CASE REPORT

A 40-year-old Saudi male, previously healthy, presented with new progressive painful eruption that had persisted for 3 weeks. Skin examination showed a tender punched-out ulcer on the lower portion of the left leg measuring 5 cm in diameter (Fig 1). The ulcer had undermined borders with fibrinous exudate at the base. The patient denied any history of medical illnesses, including inflammatory bowel disease, gastrointestinal symptoms, insect bites, local trauma, or injections. Results of the following tests were either normal or negative: complete blood count, complete metabolic panel, liver function test, antinuclear antibody, glucose-6-phosphate dehydrogenase, and reticulocyte count.

A punch biopsy sample obtained from the ulcer showed epidermal necrosis, with infiltration of mixed inflammatory infiltrate with lymphocytes and neutrophils (Fig 2). There were significant vasculopathic changes in surrounding blood vessels, with fibrinoid necrosis and thickening of blood vessel walls but no karyorrhexis and no frank vasculitis.

A diagnosis of vasculitis ulcer was rendered, and the patient was treated with prednisolone 40 mg/d, which was later increased to 60 mg/d in 2 weeks because of inadequate response. At 1 month after starting the steroids, there was no improvement, and dapsone was added as an adjuvant therapy in a dose of 25 mg/d, which was later increased to 50 mg/d. However, the ulcers did not respond to this regimen. The patient declined to start methotrexate or add other immunosuppressants. The patient was seen by rheumatologists, and there was no evidence of generalized vasculitis.

Timolol 0.5% ophthalmic drops were used sparingly in 5 drops 3 times/day installed to the base and the borders on the leg ulcer. Timolol resulted in significant and clear improvement of the ulcer in all aspects at weekly evaluations (Fig 3). Over the next 6 weeks, the borders of the ulcer became less inflamed with significant reduction of pain, followed by healing of the ulcer. No significant changes in blood pressure or blood potassium were seen during the treatment.

Table I shows the wound characteristics during the treatment period.

DISCUSSION

Wound healing is a well-organized, normal biological process achieved through hemostasis, inflammation, proliferation, and remodeling. It requires the orchestrated migration and proliferation of keratinocytes and fibroblasts, as well as other cell types. Improving and enhancing the wound healing process was and still is the target of many laboratory studies, with many topical and systemic agents investigated. The skin is believed to have an autocrine and paracrine β-adrenergic receptor (β-AR) network in the epidermis and dermis. The first clues to a biological function for β2-AR in wound repair came from an early study showing that

From the Department of Pharmacology and Toxicology, College of Pharmacy; Dermatology Department and Pathology and Laboratory Medicine Department, College of Medicine, King Saud University; and King Abdulaziz Medical City, Riyadh. Funding sources: None. Conflicts of interest: None disclosed. Correspondence to: Salman M. Alsaad, MD, PO Box 2529, Riyadh 11461, Kingdom of Saudi Arabia. E-mail: salmanalsaad@gmail.com.

JAAD Case Reports 2019;5:812-4. 2352-5126 © 2019 by the American Academy of Dermatology, Inc. Published by Elsevier, Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/). https://doi.org/10.1016/j.jdcr.2019.07.016

812
β-AR agonists delay skin wound healing in newt limbs. Later, Pullar et al showed that β-AR antagonists promote wound re-epithelialization by blocking the autocrine β2-AR network within the epidermis. Clinically, nonselective β-AR antagonists were shown to improve wound healing in many studies. Nayak et al showed significantly decreased epithelialization time with a beta-blocker (carvedilol and propranolol) compared with control and alpha-blocker phentolamine. In a double-blind randomized controlled trial, patients who received oral propranolol had a shorter time to healing of superficial wounds and were quicker to receive skin grafts in deeper injuries. Also, topical beta-blocker timolol was shown to promote healing of chronic wounds of various causes. Oberbeck et al explained the immunomodulatory effects of topical timolol. Catecholamines have been shown to have many immunosuppressive activities. Administration of norepinephrine in humans transiently increases the numbers and the activity of circulating natural killer cells and T lymphocytes (SKN-1). Also, elevated levels of circulating epinephrine are associated with an increased lymphocyte proliferation. All of these are inhibited and blocked by a β-adrenergic antagonist such as timolol, thus exhibiting an anti-inflammatory action.

The proposed mechanisms for β2-AR antagonist-promoted wound healing is not known, but theories include, but are not limited to, (1) enhanced keratinocyte migration and re-epithelialization, (2) increased extracellular signal–related kinase phosphorylation and electric field–mediated directional

![Fig 1. Photograph showing the ulcer on the left leg before treatment with timolol drops.](image1)

![Fig 2. Vasculitis in the mid-dermis (lymphocytic infiltration and focal fibrin deposition).](image2)

Table 1. Wound characteristics during the treatment period

| Treatment                      | Ulcer response                                      |
|--------------------------------|------------------------------------------------------|
| Oral prednisolone 40 mg/d     | No changes                                          |
| Oral prednisolone 60 mg/d +   | No changes                                          |
| dapsone 25 mg/d               |                                                      |
| Oral prednisolone 60 mg/d +   | No changes                                          |
| dapsone 50 mg/d               |                                                      |
| Oral prednisolone 60 mg/d +   | The wound started to heal within one week of initiating treatment and was completely healed by the 6th week |
| dapsone 50 mg/d +             |                                                      |
| timolol drops 3 times/d       |                                                      |

![Fig 3. At 6 weeks, showing complete closure of the wound.](image3)
migration (galvanotaxis), (3) enhanced fibroblast migration, (4) reduced local inflammatory response, and (5) enhanced angiogenesis.  

In conclusion, the use of a topical or systemic beta-blocker is a promising, inexpensive, noninvasive new option to enhance wound healing in complicated ulcers and wounds. Here, the use of topical timolol resulted in complete healing of our patient’s resistant vasculitis ulcer. Further randomized clinical studies are needed to help dermatologists dealing with this disease.

REFERENCES

1. Nayak V, Chogtu B, Parimi MRA, Mahapatra AK, Vaishnav RL. Comparison of different adrenergic blockers on cutaneous wound healing in Wistar rats. Br Biomed Bull. 2014;2(2):371-375.
2. Pullar CE, Rizzo A, Isseroff RR. beta-Adrenergic receptor antagonists accelerate skin wound healing: evidence for a catecholamine synthesis network in the epidermis. J Biol Chem. 2006;281(30):21225-21235.
3. Pullar CE, Le Provost GS, O’Leary AP, Evans SE, Baier BS, Isseroff RR. beta2AR antagonists and beta2AR gene deletion both promote skin wound repair processes. J Invest Dermatol. 2012;132(8):2076-2084.
4. Donaldson DJ, Mahan JT. Influence of catecholamines on epidermal cell migration during wound closure in adult newts. Comp Biochem Physiol C. 1984;78(2):267-270.
5. Mohammadi AA, Bakhshaeekia A, Alibeigi P, et al. Efficacy of propranolol in wound healing for hospitalized burn patients. J Burn Care Res. 2009;30(6):1013-1017.
6. Braun LR, Lamel SA, Richmond NA, Kirsner RS. Topical timolol for recalcitrant wounds. JAMA Dermatol. 2013;149(12):1400-1402.
7. Liu DY, Fischer R, Fraga G, Aires DJ. Collagenase ointment and topical timolol gel for treating idiopathic pyoderma gangrenosum. J Am Acad Dermatol. 2014;71(5):e225-e226.
8. Moreira C, Lopes S, Cruz MJ, Azevedo F. Topical timolol for the treatment of pyoderma gangrenosum. BMJ Case Rep. 2017;2017:bcr2016218589.
9. Oberbeck R, van Griensven M, Nickel E, Tschernig T, Wittwer T, Pape H. Influence of beta-adrenoceptor antagonists on hemorrhage-induced cellular immune suppression. Shock. 2002;18(4):331-335.