Combination Doxycycline and Topical Corticosteroids in the Treatment of Ulcerative Pyoderma Gangrenosum: A Case Report

Doha Mae Laurisse M. Manalo-Legas, MD, MPM-HSD, Erickah Mary Therese D. Calayag, MD and Eillen Luisa A. Chen, MD

Department of Dermatology, Philippine General Hospital, University of the Philippines Manila

ABSTRACT

Pyoderma gangrenosum (PG) is a chronic inflammatory neutrophilic dermatosis often presenting as a solitary enlarging painful ulcer with red to violaceous undermined borders. This report delves into the role of doxycycline in the treatment of PG in a 44-year-old male COVID-19 positive patient who has concomitant active tuberculosis infection and end-stage kidney disease, for which both first-line treatments (systemic corticosteroid and cyclosporine) are contraindicated. After three months on doxycycline and topical corticosteroids, there was resolution of the ulcers and no note of recurrence up to three months from completion of the treatment regimen.

Keywords: pyoderma gangrenosum, doxycycline, nonhealing ulcer, neutrophillic dermatosis

Virtual Abstract Presentation with Oral Presentation (finalist) – PGH Research Forum 2022 (Won First Place in Resident Case Report Category), October 15, 2022, University of the Philippines-Philippine General Hospital, Manila, Philippines.

Poster Presentation – EADV 31st Congress 2022, September 7-10, 2022 (Online); Regional Congress of Dermatology, October 26-28, 2022, Manila, Philippines.

eISSN 2094-9278 (Online)
Published: September 30, 2024
https://doi.org/10.47895/amp.v58i17.7462

Corresponding author:
Doha Mae Laurisse M. Manalo-Legas, MD, MPMHSD
Department of Dermatology
Philippine General Hospital
University of the Philippines Manila
Taft Avenue, Ermita, Manila 1000, Philippines
Email: dmmanalo@up.edu.ph
ORCiD: https://orcid.org/0000-0001-9940-8695

INTRODUCTION

Pyoderma gangrenosum is an uncommon chronic inflammatory neutrophilic dermatosis commonly presenting as a solitary enlarging painful ulcer with violaceous undermined borders.[1] Diagnosis is clinical and done upon exclusion of other causes of non-healing ulcers such as chronic bacterial and deep fungal infections, vasculitis and other vascular problems, and malignancy. History of pathergy and histologic findings of dense neutrophilic infiltrate, as well as pustule and abscess formation will support this diagnosis.[2]

Treatment for pyoderma gangrenosum is mainly medical, with mild localized or unilesional forms of the disease with <5% body surface area (BSA) involvement responsive to topical/intralesional immunosuppressants like corticosteroids and calcineurin inhibitors (Level 2B Evidence). More severe disease with three or more lesions or those with more than 5% BSA involved require systemic therapy, with systemic corticosteroid and/or cyclosporine as first-line (Level 1B Evidence).[3] Despite several treatment options for pyoderma gangrenosum, its prognosis varies from case to case; some would require chronic pharmacologic treatment and some would respond to medications but would still relapse.[4] Systemic treatments for pyoderma gangrenosum, when chronic use is indicated, would require close monitoring for adverse effects.

CASE PRESENTATION

This is a case of a 44-year-old male with a six-week history of gradually enlarging ulcers on his right calf, admitted for

severe COVID-19 infection. He had Stage 5 chronic kidney disease from hypertensive kidney disease for the last eight years but was non-compliant to maintenance hemodialysis and his prescribed medications namely: calcium carbonate, calcitriol, telmisartan, spironolactone, carvedilol, atorvastatin, and enoxaparin. He had a history of cerebrovascular disease 15 years ago with left-sided residuals. Both his parents had diabetes, hypertension, and a history of stroke. He was a former occasional smoker and alcoholic beverage drinker, had been unemployed since he was diagnosed with chronic kidney disease (CKD), and lived with his daughter and her family who were his primary carers and financially supported his treatments.

During the admission, he had an incidental diagnosis of pulmonary tuberculosis infection (PTB) and was started on anti-tuberculosis medications. Patient was also diagnosed with uncontrolled diabetes further contributing to his CKD and for which hemodialysis was initiated. The non-healing wound was initially managed as a case of cellulitis with several antibiotic regimen including: ceftriaxone, clindamycin, piperacillin-tazobactam, meropenem, and levofloxacin, providing no resolution of the lesion. Wound discharge culture studies done prior to starting antibiotics revealed no growth after five days. He also underwent regular wound debridement while admitted, but in the interim, the ulcer continued increasing in size and depth, and becoming more exudative. Upon referral to dermatology, multiple well-defined irregularly-shaped tender ulcers with hyperpigmented undermined borders localized on the right leg were appreciated (Figures 1A and 2A). Punch biopsy was taken from the edge of an ulcer, which revealed dermal edema and diffuse dense infiltrate composed mostly of neutrophils, with accompanying eosinophils, histiocytes, and plasma cells, and areas of hemorrhage/extravasated erythrocytes superficial to deep dermis (Figures 3A and 3B), consistent with pyoderma gangrenosum. Tissue culture studies revealed no growth. Since patient was not cleared to receive systemic steroids, he was prescribed doxycycline 100 mg/capsule twice daily combined with halobetasol propionate 0.05% cream applied twice daily. He was discharged from the hospital after two weeks and instructed to continue with his treatments at home.

After one month on this regimen, there was significant re-epithelialization of the ulcer noted on out-patient follow up (Figures 1B and 2B). Dose was decreased to 100 mg daily for two more months, allowing the ulcer to heal completely (Figures 1C-D and 2C-D). Patient reported that he was able to take doxycycline as prescribed and his caretaker helped him with the application of halobetasol throughout the treatment course. No significant side effects (e.g., abdominal discomfort, nausea, cutaneous drug reactions, photosensitivity, diarrhea, etc.) were noted throughout the treatment and no recurrence was noted up to three months after the completion of treatment.

DISCUSSION

High-dose systemic corticosteroids (e.g. prednisone 1 mg/kg/day) is indicated in pyoderma gangrenosum. Fifty percent reduction in ulcer size is expected within one month on this regimen and is actually considered one of the minor criteria in the diagnosis of the disease. Cyclosporine is the alternative first-line medication for pyoderma gangrenosum but was also contraindicated in this case due to the concomitant renal failure.[5] If the response to corticosteroid or cyclosporine is not sufficient, other anti-inflammatory steroid sparing agents like minocycline, dapsone, mycophenolate mofetil and azathioprine are given as alternative or adjunct.[6] Although there are other cases of pyoderma gangrenosum associated with chronic renal failure

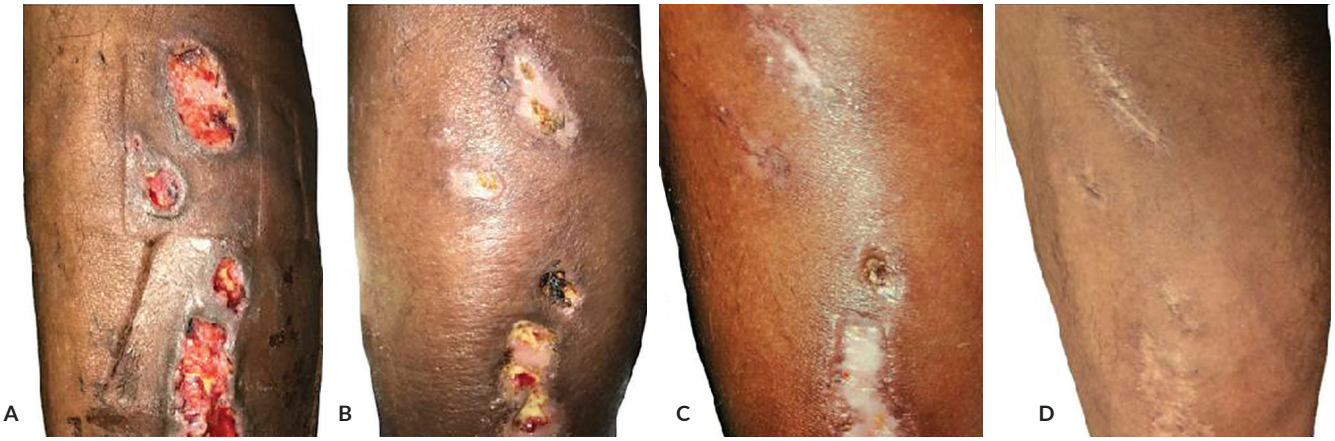

Figure 1. ***Ulcerative pyoderma gangrenosum, superior portion of the wound.*** **(A)** Baseline photo on day of dermatology referral; **(B)** Photo after one month of doxycycline 100 mg twice a day and halobetasol propionate 0.05% cream twice a day; **(C)** Photo following month 2 on doxycycline 100 mg once a day and halobetasol propionate 0.05% cream twice a day; **(D)** Photo following month 3 on doxycycline 100 mg once a day and halobetasol propionate 0.05% cream twice a day.

Figure 2. ***Ulcerative pyoderma gangrenosum, inferior portion of the wound.*** **(A)** Baseline photo on day of dermatology referral; **(B)** Photo after one month of doxycycline 100 mg twice a day and halobetasol propionate 0.05% cream twice a day; **(C)** Photo following month 2 on doxycycline 100 mg once a day and halobetasol propionate 0.05% cream twice a day; **(D)** Photo folllowing month 3 on doxycycline 100 mg once a day and halobetasol propionate 0.05% cream twice a day.

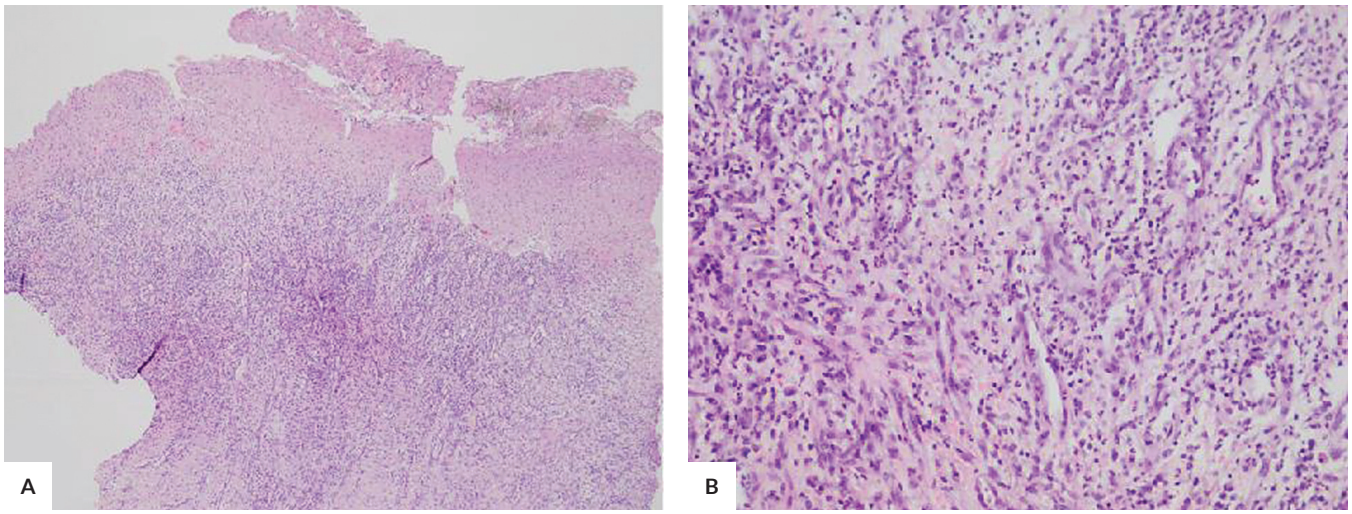

Figure 3. ***Histopathologic results, punch biopsy taken from the edge of the ulcer.*** **(A)** LPO view shows dermal edema and a dense diffuse infiltrate from the superficial to deep dermis **(B)** HPO view reveals that the dense infiltrate is composed mainly of neutrophils, with accompanying eosinophils, histiocytes, plasma cells, and extravasated erythrocytes.

reported in literature, the presence of concomitant infections posted a challenge in the management of our case.[7,8]

Tetracyclines like doxycycline have been used as a steroid-sparing agent due to its anti-inflammatory properties in certain conditions like rosacea, bullous pemphigoid, perioral dermatitis, and in granulomatous and other neutrophilic dermatoses.[9,10] Furthermore, its use in neutrophilic dermatoses like pyoderma gangrenosum can be attributed to its synergistic ability to inhibit monocyte chemoattractant protein-1 (MCP-1), one of the key chemokines responsible for neutrophil migration; and decrease pro-inflammatory cytokine interleukin-8 (IL-8), a neutrophil chemotactic factor.[11] Doxycycline is mainly excreted extrarenally, hence, is considered relatively safe to give to patients with renal failure.[9] Although minocycline is considered as an adjunctive treatment for PG, the response of PG to other tetracyclines like doxycycline as monotherapy is poorly documented in literature.[10] To the authors' knowledge, this was the only documented case of extensive ulcerative pyoderma gangrenosum in the Philippines that was managed without the use of any of the first-line

systemic treatments. Doxycycline was the alternative non-immunosuppressive treatment given in this case, which provided a rapid and dramatic response, but could have been confounded by the concomitant use of topical halobetasol.

CONCLUSION

This report suggests that the anti-inflammatory effect of doxycycline has a role in the treatment of pyoderma gangrenosum in patients with contraindications to receiving systemic steroids and cyclosporine. It is an easily accessible and affordable medication, which is relatively safe to prescribe to patients with active tuberculosis and COVID-19 infection. Clinical trials would better compare the efficacy and safety of the doxycycline and systemic steroids in patients with pyoderma gangrenosum.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

All authors declared no conflicts of interest.

Funding Source

None.

REFERENCES

1. Jourabchi N, Lazarus GS. Pyoderma Gangrenosum. In: Kang S, Amagai M, Bruckner AL, Enk AH, Margolis DJ, McMichael AJ, et al (eds). Fitzpatrick's Dermatology, 9th ed. New York: McGraw-Hill Education; 2019. pp. 605-607.
2. George C, Deroide F, Rustin M. Pyoderma gangrenosum - a guide to diagnosis and management. Clin Med (Lond). 2019 May;19(3): 224-8. doi: 10.7861/clinmedicine.19-3-224. PMID: 31092515; PMCID: PMC6542232.
3. Maronese CA, Pimentel MA, Li MM, Genovese G, Ortega-Loayza AG, Marzano AV. Pyoderma gangrenosum: An updated literature review on established and emerging pharmacological treatments. Am J Clin Dermatol. 2022 Sep;23(5):615-634. doi: 10.1007/s40257-022-00699-8. PMID: 35606650; PMCID: PMC9464730.
4. Wollina U. Pyoderma gangrenosum--a review. Orphanet J Rare Dis. 2007 Apr 15:2:19. PMID: 17433111; PMCID: PMC1857704.
5. Dissemond J, Marzano AV, Hampton PJ, Ortega-Loayza AG. Pyoderma gangrenosum: treatment options. Drugs. 2023 Sep;83(14): 1255-67. doi: 10.1007/s40265-023-01931-3. PMID: 37610614; PMCID: PMC10511384.
6. Romańska-Gocka K, Cieścińska C, Zegarska B, Schwartz RA, Cieściński J, Olszewska-Słonina D. Pyoderma gangrenosum with monoclonal IgA gammopathy and pulmonary tuberculosis. Illustrative case and review. Postepy Dermatol Alergol. 2015 Apr;32(2): 137-41. doi: 10.5114/pdia.2014.40974. PMID: 26015785; PMCID: PMC4436233.
7. Goto M, Okamoto O, Fujiwara S, Yanagi T, Komada S, Yokoyama S, et al. Vegetative pyoderma gangrenosum in chronic renal failure. Br J Dermatol. 2002 Jan;146(1):141-3. doi: 10.1046/j.1365-2133.2001.04510.x. PMID: 11841382.
8. Sangiray H, Nguyen JC, Turiansky GW, Norwood C. Pyoderma gangrenosum occurring near an arteriovenous dialysis shunt. IntJ Dermatol.
9. Sapadin AN, Fleischmajer R. Tetracyclines: nonantibiotic properties and their clinical implications. J Am Acad Dermatol. 2006 Feb;54(2):258-65. doi: 10.1016/j.jaad.2005.10.004. PMID: 16443056.
10. Vojtová V, Urbánek K. Farmakokinetika tetracyklinů a glycylcyklinů [Pharmacokinetics of tetracyclines and glycylcyclines]. Klin Mikrobiol Infekc Lek. 2009 Feb;15(1):17-21. PMID: 19399726.
11. Navarro-Triviño FJ, Pérez-López I, Ruíz-Villaverde R. Doxycycline, an antibiotic or an anti-inflammatory agent? The most common uses in dermatology. Actas Dermosifiliogr (Engl Ed). 2020 Sep;111(7): 561-6. doi: 10.1016/j.ad.2019.12.006. PMID: 32401726.