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Leukocytoclastic Vasculitis Induced by Cocaine Adulterated with Levamisole

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ABSTRACT

Leukocytoclastic vasculitis is a cutaneous, small-vessel vasculitis. In 50% of cases the aetiology is idiopathic but it can be linked to drugs, infections, autoimmune disorders and various types of cancer. Levamisole is used as an adulterant in cocaine and heroin and has been associated with the development of leukocytoclastic vasculitis. We describe an atypical presentation of a patient with levamisole-induced leukocytoclastic vasculitis who presented with diffuse skin abscesses and a purpuric rash of the upper and lower limbs.

LEARNING POINTS

- In patients with intravenous drug consumption and a clinical presentation of leukocytoclastic vasculitis, it is important to consider levamisole as a possible contributing factor.
- Negative screening for MPO-ANCA and PR3-ANCA antibodies does not exclude levamisole-induced leukocytoclastic vasculitis.
- Diagnostic criteria for leukocytoclastic vasculitis induced by levamisole have not yet been established.

KEYWORDS

Leukocytoclastic vasculitis, cocaine, heroin, levamisole

CASE DESCRIPTION

A 61-year-old woman with a medical history of intravenous heroin and cocaine consumption, previous viral hepatitis B and C infection and previous laryngeal carcinoma presented to the Emergency Department with painful swellings on both arms and a diffuse skin rash on both legs. She stated that she had injected heroin and cocaine in multiple sites of her upper and lower limbs in the past week. She denied any other systemic symptoms and denied the ingestion of any other drugs. Her prescription drug therapy included methadone, zolpidem and midazolam.

During clinical evaluation in the Emergency Department, the patient's vital signs were normal. Clinical examination of the skin showed several superficial and deep skin abscesses, localised more to the upper than to the lower limbs (*Fig. 1*).

A diffuse palpable purpura with a few haemorrhagic bullae was also present on both lower legs (*Fig. 2*). The rest of the clinical examination, with particular attention to the mucosae, was unremarkable.

Laboratory tests showed an inflammatory state associated with a high C-reactive protein (CRP) level of 115 mg/l (n.v. <5 mg/l) and an elevated D-dimer level of 17.85 mg/l (n.v. <0.50 mg/l). A complete blood count and liver and kidney function tests were normal. Urine microscopy was unremarkable, while urinary toxicology screening confirmed the presence of cocaine, opioids and methadone. Duplex ultrasound was performed and excluded superficial and deep vein thrombosis in all four limbs. Pulmonary CT angiography also excluded pulmonary embolism.

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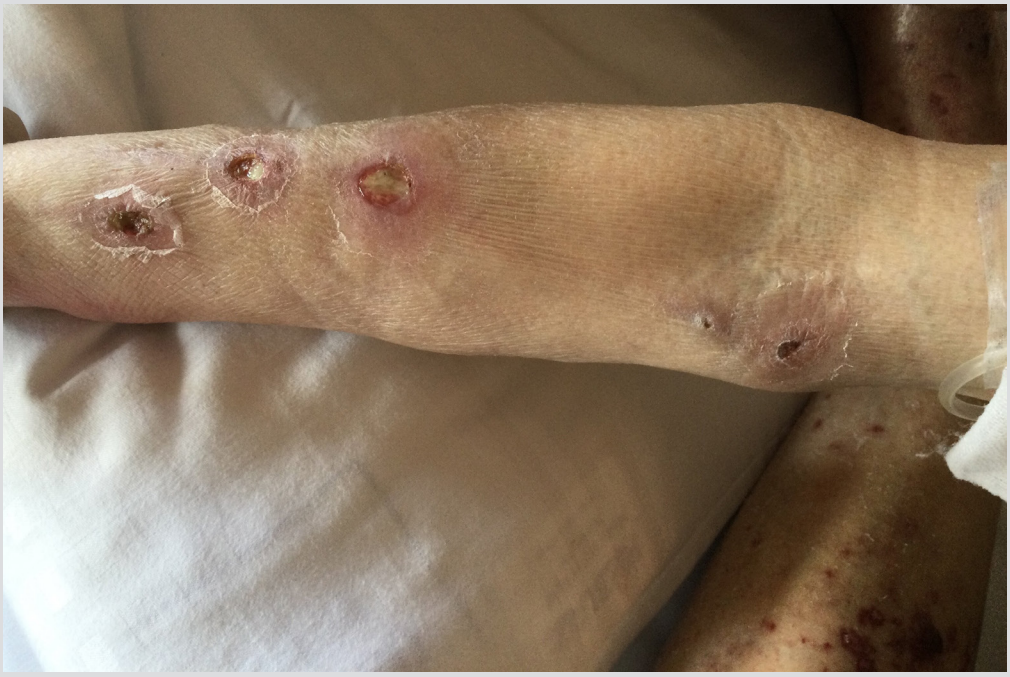

Figure 1. Multiple skin abscesses on the right upper arm.

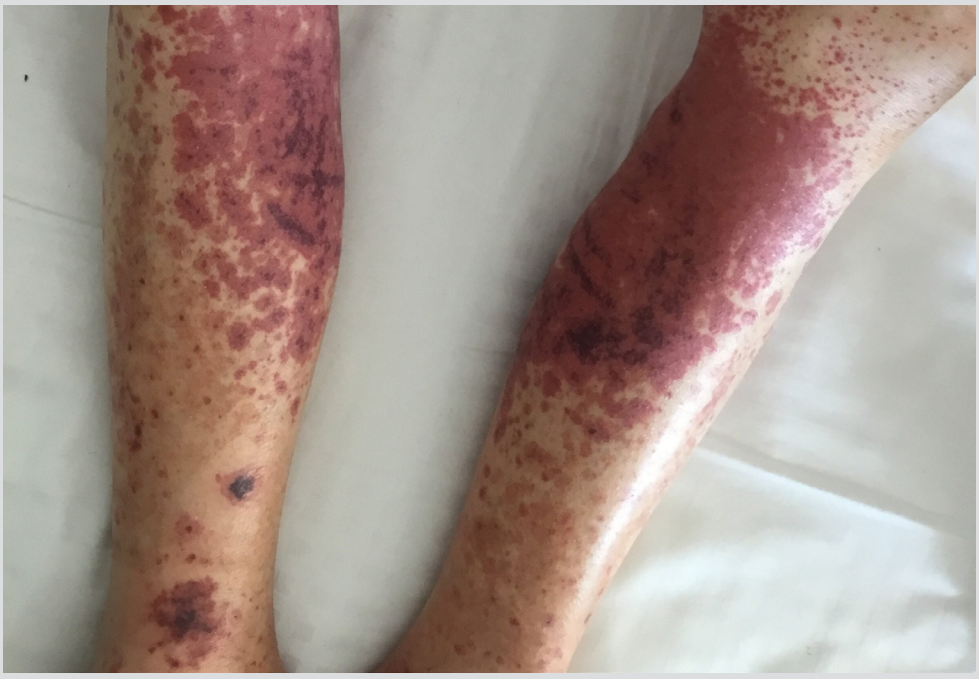

Figure 2. Purpuric skin rash on the lower limbs (clinical presentation on admission to hospital)

The three largest abscesses on both arms were surgically drained and pus was evacuated. The patient was started on empirical antibiotic therapy with intravenous amoxicillin-clavulanate. Three sets of blood cultures yielded no significant growth (one bottle was contaminated with *Streptococcus mutans*). Microbiological cultures taken from the skin abscesses showed growth of MSSA, *Enterobacter cloacae* and *Pantoea agglomerans* and considering the persistence and recurrence of abscesses, antibiotic therapy was switched to imipenem-cilastatin with complete resolution of the abscesses.

Further in-depth investigations of the non-thrombocytopenic palpable purpura with haemorrhagic bullae of the lower limbs were conducted. Serological tests for HIV and *Treponema pallidum* were negative, while HBV DNA and HCV RNA were undetectable. Autoimmune screening was negative for PR3-ANCA and MPO-ANCA. Repeated laboratory tests showed normal renal function, platelet count and white blood

cell count. We carried out a full-thickness punch skin biopsy that showed cutaneous leukocytoclastic vasculitis with abundant eosinophils. The clinical presentation, the diagnostic work-up and the hypothesis of consumption of adulterated cocaine or heroin led to the possible diagnosis of levamisole-induced leukocytoclastic vasculitis.

After specialist dermatological evaluation, topical clobetasol propionate was applied to both legs for 14 days with an excellent response and complete resolution of the lesions (*Fig. 3*). No new lesions developed.

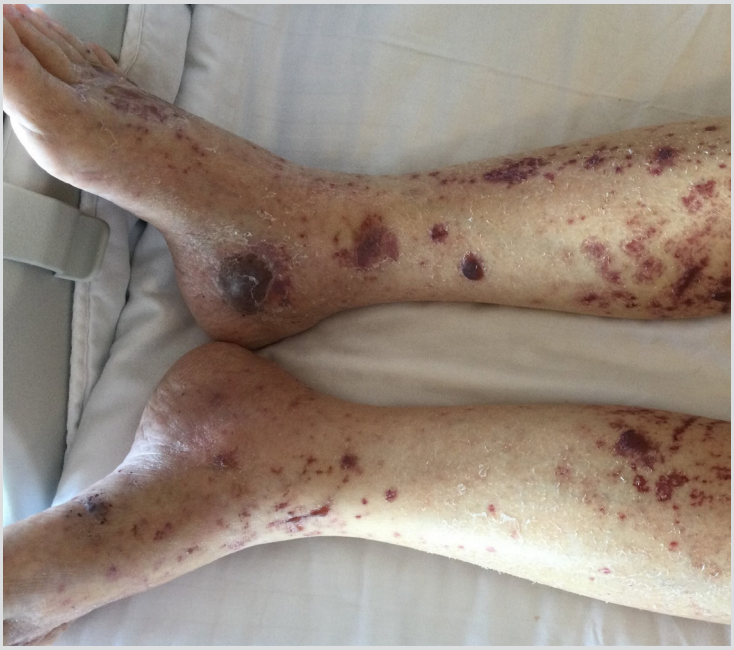

Figure 3. Improvement of purpuric skin rash during treatment with topical steroids

DISCUSSION

Estimates of drug consumption in Europe during 2019 showed that approximately 5 million people (or 0.92% of those aged 15–64 years) had used cocaine during that year. Its use was much higher in Central and Western Europe, than in South-Eastern and Eastern Europe (1.39% vs. 0.26%). Data suggest an overall increase in the use of this drug in Europe, which is reinforced by wastewater analysis that estimates cocaine consumption [1]. In contrast, data on opioid consumption in Europe in 2019 confirmed stable use compared with previous years, with approximately 3.6 million people (or 0.66% of those aged 15–64 years) consuming opioids. Heroin was stated as the main opioid used [1].

Levamisole is an anthelminthic drug used in veterinary medicine against intestinal nematodes. In the past it was used in humans to treat various tumours, such as breast and colon cancer, and many other conditions such as rheumatoid arthritis, Behcet's disease and ankylosing spondylitis due to its immunomodulating effects [2]. Levamisole is added to cocaine to increase its volume and to enhance its stimulatory effects by acting on dopaminergic synapses. The material and chemical characteristics of this substance make it an effective cocaine additive, as it bears a strong resemblance to cocaine itself and is difficult to identify [3]. It is estimated that more than 80% of cocaine used in the USA is adulterated with levamisole. The lack of laboratories specialised in the identification of levamisole and the high costs of analysis prevent investigation for this adulterant in cocaine samples throughout Europe. Nonetheless, it is estimated that its use is probably lower than in USA but is steadily increasing [4]. Although more common as a cocaine adulterant, levamisole has also been found as an additive in heroin [5].

Levamisole was withdrawn from the market by the Food and Drug Administration at the end of the last century because of side effects such as agranulocytosis and vasculitis. The pathogenesis of levamisole-induced vasculitis is not entirely clear. It is likely that the drug acts as a hapten that generates an immune response against self-antigens, resulting in the formation and deposition of immune complexes in the vascular wall. There are no defined diagnostic criteria for levamisole-induced vasculitis. Typical cutaneous manifestations are purpuric lesions on the lower extremities, face and ear lobes that may progress to necrosis, ulcers and superinfections. Two common histological patterns are associated with levamisole: a leukocytoclastic vasculitis and a small-vessel thrombotic vasculopathy of the deep and superficial dermis. Microscopy usually shows mixed angiocentric cell infiltrates of neutrophils, eosinophils and lymphocytes. Histological analysis performed on our patient showed the leukocytoclastic type with abundant eosinophils [6].

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Laboratory findings often show neutropenia, leukopenia, and high levels of CRP [6]. In particular, most patients with levamisole-induced vasculitis are positive for MPO-ANCA (66–100%) or PR3-ANCA (50–66%) [7, 8], with both MPO-ANCA and PR3-ANCA positive in 43% of patients [8]. The peculiarity of our clinical case is that we did not observe the pathognomonic laboratory findings, with MPO-ANCA and PR3-ANCA antibody screening that was negative and a white blood cell count in the normal range.

Levamisole can be detected in blood and urine specimens by gas and liquid chromatography with mass spectrometry. However, the cost of these analyses is high and not available in all laboratories. In our case, we did not perform this specific investigation and the patient knew nothing about the existence of a drug called levamisole, nor that it could have been mixed with the cocaine or heroin she had consumed.

Therefore, our diagnosis of levamisole-induced leukocytoclastic vasculitis was assumed due to the association between cocaine and heroin consumption and the clinical and histological picture, despite the absence of MPO-ANCA and PR3-ANCA antibodies.

CONCLUSION

The incidence of levamisole-induced leukocytoclastic vasculitis is likely to rise due to increased cocaine consumption and increased use of levamisole as an adulterant in cocaine and heroin. There are no definitive diagnostic criteria and blood or urinary screening for levamisole is not routinely performed.

This condition should therefore be considered in any patient presenting with a purpuric rash and a history or test confirming cocaine or heroin consumption. Histopathological features and MPO-ANCA or PR3-ANCA positivity may support the diagnosis, Nonetheless, negative screening for MPO-ANCA and PR3-ANCA antibodies does not exclude a diagnosis of levamisole-induced leukocytoclastic vasculitis.

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