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Is Levamisole-Induced Vasculitis a Relegated Diagnostic Possibility? A Case Report and Review of Literature

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Patient: Female, 38
Final Diagnosis: Levamisole induced vasculitis
Symptoms: Skin and joint
Medication: —
Clinical Procedure: None
Specialty: Toxicology

Objective: Unusual clinical course





Background: Levamisole, a veterinary anti-helminthic, is a common adulterant in cocaine. Levamisole-induced vasculopathy (LIV) is a relatively new entity, and is being increasingly recognized since it was first reported in 2010. Although cutaneous findings, agranulocytosis, and positive antineutrophil cytoplasmic antibodies (ANCA) are characteristic, the full clinical picture and appropriate management remain unclear.

Case Report: A 38-year-old woman presented with malaise and a pruritic, painful rash on all extremities, right ankle pain, and effusion and necrosis of the right 2nd and 3rd finger tips. After extensive work-up, we determined that she had LIV.

Conclusions: Arthritis-dermatitis syndrome in cocaine users should raise suspicion for LIV. Although some features are characteristic, the full clinical spectrum is yet to be described. Management is supportive.

MeSH Keywords: Arthritis • Cocaine • Dermatitis • Drug Contamination

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Background

More than 5 million Americans abuse cocaine in various forms [1]. Levamisole, a veterinary anti-helminthic drug, is a common adulterant in cocaine due to its physical similarity [2]. In a recent estimate by the US Drug Enforcement Agency, 69% of samples of illicit cocaine reaching the United States were adulterated with levamisole [3]. More than three-quarters of cocaine users tested positive for both cocaine and levamisole [2–5].

Levamisole-induced vasculitis (LIV) in cocaine abusers is a relatively new entity, and is being increasingly recognized since the first report in 2010 [6]. Although characterized by typical cutaneous findings, agranulocytosis/ neutropenia, and a positive anti-neutrophil cytoplasmic antibody (ANCA) [7], the full clinical picture and appropriate management remains unclear. In an analysis by Pearson et al. in 2012, 55 cases of Levamisole-induced vasculopathy (LIV) with classic cutaneous lesions, neutropenia, and ANCA positivity had been reported [8]. Despite the increasing number of reported cases, the full picture and appropriate management of LIV remains unclear. In this case report, we describe a case of levamisole-induced vasculitis and review the literature.

Case Report

A 38-year-old African-American woman patient presented with a two-week history of dark and painful discoloration of her right second and third finger tips. She also had one-day history of generalized body aches, a pruritic, painful rash on all extremities, right ankle pain, erythema, and edema affecting her ambulation. She also complained of a whitish vaginal discharge. Past medical history was significant for prior episodes of gonorrhea, poly-substance abuse (alcohol, opioid, and inhaled cocaine), depression, and anemia. She denied fever, chills, dyspnea, nausea, vomiting, or diarrhea. She stated that her last cocaine use was two weeks prior to her symptom onset. On physical examination, vital signs were normal. Multiple coin-like, erythematous tender indurated swellings with a central pustule or vesicle were noted, particularly on the lower extremities (Figure 1A–1C). The right ankle was red, tender, and swollen, and a joint effusion could be palpated. She had right-ankle arthritis with decreased range of motion. The distal right hand second and third fingertips were necrotic and draining frank pus, which suggested super-added infection (Figure 2). Chest, abdominal, and neurological examinations were unremarkable. Pelvic examination showed whitish discharge without cervicitis. Metabolic panel and complete blood count with differential were unremarkable except for mild iron-deficiency anemia. Total WBC count was normal ($8.7 \times 10^3/\text{mcl}$). Differential count revealed mild eosinophilia 7.1%. Erythrocyte sedimentation rate was 59 mm/h and C-reactive protein was elevated

to 19.4 mg/ L (normal 0–5 mg/L). Urine drug screening was negative for cocaine, cannabis, amphetamines, barbiturates, and benzodiazepine.

She was initially treated with daily Ceftriaxone because we suspected disseminated gonococcal infection (DGI). However, multiple sets of blood cultures were negative. Urine, throat, and vaginal cultures were also negative. Urine gonococcal and chlamydia DNA nucleic acid amplification tests were negative, making DGI unlikely.

Further laboratory testing showed negative hepatitis screen, HIV screen, and negative RPR. Lyme disease panel was negative. Right ankle joint fluid analysis did not show any evidence of bacterial infection or crystal-induced arthropathy (white cells 1.9 cells/ cu mm, 70% lymphocytes, 26% monocytes/macrophages, 4% meso, negative for crystals). Serological testing showed negative antinuclear antibody (ANA <1:80, cytoplasmic type), a positive perinuclear anti-neutrophil cytoplasmic antibody (pANCA) at titer of 1:640, and elevated antiproteinase-3 (18.8 units/ml), thereby supporting the diagnosis of LIV. Cytoplasmic ANCA (c-ANCA) and anti-myeloperoxidase antibodies (MPO) were negative. C3 complement was normal at 119.4 (normal 83–193) and C4 complement was mildly low 13.6 (normal 15–53). Rheumatoid factor was negative.

Appropriate antibiotics for the fingertip infection and supportive therapy were instituted. On further questioning, she endorsed having had a similar but milder rash on her lower extremities in the past, for which she had never sought any medical attention. The patient recovered well over the next few weeks.

Discussion

Because our patient had a history of poly-substance abuse and presented with painful rashes, arthralgia, and digital necrosis, we suspected some type of vasculitis as the first clinical possibility.

The initial differential diagnosis for any arthritis-dermatitis syndrome should include common entities such as vasculitides, tick-borne diseases (e.g., tick-borne typhus and Lyme disease), infective endocarditis, disseminated gonococcal infection, and reactive arthritis. The striking digital necrosis in our patient could not be explained by gonococcemia or tick-borne diseases. Complicated endocarditis, or cryoglobulinemia, were considered as other potential processes that could possibly account for this manifestation. However, the clinical presentation did not suggest infective endocarditis, and she did not meet the Duke's criteria. As such and because our patient had used cocaine, levamisole-induced vasculitis was considered a very strong clinical possibility. The negative urine report is not



Figure 1. (A) Photograph showing multiple coin-like indurated lesions on the arm, with central ulceration. (B) Some of the lesions showed intact fluid-filled vesicles. (C) Enlarged image of the rash.

surprising since the cocaine abuse was 2 weeks prior to presentation. We did not assess the serum levels of Levamisole nor did we perform tandem mass spectroscopy testing to prove presence of Levamisole. The diagnosis was based on exclusion of other possibilities, serology, and a strong positive history of drug abuse. We did not perform biopsy of the skin lesions as the patient declined the procedure. Moreover, she started to show improvement in a few days with supportive management. Some authors have suggested that using sensitive techniques like tandem mass spectroscopy or gas chromatography may be helpful to prove Levamisole contamination, but these tests are not universally available [9].

Levamisole is an imidazothiazide derivative that was previously used as an immunomodulatory drug in the treatment of cancer and collagen vascular disease. It was withdrawn from the market in 1999 due to severe adverse effects, the most serious of which was agranulocytosis [10]. Currently, it remains available as a veterinary anti-helminthic drug. Because of its physical similarity to cocaine and independent neuro-stimulatory effects, it is often used as an adulterant to increase the bulk of the distributed product as well as to get additional stimulant effects. Recently, there have been increasing reports of LIV among cocaine users. An LIV-like syndrome was



Figure 2. Photograph showing necrotic lesions on the tips of the fingers.

first described in 1978 in children on Levamisole for treatment of nephrotic syndrome, with characteristic cutaneous lesions (e.g., retiform purpura), agranulocytosis, neutropenia, arthralgia, and abnormal antibodies in serum [11]. Among cocaine abusers, Levamisole-induced vasculitis (LIV) was first reported in 2010, and was characterized by typical cutaneous findings, agranulocytosis/neutropenia, and a positive anti-neutrophil cytoplasmic antibody (ANCA) [6]. Since that report there were several similar case reports in the literature. Both snorting and smoking cocaine also have been associated with this syndrome, which may develop even after 1 year of using levamisole-contaminated cocaine [3,12].

Cutaneous manifestations characteristically include reticulated purpuric lesions and hemorrhagic bullae. These stellate lesions tend to have bright erythematous borders with a necrotic center. Cutaneous lesions may resolve spontaneously within a few weeks of drug use cessation, but can recur on subsequent exposure. In an analysis of 55 cases, lower limbs (84%) and ears (73%) were the most affected areas. Upper extremity, face, trunk, nose, and mouth involvement has also been reported [5]. Necrotic lesions on the fingers are thought to be due to vasculitis, which is believed to be immune-mediated because IgM, IgA, IgG, and C3 complexes are demonstrated on the biopsy of these lesions [8,9,13,14].

Some authors emphasize that levamisole does not cause destructive damage to the nose, sinuses or palate, while midline destructive lesions are peculiar to the direct effects of cocaine. Granulomatosis with polyangiitis (GPA) may sometimes be confused with LIV due to the above-mentioned features [3,10,11,15,16]. A variety of immunological disturbances are described with LIV. It has been recently reported that levamisole may cause increased formation of antibodies to various antigens, as it has the ability to act as a hapten, and therefore lead to an immune response [17].

In 1999, Rongioletti et al. reported the occurrence of necrotic lesions on ears of all the 5 children with nephrotic syndrome being treated with levamisole [13]. Biopsy of such skin lesions often shows thrombotic vasculopathy, vasculitis, or a combination of the two. The vasculitis is believed to be immune-mediated because several immunoglobulins and C3 complexes are demonstrated in these lesions [14,18,19]. Analysis of cases of LIV in the past few years revealed a fascinating auto-antibody profile. High-titer peri-nuclear anti-neutrophil antibodies (p-ANCA) were found in 86–100% of patients with LIV and cytoplasmic antineutrophil antibodies (c-ANCA) were found in about 50% of cases [7,20]. The responsible antigens have not yet been identified. The common antibodies detected are anti-myeloperoxidase (anti-MPO), antiphospholipid antibodies, antinuclear antibodies, and antiproteinase-3 (anti-PR3) [5,21]. In those with cocaine-induced midline destructive lesion (CIMDL),

antihuman neutrophil elastase (anti-HNE) antibody was detected in 84% of the patients, but was absent in other autoimmune disorders, including GPA [7]. Other immune abnormalities include elevation of ANA, PR3, ANCAs, dsDNA, and lupus anticoagulant [22]. In an observation by Pearson et al., p-ANCA was seen in 88% and cytoplasmic ANCA in 21% of cases. Antibodies against MPO and PR3 are positive in about two-thirds of cases, usually concomitantly, and we believe that positivity of p-ANCA, MPO, or PR3 antibodies strongly suggest LIV [8]. Multiple ANCA differentiate LIV from other vasculitides. LIV commonly causes several hematological changes and musculoskeletal abnormalities. Although leukopenia occurs in only 50–60% of cases, agranulocytosis and neutropenia are described as typical findings in most case reports [4,5,8,23]. Arthralgia can occur in about one-third of patients with LIV [8]. Recently, a syndrome of leukopenia, arthralgia or arthritis, and vasculitis has been described in abusers of levamisole-contaminated cocaine [6,24]. A predilection for joint involvement of any one or any group of joints has not been described. Systemic effects on the heart, lung, liver, and kidney are believed to be extremely rare. It is suggested that the absence of end-organ involvement, along with a typical skin lesions and serologic profile, differentiates cocaine-levamisole cutaneous vasculopathy from idiopathic systemic vasculitis [25]. Hypersensitivity pneumonitis is also reported in the case series reported by Ulrich et al. [22].

McGrath et al. described 30 patients with ANCA-positivity who had used levamisole-contaminated cocaine. Abnormal urinalysis (defined as dipstick proteinuria, hematuria, or the presence of cellular casts on microscopy) was present in about one-third of patients at diagnosis. They, however, did not report nephrotic syndrome [26]. Diaz et al. reported a case of nephrotic syndrome caused by levamisole, in which the result for cryoglobulin was negative and anti-nuclear antibody (ANA) was positive at 1:80 dilution in a homogeneous pattern [27].

Besides stopping further exposure to the offending agent, management of LIV is supportive, including wound dressing and antibiotics in superimposed infections. Without specific treatment, some of the cutaneous lesions may regress in a few weeks after stopping cocaine use. Corticosteroids are reserved for the management of persistent cases not responding to supportive therapy alone. Pearson et al. opined that although routine use of corticosteroids is not supported by evidence, they may be considered for debilitating arthropathy, a strikingly elevated CRP, or a biopsy-proven vasculitis. In their analysis of 43 patients, 58% received glucocorticoids. In their analysis of 35 patients with follow-up data, 31 improved irrespective of the steroid therapy. Currently, there is no evidence that systemic corticosteroids modify the clinical course [8]. A few severe and fatal cases have sometimes been reported. One of the two cases described by Abdul Karim et al. died due to severe vasculitis [20].

Conclusions

Levamisole-induced vasculitis is an emerging public health concern. In an arthritis-dermatitis syndrome in a cocaine user, levamisole-induced toxicity should be considered. A typical clinical syndrome with lesions on the lower limbs and ears, ANCA

positivity, and anti-HNE antibodies makes it a distinct entity, unlike other autoimmune vasculitides.

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None.

Disclosures of conflict of interest