Curr Rheumatol Rep (2017) 19: 36
DOI 10.1007/s11926-017-0653-9

VASCULITIS (L ESPINOZA, SECTION EDITOR)

Cocaine-Levamisole-Induced Vasculitis/Vasculopathy Syndrome

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Published online: 13 June 2017

Abstract
Purpose of review To understand the clinical spectrum of cocaine-levamisole-induced vasculitis. Worldwide recreational drug consumption is high among the adult population from various social strata. The use of cocaine with levamisole, a frequently added antiparasitic diluent, favors the manifestations of vasculitic lesions, especially in the skin.
Recent findings New insights into immunological mechanisms involved in the pathogenesis of the disease. There are still many unknown aspects in the pathogenesis of this disease, such as the immune system interaction with *p*-ANCAs and the release of inflammatory NETs (neutrophil extracellular traps), which are the origin of auto-antigens and tissue damage, manifesting as vasculitic purpura on the skin. The clinical presentation constitutes a challenge for the clinician to be able to distinguish it from small-vessel vasculitides.
Summary This paper intends to improve the understanding of this condition, exhibiting the broad clinical spectrum of local and systemic manifestations of cocaine-levamisole-induced vasculitis, to facilitate a timely diagnosis, in order to take corrective measures and avoid sequelae, along with tissue damage and the consequent deformities and permanent scars.

Keywords Cocaine-related disorders · Levamisole · Vasculitis · Leukocytoclastic · Cutaneous · Anti-neutrophil cytoplasmic antibody-associated vasculitis

This article is part of the Topical Collection on *Vasculitis*

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Introduction

Cocaine use has remained globally stable from 1998 to 2014, ranging between 0.3 and 0.4% of the population aged 15–64 years [1]; however, it has become a public health problem in recent decades for its organic and psychosocial consequences which can lead to a fatal outcome. Cocaine has an idiosyncratic effect, can cause multisystem manifestations and can simulate rheumatologic autoimmune diseases.

Levamisole, a former antiparasitic and immunomodulatory drug, has been used as a cocaine adulterant, because of its euphoric and stimulating effects which enhance its psychotropic properties, but it also has deleterious and deadly effects. It is responsible for the development of extensive necrotic lesions and retiform purpura, usually localized in the ear lobes, with the presence of *p*-ANCA, antinuclear and antiphospholipid antibodies, and neutropenia. Levamisole is the main cocaine adulterant, used between 70 and 88% of cases, in concentrations ranging between 1.5 and 10% [2].

Cocaine and Levamisole

Cocaine is extracted from the coca tree of the *Erythroxylum coca* plant. It is a local anesthetic with potent stimulant and vasoconstrictor properties, which after oral, intravenous or inhaled administration, generates behavioral changes and psychological effects, due to its coneffectssequences on the central nervous system (CNS), and it increases dopamine concentrations in the synaptic cleft by inhibiting its reuptake. Levamisole, a nicotinic antagonist, releases glutamate and thus potentiates the dopaminergic effect of cocaine; these central and peripheral effects act synergistically to promote cocaine addiction [3].

Levamisole is a synthetic derivative of imidazothiazole, which is used as an antiparasitic for intestinal nematodes in veterinary medicin, and has been used in humans as an immunomodulator in rheumatoid arthritis, ankylosing spondylitis, Behcet's disease, lichen planus, Crohn's disease, and vitiligo and as an adjuvant in chemotherapy for breast, colon and melanoma cancer. The first reports of leukocytoclastic vasculitis, nephropathy and agranulocytosis associated with levamisole were published in 1978, but since 2009 there have been numerous reports on vasculitis associated with cocaine consumption adulterated with levamisole, characterized by retiform purpura, neutropenia, thrombosis, crescentic glomerulonephritis and the presence of ANCA and other antibodies; thus, its use in humans has been restricted, but it continues in veterinary medicine [4–6].

Levamisole is used to increase the volume of cocaine and to augment its stimulating and euphoric properties mediated by increased brain dopamine levels and the production of a metabolite with amphetamine-like action. The physicochemical properties of levamisole make it favored as a cocaine adulterant, since it has an iridescent brightness which resembles it, along with stability at high temperatures, undetectable on impurities test, short half-life (5.6 h), and its quantification can only beperformed in specialized laboratories by liquid chromatography or tandem mass spectrometry [7].

Clinical manifestations of cocaine-levamisole use are multiple and can be local or systemic [8–10] (Table 1).

Table 1 Manifestations associated with cocaine and levamisole consumption [8–10]

Cocaine	Levamisole
Local:	Local:
Granulomas, necrosis and septal perforation	Hemorrhagic blisters
Cocaine-induced midline destructive lesions (CIMDL)	Retiform purpura
Erosion of dental enamel	Purpuric plates
Acute generalized exanthematous pustulosis	
Digital infarctions	
Necrotizing vasculitis	
Raynaud's phenomenon	
Lichenoid eruption	
Stevens-Johnson syndrome	
Oral thrush	
Corneal ulcers	
Systemic:	Systemic:
Delirium	Leukopenia, agranulocytosis
Hepatitis	Arthralgia
Granulomatosis with polyangiitis	Necrotizing and crescentic pauci-immune glomerulonephritis; renal failure
Thromboangiitis obliterans	
Urticarial vasculitis and other vasculitis	Alveolar hemorrhage, pulmonary hypertension Leukoencephalopathy and seizures

Pathogenesis

The vasculopathy associated with cocaine adulterated with levamisole is characterized by unusual high titers of *p*-ANCA directed against atypical antigens within the neutrophil granules, such as human neutrophilic enolase (HNE) and not against myeloperoxidase (MPO), the main target of *p*-ANCA [11, 12]. These findings differentiate it from typical ANCA vasculitis that share similar clinical manifestations, but with low-ANCA titers specifically directed against a single neutrophil antigen rather than against several.

Cocaine alone may induce ANCA-like polyangiitis with granulomatosis vasculitides, similar to the primary form of idiopathic *c*-ANCA and PR3 (proteinase 3)-positive antibodies, unlike the pattern observed with levamisole, which is predominantly *p*-ANCA [13•].

There are very few reported cases in the literature of levamisole-induced vasculopathy not related to cocaine use. Tello et al. described the case of an adult patient on treatment with levamisole for vitiligo, who presented with extensive cutaneous necrosis, coagulopathy, thrombocytopenia and intracranial bleeding associated with positive *p*-ANCA and lupus anticoagulant, with persistence of the latter 4 years later, demonstrating that there is a subgroup of patients who may develop levamisole-associated autoimmune disease, requiring observation and treatment for long periods of time [14].

There is no clarity in the pathogenesis of levamisole-induced vasculopathy/vasculitis, yet it is known that there is activation of the immune cascade with loss of tolerance to self - antigens in genetically predisposed individuals [14–16] (Table 2).

Both cocaine and levamisole induce the formation of neutrophil extracellular traps (NETs), a potential source of self-antigens, such as neutrophil enolase, the arget of ANCA in cocaine users; they also increase the release of B-cell activating factor [17••].

Other mechanisms involved in the pathogenesis of tissue ischemia attributed to cocaine are: vasospasm, endothelial dysfunction and thrombophilia, by increased platelet factor 4, thromboglobulin, P-selectin, endothelin-1 and decreased nitric oxide [18].

Table 2 Immunological mechanisms of levamisole

- Formation of antibodies with increased B and T cells
- Chemotaxis and increased neutrophil response
- Deposit of immune complexes in the blood vessel wall
- Degranulation and release of oxygen metabolites causing vascular injury
- Neutropenia secondary to antibody production that bind neutrophils or cytotoxic antibodies
- Autoimmunity, coagulopathy and antiphospholipid syndrome induction
- Clinical manifestations improve within 2–3 weeks after removal or withdrawal of levamisole, but serology persists up to 14 months

A subset of patients predisposed to ANCA production, particularly against HNE, develop cocaine-induced midline destructive lesions secondary to necrotizing inflammatory response triggered by this alkaloid [12].

The mechanism by which only a few individuals present with levamisole-associated agranulocytosis and neutropenia is not fully understood. With human therapeutic use, they occur in up to 20% of cases and there seems to be susceptibility to these complications in HLA-B27-positive subjects, which can be observed in up to 75% of them [19, 20].

The presence of neutropenia and agranulocytosis is a key to differentiate ANCA vasculitis produced by cocaine-levamisole and that produced by other drugs [13•]. This finding may or may not be related to skin purpura, and the presence of both occurs in 47% of cases [10].

Clinical Manifestations

A cocaine-levamisole-induced vasculopathy syndrome has been described, distinguished by cutaneous manifestations, neutropenia and ANCA positivity [21, 22], mainly attributed to the vasoconstrictor effect of cocaine and antibody production induced by levamisole [15]. All manifestations reappear with each exposure; thus, the best treatment relies on abstinence.

Most cases present almost exclusively in the skin, but some have involvement in other organs, such as: kidney, lung, liver and brain. There may be constitutional symptoms, such as fever, arthralgia, symmetric polyarthritis similar to rheumatoid arthritis, fatigue, asthenia, and flu-like symptoms [23] (see Table 1).

In 91% of cases, the presentation is cutaneous, with retiform purplish plaques with a bright erythematous edge and necrotic center [24], and painful hemorrhagic blisters which appear suddenly and simultaneously in any part of the body, with a predilection for lower limbs, ears [9–11], zygomatic archs and nose (Fig. 1). The lesions may progress to ulcers with necrosis and superinfection.

Mucosal involvement may present as a midline destructive lesions present in up to 4.8% of cases seen in inhaled cocaine users. The most frequent location is the nasal septum but it can affect the turbinates and the hard palate. Patients may have epistaxis, hyposmia or facial pain, which can be reversed if detected and treated in a timely manner [25••].

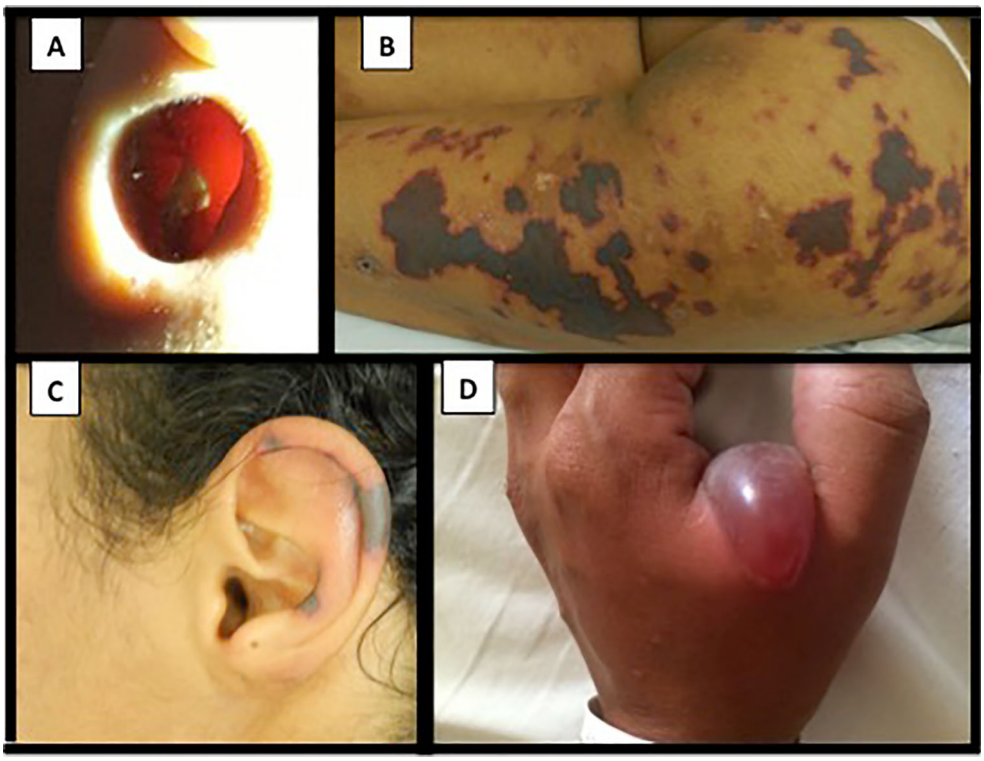

Fig. 1 Characteristic manifestations: Perforated nasal septum (**a**), retiform purpuric plaques in extremities with a necrotic center (**b**), involving the helix of the ear (**c**) and painful hemorrhagic blisters (**d**)

Diagnosis

The diagnosis is of exclusion and is based on the clinical suspicion of the sudden appearance of retiform purpuric lesions with central necrosis, with a special predilection for the earlobes, associated with general symptoms such as fever, arthralgia and fatigue. In patients with cutaneous disease, hematologic abnormalities occur in up to 60% of cases and between 95 and 100% are ANCA- positive [5].

Among the hematological findings, the presence of agranulocytosis, leukopenia, neutropenia, increased globular sedimentation rate, and hyponatremia can be observed.

The most important serological study is ANCA, *p*-ANCA and/or *c*-ANCA positivity, which may have multiple antigenic specificities, such as MPO and PR3. The most frequent are atypical ANCA directed against HNE, lactoferrin and cathepsin G. In addition, low titers of antinuclear and antiphospholipid antibodies can be found [4, 26].

Leukocytoclastic vasculitis, thrombotic vasculopathy or both may be observed in skin biopsies. There is typically involvement of superficial and deep dermis vessels, associated with mixed angiocentric inflammatory infiltrate with predominance of neutrophils, and sometimes eosinophils. There is infiltration of the vessel wall, leukocytoclasis, fibrinoid necrosis and extravasation of red blood cells (RBCs) [13•, 27]. Some cases present vascular occlusion by fibrin thrombi and epidermal necrosis without vasculitis [7, 28].

Treatment

The discontinuation of cocaine use is the first line of treatment associated with supportive measures, including skin care with proper wound healing and dressings, antibiotics for infected lesions and analgesics. Some patients require surgical management with debridement, grafting, and amputation.

The use of immunosuppressants has been reported in some cases. Corticosteroids are reserved for individuals who do not improve with general measures or those with debilitating joint disease, very high C-reactive protein (CRP) values or histopathology-proven vasculitis [29]. The role of other immunosuppressants is controversial, mainly when there is agranulocytosis or neutropenia. There are case reports on colchicine, methotrexate, anticoagulants, dapsone, pentoxifylline, immunoglobulin, plasmapheresis, mycophenolate mofetil, cyclosporine, cyclophosphamide and thalidomide, with varying results [26, 30, 31]. Recently, the case of a patient who did not stop cocaine consumption and was treated with prednisolone, aspirin and vardenafil was published [32••].

The prognosis of cocaine-levamisole-induced vasculopathy syndrome is generally good; most patients have a non-aggressive, predominantly cutaneous course, but, when associated with extensive or extracutaneous involvement, morbidity and mortality are higher. It is mandatory to monitor and prevent superinfection of the lesions.

After having discontinued consumption, skin lesions begin to improve within 2–3 weeks and neutropenia in 5–10 days, but the serological profile may persist for up to 14 months [25••, 33].

Conclusion

Clinical and laboratory manifestations secondary to cocaine use combined with or without levamisole constitute a syndrome that requires high clinical suspicion, early diagnosis and rapid suspension of consumption due to the high probability of complications and the possible development of autoimmunity in predisposed individuals, In turn, it is important to provide education and psychosocial support to the patient as well to prevent the use of unnecessary treatments,.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any human or animal studies performed by any of the authors.

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