosis, and bulla formation of the trunk and upper and lower limbs
Skin biopsy	Gangrenous necrosis with acute inflammation and fibrosis	Leukocytoclastic vasculitis with fibrinoid necrosis of the blood vessel walls and subepidermal bullae formation
Treatment	Short course of high-dose prednisone	Mechanical ventilation; steroid tapering induced worsening of her respiratory status and skin lesions
Outcome	Spontaneous resolution of skin lesions	Deep eschars of the face with extensive destruction of nasal and ear cartilages; death after 60 days in the hospital

ESR indicates erythrocyte sedimentation rate; CRP, C-reactive protein; c-ANCA, cytoplasmic antineutrophil cytoplasmic antibody; p-ANCA, perinuclear antineutrophil cytoplasmic antibody; anti-PR3, anti-proteinase 3 antibody; anti-MPO, anti-myeloperoxidase antibody; ELISA, enzyme-linked immunosorbent assay.

effect of cocaine. Levamisole metabolites also have a stimulatory effect. Very importantly, levamisole reacts as cocaine in the “bleach test,” a quick, widely utilized street test for cocaine purity. Therefore, it adds bulk to illicit cocaine without reducing the native drug’s apparent purity, as occurs with other bulking agents such as sugar or lidocaine (2). Both snorting and smoking levamisole-contaminated cocaine have been associated with the vasculitic syndrome (4).

Levamisole-induced syndrome has a characteristic presentation (2, 4). The distinctive vasculopathic purpura typically

involves the ears, but purpura can also be observed on the nose, cheeks, extremities, and diffusely. Cutaneous lesions tend to be stellate with a bright erythematous border and necrotic center. This lesion usually resolves spontaneously within a few weeks of drug discontinuation and recurs with subsequent contaminated cocaine abuse.

The half-life of levamisole is 5.6 hours, and only 3% to 5% of the drug is found in urine within 48 hours of last use. Leukopenia can occur in 50% to 60% of cases (3) and can first develop after as long as 12 months of continuous use (5). Agranulocytosis has also been reported in patients with cocaine/levamisole abuse (6).

The syndrome has a very interesting spectrum of autoantibody findings. High-titer perinuclear antineutrophil antibodies (p-ANCA) are almost always found (86%–100%), and about 50% of the cases also have cytoplasmic antineutrophil antibodies (c-ANCA) (4–10). However, the specific antigens responsible for generating these positive ANCA fluorescent patterns are not yet clearly defined. Antibodies against proteinase-3 (anti-PR3), the autoantibody most commonly associated with a c-ANCA pattern, are present in about 50% of these patients, while antibodies against myeloperoxidase (anti-MPO), the antibody most often responsible for a p-ANCA pattern, are found in almost every case (3, 10). In addition, antiphospholipid antibodies and antinuclear antibodies are also often present. The Mayo group has reported another antibody in these patients that is directed against human neutrophil elastase. Anti-human neutrophil elastase (anti-HNE) is also present in most patients with cocaine-induced midline destructive lesions, but not in patients with classic ANCA vasculitis (4, 9). Both PR3 and HNE belong to the same family of serine proteases, and cross-reactivity between these antibodies/antigens may occur. These two cocaine abuse–associated syndromes are distinctly different. Cocaine-induced midline destructive lesions may be caused by the cocaine itself and do not generate the distinctive skin involvement that occurs with the levamisole-related condition

(11). Conversely, the levamisole-related vasculitis does not usually cause destructive damage to the nose, sinuses, and palate.

The histology of cutaneous lesions typically shows thrombotic vasculitis or leukocytoclastic vasculitis with or without vascular occlusion (2–4). The natural history of levamisole-induced vasculitis is spontaneous resolution without treatment when the levamisole is withdrawn. Immunologic abnormalities generally resolve within 2 to 14 months of withdrawal of the levamisole (2). However, some severe cases may not improve, as in our second patient, who had a fulminant form of vasculitis

and a fatal outcome. Although steroids have been used for treatment of this syndrome, it is unclear if they provide any benefit. The side effects may be harmful, especially since most reported cases had no internal organ involvement (3, 4).

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