Widespread cutaneous vasculopathy associated with levamisole-adulterated cocaine

Sir,

A 53-year-old woman presented to the emergency department with a two day history of extensive, painful cutaneous lesions. Physical examination revealed patches of retiform purpura symmetrically affecting the upper arms, lower extremities, buttocks and abdomen, covering 40–45% of total skin surface area [Figure 1]. The patient was afebrile and hemodynamically stable. She reported regular cannabis use and occasional inhaled cocaine. Laboratory investigations revealed neutropenia (1600 cells/mm^3), thrombocytopenia (110,000/mm^3) and elevated C-reactive protein levels (13 mg/dL). Coagulation panel, liver function tests and urinalysis were unremarkable. Screening for lupus anticoagulant, anticardiolipin antibody and cryoglobulins was negative. Serological study was positive for antineutrophil cytoplasmic antibodies (c-ANCA) against proteinase three (PR3). Hepatitis viruses, syphilis and HIV tests were negative. Further workup ruled out infections and other etiologies of vasculitis. Urine drug test was positive for cocaine and cannabis. Histopathological examination revealed intraluminal thrombi within the superficial and deep dermal vessels. No inflammatory infiltrate was observed around the vessels. These findings were consistent with a thrombotic vasculopathy [Figure 2]. Therefore, based on the characteristic retiform cutaneous lesions, histological results and antineutrophil cytoplasmic antibodies positivity, a levamisole-induced vasculitis in a patient with a history of cocaine abuse was suspected. Despite treatment with systemic corticosteroids (1 mg/kg/day), skin lesions rapidly progressed to large confluent areas of necrosis and ulceration [Figure 3]. The patient was admitted to the burn intensive care unit to be closely monitored, ensure fluid replacement and supportive care and achieve better pain control with morphine. Colchicine and prophylactic systemic antimicrobial therapy were also initiated. The extension of the ulceration mandated surgical debridement of the necrotic tissue and coverage with skin grafts. Despite the severity of the cutaneous lesions, the patient remained hemodynamically stable and there was no

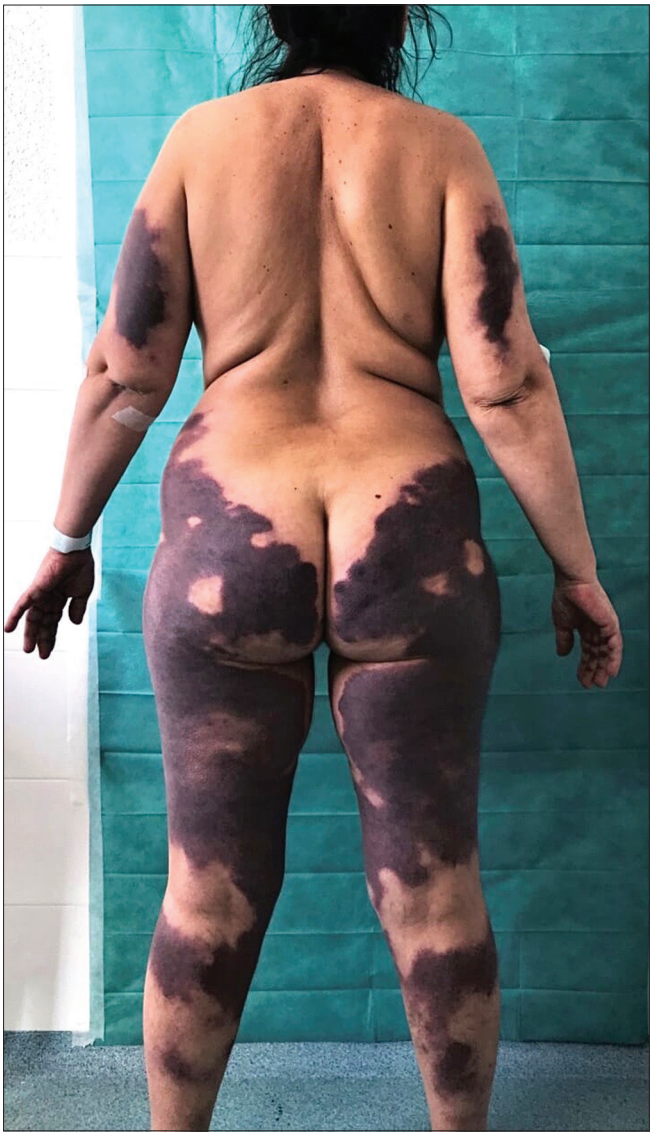

Figure 1: Widespread violaceous patches of retiform purpura symmetrically affecting the upper and lower extremities and buttocks covering at least 40% of total body surface area

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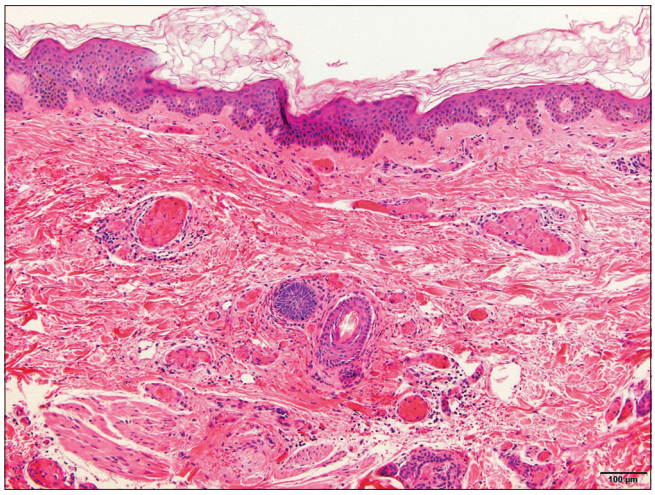

Figure 2: Intraluminal thrombi within the superficial and deep dermal vessels. No inflammatory infiltrate was observed around the vessels. These findings were consistent with a thrombotic vasculopathy (H and E, ×100)

Figure 3: Skin lesions rapidly progressed to large areas of necrosis and ulceration

evidence of systemic disease. Subsequently, she improved and was discharged in a good general condition.

Differential diagnosis of retiform purpura is broad and includes vasculitis, infectious and embolic phenomenon, warfarin induced skin necrosis, disseminated intravascular coagulation, cryoglobulinemia and anti-phospholipid antibody syndrome.[1]

A cutaneous vasculopathy syndrome has been described in users of cocaine contaminated with levamisole. This distinctive clinical entity is characterized by the presence of retiform purpura with a predilection for the ears and extremities, thrombosis of the small vessels, antineutrophil cytoplasmic antibodies positivity and leukopenia.[2] Histologically, skin lesions demonstrate a thrombotic vasculopathy and/or leukocytoclastic vasculitis involving small- or medium-sized vessels. Accordingly, we established our diagnosis based on these criteria. Levamisole is the most common cocaine adulterant in Spain and all over the world. It was formerly used as an immunomodulatory agent for the treatment of autoimmune diseases and various cancers. The vast majority of cases of levamisole induced vasculitis in cocaine users did not have levamisole exposure confirmation. This link was based on the presence of levamisole in approximately 69% of the cocaine entering in the US[2] and the typical clinical scenario. Moreover, its detection is difficult because not every center has the provision to test for levamisole using gas chromatography and mass spectrometry; besides, it has a short elimination half-life of 5.6 h. Consequently, many authors do not consider a positive test for levamisole necessary to establish the diagnosis of this syndrome.[2] Finally, there are important clinical features that support the diagnosis of levamisole-contaminated cocaine-induced vasculopathy versus cocaine-induced vasculopathy. Vasculopathy due to levamisole has a very distinct presentation with purpuric lesions over the extremities and acral sites, neutropenia and p-ANCA or c-ANCA positivity. However, cocaine alone-induced vasculopathy does not present with ear necrosis, leukopenia or neutropenia and its typical mucocutaneous manifestations are cocaine-induced midline destructive lesions.

Due to the severity of the cutaneous lesions, our patient required intensive care nevertheless, she remained hemodynamically stable, there was no evidence of systemic disease, and she was discharged in a good general condition. On the contrary, most cases present with cutaneous lesions limited to the nose, ears, cheeks or thighs and experience resolution with the discontinuation of cocaine. Only a few cases of extensive necrosis have been described, however, most of them developed infectious complications and septicemia[3-5] required amputations[3,4] or eventually died.[5] Surprisingly, in the current case, no systemic complications arose, and no amputations were needed. This is an unusual clinical evolution and it arises the idea that prognosis may be good, despite the extension of the cutaneous lesions. Dermatologists should keep in mind this clinical picture and the typical laboratory findings when assessing a retiform purpura and always rule out systemic complications such as renal failure, pulmonary hypertension, intra-alveolar hemorrhage or interstitial pneumonia[5] which can lead to a fatal outcome.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Stevens-Johnson syndrome/toxic epidermal necrolysis induced by pirfenidone

Sir,

A 78-year-old woman presented with a 24 h history of a pruriginous cutaneous rash along with odynophagia and photophobia. She had a personal history of idiopathic pulmonary fibrosis (IPF) and had recently started therapy with pirfenidone (Esbriet®) two weeks ago. Besides pirfenidone, the patients' usual medications consisted of levothyroxine and pantoprazole as treatment for hypothyroidism and dyspepsia since many years. Physical examination showed an eruption of erythematous macules and papules with scarce incipient vesicles distributed over the patient's trunk and proximal extremities. There was ophthalmological involvement with intense conjunctival hyperemia with pseudomembranes [Figure 1a]. Oral examination revealed extensive erosions on the buccal and palatal surfaces [Figure 1b]. The genital mucosa was not involved. Over the next few hours, the eruption evolved rapidly, becoming confluent. Dusky areas with epidermal detachment were observed [Figure 1c], while oral lesions extended to lingual and labial mucosae. A severe cutaneous adverse reaction to pirfenidone was suspected and a skin biopsy was performed. Histopathology revealed full-thickness epidermal necrosis with a minimal lymphocytic infiltrate in the dermis [Figure 2]. These findings were consistent with the diagnosis of Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) related to pirfenidone. The patient was promptly transferred to a burn center with life support

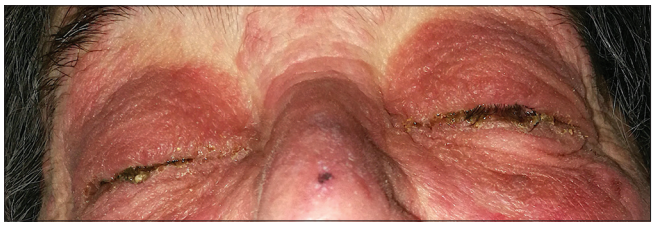

Figure 1a: Physical examination 48 h after the onset of skin symptoms. Prominent conjunctival involvement with profuse secretion and crusting

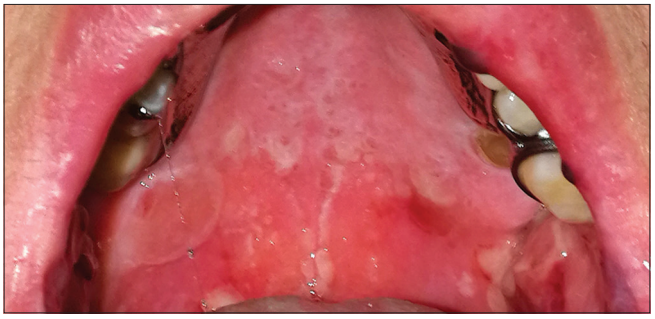

Figure 1b: Physical examination 48 h after the onset of skin symptoms. Extensive erosions on the palatal mucosa.

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