CHAPTER **34**

Application of Placental Membrane Graft in Management of Recalcitrant Venous Ulcer: A Case Report

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PRESENTATION

An 84 year-old Hispanic man with a history of chronic venous insufficiency presented with reports of chronic left leg ulceration. The ulcer was located approximately 1 cm superior to the lateral malleolus. The patient was treated with local wound care and compression therapy for almost 7 months. However, his leg ulcer failed to heal. The patient presented to our service for a second opinion in hopes of healing the ulcer. A thorough evaluation and examination were performed. The patient's work-up included left leg and ankle radiographs, a noninvasive vascular study, complete blood count, basic metabolic panel, erythrocyte sedimentation rate, C-reactive protein level, aerobic and anaerobic cultures, and biopsy.

PHYSICAL EXAMINATION

Physical examination revealed an oval-shaped full-thickness ulcer measuring 4.6 cm × 2.3 cm × 0.1 cm in diameter with sharply demarcated borders. It was located approximately 1 cm above the lateral malleolus of the left leg. The ulcer base was healthy and granular with no evidence of bone exposure (Figure 1). Changes indicative of chronic venous insufficiency changes (hemosiderin hyperpigmentation, stasis dermatitis, varicosities, non-pitting edema, and lipodermatosclerosis) were revealed during the physical examination. Vascular examination revealed palpable pedal pulses with intact capillary refill time. Neurological examination indicated normal deep tendon reflexes. Vibratory and sharp-dull sensations were intact. Orthopedic examination revealed normal range of motion at all major joints of the foot and leg. Muscle strength was adequate.

DIAGNOSIS

Wound infection and osteomyelitis were excluded based on the results of the blood work, wound cultures, and radiographs. Mild peripheral arterial disease was discovered during the noninvasive vascular study; however, the vascular surgeon cleared the patient and did not recommended vascular intervention. The patient had adequate circulation to heal the ulcer. Biopsy results indicated chronic inflammatory cell infiltration without evidence of malignancy or vasculitis. The final diagnosis was recalcitrant venous leg ulcer.

Figure 1. Initial presentation.

Figure 2. Appearance after the first application of amniotic membrane.

Figure 3. Ulcer size has been reduced 50% after the third application.

Figure 4. Appearance after the fourth application.

Figure 5. Appearance after the fifth application.

Figure 6. Complete wound closure after the sixth application.

TREATMENT

The patient's medical and nutritional conditions were optimized and compression therapy, surgical debridement, and local wound care were initiated. The patient was monitored closely and evaluated on a regular basis. Despite the numerous wound care therapies initiated, the ulcer continued to be recalcitrant. After several weeks of follow-up, no significant improvement in the ulcer healing noted. At that time, bio-engineered skin and soft tissue substitutes were recommended and discussed with the patient. Once the wound bed was well prepared, cryopreserved placental membrane graft was applied to the wound bed in combination with compression therapy and surgical debridement.

RESULTS

After 3 applications of cryopreserved placental membrane graft to the venous ulcer, dramatic reduction in the wound size was achieved (Figures 2, 3). Application of the graft was combined with surgical debridement and compression therapy. Complete wound healing was accomplished after a total of 6 applications (Figures 4-6). Once the venous ulcer had completely healed, compression therapy was maintained to control the edema.

DISCUSSION

When a wound fails to respond to traditional therapy and becomes chronic, clinicians should re-evaluate the wound and consider other possible etiologies. In this case, the medical and nutritional conditions were stabilized and a full workup was performed. Arterial insufficiency was excluded. A wound biopsy sample was taken to exclude other underlying etiologies and to confirm the diagnosis. In this case, the primary goal was early wound closure to reduce the incidence of the complications. Once the final diagnosis was confirmed as recalcitrant venous ulcer, compression therapy in combination with debridement was started. After approximately 4 weeks of treatment, the ulcer failed to heal. At that time, advanced wound care modalities were considered. Cryopreserved placental membrane graft was

selected since it contains growth factor and components of extracellular matrix. Application of the graft combined with compression therapy and debridement to control the edema, stimulated granulation and facilitated early wound closure.

LITERATURE REVIEW

Venous insufficiency ulceration makes up the largest chronic ulcer group (1). These ulcers are notorious for having high recurrence rates (2). Venous insufficiency is the inability of the veins of the lower leg to pump blood back towards the heart. The veins in the lower legs are equipped with one-way valves that allow them to pump blood to the heart against gravity. The calf muscles especially in ambulatory individuals also help this pumping action. Venous insufficiency results when there is a failure of the calf muscle as well as valvular incompetence. Valvular incompetence results when the one-way valves start allowing back-flow of blood. This reflux leads to blood pooling in the legs and increased pressure. The resulting venous hypertension leads to edema. Due to the edema and increased pressure the red and white blood cells tend to aggregate in tissues. The extravasation of blood cells leads to inflammatory changes in the tissue and ultimately its breakdown (3).

The hallmark for the treatment of venous legs ulcers is compression, which is most commonly achieved by a short-stretch bandage like an UNNA boot (4). The non-elastic, rigid design of the UNNA boot allows it to be very effective in providing adequate compression for ambulatory patients with venous leg ulcers (4). This results in reduced edema and pain. The compression of the UNNA boot works on improving the calf muscle pump, therefore it should be noted that this particular type of compression is designed for patients that are ambulatory (1). Due to the changing pressure, it is crucial that clinicians understand how to change the degree of compression along the lower extremity (5). For instance, the pressures at the ankle tend to be higher than the pressures above the ankle. Therefore, when compression is applied, care must be taken to apply greater pressure at the ankle (6). Research has shown that compression can be extremely effective in reducing edema when applied correctly (2). Clinicians run into challenges when the compression cannot be applied to certain patients due to other co-morbidities such as obesity and arterial disease.

It is recommended that venous leg ulcers that do not respond well to compression therapy should be biopsied (1). The biopsy results can be used to aid the clinicians in proper diagnosis and the appropriate treatment (3). Venous ulcer beds often contain fibrinous tissue and exudates, which need to be debrided on a regular basis (7). Without proper wound bed preparation, it becomes difficult for wound care modalities to penetrate the wound bed (1). It is imperative that a patient's vascular status is evaluated prior to sharp debridement with a surgical blade. Patients who are not good candidates for surgical debridement due to underlying arterial disease or their nutritional status can benefit from chemical and/or enzymatic debridement. Enzymatic debridement consists of the application of topical agents that aid in digesting the proteins that hinder wound closure such as high levels of bio-burden and matrix-metalloproteases (3).

The use of growth factors and cryopreserved products is becoming popular in the management of chronic wounds. It is also imperative that clinicians understand the importance of early wound closure. Research has shown that the longer a wound stays open, the more likely it is to become chronic (8). Clinicians are often faced with the question of when to use advanced wound care products. Surrogate end-points allow clinicians to keep the treatment progress of the wound in check. It is recommended that clinicians use surrogate end points to assess the progress of the wounds (8). If a wound has stalled or has gotten worse since its initial presentation, then clinicians should take another look at wound and try to determine why the wound is not responding to traditional therapy. The use of surrogate end-points is also helpful in the treatment of diabetic foot ulcers (9). These end points allow clinicians to use advanced treatment modalities in a timely manner. The mistake of delaying advanced treatment modalities is often made as clinicians wait too long to use them.

Chronic ulcers are often stuck in the inflammatory phase of wound healing (4). Care must be taken in order to stimulate the wound back on the track of the healing progress. Chronic wounds are known to have an imbalance of growth factors and proteases (4). New research is directed towards the development and efficacy of wound care products that contain biologic products designed to provide chronic wounds with the help they need to progress towards closure. A bioengineered living skin equivalent product that is approved by the Food and Drug Administration for diabetic and venous leg ulcers is Apligraf. The efficacy of Apligraf has been tested in randomized controlled clinical trials (1). Studies show that the use of graftskin is highly effective in the treatment of chronic venous ulcers that have been present for longer than a year (10).

Cryopreserved placental membrane graft is being used for the treatment of chronic diabetic and venous ulcers. This type of graft is unique in design in that it not only contains growth factors but also components of the extra-cellular matrix (11). It is also known for its anti-inflammatory and anti-microbial abilities (10). The ability of the graft to stimulate wound closure also arises from the underlying mesenchymal stem cells that it contains (10). Amniotic membrane is also rich in collagen, which can be beneficial for the closure and the maintenance of ulcers because collagen plays a key role in the tensile strength of the wound (6).

Lavery et al showed the efficacy of amniotic membrane in the closure of diabetic foot ulcers as well as venous leg ulcers (10). Research shows that the use of advanced wound care products such as cryopreserved placental membrane along with compression therapy can facilitate wound closure, reduce pain, and stimulate granulation of the wound bed as well as its epithelialization (2).

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