Using Amniotic Membrane Allografts in the Treatment of Neuropathic Foot Ulcers

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Neuropathic foot ulcers are a common complication in patients with diabetes. These ulcers are often slow to heal and can lead to infection, further tissue destruction, osteomyelitis, and amputation. These patients pose a challenge to clinicians who must determine the best treatment options while balancing the risks, benefits, and costs. Conservative therapies often present disappointing results, and a number of newer ''biologic bandages'' have been developed to better assist the healing process. We describe results from diabetic patients with neuropathic foot ulcers treated with a new amniotic membrane–based allograft. (J Am Podiatr Med Assoc 104(2): 198-202, 2014)

Diabetes mellitus is an extremely common clinical condition, affecting between 5% and 10% of the general population. In the United States, the numbers of diabetic individuals and their healthcare costs are expected to more than double in the next 25 years. By 2034, it is estimated that more than 44 million people will be living with diabetes.[1] Among patients with diabetes, peripheral arterial disease, peripheral neuropathy, deformity, callus, and trauma often lead to foot ulcers, which can become chronic in nature, leading to severe morbidity.[2] Diabetic individuals have a 15% to 25% risk of developing a foot ulcer in their lifetime. Approximately 15% of diabetic foot ulcers (DFU) result in lower-extremity amputation.[2,3]

Because healing time is prolonged, there is an increased risk of morbidity, infection, hospitalization, and amputation; thus the primary goal of DFU treatment is rapid wound closure. Standard treatments include management of underlying disease, wound debridement, infection control, off-loading, and hyperbaric oxygen therapy.[2] Despite appropriate conservative wound management, many diabetic foot ulcers do not heal. Indeed, Margolis et al[4] reported neuropathic ulcer healing rates of only 24.2% at 12 weeks and 30.9% at 20 weeks. It is suggested that advanced therapies such as human skin equivalents, wound modulators, and growth factors be considered if wound area is not reduced by 50% after 4 weeks of conservative management. We report results of incorporating EpiFix (MiMedx Group Inc, Marietta, Georgia), a dehydrated amniotic membrane allograft, as part of the treatment plan in patients with nonhealing DFU.

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Materials and Methods

Patients diagnosed with insulin dependent or non-insulin–dependent diabetes, who were receiving conservative treatment for a DFU at a single wound care center were eligible for inclusion. Excluded from eligibility were those patients with end-stage renal failure, a history of prior graft failure, signs of infection, or autoimmune disease.

Advanced therapies are considered if a patient's wound size has not decreased by at least 50% after 4 weeks of conservative management. Conservative treatments were based on clinical evaluation and judgment and may have included sharp debridement, wet-to-moist dressings, application of an enzymatic agent, and the application of standard dressings. After 4 weeks of conservative management, use of EpiFix was discussed with those patients eligible for advanced treatment. Included in this report are those patients with a nonhealing DFU who agreed to the use of EpiFix, and who provided written consent for the use of their personal health information and images in accordance with the St. Francis Hospital Institutional Review Board (Columbus, Georgia) policy. EpiFix was provided free of charge from MiMedx Group for use in this study.

Each patient had a complete review of past medical history and previous treatments and was assessed for appropriate treatment of relevant comorbidities. Lower-extremity, circulatory, and neurologic examinations were conducted to deter-

mine wound healing support. EpiFix was applied to the wound after subcutaneous debridement to bleeding was performed. An appropriate dressing was then applied and off-loading device was prescribed. Patients were asked to return to the wound center weekly for evaluation of wound healing.

Case 1

Case 1 was a 74-year-old male with a nonhealing neuropathic ulcer of the right great toe. The patient was an avid golfer and had been initially self-treating a callus at the site. On presentation, the wound was a Wagner grade 2 full-thickness plantar right hallux wound that had been present for 4 months. The size of the wound was $0.7 \times 0.6 \times 0.2$ cm on initial presentation. His past medical history was remarkable for non-insulin–dependent diabetes mellitus, hypertension, and hyperlipidemia. Previous medical treatment included over-the-counter topical medications and oral antibiotics. Objective findings on examination showed no signs of infection, pain, or drainage. There were strong palpable pulses. Epicritic gross sensation of the lower extremity was diminished to absent. The condition of the wound prior to debridement is shown in Figure 1A.

The patient underwent the standard procedure with initial debridement and application of the EpiFix amniotic membrane. Figure 1B shows the wound after debridement; Figure 1C, after application of the allograft.

Four weeks postoperatively, the patient showed gradual healing with eventual complete resolution of the wound (Fig. 1D). Hematoxylin and eosin (H&E) stain showed initial inflammatory cells

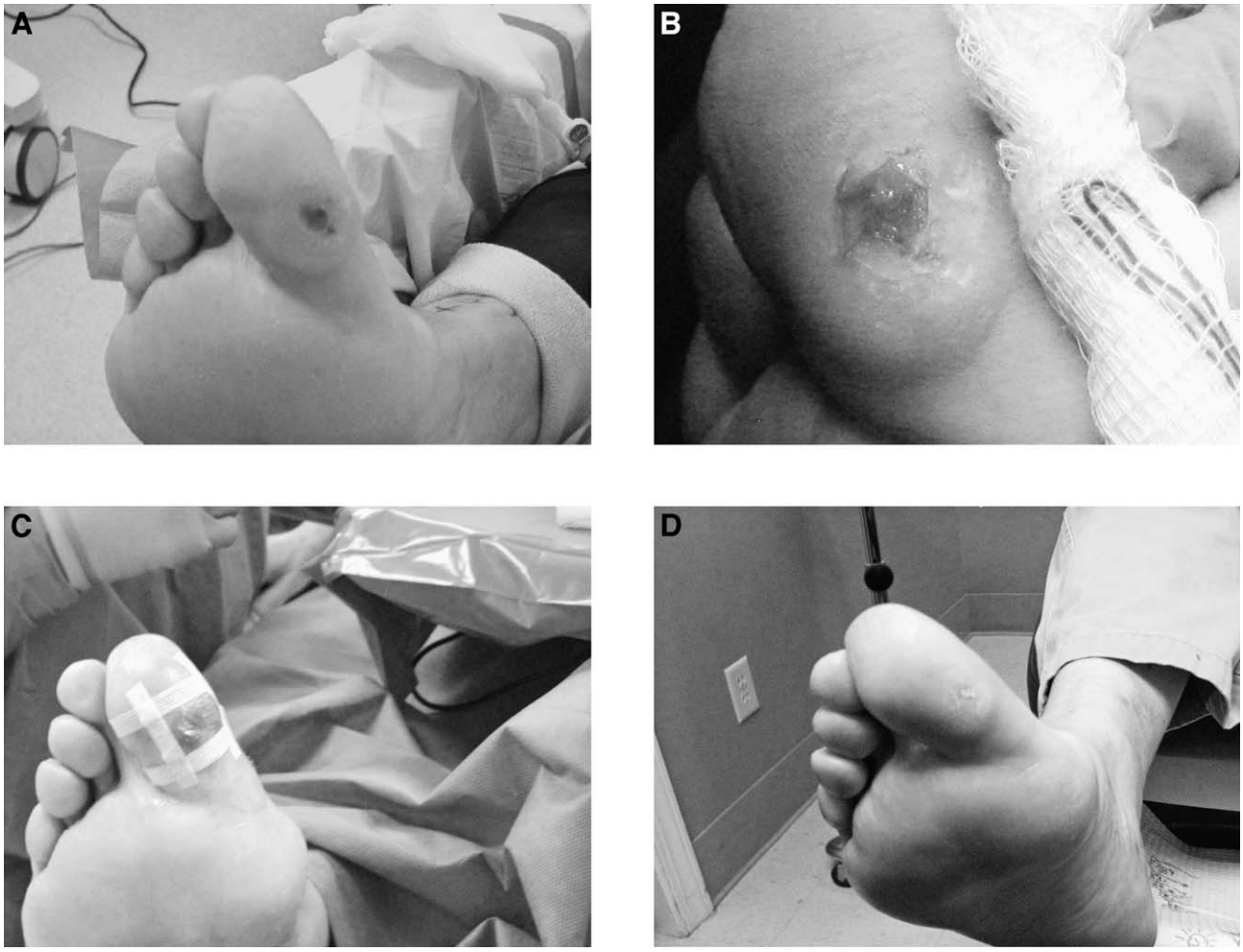

Figure 1. Condition of the wound discussed in Case 1 prior to debridement (A), after debridement (B), after application of EpiFix allograft (C), and 4 weeks after application of EpiFix allograft (D).

moving to subsequent deposition of dense collagen and graft healing with minimal inflammatory response at the site.

Case 2

The second case was a 70-year-old female with a nonhealing neuropathic ulcer of the plantar left heel. Previous treatment included over-the-counter topical medication and oral antibiotics. The patient presented with a past medical history of insulin-dependent diabetes, hypertension, and peripheral vascular disease (ankle-brachial index of less than 0.9). Objective findings included no signs of infection, pain, or drainage. Weak palpable pulses were present but audible on Doppler with a biphasic sound. The wound presented as a Wagner Grade 2 full-thickness left heel wound that had been present for 7 to 8 months (Fig. 2A). The wound measured $1.9 \times 1.8 \times 0.3$ cm on initial presentation.

Following irrigation and hemostasis, a 4×4-cm nonhydrated amniotic membrane graft was applied to the wound site. At the first postoperative week, observation showed evidence of full graft uptake with healthy granulation tissue within the wound bed. Evidence of a decrease of the wound margins was also noted. At the fourth postoperative week, the wound measured $1.0 \times 0.8 \times 0.1$ cm with a resulting 50% reduction in overall wound volume and marked wound healing progression (Fig. 2B).

Case 3

The third case was a 58-year-old male presenting with a nonhealing neuropathic ulcer of the lateral left foot transmetatarsal stump. Previous therapies included topical medication, off-loading, and surgical resection of the underlying metatarsal. Past medical history was remarkable for insulin-dependent diabetes mellitus and hypertension. Objective findings on examination showed no signs of infection, pain, or drainage with strong palpable pulses but an abnormal gait. The Wagner Grade 2 full-thickness wound had been present for 3 months and measured $1.2 \times 1.1 \times 0.1$ cm on initial presentation (Fig. 3A). The epicritic gross sensation of the lower extremity was diminished to absent.

The patient was prepped and underwent subcutaneous soft-tissue debridement and the EpiFix dressing was placed. At the second postoperative week the wound measured $1.0 \times 0.9 \times 0.2$ cm with full graft uptake and a decrease in wound margins (Fig. 3B). By the fourth postoperative week, the wound measured $0.5 \times 0.6 \times 0.1$ cm, with a greater than 50% reduction in overall wound volume and marked progression in healing. By postoperative week 5.5, the wound had closed (Fig. 3C).

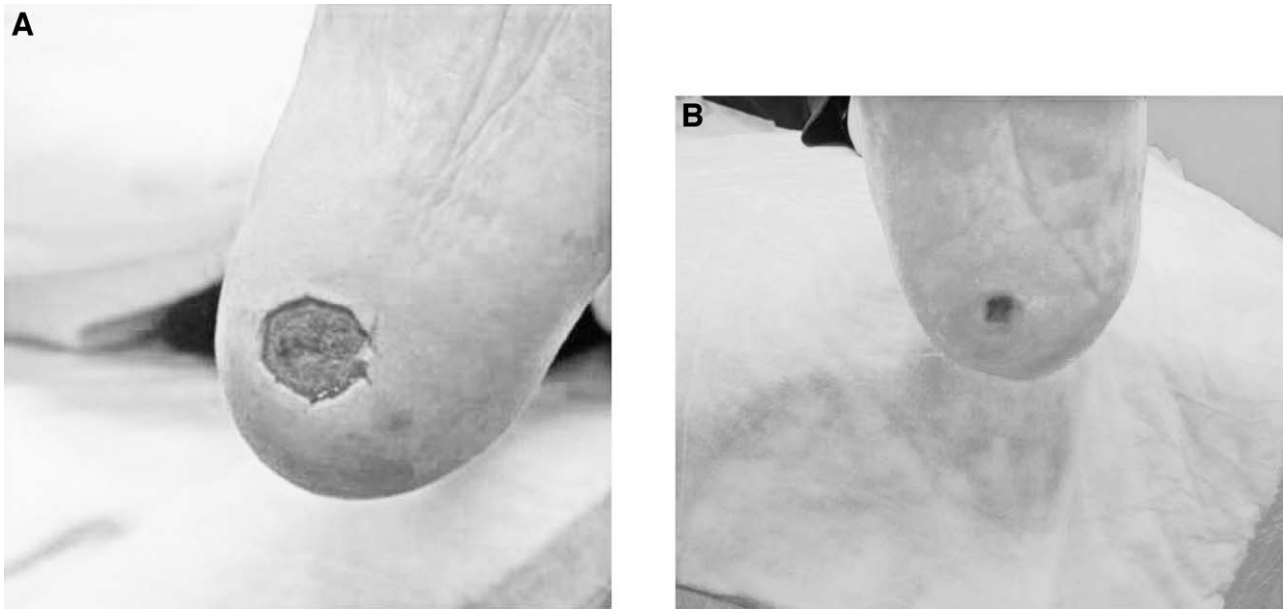

Figure 2. Full-thickness heel wound discussed in Case 2, at presentation for treatment with EpiFix allograft (A) and 4 weeks after application of EpiFix (B).

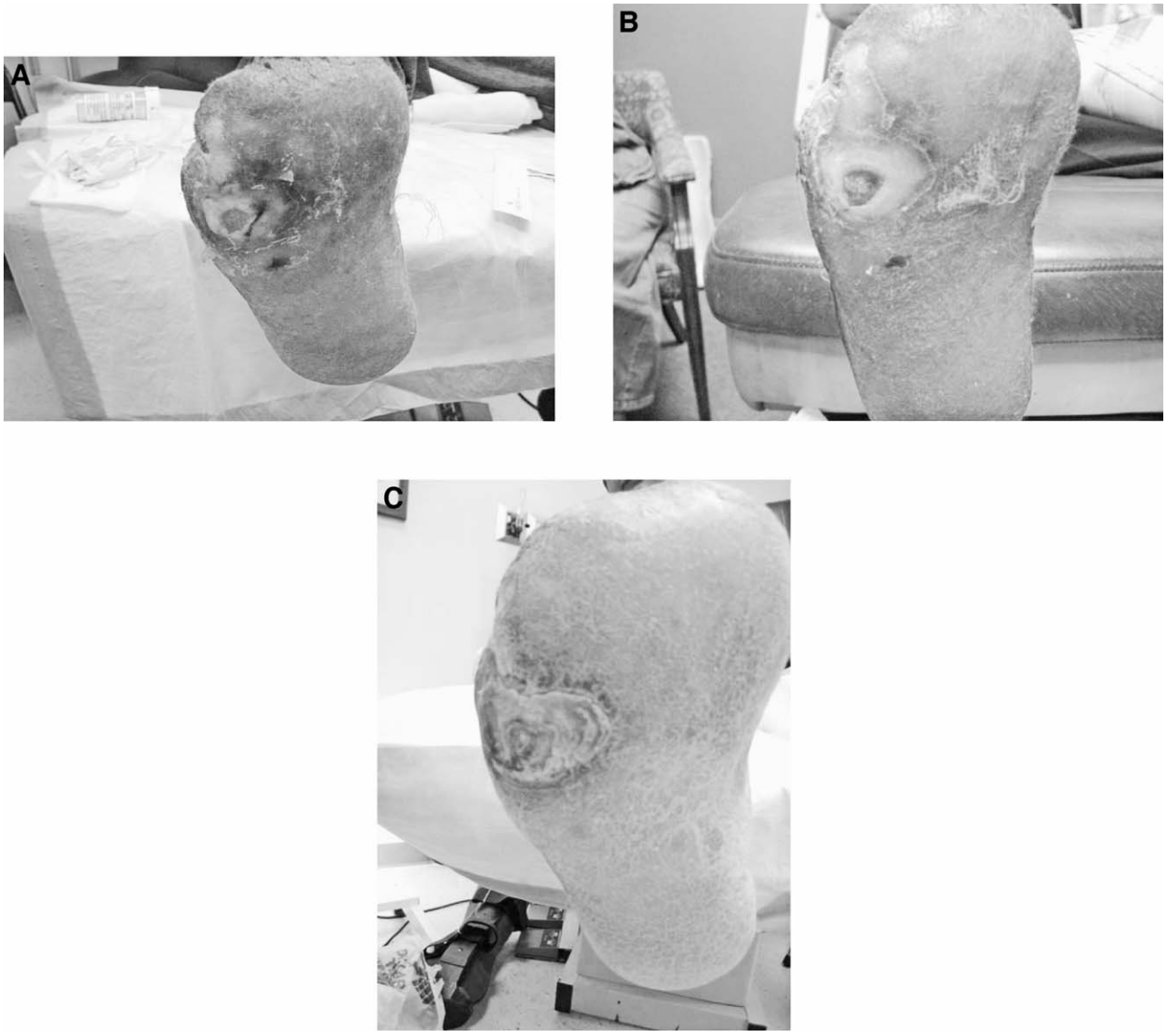

Figure 3. Condition of wound discussed in Case 3, prior to debridement (A), 2 weeks after application of EpiFix allograft (B), and 4 weeks after application of EpiFix (C).

There was continued wound-care treatment after closure for improvement of skin integrity before returning to a custom-molded diabetic shoe.

Discussion

The presented cases illustrate results obtained by using EpiFix to enhance wound healing in patients with lower-extremity neuropathic ulcers refractory to conservative treatment measures. Given the poor prognosis for healing in patients with chronic DFU, it is important that clinicians remain abreast of new techniques, technology, and products that can assist in their efforts to provide optimal care and promote positive outcomes for these difficult wounds.

Use of advanced therapies should be considered if the wound size has not been reduced after 4 weeks of standard wound care. Bioengineered skin substitutes and wound care technologies, such as the topical gel becaplermin (Regranex, Systagenix Wound Management), and living skin equivalents such as Apligraf (Organogenesis) and Dermagraft (Advanced Bio-Healing), have been shown to accelerate the healing process but are not a panacea; no perfect skin substitute exists for all patients in all situations.[5]

Human amniotic membrane has been used for a variety of reconstructive surgical procedures since the early 1900s. Amniotic membrane has recently been identified as a potent facilitator of wound healing in a variety of conditions including lower-extremity vascular ulcers, but also in a variety of other applications including eye surgery, burns, gynecologic surgery, and orthopedics.[6-11] The amniotic membrane is a nonvascular tissue comprised of the innermost layer of the placenta, and consists of a single layer that is attached to a basement membrane. Histological evaluation shows that the membrane layers consist of epithelium cells, thin reticular fibers (basement membrane), a thick compact layer, and fibroblast layer. The fibrous layer of the amnion contains cell-anchoring collagen types: IV, V, and VII. The membrane serves as a substrate material, more commonly referred to as a biological dressing or patch graft.

In wound care, amnion may influence all three major phases of wound healing: inflammatory, proliferation, and maturation stages. As a grafting material, amnion also has some unique characteristics that provide a matrix for cellular migration/proliferation, create a natural biological barrier, is non-immunogenic, and contains growth factors that promote healing.[6,12-14] Although human amniotic membrane has been used successfully in a variety of wounds,[15] difficulty in obtaining, preparing, and storing the material, as well as a concern of the potential for infectious disease transmission, has precluded its widespread use.[5] EpiFix, a sterilized, dehydrated form of human amniotic membrane, with a 5-year shelf life, addresses many of these issues.

The clinical cases outlined demonstrate the typical course seen in patients with refractory neuropathic ulcers when treated with an EpiFix amniotic membrane allograft. EpiFix should be considered as a viable treatment option in the wound-care market.

Financial Disclosure: None reported.
Conflict of Interest: Dr. Shah is on the Medical Advisory Board of MiMedx, the manufacturer of EpiFix.

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