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Improvement of Ulcerations in Treatment-Resistant Chronic Scarring in a Patient with Pyoderma Gangrenosum After Improving Vascular Insufficiency, Gently Removing Necrotic Debris, and Decreasing Wound Fluid

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Conflict of interest: None declared

Patient: Male, 44
Final Diagnosis: Pyoderma gangrenosum
Symptoms: Pain • ulceration • scarring • exudate • necrosis
Medication: Clobetasol 0.5% ointment • Cadexomer iodine • Pentoxifylline
Clinical Procedure: Compression stocking application • leg elevation at night
Specialty: Family Medicine

Objective: Rare disease

Background: Classical pyoderma gangrenosum is a rare, inflammatory, neutrophilic dermatosis that commonly presents with severe ulcerations on the lower extremities and is often misdiagnosed and mistreated. Delay in treatments can lead to worsening of the ulcerations and allows for multiple comorbid factors. Pyoderma gangrenosum is most commonly treated with immunosuppressants or anti-inflammatory agents and is often worsened by surgical procedures due to the presence of pathergy. In acute cases, a course of anti-inflammatory treatments works well in alleviating symptoms and reducing ulcerations and residual scarring. However, in chronic cases with the presence of severe scarring and necrotic ulcerations, the simple implementation of systemic immunosuppressants is frequently ineffective alone. Although not mentioned in most case reports on pyoderma gangrenosum, the chronicity of its inflammatory component can lead to necrosis and scarring and subsequent vascular insufficiency.

Case Report: We present a severe case of chronic ulcerative pyoderma gangrenosum in a patient who had treatment-resistant ulcerations and cribriform edematous scarring with subsequent vascular insufficiency of the right lower extremity. This patient, while receiving topical clobetasol, had marked improvement in the healing of his ulcerations only after starting a novel course of cadexomer iodine, compression stockings, and pentoxifylline.

Conclusions: The efficacy of non-anti-inflammatory treatments indicates that chronic pyoderma gangrenosum with extensive scarring is commonly associated with the comorbid factors of vascular insufficiency, necrotic debris, and extensive wound fluid. In cases of ulcerations in chronic pyoderma gangrenosum that are resistant to anti-inflammatory treatments alone, one should identify and address other compounding factors that may inhibit wound healing.

MeSH Keywords: Cicatrix • Clobetasol • Iodine Compounds • Pentoxifylline • Pyoderma Gangrenosum • Venous Insufficiency

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Background

Pyoderma gangrenosum (PG) is classified into distinct variants such as ulcerative (the most prevalent), pustular, bullous, and vegetative [1–4]. Ulcerative PG is characterized by neutrophilic inflammation that results in ulcerations with necrosis [5]. The true etiology of the disease is still unknown, and PG has an occurrence rate of about 3 in 1 million [3]. Since there are no specific diagnostic criteria, PG is often misdiagnosed [6]. The delay in both diagnosis and treatment can lead to extensive scarring [7,8]. Many of the cases involving PG express comorbidity with other diseases like inflammatory bowel disease, malignancies, paraproteinemia, and arthritis [1,5,7,8].

We introduced a prolonged case of PG in a male whose right lower extremity (RLE) presented with painful ulcerations, scarring, ulcer drainage, necrosis, and edema. Early in his course of treatments, he reported that systemic anti-inflammatory agents improved his condition. As his case became more chronic, these same anti-inflammatory agents alone were unable to ameliorate his condition. During the chronic phase of his PG ulceration, systemic treatments to reduce inflammation showed minimal to no effect. A marked improvement in the healing of the patient's ulceration occurred only after employing treatments that improved vascular capacity, ulcer fluid removal, and necrotic tissue debridement with immunosuppression.

Case Report

A 44-year-old man with a history of ulcerative colitis came to our clinic with a 22-year history of non-healing necrotic ulcerations of the RLE. The ulcerations were preceded by the formation of inflammatory papules or pustules. The patient reported that while he was living in China, he had multiple surgical debridements that worsened his ulcerations. He stated that he took bouts of cyclosporine, prednisone, and methotrexate that initially helped his ulcerations. As his case became more chronic over several years, none of the aforementioned immunosuppressants drastically decreased the size of his ulcerations. After coming to the United States, he stated that he was diagnosed with pyoderma gangrenosum at a major academic center in Los Angeles and was scheduled to receive rituximab. However, due to a job relocation to San Diego and health insurance change, he was unable to receive rituximab.

On examination at our clinic, his entire RLE was covered with boggy edema, nodular scarring, and 3 large, painful ulcerations that each had mild peripheral erythema (Figures 1A, 2A). The ulcer bases had drainage and fibrinous, necrotic debris. The edges of the ulcers were very steep, and in some cases undermined. He also had no palpable pedal pulses of the RLE.

Initial labs, including antinuclear antibodies, antineutrophil cytoplasmic autoantibodies, rheumatoid factor, panel for hepatitis B and C, and syphilis, were within normal limits. Tissue cultures from the ulcerations showed no presence of infection. Multiple wedge excision biopsies encompassing the ulcer base, edge, and non-affected skin were performed. A pathology report from an ulcer edge on the medial side of the RLE showed chronic scarring with ulceration, lobular proliferation of blood vessels with intervening spindled cells and thickened collagen fibers, and acute and chronic inflammation. He had no known drug allergies.

The patient also indicated to us that he did not want to go on the aforementioned systemic agents, as they did not dramatically change his condition and he was afraid of their adverse effects. Over a 6-month treatment course, the patient used a combination of topical clobetasol (0.5%) ointment application to the ulcers, leg elevation when sleeping, wearing compression stockings (15–20 mm Hg), applying topical cadexomer iodine (CI) to his ulcers, and taking pentoxifylline 800 mg 3 times a day. To reduce inflammation, the patient applied topical clobetasol to the edges of the ulcers daily under a non-adherent pad and compression stocking. In a similar fashion, CI was applied to the central bases of the ulcers daily and washed out after 8 h. In sites where the necrotic debris had been mostly removed, daily applications of the clobetasol ointment were applied into the bases and at the edges of the ulcers. If the ulcers reverted to a more necrotic debris-filled state, the patient switched to the course combining daily applications of CI centrally and clobetasol peripherally. During this course, the patient's ulcers exhibited increased wound healing, decreased debris, and reduced pain, which resulted in the closure of 2 of the 3 ulcers, and a dramatic reduction in size of the third ulcer (Figures 1B, 2B).

Discussion

Due to the absence of conclusive histopathologic criteria, PG is usually diagnosed after ruling out other causes of ulcers such as infection, vasculitis, or malignancy [4]. In many cases of PG, numerous misdiagnoses of this disease occur [2,4,7,9]. However, recent publications have suggested that PG should have diagnostic criteria that is based on clinical course, history and visual presentation, pathology, and pattern of improvement [5, 6]. Our case has met the diagnostic criteria of PG as suggested by Maverakis et al. [5]. Our patient had no evidence of infection in cultures or pathology. Moreover, there was a history of pathergy with surgical debridement. The patient also has a history of inflammatory bowel disease-ulcerative colitis. In addition, he reported a history of inflammatory pustules and papules preceding the onset of the ulceration of the lower extremity. His ulcer edges had erythema, tenderness/pain, and

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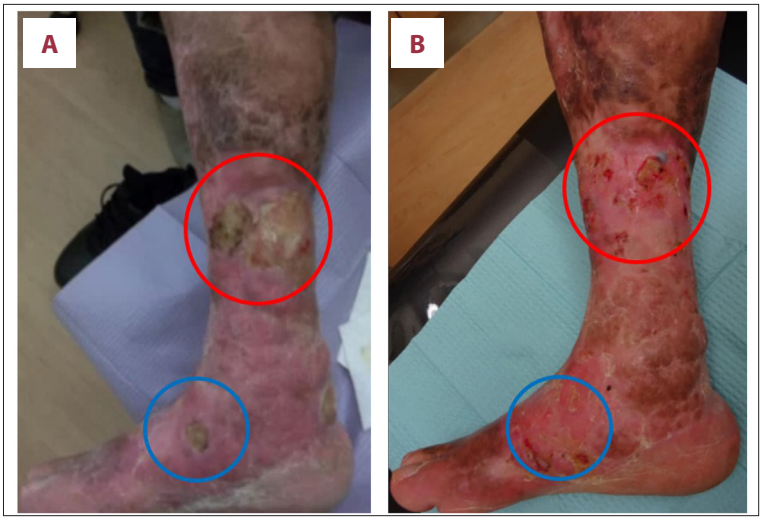

Figure 1. View of medial aspect of RLE with edematous scarring before and after treatments with cadexomer iodine, clobetasol ointment, compression stockings, and pentoxifylline. (**A**) *Before treatments:* There is edematous scarring and a steep-edged ulcer on the medial middle aspect, which measured 13.5 cm by 7.3 cm (red circle). There is another ulcer on the medial superior aspect of the right foot measuring 3.3 cm by 2.2 cm (blue circle). (**B**). *After treatments (6 months*): There is partial closure of the ulcer on the medial middle aspect of the RLE, measuring 2.3 cm by 1.6 cm (red circle). The ulcer on the medial superior aspect of the right foot closed completely (blue circle).

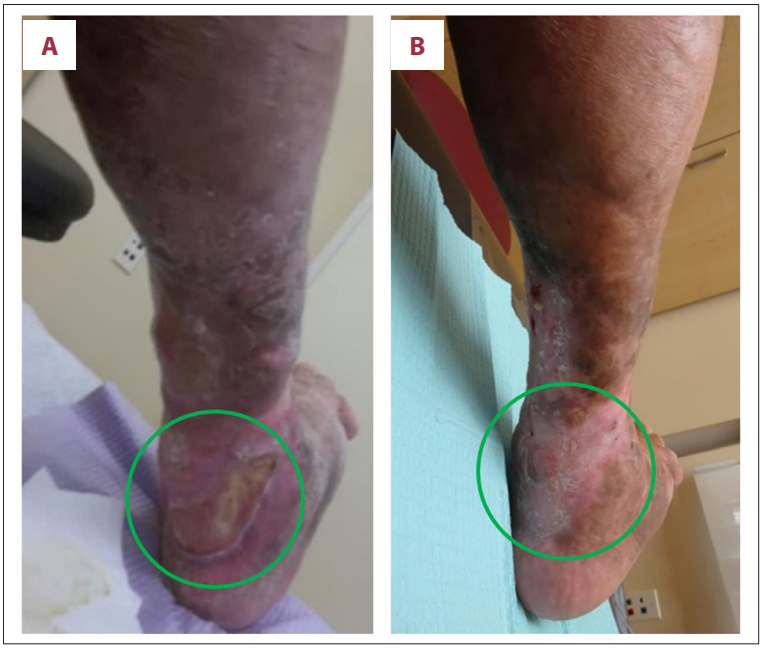

Figure 2. Posterior view of RLE before and after treatments. (**A**) *Before treatments:* There is a large ulcer with necrotic debris measuring 6.8 cm by 4.3 cm (green circle) covering the Achilles area and extending to the lateral superior ankle area. (**B**) *After treatments (6 months):* There is a complete closure of the ulceration of the Achilles and lateral superior ankle areas (green circle).

undermining. He presented with 3 ulcerations on the lower leg. At sites of healing, there was cribriform appearance and there was a history of improvement of ulcerations with immunosuppressive mediations. Finally, pathology demonstrated an inflammatory infiltrate.

There is no definitive standard of treatment for PG due to its rarity and lack of data; however, the main goal when dealing with any case of PG in the literature is to reduce the neutrophilic inflammation leading to ulcerations [7,10,11]. A common way to reduce inflammation was to use systemic anti-inflammatory drugs such as prednisone, cyclosporine, dapsone, thalidomide, minocycline, doxycycline, sulfasalazine, methotrexate, and tacrolimus [9,11,12]. Recently, newer biologic agents such as ustekinumab, adalimumab, etanercept, and infliximab, which target TNF, IL-12, and IL-23, have been used in the treatment of PG [13–16]. The use of rituximab is controversial as there are cases of PG being induced by rituximab therapy [17,18]. The use of heparin has been shown to aid in PG. It is thought that increased stickiness of either the neutrophils or the vascular endothelium in PG could be aided by the use of heparin [19].

Topical steroids like clobetasol and topical immunosuppressive agents like tacrolimus can be used to effectively treat the acute inflammatory stages of ulcerations, but they have response rates drastically lower than that of systemic immunosuppressants [7,11,20,21]. Although the anti-inflammatory

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agents are effective early on in a course of PG, these agents are not entirely sufficient in treating all chronic cases of PG due to the presence of necrotic debris and vascular insufficiency. As a result, these prolonged cases of ulcerative PG require a different approach to treatment.

In this case, the patient had major chronic tissue scarring, considerable boggy swelling with wound drainage, and a lack of pedal pulses, which either indicated arterial compromise or severe edema. Years of inflammatory attacks and subsequent scarring were also responsible for the patient's poor venous response. Although the patient's condition did not improve with previous use of systemic agents, all cases of PG that have dysregulation and abnormal recruitment of neutrophils should have some anti-inflammation or neutrophilic suppression treatment. Due to the patient's current disinclination towards systemic anti-inflammatory agents, we opted to use topical clobetasol (0.05%) ointment to reduce inflammation in the ulcerations. Clobetasol ointment was chosen because it is a class 1 steroid, and the ointment vehicle, in comparison to other vehicles, has the greatest ability for local steroid penetration.

Surgical treatments such as surgical debridement or grafting have been controversial due to the occurrence of pathergy, which can worsen the ulcers caused by PG [7,15,22]. In our patient, multiple prior surgical debridements may have exacerbated his ulcerations. Because our patient's ulcerations were resistant to treatment, in part due to venous insufficiency and a poor wound healing state, removing debris from his ulcers in a non-traumatic fashion was paramount. For healing to occur in chronic wounds, the cellular milieu must resemble that of an acute wound [23]. Necrotic, non-viable tissue promotes a non-healing wound environment and therefore must be removed [24]. To prevent the wound environment of chronic ulcers from reverting to an unhealthy state, repeated non-traumatic debridement must be performed to allow the ulcers to heal [25]. We therefore decided to use CI due its ability to act as an antimicrobial, wound fluid removal, and desloughing agent. CI consists of polysaccharide beads that release iodine in a non-toxic fashion and absorb exudative wound fluid, necrotic debris, and bacteria [26,27]. Constant daily applications and removal of CI from the ulcers allow for this non-pathergy-inducing type of maintenance debridement.

With the continuous trauma and inflammation of chronic PG, eventual venous and arterial insufficiency is bound to occur in this condition. This state is corroborated by the absence of pedal pulses and the presence of edema and wound drainage. Pentoxifylline was used to help with the vascular insufficiency of ulcerations. which reduces blood viscosity and decreases platelet aggregation by effecting the shape deformation in erythrocytes [28]. Pentoxifylline at 800 mg 3 times a day, compression therapy, and leg elevation while sleeping was shown to aid in the healing of venous ulcerations [29,30]. For our patient, the pressure of the compression stocking was kept at 15–20 mm Hg as we were unsure of how much arterial insufficiency was present. Using a higher-pressure compression stocking could have led to arterial complications. In addition, the act of leg elevation while sleeping was an additional aid alleviate the venous insufficiency [31].

PG is a neutrophilic dermatosis. Neutrophilic dermatoses are characterized by neutrophilic infiltration of the epidermis and dermis of the skin. They also include Sweet's syndrome, Sneddon-Wilkinson disease, erythema elevatum diutinum, and neutrophilic eccrine hidradenitis [14,32]. Systemic manifestations such as ulcerative colitis, Crohn's disease, rheumatoid arthritis, and other inflammatory conditions could be related to the inflammatory storm of interleukins and other inflammatory mediators, of which neutrophilic dermatoses such as PG may be a part [22,33]. Unlike other neutrophilic dermatoses, PG has inflammation that leads to scarring. For example, although Sweet's syndrome has cutaneous lesions with neutrophils, it does not lead to scarring. Repeated induction of scarring with the ulceration and chronic tissue damage in the lower extremities eventually leads to compromise of the check valves that are present throughout the venous system. Since these microvalves are made incompetent, the venous system becomes compromised. The venous oncotic pressure subsequently leads to lower-extremity edema. This edema with accumulation of excessive ulcer fluid has deleterious effects on the state of wound healing. There are as of yet unknown macromolecules in the edema and ulcer fluid that lead to the compromised healing state. It is thought that these macromolecules trap growth factors and matrix materials, which then become unavailable for wound repair and promotion of skin tissue integrity [34].

This combination of therapies improving vascular capacity and wound debridement provided optimal results that led to an improvement in the "edge effect" of the ulcerations. The edge effect refers to the sharp, dramatic, cliff-like edges seen with ulcerations that are unable to heal [35]. The edges of each ulcer during the treatment course went from a steep to a more tapered appearance. The appearance of the edge is a primary indicator of the capacity of the ulcer to heal. Thus, the improvement in the edge effect and the decrease in the sizes of the ulcerations with the discussed treatments demonstrate that profound vascular insufficiency can occur in chronic cases of PG.

Conclusions

Acute ulcerations with PG arise from dysregulation of the inflammatory response. Necrotic ulcerations with scarring, as seen in our chronic case of PG, can be compounded by both

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venous and arterial insufficiency. As such, the chronic ulcers seen in chronic cases of PG should be treated in a distinct fashion from acute ulcers. In addition to anti-inflammatory treatments, chronic ulcerative cases of PG should be evaluated for other comorbid wound healing factors and those factors should be addressed for optimal healing.

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