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Levamisole-Adultered Cocaine: Vasoconstrictive and Vasculitis Effects Occurring Simultaneously

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Abstract

This case presents a rarely seen combination of two Cocaine-induced syndromes occurring simultaneously. Levamisole-adultered cocaine leads to Levamisole-induced Vasculitis (LIV), while cocaine's vasoconstrictive effect causes destruction of the osteo-cartilaginous structures of nose called Cocaine-induced midline destructive lesions (CIMDL). This case raises awareness of a new pattern of recognition in order to avoid misdiagnosis. We present a case of a 51-year-old male cocaine user who developed severe left-sided ear pain and yellowish secretions with circular necrotic lesions in the nose, right earlobe, and dorsum of feet bilaterally. An extensive workup to assess purpuric lesions' etiology, including vasculitis, collagen vasculitides, anti-phospholipid syndrome, hypercoagulable state and infectious process, was performed and found negative. He developed bilateral tympanic membrane perforation and purpuric necrotic skin lesions, at the same time, due to CIMDL and LIV, respectively. These two syndromes rarely present simultaneously in a patient. This case report exhibits a new Cocaine-induced clinical presentation that will help hospitalists recognize the disease and avoid misdiagnosis leading to unnecessary tests, prolonged hospitalization, and higher healthcare costs. Diagnosis is challenging, as it consists of establishing a temporal relationship between cocaine ingestion and symptoms' onset. This disease usually has a benign progression because symptoms frequently resolve without intervention.

Keywords

Levamisole-Induced Vasculitis, Cocaine-Induced Midline Destructive Lesions, Cocaine's Side Effect Spectrum

1. Introduction

Levamisole is a synthetic anthelminthic agent that acts as a cocaine diluent, which intensifies the euphoric feeling of cocaine by inhibiting the monoamine oxidase and catechol-*O*-methyltransferase, prolonging the synaptic transmission [1]. It has been found in cocaine as an adulterant since 2003, and up to this date, 70% of street cocaine is contaminated with Levamisole [1]. Levamisole was once used in cancer treatments and as an immunomodulator due to its ability to induce interferon synthesis and intensify the effect of steroids. Nevertheless, it was removed from the human pharmaceutical market in 1999 due to its side effects. Now, it is only used as a deworming drug in animals [2]. Snorting and smoking Levamisole contaminated cocaine has been associated with two characteristic presentations: Agranulocytosis and Levamisole-induced Vasculitis (LIV). On the other hand, cocaine itself can cause extensive destruction of the osteo-cartilaginous structures of the nose, sinuses and palate called Cocaine-induced midline destructive lesions (CIMDL). This case presents a rarely seen combination of two Cocaine-induced syndromes occurring simultaneously. Levamisole-adultered cocaine can lead to Levamisole-induced Vasculitis (LIV), while cocaine's vasoconstrictive effect causes destruction of the osteo-cartilaginous structures of nose called Cocaine-induced midline destructive lesions (CIMDL). This case raises awareness of Cocaine disease's spectrum to facilitate pattern recognition and avoid misdiagnosis.

2. Case Report

The case is a 51-year-old male inmate with a history of bipolar disorder, a chronic cigarette smoker and a cocaine user who developed intermittent severe left-sided ear pain and bilateral yellowish ear drainage with days of duration. The patient referred subjective fever, hypoactivity, unintentional weight loss (unknown amount) and generalized body ache. No tinnitus or hearing loss. Incidentally, the patient also had painful black necrotizing ulcers in bilateral multiple toes for the last two months. He had no history of trauma or peripheral vascular disease (PVD). He reported a history of smoking cocaine for the past fourteen years. The last use was one month before admission. His medications included Valproic acid, Benadryl, Lithium, Trazodone and Bupropion. There was no history of prior hospitalizations or surgeries. Family history was non-contributory.

On examination, the patient was ill-appearing and cachexic. His vital signs were blood pressure (BP) of 146/98mmHg, pulse of 139 beats per minute, respiratory rate of 24 breaths per minute, temperature of 37.0˚C and oxygen saturation of 100% at room air. Cardiovascular, pulmonary, and abdominal examinations were unremarkable. ENT examination revealed bilateral tympanic membrane perforation of 15% - 20% mostly in the central aspect with purulent secretions. The patient had an erythematous hard and soft palate. Dermatological examination revealed a circular 3 cm × 2 cm plaque with central necrosis and an erythematous border on the medial portion of the R nares (**Figure 1**).

In addition, scaly erythematous circular lesions on the R side of the scalp and

in the R outer ear, both measuring 1 cm approximately (Figure 2). There was evidence of extensive black discoloration and necrosis in the plantar region of both feet (Figure 3).

Laboratory findings revealed polycythemia (Hgb of 21.4 g/dL), and thrombocytopenia (Platelets = 71 U × 1000/mm^3). No leukocytosis (WBC = 7.62 U × 1000/mm^3) but neutrophilic predominance (N = 83.6%) and left shifting. Renal

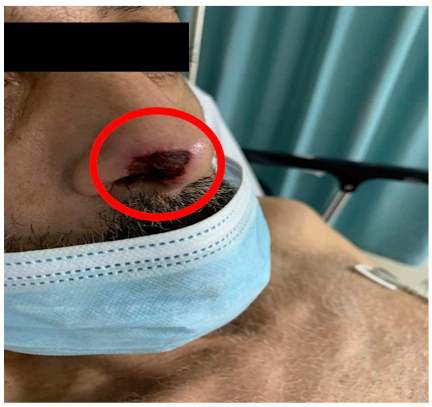

Figure 1. Circular 3 cm × 2 cm plaque with central necrosis and erythematous border on the medial portion of the R nares.

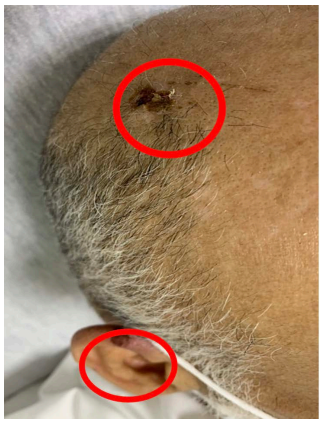

Figure 2. Scaly erythematous circular 1 cm lesion in the R side of the scalp and in the R ear's helix.

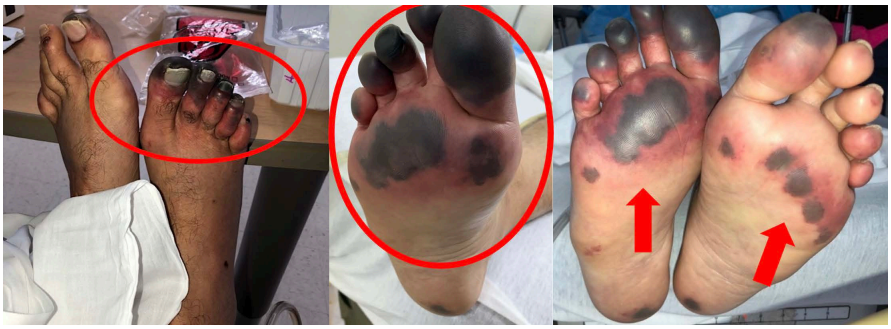

Figure 3. Extensive black discoloration and necrosis from 1st to 4th digits of Right foot and 1st digit of Left foot extending to the interphalangeal joint from the plantar and dorsal area. Also, circular necrotic patches in the superior plantar aspect of both feet (Red arrows).

function panel was essentially unremarkable. There was evidence of high inflammatory markers (CRP of 164 (<5) and ESR of 6 (0-15)). Blood cultures were negative and urine toxicology was negative for cocaine. Serum Levamisole was not available in our Institution. Head CT and Temporomandibular (TMJ) Joint CT were performed, both revealing bilateral partial opacification of the internal acoustic meatus, although worse on the left side with thickening of the tympanic membrane, suggestive of acute otitis media (Figure 4).

An extensive workup to assess the etiology of purpuric skin lesions was performed and found to be negative except for positive low titter RF, which upon laboratory repetition was found to be negative (Figure 5). The Transesophageal Echocardiogram (TEE) was performed and found negative for intracardiac

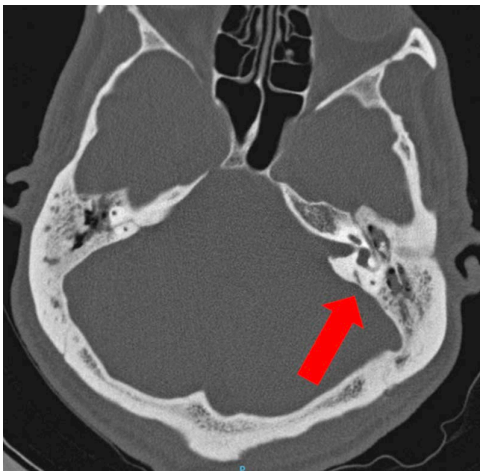

Figure 4. TMJ CT Scan showed bilateral partial opacification of the internal acoustic meatus worse on the left side about the level of the auditory ossicles with thickening fo the tympanic membrane, suggestive of acute otitis media (Red arrow).

	Laboratories	Results
Vasculitis	ANCA- PR3 ANCA- MPO Cryoglobulins x 2	Negative
Rheumatologic Tests	ANA Anti-Smith Anti-scleroderma-70 Anti-dsDNA C3 and C4 complements RF	Negative 1st 24.7 IU/mL (< 14), 2nd: Negative
Anti-Phospholipid Syndrome	Anti-Lupus Anticoagulant Anti-cardiolipin IgM/IgM Anti-Beta 2 glycoprotein IgM/IgG	Negative
Hypercoagulable State	Antithrombin III Factor V Leiden VW factor Factor II, Factor V and IX	Negative
Infectious Diseases	HIV Hepatitis EBV IgM COVID-19 PCR Mycoplasma pneumonia IgM Anti-ASO antibodies Influenza type A and B	Negative

Figure 5. Main laboratories findings performed during hospitalization.

vegetations. A lower extremity CTA had no evidence of high-grade stenosis or occlusion of the arterial system. Skin biopsy revealed small vessels leukocytoclastic vasculitis. In view of negative work up to rule out embolic, autoimmune, collagen-vascular and atherosclerotic disease, but the presence of constitutional symptoms, purpura and necrotic acral lesions in typical areas (earlobes, nose and toes) on physical exam, findings of thrombotic vasculopathy and confirmed cocaine use, the patient was diagnosed with LIV and Acute suppurative Otitis media, most likely secondary to CIMDL, both happening concomitantly. He was treated with supportive management, which included removal of the offending agent, intravenous fluids, pain management and medications for chronic diseases. The patient was discharged to the correctional institution after three weeks of hospitalization. Since then, he has visited the Emergency Room on two occasions (one and four months later) due to complaints of "necrotic ulcers", which upon physical examination have remained unchanged from initial presentation due to continuous use of cocaine.

3. Discussion

Levamisole-induced vasculitis's pathophysiology is poorly understood, but it is believed to be related with immune complex deposition, neutrophil chemotaxis, release of proteolytic enzymes, and free oxygen radicals [3]. Almost all studies have reported cases of Levamisole-induced vasculitis with positive p-ANCA and c-ANCA levels of 86% - 100% and 50%, respectively [4]. Only few cases have been reported with negative serology to ANCA. Our patient had a negative serology which could be explained by the withdrawal of Levamisole one month prior to evaluation. When encountering ENT involvement with a concomitant purpuric skin lesion, ANCA vasculitis and collagen vascular disease must be within the differential diagnosis. We were able to rule out ANCA vasculitides, including granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis, microscopic polyangiitis, cryoglobulinemic vasculitis, immunoglobulin A vasculitis (IgAV and Henoch Schonlein purpura (HSP)) based of the pattern of organ involvement, as there was no lung or kidney involvement, and pertinent negative laboratories i.e negative cryoglobulinemia and ANCA. Negative blood cultures accompanied by a negative TEE ruled out infective endocarditis (IE) and embolic source. Chest Xray (CXR) and Head and Neck Computer Tomography (CT) were negative for solid tumors making nasopharyngeal carcinoma low within the differential diagnosis, and thus paraneoplastic syndromes. In view of the history of cocaine use, Levamisole-induced vasculitis was the most likely diagnosis, although it was difficult to establish a temporal relationship because the patient had denied recent use. LIV's classic presentation is often a tender purpuric rash with erythematous borders and necrotic centers in the lower extremities, ears, cheeks, and nose [1] [5]. LIV is associated with autoimmune effects and hypercoagulability leading to tissue thrombosis, and therefore, biopsy reveals leukocytoclastic vasculitis, occlusive thrombotic vascu-

lopathy or vasculitis with thrombosis [1]. Recent studies have suggested that Human Leukocyte Antigen B27 (HLA B27) is a risk factor for the development of LIV [6]. Also, there is an evident pattern of the lower threshold with repeated exposure, after an initial episode of LIV [4]. Ideally, the diagnosis of LIV would be confirmed with a positive Levamisole test in plasma and urine, however, a negative test does not rule out LIV since Levamisole has a short half-time of 5.6 hours [2].

Cocaine-induced midline destructive lesions are defined by a wide spectrum of the destruction of the osteo-cartilaginous structures of the nose, sinus, and palate [7]. CIMDL pathophysiology is thought to be related to the direct destruction of cocaine adulterers and cocaine-crystals passing through the respiratory canal at high velocities. The second mechanism is through cocaine vasoconstrictive effect [7]. Snorting cocaine damages the nasopharynx, by causing necrotizing crusted ulcerative lesions, hard/soft palate perforation, and septum destruction, especially of the inferior turbinate [8]. Adult-onset otitis media is unusual, as it is a common disease in children. Adults make up less than 20% of patients presenting with acute otitis media [9]. For acute otitis media to take place in adults, an underlying anatomic or immunologic response must be present which predisposes the patient to such disease. The Eustachian tube works as an anatomic communicator between the nasopharynx and the middle ear. It functions by protecting the middle ear from nasopharyngeal secretions, draining the secretions produced within the middle ear into the nasopharynx, and equilibrating the middle ear's air pressure [6]. Eustachian tube dysfunction is divided into Mechanical versus Functional obstruction. Mechanical Eustachian tube obstruction may be subsequently divided into Intrinsic vs Extrinsic obstruction. Intrinsic obstruction results from inflammation (secondary to infections, allergic irritants, primary mucosal disease, ciliary disorders, and drugs, including cocaine) and the extrinsic results from enlarged adenoids, nasopharyngeal tumors or secondary to radiation [6]. Snorting cocaine and continuous inflammation of the midline structures, including soft and hard palate, led this patient into developing mechanical intrinsic obstruction of the Eustachian tube, thus dysfunction leading to acute suppurative otitis media. To our knowledge, only one case of CIMLD with the erosion of Eustachian has been described in the literature [10].

4. Conclusions

This case report presents a chronic cocaine-user male patient who presents with acute suppurative otitis media and purpuric necrotic skin lesions diagnosed with CIMDL and LIV, at the same time. These two syndromes rarely present simultaneously in a patient. The significance of this case report is to exhibit a new Cocaine-induced clinical presentation in order to facilitate recognition of the disease and avoid misdiagnosis, which can lead to unnecessary tests, prologued hospitalization, and higher healthcare costs.

As of this date, there are no approved guidelines for diagnosis. Diagnosis is based on the sum of clinical, immunohistochemistry, histopathologic and imaging findings. It is also based on the exclusion of other autoimmune, collagen or infectious diseases, and hypercoagulable states. Therefore, diagnosis is challenging. According to our literature review, there is only one prevailing algorithm for diagnosis proposed [11]. It suggests that the first step should be ordering urine toxicology to assess the presence of cocaine. If negative, but with high clinical suspicion, the next step should be gas chromatography or mass spectrometry for Levamisole. If positive, the next step should be a Complete Blood Count (CBC) to assess for neutropenia, as well as ANCA titters, Cryoglobulins and APS antibodies [11]. This disease usually has a benign progression, as symptoms usually resolve without intervention. Drug abstinence remains the cornerstone of therapy [8].

Consent

A verbal informed consent was obtained from the patient for this report, including picture.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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