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Review

Cutaneous and mucosal manifestations associated with cocaine use☆

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ABSTRACT

Complications due to cocaine are a public health problem. The typical cutaneous disease is leukocytoclastic vasculitis and/or thrombotic vasculopathy affecting mainly the ears. No intense systemic involvement is usually present, but there may be several cutaneous, mucosal and systemic manifestations. Other findings associated as arthralgia, neutropaenia or agranulocytosis, low titre positive antinuclear antibodies, antiphospholipid antibody positivity and neutrophil cytoplasmic antibodies against multiple antigens help the diagnosis. This disease requires a clinical suspicion with a clinical history, a complete physical examination and a broad differential diagnosis for an early and correct diagnosis. The course is usually self-limited. In most cases the only treatment is to discontinue the use of cocaine associated with symptomatic treatment, no proven benefit of systemic corticosteroids.

Manifestaciones cutáneas y mucosas asociadas al consumo de cocaína

Palabras clave:
Cocaína
Levamisol
Vasculitis
Trombosis
Anticuerpos anticitoplasma de neutrófilos

RESUMEN

Las complicaciones secundarias a la cocaína constituyen un problema de salud pública. La manifestación cutánea característica es la vasculitis leucocitoclástica y/o la vasculopatía trombótica habitualmente poco agresiva que afecta principalmente a los pabellones auriculares. No suele presentar afectación sistémica intensa, pero puede acompañarse de múltiples manifestaciones cutáneas, mucosas y sistémicas. Otros hallazgos asociados como las artralgias, la neutropenia o la agranulocitosis, los anticuerpos antinucleares positivos a títulos bajos, y la positividad para anticuerpos antifosfolipídicos y anticuerpos anticitoplasma de neutrófilos frente a múltiples antígenos ayudan al diagnóstico. Esta entidad requiere un diagnóstico precoz, siendo fundamental la sospecha clínica, realizar una adecuada anamnesis, una exploración física completa y un diagnóstico diferencial amplio. El curso suele ser autolimitado. En la mayoría de los casos el único tratamiento necesario es la interrupción del consumo de cocaína asociado a un tratamiento sintomático, sin beneficio demostrado de los corticoides sistémicos.

Introduction

Consumption of drugs, especially cocaine, doubled in Western countries during the first decade of this century, which has meant that it has become a major public health problem.[1] The frequency of complications related to the use of these substances has increased significantly. The principle complications reported from the use of cocaine are haematological and skin, which may appear in isolation or together.[1–3]

Cocaine is a local anaesthetic and powerful vasoconstrictor that has stimulant properties. After oral, intranasal, intravenous or inhaled administration or upon being smoked, it causes behavioural changes and has certain psychological effects on the consumer because of its pharmacological effects on the dopaminergic and serotonergic neurons of the central nervous system. Although it is generally administered intranasally, there has been a gradual increase in both intravenous and inhaled use of pyrolysed materials, such as coca paste to extract the cocaine through the use of flammable solvents or by smoking cocaine in its free base form prepared with sodium bicarbonate, thus extending and/or increasing its potency and duration.[1,2]

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This has resulted in the narcotic substance not only being used as a cocaine base, but adulterated with substances such as caffeine, talc, analgesics, phenacetin, lidocaine, procaine, various sugars and especially, because of its special pharmacological properties, with levamisole. All this has led to a sharp controversy in regard to considering whether the complications described with the use of the drug are due only to cocaine in its free base form or the different products that adulterate it.[1–7]

Regarding this last point and regarding levamisole, this is an synthetic, imidazothiazole derivative drug which, because of its antiparasitic and immunomodulatory effect, was used for the treatment of rheumatoid arthritis, ankylosing spondylitis, Behcet's disease, Crohn's disease, recurrent oral aphtosis, lichen planus and various malignancies such as leukaemia, colorectal cancer, breast cancer and metastatic malignant melanoma. Its mechanism of action is unknown, but it is suggested that levamisole has an immunomodulatory effect through an increase in adhesion, chemotaxis, activity and apoptosis of neutrophils, inducing maturation of dendritic cells, increased phagocytosis by macrophages by toll-like receptors and an increase in the activity of T cells with increased antibody production. Likewise, levamisole intensifies and prolongs the stimulating effect of cocaine because of its potential inhibitory effect of the presynaptic reuptake of catecholamines.[1–13]

It is estimated that between 70 and 88% of the cocaine consumed today is adulterated with levamisole and that the dopant concentrations present in cocaine range between 1.5 and 10%. Levamisole was withdrawn from use by humans in 2000 because of its serious side effects and lack of knowledge of the exact toxic dose.[1–3]

Skin manifestations

Skin manifestations appear in 0.5–3% of consumers and occur between 24 and 96 h after consumption. Lesions occur regardless of how the drug was administered, whether intravenously, injection or inhaled. Women show a higher frequency, with an average age of onset of 42.7 years (range 18–64).[1–13]

Its manifestations have a broad clinical spectrum (Table 1).[1–40] The most frequent clinical forms and characteristics are leukocytoclastic vasculitis and/or thrombotic vasculopathy[1,3,6,8–31] in the form of an acute outbreak of purpuric lesions that are usually painful. The lesions appear as maculopapular or erythematous edematous and indurated plaques with erythema violaceous edges. The centre of the lesions show increased activity with the development of blood blisters, necrosis and ulcers with risk of secondary infection. By confluence, injuries can take a reticulated, starry or angular shape (Fig. 1). In most patients, lesions appear in bilaterally and with a very selective placing in the helix or the lobe of the ear (Fig. 2). Other affected areas are the cheeks, the nasal dorsum and acral areas of the lower limbs, but it can also be located in any area of the skin. In 16% of patients, the dermatologic profile is accompanied by joint pain, but this does not usually present a clear systemic involvement.

Histological findings show lesions of small and/or medium sized vessels of the skin and occasionally hypodermis. Extravasation of red blood cells is frequent, as well as the presence of a diffuse neutrophilic dermal infiltrate with isolated eosinophil. Leukocytoclastic vasculitis with or without fibrinoid necrosis can be observed, as can occlusive thrombotic vasculopathy thrombotic or a thrombotic vasculitis, which is a characteristic but not specific histological finding (Fig. 3). These findings may be helpful in the differential diagnosis.

The aetiologic mechanism is unknown, but is believed to be a multifactorial process that is predominantly immunologically mediated with a deposit of antigen-antibody complexes in the

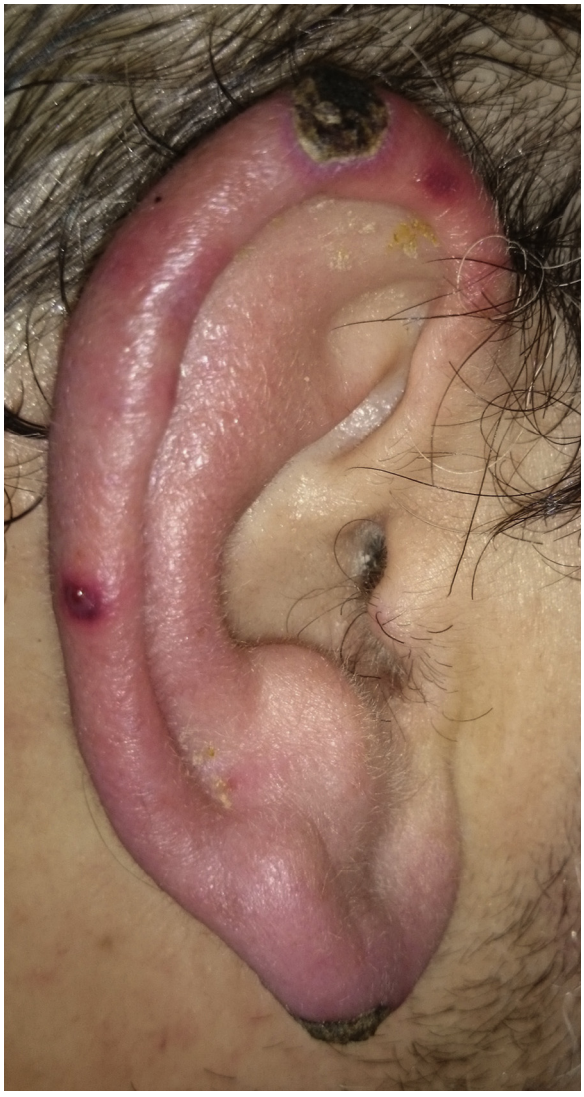

Fig. 1. Surface necrotic purpuric plates confluent with reticulated distribution in the lower limbs.

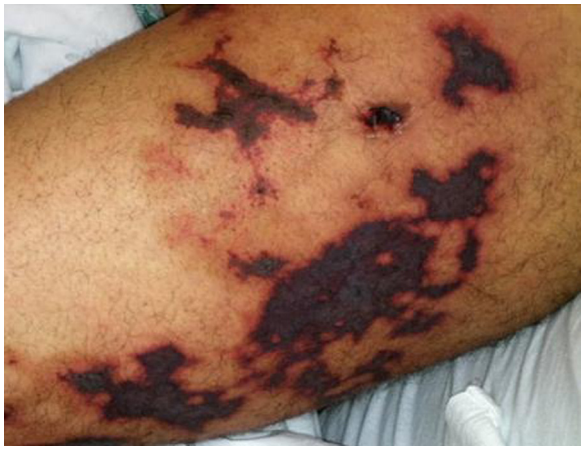

Fig. 2. Necrotic plates with violet edges on the helix and earlobe.

Table 1
Cutaneous and mucosal manifestations associated with cocaine use.

Vascular diseases	Digital vasospasm, digital or limb gangrene, acral ulcerations Raynaud's phenomenon Livedo reticularis, livedo racemosa Urticaria vasculitis Buerger's disease
Skin rashes	Morbilliform or maculopapular erythematous, scaly skin outbreak, usually widespread and non-pruritic Urticaria with angioedema Lichenoid eruption Fixed-drug eruption Acute generalised exanthematous pustulosis Stevens-Johnson syndrome
Bullous diseases	Bullous erythema multiforme Vegetating pemphigus
Skin and soft tissue infections	Skin abscesses Fournier gangrene
Neutrophilic dermatosis	Gangrenous pyoderma
Other dermatoses	Alopecia Anetoderma
Oral manifestations	Pharyngitis, sore throat, oral candidiasis Oedema of uvula Hyperpigmentation and hyperkeratotic papules and plates coalescing as a round morphology on the tongue dorsum
Nasal manifestations	Nasopharyngeal ulcerations Abscesses Gangrenous pyoderma with nasal piercing Fungal rhinosinusitis angioinvasive
Ocular manifestations	Corneal ulcers, ulcerative keratitis and bacterial or fungal keratitis

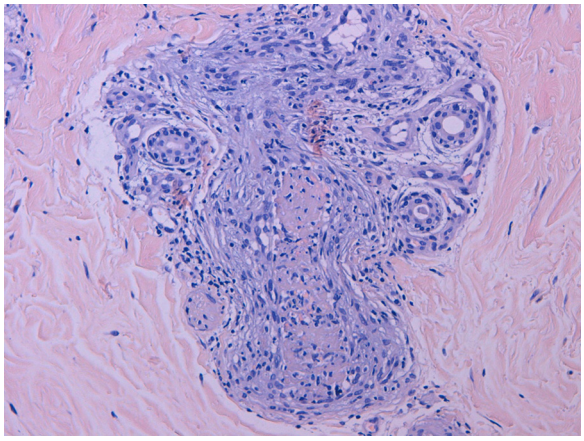

Fig. 3. Leukocytoclastic vasculitis with thrombosis and small dermal vessels (haematoxylin-eosin, 20×).

vascular wall of individuals who are genetically predisposed. Ultimately ischaemia and an inflammatory reaction develop.

Mucosal manifestations

Different clinical conditions have been reported regarding mucous due to cocaine use, including oropharyngeal, nasal and eye mucosa (Table 1). Orofacial manifestations that are most frequent from the use of inhaled cocaine is midline destructive lesions, which can occur in up to 4.8% of consumers.[1,6,9,28,30] The most common site is the nasal septum, followed by the turbinates and hard palate, although it can affect any osteochondral structure or soft tissue. Clinically it presents in the form of epistaxis, hyposmia or anosmia accompanied by nasal or facial pain. In its evolution, ulceronecrotic lesions develop that produce communications between the different nasal, oral and sinus cavities. Lesions can be reversed if detected early and cocaine use is discontinued. The origin is unknown, but it has been suggested that endothelial damage through a direct toxic effect or by prolonged vasoconstriction could cause ischaemic tissue necrosis.[32–40] Another common complication is canker sores, which have an unknown origin and may appear regardless of the presence of haematological abnormalities.[1,6,9,32]

Table 2
Systemic manifestations associated with cocaine use.

Pulmonary manifestations	Laryngitis Flu-like episodes Respiratory distress Pulmonary haemorrhage Arterial pulmonary hypertension
Rheumatological manifestations	Polyarthritis/polyarthralgia Diffuse sclerosis and CREST-like syndrome
Digestive symptoms	Hepatitis Anorexia, nausea, vomiting, diarrhoea Dysgeusia Gastric perforation and ulcer
Systemic vasculitis	Cerebral vasculitis Churg-Strauss syndrome Wegener's granulomatosis Henoch-Schönlein Vasculitis
Other manifestations	Glomerulonephritis Secondary amyloidosis Delusional infestation Multifocal inflammatory leukoencephalopathy Type 1 and 3 hypersensitivity reactions Inappropriate antidiuretic hormone secretion (SIADH)

Systemic manifestations

Parenteral administration of cocaine is associated with a systemic clinical profile that includes fever and visceral multiorgan involvement with pulmonary, haematologic, gastrointestinal and vasculitis repercussions (Table 2).[1,3,6,8–10,12,18,19,21,25,31,41] The toxicity of cocaine produces hypertension, tachycardia, tonic-clonic seizures, dyspnoea and ventricular arrhythmia. These events are not only associated with the use of intravenous cocaine, but also through inhalation when it is smoked in the form of coca paste and can cause serious lung disease due to a direct effect of the substance or solvents used.[41]

Laboratory findings

From a haematological perpective, neutropenia is a frequent and characteristic finding that appears in 4% of consumers 24 h to 3 weeks after the last administration. The figures return to normal after cessation of drug use within 5–10 days. In addition, it is believed that the presence of neutropenia can cause a trigger effect for vascular disease associated with cocaine use.[1,6,7,9,12,13,20,24–30,42–49] The aetiologic mechanism is not fully established, but it is thought that it might be due to either a direct toxicity on neutrophils or a process mediated by antibody formation.[24,49] Other changes described are thrombocytopaenia, eosinophilia and agranulocytosis, which is a rare, idiosyncratic and very serious side effect that occurs in 0.5% of consumers and is usually reversible.[1,6,7,9,12,30,42–47] A bone marrow biopsy is not necessary in these patients.

Regarding serologic findings, the most frequently encountered autoantibodies are antiphospholipid antibodies, especially IgM anticardiolipin, lupus anticoagulant and antineutrophil cytoplasmic antibodies (ANCA) with a cytoplasmic fluorescence (c-ANCA) or perinuclear (p-ANCA) pattern.[7,9,12,19,22,23,25,34,35,50–52] While c-ANCA are directed against proteinase antigen 3 (PR3), the p-ANCA

bind to different antigens, including myeloperoxidase, lactoferrin, cathepsin G, K catalase, azurocidin, the protein that increases bacterial permeability and human neutrophil elastase (HNE). These findings are relevant but are not specific, they may appear in other vasculitis that show positive for ANCA caused by medications. However, detection of ANCA against HNE is considered a specific serological marker associated with cocaine use. It has been suggested that ANCA stimulate the degranulation of neutrophil and apoptosis and with direct or indirect endothelial damage. The ANCA titre appears to correlate with clinical activity of vasculitis.[52–54]

Other laboratory abnormalities described include low titre positivity for anti-DNA and antinuclear antibodies (ANA) together with positive Coomb's test.[1,6,13,20,24–28,46,48,49] Sera supplement levels are usually normal, although a decline in C3 and C4 has been reported.[24,53] An activated partial thromboplastin time and prothrombin time may be elevated due to the hypercoagulable state in these patients. Protein C and S levels may be decreased.[25] It has also been shown that the expression of HLA could be a risk factor for the development of complications, especially agranulocytosis, but this latter one has not yet been fully confirmed.[1,6,13,20,24,25,46,48,49]

Toxicological analysis[6,9,13,26–28]

Cocaine has a short plasma half-life of approximately 6 h. In humans, cocaine is metabolised through plasma esterases to benzoylecgonine and ecgonine methyl ester, which has an average life of 12 h and is excreted through urine. The drug can be detected in routine urine toxicology tests up until 3 or 4 days after the last administration, although the highest diagnostic yield is obtained in the first 24–48 h after consumption. It is possible to detect in hair samples up to one month after cessation of administration, but this method is not used regularly. The simultaneous intake of alcohol and cocaine is a common form of use which induces the presence of cocaine in blood and urine of a metabolite, ethylcocaine, a prominent inducer of cardiovascular alterations associated with the drug.

Regarding levamisole, this has a half life of only 5.6 h, and only between 2 and 5% of the product can be detected in urine. Obtaining serum and urine samples within 48 h after consumption is necessary, special methods are fundamental for detection such as gas chromatography and mass spectrometry. The sensitivity of the test is low and is only available in some centres, such that analysis is not always done systematically.

Diagnosis

The diagnosis of purpuric rash outbreak because of use of cocaine adulterated with levamisole is mainly clinical and exclusion. Initially, the patient usually does not admit prior drug use, so a high index of suspicion and properly directed anamnesis is required along with a complete clinical examination.

In the presence of a suspicious skin condition, we must establish several differential diagnoses (Table 3).[6,8,9,12,20,26,27,54,55] A clinical picture of a purpuric or necrotic rash outbreak with acral predominance, without a marked systemic involvement, including the presence of neutropenia, agranulocytosis, ANCA positivity, antiphospholipid antibodies or ANA at low titres are findings that should be treated with suspicion.

Ulceronecrotic oronasofacial lesions have several differential diagnoses (Table 3).[6,8,9,12,20,26,27,54,55] Wegener's granulomatosis is the main differential diagnosis as it can present a very similar clinical picture. Determining pANCA against HNE and PR3 antigens can be a differentiating factor, as it tests positive in profiles induced by cocaine while in Wegener's granulomatosis it would test positive for c-ANCA.

Table 3
Main diagnostic differences to consider when dealing with a purpuric rash outbreak and ulceronecrotic oronasofacial lesions.

Autoimmune connective tissue diseases	Systemic lupus erythematosus Antiphospholipid syndrome
Viral infections	HIV, hepatitis B and C
Fungal infections	Blastomycosis, mucormycosis, aspergillosis in immunosuppressed patients
Parasitic infections	Disseminated strongyloidiasis
Bacterial infections	Septicemia by staphylococci, streptococci and vibrios Ecthyma gangrenosum due to *Pseudomonas aeruginosa* Tuberculosis Tertiary syphilis
Other causes of vasculitis	Secondary to neoplasias or medication, atypical exudative erythema multiforme, polyarteritis nodosa, microscopic polyarteritis, Churg-Strauss syndrome, Wegener's granulomatosis, sarcoidosis, cryoglobulinemias, cryofibrinogenemia
Coagulation disorders	Protein C and S deficiency, hyperhomocysteinaemia, purpura fulminans due to disseminated intravascular coagulation, skin necrosis induced by warfarin or heparin
Vascular disorders	Livedoid vascular disease, Kaposi's sarcoma, oxalate crystal deposition disease or cholesterol emboli, embolisation bue to marantic endocarditis or atrial myxoma, cutaneous calciphylaxis
Haematological diseases	Thrombocytosis secondary to myeloproliferative disorders, severe haemolytic anaemia, sickle cell disease, paroxysmal nocturnal haemoglobinuria, idiopathic thrombocytopenic purpura, leukaemia, T-cell lymphoma angiocentric
Neoplasms	Squamous cell carcinoma of head and neck

When clinical suspicion of cocaine-induced vasculitis exists, a study protocol similar to that of drug-induced vasculitis should be requested,[1,3,6,9,12,20] including a red blood count, basic biochemical analysis (liver and kidney function tests), erythrocyte sedimentation rate, urinalysis, posteroanterior and lateral chest plain radiographs, histopathological study through biopsy punch of skin with or without direct immunofluorescence, antiphospholipid antibodies (lupus anticoagulant and anticardiolipin antibodies), hypercoagulable study (homocysteine levels and protein C and S), cryoglobulins, ANCA, ANA and anti-DNA serum levels, rheumatoid factor and complement, and serology for hepatitis B and C and HIV.

Blood, urine and skin cultures may be necessary to exclude an infectious aetiology. Finally, depending on the patient's clinical history, faecal occult blood can be tested.

Evolution and treatment

Cocaine-induced vasculitis evolution is not usually very aggressive, with predominantly cutaneous involvement and an absence of clinical or laboratory visceral damage. However, in some cases, cutaneous and systemic involvement can be extensive and severe with a high rate of morbidity and mortality. Cases of extensive skin necrosis, neutropenia and/or agranulocytosis could result in hydroelectrolyte disorders, loss of proteins, and opportunistic infections, which could develop into sepsis and multiorgan failure.

In most cases this entity has a complete spontaneous resolution of skin lesions two to three weeks after cessation of cocaine use, with no long-term sequelae. Some patients may have significant sequelae scarring. Elevated serological markers tend to normalise over a period of time that can vary between 2 and 14 months, while neutropenia usually normalises within between 5 and

10 days. Re-exposure to cocaine can cause an intense recurrence of the disease.[6,8–10,12,13,19,20,26–28,47,49]

In regard to treatment, there is no consensus nor established clinical guideline. The most significant therapeutic measure that can reverse the process and prevent relapse is cessation of cocaine use and prevention of re-exposure. In most cases the only necessary process is the interruption of cocaine use, usually associated with symptomatic and supportive treatment and close ambulatory monitoring. NSAIDs are useful for articular symptoms, and colchicine and oral antihistamines for skin symptoms, with good response.[6,8–10,12,13,19,20,26–28,30,47,49]

Systemic glucocorticoids are often used as a treatment, but their benefit is not proven, and should be used with caution because of an increased susceptibility to infections and systemic adverse effects. When mild systemic involvement occurs, glucocorticoids can be used alone or in combination with other immunosuppressive drugs with caution. In cases of severe systemic involvement other medications have been used such as dapsone, pentoxifylline, intravenous immunoglobulin, plasmapheresis, mycophenolate mofetil, cyclosporine, methotrexate, cyclophosphamide and thalidomide, although it is unclear whether these treatments affect prognosis.[8,46,53,56]

Patients who develop agranulocytosis or symptomatic or febrile neutropenia require hospitalisation and also broad-spectrum antibiotics. Granulocyte-colony stimulating factor is recommended for these patients in cases of evidence of infection or added immunosuppressive comorbidity.[42–49] In some cases, anticoagulation measures may be required. Extensive skin necrosis may require hospitalisation in burn units for extensive debridement and the need for skin grafts or amputation.[57]

Conclusion

Complications associated with cocaine use are underestimated and underdiagnosed and require proper and early diagnosis in order to interrupt its consumption and prevent the use of unnecessary and potentially dangerous treatments, such as intensive immunosuppressive therapy. The risk of recurrence is high in symptomatic patients and preventive advice is essential for the cessation of cocaine use.

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Conflicts of interest

The authors declare no conflict of interest.

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