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A CASE OF PYODERMA GANGRENOSUM

Christopher T. Miller, MD

Case Report

A 60-year-old man with past medical history of hypertension, post-traumatic stress disorder, major depression, hepatic steatosis, chronic kidney disease, and untreated hepatitis C virus (genotype 1b) initially presented to the outpatient primary care clinic with a chief complaint of an extremely painful right lower extremity ulcer that had developed and grown progressively larger after mild trauma against a metal corner 4 months prior to the appointment. He admitted to picking at the granulation tissue that would develop over the ulcer. He was treating the ulcer with antibiotic ointment. On initial exam, the ulcer was about 2x2 cm, located a few inches above the ankle on the lateral right leg, and associated with some lower extremity edema. His primary care physician was concerned at the time for a venous stasis ulcer. Initial plain films of the leg were obtained, and these did not show any evidence of osteomyelitis. A lower extremity doppler ultrasound did not reveal a deep vein thrombosis that could account for the edema. He had no signs of heart failure, ascites, or volume overload otherwise. He was referred to podiatry and wound care.

The patient was assessed by podiatry about 2 weeks later. The podiatrist noted mycotic toenail infection on both feet, mild 1+ edema, and noted that the lesion had a small eschar. He also felt the wound was a venous stasis ulcer and recommended daily collagenase covering for enzymatic wound debridement.

The patient was subsequently seen over the next few weeks at wound care clinic. There, the ulcer was noted to have a bit of sloughing material which was removed with scissors each time. The wound did not clinically appear infected at any of these appointments. The patient noted worsening pain with each mechanical debridement.

The patient was seen by surgery who also initially felt the patient had a vascular ulcer. Compression wrappings and Dermagraft were employed as treatment. The patient had an ankle-brachial index calculated with ultrasound. The results of this study were normal. An arteriogram of the extremity was roughly normal. Surgery noted that with each mechanical debridement, that patient returned to clinic in more pain with more necrotic material, and the ulcer increased in size and depth with each appointment.

The possibility of pyoderma gangrenosum was eventually considered by surgery. A biopsy of the ulcer was performed, and the patient was referred to rheumatology about 7 months after initial presentation. His wound appeared significantly more edematous and inflamed after the biopsy. A tendon was found to be exposed at the wound base in rheumatology clinic. The patient was tested for vasculitis, but was negative for cryoglobulins, rheumatoid factor, and anti-neutrophil cytoplasmic antibodies (ANCA). Biopsy results were consistent

with pyoderma gangrenosum. He was started on prednisone, but the wound became foul-smelling. The patient was directly admitted to the inpatient medicine floors after a rheumatology follow-up exam and was started on antibiotics. He was seen as an inpatient by an infectious disease specialist and was diagnosed with cellulitis.

The patient was successfully treated for the cellulitis with a course of antibiotics. Dermatology was consulted and felt the biopsy results in addition to history of wound pathergy (worsening lesion with mechanical manipulation or mild trauma) was consistent with a diagnosis of pyoderma gangrenosum.

The overall concern of the medical team was that his exposed tendon would become infected and track infection to other areas of the leg. The team felt the tendon should be excised, but there was concern further debridement could lead to further wound pathergy. The consensus was that he should be sufficiently immune-suppressed before surgical therapy, then have the tendon removed before attempting possible skin graft.

The patient was continued on steroids. He was also considered for concurrent cyclosporine; however, he was deemed to not be a candidate secondary to decreased renal function. He was considered for infliximab as a second-line treatment. Incidentally, the patient had had close contact with a relative with active tuberculosis (TB) within the past 5 years, so there was concern that infliximab could precipitate reactivation of latent tuberculosis. Although he had a negative purified protein derivative (PPD) test, the patient was on corticosteroids, and the infectious disease team felt the likelihood of a false-negative in this setting was high. He was therefore started on empiric isoniazid for latent TB infection and was to begin infliximab 1 month into this treatment. He was to follow up with rheumatology and surgery. To date, his wound appears to be accumulating granulation tissue indicating recovery after a single infusion of infliximab.

Discussion

Pyoderma gangrenosum (PG) is a neutrophilic dermatosis that causes skin papules or vesicles that eventually progress to ulcerations. Lesions are usually located on the lower extremities and are often multiple in number. Ulcerations are painful (pain is usually out of proportion to exam) and generally have a purulent base with rough, violaceous border. Tendons and muscles can become exposed in the wound. Wounds can demonstrate pathergy, or wound exacerbation with mechanical manipulation.

The pathophysiology of PG is incompletely understood. A better understanding may come with further study of the inflammasome. Inflammasomes are intracellular macromolecules that sense foreign or pathologic material and cause

cellular release of “warning” mediators. Their study has led to a better understanding of a multitude of familial autoimmune diseases. One particular mutation to the proline-serine-threonine phosphatase interacting protein1 (PSTPIP1) gene has been associated with PAPA (pyogenic arthritis with pyoderma gangrenosum and acne syndrome). Mutations in PSTPIP1 are believed to cause increased interaction with the molecule pyrin. The exact signaling cascade of this interaction is not yet certain, however, the consequence appears to be increased release of the inflammatory mediator IL-1 β . Targeted therapies against IL-1 β , however, have only been reported in limited anecdotal accounts, so the PSTPIP1 mutation may cause additional consequences that are not yet known.

PG is associated with systemic disease in 50% or more of cases. (Debade et al 2011) Examples include inflammatory bowel disease (IBD), rheumatoid arthritis (RA), and acute myeloblastic leukemia (AML) or lymphoproliferative disease (PG can sometimes be a paraneoplastic disorder in these cases). It can also occur in idiopathic cases.

PG can be classified into 4 different subtypes based on clinical presentation and histopathology: ulcerative, pustular, bullous, and vegetative. Patients typically present with one subtype of PG.

Ulcerative PG is characterized clinically by ulcers with eroded borders and surrounding inflammation and histologically by centrally neutrophilic abscess and marginal lymphocytic angiocentric infiltrates. This disease subtype generally presents with progression of small papules into the aforementioned ulcerations, which can be fatal in its most severe form.

Pustular PG has clinical findings of inflammatory pustules (measuring less than 8mm) and dense neutrophilic infiltrates in perifollicular, follicular, and dermal zones on histology. It is often associated with IBD flares. This disease subtype generally manifests similarly to the ulcerative subtype, but does not progress to such a severe extent.

Bullous PG has a clinical presentation of superficial painful, sometimes inflamed bullae that can progress to ulcers. Histologically it appears as a subepidermal bulla with intraepidermal and dermal neutrophils. It often heralds a poor prognosis if associated with hematologic malignancy.

Vegetative PG is characterized by a painless single shallow ulcer with slow progression. It shows pseudoepitheliomatous hyperplasia, dermal neutrophilic abscess, sinus tracts, and palisading granulomas on histology. It is usually associated with idiopathic cases. It is generally nonaggressive.

Differential diagnoses for PG include vascular insufficiency, atypical mycobacterium, fungal infection, spider or insect bite, vasculitis, gummatous syphilis, gangrene, drug reaction, malignancy, antiphospholipid syndrome, amebiasis, halogenoderma (superficial reaction to halogen compounds), factitial disorder, and viral infection (like Herpes simplex virus).

Diagnosis is established by history and biopsy consistent with PG, and exclusion of other disorders.

Treatment for PG is generally based on case reports and expert opinion, as so few cases have been diagnosed and documented that only one double-blinded, randomized study exists to date. For the purposes of this case report, a treatment algorithm suggested in early 2011 in *Dermatologic Therapy* has been referenced as one of the most up-to-date references. The algorithm consists of both local and systemic therapy. Local therapy alone may be considered in mild cases. Local treatments include topical immunosuppressants such as corticosteroids (clobetasol) or tacrolimus. Numerous dressing types can be applied with a goal of a moist, but not overtly wet or dry lesion. Mechanical or chemical debridement is contraindicated due to pathergy. Systemic treatment, generally with corticosteroids, is first line therapy in most cases of PG. Although experts generally consider steroids the first line therapy, no randomized, double-blind trials exist to support their use. Prednisone is commonly used and is historically initiated at 1-2mg/kg. During initiation of therapy, underlying systemic disease like IBD or RA should be treated as well if uncontrolled. This can often lead to improvement in PG, although treatment specifically targeted at PG should continue, as flares of PG and systemic disease may occur independently despite coexistence in a single patient. After treatment initiation, improvement of wound pain, decrease in the violaceous appearance of the wound, and flattening of wound borders indicates healing. No new lesions should appear if the disease process is adequately controlled. At this point, steroid tapering should be considered. A steroid-sparing agent may be added if there is any recurrence.

In refractory cases of PG, diagnostic steps should be reviewed or even repeated to determine if the diagnosis of PG is correct. If diagnosis is felt to be certain, steroids should be pulsed or a second-line therapy added. The aforementioned assessment of healing and disease control remains a guidepost to determine when immunosuppressants can be tapered. Second-line treatments are numerous. Cyclosporine is one of the most widely used agents, as it is historically backed by some of the most literature amongst treatments. Infliximab, an anti-TNF immunomodulator, is the only PG treatment to date that has been examined in a randomized, double-blinded study.¹ Published in 2006 by Brooklyn et al, this 30-patient study compared infliximab to placebo and was found to be superior, even in patients without known underlying concurrent disease (although this study did not compare infliximab head-to-head with first line therapy like steroids or cyclosporine). Other second-line systemic treatments that have been described include methotrexate, azathioprine, cyclophosphamide, mycophenolate mofetil, tacrolimus, dapsone, chlorambucil, IVIG, colchicine, interferon alpha, etanercept, adalimumab, and alefacept. The use and efficacy of these therapies is largely anecdotal. Hyperbaric oxygen, skin grafting, and plasmapheresis are amongst additional tertiary therapies that have

been described and may be considered as concurrent therapy to the algorithm suggested above. Consensus expert opinion has generally advised against surgical intervention, however, when necessary, it should be postponed until sufficient immunosuppression and disease control has been established.

Conclusion

PG is a rare, painful, ulcerating skin disorder that often affects the lower extremities. The lesions can demonstrate pathergy and may be associated with an underlying systemic disease such as IBD, RA, or various hematologic disorders. Diagnosis is based on clinical history, biopsy, and exclusion. Treatment consists of local topical immunosuppressants and wound care, avoidance of debridement, and usually systemic corticosteroids. Treatment failure or relapse is treated with a second-line agent such as cyclosporine or infliximab, usually in conjunction with corticosteroids. Infliximab is the only therapy that has demonstrated efficacy in a randomized, double-blinded, placebo-controlled trial, although significant literature exists to support the use of corticosteroids, cyclosporine, and many other agents. Surgical intervention should only be considered if adequate therapy has been established by symptoms and signs of decreasing pain, decreased wound discoloration, wound margin flattening, and lack of appearance of new lesions.

Our patient in this case had a history and biopsy consistent with PG. His wound demonstrated pathergy and continued to worsen as aggressive mechanical debridement was pursued under the assumed diagnosis of venous insufficiency. When the diagnosis was established, he did not initially respond to steroids. Investigation for other systemic diseases was unfruitful. He was deemed to not be a candidate for cyclosporine due to compromised renal function, so infliximab was added instead. He appears to be responding to this combined treatment regimen.

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"Flower of Hope"

Painting by Mahmoud Gaballa, MD