CLINICAL VIGNETTE

A Case of Levamisole-Induced Vasculitis

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A 36-year-old Asian female with a history of Sjogren's syndrome, seizure disorder, and vasculitis of unknown etiology was referred to the Emergency Room for progressively worsening facial ulcerations. Per the patient, these ulcerations had first appeared approximately three years earlier in her posterior pharynx. Shortly thereafter, she began to develop minor ulcerations on her face that grew progressively larger and deeper over the course of several months. She presented to her primary care physician who prescribed a number of topical preparations, including hydrocortisone and neomycin, without improvement. She was eventually referred to a rheumatologist, who initiated prednisone 30mg daily for presumed autoimmune vasculitis, which was diagnosed by serology at that time. She reported significant improvement in the ulcerations with prednisone, though she never achieved full remission. She continued to receive prednisone 20mg, in addition to mycophenolate 500mg daily, for maintenance therapy. On the day of admission, the patient was seen in rheumatology clinic, where it was determined that the facial ulcerations were so severe that they had the potential for permanent disfigurement, complete destruction of her sinuses, and eventual brain involvement, requiring immediate inpatient management.

The patient's past medical history is significant for Sjogren's syndrome and seizure disorder, currently managed with marijuana prophylaxis alone. She has no significant family history. Social history is significant for a history of cocaine use, with last reported use more than 11 years ago.

Vital signs in the ED were T 37.1C, HR 98, RR 17, BP 138/100, and oxygen saturation 98% on room air. The physical examination was notable for several large, ovoid-to-angulated, deep, suppurative ulcerations with undermined violaceous borders across the face and neck, saddle nose deformity, and purulent yellow drainage in posterior pharynx.

Initial laboratory examination revealed a WBC of 12.7 and a global lymphopenia with a low CD4/CD8 ratio. HIV testing was negative. Toxicology screen was positive for both cocaine and cannabinoids, with subsequent urine testing also positive for levamisole. Skin biopsy of the facial lesions showed granulation tissue with abscess formation in the dermis, as well as vasculopathic changes with extravasated fibrin, edema, and hemorrhage in the dermis. Further serology showed both proteinase-3 and myeloperoxidase antibody positivity.
On further questioning, the patient disclosed that she had been regularly using cocaine over the past 11 years, with most recent use occurring in the days leading up to presentation. She was admitted to the hospital for initiation of rituximab immunotherapy for presumed levamisole-induced vasculitis and lymphopenia, and administration of antibiotics for sinusitis. After extensive counseling regarding cessation of further cocaine use, she was discharged from the hospital with close follow-up in rheumatology for additional rituximab.

Discussion

Recent surveys show that there are approximately 1.5 million current (past-month) cocaine users aged 12 or older in the United States, a number that has been relatively stable since 2009.[1] Cocaine remains among the most common causes of acute drug-related emergency department visits in the country. It is well known that cocaine can produce end-organ toxicity in virtually every organ system in the body, with common manifestations including hypertension, arterial vasoconstriction, thrombus formation, and psychomotor agitation. Additionally, levamisole, a common adulterant found in cocaine in the United States, can cause agranulocytosis, leukoencephalopathy and a cutaneous necrotizing vasculitis.

Originally developed as an antihelminthic agent in the 1960s, levamisole has been used to treat a number of autoimmune disorders, including rheumatoid arthritis, nephrotic syndrome, and ankylosing spondylitis, as well as various cancers in humans.[2] Although the mechanism by which levamisole activates the immune system is not fully understood, it is thought to promote the normal activities of macrophages and T-lymphocytes, including chemotaxis and phagocytosis, as well as to inhibit the production of various endogenous immunosuppressive factors. Additionally, it can act as a hapten, leading to an immune response resulting in the opsonization and destruction of leukocytes. It was voluntarily withdrawn from the market for use in humans in 1999 due to its adverse effects, particularly agranulocytosis. However, it is still available as an antihelminthic agent for veterinary use in the USA, Canada, and South America.[3]

In recent years, use of levamisole as a contaminant in street cocaine has become increasingly prevalent. This was first reported by the US Drug Enforcement Agency in 2003, with as much as 69% of seized cocaine in 2009 containing levamisole.[4] Multiple factors likely account for the common use of levamisole as a contaminant in cocaine. Studies have shown levamisole to inhibit both monoamine oxidase and catechol- *O*

-methyltransferase activity, thereby prolonging the presence of catecholamine neurotransmitters in the synapse and adding to the reuptake-inhibition effect of cocaine. Levamisole metabolites may also have independent stimulatory effects at nicotinic receptors. Additionally, it is a cheap, widely available white powder that can easily be mixed with cocaine to increase bulk.[5]

Cocaine use is becoming increasingly associated with a levamisole-induced vasculitic syndrome. This syndrome has a characteristic presentation, with distinctive vasculopathic purpura most commonly involving the ears, nose, and cheeks, but that can also be seen on the trunk or diffusely across the body. The rash typically presents as purpuric plaques in a retiform, reticular, or stellate pattern with central necrosis or ulceration.[3] Laboratory findings associated with the syndrome almost always include perinuclear-antineutrophil autoantibodies (86%-100% of cases in some studies), with about half of cases also having cytoplasmic-antineutrophil antibodies. The specific antigens responsible for these autoantibody populations are less well defined, but have most commonly included proteinase-3 (typically, c-ANCA) and myeloperoxidase (typically, p-ANCA).[6] Urine toxicology can confirm cocaine use if the patient used cocaine in the preceding 2-3 days. Additionally, both serum and urine tests are commercially available for levamisole, but the short half-life of 5.6 hours makes the drug difficult to detect.[7] Therefore, a thorough drug-history is essential with any patient presenting with the characteristic features of this syndrome.

There is controversy over the best treatment strategy for levamisole-induced vasculitis. A number of studies reported improvement without specific intervention, implying that the natural course of the syndrome is self-limited. Although steroids have been used for treatment in the past, it is unclear if they provide any clinical benefit. Therefore, clinicians should consider waiting before pursuing aggressive immunosuppressive therapy, given the many adverse effects associated with steroid use.[3] Cessation of cocaine use is of utmost importance, as it is associated with more rapid resolution of symptoms, while continued use of the drug and/or relapse following cessation of drug use are likely to lead to re-emergence of the cutaneous lesions.[8]

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