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Short Review

Pyoderma gangrenosum-like ulcer association in small vessel vasculitis (Vasculitis presenting as pyoderma gangrenosum-like ulcer)

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ABSTRACT

Pyoderma gangrenosum (PG) was first described by French Dermatologist Louis-Anne-Jean Brocq as a "rapidly spreading ulceration of soft tissue".[1] Histologically, PG is a neutrophilic dermatosis presenting as painful ulcerations. It is known to be associated with autoimmune-mediated disorders such as vasculitis.[2] Timely confirmatory diagnosis with tissue biopsy and management with immunosuppressive agents are critical.[1] We report a unique case of a PG-like lesion related to small vessel vasculitis in a 47-year-old man. Following the initiation of methotrexate (Methotrexate) therapy, the patient's lesions improved significantly, highlighting the importance of recognizing PG-like lesions associated with vasculitis.

Case presentation

A 47-year-old man with past medical history of diabetes mellitus presented to the clinic for evaluation of recurrent pyoderma gangrenosum (PG). He had a medical history of biopsy-proven PG (Fig. 1A and B) that was previously treated with clobetasol and an intralesional steroid injection. Clinical examination revealed an ulcer measuring approximately 6 cm in the left lower extremity that was consistent with PG (Fig. 2A). Blood tests revealed an elevated erythrocyte sedimentation rate (ESR) of 59MM/HR and C-reactive protein (CRP) of 9.95 mg/dL Results for antinuclear antibody (ANA), rheumatoid factor (RF), anti-cyclic citrullinated antibodies (anti-CCP), myeloperoxidase (MPO), proteinase 3 (PR3), and cryoglobulin were negative. Complement levels were within normal limits, and protein electrophoresis showed no abnormalities. A basic metabolic panel demonstrated normal kidney function, and urinalysis revealed no hematuria or proteinuria, A1c 7.9 %, X-ray of the chest was unremarkable, colonoscopy showed no ulceration or perforation observed, transthoracic echocardiogram unremarkable with no pericardial effusion or aortic aneurysm. The infectious workup was unremarkable, with non-reactive results for HIV 1 and 2, and negative findings for tuberculosis, hepatitis B and C, and syphilis. Duplex venous ultrasonography did not indicate deep vein thrombosis. The patient underwent biopsy that revealed small- and medium-vessel neutrophilic vasculitis with ulceration and fat necrosis. The patient was initiated on prednisone (1 mg/kg) with a gradual taper, in combination with methotrexate (Methotrexate). He is currently taking methotrexate (Methotrexate) at 20 mg once a week, with healing of the ulcer at one and a half months (Fig. 2B) and near resolution after six months of follow-up.

Epidemiology

PG is rare, and its accurate diagnosis is challenging due to its clinical mimickers. Based on this, the precise estimates of its incidence and prevalence are limited. However, available studies indicate that its incidence is estimated to be three to ten cases per million individuals per year.[1,2] It is common in people aged 50 years and older, with a higher incidence and prevalence in women than in men.[3]

Based on a population study conducted in the UK, PG carries a threefold risk of mortality when age and sex are matched in comparison to other inflammatory conditions.[4] Therefore, timely diagnosis and treatment are imperative.

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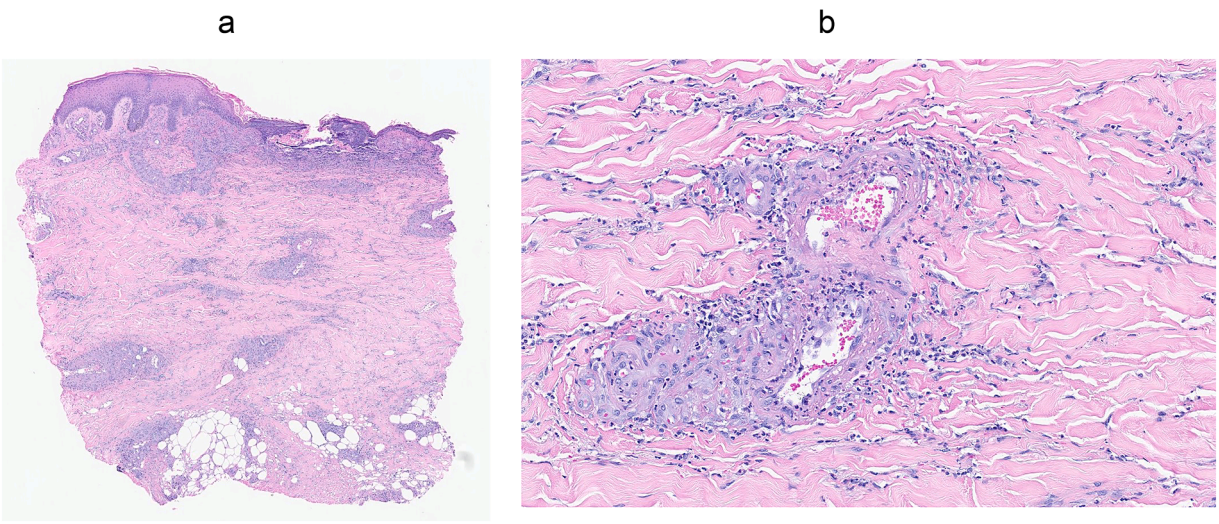

Fig. 1. A: Scanning magnification (H&E, 20x) demonstrates focal ulceration with a superficial and deep perivascular and interstitial inflammatory infiltrate. **Figure 1B:** Higher power magnification (200x) reveals interstitial and perivascular neutrophils, with infiltration of vessel walls, leukocytoclasis, and hemorrhage. *Abbreviations: H&E, Hematoxylin and Eosin stain.*

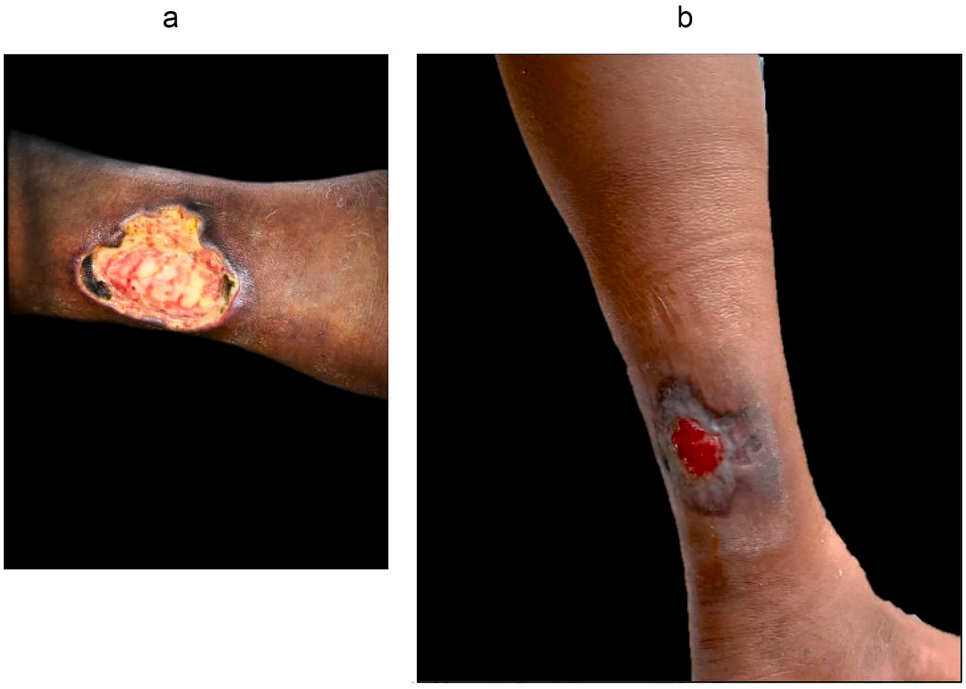

Fig. 2. A: Large ulcer on the left lower extremity and elevated borders with erythema around the wound consistent with pyoderma gangrenosum. **Figure 2B**: At one and a half months follow-up, response to therapy with healing of the ulcer is visualized.

Diagnosis

Variable PG presentation makes diagnosis challenging, with reports of ulcers believed to be PG with an alternative diagnosis.[1] Hence, careful evaluation of suspected PG or PG-like lesions is vital for accurate diagnosis, involving a thorough medical history and attention to patient risk factors such as history of autoimmune inflammatory conditions or malignancy. Furthermore, establishing a timeline for the onset of the lesion, while noting color, borders, and presence or absence of scars at sites of previous ulcerations, is important.[1] Various diseases can present as PG-like lesions, including drug-induced PG, neutrophilic dermatosis of the dorsal hands (also known as 'pustular vasculitis'), and necrotizing neutrophilic dermatosis.[1] Given the need for accurate diagnosis, the international diagnostic criteria of PG was created with four primary criteria that include histology, history, clinical examination, and response to therapy, with a score above five supporting the clinical diagnosis of PG.[5]

Management

PG pathogenesis is complex, with most of its complexity arising due to the marked imbalance in innate and adaptive immunity activation.[6] Despite its multi-component pathophysiology, the initial understanding of its molecular pathway has cemented the way for current treatment with immunosuppressive agents as the mainstay therapy.[6] An updated literature review on established and emerging pharmacological

treatments for PG, identifies systemic corticosteroids as a first-line therapy, supported by a level 1B[6] evidence. Corticosteroids are potent agents in PG due to their effects on the downregulation of proinflammatory cytokines, where a dose of 0.5–1 mg/kg/day has yielded a clinical response in 40–50 % of patients with PG.[7] Additionally, cyclosporine (Cyclosporine capsules), an immunosuppressive agent, is well documented in the literature as a first-line choice in PG and has demonstrated to be highly effective with the level of evidence 1B.[6]

Notably, evidence regarding methotrexate (Methotrexate), an immunomodulating agent, indicates that efficacy in the context of PG has been limited.[6] methotrexate (Methotrexate) is widely used in chronic inflammatory skin conditions, but its effectiveness depends on the administration route and other comorbidities with PG. For example, intralesional methotrexate (Methotrexate) resulted in drastic improvements in patients with ulcerative PG, whereas oral methotrexate (Methotrexate) was more effective in patients with PG and concurrent psoriatic arthritis.[6] Despite emerging treatments, treatment of PG remains solely dependent on clinical experience.

Discussion

PG manifests as cutaneous ulceration characterized by painful ulcers classified within the neutrophilic dermatosis entity.[8] Understanding its exact pathogenesis remains narrow, with proinflammatory cytokine release and increased neutrophil granulocyte activity proposed as the pathophysiological drivers of skin inflammation.[8] Despite attempts to understand the pathophysiology, diagnosis remains challenging, with misdiagnosis rates up to 39 %.[9] The most commonly reported etiology of PG is the 'pathergy phenomenon' that is the formation of new ulcers post-minor trauma such as needle injury.[8] However, misdiagnoses occur due to similar clinical presentations of PG and PG-like lesions associated with inflammatory conditions such as vasculitis, vasculopathy, and factitial ulcers.[8]

PG-like lesions have been documented in association with small vessel vasculitis, particularly GPA.[10] According to a nine-case series by Shakshouk and Gibson, certain features were proposed that favor PG-like lesions versus PG, with a notable emphasis on obtaining histopathological evidence via skin biopsy.[11] While PG has been well documented in the literature to be associated with anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV), PG-like ulcers associated with vasculitis remain an unclear entity. Additionally, first-line management of PG involves corticosteroids and cyclosporine (Cyclosporine capsules), with the rare use of methotrexate (Methotrexate); however, in our unique case, the patient exhibited a remarkable clinical response to methotrexate (Methotrexate). The significant clinical response is owed to methotrexate (Methotrexate)'s mechanism of action, which decreased neutrophil migration and chemotaxis, a process that is well evidenced to be dysregulated in PG.[12] Additionally, a retrospective case series that evaluated thirty-three biopsy-proven PG cases from 2012 to 2022, found that 10 patients,30 %, had a complete response with methotrexate (Methotrexate) with six of the 10 tapered off methotrexate (Methotrexate) without relapse.[13] The latter signals methotrexate (Methotrexate)'s efficacy and future potential in the reduction of steroid burden in the management of PG.

Prospective studies examining the underlying pathophysiology and molecular makeup of PG, its prognosis, and new targeted therapies are necessary to distinguish between PG- and PG-like ulcers associated with vasculitis.

Conclusions

PG manifests as cutaneous ulceration characterized by painful ulcers and deep neutrophilic dermatosis that can be associated with rheumatic diseases.[11] Small vessel vasculitis, particularly ANCA-associated vasculitis, has been reported to cause pyoderma gangrenosum-like lesions in the legs.[10] Corticosteroids and oral cyclosporin are widely used as first-line treatment for PG.[8] methotrexate (Methotrexate) is rarely used for PG; however, in our unique case, methotrexate (Methotrexate) has exhibited excellent treatment efficacy.

Disclosures

Fully informed consent for publication was obtained

Declaration of competing interest

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