Vasculitis inducida por cocaína-levamisol con manifestaciones cutáneas, articulares y abdominales: reporte de caso

Cocaine-levamisole induced vasculitis with cutaneous, joint and abdominal manifestations: case report

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Abstract

Levamisole is an antiparasitic agent for veterinary use. Currently it is used to increase the volume and potency of cocaine. Levamisole and cocaine combined result in the septum nasal perforation and small-vessel vasculitis in the ears and nasal cartilage. These findings are known as cocaine levamisole-induced vasculitis and can progress to necrosis and even skin ulceration, which is associated with agranulocytosis, arthralgia, and glomerulonephritis. This article describes the case of a patient with a history of substance abuse in whom palpable purpuric lesions were found in the upper and lower limbs, trunk, and ears. A clinical condition suggestive of vasculitis induced by cocaine-levamisole was considered, given the history of substance consumption. In the diagnostic process, entities such as Anti-neutrophil Cytoplasmic Antibodiy (ANCA) vasculitis and cryoglobulinemia, among other possible condi-

tions, were ruled out. Steroid treatment was carried out, to which the patient had an adequate response, but then symptoms recurred, particularly abdominal, which were associated with vasculitis. Additional management with cyclophosphamide and new steroid pulses were provided, and with those symptom control was achieved. In this case report highlights the diagnostic and clinical exercises in cocaine levamisole vasculitis and is suggested the consideration of abdominal symptoms as a possible component of the vasculitis flare.

Key words: Substance use disorder, vasculitis, cocaine, levamisole.

Resumen

El levamisol es un antiparasitario de uso veterinario que actualmente es empleado para aumentar el volumen y la potencia de la cocaína. La mezcla de estas dos sustancias puede causar un cuadro caracterizado por lesiones propias de la cocaína, como la afección del cartílago septal con perforación del tabique nasal, y vasculitis cutánea de pequeños vasos con afectación de los pabellones auriculares y del cartílago nasal, afección conocida como vasculitis inducida por cocaína-levamisol (VICOL) que puede avanzar a necrosis e incluso ulceraciones cutáneas, asociadas a agranulocitosis, artralgias y glomerulonefritis . En el presente artículo se describe el caso de un paciente con historia de consumo de sustancias en quien se encontraron lesiones purpúricas palpables en miembros superiores, tronco, pabellones auriculares y miembros inferiores. Se consideró una clínica sugestiva de VICOL dado el antecedente de consumo de sustancias. En el proceso diagnóstico se descartaron entidades como la vasculitis por anticuerpos contra el citoplasma de los neutrófilos (ANCAs) y crioglobulinemia, entre otras posibles afecciones. Se llevó a cabo un tratamiento con esteroides y con ello presentó una respuesta adecuada, pero luego recurrieron los síntomas, particularmente abdominales, los cuales se consideraron asociados con vasculitis. Se le brindó manejo adicional con ciclofosfamida y nuevos pulsos de esteroides, con que se logró el control total de los síntomas. A través este caso se resaltan entonces los ejercicios diagnósticos y clínicos en la vasculitis cocaína- levamisol, y se sugiere la consideración de los síntomas abdominales como posible componente del cuadro vasculítico.

Palabras claves: trastornos relacionados con sustancias, vasculitis, cocaína, levamisol.

1. Introduction

Cocaine-levamisole induced vasculitis (CLIV) generates a set of systemic symptoms characterized by midline lesions, small vessel vasculitis, agranulocytosis, fever, arthralgia, earlobe necrosis and includes rheumatologic manifestations (1). The diagnosis is clinical but can be supported by laboratory tests in order to rule out differential diagnoses. The objective of this case report is to inform the readers about a disease that is becoming more common in our environment, to emphasize atypical manifestations such as abdominal symptoms and to alert about the need to make a timely diagnosis and treatment to avoid complications and even death.

2. Case Report

A 21-year-old man with a history of immune thrombocytopenic purpura in childhood, with no evidence of relapses since then. He consulted for a clinical picture of four days of evolution consisting of the appearance of palpable and pruritic purpuric lesions on the right forearm that later expanded to the whole of both upper limbs, trunk, and auricular pavilions. In addition, he presented edema in the lower limbs, ulcers in both malleoli and intense joint pain, for which the patient decided to self-medicate with 15 mg/day of prednisolone for four days. When he did not notice any improvement in his symptoms, he decided to consult a physician. In the examination, the patient reported regular use of marijuana but denied the use of other substances of abuse. On physical examination, the main findings were confluent exanthema on upper and lower limbs, purpuric lesions on both pinnae **(Image 1)** and ulcers on both external malleolus with grade I edema of the lower limbs **(Image 2).**

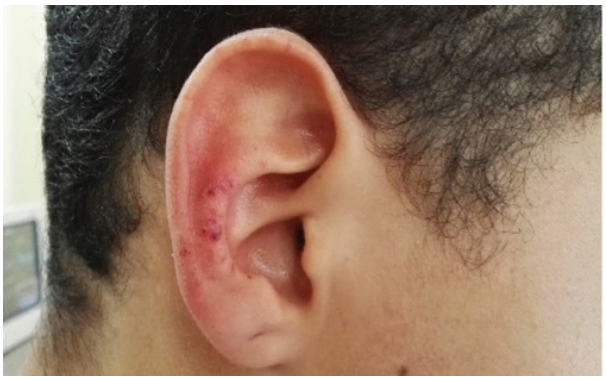

Image 1. Purpuric lesions in the pinna.

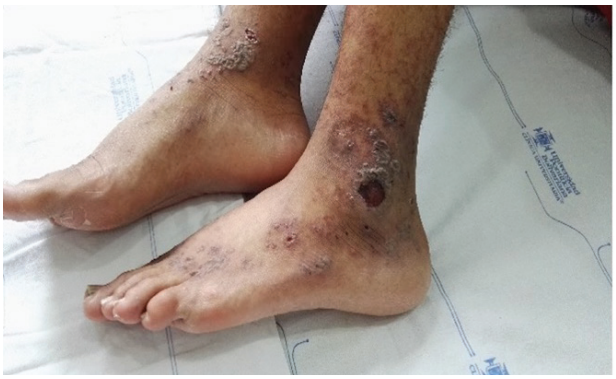

Image 2. Ulcer and purpuric lesions on external malleolus.

On initial examinations, he was found to have a discrete elevation of C-reactive protein and leukocytosis at the expense of neutrophils. The rest of the paraclinical, including liver and renal function tests, urinalysis, coagulation

times and rheumatological tests such as cryoglobulins, ANCAs, antinuclear antibodies (ANAs), extractable nuclear antibodies (ENAs), rheumatoid factor, hepatitis C antibodies, hepatitis B antibodies, lupus anticoagulant, anticardiolipin antibodies and complement C3 and C4, were in normal ranges. However, due to the lesions highly suggestive of cocaine consumption contaminated with levamisole, it was decided to perform a urine toxicity test, which was positive for marijuana and cocaine. With this result, the patient was questioned again and then admitted regular cocaine use.

Treatment was started with methylprednisolone 500 mg/day pulses for three days and continued with prednisolone 50 mg/day, achieving a significant improvement of the skin lesions. However, five days after discharge, the patient returned to the emergency room complaining of severe abdominal pain, so CT scan of the abdomen was requested, the results of which showed no abnormalities. However, due to the early clinical picture after discharge, the symptoms and the high suspicion of vasculitis, the treatment was complemented with cyclophosphamide 750 mg single dose and methylprednisolone 500 mg/day pulses were restarted for three days, with this treatment a complete improvement of the symptoms was achieved, the patient was discharged without complications and had no need for new admissions to the institution.

Ethical considerations:

For the preparation of this case report, the patient signed an informed consent form authorizing the review of his clinical history and the photograph taking. Likewise, institutional permission was obtained from the Clínica Universitaria Bolivariana (Medellín, Colombia) to access the patient's information and approval was obtained from the Health Research Ethics Committee of the Universidad Pontificia Bolivariana (Medellín, Colombia).

3. Discussion

In its 2021 report, the United Nations Office on Drugs and Crime (UNODC) reported that by 2019 approximately twenty million people worldwide had used cocaine in the previous year. Over the period 2010-2019 the estimated prevalence of cocaine use remained stable, but because of population growth there was a 22% increase in the number of people who had used cocaine in the previous year (2). For its 2020 report, the International Narcotics Control Board (INCB) reported that in South America there was a growing trend of coca paste use and a high percentage of patients in treatment for substance use disorders were cocaine users (3). In Colombia, the 2019 Na-

tional Study of Psychoactive Substance Use reported that 10.3% of the Colombian population reported having used an illicit substance at least once in their lifetime, and that 2.1% of respondents (about 136,000 people) reported having used cocaine at least once in their lifetime (4).

Nowadays, in many countries there is a problem with the combination of cocaine with levamisole and it is difficult to define when this mixture began to be used. Initially, it is possible that it was used because of its physical properties that allow expanding the volume of the commercialized product. Subsequently, it was found to have a cocaine potentiating effect because it increases endogenous levels of the alkaloid and because it prolongs the action of catecholamines in the synapse by reinforcing the inhibitory process of their reuptake and blocking monoamine oxidase (5,6).

Levamisole is an antiparasitic discovered in 1966 and was widely used for its efficacy in the treatment of gastrointestinal and pulmonary helminthiasis in humans and animals. In the 1970s, it was discovered to have immunomodulatory properties useful in multiple rheumatic diseases. However, in the 1980s, interest in this drug was lost due to inconclusive study results regarding its benefits. Then, in the 1990s, the molecule was reanalyzed due to three multicenter studies that revealed its role as an adjunctive therapy in melanoma and colon cancer (7-9), although later, due to adverse effects such as agranulocytosis, its use in humans was banned (10). Today it is only used in veterinary medicine.

The pathophysiology of CLIV is not yet fully established. It is known that the immunologic target of this reaction is neutrophil elastase (NE), a major component of neutrophil extracellular traps (NETs). NETs are formed by a complex immune process consisting of a type of programmed neutrophil death in which nuclear or mitochondrial deoxyribonucleic acid (DNA) is expelled, forming networks that play a fundamental immunological role in the trapping of invading extracellular microbes, as well as other different pathogenic functions in inflammatory, autoimmune, and thrombotic diseases (11).

When cocaine contaminated with levamisole is consumed, the formation of NETs is induced with the release of mitochondrial DNA, B-cell survival factor (BAFF) and neutrophil elastase, the main target antigen of ANCAs in cocaine users (12). All this breaks the immunological tolerance and increases the thrombotic state of the patient, which generates the CLIV.

Both compounds can produce systemic and rheumatologic symptoms, so it is difficult to individualize their effects. Cocaine use generates midline le-

sions including ischemic necrosis of the septal cartilage and perforation of the nasal septum, which are caused by its vasoconstrictor effect, by the trauma induced by the crystals and by the irritation generated by the substance directly in the tissue. These lesions may simulate a granulomatosis with polyangiitis (13).

The manifestations of levamisole consumption are associated with agranulocytosis, cutaneous vasculitis of small vessels, fever, arthralgias and occasionally glomerulonephritis. This vasculitis is characterized by being rapidly progressive and painful and begins with purpuric lesions that may progress to cutaneous necrosis and ulceration, with involvement of the ears, cheeks, trunk and extremities. There may also be gastrointestinal involvement, but this is infrequent (1,14,15). When both compounds are combined, a syndrome is generated which, in addition to inducing midline lesions, can generate systemic manifestations mainly attributed to levamisole.

In our environment, one of the largest studies published to date is that of Muñoz-Vahos et al (16), which reported the characteristics of thirty patients from two Colombian cities and four high complexity institutions, with an average age of 31 years and a symptom onset time of twelve months. The most frequent manifestations were lesions in the pinna, in 73% of the cases, and retiform purpura in 83%. The most common location of this purpura was the upper limbs. Of these patients, 57% developed renal involvement, 40% joint involvement and 23% fever (16).

Within the differential diagnosis, special consideration should be given to vasculitis. Patients may present positivity in some rheumatological tests such as anticardiolipin antibodies in up to 63% of cases, cryoglobulins in 65%, ANAs between 20 and 30%, lupus anticoagulant in 51% and positive anti-DNA and ribonucleoprotein (RNP) antibodies less frequently (1,17,18). The series of Muñoz-Vahos et al. shows this specific characteristic, which is positivity in multiple unrelated tests, and which constitute what the Anglo-Saxon literature calls “red herrings” or false leads. Thus, in this series 73% of patients had lupus anticoagulant, 24% cardiolipin IgM, 15% cardiolipin IgG, 57% ANAs and 35% anti DNA. This is then something that leads to suspect this condition: the presence of a rheumatologic disease of the vasculitis subtype with positivity for multiple paraclinical (16).

Among all the rheumatologic tests, the one most frequently found positive in these cases is that of ANCAs performed by immunofluorescence, which is present in up to 93% of patients. The pattern reported is an atypical pattern

(X-ANCA), although in laboratories with little experience in its measurement perinuclear patterns can be reported (p-ANCA), which makes the diagnostic process more difficult (13,19).

In patients with suspected CLIV, enzyme-linked immunosorbent assay (ELISA) tests for proteinase-3 and myeloperoxidase, which are specific for ANCA-positive vasculitis, should be additionally requested. This would point to primary vasculitis and not to CLIV. Other antibodies that may be useful are anti-elastase antibodies, as an antigenic target in CLIV, but they are not always available (20). Local data show ANCA positivity by indirect immunofluorescence or ELISA in 85%, predominantly of perinuclear pattern (93%), and in 7% of mixed pattern (perinuclear and cytoplasmic), with double positivity by ELISA for both proteinase 3 and anti-myeloperoxidase antibodies (57%) and in 43% positive only for anti-myeloperoxidase antibodies (16).

On the other hand, the presence of levamisole in urine can be confirmed by gas chromatography-mass spectrophotometry, but since the levamisole half-life is short (5.6 hours), its identification is difficult, even with a positive result for cocaine in blood or urine, which in this case can be detected by this same diagnostic method up to 48 hours after consumption (21,22).

The mainstay of treatment is withdrawal from the use of the substance and wound management should also be done considering the need for surgical debridement or antibiotic treatment. If with these measures and abstinence from consumption there is no improvement, or if there are severe manifestations, short courses of steroids can be used (15).

The results of investigations are variable for other treatments with colchicine, methotrexate, anticoagulants, dapsone, pentoxifylline, immunoglobulin, mycophenolate mofetil, cyclosporine, cyclophosphamide, and thalidomide (19); even in the case of severe compromises, plasmapheresis has been used (23). Some other complications such as leukopenia due to levamisole have been successfully treated with colony-stimulating factor (18).

After treatment, clinical improvement is observed in the first 48 hours. Neutropenia may disappear in five to ten days and skin lesions may completely heal in two to three weeks. However, immunological alterations may

«Both compounds can produce systemic and rheumatologic symptoms, so it is difficult to individualize their effects. »

persist for up to fourteen months after stopping consumption, and if there is a relapse in consumption, a more intense immunological response may be generated (24).

In conclusion, we report a case of cocaine-levamisole-induced vasculitis with typical cutaneous and joint manifestations, in addition to abdominal manifestations, which were completely resolved with immunosuppressive treatment with methylprednisolone and cyclophosphamide pulses at the doses described. The involvement of the auricular pavilion was fundamental for the diagnosis since it is not always possible to have an anamnesis in which the patient openly acknowledges the consumption of this substance. Therefore, a high diagnostic suspicion and clinical expertise is required, and in some cases, diagnostic aids to rule out other possible differential diagnoses. It is also suggested to consider abdominal symptoms as a possible component of the clinical symptoms of vasculitis.

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