

# Retiform Purpura Associated with Levamisole-adulterated Cocaine. Do Procoagulant Genetic Alterations May Influence?

Silvia Méndez-Flores<sup>1</sup>, Lilly Esquivel-Pedraza<sup>1,2</sup>, Judith Domínguez-Cherit<sup>1</sup>

<sup>1</sup>Department of Dermatology, Instituto Nacional de Ciencias Médicas y Nutrición “Salvador Zubirán” (INCMNSZ), Mexico City, Mexico, <sup>2</sup>Department of Health Care, Universidad Autónoma Metropolitana-Xochimilco, Mexico City, Mexico

## ABSTRACT

Levamisole-contaminated cocaine may induce a syndrome characterized by retiform purpura, cutaneous necrosis, intravascular thrombosis, neutropenia, and anti-neutrophil cytoplasmic antibodies. We describe a case study of retiform purpura and neutropenia associated to the consumption of levamisole-contaminated cocaine and simultaneous presence of Factor V Leiden.

**Key words:** Leukocytoclastic vasculitis, levamisole, cocaine, Factor V Leiden, cutaneous markers, clinical dermatology

## INTRODUCTION

Levamisole is a synthetic imidazothiazole derivative that has been used as an immunomodulatory drug, chemotherapy adjuvant and anthelmintic treatment.

The use of adulterants to increase profit in the drug market is a common practice and during the last decade levamisole has been the most frequently used by cocaine producers in the United States of America (USA).<sup>[1]</sup>

Approximately 80% of cocaine samples in the USA are contaminated with levamisole; however, few cases of levamisole-induced vasculitis have been reported.<sup>[2]</sup>

We report a case of vasculitis related to use of levamisole-contaminated cocaine, and coagulation tests with factor V Leiden (FVL) mutations. In this manuscript, we discuss if the presence of a genetic alteration in a coagulation factor is a predisposing factor in the development of this vasculopathy.

## CASE REPORT

A 31-year-old male patient, with a history of marijuana and cocaine consumption for 15 years was seen due to painful

ulcers of 7–10 cm in diameter on lower extremities, of 6 months of evolution, and presence of tender, stellate, purpuric patches, and plaques with reticular appearance, some of them showing central necrosis, predominantly located at nose tip, ear lobes, and distal regions of lower limbs [Figures 1a-d].

Skin biopsy specimens revealed extensive occlusion of small superficial and deeper blood vessels with fibrin thrombi without vasculitis, but leukocytoclastic vasculitis with mural fibrin deposits in some small vessels [Figures 1e and f].

Relevant laboratory data showed: Leukocytes 3200 cells/ $\mu$ L, absolute neutrophil count 1700 cells/ $\mu$ L, microcytic hypochromic anemia (hemoglobin 10.7 g/dL), erythrocyte sedimentation rate: 53 mm/h, and antineutrophil cytoplasmic antibodies (ANCA) directed against myeloperoxidase: 91.4 EU/mL (normal values: <0.4 EU/mL) and directed against proteinase-3: 106.5 EU/mL (normal values: <0.4 EU/mL). The anti-dsDNA, lupus anticoagulant, and anticardiolipin (IgM and IgG) tests were negative. The presence of FLV was positive.

## DISCUSSION

Cases of retiform purpura and skin necrosis associated to ANCA and severe neutropenia, in children with nephrotic

### Address for correspondence:

Silvia Méndez-Flores, Department of Dermatology, INCMNSZ, Vasco de Quiroga 15, Col. Sección XVI, Tlalpan 14000, Mexico City, Mexico. E-mail: silvia.mendezflores@gmail.com

© 2018 The Author(s). This open access article is distributed under a Creative Commons Attribution (CC-BY) 4.0 license.



**Figure 1:** (a-d) Clinical images of the patient show purpuric rash in a retiform with central necrosis involving the extremities, nasal tip, digits, and ears, (e) histopathology shows a thrombosed vessel with the formation of fibrin deposition within the vessel lumen; there is no damage to the vessel wall or inflammation, (f) the image shows a leukocytoclastic vasculitis characterized by a thrombosed vessel with the formation of fibrin deposition within the lumen, associated with an inflammatory neutrophilic infiltrate with leukocytoclasia, fibrinoid necrosis of the vessel wall, and extravasated erythrocytes (Photomicrography courtesy Dr. Marcela Saeb-Lima, H and E stain,  $\times 400$ )

syndrome treated with levamisole, have been described since 1999. In 2010, patients with the same characteristics and history of levamisole-contaminated cocaine consumption were also reported. Due to its stimulating effects, levamisole is used to thin down cocaine and has been held responsible for the damage and thrombosis of small blood vessels, leading to the above-mentioned skin symptomatology and ANCAs formation. However, levamisole has been widely used to treat diverse conditions (e.g., adjuvant colon cancer therapy, pediatric nephrotic syndrome, and rheumatoid arthritis), and occasionally, in retiform purpura cases associated to the presence of ANCAs.<sup>[1]</sup>

Recently, the incidence of this type of vasculopathy has increased as a result of the use of levamisole associated to cocaine, because of vasoconstricting and procoagulant effects; nevertheless, this adverse effect is scarcely seen, considering the high prevalence of exposure to

contaminated cocaine of the global population.<sup>[2]</sup> Thus, although levamisole has proved to be a causal trigger of the ANCAs-associated retiform purpura pathophysiology, a predisposing factor must be present for this disorder development.

In the present case, the patient was examined for alterations in blood-clotting proteins and factors, and through polymerase chain reaction technique, the presence of FVL was demonstrated, and the patient proved to be heterozygous for the trait. In 2002, Powell *et al.*<sup>[3]</sup> reported nephrotic syndrome in a child who was treated with levamisole and developed skin symptoms, characterized by retiform purpura and distal necrosis associated to neutropenia and ANCAs. The child also proved to be positive for FVL in peripheral blood. To the best of our knowledge, no other reported cases have determined FVL or searched for alterations in blood-clotting factors.

Nearly 5–7% of individuals of European descent and up to 2% of individuals from other ethnic groups are heterozygous for FVL. FVL confers a 3-to 4-fold increased risk of the occurrence of venous thromboembolism, but most affected individuals are asymptomatic and require additional risk factors to develop venous thrombosis.<sup>[4]</sup>

In previously published cases,<sup>[5]</sup> skin biopsy showed both leukocytoclastic vasculitis and occlusive vasculopathy of small vessels; however, image studies revealed neither superficial nor deep venous thrombosis, as observed in our patient.

We consider that a heritable thrombophilic defect (positivity to FVL in our case) could be the predisposing factor for the development of vasculopathy in the presence of the triggering factor of levamisole. This drug also leads to transitory immunological anomalies such as the formation of ANCAs and vascular deposit of immune complexes. Thus, in some cases, this association could explain the presence of leukocytoclastic vasculitis.

## REFERENCES

1. Oh J, Kemper MJ. Second-line options for refractory steroid-sensitive and resistant nephrotic syndrome. *Expert Rev Clin Pharmacol* 2010;3:527-37.
2. Lapachinske SF, Okai GG, dos Santos A, de Bairros AV, Yonamine M. Analysis of cocaine and its adulterants in drugs for international trafficking seized by the Brazilian federal police. *Forensic Sci Int* 2015;247:48-53.
3. Powell J, Grech H, Holder J. A boy with cutaneous necrosis occurring during treatment with levamisole. *Clin Exp Dermatol* 2002;27:32-3.
4. Campello E, Spiezia L, Simioni P. Diagnosis and management of factor V Leiden. *Expert Rev Hematol* 2016;9:1139-49.
5. Salehi M, Morgan MP, Gabriel A. Levamisole-induced leukocytoclastic vasculitis with negative serology in a cocaine user. *Am J Case Rep* 2017;18:641-3.

**How to cite this article:** Méndez-Flores S, Esquivel-Pedraza L, Domínguez-Cherit J. Retiform Purpura Associated with Levamisole-adulterated Cocaine. Do Procoagulant genetic Alterations May Influence? *Clinic Res Dermatol* 2018;1(1):1-3.