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# PYODERMA GANGRENOSUM AND HAEMATOCHEZIA IN A PATIENT WITH PREVIOUS COCAINE ABUSE

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## ABSTRACT

*Introduction:* Pyoderma gangrenosum (PG) is an autoinflammatory neutrophilic dermatosis that may rarely occur in association with granulomatosis with polyangiitis (GPA). Management of refractory disease remains challenging.

*Case description:* A 48-year-old man with a history of previous cocaine abuse was admitted due to impaired feeding in the context of a chronic hard palate perforation and a large oro-sinus fistula. During hospitalisation, he developed haematochezia and painful ulcerative skin lesions involving the right upper limb and lower extremities. Upper and lower gastrointestinal endoscopy revealed a Forrest IIc gastric lesion and a non-bleeding ileocecal ulcer. Histopathological examination of skin lesions demonstrated dense neutrophilic infiltration consistent with PG, while gastrointestinal biopsies excluded inflammatory bowel disease. An extensive evaluation excluded infection, antiphospholipid syndrome, cryoglobulinaemia, malignancy and vascular occlusive disease, all of which may mimic PG. Autoimmune screening workup yielded positive for anti-proteinase-3 antibodies (C-ANCA). The patient initially received high-dose methylprednisolone followed by mycophenolate mofetil and infliximab. Despite treatment, disease activity persisted with recurrent relapses, requiring hospitalisations. Upadacitinib was subsequently introduced, resulting in rapid clinical improvement, near-complete healing of skin lesions and successful glucocorticoid withdrawal.

*Conclusion:* The coexistence of PG and GPA is rare and presents substantial diagnostic and therapeutic challenges. JAK inhibition with upadacitinib may represent a promising therapeutic option in refractory cases.

## KEYWORDS

Pyoderma gangrenosum, granulomatosis with polyangiitis, upadacitinib, JAK inhibitor, ANCA-associated vasculitis

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## LEARNING POINTS

- Pyoderma gangrenosum may rarely coexist with granulomatosis with polyangiitis, creating significant diagnostic and therapeutic challenges.
- A history of cocaine abuse may complicate the diagnostic evaluation because cocaine-induced vasculitis can mimic ANCA-associated vasculitis.
- Upadacitinib may represent a promising steroid-sparing therapeutic option in refractory pyoderma gangrenosum associated with granulomatosis with polyangiitis.
- Pyoderma gangrenosum is a diagnosis of exclusion for which no confirmatory test exists; approximately 10% of patients given the diagnosis are subsequently found to have an alternative condition, so mimickers must be actively excluded before and during treatment.

## INTRODUCTION

Pyoderma gangrenosum (PG) is an autoinflammatory ulcerative disorder characterised by neutrophilic infiltration of the skin and underlying soft tissues. PG has been associated with several systemic diseases, including inflammatory bowel disease and inflammatory arthritis[1,2]. However, its association with granulomatosis with polyangiitis (GPA) is uncommon (3–10 cases per million people per year)[3,4].

GPA is a necrotising ANCA-associated vasculitis with multisystem involvement, most commonly affecting the upper respiratory tract, lungs and kidneys[5]. The coexistence of PG and GPA presents significant diagnostic and therapeutic challenges[3,4]. Furthermore, a history of cocaine use may complicate the clinical picture, as cocaine-induced vasculitis may mimic GPA and can present with ANCA positivity[6-8].

Janus kinase (JAK) inhibitors have recently emerged as targeted therapies in several immune-mediated diseases. Their role in refractory PG and GPA remains under investigation[9].

## CASE DESCRIPTION

A 48-year-old man was admitted to the otorhinolaryngology department because of a hard palate perforation and a large oro-sinus fistula, causing significant feeding impairment. His medical history was notable only for previous cocaine abuse, which had ceased several months before admission.

The patient received nutritional support and treating physicians administered oral amoxicillin/clavulanic acid for underlying sinusitis, scheduling the occlusion of the hard palate fistula with a palatal obturator synthetic device. During hospitalisation, he developed multiple episodes of haematochezia without haemodynamic compromise. Internal medicine consultation was requested, and physical examination revealed painful ulcerative skin lesions involving the right upper extremity, right thigh and right lower extremity *(Fig. 1)*. The presence of concomitant gastrointestinal haemorrhage and painful skin lesions was suggestive for possible underlying inflammatory bowel disease or cocaine-induced ischaemic colitis. Upper and lower gastrointestinal endoscopy was performed and demonstrated a Forrest IIc lesion in the gastric antrum and a non-bleeding ileocecal ulcer, from which biopsied were obtained. Histological examination of gastrointestinal biopsies was not suggestive of inflammatory bowel disease but showed a colon ulcer with reactive mucosal lesions. Given the patient's painful cutaneous ulcers and gastrointestinal involvement, a broad differential diagnosis was considered. Infectious causes included bacterial *(Pseudomonas spp.)*, fungal, mycobacterial and viral infections (e.g. herpes simplex virus), as syphilitic and deep fungal ulcers may clinically mimic pathergy-associated lesions but typically respond to appropriate antimicrobial therapy. Autoimmune and inflammatory disorders, including ANCA-associated vasculitis, Behçet's disease, sweet syndrome and antiphospholipid syndrome, were also considered because of their potential to present with both cutaneous ulceration and systemic manifestations. In addition, inflammatory bowel disease remained an important differential in view of the gastrointestinal ulceration and skin lesions, although characteristic histopathological features were absent. Cocaine-induced ischaemic colitis was likewise considered because of the patient's history of cocaine use. Finally, neoplastic and other non-inflammatory conditions, including cutaneous squamous cell carcinoma or skin



***Figure 1.*** *Ulcerative skin lesion of lower extremity prior to treatment.*



*Figure 2. Lower extremity skin lesion refractory to glucocorticoid therapy.*

lymphoma, were not likely; however, further imaging and histopathology investigation was needed to exclude them.

Due to rapid progression of the skin lesions with significant skin necrosis and fever absence, with persistent high inflammatory markers, antimicrobial therapy was upscaled with administration of empirical broad-spectrum intravenous antibiotics (piperacillin/tazobactam and vancomycin) without clinical improvement. A skin biopsy and skin tissue culture (for common bacteria/mycobacteria) was then performed, and empiric intravenous methylprednisolone pulses (1 gram daily for five days) were initiated empirically for treatment of possible PG, due to compatible skin lesion morphology. Empiric corticosteroid treatment was associated with the patient's significant pain improvement.

Moreover, further investigation of necrotic skin lesion aetiology followed with autoimmune screening workup that yielded positive for anti-proteinase-3 antibodies (immunofluorescence C-ANCA: 1/20). Further investigations, including magnetic resonance enterography, viral serology, tuberculin testing and serum angiotensin-converting enzyme levels, and tissue cultures for bacteria, fungi and mycobacteria, were negative. In addition, an antiphospholipid antibody panel and serum cryoglobulins were negative, and arterial and venous Doppler studies of the affected limbs were normal, thereby excluding antiphospholipid antibody syndrome, cryoglobulinaemia, deep fungal infection and vascular occlusive or venous disease. The skin lesion histopathology, taken from the advancing ulcer edge, revealed a dense dermal neutrophilic infiltrate with epidermal ulceration and dermal oedema, in the absence of true vasculitis, vascular thrombosis, granulomata or an atypical lymphoid infiltrate. These appearances, together with the exclusion of the alternative diagnoses listed above, supported a diagnosis of PG.

A multidisciplinary evaluation involving internal medicine, rheumatology, plastic surgery and pathology teams established a working diagnosis of PG associated with granulomatosis with polyangiitis. Initial treatment of intravenous methylprednisolone pulses was followed by intravenous methylprednisolone 62.5 mg daily and atraumatic wound care. The patient was discharged, after 26 days on corticosteroid treatment, on oral methylprednisolone 64 mg daily after manifesting clinical skin lesion improvement and inflammatory marker normalisation.

During outpatient follow-up, mycophenolate mofetil was added to the therapeutic scheme. Due to inadequate and slow clinical response *(Fig. 2)* and new painful skin lesions, infliximab was subsequently introduced as a second-line, steroid-sparing agent. Nevertheless, the patient experienced persistent disease activity with recurrent hospitalisations, manifesting fever and new migrating painful PG skin lesions on trunk and extremities associated with elevated inflammatory markers. Due to the refractory disease nature and ongoing glucocorticoid dependence, upadacitinib was initiated following multidisciplinary consensus.

Clinical improvement became evident within four months of treatment initiation. By six months, inflammatory



*Figure 3. Marked healing of skin lesions after six months of upadacitinib treatment.*

markers had normalised, ulcer size and pain had markedly decreased and no new lesions had developed *(Fig. 3)*. Glucocorticoids were successfully tapered and eventually discontinued without disease relapse or need for hospitalisation.

## DISCUSSION

This case illustrates the rare coexistence of PG and granulomatosis with polyangiitis[3,4], initially presenting with upper airway involvement followed by gastrointestinal and cutaneous manifestations.

The principal differential diagnoses included inflammatory bowel disease, infection, necrotic small-vessel vasculitis and cocaine-associated vasculitis. Although haematochezia raised suspicion initially for inflammatory bowel disease, histopathological findings and magnetic resonance enterography were not supportive. Infectious causes were excluded by negative microbiological investigations and the absence of clinical response to broad-spectrum antimicrobial therapy.

Critically, there is no confirmatory laboratory, radiological or histological test for PG: the diagnosis remains one of exclusion[10], supported by compatible clinicopathological features and by response to immunosuppression. Misdiagnosis is consequently common and carries real harm[10]. In the landmark series reported by Weening et al.[10], 15 out of 157 consecutive patients (10%) treated for presumed PG at a single academic centre, were ultimately found to have an alternative diagnosis; among 95 patients with ulcers clinically resembling PG, the eventual diagnoses comprised vascular occlusive or venous disease, vasculitis, malignancy, primary cutaneous infection, drug-induced or exogenous tissue injury and other inflammatory disorders. Of those treated as PG, the ulcers of 36% failed to respond and those of a further 12% were exacerbated by that treatment[10]. Entities most frequently mistaken for PG include antiphospholipid antibody syndrome – among the commonest – venous stasis ulceration, granulomatosis with polyangiitis, factitial ulceration, sporotrichosis and other deep fungal infections, polyarteritis nodosa, angiocentric T-cell lymphoma, cryoglobulinaemia, cutaneous Crohn's disease and ulcerative necrobiosis lipoidica[10]. The overlap of this list with this case is striking, since our patient carried an established diagnosis of granulomatosis with polyangiitis, presented with lower-limb ulceration and had a history of illicit drug use – a combination in which each recognised mimicker was a genuine competing possibility rather than a theoretical one.

We therefore implemented a deliberately exhaustive exclusion strategy before accepting PG. Applying the Delphi consensus criteria retrospectively, our patient fulfilled the major criterion of an ulcer-edge biopsy. He demonstrated a neutrophilic infiltrate, together with the minor criteria of exclusion of infection, multiple ulcerations with at least one on an anterior lower leg, peripheral erythema with an undermined and tender ulcer border, and a decrease in ulcer size within one month of starting immunosuppressive therapy. The Paracelsus score, which similarly weights assessment of differential diagnoses as a major criterion, was likewise consistent with PG. We would emphasise that in such patients the diagnosis should be treated as provisional and reviewed at every relapse, since failure to respond to immunosuppression – or deterioration on it – should prompt re-biopsy and reconsideration of the alternatives rather than escalation of therapy alone.

The patient's history of previous cocaine abuse further complicated the diagnostic process, as cocaine-induced vasculitis may mimic GPA clinically and serologically. The relapsing nature of the PG skin lesions however, in the context of cocaine abstinence, were supportive of an alternate diagnosis.

Treatment of PG associated with GPA remains challenging. While high-dose glucocorticoids remain the cornerstone of therapy, prolonged corticosteroid exposure is associated with substantial morbidity. In this case, disease activity persisted despite treatment with mycophenolate mofetil and infliximab.

The favourable response observed after initiation of upadacitinib highlights the potential role of JAK-STAT pathway inhibition in refractory neutrophilic dermatoses and ANCA-associated vasculitis[9]. Additional studies are required to clarify the efficacy and safety of JAK inhibitors in these conditions.

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