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# Successful Treatment of Chronic Lower Extremity Ulcers with Allogeneic Platelet-Rich Plasma and Artificial Dermis: A Case Report

Qiannan Zhao, MA; Yuanyuan Ma, MD; Yuquan Lu, PhD; Yuan Chai, MD; and Yuemin Zhou, PhD, MD

## ABSTRACT

Hydroxyurea is an oral medication associated with painful, nonhealing ulcers, for which there is no effective treatment but permanent discontinuation of hydroxyurea. The authors present a case of leg ulcers that likely occurred as a result of hydroxyurea use in a patient with essential thrombocythemia. Topical treatment with allogeneic platelet-rich plasma and artificial dermis completely healed the leg ulcers without hydroxyurea cessation.

**KEYWORDS:** artificial dermis, chronic ulcer, hydroxyurea, leg ulcer, platelet-rich plasma, thrombocythemia

ADV SKIN WOUND CARE 2019;32:550–2.

## CASE REPORT

A 64-year-old woman presented with two painful CLEUs on the lateral malleolus of her left lower limb and the instep of her left foot that had persisted for 3 months. This patient had been previously diagnosed with ET, which was well controlled by HU therapy for approximately 12 years at a dosage of 1 g/d. She also had a history of foot ulcers that healed with local treatment. The ulcers began after scratching a mosquito bite and enlarged despite oral antibiotic treatment. She was admitted to the authors' clinic and diagnosed with CLEUs.

Given the risk of deterioration, surgical debridement was performed after admission.<sup>4</sup> Postoperative pathologic examination demonstrated epidermal atrophy and perivascular lymphocytic infiltrate in the corium layer with infiltration by plasma cells and neutrophils (Figure 1). Topical treatment was applied, with dressing changes every 2 days and intermittent debridement for approximately 3 weeks. Healthy granulation tissue did not form, and wound contraction was not observed (Figure 2 A0, 2B0).

Because of the nature of thrombocytosis, providers knew that autologous PRP was not an option. Instead, after obtaining informed consent from the patient and her daughter, the authors designed a treatment involving allogeneic PRP and artificial dermis.<sup>5</sup> The treatment conformed to ethical guidelines and was approved by the institutional ethics committee. The patient signed a written release for the case and the relevant images.

Briefly, 20 mL of venous blood from the patient's daughter was collected, 15 mL of which was used to prepare PRP. The other 5 mL was used to prepare autologous thrombin.<sup>6</sup> The PRP was mixed with the autologous thrombin/calcium activator until a gelatinous mixture was obtained. In addition, testing for hepatitis B and C, HIV, and syphilis was conducted before application. The necrotic tissue on the ulcer surfaces was debrided, and the wounds were rinsed with iodine and saline. The unconsolidated portion of the PRP was injected into the inner walls of the ulcers, and the PRP gel

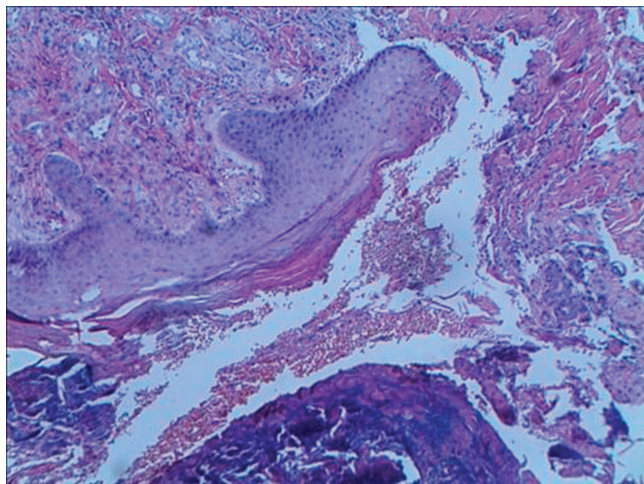
## INTRODUCTION

A cell cycle-specific inhibitor, hydroxyurea (HU) is an oral medication commonly used to treat myeloproliferative disorders such as essential thrombocythemia (ET), which is characterized by persistent platelet elevation and functional disturbance. However, HU is associated with various adverse reactions, such as bone marrow depression, systemic adverse effects (including fatigue, headache, and gastrointestinal symptoms), and dermatologic reactions (including skin atrophy, dryness, and skin ulcers).<sup>1</sup> Chronic lower extremity ulcers (CLEUs) are a rare adverse reaction, and only approximately 5% of patients are affected.<sup>2</sup> Multiple or bilateral ulcers usually present in the perimalleolar region and are accompanied by peripherally atrophic, intense pain.<sup>3</sup>

Treatment regimens such as debridement and wound care all require discontinuation of HU. In patients for whom discontinuation of HU is not suitable, such as those who cannot tolerate alternative treatments, there is no effective cure for these ulcers. Here, researchers describe a patient with CLEUs associated with ET and HU therapy, who experienced complete healing of the ulcers after four rounds of allogeneic platelet-rich plasma (PRP) therapy.

At the Huaihe Hospital of Henan University, Kaifeng, China, Qiannan Zhao, MA, is a graduate student, Department of Reconstructive and Plastic Surgery; Yuanyuan Ma, MD, is a plastic surgeon, Department of Reconstructive and Plastic Surgery; Yuquan Lu, PhD, is a professor, International Joint Research Laboratory for Cell Medical Engineering; Yuan Chai, MD, is a plastic surgeon, Department of Reconstructive and Plastic Surgery; and Yuemin Zhou, PhD, MD, is a professor, Department of Reconstructive and Plastic Surgery. Copyright © 2019 the Author(s). Published by Wolters Kluwer Health, Inc. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal. **Acknowledgments:** This work was supported by the Medical Science and Technology Research Project of Henan Province (1721102410005). The authors have disclosed no financial relationships related to this article. Submitted April 12, 2019; accepted in revised form July 9, 2019.

**Figure 1.**  
**HISTOLOGY ANALYSIS OF SKIN BIOPSY**



Presentation shows epidermal atrophy and perivascular lymphocytic infiltrates in the corium layer with infiltration by plasma cells and neutrophils.

was applied to the surface of the wounds. A wound-size sheet of PRP-impregnated artificial dermis (Pelnac; Gunze Limited, Kyoto, Japan) was placed on the wounds and covered with a polyurethane film (Mepore Film; Mölnlycke Wound Care AB, Gothenburg, Sweden). This PRP treatment was performed once a week for 4 weeks.

The patient reported notable pain relief and marginal erythema and edema reduction after the first PRP treatment. Fresh granulation tissue appeared, and the wounds contracted after the second PRP treatment. The wounds showed active granulation tissue growth, increasing in local angiogenesis and significant contraction after the third PRP treatment. In addition, the surface of the wound defects was even, and the lesions had decreased in size 2 weeks after the fourth PRP treatment (Figure 2A1, 2B1).

The PRP treatment was changed to a general dressing (including iodophor disinfection, saline cleaning, and gauze replacement). During this time, the patient discontinued the HU for 1 week and concealed this information from her doctors. Because of the short-term discontinuation and excellent results of the PRP treatment, it is unlikely that this drastically affected the patient outcomes.

The authors examined the ulcers at 1 month after the fourth PRP treatment and found that they were completely healed (Figure 2A2, 2B2). Providers followed up with the patient for 6 months, and no recurrence was noted. During the follow-up period, the patient's platelet levels were monitored regularly and remained around 300 to  $500 \times 10^9/L$ .

## DISCUSSION

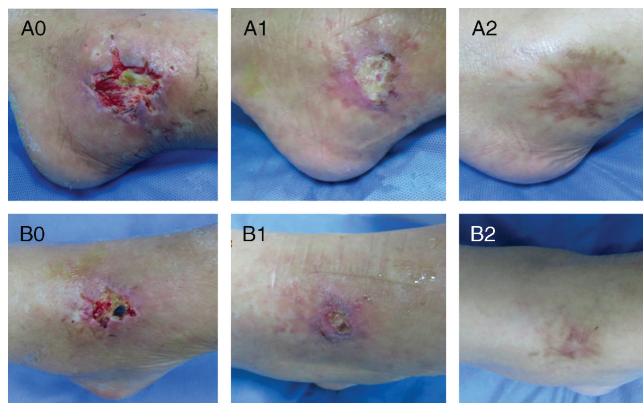
The clinical diagnosis of this patient was perplexing. She had been diagnosed with ET and was receiving HU treatment. Providers

ruled out hypertension and thrombosis caused by ET as major contributors to ulcer formation because the patient's previous ulcers healed after HU cessation and reformed after restarting HU therapy. Further, the patient's platelet index and BP were well controlled during the administration of HU, so they were also unlikely to be the main cause of the ulcers. Based on these findings, the patient was eventually diagnosed with HU-associated ulcers, which is consistent with the literature.<sup>1</sup>

Hydroxyurea can inhibit the functions of ribonucleotide reductase, which in turn causes a decrease in cellular DNA production and induces cell death. In addition to inhibiting DNA synthesis, HU has significant antiangiogenic properties.<sup>7</sup> In many patients, CLEUs are a severe adverse reaction to long-term HU treatment at a dose of at least 1 g/d. These ulcers tend to localize in the malleolar region and heal spontaneously when HU is discontinued.<sup>3</sup> Treatment methods mostly involve discontinuation of drugs, as well as standard debridement and wound care. However, when medication cessation is not an option, a simple debridement and dressing may not heal these ulcers, which can become cancerous if they persist.<sup>7</sup>

To the authors' knowledge, this is the first reported case of successful application of allogeneic PRP from lineal consanguinity in HU-related CLEUs with a favorable effect. Vascular ulcers are often associated with pain, and the researchers found that (consistent with previous reports<sup>8</sup>) PRP therapy was particularly effective for this patient's pain.<sup>8</sup> By promoting safe and natural healing, PRP offers a promising alternative to the current standard of care. The PRP is derived from density-gradient centrifugation of peripheral venous blood to obtain plasma rich in platelets. It contains a

**Figure 2.**  
**CLINICAL PRESENTATION OF ULCERS BEFORE AND AFTER TREATMENT**



A0, B0, Two chronic lower extremity ulcers were observed on the left lower limb and left foot in the initial presentation. A1, B1, Significant improvements in the skin lesions were observed after the fourth treatment. A2, B2, Good cosmetic and therapeutic outcomes were observed 1 month later.

variety of growth factors, mesenchymal stem cells, fibroblasts, and leukocytes.<sup>9</sup> Studies have confirmed that it can promote wound healing, improve angiogenesis, inhibit the growth of certain bacteria, and reduce postoperative pain.<sup>10,11</sup> However, there is no uniform standard for the preparation and quality of PRP.

The success of this case may be attributable to a few different factors. First, PRP contains many bioactive molecules, such as fibroblast growth factors, mesenchymal stem cells, and leukocytes that promote wound healing and improve angiogenesis and pain relief.<sup>12</sup> Further, allogeneic PRP offers all of the same functional factors as normal PRP.<sup>13</sup> Third, artificial dermis improves nonhealing cutaneous ulcers, such as diabetic foot ulcers.<sup>5</sup>

## CONCLUSIONS

This case provides the first evidence for the validity and utility of allogeneic PRP from a blood relative in healing HU-associated ulcers. However, future studies including more wounds are required to confirm the utility of this treatment and any adverse reactions. Nonetheless, further research is needed to investigate possible differences in clinical efficacy. ●

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