Pyoderma gangrenosum–like facial ulcers in a woman associated with cocaine use and cANCA/anti-PR3⁺, pANCA/anti-MPO⁻ serology

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INTRODUCTION

Several reports indicate that cocaine use (particularly if levamisole contaminated) is associated with development of vasculopathy, vasculitis, or skin necrosis. The classic presentations shown for levamisole-induced skin lesions are of purpuric or necrotic, pyoderma gangrenosum–like lesions involving the ears, face, and extremities. Furthermore, serologies in these patients are most often positive for perinuclear antineutrophil cytoplasmic antibody (pANCA), corresponding to positive antiproteinase [MPO] titers, more so than cytoplasmic antinuclear cytoplasmic antibody (cANCA), or both together. Conversely, patients are rarely cANCA positive (corresponding to antiproteinase [PR3] titers) while negative for pANCA (anti-MPO). However, there is clinical and serologic variability in how these patients present. Here, we present a case of large ulcers forming on the face and body, without involvement of the ears, of a previously healthy woman who was simultaneously using cocaine. Furthermore, she was positive for cANCAs and negative for pANCAs, which is the more rare serologic profile. The patient responded well to intravenous and oral steroids, 3 rituximab infusions, and drug cessation with intent to permanently stop using cocaine. However, the patient ended consistent follow-up, began using cocaine again, and severely relapsed.

CASE REPORT

Here, we present a case of large, bilateral facial pyoderma gangrenosum–like ulcers in a 30-year-old woman. Two years before the ulcer formation (when the patient was 28 years old), she was healthy with no known medical problems. She had clear skin and no facial lesions. The patient had a history of cocaine use before the eruption of ulcers. Months later, the patient had enlarged facial ulcers with necrotic-appearing centers and violaceous peripheral borders (Fig 1). The patient had enlarging ulcerations on face, arms and back, with no involvement of the ears and no oral involvement. Review of systems was bland, with the exception of positivity for intermittent fever, headaches, and anxiety. The patient denied hematuria, gastrointestinal distress, or other neurologic symptoms. She was seen previously at outside hospitals and treated with a broad range of antibiotics, including anti–methicillin-resistant Staphylococcus aureus (MRSA) antibiotics (intravenous vancomycin and oral trimethoprim-sulfamethoxazole) and antipseudomonal antibiotics (including cefalosphorins) with no significant effect on wound healing.

The patient then presented to our academic medical center, where we performed biopsies of the face and body ulcers at the wound centers

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and borders, which found neutrophil-rich and lymphocyte-rich dermal inflammation with no clear evidence of vasculitis or vasculopathy (Fig 2). Superficial bacterial cultures were negative for MRSA. Deeper tissue cultures were negative for bacterial, viral, fungal, or mycobacterial organisms. Urinalysis found intermittent hematuria (positive, then negative on repeat). Complete blood count and metabolic panels were unremarkable. C-reactive protein and erythrocyte sedimentation rate were consistently elevated. Urine toxicology was positive for cocaine. Serology was performed for autoantibodies (Table I). The patient was positive for cANCA/anti-PR3 and negative for pANCA/anti-MPO. On computed tomography imaging, the patient had radiologic evidence of a nasal septal defect, which was suspected to reflect her history of cocaine use. Computed tomography of the chest found small pulmonary nodules (which were stable on repeated imaging). The patient was negative for hepatitis B and C and negative for HIV.

The patient was admitted to the hospital and responded to intravenous steroids (1 g methylprednisolone x 3 over the course of 3 days), outpatient steroid taper (starting at 60 mg/d, tapering by 10 mg/wk every 2 weeks), and outpatient rituximab infusions. The target dose of rituximab was 375 mg/m² and based on when the patient could comply with outpatient infusions: first dose: intravenous rituximab, 500 mg, followed by a second dose of intravenous rituximab, 500 mg, 14 days later. The rituximab regimen was interrupted by patient noncompliance to infusions in the outpatient setting. The patient was then admitted to the hospital 2 months later for another round of pulse intravenous steroids and intravenous rituximab, 500 mg, and prophylactic trimethoprim-sulfamethoxazole (to prevent pneumocystic jiroveci pneumonia and staphylococcal infection of the wounds). After treatment, the patient’s ulcers healed with scarring and scant overlying crust (Fig 3). The patient was counseled and voiced understanding that cocaine contributed to her disease and that she intended to stop the drug use. She was scheduled for multispecialty outpatient follow-up, including with the dermatology, rheumatology, and nephrology departments to monitor healing and any potential systemic involvement.

After being lost to clinical follow-up for nearly 1 year and restarting cocaine use, the patient relapsed, and subsequently presented to the emergency room with a worsened clinical presentation (Fig 4). The facial ulcers reformed in the same and new locations (back, arms, genital areas) and became larger. Clinical findings mimicked granulomatosis with polyangiitis. Oral examination found strawberry gums, and her nose had a saddle-nose deformity. Urine toxicology was positive for cocaine. There were no findings of purpura or ulcerations of the ears. She had no evidence of renal involvement (creatinine levels were normal and urinalysis was unremarkable). Complete blood counts remained unremarkable. The patient had sustained elevation in C-reactive protein and erythrocyte sedimentation rate. She had sustained anti-PR3 titers and negative anti-MPO titers.
After the latest inpatient hospitalization and 1 week of treatment with intravenous steroids and anti-MRSA antibiotics, the patient’s ulcers began to show signs of healing (Fig 4). The patient was discharged with a steroid tapering regimen and intention for close follow-up for continuation of steroid-sparing therapy.

**DISCUSSION**

Rapid development of pyoderma gangrenosum—like facial wounds on a young, otherwise healthy woman should raise the clinical suspicion for ANCA-mediated disease. Substance abuse should be ruled out. Cocaine is a commonly abused drug in North America; its stimulatory effects are via blockage of norepinephrine and dopamine reuptake at the synaptic nerve endings. It has both vasoconstrictive and procoagulant effects, raising the risk of vasculopathy development. Cocaine abuse has been associated with elevated inflammatory markers, cold agglutinin positivity, both pANCA and cANCA positivity, and hematologic abnormalities (eg, cytopenias). Many reports associate levamisole as a suspected cause of vasculitis, vasculopathy, or direct skin necrosis. Although our patient was never directly found to be positive for levamisole biochemically, the high probability of

| Test                  | Result                          |
|-----------------------|---------------------------------|
| Antinuclear antibody  | 1:40, homogenous and speckled pattern |
| Anti-dsDNA            | Negative                        |
| Anti-Sc70             | Negative                        |
| Anti-Smith            | Negative                        |
| Anti-centromere       | Negative                        |
| Anti-Jo1              | Negative                        |
| Anti-mitochondrial    | Negative                        |
| Anti-ribosomal        | Negative                        |
| Anti-chromatin        | Negative                        |
| cANCA                 | Positive x 3                    |
| pANCA                 | Negative x 3                    |
| anti-PR3              | Positive, 7.7 AI (<1.0 normal range) |
| anti-MPO              | Negative, <1.0 AI (<1.0 normal range) |

cANCA and anti-PR3 antibodies were positive (bolded).
cocaine and levamisole playing a role in the
development, progression, and relapse of her dis-
ease cannot be ignored.

Of note, levamisole is an antihelminth drug that
was estimated to contaminate approximately 70%
of cocaine samples in the United States (Drug
Enforcement Administration’s Cocaine Signature
Program, 2009 data). Levamisole-contaminated
cocaine has been associated with development of
ANCA-positive disease, particularly the development
of vasculitis in the skin, kidney, and lungs. Levamisole has a half-life of approximately 5 hours,
and may become undetectable in the urine in as little
as 48 hours after exposure. Traditionally, when
levamisole was used as a therapeutic, known side
effects included neutropenia, liver toxicity, gastroin-
testinal upset, and development of purpuric and
necrotic lesions. Cocaine, independent of levami-
sole, may itself be associated with development of
autoimmunity; thus, both drugs may be contributing
to development of ANCA-associated disease via
the formation of neutrophil extracellular traps in sus-
ceptible individuals. In a case series of 8 patients with cocaine-
associated skin disease in Ottawa, Canada, only 1
had purpura of the cheek, and none with necrotic
ulcers involving the face. Only 3 of the 8 patients
lacked a medical history before the development
of skin lesions, similar to our patient, whereas
some had hepatitis B or C, systemic lupus, or
Sweet syndrome documented before their cocaine-
associated skin disease. Three of 8 patients had
involvement of the ear; 5 of 8 had involvement of the
mouth. All patients had positive pANCA, and 5
of 8 had cANCA positivity. Of note, no patient had
positive cANCA (anti-PR3) coupled with negative
pANCA (anti-MPO), as our patient had consistently. Two of the 8 patients had neutrophilic
infiltrates predominately on biopsy, as our patient
had.

In addition to steroids and prophylactic antibi-
otics, we chose to treat the patient with rituximab.
Rituximab is found to be as effective as cyclophos-
phamide in treating cANCA-associated vasculitis but
with a better side effect profile versus cyclophos-
phamide, especially in our patient’s demographic. It is not clear how patients may benefit from
rituximab with recent drug use (although our patient
appeared to experience no side effects from ritux-
imab infusions). It is imperative the patient stops
drug use before initiation of consistent rituximab
infusions. Given that rituximab may be superior in
relapsing cANCA-mediated disease versus cyclo-
phosphamide, we recommended a combination
of prednisone initially, followed by rituximab along
with absolute cessation of cocaine, with local wound
care (mupirocin) and prophylactic trimethoprim-
sulfamethoxazole to prevent Pneumocystis jiurovei
pneumonia and *S. aureus* infections. This regimen should allow patients, such as ours, to experience effective wound healing (as she did, before relapse with continued drug use and medication noncompliance).

Our case highlights the more rare ANCA profile (cANCA/anti-PR3**, pANCA/anti-MPO**) that can exist in previously healthy patients with simultaneous cocaine use presenting with granulomatosis with polyangiitis-like clinical features (but without ear involvement). The biopsies from these patients can lack vasculitis or vasculopathy (either because it is not present or it was not captured in the biopsies). Wounds may be mostly neutrophil and lymphocyte rich. Patients need extensive drug counseling as the most important limiting factor before the ANCA-mediated disease can be fully contained.

**Fig 4.** Relapse of patient’s ulcers. A, Right and B, left side of face. C and D, Inflamed “strawberry” gums. E and F, One week after inpatient treatment (intravenous/systemic steroids and anti-MRSA antibiotics). F, Note saddle-nose deformity.
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