Cocaine-Induced Delayed Recurrent Vasculitis: A 4-Year Follow-Up

Meera Yogarajah
Mona Pervil-Ulysse
Bhradeev Sivasambu

Corresponding Author: Meera Yogarajah, e-mail: myogarajah@interfaithmedical.com
Conflict of interest: None declared

Patient: Female, 51
Final Diagnosis: Cocaine induced vasculitis
Symptoms: —
Medication: —
Clinical Procedure: None
Specialty: Rheumatology
Objective: Rare disease

Background: Cocaine is a highly abused substance in United States with almost 70% of cocaine adulterated with levamisole. It is known to cause vasculitis involving multiple organs due to its direct toxic effect and by the contribution of levamisole or a combined effect of both.

Case Report: A 51-year-old woman complained of painful erythematous rash in her hands and lower extremities that started few hours after smoking cocaine and progressed to blistering dark lesions in her lower extremities. She denied any other systemic complaints. Although she has been smoking cocaine for more than 35 years, these skin eruptions started only 4 years ago. Examination revealed tender retiform purpura in the hand and tender retiform purpura with hemorrhagic bulla in the legs. Initially, she had only a significantly positive atypical p-ANCA and later developed combined positivity of both Myeloperoxidase (MPO) and Anti-proteinase-3 (PR3) antibodies with a p-ANCA pattern on immunofluorescence. We report a unique case of cocaine (likely contaminated with levamisole)-induced delayed recurrent vasculitis with varying vasculitic antibodies over the years.

Conclusions: This case highlights the fact that patients can develop cocaine-related vasculitis after many years of uneventful abuse. Cocaine, with its adulterant levamisole, has the propensity to trigger diverse immunological reactions, which is evident by the varying antibody profile seen in the same patient over time.

MeSH Keywords: Cocaine • Levamisole • Vasculitis

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**Background**

In 2013 the National Survey on Drug Use and Health (NSDUH) estimated that there were 1.549 million current cocaine users in the USA [1]. Thirty percent of the cocaine seized by the DEA (U.S. Drug Enforcement Agency) from July to September 2008 was found to be adulterated with levamisole, which dramatically increased to 70% by July 2009 [2,3]. Given the high prevalence of cocaine use and the rising trend of adulteration with levamisole, knowledge and awareness of related complications becomes vital for practicing physicians. The toxic effects of cocaine had increased since the adulteration of cocaine with levamisole. Vasculitis due to direct effects of cocaine and its contaminant levamisole has been reported in the literature; however, we report a case of delayed cocaine-induced vasculitis, with a follow-up of over 4 years, with varying antibodies. This case signifies the potential of cocaine to trigger vasculitis after many years of abuse and the diverse immunomodulatory properties predicted by the diverse antibody profile during each exacerbation in the same patient.

**Case Report**

A 51-year-old woman complained of painful erythematous rash that started a few hours after smoking cocaine and progressed to blistering dark lesions involving her lower extremities and hands. She had similar episodes of skin eruptions in the past that always occurred after cocaine use, but she was not on any long-term treatment. Although she has been smoking cocaine for more than 35 years, these skin eruptions started 4 years ago, after which she had similar several skin eruptions after smoking cocaine. Two years ago, she had a severe skin eruption with necrosis, which required skin grafting. Her other medical problems were hepatitis C, for which she never received treatment, and she had an excision of melanoma 10 years ago. She denied any joint pain, hair loss, oral ulcers, nasal ulcers, rash on the face, photosensitivity, discoloration of finger tips in cold weather, hemoptysis, or shortness of breath.

Examination revealed tender retiform purpura in the hand (Figure 1) and tender retiform purpura with hemorrhagic bulla in the legs (Figure 2). There were no skin lesions on the other parts of the body. Other system examination was unrevealing. Her initial laboratory results showed mild hypochromic microcytic anemia with a hemoglobin of 10.9 g/dl, with evidence of iron deficiency in the iron panel. The white blood cell count of 4.3 K/ul with a neutrophil count of 2.6 K/ul and platelet count was 212 000. The electrolytes, renal function test, liver function test, and coagulation profile was normal. Urine analysis showed microscopic hematuria with red blood

**Figure 1.** Retiform purpura of both hands.

**Figure 2.** Retiform purpura with hemorrhagic bullae and healed scars.
cells of 5–15 with mild proteinuria. There was no evidence of hepatitis B infection and the rapid plasma reagin was negative. She was tested for human immunodeficiency virus (HIV) 1 month ago and was found to be negative. The urine toxicology was positive for cocaine. Levamisole levels were not done. The concerns were cocaine or levamisole-induced vasculitis, ANCA-associated vasculitis, cryoglobulinemic vasculitis related to hepatitis C, and connective tissue disease-related vasculitis.

A vasculitic panel revealed high levels of anti-PR3 antibody and anti-MPO antibody with a p-ANCA pattern. Her cryoglobulins were negative. Further autoimmune work-up showed a positive antinuclear antibody (ANA) with a titer of 1:80 and homogenous pattern. The rheumatoid factor (RF) and anticardiolipin IgM antibody were also positive. Anti-Smith antibody, anti-double-stranded DNA antibody (ds DNA antibody), anti-citrullinated protein antibody (Anti CCP antibody), anti-SS-A antibody, anti-SSB-antibody, and anticardiolipin IgG were negative. There was decreased C3 with normal C4 levels. Erythrocyte sedimentation rate was 53 mm/Hr. C-reactive protein was 65.9 mg/L (normal range 0–4.9) (Table 1).

We also reviewed the autoimmune work-up and vasculitic work-up from previous admissions and current admission over the last 4 years (Table 2).

In 2010, a vasculitic panel revealed a positive atypical p-ANCA with negative anti-proteinase 3 antibody (PR3 antibody) and anti-myeloperoxidase antibody (MPO antibody). However, in 2013 the patient had developed anti-PR3 antibody but had negative anti-MPO antibody. ANCA pattern on immunofluorescence was not done in 2013. During this presentation in 2014, the patient had a very high level of anti-PR3 antibody and went on to develop anti-MPO antibody with a p-ANCA pattern. However, she did not demonstrate a c-ANCA pattern. Her skin biopsy revealed vasculitis with fibrin thrombi.

She was treated with steroids during this admission and the skin lesions improved significantly. She was counseled on cessation of cocaine to prevent recurrent similar skin lesions.

### Discussion

Cocaine is known to cause vasculitis involving multiple organs and has been described in the literature, but still is a rare phenomenon. The etiopathogenesis still remains obscure and it is not known why a subset of cocaine abusers develops vasculitis. Many patients can present like a typical case of granulomatosis with polyangiitis with positive cytoplasmic-staining antineutrophil cytoplasmic antibody (c-ANCA) with specificity
for the target antigen proteinase-3 (PR-3) [4]. Chronic intranasal use of cocaine can cause cocaine-induced midline destructive lesions, which may be difficult to differentiate from granulomatosis with polyangiitis [5], but a positive human neutrophil elastase (HNE-ANCA) is more suggestive of cocaine-induced vasculitis [5]. Cocaine use is also associated with cerebral an- gitis [6], scrotal vasculitis [7], urticarial vasculitis [8], IgA ne- phropathy, and Churg-Strauss vasculitis [9]. Although many of these cases were ANCA-negative, some patients demonstrated perinuclear ANCA (p-ANCA) with paradoxical specificity to PR3. 

Vasculitis in cocaine abuse could be a direct effect of cocaine or due to contamination with levamisole and a combined ef- fect of both. In 2003 levamisole was first detected as a co- caine adulterant and is believed to be added by the manufac- turers for its stimulant properties. Around 70% of the cocaine seized in the United States is adulterated with levamisole [2,3]. Levamisole is a veterinary anti-helminthic agent that was also used as a therapeutic agent for autoimmune disorders and cancers due to its immunomodulatory action. It was withdrawn from human use in 1999 due to its adverse effects such as agranulocytosis and cutaneous vasculitis. The first case of levamisole-induced vasculitis was reported in 1978 in a patient with rheumatoid arthritis [10].

ANCA-associated vasculitis could be triggered by a variety of drugs, including hydralazine, propylthiouracil, and minocycline. Significantly high titers of anti-MPO antibody are found in these patients and, rarely, dual positivity of both anti-MPO and anti-PR3 antibodies are found, but is extremely scarce in other conditions. Our patient had combined positivity and signifi- cantly elevated anti-PR3 antibody with a 2-fold increase in anti-MPO antibody. Similar phenomena of dual positivi- ty have been described in a study at Massachusetts General Hospital’s ANCA laboratory on cocaine-positive patients; 50% (15/30) of the patients were positive for both of these anti- bodies [11]. However, these patients demonstrated both p-AN- CA and c-ANCA pattern, whereas our patient only demonstrat- ed the p-ANCA pattern.

The clinical manifestations of levamisole-induced vasculitis is usually limited to skin with tender purpuric papules with reticular pattern, which could progress to skin necrosis com- monly involving the ears, face, and extremities. Levamisole has rarely been associated with pulmonary [11,12], and renal [12,13] involvement. Laboratory tests could be positive for various antibodies such as ANCA antibodies, ANA, and lu- pus anticoagulant. Levamisole can also cause agranulocytosis [14]. Skin biopsy shows either a mixed pattern of leukocy- tolastic and thrombotic vasculitis or an isolated thrombotic vasculopathy. Levamisole can be detected in specialized labo- ratories using liquid chromatography tandem mass spectros- copy, but it has a short half-life of 5.6 hours [15]. Our patient had only skin manifestations involving the extremities, likely secondary to levamisole-contaminated cocaine, with charac- teristic retiform lesions, but the limitation is that levamisole levels were not checked.

### Table 2. Antibody panel over 4 years.

| Test                        | Normal range | 2010   | 2013   | 2014   |
|-----------------------------|--------------|--------|--------|--------|
| Anti-nuclear antibody       | <7.5 IU/ml   | Positive | Positive | Positive |
| Anti-cardiolipin IgG        | 0-14 U/ml    | Not done | Negative | 11     |
| Anti-cardiolipin IgM        | 0-12 U/ml    | Not done | Negative | 62     |
| Cryoglobulin                | Negative     | Not done | Negative | Negative |
| Complement C3               | 90-180 mg/dl | 64     | 87     | 57     |
| Complement C4               | 9-36 mg/dl   | 18     | 30     | 18     |
| Rheumatoid factor           | <13.9 IU/ml  | Negative | Negative | 20.7   |
| Cyclic Citrullinated Peptide antibody | <19 U | Not done | Not done | Negative |
| Aypical p-ANCA              | <1.20 titer  | 1:640  | Not done | Negative |
| p-ANCA                      | <1.20 titer  | Negative | Not done | >1:640 |
| c-ANCA                      | <1.20 titer  | Negative | Not done | Negative |
| Anti-proteinase 3 antibody  | <3.5 U/ml    | Negative | 57     | >100   |
| Anti-myeloperoxidase antibody | <9 U/ml  | Negative | Negative | 23.6   |

Al – antibody index; U – units; IU/ml – international units/milliliter; U/ml – units/milliliter.
Primary management of cocaine-induced vasculitis is abstinence from cocaine consumption. Steroids have been used in some patients, but further studies are needed on long-term management. Our patient received steroids and showed improvement in skin lesions. Although vasculitis and causal relationship with cocaine and levamisole has been described, the possibility of delayed vasculitis and varying ANCA antibodies in the same patient over time has not been described in the literature and we report this unique case.

Conclusions

Cocaine abuse is very prevalent and is a commonly encountered illicit drug; given the increase in levamisole adulteration in recent years, it is a major health hazard. This case highlights the fact that patients can develop cocaine-related vasculitic complications after many years of uneventful abuse. Cocaine, with its adulterant levamisole, has the propensity to trigger diverse immunological reactions, which is evident by the varying antibody profile seen in the same patient over time.

Disclosure of interest

None of the authors have any conflicts of interest to declare.

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