Case Report

ANNALS OF MEDICINE & SURGERY

OPEN

Ulcerative colitis and pyoderma gangrenosum refractory to treatment successfully managed with pentoxifylline: a case report

Miguel A. Jiménez-Luévano, MD, PhD[a], Ana E. Jiménez-Partida, MD[a], Miguel A. Jiménez-Partida, MD[a], Georgina Hernández-Flores, PhD[b], César R. Cerda-Cruz, MD[b], Alejandro Bravo-Cuellar, MD, PhD[b,d], María M. Villaseñor-García, PhD[b,c,*]

Introduction and importance: Pyoderma gangrenosum is an unusual inflammatory pathology, with neutrophilic dermatosis, of unknown etiology. It is associated with diseases such as bowel disease. Generally, it is treated with anti-inflammatory drugs, corticosteroids, immunosuppressants, and antibodies against tumor necrosis factor, but relapse and adverse effects are persistent. Pentoxifylline is a drug with immunoregulatory and anti-inflammatory properties.

Case presentation: A 47-year-old male with a diagnosis of ulcerative colitis initially managed favorably for 7 years with mesalazine. At 3 years of treatment, he presented a sudden ulcer that affected skin and subcutaneous tissue (13 × 10 cm) in the lower right limb. During the last 2 years, he was treated with mesalazine and infliximab with partial results and permanent relapses. Therefore, pentoxifylline was added to his treatment.

Clinical discussion: The justification for the addition of pentoxifylline is mainly its action as an inhibitor of Nuclear Factor-kappa Beta (NF-κB) transcription, which stimulates the expression of proinflammatory interleukin genes such as IL-1, IL-6, IL- 8, and TNF-α and showing immunoregulatory and antioxidant activities.

Conclusion: With pentoxifylline, this lesion healed at 6 weeks without relapses after 2 years.

Keywords: case report, pentoxifylline, pyoderma gangrenosum, treatment

Introduction

Pyoderma gangrenosum is an unusual inflammatory pathology, with neutrophilic dermatosis, of unknown etiology. It occurs mainly between the ages of 25 and 54 years and in males[1]. It has a prevalence of 3–10 cases in 100 000 inhabitants worldwide. Autoimmune factors, microbiota, and the alteration of dysbiosis play an important role[2].

Thus, it manifests itself in 70% in systemic inflammatory diseases, being mainly associated with inflammatory bowel disease, ulcerative colitis (UC) and, to a certain extent, Crohn's disease in up to 20–30% of cases, reaching under these circumstances a mortality of up to 70%[3]. It has also been related with a traumatic antecedent (pathergy) in 30% of cases, and with other pathologies of diverse origins.

This clinical entity can affect any part of the economy of the body, with the skin main organ affected (in up to 40–50% of cases). The following extracutaneous manifestations have been reported, such as in oral aphthosis and in the ulcerative involvement of the larynx, pharynx, eyes, vulva, and cervix, while other extraintestinal presentations include lungs, heart, liver, spleen, lymph nodes, and the central nervous system.

Diagnosis is based on clinical manifestations and by the exclusion of microbial and fungal infections[4]. There are several

HIGHLIGHTS

- Pyoderma gangrenosum is an unusual inflammatory pathology of unknown etiology.
- Diagnosis is based on clinical manifestations and by the exclusion of microbial and fungal infections. Currently, there is no definitive cure of this disease.
- We present a case of pyoderma which an ulcer in the lower right limb, affecting the skin and subcutaneous cellular tissue (13 × 10 cm).
- Over the past 2 years, he was treated with mesalazine and infliximab, yielding partial results and persistent relapses.
- Pentoxifylline, a drug with immunoregulatory and anti-inflammatory properties, was added to his treatment, leading to the healing of the lesion within 6 weeks, and no relapses occurred in the subsequent 2 years. These results encourage further studies.

[a]Servicio de Gastroenterología, Hospital Regional 'Dr. Valentín Gómez Farías', ISSSTE Zapopan, [b]Centro de Investigación Biomédica de Occidente, Instituto Mexicano del Seguro Social, [c]Centro Universitario de Ciencias Exactas e Ingenierías, Universidad de Guadalajara, Guadalajara and [d]Centro Universitario de los Altos, Universidad de Guadalajara, Tepatitlán de Morelos, Jalisco, México

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

*Corresponding author. Address: Centro de Investigación Biomédica de Occidente, IMSS, Sierra Mojada 800, Col. Independencia, CP 44340 Guadalajara, Jalisco, México. Tel.: +52333 809 9804. E-mail: mvillasr@gmail.com (M.M.Villaseñor-García).

Annals of Medicine & Surgery (2024) 86:1144–1146

Received 17 August 2023; Accepted 8 December 2023

Published online 3 January 2024

http://dx.doi.org/10.1097/MS9.0000000000001637

clinical presentations, including ulcerative (the most prevalent), pustular, bullous, vegetative, and ostomal[5].

On the other hand, it is important and noteworthy that inflammation and the immune process play a central role in this clinical entity regardless of the pattern of its presentation.

Currently, there is no definitive cure for this disease; it is generally is treated with immunosuppressants, such as cyclosporine, azathioprine, mezalasine, and glucocorticoids, as well as antibodies against tumor necrosis factor (TNF), but these show partial results with a higher risk of relapse as high as 40% or more and with risks of severe adverse effects.

Pentoxifylline is a methylxanthine utilized in vascular diseases. It also possesses anti-inflammatory, immunomodulatory, antioxidant, antifibrotic, and antiapoptotic effects. Pentoxifylline exhibit the inhibition of angiogenesis in degenerative processes, it also inhibits proinflammatory cytokines, particularly Interleukin 1 (IL-1), IL-6, IL-8, and TNF alpha (TNF-α). It also decreases the production of growth factors and C-reactive protein. It has been employed with success in vascular and severe inflammatory diseases such as fulminant hepatitis[6], in oncology[7], and as a radioprotective and chemoprotective agent[8].

Therefore, we decided to use pentoxifylline for up to 24 months in a patient who had not responded to and who experienced relapses every 4 weeks with treatments such as mesalazine, topical and systemic corticosteroids, immunosuppressants, and anti-TNF (infliximab and adalimumab), This work has been reported in line with the Surgical CAse REport (SCARE) 2023 Criteria[9].

Clinical case

A 47-year-old male of hispanic origin occupation professor with a diagnosis of UC, managed for 7 years with mesalazine, responding favorably. At 3 years of treatment, he presented a sudden, painful, pretibial necrotic ulcer in anterior aspect of the right lower limb with irregular friable edges that affected the skin and the subcutaneous tissue of ~13 × 10 cm. The patient was subjected to cultures, biopsies, and multiple treatments involving the following: topical corticosteroids; antibiotics; debridations, and systemic treatments including anti-inflammatory drugs, mesalazine (1 gr/8 h *per os)*, corticosteroids (prednisone 1 mg/kg of weight), and pulses of methylprednisolone 1 g/day *per os* in the absence of response. After 8 weeks, cyclosporine (100 mg/12 h *per os)* were added, to which there was an improvement for short periods of time (2–3 weeks). After 12 months, azathioprine 1–2 mg/kg of weight/day *per os* was added. Moreover, due to the multiple relapses, treatment is initiated with anti-TNF antibodies and infliximab 5 mg/kg of weight, observing a more extended response (up to 4–6 weeks). Finally, adalimumab 40 mg/week was started, without improvement. The patient's last treatment had included mesalazine and infliximab for 2 years with partial results and permanent relapses. Pentoxifylline was added to the conventional treatment at a dose of 400 mg /12 h *per os* during the entire observation time of the 2 years without side effects. The patient responded favorably, with the healing of this lesion healing at 6 weeks without relapses after 2 years (Fig. 1).

Discussion

This is a case of pyoderma gangrenosum associated with UC in a patient who had been unsuccessfully multitreated during 2 years with monotherapy or therapy in combination with anti-inflammatory drugs and anti-TNF antibodies without improvement, so the relapse of the ulcer lesion was permanent. Finally, pentoxifylline was added to the treatment with mesalazine and infliximab, with a surprising response 6 weeks after starting treatment, with complete healing and without relapse during this entire time (Fig. 1).

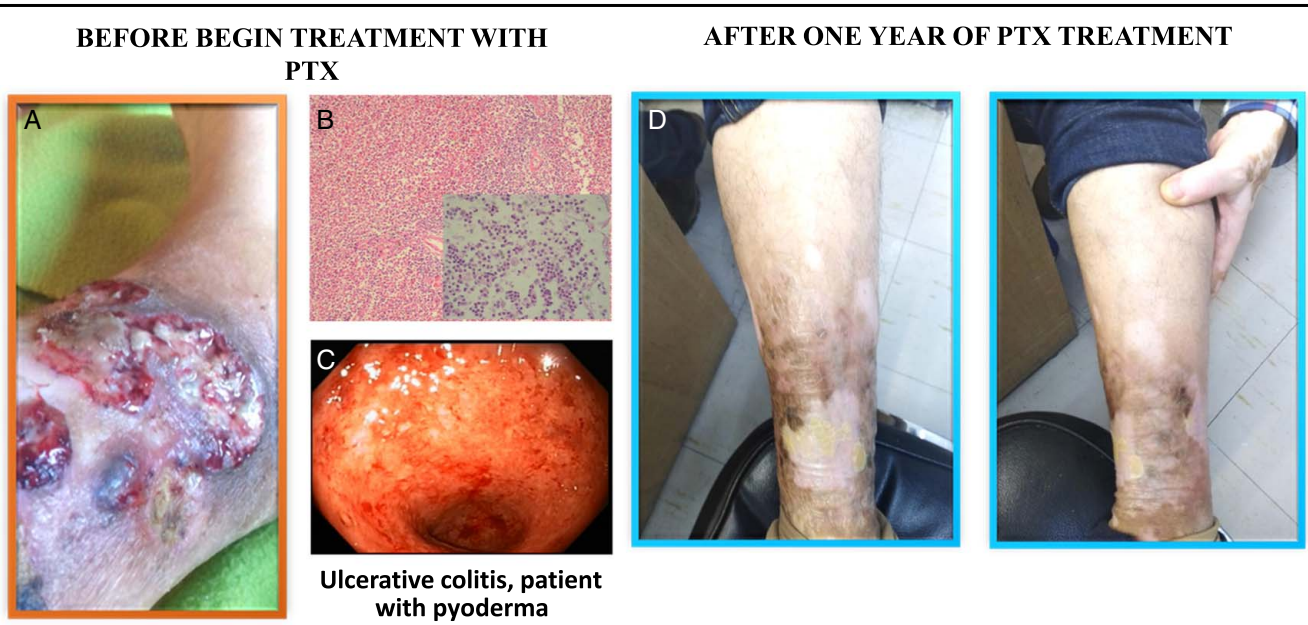

Figure 1. Patient with ulcerative colitis and pyoderma treated with pentoxifylline. A. Ulcerative lesion with purulent, hemorrhagic and painful exudate that affects the dermis, hypodermis and fascia. B. Histological image of pyoderma gangrenosum with neutrophilic infiltrate. C. Gastric endoscopic image with ulcerative colitis. D. Image of the ulcerative lesion 1 year after treatment.

The results may be explained by the inhibition of the transcription Nuclear Factor-kappa Beta (NF-KB), which stimulates the expression of the genes of proinflammatory interleukins such as IL-1, IL-6, Il-8, and TNF-α and which shows immunoregulatory and antioxidant activities[7].

Pentoxifylline exhibits a wide margin of safety, it and has even been used with minimal adverse effects in pediatrics for the treatment of leukemias[10].

It is evident that the main limitation of the work is the inclusion of only one patient. However, it is important to consider the low incidence of this pathology, making it challenging to gather a large series of patients. On the positive side, the study's strengths lie in its results, the extended duration of ulcer-free lesions, and the low toxicity of PTX, which encourages its study.

Conclusion

Pentoxifylline could be a therapeutic adjuvant option for this eventually fatal dermatosis. Due to its anti-inflammatory, antioxidant, and antifibrotic effects, more studies are necessary.

Ethical approval

None.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Sources of funding

None.

Author contribution

All authors contributed in study concept, data collection, writing the paper, and making the revision of the manuscript following the reviewer's instructions, reviewing, and validating the manuscript's credibility.

Conflicts of interest disclosure

There are no conflicts of interest.

Research registration unique identifying number (UIN)

1. Name of the registry: not applicable.
2. Unique identifying number or registration ID: not applicable.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): not applicable.

Guarantor

Jiménez-Luévano Miguel Ángel.

Data availability statement

Data sharing is not applicable to this article.

Provenance and peer-review

Not commissioned, externally peer-review.

Acknowledgements

None.

References

[1] Sasor SE, Soleimani T, Chu MW, *et al*. Pyoderma gangrenosum demographics, treatments, and outcomes: an analysis of 2,273 cases. J Wound Care 2018;27(Sup1):S4–8.
[2] Ahronowitz I, Harp J, Shinkai K. Etiology and management of pyoderma gangrenosum: a comprehensive review. Am J Clin Dermatol 2012;13:191–211.
[3] da Silva BC, Lyra AC, Rocha R, *et al*. Epidemiology, demographic characteristics and prognostic predictors of ulcerative colitis. World J Gastroenterol 2014;20:9458–67.
[4] White M, Adams L, Phan C, *et al*. Disseminated sporotrichosis following iatrogenic immunosuppression for suspected pyoderma gangrenosum [published correction appears in Lancet Infect Dis. 2019;19:e370]. Lancet Infect Dis 2019;19:e385–91.
[5] Afifi L, Sanchez IM, Wallace MM, *et al*. Diagnosis and management of peristomal pyoderma gangrenosum: a systematic review. J Am Acad Dermatol 2018;78:1195–1204.e1.
[6] Jiménez-Luévano MR-FS, Sepúlveda-Castro R, Jiménez-Partida AE, *et al*. Fulminant hepatitis managed with Pentoxifylline. J Clin Exper Pharmacol 2020;10:1–6.
[7] Lerma-Díaz JM, Hernández-Flores G, Domínguez-Rodríguez JR, *et al*. In vivo and in vitro sensitization of leukemic cells to adriamycin-induced apoptosis by pentoxifylline. Involvement of caspase cascades and IkappaBalpha phosphorylation. Immunol Lett 2006;103:149–58.
[8] Niderla-Bielinska J, Bartkowiak K, Ciszek B, *et al*. Pentoxifylline inhibits angiogenesis via decreasing Dll4 and Notchl expression in mouse proepicardial explantcultures. Eur J Pharmacol 2018;827:80–7.
[9] Sohrabi C, Mathew G, Nicola M, *et al*. The SCARE 2023 guideline: updating consensus Surgical CAse REport (SCARE) guidelines. Int J Surg 2023;109:1136–40.
[10] Meza-Arroyo J, Bravo-Cuellar A, Jave-Suárez LF, *et al*. Pentoxifylline added to steroid window treatment phase modified apoptotic gene expression in pediatric patients with acute lymphoblastic leukemia. J Pediatr Hematol Oncol 2018;40:360–7.