In recent years, the immunomodulating agent levamisole has been increasingly used as a cutting agent in cocaine. This contaminant has led to numerous reported cases of levamisole-induced vasculopathy. With the increased use of levamisole-adulterated cocaine, physicians should be aware of the various cutaneous manifestations associated with levamisole toxicity. We describe the case of a chronic cocaine user who presented with extensive hemorrhagic retiform purpura involving the ears, upper extremities, and trunk. Levamisole-induced vasculopathy should always be included in the differential diagnosis of a patient with evidence of vasculitis and history of cocaine abuse. This case emphasizes the importance of timely recognition and proper counseling in order to prevent recurrent episodes of levamisole-induced skin necrosis.

INTRODUCTION

A 44-year-old woman with a past medical history of untreated, chronic hepatitis C presented to the emergency room with acute onset of a widespread rash on her bilateral helices, abdomen, buttocks, and bilateral upper extremities. She was initially seen at an outside hospital one week prior where she was treated with topical permethrin for a presumptive diagnosis of scabies. Subsequently, the tender lesions which had appeared initially on her abdomen and right upper extremity quickly spread to involve the buttocks, posterior thighs, and external ears. She returned to the hospital and was given an additional dose of permethrin cream and tramadol. However, the patient’s cutaneous lesions did not improve and continued to evolve into larger more necrotic plaques. At that point, she presented to our facility. On further evaluation, she admitted to cocaine use on the night prior to onset of her skin findings. She also endorsed history of a similar purpuric eruption that occurred on both lower extremities three years prior after cocaine use.

Her vital signs upon presentation included a temperature 98.8 °F, blood pressure 137/79 mmHg, heart rate 112 beats per minute, respiratory rate 18 breaths per minute, and a body mass index of 26.9. Physical examination revealed large, retiform, purpuric plaques with erythematous, inflammatory borders and central hemorrhage and necrosis (Figure 1). Lesions involved the bilateral helices of the ears (Figure 2), bilateral upper arms, forearms, buttocks, and posterior thighs. Multiple faintly hyperpigmented to violaceous macules were scattered over her abdomen and back (Figure 3). The purpuric lesions had a stellate pattern with a notable central necrosis.

Laboratory analysis revealed a leukopenia with a WBC count of 3,000 per UL (4,500-11,000 per UL), with an absolute neutrophil count of 1900 per UL (1800-8000 per UL). Laboratory workup also revealed a microcytic anemia with hemoglobin levels of 10.6 GM/DL (12-16 GM/DL), and a MCV of 74.7 FL (80-100 FL). Inflammatory markers were elevated with a C-reactive protein level of 12.6 MG/DL (<0.90 MG/DL) and an erythrocyte sedimentation rate of 67 MM/HR (0-20 MM/HR ). Blood cultures and HIV tests drawn at admission returned negative. Toxicology screening of the urine was positive for cannabinoids, cocaine, and levamisole.

Based on the patient’s recent cocaine use and the characteristic clinical presentation, a presumptive diagnosis of levamisole-induced vasculitis was made. Further immunological workup revealed positive p-ANCA antibodies with a titer of 1:640 (<1:20 titer). C3 complement levels were within normal range, however a low C4 complement of 17 MG/DL (18-55 MG/DL) was present. Additional laboratory tests that were negative included: cryoglobulins, c-ANCA, anticardiolipin panel, rheumatoid factor, antinuclear antibodies, and an extractable nuclear antigen (ENA) panel. Dermatology was consulted, and a punch biopsy of a purpuric lesion on the left forearm was obtained. Histopathology of the punch biopsy revealed multiple fibrin thrombi distributed throughout the superficial and deep dermis. Dermal hemorrhage along with perivascular neutrophilic inflammation was also present. Treatment consisted of supportive care and complete withdrawal of cocaine. The patient’s lesions slowly improved, and she was discharged home following counseling on the importance of cocaine cessation.

EPIDEMIOLOGY

Drug-induced vasculitis is one of the most common causes of vasculitis in adults. It can be a diagnostic challenge to differentiate between the various idiopathic cutaneous vasculopathies. Illicit
drug use in the United States has been steadily increasing and in 2013 up to 24.6 million Americans reported the use of an illicit drug in the past month.\(^1\) Cocaine abuse is widespread in our society with over 5 million Americans using some form of the drug.\(^2\)

Levamisole is an immunomodulatory drug, developed in the 1960s, that was initially used as an adjuvant agent in the treatment of colorectal cancer and rheumatoid arthritis.\(^3\,\,6\) The first case of cutaneous necrotizing vasculitis caused by levamisole was described in 1978.\(^4\) It was subsequently banned due its severe side-effect profile which included agranulocytosis and vasculitis.\(^5\,\,6\) It is now currently used as an anthelmintic agent in veterinary medicine.\(^5\) In recent years, levamisole has been used as a bulking agent in cocaine due to its physical similarities and its ability to potentiate the effects of cocaine. It has been thought to potentiate the stimulatory effects of cocaine by increasing the amount of dopamine in the brain and having cholinergic effects. According to U.S. Drug Enforcement Agency (DEA) estimates, up to 69% of cocaine imported into the United States is contaminated with levamisole.\(^6\)

In 2009 the Centers for Disease Control and Prevention (CDC) first reported the link between agranulocytosis and cocaine abuse\(^5\), and in 2010, the first case of levamisole-induced vasculitis in a cocaine abuser was reported.\(^8\) Over the following years, a rise in the number of cases of levamisole-induced vasculitis has been reported. According to previous reports, levamisole-induced cutaneous vasculitis is more commonly seen in women with a median age of 45 years.\(^9\) The pathogenesis of levamisole-induced necrotizing vasculitis is still unknown, but some postulate that immune complexes are formed. A common theory is that the induced autoantibodies stimulate immune cells to release cytotoxic agents causing cellular destruction.\(^10\) With the widespread use of levamisole-adulterated cocaine, early recognition of levamisole-induced vasculitis is important in order to prevent recurrent episodes in the future that can lead to significant complications.

**CLINICAL PRESENTATION AND DIAGNOSIS**

Levamisole-induced Vasculitis (LIV) presents with a unique clinical picture that is characterized by reticulated purpuric lesions and hemorrhagic bullae with concurrent central necrosis occurring most commonly on the lower extremities and ears.\(^9\) The predilection for the ears is a specific finding for LIV and is thought to possibly arise due to the lower temperature and smaller vessels favoring the deposition of immune complexes.\(^10\) These necrotizing vasculitic lesions with an erythematous base are also found on the upper extremities, trunk, face, nose, and oral region.\(^11\) Arthralgias of the large joints are commonly reported clinical manifestations. Many patients also have constitutional symptoms including fever, weight loss, night sweats, myalgia, and malaise.\(^12\) Rhinorrhea and recurrent sinusitis have also been reported, most likely related to the nasal inhalation of cocaine. Levamisole has immunomodulatory effects that lead to the increase of multiple autoantibodies. Elevated Perinuclear ANCA (p-ANCA) has the strongest association in LIV, with cytoplasmic ANCA (c-ANCA), anti-myeloperoxidase (anti-MPO), anti-proteinase-3 (anti-PR3) and human neutrophil elastase antibodies also elevated in some patients. Studies have also shown elevated titers of lupus anticoagulant, antinuclear,
anti-cardiolipin, and anti-double-stranded DNA antibodies. Of note, a number of other drugs including propylthiouracil, hydralazine, and minocycline have also been associated with ANCA-associated vasculitis. Other common laboratory findings of LIV include agranulocytosis and neutropenia.

Histopathologic evaluation of skin biopsy in LIV typically reveals a leukocytoclastic vasculitis of the small vessels as well as vasculopathic features including intravascular thrombi. There is a predominantly neutrophilic inflammatory infiltrate that invades the vessel walls spreading into the perivascular area. A high number of eosinophils is also a common finding. Fibrinoid necrosis along with the extravasation of red blood cells is frequently seen as well.

MANAGEMENT

Treatment of levamisole-induced cutaneous vasculitis requires supportive care and counseling on cocaine cessation which, in most cases, leads to resolution of symptoms. There is no strong evidence that steroids are needed for the treatment of LIV cutaneous lesions. Steroid use should be withheld due to the possibility of infections in patients who are neutropenic. Patients must be educated on the recurrence of the necrotizing lesions if cocaine use is resumed. In some patients, extensive tissue involvement can lead to amputation and severe infection.

REFERENCES


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