CASE REPORT

Levamisole-contaminated cocaine: a hairy affair

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SUMMARY

Levamisole-contaminated cocaine can induce severe systemic vasculitis. The diagnosis can be challenging, especially when substance abuse is uncertain. We present the case of a 42-year-old woman suffering from vasculitis due to levamisole-contaminated cocaine, who persistently denied substance abuse. Symptoms included ulcerating skin lesions, arthralgia and myalgia, and the occurrence of an ileal intussusception. The definitive diagnosis was made using hair testing for toxins. She recovered through cocaine abstinence, but re-exposure resulted in a severe relapse with glomerulonephritis. Importantly, at time of the relapse, the patient became positive for both myeloperoxidase-antineutrophil cytoplasmic antibody (ANCA) and proteinase 3-ANCA. Cocaine–levamisole-induced vasculitis poses a great clinical challenge. The proper diagnostic strategy and therapy is still controversial. We highlight our diagnostic and therapeutic considerations, including hair testing for definitive proof of exposure.

BACKGROUND

Cocaine use is widespread and all clinicians should be aware of the diverse symptoms the drug can bring about. In the last decade, levamisole-contaminated cocaine was recognised as a cause of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. The condition has a versatile character and can present with symptoms involving almost any organ system. Our patient suffered from ulcerating skin lesions, as well as from several other symptoms. Over the course of her illness, she suffered diverse complications, most importantly glomerulonephritis and ileal intussusception. The latter has not been reported previously in ANCA-associated vasculitis. Diagnostic uncertainty remained when the patient persistently denied substance abuse. Definitive proof was obtained by testing the patient's hair for toxins, an uncommonly used technique that holds promise for wider application. ANCA-autoantibodies can also be an important diagnostic aid. The proper therapeutic strategy is still disputed, but immunosuppressive therapy can be indicated in case of severe organ involvement.

CASE PRESENTATION

A 42-year-old woman of Hispanic ancestry presented at the rheumatology outpatient clinic with severe arthralgias, myalgias, intermittent abdominal pain and skin lesions. Her history was unremarkable except for a recurrent urinary tract infection. She was not using any medication at the time of presentation or over the past 6 months. She was

admitted to the clinic under suspicion of a systemic inflammatory disease.

At examination, she had violaceous ulcerating skin lesions, predominantly on the upper legs (figure 1), and an episcleritis of the left eye.

INVESTIGATIONS

Rheumatoid factor, anticyclic citrullinated peptide, antinuclear antibody/extractable nuclear antigens, proteinase-3 (PR3)-ANCA, myeloperoxidase (MPO)-ANCA, lupus anticoagulant, anticardiolipin antibodies and cryoglobulins were all negative. However, human neutrophil elastase antibodies (HNE-ANCA) were detected.

Biopsy of a representative skin lesion showed purulent inflammation and a perivascular lymphocytic infiltrate, but no definite vasculitis. Chest X-ray was normal. Otorhinolaryngological examination showed perforation of the nasal septum suggestive of cocaine abuse, which the patient at first denied. Her abdominal pain worsened and an ileal-ileal intussusception was diagnosed, for which the patient underwent an emergency ileocecal resection. The resected specimen showed extensive ulceration due to prolonged ischaemia, but no clear vasculitis. The patient finally admitted to cocaine abuse in the past, but persistently denied any recent use. Several urine samples tested negative for cocaine metabolites. The patient agreed to hair testing for toxins, which was carried out by Laboratoire ChemTox, Illkirch, France, using high-performance liquid chromatography with mass spectrometric detection. The hair tested positive for cocaine and levamisole, and negative for amphetamines. Levamisole and cocaine concentrations were 18.3 and 11.8 ng/mg, respectively, in hair segments closest to the scalp. This finding demonstrated recent use of levamisole-contaminated cocaine.

Figure 1 Violaceous ulcerating skin lesions on the upper legs.

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DIFFERENTIAL DIAGNOSIS

At this point, the differential diagnosis consisted of either levamisole-adulterated cocaine-induced ANCA-associated vasculitis, or midline destructive disease with levamisole-adulterated cocaine-induced skin necrosis.

TREATMENT

The patient recovered after complete cocaine abstinence with only wound care and supportive therapy. Two months later, however, she relapsed in cocaine abuse and had recurrent arthralgias. Decreased kidney function was found in combination with erythrocyturia and proteinuria. Now both MPO-ANCA and PR3-ANCA were positive and a kidney biopsy showed necrotising crescentic glomerulonephritis. The diagnosis of levamisole-adulterated cocaine-induced ANCA-associated vasculitis was made. High-dose corticosteroids and cyclophosphamide were started.

OUTCOME AND FOLLOW-UP

Subsequently, the patient's symptoms resolved and kidney function normalised completely over the course of a few days. After 1 year of follow-up, her condition has remained stable on maintenance therapy consisting of azathioprine and prednisolone. ANCA titres became negative. Further use of cocaine was denied.

DISCUSSION

During the last decade, it has been established that cocaine may induce ANCA-associated vasculitis.^{1 2} The adulterant levamisole has been indicated as the culprit.³ Symptoms include cutaneous manifestations, arthralgia, neutropenia and/or nasal midline destructive disease. A biopsy of the affected tissue often fails to prove vasculitis.² Kidney involvement demonstrating necrotising crescentic glomerulonephritis may be another serious manifestation. This is the first reported case to develop an ileal intussusception, which is likely a consequence of intestinal involvement.

It is often difficult to confirm exposure to cocaine and/or levamisole using standard techniques. Cocaine metabolites are detectable in urine for 2–4 days after consumption. The plasma elimination half-life of levamisole is 3–6 h and only about 3% of levamisole is excreted unchanged in urine. When diagnostic uncertainty remains, toxicological screening of hair should be considered. This has the ability to retrospectively confirm exposure to cocaine, levamisole and other substances of abuse such as amphetamines.^{4 5} The type of ANCA antibodies can be an aid to the diagnosis and distinguish the entity from idiopathic autoimmune ANCA-associated vasculitis. Indicative for cocaine–levamisole-induced vasculitis is the presence of both MPO-ANCA and PR3-ANCA simultaneously. Furthermore, cocaine abusers are often positive for HNE-ANCA, which in these patients is indicative of cocaine-induced nasal midline destructive disease.⁶

No consensus on treatment has been established for cocaine–levamisole-induced vasculitis other than cocaine abstinence. In case reports and case series, symptoms often resolve after discontinuation of cocaine use. Sometimes specialised wound care is necessary.⁷ Successful use of corticosteroids and immunosuppressives has been reported.^{2 8} We believe immunosuppressive therapy should be considered in case of severe organ involvement, as in idiopathic ANCA-associated vasculitis.⁹ Our patient was finally treated aggressively with corticosteroids and cyclophosphamide to prevent permanent kidney damage, according to vasculitis guidelines.⁹ In case of necrotising crescentic

glomerulonephritis, this has previously been reported to cause rapid improvement, though it can still leave the patient with permanently decreased kidney function.^{10 11} Relapse at re-exposure is common. Of note, the first episode of the disease resolved after cocaine abstinence and a more severe form of vasculitis recurred after rechallenge. A more severe relapse was recently also described in a patient with statin-induced vasculitis.¹² It is unknown if relapses are generally more severe in levamisole-adulterated cocaine-induced vasculitis. Still, it seems that kidney involvement and other systemic symptoms only occur after prolonged and repeated exposure, as was also the case in four patients described by Carlson *et al.*¹¹ Interestingly, our patient became both MPO-ANCA and PR3-ANCA positive at the time of relapse.

A promising new approach could be antiaddiction vaccination, which prevents the drug from having an effect.¹³ Whether vaccination is helpful for abstinent patients, however, is still uncertain. As always, patient education and compliance remain the cornerstone of treatment, even when this is hardest to accomplish.

Learning points

- ▶ Levamisole-contaminated cocaine can cause antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, often presenting with skin lesions, arthralgia, neutropenia or nasal midline destructive disease.
- ▶ Human neutrophil elastase-ANCA is indicative of cocaine-induced disease, as well as simultaneous presence of myeloperoxidase-ANCA and proteinase 3-ANCA.
- ▶ Hair testing for toxins can provide definitive proof of cocaine and levamisole exposure.
- ▶ Cocaine abstinence is key, although immunosuppressive therapy can be indicated in case of severe organ involvement such as glomerulonephritis.
- ▶ Ileal intussusception can occur and is likely due to intestinal involvement.

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Contributors TVV was involved in manuscript drafting and patient care. EP was responsible for diagnostic expertise (toxicology) and editing. JWCT was responsible for diagnostic expertise (antibodies) and editing. L-AK was responsible for final editing and physician primarily responsible for the patient.

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