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Successful Treatment of Pyoderma Gangrenosum with Cryoglobulinemia and Hepatitis C

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient: Male, 68
Final Diagnosis: Pyoderma gangrenosum
Symptoms: Worsening lower extremity wound
Medication: —
Clinical Procedure: —
Specialty: Infectious Diseases

Objective: Rare disease





Background: Pyoderma gangrenosum is a rare, ulcerative cutaneous condition that was first described by Brocq in 1916. This diagnosis is quite challenging as the histopathological findings are nonspecific. Pyoderma gangrenosum is usually associated with inflammatory bowel disease, leukemia, and hepatitis C. We describe a rare clinical case of a patient with hepatitis C (HCV), mixed cryoglobulinemia, and pyoderma gangrenosum, which was successfully treated with prednisone in combination with the new antiviral medication ledipasvir/sofosbuvir.

Case Report: A 68-year-old male with a history of untreated HCV presented to the clinic with a left lower extremity ulcer that had progressively worsened over 4 days after the patient sustained a minor trauma to the left lower extremity. Examination revealed a 2×3 cm purulent ulcer with an erythematous rim on medial aspect of his left lower leg. HCV viral load and genotype analysis revealed genotype 1A with polymerase chain reaction (PCR) showing viral counts of 9,506,048 and cryoglobulinemia. With a worsening and enlarging erythematous ulcer and failure of IV antibiotic therapy, the patient underwent skin biopsy, which showed acanthotic epidermis with superficial and deep perivascular lymphoplasmacytic dermatitis admixed with mild neutrophilic infiltrate. The patient was subsequently started on ledipasvir/sofosbuvir and prednisone with a high suspicion of pyoderma gangrenosum. At one-month follow-up at the hepatology clinic, the patient demonstrated a near resolution of the lower extremity ulcer with undetectable viral load.

Conclusions: Pyoderma gangrenosum is an inflammatory process of unknown etiology, and establishing the correct diagnosis can be a difficult task. For this reason it is prudent for clinicians to consider Pyoderma gangrenosum in their differential diagnosis, especially in the setting of a nonhealing surgical wound or skin infection.

MeSH Keywords: Cryoglobulinemia • Hepatitis C, Chronic • Pyoderma Gangrenosum

Full-text PDF: <http://www.amjcaserep.com/abstract/index/idArt/898611>

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Background

Pyoderma gangrenosum (PG) lesions are rare necrotic ulcerations of unknown etiology. Pyoderma gangrenosum is typically associated with ulcerative colitis, Crohn's disease, and hepatitis C (HCV). The Centers for Diseases Control and Prevention estimates that approximately 3.5 million people in United States are living with HCV infection. Dermatologic manifestations of HCV include psoriasis, porphyria cutanea tarda, lichen planus, and PG. A study conducted by Hopital La Pitié-Salpêtrière showed that 38% of patients with chronic HCV had at least one extrahepatic manifestation [1]. We describe a rare clinical case of a patient with HCV, mixed cryoglobulinemia, and PG, which was successfully treated with the new antiviral medication ledipasvir/sofosbuvir.

Case Report

A 68-year-old Caucasian male with a history of untreated HCV presented to the clinic with a left lower extremity ulcer that had progressively worsened over 4 days after the patient sustained a minor trauma to the left lower extremity. Examination revealed a 2×3 cm purulent ulcer with an erythematous rim on the medial aspect of his left lower leg (Figure 1). The patient was started on a 7-day course of Augmentin and Bactrim therapy for presumptive uncomplicated cellulitis after wound cultures detected methicillin-resistant *Staphylococcus aureus* and *Citrobacter* species. Upon re-evaluation, the patient was noted to have worsening and enlarging erythematous ulcer of his left lower extremity without satisfactory healing (Figure 2). The patient was subsequently admitted to the hospital, and intravenous vancomycin and cefepime were initiated. On physical examination he was noted to have a low grade temperature of 100.7°F (38.2°C), heart rate of 107, and blood pressure of 146/80 mm Hg. A well-defined angulated ulceration with punched-out margins and crusted exudate was noted on the medial aspect of the left lower leg. The base of the ulcer appeared erythematous with granulation tissue (Figure 2). Laboratory evaluation revealed the following: leukocyte count $2.7 \times 10^3/\mu\text{L}$, hemoglobin 10.7 g/L, and platelets $183 \times 10^3/\mu\text{L}$; chemistry values on liver function test were within normal limits. Wound cultures detected *Pseudomonas aeruginosa*, *Serratia marcescens*, methicillin-resistant *Staphylococcus aureus*, and *Streptococcus agalactiae* with no evident growth of mycobacterium. Antinuclear antibody testing was insignificant, and erythrocyte sedimentation rate was 9. Hepatitis C viral load and genotype analysis revealed genotype 1A with polymerase chain reaction (PCR) showing highly elevated viral counts of 9,506,048. Blood testing was also positive for cryoglobulinemia. Biopsy specimens from the active border of the ulcer revealed acanthotic epidermis with superficial and deep perivascular lymphoplasmacytic dermatitis admixed with mild

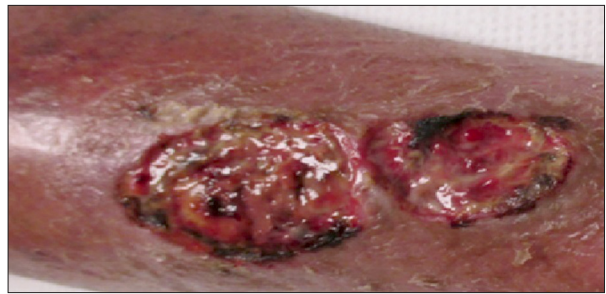


Figure 1. Ulcer with red granular moist tissue, with yellowish necrotic tissue at the wound bed with surrounding erythema.



Figure 2. Full thickness ulcer with red nongranular base and fibrinous tissue over the top with uneven borders.

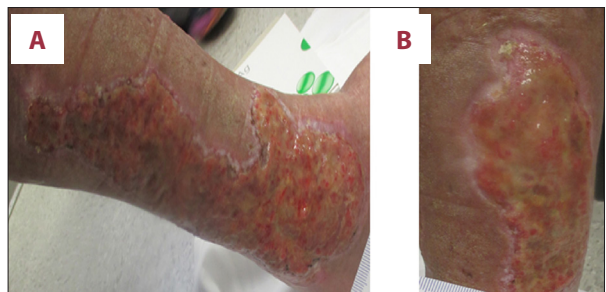


Figure 3. (A, B) Healing of ulcer with growth of pale and red tissue at ulcer bed, with formation of pink epithelial tissue at the borders.

neutrophilic infiltrate, with no evidence of stasis dermatitis suggestive of the early phase of PG (Figures 4–6). The patient was started on prednisone with a high suspicion of PG. Seventy-two hours after steroid therapy, he exhibited significant improvement regarding lower extremity pain and erythema, and he was subsequently discharged with a long taper of steroids and ledipasvir/sofosbuvir. At one-month follow-up at the hepatology clinic, patient demonstrated a near resolution of lower extremity ulcer with undetectable viral load (Figure 6A, 6B).

Discussion

Pyoderma gangrenosum is a very rare clinical entity with an incidence of 3 per million people per year [1]. First described by Brocq in 1916, it was believed to be a disseminated form of

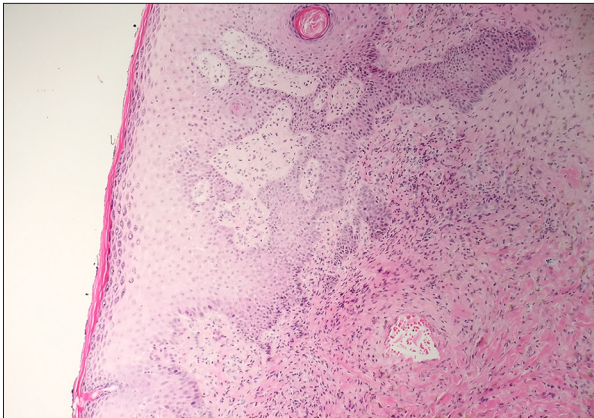


Figure 4. Low power view depicting acanthosis with lymphoplasmacytic and histiocytic infiltrate and focal hemosiderin deposition.

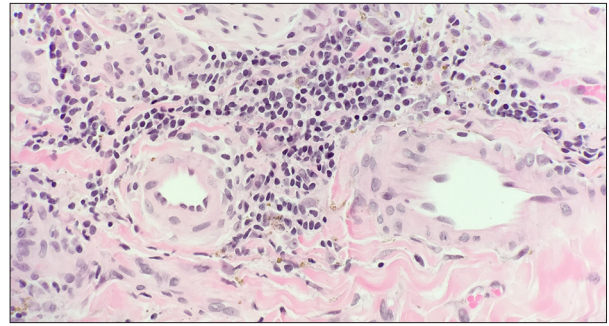
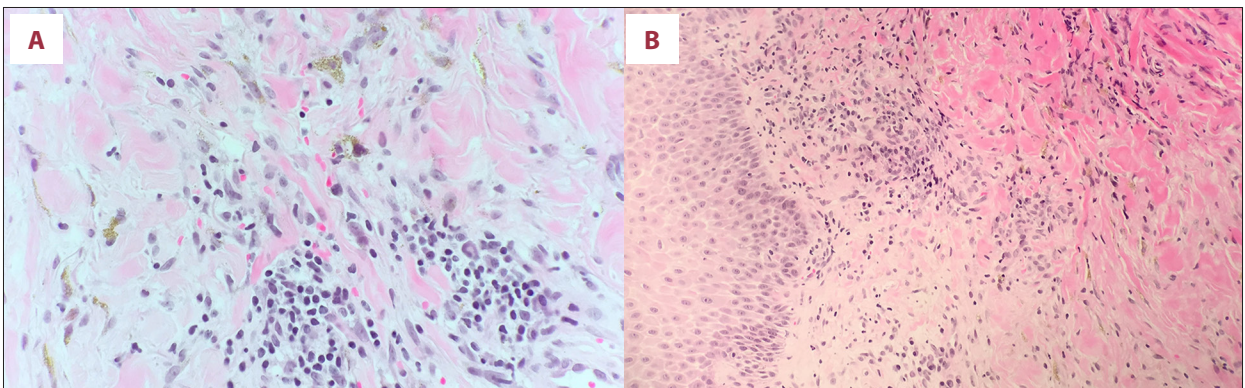


Figure 5. High power view depicting prevascular inflammation.



Figures 6. (A) High power view showing hemosiderin deposition and chronic inflammatory cells. (B) Acanthotic epidermis with superficial and deep perivascular lymphoplasmacytic dermatitis admixed with mild neutrophilic infiltrate, with no evidence of stasis dermatitis.

an infection such as bowel in ulcerative colitis or lungs in empyema [2]. While PG may manifest in individuals of any age, it most commonly occurs in young and middle-aged adults with an average age of 40-60 years and a female predominance [3,4]. The exact cause of PG is poorly understood, but abnormal neutrophil functioning, genetic variation, and innate immune system dysregulation are all considered to be part of the etiopathogenesis of PG [5,6].

The lesions of PG are progressive in nature and initially present as inflammatory papules, pustule vesicles, or nodules [1]. These lesion(s) rapidly and at times painfully advance to ulcerative erosions with tissue necrosis [7]. The ulcerations are the hallmark for the classic ulcerative form of the disease, and the ulcers have well-defined borders extending peripherally in rough, serpiginous configuration [8]. Typically the lesions involve the lower limbs, but atypical PG tends to involve the upper extremities, head, neck, and even the genital area [9].

Establishing the correct diagnosis can be a difficult task. Pyoderma gangrenosum is histologically classified as a neutrophilic dermatose and displays dermal inflammatory infiltrates of neutrophils without any evidence primary vasculitis [10]. However, the clinical and histopathological findings of PG are nonspecific and can mimic a variety of conditions. For this reason other causes for cutaneous ulcerations have to be excluded, as nearly 50% of PG cases are in close association with systemic diseases. To date, more than 500 case studies of PG have been published; it is most commonly associated with inflammatory bowel disease, arthritis, and hematologic diseases. Although the association of PG and chronic liver disease is frequently reported, only a few cases of PG and HCV have been recorded in the medical literature [11].

Two proposed diagnostic criteria for PG are currently in existence, neither of which is universally accepted and validated [12,13]. While the clinical history, physical examination, and skin biopsy findings are not of individual diagnostic value, they do provide valuable information in identifying and narrowing

the differential diagnosis. The proposed criteria consist of two major criteria and two minor criteria, which must be present to help establish a correct diagnosis. One major criterion is the clinical presentation of rapid progression of a painful necrotic ulcer that increases by 50% in size in the span of a month. The other major criterion is the exclusion of relevant differential diagnoses such as arterial/venous ulcers, vasculitis, hematologic malignancies, and so forth. The minor criteria includes history of suggestive of minor trauma, systemic disease associated with PG, histopathological; sterile dermal neutrophilia, and/or clinical improvement with systemic glucocorticoid treatment. Additional laboratory testing should also be considered once there is a clinical suspicion of PG in an effort to evaluate for underlying causative disorders.

However, due to the lack of a definitive test, PG is a commonly missed diagnosis. Two of the most common mistaken diagnoses are antiphospholipid-antibody syndrome and venous stasis ulcers [14]. For this reason, it is vital to reexamine a diagnosis if patients fail to respond to therapy as failure to do so can lead to long-term complications such as pain, scarring, and prolonged immunosuppressive therapy. Unfortunately our patient's wound worsened following surgical debridement through a phenomenon called pathergy. Abnormal Gram stain and culture findings further obscured our judgment, leading us to treat the patient with antibiotic therapy for presumptive complicated cellulitis. It was not until the failure of antibiotic treatment that we considered PG as the possible disease process.

It is essential to exclude other etiologies of cutaneous ulceration before initiating treatment for PG. The hallmark of PG therapy is addressing both disease components: the systemic inflammatory component and the wound component. This can be achieved through a combination of local wound care and topical and/or systemic therapy.

Wound care should include appropriate dressing; prior to each dressing change, wounds should be washed with saline [7]. Absorptive dressing such as hydrocolloid is an effective way to manage purulent and exudative lesions, while nonpurulent lesions may require moisture-retentive dressings [15]. Wound care must also include monitoring for signs of infection including skin warmth, edema, erythema and lymphangitic streaking, foul odor, increased drainage, and pain.

The choice of appropriate modality of therapy depends initially on the number, size, and extension of the lesions and then on the patient's response to therapy.

For small and slowly progressive lesions, topical therapy is the first line of treatment. There is general agreement that cornerstones of topical treatment include topical corticosteroids and

topical tacrolimus [16]. Investigators recommend the use of topical agents specifically at the inflamed border of the ulcer and not within the ulcer base. A few case reports describe the use of intralesional corticosteroids with success [17]; however this modality should be used with extreme caution as excessive injections or a high concentration of corticosteroid can lead to pathergy and delay wound healing.

Large and rapidly progressive lesions and small lesions resistant to local treatment require a different approach; systemic therapy is preferred as the first line of treatment. The choice of agent requires consideration of the underlying disease and the possible side effects. Systemic steroids are considered the treatment of choice [18]. Cyclosporine is an alternative first-line agent that is beneficial in patients who can't tolerate steroids or who fail to respond to steroids. Case reports and small case series describe success with using antineutrophilic agents such as dapsone as monotherapy or adjunctive treatment with steroids [15].

In patients with severe PG who fail to respond to conventional therapy, intravenous immune globulin and alkylating agents are the preferred option [19, 20]. However, it is important to keep in mind the high cost burden of intravenous immune globulin and the adverse side effects of alkylating agents.

Infliximab is emerging as an effective therapy in PG and is the only biologic agent that has shown efficacy in a randomized, double-blind, controlled trial [21]. Given its efficacy in Crohn's disease, infliximab may be particularly useful in the population of patients with PG who also suffer from refractory Crohn's disease.

The role of surgical treatment in PG is controversial, as 25–50% of PG lesions demonstrate pathergy and theoretically could worsen with surgical intervention [22] Pichler et al. reported a multicenter case series of 15 patients with PG who were treated successfully with surgery under adequate immunosuppression, with split thickness skin graft secured by negative pressure wound therapy [23].

In general, surgical intervention should be considered on a case-by-case basis and should never be used as a sole treatment for PG.

Conclusions

Pyoderma gangrenosum is an inflammatory process of unknown etiology. It is considered a diagnosis of exclusion, and the greatest challenge lies in the clinician's ability to rule out other causes of necrotic ulcerations. Pyoderma gangrenosum is very commonly mistaken for an infection, and such misdiagnosis

can lead to a delay in treatment or even severe complications. For this reason, it is prudent for clinicians to consider PG in their differential diagnosis, especially in the setting of a non-healing surgical wound or skin infection.

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Statement

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