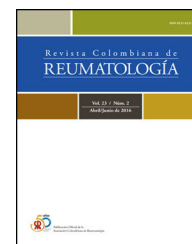




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Case Report

Toxics and atypical manifestations. Vasculitis associated with levamisole-adulterated cocaine. A case report

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ABSTRACT

Clinical case: A 57-year-old patient with active inhaled cocaine consumption consulted for asthenia, sweating and elevated inflammatory parameters. A positive result was obtained in anti-neutrophil cytoplasmic antibodies (ANCA) type PR 3, without evidence of uptake on positron emission tomography with fluorodeoxyglucose (PET-CT). The study was completed with a renal biopsy that demonstrated a focus of acute tubular necrosis within an area of lymphoplasmacytic interstitial infiltrate with the absence of proliferative signs. The presumptive diagnosis of vasculitis associated with the consumption of toxins, cocaine adulterated with levamisole, was established.

Discussion: Since 2010, cases of levamisole-adulterated cocaine-induced vasculitis have been reported, frequently manifesting with skin lesions, the appearance of purpuric lesions on the ears being typical. The presence of renal involvement associated with pauci-immune glomerulonephritis has been described. Treatment will be abstinence from toxins; however, steroids or immunosuppressive drugs may become necessary without consensus in the clinical practice guidelines on their indication.

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Tóxicos y manifestaciones atípicas. Vasculitis asociada con cocaína adulterada con levamisol. A propósito de un caso

RESUMEN

Caso clínico: Una paciente de 57 años con consumo activo de cocaína inhalada consultó por un cuadro de astenia, sudoración y elevación de parámetros inflamatorios. Se obtuvo un

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Levamisol
ANCA

resultado positivo en anticuerpos anticitoplasma de neutrófilos (ANCA) de tipo PR 3, sin evidencia de captación en una tomografía por emisión de positrones con fluorodesoxiglucosa (PET-TAC). Se completó el estudio con una biopsia renal que demostró un foco de necrosis tubular aguda dentro de un área de infiltrado intersticial linfoplasmocítico con ausencia de signos proliferativos. Se estableció el diagnóstico de presunción de vasculitis asociada con el consumo de tóxicos, cocaína adulterada con levamisol.

Discusión: Desde el año 2010 se han reportado casos de vasculitis inducida por cocaína adulterada con levamisol, que frecuentemente se manifiesta con lesiones cutáneas, siendo típica la aparición de lesiones purpúricas en las orejas. Se ha descrito presencia de afectación renal asociada con glomerulonefritis pauci-inmune. El tratamiento de elección será el abandono del consumo de tóxicos, sin embargo, pueden llegar a ser necesarios esteroides o fármacos inmunosupresores, sin existir consenso en las guías de práctica clínica sobre su indicación.

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Introduction

Since 2003, the presence of Levamisole in cocaine has been detected, having increased the proportion of use from 10% in 2008 to 82% in 2011.^{1,2} The importance lies in the association of cocaine, as well as adulteration with levamisole, as a trigger for the development of vasculitis mediated by anti-neutrophil cytoplasm antibodies (ANCA).^{1,3}

Clinical observation

We present the case of a 57-year-old woman, native of Spain, an administrative worker with a personal history of arterial hypertension, chronic toxic rhinitis with active use of inhaled (snorted) cocaine, who consulted for asthenia, night sweats and shivering associating elevation of inflammatory parameters in laboratory tests. On physical examination, she presented a cushingoid morphotype, was afebrile, without lymphadenopathy or palpable visceromegaly, and did not associate skin lesions. The patient was being treated with oral methylprednisolone for a long time, since it had been indicated some time before, without having stopped it at any time.

Eighteen months before, she visited another center due to a clinical condition that overlapped the current one, with positive analytical results for ANCA anti-proteinase antibodies (PR3) 122 U/ml and a cranial-thoraco-abdominal-pelvic computerized tomography (CT), which showed only changes sinus inflammation and septum perforation. The study was completed with a fluorodeoxyglucose positron emission tomography scan (PET-CT) with no evidence of uptake tissue.

The hemogram showed 19,220 leukocytes, Hb 9.8 g/dL (MCV 87.5 fl, ferritin 40 ng/ml, transferrin 251 mg/dL, saturation index of 14%). It should be highlighted an elevated creatinine (1.45 mg/dL, with a calculated glomerular filtration rate of 37 ml/min/1.73 m²) with mild urine proteinuria (creatinine protein ratio 313.5 mg prot/g creates). The autoimmunity panel revealed positive ANCA antibodies at 1/20 titers with PR-3 specificity of 8 IU/ml. No other antibodies were positive.

An ultrasound-guided percutaneous renal biopsy was performed, which demonstrated the absence of proliferative signs (mesangial, endocapillary or extracapillary), with no active extracapillary lesions indicating glomerular involvement due to active or past outbreak of ANCA antibodies. The acute involvement consisted of foci of acute tubular necrosis within an area of lymphoplasmacytic interstitial infiltrate without atypia, surrounded by foci of chronic involvement, with an index of tubular atrophy and interstitial fibrosis of approximately 15%. The direct immunofluorescence study revealed an absence of binding for IgG, IgA, C3, C1q, Kappa, lambda, fibrinogen, and albumin.

Initially, the presence of granulomatosis with polyangiitis with otorhinolaryngological involvement was considered. However, it has recently been described in the literature a picture of vasculitis associated with the consumption of toxics. In this case the patient confirmed the adulteration of the cocaine consumed with levamisole, which supported the diagnosis of levamisole-adulterated cocaine-induced vasculitis. A decrease in steroids was initiated without achieving the abandonment of toxic substances, for which Azathioprine was introduced as a corticosteroid-sparing drug, with resolution of the clinical picture.

Discussion

Cocaine is an alkaloid ester derived from *Erythroxylum coca* Lam and *Erythroxylum novogranatense*, with intravenous as well as intranasal (snorted) administration being the most frequent form of consumption. The rate of elimination of cocaine is independent of the route of administration, being metabolized predominantly into benzoylecgonine and methyl ester ecgonine.⁴

Currently in Spain the rate of cocaine use at some point in life is around 11.2%, while the analysis of the last 12 months describes a consumption of 2.5% of the population.⁵

Levamisole is a veterinary anthelmintic drug used for clinical indications such as rheumatoid arthritis, nephrotic syndrome in children or as an adjunct to chemotherapy treatment which was withdrawn due to the profile of adverse effects. Among these, it has been associated with

agranulocytosis, neutropenia, liver toxicity, as well as vasculitic purpura and necrosis in the ears.⁶ Due to its pharmacokinetic profile, it is difficult to detect Levamisole in biological samples since it has a half-life of 5.5 h and only 2–5% is excreted in the urine, also presenting a high degree of difficulty for its diagnosis by standardized techniques.^{1,6}

Skin lesions have been found in up to 90% of the total in reported cases as initial manifestations. Purpuric lesions on the ears are considered typical, however, the lower extremities are the most affected anatomical region.^{7,8} Skin biopsies have demonstrated thrombotic vasculopathy as the predominant form, as well as leukocytoclastic or necrotizing vasculitis.^{1,3} Other forms of skin involvement described include digital necrosis that required amputation in some cases and even genital necrosis in a higher percentage than previously reported.⁹ It must be differentiated from patients with destructive midline lesions associated with cocaine, which usually present with local symptoms. In these cases, nasal mucosa biopsies show granulation tissue, necrosis and inflammatory infiltrates, which together with the absence of granulomas can serve to differentiate from other forms of ANCA vasculitis.² Systemic symptoms such as arthralgia, fever, night sweats and weight loss have also been described.⁷

Renal involvement affects a minority of patients and may lead to the presence of pauci-immune glomerulonephritis. Simultaneous renal and pulmonary manifestation is not considered frequent in the series described.⁶ The etiologies range from rhabdomyolysis, pauci-immune glomerulonephritis, acute interstitial nephritis as well as thrombotic microangiopathy.¹⁰

Regarding to the immunological pattern there may be positivity for both anti-MPO and anti-PR3 antibodies, the combination of both is extremely rare in another context. Anti-MPO antibody titers can be up to 10 times higher than those described in idiopathic cases.⁶

Treatment is based on the abandonment of toxics consumption, however, in the series described many of the patients have required treatment with glucocorticoids alone or in combination with immunosuppressive drugs, with no standardized indication in clinical practice guidelines.^{3,7}

Conclusions

In summary, we present the case of a patient with destructive otorhinolaryngological involvement with inflammatory changes which improved with methylprednisolone and when cocaine use decreased. When it was detected the presence of ANCA antibodies, we considered a possible levamisole-adulterated cocaine-induced vasculitis that the patient confirmed as the substance that adulterated the cocaine she was consuming.

Levamisole-adulterated cocaine-induced vasculitis should be considered as one of the entities to be included in the differential diagnosis in the case of patients with systemic

symptoms, skin involvement and positivity for ANCA antibodies. Treatment will be based on the abandonment of the consumption of toxics and in some cases immunosuppressive treatment will be necessary.

Ethical considerations

This is a clinical case where patients remain anonymous, with no recognizable personal data and a review of the literature.

Conflict of interest

The authors declare that they have no conflict of interest.

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