CHAPTER **18**

Levamisole-Induced Vasculitis Affecting the Lower Extremity From Contaminated Cocaine

Mark B. Ellis, DPM
William D. Fishco, DPM

Levamisole is an immunomodulator used in veterinary medicine as an anthelmintic agent. Formerly used to treat nephritic syndrome, autoimmune disorders, various cancers and some skin conditions in humans, (1-7) it was removed from the US market in 1999 (8) secondary to leukopenia, agranulocytosis, and skin vasculitis. Recently, levamisole is becoming more prevalent in the medical literature because of its widespread use as an adulterant to street cocaine. Reports from the Centers for Disease Control and prevention indicate 69% of cocaine is contaminated with levamisole (9), with other sources estimating even higher percentages (10). The incidence of cutaneous vasculopathy has seen concordant growth in emergency department encounters and in the medical literature (10). In addition to the pathognomonic cutaneous lesions of the nose and ears, research done at Maricopa Medical Center in Phoenix, Arizona has shown an 87.5% predilection for the lower extremity, which is similar to other published data (11). Therefore with the increased incidence and the implications for the lower extremities, foot and ankle specialists taking emergency room call need to know how to recognize and treat these lesions.

The emergence of this cutaneous vasculopathic condition is relatively recent, despite cocaine's use since the 1800s. Currently, cocaine use is well-documented to be widespread in the US. With an estimated 2-5 million users (12,13), the US is the world's largest consumer of cocaine (14). In July of 1999, the DEA reported that 69% of all cocaine seized at US borders contained levamisole at a concentration of approximately 10% (9). Various hypotheses regarding the addition of levamisole to cocaine have been proposed, but a recent study found that its metabolite, aminorex is a powerful inhibitor of dopamine and norepinephrine reuptake, increases release of serotonin, and enhances synaptic catecholamine activity, which may enhance or prolong the effects of cocaine (15). As the presence of the contaminant and the frequency of cocaine use have increased, so have the associated numbers of levamisole-related adverse effects.

Agranulocytosis is uncommon (7.2 cases per 1 million population per year, excluding patients with cancer and patients receiving cytotoxic drugs), carries a risk for opportunistic infections, and can be fatal in approximately 7-10% of cases (16). Cocaine use alone does not evoke agranulocytosis, neutropenia, and characteristic vasculitis, but these have been shown to be caused by oral levamisole in up to 13% of patients using levamisole clinically (17).

As more cases were seen, the condition was given varied agnomen in the medical literature: Levamisole-Induced Cutaneous Vasculopathy (LICV), Levamisole-Induced Vasculitis (LIV), Cocaine-Induced Pseudovasculitis (CIP), and Levamisole-Induced Pseudovasculitis (LIP). Initial clinical findings are characterized by tender purpuric lesions in retiform distribution with erythematous borders and areas of central necrosis, often accompanied by bullae (Figures 1, 2).

Pediatric patients receiving long-term oral levamisole have been reported to have nonspecific rash or lichenoid eruptions with a documented latency of up to 5 years (18). The most commonly affected locus is the lower extremity (84-87.5%) (11,19). Other differentials of florid vasculopathy in the extremities include septic emboli and cryoglobulinemia. Affected ears, specifically the helix, are pathognomonic due to the fact that they are uncommonly affected by other vasculitities (11,20) and occur in 73% of patients (Figure 3). The upper extremities and hands are also commonly affected. Other areas of the face including the cheeks, nose, and oral region are also noted. The presence of cutaneous involvement of large areas of the lower extremities and ear involvement raises the index of suspicion for LIV.

Initial work up includes a thorough patient history including present or prior cocaine use, which raises the index of suspicion. Laboratory studies may include toxicology screen, complete blood count, chest radiograph, c-/p- antineutrophil cytoplasmic antibody (c-/p-ANCA), antinuclear antibody (ANA), proteinase 3 (PR3), antimyeloperoxidase (anti-MPO), and direct immunofluorescence (DIF).

Laboratory findings show leukopenia (white blood cells <4000/µl) and/or neutropenia (absolute neutrophil count <1500/µl) in 60-63% of cases (11,19). Although neutropenia is a published complication of levamisole causing agranulocytosis in 2.5 to 13% of patients on long-term use (17), it is not necessary to make the diagnosis (21). Direct confirmation of levamisole via gas chromatography

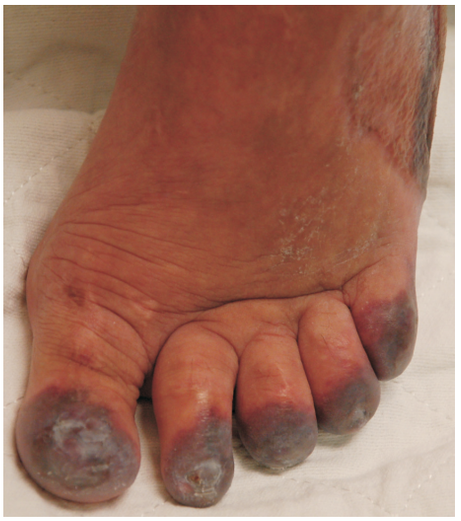


Figure 1. Vasculitis of the distal toes in a patient with levamisole-induced vasculitis.

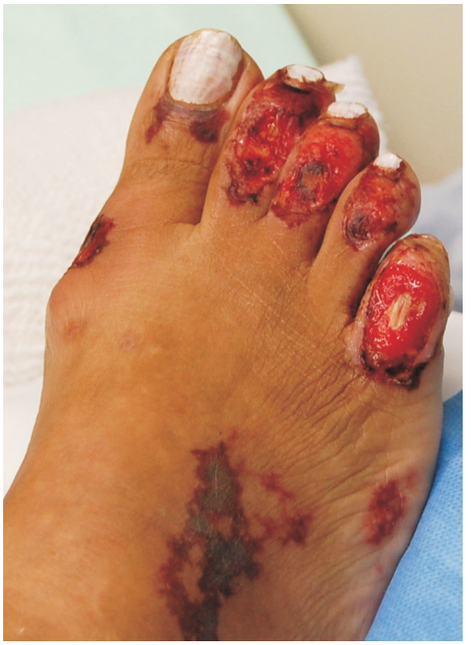


Figure 2. Patches of vasculitis with purpura in addition to full-thickness skin ulcerations in the same patient at a different hospital admission encounter.

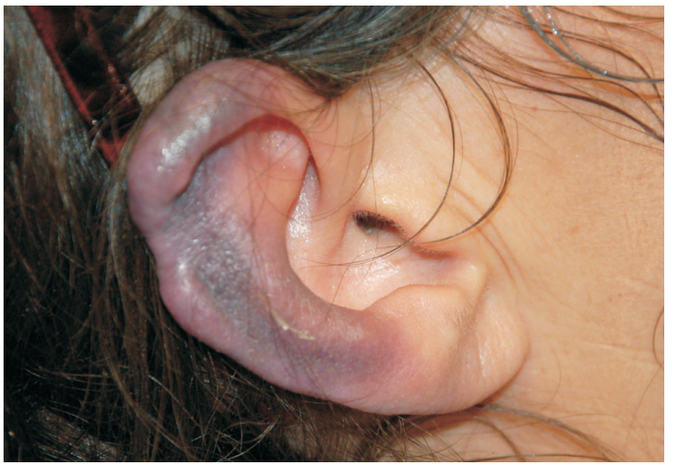


Figure 3. Vasculitis of the helix of the ear is pathognomonic for levamisole-induced vasculitis due to the rarity of the affected area in other types of vasculitis.

and mass spectrometry require urine samples within 5.6 hours of substance abuse (22), which shows high prevalence of levamisole with cocaine use (68% of 300 toxicology samples (23), but is not always feasible due to the half-life of levamisole and poor availability of labs equipped to perform gas chromatography. If this window of time has elapsed, antihuman neutrophil elastase (anti-HNE) can help confirm levamisole/cocaine, being found in higher prevalence in levamisole/cocaine patients over granulomatosis with polyangiitis (Wegener's) (11,19,24).

Small-vessel leukocytoclastic vasculitis may occur in association with a variety of conditions: sepsis, cryoglobulinemia, drug allergy, Henoch-Schonlein purpura, connective tissue disease, systemic vasculitis, inflammatory bowel disease, streptococcus infection, viral hepatitis, other infections, systemic malignancy, and other systemic disorders. It is therefore imperative to differentiate the cutaneous presentations of levamisole-contaminated cocaine use from that of true vasculitic diseases such as granulomatosis with polyangiitis (Wegener's), cutaneous polyarteritis nodosa (cPAN), and Churg-Strauss Syndrome (CSS) because the treatments are remarkably different. Onset in classical vasculitic diseases is more gradual. Histologic analysis of skin biopsies shows thrombotic vasculopathy, vasculitis, or a combination of thrombosis with vasculitis. With rare exception, granulomas typically found in granulomatosis with polyangiitis (Wegener's) and CSS are not found in levamisole/cocaine induced cutaneous lesions (20,25). ANCA testing by either immunofluorescence or ELISA usually shows more frequent positivity of perinuclear (p-ANCA) than c-ANCA, or a combination of the two. Although not specific, positive p-ANCA, MPO, and PR3 are consistent with levamisole-induced vasculitis (11,26). Anti-HNE (antihuman neutrophil elastase) is a very high indicator of levamisole involvement. A 2012 review of all published cases and reports to date found 100% correlation in a small accumulative cohort (11). Levamisole is also suspected to cause positive lupus anticoagulant antibodies in some patients (18,20,27). If toxicology screen, anti-HNE, and/or levamisole screens are positive, the physician should suspect LIV (11,19,20,24).

When mild lesions present for the first time and cocaine use is abandoned, the skin lesions are short-lived, resolving usually in a matter of weeks by secondary intention. Treatment with topical steroids is controversial. Advanced lesions may require more aggressive tangential excision and debridement with temporary allograft or xenograft in

preparation for appropriate permanent coverage via split-thickness autograft. Judicious timing is paramount to ensure that antibody profiles have returned to baseline prior to skin grafting. Continued vasculitic activity carries risk of continued tissue necrosis and therefore graft failure.

Lower extremity specialists must be aware of this emerging condition as the presence of levamisole-contaminated cocaine becomes more widespread, and increased use translates into growing patient encounters. It is crucial to distinguish the untoward effects of levamisole from other cutaneous vasculidities.

REFERENCES

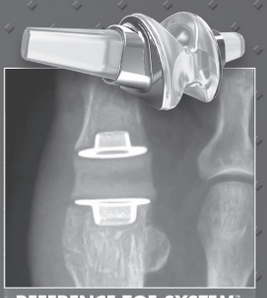
1. Ching JA, Smith DJ,Jr. Levamisole-induced necrosis of skin, soft tissue, and bone: case report and review of literature. J Burn Care Res 2012;33:e1-5.
2. Donia AF, Ammar HM, El-Agroudy A, Moustafa F, Sobh MA. Long-term results of two unconventional agents in steroid-dependent nephrotic children. Pediatr Nephrol 2005;20:1420-5.
3. Abdul-Karim R, Ryan C, Rangel C, Emmett M. Levamisole-induced vasculitis. Proc (Bayl Univ Med Cent) 2013;26:163-5.
4. Amery WK, Bruynseels JP. Levamisole, the story and the lessons. Int J Immunopharmacol 1992;14:481-6.
5. Runge LA, Pinals RS, Lourie SH, Tomar RH. Treatment of rheumatoid arthritis with levamisole: a controlled trial. Arthritis Rheum 1977;20:1445-8.
6. Christensen KD. Treatment of seronegative spondylarthritis with levamisole: a double-blind placebo-controlled study. Int J Immunopharmacol 1979;1:147-50.
7. Tanphaichitr P, Tanphaichitr D, Sureeratanan J, Chatasingh S. Treatment of nephrotic syndrome with levamisole. J Pediatr 1980;96:490-3.
8. Chang A, Osterloh J, Thomas J. Levamisole: a dangerous new cocaine adulterant. Clin Pharmacol Ther 2010;88:408-11.
9. Centers for Disease Control and Prevention (CDC). Agranulocytosis associated with cocaine use-four states, March 2008-November 2009. MMWR Morb Mortal Wkly Rep 2009;58:1381-5.
10. Dr. Dan Quan, MD, Toxicologist at Maricopa Medical Center; personal communication, 5/2013.
11. Pearson T, Bremmer M, Cohen J, Driscoll M. Vasculopathy related to cocaine adulterated with levamisole: a review of the literature. Dermatol Online J 2012;18:1.
12. Vagi SJ, Sheikh S, Brackney M, et al. Passive multistate surveillance for neutropenia after use of cocaine or heroin possibly contaminated with levamisole. Ann Emerg Med 2013;61:468-74.
13. Walsh NM, Green PJ, Burlingame RW, Pasternak S, Hanly JG. Cocaine-related retiform purpura: evidence to incriminate the adulterant, levamisole. J Cutan Pathol 2010;37:1212-9.
14. CIA.gov. Field Listing- Illicit drugs (by country). URL: www.cia.gov/library/publications/the-world-factbook/fields/2086.html.
15. Hofmaier T, Luf A, Seddik A. Aminorex, a metabolite of the cocaine adulterant levamisole, exerts amphetamine like actions at monoamine transporters. Neurochem Int 2013;73:32-41.
16. Ibanez L, Vidal X, Ballarin E, Laporte JR. Population-based drug-induced agranulocytosis. Arch Intern Med 2005;165:869-74.
17. Thompson JS, Herbick JM, Klassen LW, et al. Studies on levamisole--induced agranulocytosis. Blood 1980;56:388-96.
18. Rongioletti F, Ghio L, Ginevri F, et al. Purpura of the ears: a distinctive vasculopathy with circulating autoantibodies complicating long-term treatment with levamisole in children. Br J Dermatol 1999;140:948-51.
19. Arora NP. Cutaneous vasculopathy and neutropenia associated with levamisole-adulterated cocaine. Am J Med Sci 2013;345:45-51.
20. Lutfy J, Noland ME, Jarmuske M. How to spot cocaine-induced pseudovasculitis. Ann Plast Surg 2013;70:375-8.
21. Chai PR, Bastan W, Machan J, Hack JB, Babu KM. Levamisole exposure and hematologic indices in cocaine users. Acad Emerg Med 2011;18:1141-7.
22. Kouassi E, Caille G, Lery L, Lariviere L, Vezina M. Novel assay and pharmacokinetics of levamisole and p-hydroxylevamisole in human plasma and urine. Biopharm Drug Dispos 1986;7:71-89.
23. Buchanan JA, Heard K, Burbach C, Wilson ML, Dart R. Prevalence of levamisole in urine toxicology screens positive for cocaine in an inner-city hospital. J Am Med Assoc 2011;305:1657-8.
24. Wiesner O, Russell KA, Lee AS, et al. Antineutrophil cytoplasmic antibodies reacting with human neutrophil elastase as a diagnostic marker for cocaine-induced midline destructive lesions but not autoimmune vasculitis. Arthritis Rheum 2004;50:2954-65.
25. Gertner E, Hamlar D. Necrotizing granulomatous vasculitis associated with cocaine use. J Rheumatol 2002;29:1795-7.
26. McGrath MM, Isakova T, Rennke HG, Mottola AM, Laliberte KA, Niles JL. Contaminated cocaine and antineutrophil cytoplasmic antibody-associated disease. Clin J Am Soc Nephrol 2011; 6:2799-805.
27. Zhu NY, Legatt DF, Turner AR. Agranulocytosis after consumption of cocaine adulterated with levamisole. Ann Intern Med 2009;150:287-9.

In2Bones

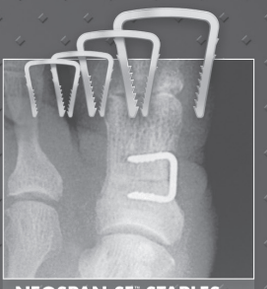
A GLOBAL EXTREMITY COMPANY

Forefoot, Midfoot, Hindfoot and Ankle

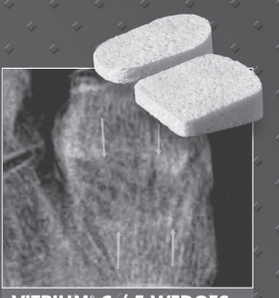
COLINK® MTP PLATE
- Cross Joint Plating System



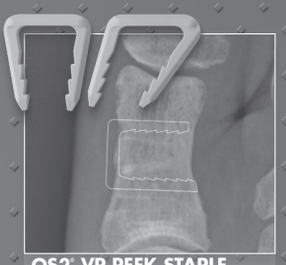
REFERENCE TOE SYSTEM®
- 1ST MTP Implant



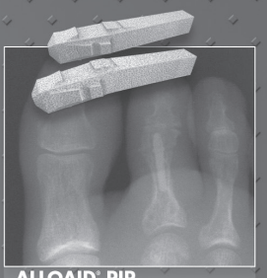
NEOSPAN SE™ STAPLES
- SuperElastic Compression 8-15mm



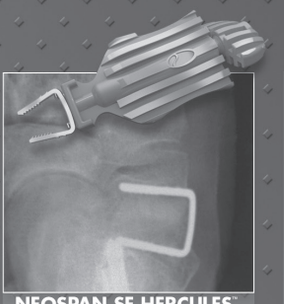
VITRIUM® C / E WEDGES
- Bioactive Glass Implants



OS2® VP PEEK STAPLE
- 9mm Compression Staple

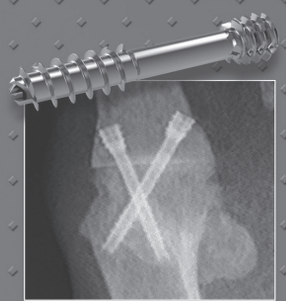


ALLOAID® PIP
- Engineered Sterile Allograft

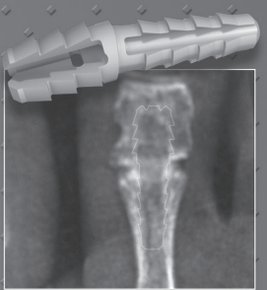


NEOSPAN SE HERCULES™
- Compression Staple 15W-25 mm

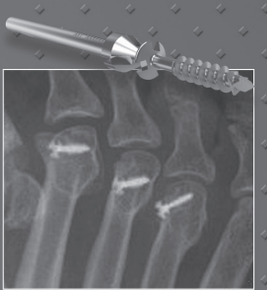
OS2® C PEEK STAPLE
- 11-13mm Compression



IBS® COMPRESSION SCREWS
- 2.0, 3.0, 3.5, 4.5, 6.5 and 8.0mm



DUAFIT® PEEK PIP
- Proximal Interphalangeal Implant



IBS® SNAP OFF SCREWS
- 2.2 and 2. 7mm Snap Offs

ALLOAID® DBM / Putty / Dermis
- Amnio Liquid / Tissue

TO LEARN MORE VISIT
www.i2b-USA.com

CALL TO SCHEDULE A SURGERY
844. 602. 6637

EMAIL US NOW
Info@i2b-USA.com