# Idiopathic Pyoderma Gangrenosum a Rare Cause of Ulcerative Lesion in the Leg: A Case Report

Jovy Louie Anthony R. Vergara, MD,[1] and Jeremyjones F. Robles, MD[1,2]

**Background:** Pyoderma gangrenosum is a rare ulcerative skin disease that can present as an ulcerative skin disease with the prominence of pain. The pathogenesis may be related to disruptions in the immune pathways. Targeted therapy is lacking and current treatment is largely empirical and consists of corticosteroids and cyclosporine first line. Early recognition can improve clinical outcomes.

**Case:** This case is a 67-year-old male diabetic who was admitted for a progressive ulcerative lesion on the right leg. Arterial Doppler studies and CT angiogram of the right lower extremity were normal. Blood and deep wound cultures of the lesion showed *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*. Multiple antibiotic regimens were given with no improvement of the ulcerating lesions of the leg. Pain on the lesion remained persistent. The tissue biopsy of the lesion taken during debridement revealed that it was a pyoderma gangrenosum with dystrophic sclerosis. Oral prednisone at 1 mg/kg was added to the regimen which improved pain but the lesion did not improve. The persistence of the pain and progression to sepsis during the hospital course prompted the decision to do an above-knee amputation of the right leg. He was discharged improved.

**Conclusion:** Pyoderma gangrenosum is a rare non-infectious cause of an ulcerative lesion in the lower extremity. Diabetes is a strong risk factor for this disease. The course is prolonged with the possibility of secondary infections. Upon histopathologic confirmation, an anti-inflammatory regimen could help improve outcomes.

**Keywords**: Pyoderma gangrenosum; diabetic foot; leg ulcer; inflammation; anti-bacterial agents; amputation

## Introduction

Pyoderma gangrenosum (PG) is a rare ulcerative skin disease, first described over 80 years ago. Ulcers can occur anywhere on the body, most classically pre-tibial/calf, and often leave unpleasant cribriform scars. There are no specific serological or histological markers, and diagnosis is predominantly clinical.[1,2]

We present a case of PG as one of the considerations in patients presenting with progressive non-healing ulcerative lesions, refractory to multiple antibiotics. This record serves as a guide for the diagnosis of PG through the exclusion of other common differentials, imaging techniques, serum analysis, microbial studies, and histopathologic examination. The case report's significance is the emphasis on other possible, albeit rare causes of non-healing wounds other than diabetic foot and ulcerating lesions due to vessel damage, may it be arterial or venous in causality.

## Case Presentation

This is the case of a 67-year-old male, from Zamboanga, Philippines, presenting with a progressive, non-healing ulcerating lesion on the gastrocnemius area. The patient is a diagnosed hypertensive for 20 years under good control with Losartan + Amlodipine 100/5mg/tab once a day. He was also diagnosed with Type 2 diabetes mellitus 13 years ago with good glucose control on Sitagliptin+Metformin 50/500mg/tab twice a day.

The initial manifestation was a small papule less than 1cm in diameter with superficial erythema on his right calf. The patient reportedly scratched the lesion frequently causing further trauma until he noted a large blister in the same area. This lesion progressed to a coin-sized purulent ulcerating lesion on the medial area of the posterior right leg which caused the patient distress due to pain and the non-healing progressive ulcer (see *Figure 1*). The patient noted severe pain in the area of the lesion, described as a persisting sharp pain, moderately severe

[1] Department of Internal Medicine, Cebu Institute of Medicine – Cebu Velez General Hospital, Cebu City, Philippines
[2] Section of Endocrinology, Diabetes, and Metabolism, Department of Internal Medicine, Chong Hua Hospital, Cebu City, Philippines
Corresponding author: Jeremyjones F. Robles, MD
eMail: Doc_jer_cebu@msn.com

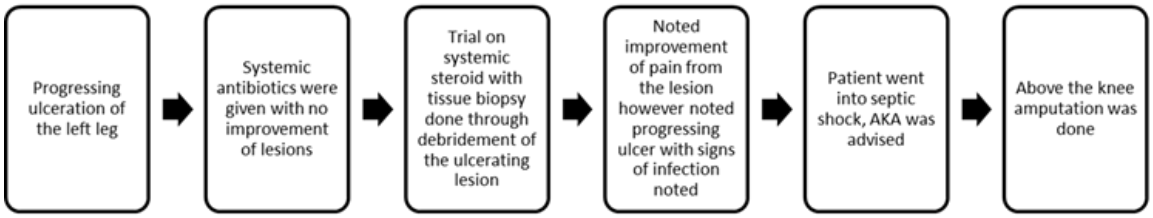


**Figure 1. Chronology of Patient Events**

**Table I. Clinical Laboratory Results of Patient Upon Admission.**

| CBC | Results | Serum | mg/dl |
|---|---|---|---|
| WBC (x10$^3$/mL) | 15.5 | Creatinine | 1.37 |
| Neu | 88.3% | Blood urea nitrogen | 23.3 |
| Lym | 7.91% | Na | 140 |
| Mono | 3.49% | K | 4.8 |
| Eos | 0.061% | SGPT | 56.9 |
| Baso | 0.283 | Albumin | 3.79 |
| Hgb | 13.9 g/L | INR | 1.04 |
| Hct | 41.2% | Uric Acid | 7.5 |
| Plt (x10$^3$/mL) | 177 | HbA1c | 5.8% |

in intensity (pain score 6-10.) The size of the ulcer continued to grow to about 10x8 cm with irregular well-defined borders, with increasing depth encroaching past the subcutaneous layer. There were no other medications taken other than unrecalled pain medications and maintenance medications. The pain persisted with the significant progression of the lesion and this prompted them to seek admission.

The patient was ambulatory but with limitation of movement due to severe pain in his right leg where the lesion is located. Vital signs showed BP=130/80mmHg, PR=75bpm, RR=24cpm, T=36.5°C, and oxygen saturation at 98% on room air. Physical examination revealed a 14x7cm purulent ulcerating lesion with necrotic, well-defined borders at the right posterior medial gastrocnemius area. Head and neck examinations were unremarkable. The chest examination was normal. He had clear breath sounds. Cardiovascular examination was also normal. Neurologic examination was only significant for the pain on the lesion but otherwise everything was within normal limits. The primary impression was an infected wound on the right calf area probably a complication of Type 2 diabetes mellitus. Admitting CBG was 123mg/dL. Baseline laboratories are presented in *Table I*.

The patient's laboratories showed leukocytosis with neutrophilic predominance, with elevated serum creatinine and decreased creatinine clearance probably

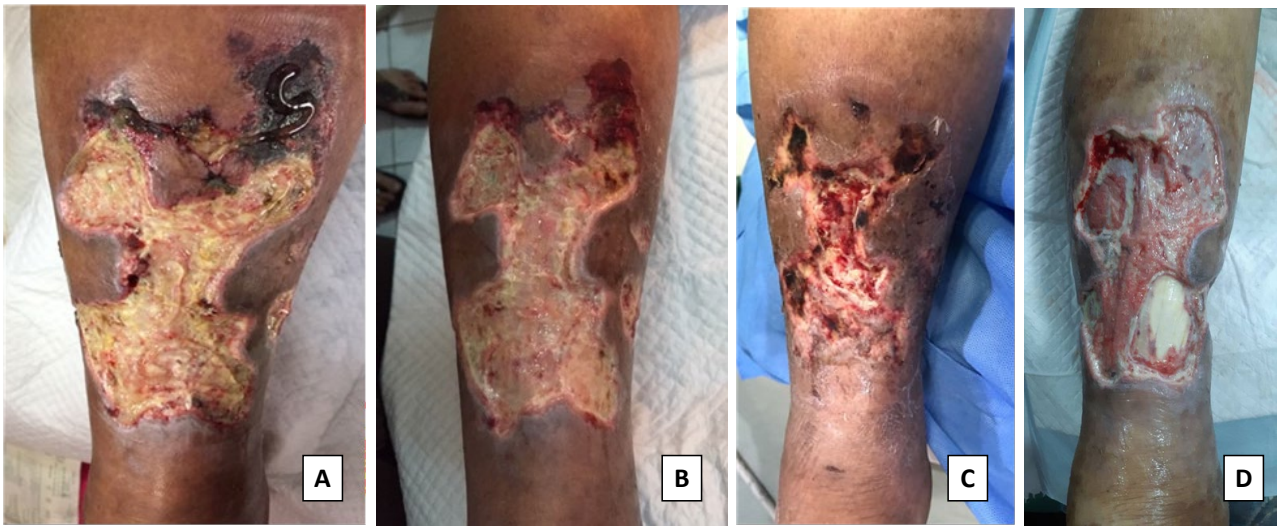


**Figure 2. A. Photo of the right posterior leg with a large ulcer and necrotic tissues on admission. B. Photo of the right posterior leg with a large ulcer status-post debridement and steroid therapy. C. Photo of the right posterior leg with a large ulcer and necrotic tissues on the second admission D. Photo of the right posterior leg with a large ulcer and necrotic tissues on second admission status post multiple debridement procedures**

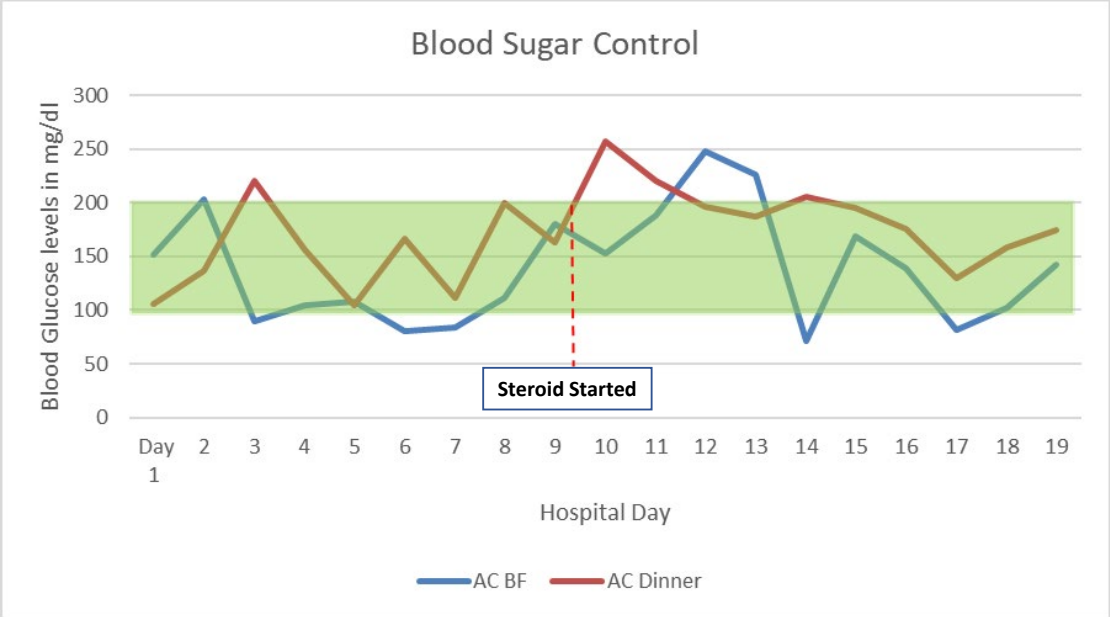


**Figure 3: Blood sugar range of the patient during the hospital course.**

secondary to long-term complications related to hypertension and diabetes. Other laboratories were unremarkable. Empirical treatment was started with IV tigecycline 50mg IV q 12h in consideration of *Staphylococcus* infection. The patient was started on febuxostat 40mg/tab once a day for the hyperuricemia and was started on pre-mixed insulin Aspart 35 units before breakfast and 25 units before dinner. Nebivolol 5mg/tab 1 tab once a day was added to Losartan + Amlodipine.

The patient underwent debridement of the lesion twice which resulted in granulation of the wound with effective removal of necrotic tissue. A tissue sample from the wound was taken for microbial culture and antimicrobial susceptibility yielded growth of *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* which were sensitive to multiple antibiotics. Patient was then started on ciprofloxacin XR 1gm/tab once a day for pseudomonal coverage. However there was still no relief of the pain with further progression of the extent of the ulceration.

Since the patient was diabetic, serial blood sugar monitoring was done. The glycemic status of the patient was controlled with premixed insulin Aspart titrated according to blood sugar levels and maintenance of Sitagliptin + Metformin 50/500mg/tab twice a day (*Figure 3*).

There was no noted visible improvement in the appearance of the wound despite antibiotics and several debridements. The lesion persisted. Subsequent wound cultures did not isolate other microorganisms.

Management was now directed to possible ischemic pathology. Arterial and venous Doppler examination of both lower extremities was normal. CT angiogram of the right lower extremity was also normal.

Histopathologic studies showed PG with medial calcific sclerosis or dystrophic calcinosis or panniculitis (*Figure 4*).

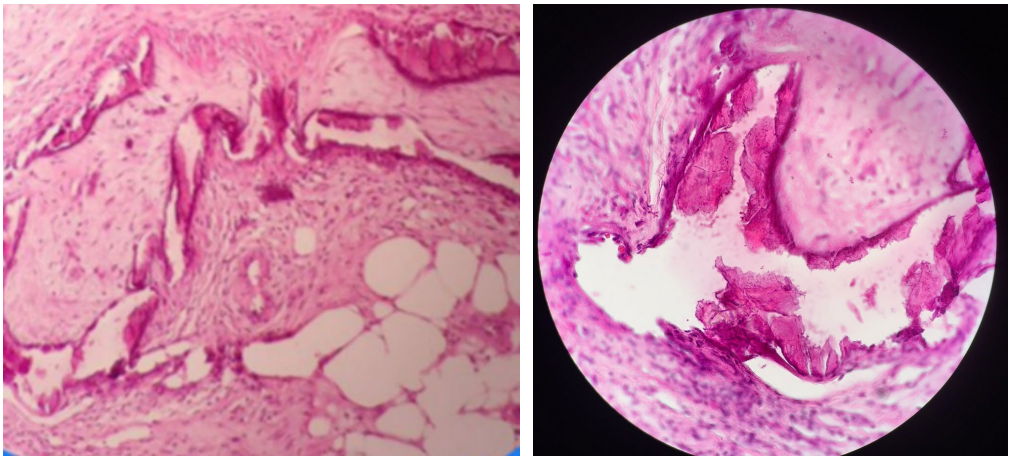

**Figure 4. Histopathologic studies shows focal epithelial ulceration with severe inflammation extending deep into the underlying tissue**

This was consistent with the clinical suspicion of the dermatologist who discussed this possibility with the gross appearance of the lesion and the pattern of the patient's presentation (failure of multiple antibiotics, no vascular anomalies seen, with good control of comorbidities).

Arterial duplex scan showed intermittent small plaques along the arteries of the lower extremities with no significant luminal narrowing. There were no localized color turbulence seen in any segment. The right and left distal posterior tibial artery flow were biphasic.

Venous duplex scan showed no evidence of acute proximal deep venous thrombosis, bilaterally. There was note of deep vein valve reflux involving the bilateral common femoral veins, left femoral vein, and left popliteal vein. Superficial vein valve reflux was also seen, involving the left great saphenous vein.

The patient was placed on systemic corticosteroids (prednisone 1mg/kg daily) with marked improvement in pain severity and cessation of progression of the lesion after four days of treatment. The patient was discharged improved with tapering of corticosteroids for 1 month. The patient did not report any intolerance or side effects relating to the medications and was fairly compliant with treatment.

However, the patient was re-admitted for recurrence of the lesion on the right leg after three months since previous discharge. He was off the prednisone for two months. A similar lesion was also noted now on the left leg, about 11 x 7cm in size similar to the presentation of the preceding lesions in the right leg, ulcerating with well-defined necrotic borders and purulent discharge (*Figure 2*). The patient was already in septic shock at this time with hypotension, tachycardia, and tachypnea noted. Cultures, both blood, and deep wound cultures were taken which revealed MDR pathogens (*K.pneumoniae* and *Morganella morganii*) which were treated with 21 days of meropenem 500mg every 12h IV and colistin IV 200mg every 24 hours. Blood glucose was still under control with the use of premixed insulin Aspart® with rapid-acting insulin analog boluses for postprandial coverage. Poor resolution of lesions, accompanied by severe pain sensation on the right leg with the occurrence of sepsis secondary to the gangrenous/necrotic lesions of the right leg resulted in above the knee amputation.

Pathologic examination of the severed right leg noted gangrene with skin ulcerations on gross examination and dystrophic calcifications and narrowing of arteries and arterioles on microscopic examination of tissues. This was consistent with PG. Signs and symptoms related to sepsis abated, with significant improvement of reported pain sensation on the right leg post-amputation. There were no new lesions reported proximal to the amputated leg. Left leg lesions did not progress upon discharge of the patient, however, was managed as an outpatient with daily wound dressings and office debridement by an orthopedic surgeon. On patient follow-up patient's overall condition was improved with good healing noted on the stump post-AKA.

## Discussion

PG is a rare and serious skin disease in which a painful nodule breaks down to form a progressive enlarging ulcer and leads to a severe and significant increase in morbidity and mortality.[3,10] The exact prevalence of PG has not been systematically reviewed and is available only for the US and Europe. In a systematic review of the incidence and prevalence of PG outside the US and Europe, a qualitative review of case reports and case series was carried out, and 2423 cases of PG were reported.[4,10] The patient was the first reported case of PG in our institution. Also, aggravating comorbid factors resulting in PG were found; in the case of Japan, PG was mostly associated with Takayasu's arteritis, and in Canada, PG is mostly seen in association with Crohn's disease and arthritis. The case however did not present with features to suspect any autoimmune disease. He is, however, a diabetic, likely Type 2. Similarly, cases from the Middle East region, South Africa and the Asia Pacific were also analyzed, with Chile and Tunisia reported to have the highest number of classical PG cases.[5,7]

In the Philippines, as of 2015, there were only two reported cases of PG, one of whom had an unknown type of PG and the other categorized as non-classical. Our case is consistent with features of classical idiopathic PG with ulcerative lesions. He is does not have systemic illnesses that have strong correlation to classic PG such as IBD, arthritis, or monoclonal gammopathies. Approximately 50% of cases of PG are associated with a systemic disease, the rest being idiopathic.[2] As mentioned, our case has the systemic disease identified as Type 2 diabetes mellitus.

Five known classes of PG are as follows, with variants often overlapping.[2]

- Ulcerative PG or classic PG, is the most common variant, presenting as described previously, and associated most commonly with other systemic illnesses such as IBD, arthritis, or monoclonal gammopathies.
- Pustular PG is a more superficial variant, mostly associated with IBD. Lesions appear as small discrete pustules surrounded by normal skin, and do not progress, remaining in the pustular stage for several months.
- Bullous PG is another superficial type, characterized by painful bullae, occurring more commonly on the upper limbs and face, and commonly associated with a hematological malignancy.
- Vegetative PG is usually a less aggressive variant, following a more indolent course with fewer symptoms, and generally responsive to milder therapies. Lesions are often solitary and do not show the violaceous undermined border or purulent base of ulcerative PG.[2,6,8]
- Peristomal PG may occur after ileostomy or colostomy in patients with IBD, probably as a result of pathergy evoked either by the initial surgical procedure itself or

by subsequent irritation of the skin by stoma apparatus or leakage of feces.[2]

PG is a "diagnosis of exclusion", and should be considered in any patient with non-healing ulceration, particularly in the context of associated systemic diseases.[2,9] Our patient was managed initially as a case of diabetic foot which did not respond accordingly to standard treatment, prompting further workup. There are no specific serologic markers, so diagnosis relies on clinical history and examination. Lesion biopsy should be taken to exclude other cutaneous diseases presenting similarly, importantly malignancy and vasculitic conditions which were ruled out in this case. The undetected associated systemic disease should be sought.[2]

Histopathology of PG is non-specific, but a biopsy may be necessary to exclude other causes of ulceration. The ulcer center shows inflammation throughout the dermis and subcutaneous tissue, with dense neutrophilic infiltration and accumulation of histiocytes and macrophages, leading to abscesses, matrix disintegration, and necrosis. Later, lymphocytes predominate, with dermal and epidermal infiltration, and more prominent hemorrhage, infarction, necrosis, and fibrosis. The ulcer border shows epidermal cell hyperplasia. As the lesions regress, macrophages and plasma cells invade the dermis, leading to fibrosis.[2,4]

The diagnosis of PG involves major and minor criteria to meet before a diagnosis can be made (*Table II*). Major criteria are: 1) a painful rapidly progressing cutaneous ulcer and 2) exclusion of other causes of ulceration. Minor criteria include: 1) presence of systemic diseases associated with PG 2) history suggestive of pathergy, 3) characteristic histopathological findings, and 4) response to systemic steroids or immunosuppression. Two major and at least two minor criteria must be met to make a diagnosis of PG.[11]

Treatment of PG includes systemic therapy in all cases except mild superficial localized cases. The mainstay is immunosuppression, systemic corticosteroids, and/or cyclosporin being the first line. The patient was placed on systemic corticosteroids which improved pain but did not have any effects on ulcer progression. The aggressive disease may require high doses of both. Corticosteroids are required at high doses, with pulsed therapy at suprapharmacological doses (e.g., 1g/day for 5 days) as an alternative. Prednisolone is the drug of choice and is usually started at high doses (60-120 mg) with Level B evidence. Patients exposed to these doses for a long time are at risk of steroid-related side effects. Hyperbaric oxygen therapy is reportedly helpful, even in refractory cases, and may permit the reduction of medication doses.[2]

**Table II. Diagnostic Criteria of Pyoderma Gangrenosum (Two major and at least two minor criteria)**

| Major criteria: | Minor criteria: |
|---|---|
| • A painful rapidly progressing cutaneous ulcer;<br>• Exclusion of other causes of ulceration. | • Presence of systemic diseases associated with PG;<br>• History suggestive of pathergy;<br>• Characteristic histopathological findings;<br>• Response to systemic steroids or immunosuppresion |

A randomized clinical trial that compared the two most commonly used treatments for PG showed a response to prednisolone or cyclosporine in the short term, but neither treatment is especially effective when healing at six months is considered.[5] This was also seen in our case wherein ulcerations progressed despite systemic corticosteroids being used with multiple broad-spectrum antibiotics to address an infection.

The recent therapies that may be recommended which are safe and effective for steroid-induced hyperglycemia include DPP-4 inhibitors, metformin, and weight-based NPH insulin. There is good prognosis for patients with transient elevations of blood sugars secondary to steroid therapy with blood glucose reverting to normal after steroids are discontinued.[12] In this case, steroid therapy on top of diagnosed diabetes mellitus complicated treatment strategies and could increase the risks of diabetes-related complication

## Conclusion

PG must be considered in any patient with enlarging, sterile, necrotic lesions that are unresponsive to prolonged antibiotics. Inflammation is the basis of the disease process, but pathophysiological mechanisms and subsequent targeted therapies for PG with more robust studies are yet to be elucidated. The case may present with features that could otherwise be the more common cause of ulcerating lesions in the leg, such as diabetic foot or arterial or venous disease, but may also not be the case in rare instances and other conditions such as PG must be considered in response to standard treatment of common causes showing poor response. Treatment should focus on both the diagnosis and management of an underlying systemic disease with a multidisciplinary approach to wound care and prevention of secondary infection. The recent development of validated diagnostic criteria and the availability of biologic agents will optimize diagnosis and treatment options for severe and refractory PG.

## References

1 Brooklyn, T., Dunnill, G., & Probert, C. (2006). Diagnosis and treatment of pyoderma gangrenosum. *Bmj,333*(7560), 181-184.
2 Teagle, A., & Hargest, R. (2014). Management of pyoderma gangrenosum. *Journal of the Royal Society of Medicine,107*(6), 228-236.
3 Bhat, R. (2012). Pyoderma gangrenosum: An update. *Indian Dermatology Online Journal,3*(1), 7.

4 Brooklyn, T., Dunnill, G., & Probert, C. (2006). Diagnosis and treatment of pyoderma gangrenosum. *Bmj,333*(7560), 181-184.
5 Comparison of the two most commonly used treatments for pyoderma gangrenosum: results of the STOP GAP randomized controlled trial. (2017). *Bmj*.
6 Saffie, M. G., & Shroff, A. (2018). A Case of Pyoderma Gangrenosum Misdiagnosed as Necrotizing Infection: A Potential Diagnostic Catastrophe. *Case Reports in Infectious Diseases,2018*, 1-5.
7 Soni, A., (2015). Pyoderma Gangrenosum: A Systemic Review of the Incidence and Prevalence(2015)
8 Benzaquen, M., Monnier, J., Beaussault, Y., Rouby, F., & Berbis, P. (2017). Pyoderma gangrenosum arising during treatment of psoriasis with adalimumab: Effectiveness of ustekinumab. *Australasian Journal of Dermatology,58*(4).
9 Langan SM, Groves RW, Card TR, et al. Incidence, mortality, and disease associations of pyoderma gangrenosum in the United Kingdom: a retrospective cohort study. J Invest Dermatol. 2012;132(9):2166–2170
10 Wollina U. Pyoderma gangrenosum–a systemic disease?. Clin Dermatol. 2015;33(5):527–530
11 George, C., Deroide, F., & Rustin, M. (2019). Pyoderma gangrenosum - a guide to diagnosis and management. *Clinical Medicine, Journal of the Royal College of Physicians of London*.
12 Wallace, M. D., & Metzger, N. L. (2018). Optimizing the Treatment of Steroid-Induced Hyperglycemia. In *Annals of Pharmacotherapy*.