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Pyoderma gangrenosum associated with levamisole-adulterated cocaine in a c-ANCA positive patient

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Abstract

Pyoderma gangrenosum (PG) is an inflammatory, ulcerative condition that is characterized by painful ulcers that commonly present on the lower extremities. Up to half of PG cases are associated with underlying systemic disease, including inflammatory bowel disease, various autoimmune conditions, and malignancy. Another well-known association is the manifestation of PG with recreational cocaine use, especially cocaine contaminated with the adulterant agent levamisole. Once utilized for its immunomodulatory capabilities, levamisole was withdrawn from the market in 2002. It has since been repurposed to potentiate the amphetamine-like effects and duration of cocaine and has reduced preparation cost. We present a 52-year-old woman with chronic maxillary sinusitis and cocaine use disorder presenting with a two-week history of painful ulcers on bilateral lower extremities, each with a purulent base and undermined, violaceous borders. Urine toxicology was positive for cocaine and serologic studies were positive for cytoplasmic antineutrophil cytoplasmic antibodies (c-ANCA) and lupus anticoagulant. Underlying conditions, especially that of granulomatosis with polyangiitis, were considered and ultimately ruled out. The patient's lesions exhibited a marked response with a short course of oral corticosteroids, typical of PG associated with levamisole. This case highlights the crucial role that drug abstinence plays in the prevention of recurrence.

Keywords: pyoderma gangrenosum, levamisole, cocaine, c-ANCA, p-ANCA, granulomatosis with polyangiitis, vasculitis

Introduction

Pyoderma gangrenosum (PG) is an inflammatory skin condition that commonly presents as a painful, enlarging ulcer on the lower extremities [1]. Although there are many variants of its presentation, classic PG manifests as a deep, well-defined ulcer, with undermined edges and erythematous, indurated surrounding skin [2]. Associated medical comorbidities related to PG include hematologic disease, inflammatory bowel disease, primary autoimmune disease, and arthritides [3,4].

Another well-recognized inciting factor for PG is cocaine consumption, in particular cocaine tainted with levamisole [3]. Levamisole is an antihelminth agent that was previously used to treat both cancer and inflammatory conditions in humans and animals [4]. Adverse events following levamisole treatment were initially reported in 1978 and included leukocytoclastic vasculitis, cutaneous necrotizing vasculitis, and thrombotic vasculopathy without vasculitis [4]. Levamisole was removed from the market in 2002, but has been repurposed and recognized as a bulking agent and adulterant in the United States cocaine supply since then [2]. By 2010, levamisole was estimated to be found in almost 70% of seized cocaine, with the first reports of complications in cocaine users following thereafter [5].

The diverse range of clinical presentations related to cocaine use include cocaine-induced midline destructive lesions, eruptive pyoderma gangrenosum, and vasculitis secondary to levamisole-contaminated cocaine [6-8]. Retiform purpura in conjunction with PG suggests a thrombotic state secondary to levamisole toxicity whereas the presence of petechiae and palpable purpura are consistent with a more characteristic clinical picture of vasculitis-derived ulcers. In the case of levamisole-associated PG, the lesions are tender

ulcers with necrotic beds and undermined borders. The proposed immune-mediated theory for the vasculitis and vasculopathy incited by cocaine exposure is supported by positive serologic studies (positive antinuclear, antiproteinase-3, antiphospholipid, and antineutrophil cytoplasmic antibodies) and immunofluorescence studies depicting vascular deposits of immunoglobulins and complement C3 [3].

We present a patient with pyoderma gangrenosum associated with levamisole-adulterated cocaine and discuss the significance of serological studies in diagnosis and differentiation from primary autoimmune disease and discuss special treatment considerations. Clinical improvement following cessation of levamisole exposure is an important feature and most importantly, underscores the necessity of drug abstinence in long-term care and prevention of recurrent ulcers.

Case Synopsis

A 52-year-old woman with history of chronic maxillary sinusitis and cocaine use disorder presented to the emergency room with a two-week history of multiple lower extremity ulcers. The lesions started as itchy bumps that progressed to painful ulcers. Her physical examination revealed numerous ulcers on the legs, each with a purulent base and irregular, undermined, violaceous borders (**Figure 1**). Discrete pustules with surrounding erythema were scattered on her arms, left axilla, and right temple. Additionally, there was longstanding perforation of her hard palate.

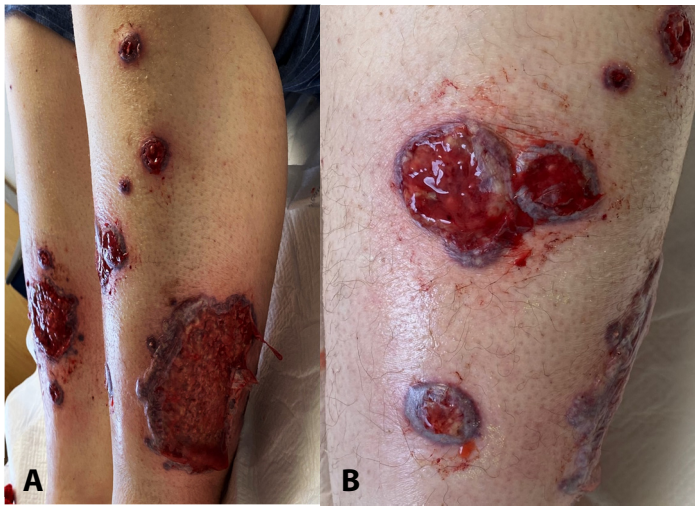

Figure 1. ***A)*** *Multiple lower extremity ulcers, each with a purulent base and undermined, violaceus borders.* ***B)*** *Close up of lower extremity ulcers, each with undermined borders, and indurated surrounding skin.*

Urine toxicology was positive for cocaine and serologic studies were positive for cytoplasmic antineutrophil cytoplasmic antibodies (c-ANCA) and lupus anticoagulant. Of note, her creatinine was normal and she denied hemoptysis, shortness of breath, and fever. Skin biopsy demonstrated a superficial neutrophil-rich dermal infiltrate with papillary dermal edema (**Figure 2**). Stains for organisms, including bacterial, fungal, and acid fast, were negative. Tissue cultures, including aerobic, acid-fast bacilli, and fungal, demonstrated no

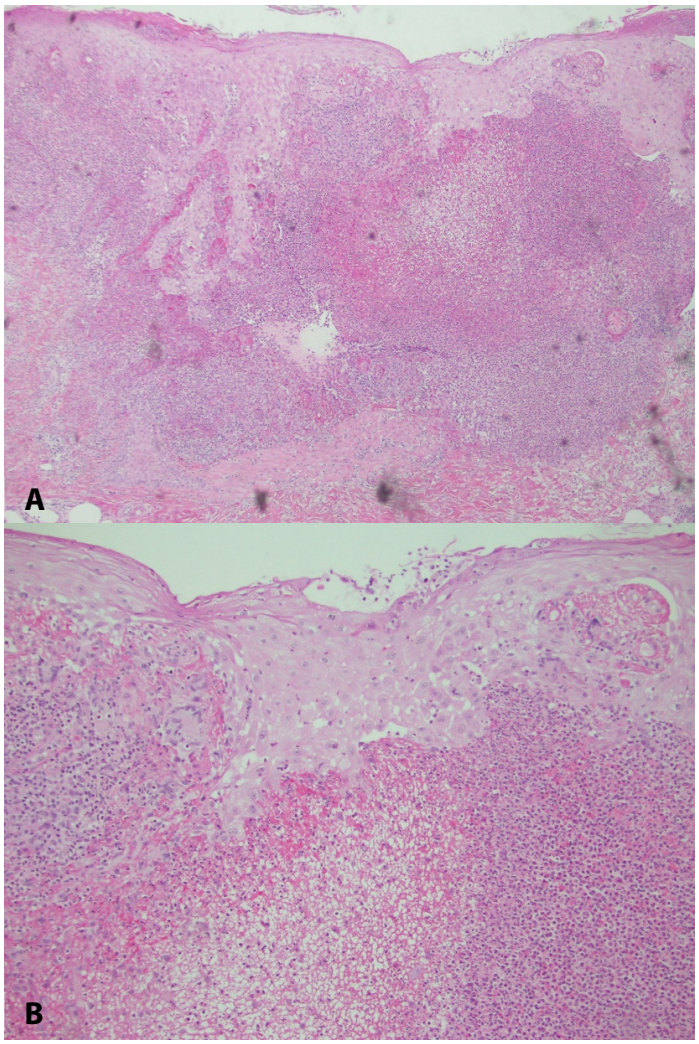

Figure 2. ***A)*** *Punch biopsy of lower extremity. Scanning view shows a dense neutrophil rich infiltrate that involves the entire dermis. H&E, 4×.* ***B)*** *Higher power shows large collections of neutrophils with edema in the upper dermis. H&E, 20×.*

growth. In the setting of the patient's c-ANCA pattern and longstanding history of nasal perforation, the differential diagnosis initially included granulomatosis with polyangiitis (GPA). She underwent biopsy of her maxillary sinus, which showed chronic sinusitis with lymphoplasmacytic infiltrate, consistent with persistent mucosal injury; no granulomas or vasculitis were seen.

The patient was treated with prednisone 100mg daily (tapered over two weeks) and topical betamethasone dipropionate 0.05% ointment. She demonstrated a marked and rapid improvement within two days. At two weeks, her ulcers were fully healed. Although additional evaluation was considered for GPA her symptoms completely resolved, which provided further reassurance that her presentation did not represent GPA.

A month later, she remained asymptomatic and did not experience recurrent ulcers. The patient unfortunately relapsed and ultimately presented with recurrence of a similar clinical picture, which resolved within one week after a repeat course of prednisone. Drug abstinence is paramount in prevention of persistent or recurrent PG, so every effort should be made to connect patients with addiction support services.

Case Discussion

Prior reports of pyoderma gangrenosum associated with levamisole-contaminated cocaine have demonstrated presence of peri-nuclear antineutrophil cytoplasmic antibodies (p-ANCA), [9]. These findings are also described in a cohort series of eight patients in whom serological studies demonstrated positivity for antiphospholipid antibodies with anticardiolipin IgM antibodies most predominantly elevated [3]. Additionally, perinuclear (p-ANCA) autoantibodies were positive in seven of the eight patients, followed by antiproteinase-3 antibodies (four of eight), [3]. The serological testing that revealed positive lupus anticoagulant was concordant in demonstrating positivity for at least one antiphospholipid antibody. In contrast to the p-ANCA findings in the aforementioned cohort, our patient exhibited c-ANCA positivity. To our knowledge, this is the first report of transient PG associated with c-ANCA positivity.

Our patient's c-ANCA positivity, along with nasal septum perforation and a history of longstanding maxillary sinusitis, present a complicated clinical picture in which GPA was also considered in the differential diagnosis. Although uncommon, cutaneous symptoms have been reported as the initial symptom of granulomatosis with polyangiitis (also known as Wegener granulomatosis), [10]. It is a multi-system vasculitis that affects the small and medium vessels with variable clinical presentation [11]. Organ systems affected include the respiratory tract, kidneys, heart, skin, eyes, and peripheral nervous system [12]. Skin lesions have been reported in nine to twenty five percent of cases, and although uncommon, cutaneous symptoms can be the initial presenting symptom of granulomatosis with polyangiitis [12,13]. Although rare, GPA presenting as PG-like lesions has been reported in one of 166 reported cases [14]. Our patient's history of cocaine abuse, which has a propensity to mimic rheumatologic conditions such as GPA, further complicated her case [15]. With a plausible clinical picture of GPA and its potential to atypically present as PG, this diagnosis was critical to rule out. As mentioned above, she underwent biopsy of her maxillary sinus, which showed chronic sinusitis with lymphoplasmacytic infiltrate, consistent with persistent mucosal injury; no granulomas or vasculitis was seen. Furthermore, though additional evaluation was considered for GPA, her symptoms completely resolved, which provided further evidence that her presentation did not represent GPA.

Levamisole potentiates the effects of cocaine through its main metabolite, aminorex, which has amphetamine-like and hallucinogenic properties [5]. Aminorex inhibits reuptake of noradrenergic neurotransmitters, which increases endogenous opioids and dopamine in the brain's reward pathway [4]. The time between cocaine consumption and the appearance of painful lesions occurs between one to four weeks [3]. Levamisole has been detected in up to 88% of urine toxicology samples in cocaine users, increasing the chances for cutaneous complications such as PG [16].

Cocaine users are susceptible to a high rate of recurrence of cutaneous symptoms, with approximately 27% experiencing recurrence upon re-exposure to contaminated cocaine [4]. With a high rate of relapse and levamisole's abilities to enhance the effects and duration of cocaine, it is likely that levamisole will remain an adulterant in cocaine, presenting a challenge for healthcare workers in its diagnosis.

The importance of timely and accurate diagnosis is key to ensuring proper treatment and prevention of recurrence. Treatments are based on consensus reports and anecdotal guidelines as no guidelines based on randomized clinical trials exist [1,2]. Differentiating the constellation of cutaneous symptoms from an underlying primary autoimmune disease and identifying levamisole-contaminated cocaine as the etiologic culprit for PG is paramount. Pyoderma gangrenosum associated with levamisole-adulterated cocaine demonstrates a rapid improvement with corticosteroids, often requiring only a one to two-week course of corticosteroids [3]. Immunosuppression is the main treatment, and symptomatic patients generally respond well to a brief course of systemic glucocorticoids, alleviating the use of other more toxic systemic immunosuppressive therapy [2]. Lastly, prior cocaine consumption increases risk of cutaneous symptom recurrence, making drug abstinence a pillar in the foundation of care for preventing future cutaneous complications.

Conclusion

Pyoderma gangrenosum associated with levamisole-altered cocaine has been reported in patients with various antiphospholipid antibodies and in p-ANCA positive positions. This case illustrates a previously unreported association with c-ANCA positivity. Because pyoderma gangrenosum is the initial cutaneous lesion for vasculitides such as GPA, this case underscores the importance of distinguishing between a multisystemic condition versus conventional PG from other causes (in this instance, cocaine abuse). The patient's complicated presentation of concurrent nasal perforation and chronic sinusitis necessitated additional workup for GPA. The improvement in cutaneous lesions with cocaine avoidance is key to differentiating PG caused by levamisole-contaminated cocaine from a primary autoimmune disease. Finally, in contrast to traditional PG, PG in the setting of levamisole-tainted cocaine responds rapidly to a short course of corticosteroids rather than an extended course of immunosuppression.

Abstinence from substance use, especially cocaine, is crucial in preventing persistent or recurrent cases of PG. A thorough clinical history with regard to substance use, a high clinical suspicion for ruling out primary autoimmune disease, and availability of addiction support services are key to the successful management of levamisole-induced PG.

Potential conflicts of interest

The authors declare no conflicts of interest.

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