

Abstract

Chronic Venous Insufficiency (CVI) is a lifelong, moribund and debilitating disease process with tremendous personal and financial costs. At its core, CVI involves blood pooling in the lower extremities secondary to inadequate venous blood return, resulting in venous hypertension and incompetence of the one-way valves in the lower extremity veins. As venous circulation slows, metabolic demands of the cells in the lower extremities increase, leading to stasis dermatitis, infection, cellular death, and venous ulceration. This case study aims to report the efficacy of Dehydrated Amniotic Membrane Allograft (DAMA) applications to a chronic right lateral ankle ulcer resulting from chronic venous insufficiency.

This case study demonstrates that the application of DAMA has the potential to act as an effective barrier to cover and accelerate wound closure time. Future non-randomized and randomized controlled trials may further establish standardized protocols for DAMA application in venous ulceration, help create treatment algorithms to predict wound closure endpoints, and encourage innovation that may further accelerate healing time.

Introduction

- Chronic venous insufficiency affects more than 25 million adults in the US [1]. 40% of the US population suffers from CVI [2].
- CVI is the cause of 80% of lower leg ulcer cases worldwide [3].
- The annual cost of healthcare for CVI is \$3 billion [4].
- Treatment costs range from \$15 to \$509,275 and include interventions from over-the-counter Tegaderm dressings to below-the-knee amputations.
- Diabetic patients with CVI ulcers warrant immediate and aggressive treatment as they precede 85% of lower extremity amputations [6].
- The Venous Clinical Severity Score is used to classify venous disease of the lower extremities [7]. zero (none) to three (severe)
- Ulceration from CVI ultimately develops due to the triad of venous hypertension, circulatory stasis, and tissue hypoxia triggering an inflammatory reaction and fibrosclerotic remodeling of the skin
- The onset of venous ulcers in CVI patients is accelerated by dry skin, dermatitis, labile edema, cellulitis, trauma, or insect bites [11].
- Clinical depression, inability to work, loss of control, loss of self-identity, insomnia, and chronic pain are all hallmarks of the CVI disease progression to venous ulceration [13]. Treatment modalities for chronic venous ulceration include mitigation of swelling, mitigation of infection, and facilitating wound closure.
- Any exposed venous ulcer is vulnerable to infection.
- Should all conservative measures fail, and the wound progress, partial wound closure, reconstructive flap surgery, or even amputation may be warranted to prevent systemic spread of infection
- Left unchecked, chronic ulcer infections can proliferate throughout the blood and lead to multi-system organ failure and death.

Methods and Materials

Following the standards established by the U.S. Food and Drug Administration (FDA) and the American Association of Tissue Banks (AATB), human amnions were obtained from consenting mothers. An independent certified laboratory tested all the donations for infectious disease per Clinical Laboratory Improvement Amendments (CLIA) of 1988, 42 CFR part 493, and FDA regulations. In addition, each birth mother was tested for Hepatitis B Core Antibody (HBcAb), Hepatitis B Surface Antigen (HBsAg), Hepatitis C Antibody (HCV), Human Immunodeficiency Virus Antibody (HIV -1/HIV-2 Plus 0), Human T-Lymphotropic Virus Antibody (HLTV-I/11), Syphilis (RPR), HIV-1/HCV/HBV, NAT, and West Nile Virus (WNV). Each test was performed with an FDA-Approval testing kit. All test results were negative or non-reactive. The donated amnion was aseptically processed and did not involve the addition of cells, tissues, or articles other than the exceptions outlined in 21 CFR Part 1271.10(a) (3). The amnion was placed on a sterile drying tray and desiccated in a high nitrogen concentration drying chamber. The sterility of the donation was tested at an independent laboratory, Eurofins VRL Laboratories. In addition, the desiccated allografts are sterilized via gamma irradiation before distribution.

Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board of the Institute of Regenerative and Cellular Medicine (protocol code IRCM-2022-311 and approved on 12 January 2022).

Application of Amniotic Membrane Allografts in Advanced Venous Leg Ulcer: A Case Study and Literature Review Matthew Regulski¹, John Shou², Naomi Lambert², Eric Vinke MS², Tyler Barrett² ¹Ocean County Foot and Ankle Center, ²Regenative Labs

Patient Outcomes



Figure 1. 1 February 2022; VLU measurements: 2.00 cm × 1.50 cm

Figure 2. 14 March 2022; VLU measurements: 1.50 cm × 1.00 cm

Patient History and Treatment

The patient of interest is a 47-year-old male who suffered from a refractory, non-healing right lateral ankle ulceration. The patient worked as an architect and often remained seated for 10 or more hours a day. He has a family history of varicose veins from both parents. The patient developed this ulceration secondary to venous insufficiency and valvular reflux. Despite 8 months of conservative treatment, the patient's venous ulcer persisted. This prompted a referral to an interventional cardiologist. The cardiologist performed a venous reflux test and diagnosed the patient with pelvic compression syndrome, prompting surgical stent placement in the right external iliac and common femoral vein. Stent placement did not resolve the patient's venous stasis ulcer, prompting a podiatric referral for a second opinion and definitive wound closure. Prior to the patient had failed a total of 10 months of conservative measures that included revascularization. Upon the initial examination, on 1 February 2022, the VLU was wet and macerated, with copious drainage, significant hemosiderosis, and lipodermatosclerosis. The wound bed was granular in appearance with significant amounts of slough and biofilm, typical of a chronically infected wound. A repeat venous flex test confirmed perforator venous incompetence. His perforator vein incompetence was subsequently treated with sclerotherapy.

Conservative treatment continued for four weeks to prepare the wound had achieved granulation, AmnioText^M, a dehydrated amniotic membrane allograft, was applied over the wound to serve as a protective barrier. Each allograft application process included AmnioText^M, silicon non-adherent dressing, BlastX, collagen, Drawtext, and Urgo2K multilayer compression bandaging. The patient was encouraged to keep his leg elevated while working and take a 30-minute walk daily. He was prescribed vitamins C and D, multivitamins, and Juven twice daily. Complete closure was achieved after four weeks of intensive wound preparation, followed by six weeks of AmnioText^M applications. After successful wound closure, the patient was encouraged to wear 30-40 mmHg compression stockings daily and to perform 30-60 minutes of aerobic exercise daily to facilitate venous return. Follow-up appointments consisted of regular assessments for an additional three months due to the high recurrence rate for venous ulceration. To date, the patient has been compliant with his post-AmnioText^M allograft application regimen and has maintained successful wound closure.

Discussion

In 2014, Stephen Barr demonstrated the benefits of using DAMA in seven patients with surgical wounds, venous leg ulcers, and diabetic foot ulcers [16]. Of the seven patients, all but one experienced at least 86% wound closure in an average of 8-14 weeks. Compared with conservative management, medical literature supports the fact DAMA used as a barrier or covering accelerates wound closure time in ulcers. CVI has a pathophysiologic basis consistent with chronic, ambulatory venous hypertension [17]. CVI is insidious and despite revascularization, may lead to venous ulceration, as presented in this case. Despite months of conservative management, this patient suffered from a treatment refractory wound. Similar observations were reported in this case study. Wound contracture was consistent and clinically evident after each of the six allograft applications. Each allograft was applied based on medical necessity. Weekly allograft applications were terminated upon wound closure, as shown in table 1. The healing process of the ulcer can be observed qualitatively in figures 1-4 and quantitatively in table 1

While amniotic membrane allografts have been shown in repeat clinical studies and case presentations to accelerate the time to wound closure in venous leg ulcers, they are also comparable in cost to the standard of care [20]. Not only is the standard of care for VLUs shown to be less effective in wound closure rate, but it is also higher in cost when considering additional quality of life metrics. When accounting for the expenses involved in treating VLU's, patient travel to and from a wound care supplies not covered by insurance, lost wages from time off work, and caregiver fees for home care nurses or aids are all out-of-pocket expenditures for patients. Extending wound closure rates by weeks or even months may result in medical bankruptcy for patients and their families.

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Figure 3. 22 March 2022; VLU measurements: 1.00 cm × 1.00 cm (Patch application shown)



Figure 4. 26 April 2022; VLU measurements: closed.



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Data

Table 1	
Date of Examination	Venous Leg Ulcer Measurement
2/1/2022	2.00 cm x 1.50 cm
2/8/2022	2.25 cm x 2.00 cm
2/22/2022	1.75 cm x 2.25 cm
3/1/2022	2.00 cm x 1.50 cm
3/8/2022	1.50 cm x 1.00 cm
3/14/2022	1.50 cm x 1.00 cm
3/22/2022	1.00 cm x 1.00 cm
3/29/2022	0.75 cm x 0.75 cm
4/5/2022	0.65 cm x 0.75 cm
4/12/2022	0.50 cm x 0.25 cm
4/19/2022	0.25 cm x 0.15 cm
4/26/2022	closed

•Wound Preparation •DAMA applications • Wound Healed

Results

Upon initial examination on February 1, 2022, the VLU measured 2.00 cm x 1.80 cm (Figure 1). The wound was open and showed clear signs of lipodermatosclerosis. The edges and outline of the ulcer were poorly defined. At the final examination on April 26th, the VLU (Figure 4) was closed. Despite wound closure evident at the final visit, a slight indentation was present in the skin topography with minimal traces of skin irritation. The patient's wound contracted consistently and clinically significantly throughout six DAMA applications, as seen in table 1. Noting that the patient's VLU had been open for ten months despite revascularization prior to the first application of DAMA, aggressive VLU management with DAMA allografting was instrumental in accelerating the time to VLU closure. Among the most important outcomes from this case study, and confirmed by other studies, the use of DAMA may decrease the risk of infection, reduce the pain associated with an open wound, and accelerate the time to wound closure.

Conclusions

The utilization of amniotic membrane allografts accelerates wound closure times in chronic VLUs and is consistent with the current medical literature. In the presented case study, the use of amniotic membrane allografts closed a 10-month-old wound, refractory to conservative measures and revascularization, in 12 weeks. The patient achieved full closure after six AmnioText™ allograft applications. Future application efforts centered on the preventative use of amniotic membrane allografts on patients with recalcitrant venous leg ulcers present a novel opportunity to reduce long-term morbidity, improve quality of life, and reduce national healthcare costs.

Future Directions

Medicare currently recognizes the medical necessity of DAMA allografts and provides some reimbursement for their application when used as an intervention for DFUs and venous stasis ulcers [21]. This assistance is critical in underserved communities where resources are limited, medical supply costs are high, availability is low, and transportation is challenging. As the population in underserved communities is generally in more frail health and suffers from multiple comorbidities, rapid treatment of venous ulcers could exponentially improve their quality of life and long-term vitality. The future of small and rural community health care is dependent on readily available and affordable treatments that are initiated proactively rather than after the patients require emergency intervention.

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