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Recurrent bilateral lower leg ulcers in an adult patient: A case report

Samuel B. Reynolds, Blake Shaffer, Hina A. Sheikh, Stacey J. Smith

ABSTRACT

Introduction: Adult patients presenting with necrotic leg ulcers at times are often diagnosed and managed for having an infection, which results in unnecessary courses of antibiotics. Early identification and management of pyoderma gangrenosum (PG), consisting, respectively, of a single biopsy with subsequent histopathology and administration of systemic steroids, leads to effective treatment and exploration into its associated conditions. Case Report: A case of a 58-year-old female presented with a 13-year history of recurrent lower leg ulcers, occurring on either leg and always provoked by minor trauma, which were repeatedly diagnosed and managed as products of bacterial infection. Collaboration with dermatopathology, however, ultimately revealed PG, a disorder of autoimmunity, to be the most likely source of her chronic condition. Conclusion: Overall, our case exemplifies how maintaining a broad differential and considering all etiologies for necrotic leg ulcers, outside of infection alone, can lead to both more effective management and to the potential discovery of previously undiagnosed autoimmune disease.

Keywords: Gangrenosum, Pathergy, Pyoderma, Ulcer

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Received: 03 May 2016
Accepted: 22 June 2016
Published: 03 August 2016

How to cite this article

Reynolds SB, Shaffer B, Sheikh HA, Smith SJ. Recurrent bilateral lower leg ulcers in an adult patient: A case report. J Case Rep Images Med 2016;2:73–77.

Article ID: 100024Z09SR2016

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doi:10.5348/Z09-2016-24-CR-17

INTRODUCTION

Pyoderma gangrenosum (PG) is a rare ulcerating skin disease, classically presenting as a deep and painful ulcer(s) on one or both of the legs with an undermined edge and surrounding indurated, erythematous skin. Systemic symptoms may also be present, including arthralgia, fever, malaise and myalgia. Pathergy, or localization of ulcerative sites to areas that have undergone surgery, minor trauma, or venipuncture occurs in a minority of cases (25%), meaning that even surgical intervention, such as biopsy or debridement, will likely worsen the disease [1]. Pyoderma gangrenosum is often seen in patients with inflammatory bowel disease, arthritis and hematologic malignancies such as leukemia. Regarding treatment, immunosuppression is generally the first step, with cyclosporine or corticosteroids being the most commonly-used initial therapies. Follow-up should include careful observation for resolution of the

ulcer(s), and appropriate management for any underlying autoimmune disease process [2]. In the end, despite the best efforts of clinicians, the diagnosis of PG is not always clear, making it vital for providers to maintain an open differential so as not to overlook atypical presentations of this dermatological disease.

CASE REPORT

A 58-year-old female was admitted to the hospital with chief complaints of an expanding ulcerative lesion on her left lower leg that had been present for approximately one week since working in her garden. Additionally, a similar, but non-ruptured, nodular lesion on her right lower leg was present on admission. The ulcerative lesion measured 8 cm in length by 4 cm in width and was present on the posterior and medial aspect of the left lower leg (Figure 1A–B). The nodular lesion was 7 cm in length by 4 cm in width by 1.5 cm in height and was present along the tibial shaft of the right distal leg (Figure 2A–B). The nodule appeared to be tense and fluid filled. Patient was started on vancomycin for a suspected cellulitis.

Initial MRI of the left lower leg (Figure 1A–B) revealed multifocal sites of myositis and small associated subcutaneous abscesses lateral to the level of the midshaft of the tibia, with no osteomyelitis appreciated. Subsequent wound culture revealed predominant MSSA (Methicillin-sensitive *Staphylococcus aureus*), which raised clinical suspicion for cellulitis with myofascial involvement and prompted the start of appropriate antibiotic coverage. When the antibiotics failed and provided no improvement, a wedge biopsy was sent to dermatopathology for workup of a potential non-infectious etiology. In the meantime, more information was gathered from the patient and discovered a much more extensive dermatologic history.

Review of past medical history found that she had been hospitalized in 2002, 2007, and in 2013 for similar lesions that would first appear as dark and pus-filled lesions that would rupture, and ulcerate. Often the lesions would envelop her lower legs, always below the knees. Interestingly, these nodules presented after minor trauma, such as an insect bite, scratching, or being pricked by a thorn (as was the case most recently while working in her garden). Patient was diagnosed with Buruli ulcers in Nairobi, Kenya in 2002. Buruli ulcers are caused by *Mycobacterium ulcerans* and are endemic to Australia and Central and Western Africa. Characteristically, they are seen in children under 15 years of age [3]. Despite not fitting the classic presentation of this infection, she was treated with surgical debridement and skin grafting, with grafts taken from her upper anterior thighs while living in Africa (physical signs of which were noted earlier in Figure 2A–B). Skin grafting was temporarily effective and the patient was hospitalized repeatedly over the next decade with the same presenting symptoms and, ultimately, the same surgical management. Given the recurrent nature of her ulcers, both in character and physical location, combined with her advanced age, it seemed unlikely that this patient's condition was secondary to infection with *Mycobacterium ulcerans*, or, more broadly, to any infection initially suspected. Reaching a new diagnosis, therefore, would be critical to this patient's clinical improvement.

Wedge biopsy taken from the left lower extremity lesion (shown earlier in Figure 1A–B) was interpreted with dermatopathology. The official report indicated a neutrophil-rich ulcerative skin lesion with numerous microabscesses present in the dermis. Also present was ulceration with adjacent epidermal thinning and undermining (low and high power images of biopsy are shown in Figure 3A–B respectively).

The biopsy was best interpreted by correlation with the clinical picture. Neutrophilic predominance in multiple skin layers is consistent with an inflammatory process. While Buruli ulcer shows ulceration, it is associated with extensive pandermal coagulative necrosis (not seen in the biopsy) making this possibility highly unlikely. This differential was further narrowed when fungal and mycobacterial cultures, specifically GMS, PAS and Fite stains, returned negative, making infection unlikely. Since the patient's wound cultures did return positive for MSSA, bacterial cellulitis was possible, however, there was no improvement despite administration of antibiotics. In the setting of chronic non-healing ulcers, prompted consideration of an underlying autoimmune process. This constellation of clinical history (recurrent bilateral lower extremity ulcers preceded by minimal inciting trauma), presenting symptoms (painful lower extremity ulcers) and findings on biopsy (neutrophilic predominance in multiple skin layers) allowed for the confirmation of pyoderma gangrenosum as this patient's underlying diagnosis.

Once diagnosed with PG, patient was placed on methylprednisolone sodium succinate, 60 mg by mouth, administered daily. This resulted in gradual healing of her left leg ulcer. Patient was discharged on steroid therapy with the goal of gradual taper as the skin lesions resolved. Images taken of her left and right lower legs at various time points throughout both her inpatient and outpatient care are shown in Figure 4.

Currently, the patient is seen regularly by wound care and is on a steroid taper, from which she has experienced no severe adverse effects. Notable laboratory findings found during continued outpatient workup include a reactive syphilis serology (clinical follow-up pending), elevations in both serum M and *Saccharomyces cerevisiae* IgG Ab, and a sigmoid polyp that was excised and determined to be a tubular adenoma (patient also has a family history significant for malignant neoplasm of the gastrointestinal tract). These findings in constellation allow us to further characterize her clinical diagnosis of pyoderma gangrenosum.

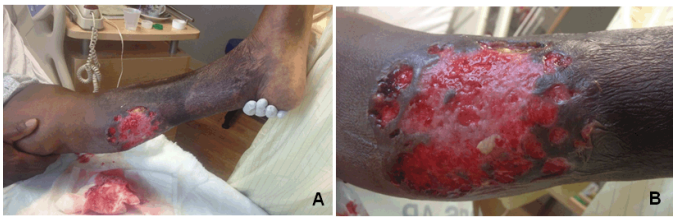

Figure 1: (A) Initial image of ulcerative lesion on patient's left leg, supported by a staff member, (B) Closer view of same lesion.

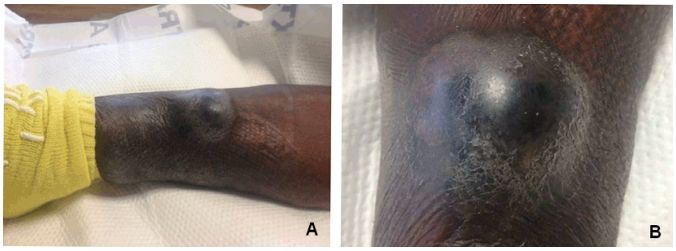

Figure 2: (A) Non-ruptured bullae on patient's right lower leg. (B) Closer, vertical image of same bullae. In both images, notes the presence of previously-implanted skin grafts.

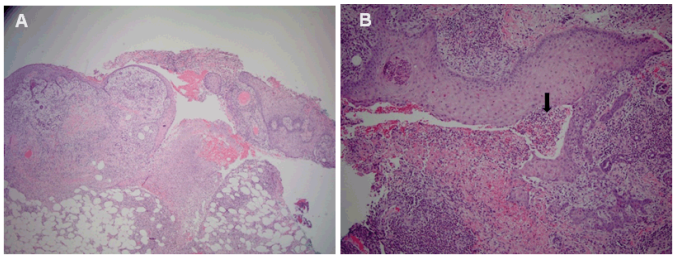

Figure 3: (A) Left lower leg wedge biopsy shown at low power; note a neutrophilic predominance in both epidermal and dermal skin layers (H&E stain, x40). (B) Higher-power image of biopsy highlighting dermal neutrophilic microabscesses (example indicated by arrow) (H&E stain, x40) (indicated by arrow).

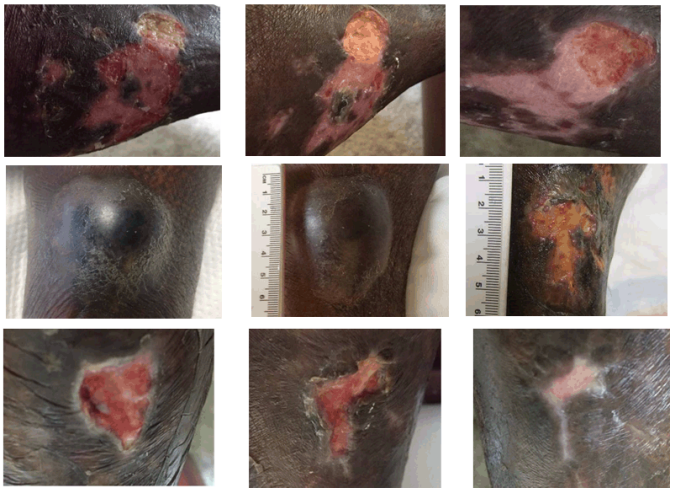

Figure 4: Sequential healing of left lower leg lesion (top six images) and right lower leg lesion (bottom six images), with time since initial administration of methylprednisolone sodium succinate 60 mg noted at the bottom of each image. Note that image positions vary, as some were taken by patient herself as an outpatient. Patient's pustule between 2 and 19 days in the bottom six images ruptured following discharge from the hospital.

DISCUSSION

Arriving at a formal diagnosis involves taking several factors into account, including clinical history, presenting symptoms/examination findings, and laboratory testing. Regarding clinical history, PG is rarely an isolated occurrence, PG occurs most often in the setting of a pre-existing autoimmune disorder, such as Crohn's disease, rheumatoid arthritis, or multiple myeloma [4]. One recent paper even reported the condition in a patient with autoimmune hepatitis [5]. The patient might also report a history of ulcerative lesions on the lower extremities that were both incited and exacerbated by minor injury, such as a mosquito bite or a rosebush thorn-prick, a process known as pathergy. Unfortunately for patients, PG lesions are often mistakenly identified as bacterial abscesses, and are subsequently incised and drained. These surgeries, while minor, involve trauma to the skin, and can worsen patients' already-disfiguring lesions. Providers therefore, should be thorough in asking if a patient suspected of having PG has ever undergone surgical instrumentation to his or her lesions, and whether or not surgery led to new or bigger lesions in the same area. Following a detailed history and physical exam, patients should undergo biopsy of their lesions. Although a relative contraindication because of the potential for PG exacerbation, the benefit of early diagnosis and management outweighs the risk of surgery. Biopsy in PG will show a neutrophil-rich lesion involving multiple skin layers, with or without the added presence of microabcesses.

The treatment of PG begins with immunosuppressive therapy, which is widely considered an effective means of symptom reduction, and should be employed to reduce ulcer growth and associated pain. What is not accepted, universally, however, is the best first-line treatment. Seeking to address this issue, researchers in 2015 published a study comparing the effects of cyclosporine and prednisolone on PG management. Using various clinical parameters, such as speed of healing, resolution of inflammation and self-reported pain, the study comparatively evaluated 112 total patients, 59 of whom received cyclosporine and 53 patients received prednisolone. Researchers ultimately found that cyclosporine and prednisolone did not produce a significant difference in clinical outcome, and that selection of initial therapy in PG would be better made based on the side effect profiles of each drug [6]. Other treatments for PG, such as interleukin-1 (IL-1) inhibitors, have also proven to have promising reduction in disease [7]. The concept behind IL-1 inhibitors is based on the autoimmune pathophysiology of genetic PG, whereby a defect affecting the NLRP3 zone of the inflammasome causes an abnormal secretion of IL-1, resulting in the classic clinical manifestations of the condition (i.e. recurrent, non-healing ulcerative lesions of the lower extremities). IL-1 inhibitors [8]. Overall, while there is no standardized treatment regimen for PG, providers should be aware of the options that do exist, and to select

therapy based on both proven efficacy and known side-effect profiles.

Returning to our patient and applying the classic presentation of PG to her case, several common features can be appreciated. Pathergy was demonstrated in this patient as she was pricked by a thorn while gardening, which produced a severe ulcerative skin reaction. Exacerbation of her condition with wound trauma is also characteristic of PG: biopsy only worsened her existing ulcer, and previous skin grafting dating back to 2002 failed as well. Additionally, the patient's location of the ulcers to her lower legs and recurrence of the disease for over a decade fit the classic presentation of PG.

Despite all of these correlations, however, the patient lacked an autoimmune condition classically seen in PG. The serologic picture was unclear in the setting of elevated CRP and ESR with a negative rheumatoid factor and ANA serologies. In light of these findings, other disease associations were considered. Pyoderma gangrenosum has been described in a patient status post treatment with lenalidomide for multiple myeloma, which ultimately produced PG on the knees bilaterally [9]. Another report from clinical and experimental dermatology reported a similar dermatologic presentation in a patient with established diagnoses of both PG and MGUS who was treated with infliximab and subsequently developed myeloma [10]. The association between monoclonal gammopathies/paraproteinemias and PG, in fact, has been well-documented in literature, largely in the form of case studies, dating as far back as the 1960s. Many of these cases, including this one, point to a key clinical phenomenon: pyoderma gangrenosum, whether or not in the setting of pre-existing monoclonal gammopathy, may be an early warning sign for the eventual development of multiple myeloma. As such, workup for systemic disease should not be limited to a few autoimmune conditions, but should be expanded to include neoplastic processes, even those that have not yet manifested clinically.

CONCLUSION

This case highlights the importance of maintaining an open differential that includes Pyoderma gangrenosum (PG) in patients presenting with history and physical exam findings that do not immediately result in a clear diagnosis.

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Author Contributions

Samuel B. Reynolds – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Blake Shaffer – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Hina A. Sheikh – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Stacey J. Smith – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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