Use of Equine Derived Pericardium as a Biological Cover To Promote Closure of a Complicated Wound With Associated Scleroderma and Raynaud’s Disease

Gerit Mulder, DPM, MS, FAPWCA and Daniel K. Lee, DPM, FACPAS

Abstract: A 39-year-old man with previously undiagnosed scleroderma was admitted to the UCSD Medical Center with bilateral, limb-threatening necrotic lower extremity ulcers extending to underlying fascia and muscle. Rather than amputate the extremities, the patient requested alternative treatment and underwent extensive tissue debridement followed by placement of an equine pericardium xenograft. Subsequent to treatment, the patient underwent weekly examinations and dressing changes without additional treatment. The patient was ambulating without assistance and with complete closure of all wounds in 10 weeks. The patient remained without wound recurrence at a recent 6-month follow-up visit.
Cutaneous manifestations include both digital ulcers that result from progressive Raynaud’s phenomenon and extremities ulcers found on bony prominences such as the olecranon, malleolus, and calcaneus. These ulcers can be very painful. Many factors appear to contribute to the etiology of these ulcerations. While digital tip ulcers are most commonly caused by ischemia, skin conditions due to fibrosis, contracture, and trauma may contribute to ulcers over bony prominence and joints. Vasculitis also is a major contributor in the large deep, painful, punched-out lower leg and malleolar ulcers.

Case Report

A 39-year-old Hispanic man was admitted to the University of California Medical Center with full-thickness ulcers that extended to underlying muscle, tendon, and fascia of the medial and lateral aspect of both ankles, the dorsum of both feet, and the digits of both feet (Figure 1).

The patient complained of the sudden appearance of these wounds and did not understand why they had developed. He stated the wounds were associated with extreme pain and heavy drainage and had been present for approximately 6 months. The patient had not sought medical treatment prior to admission through the Medical Center Emergency Department. The patient was not on any medications at the time of admission and was unaware that he had any medical problems. The remainder of his past medical history and surgical history are unremarkable and noncontributory. His family history was noncontributory. He denied any use or consumption of tobacco, alcohol, or illegal drugs. His review of systems was noncontributory, except for his history of present illness.

Subsequent to admission to the medicine service, plastic surgery, orthopedic, vascular surgery, and infectious disease consults were requested. Upon physical exam, he was found to have full-thickness ulcers with tissue and tendon necrosis of his dorsal left foot and left medial ankle extending to the gastrocnemius-soleus muscle with full-thickness ulcerations with undermining and tunneling of his medial right ankle and both lateral ankles, as well as multiple full-thickness ulcers of the digits of his right foot (Figure 2).

His diagnostic lab results supported a diagnosis of scleroderma and anemia. He had a +ANA and anti-Scl70 AB. After several consultations with different services regarding the nature of the wounds, the general consensus was to offer amputation of the left limb while attempting to salvage the right limb through surgical debridement and conservative dressing therapies. During his hospital stays, the patient was treated with vancomycin and piperacillin/tazobactam (Zosyn, Wyeth, Madison, NJ), topical bacitracin, and twice daily gauze wraps (Kerlix™, Covidien, Mansfield, MA), and kept on bedrest with bathroom privileges. After 11 days, the Wound Treatment and Research Center was consulted regarding possible conservative care and limb salvage. At the time of examination, the patient was afebrile with decreased cellulitis. There was only a minimal change in the status of the wounds.

Treatment. The patient was scheduled for wound excision, surgical debridement of all nonviable tissues, and application of acellular skin matrices. Vacuum-assisted closure was considered but not used due to the physical characteristic of the wounds and the severe pain associated with use of the negative pressure device over the damaged tissue areas.

The patient was brought to the operating theatre and administered anesthesia consisting of a popliteal block with IV conscious sedation. All nonviable tissues were removed using sharp surgical intervention and hydrotherapy (VersaJet®, Smith and Nephew, Fort Lauderdale, FL). Debridement included areas of sub tendon sinuses, cavities, and undermined wound margins. The area with deepest defect (medial left ankle), once fully debrided of all nonviable tissue, was injected with a flowable collagen-glycosaminoglycan (Integra Flowable...
Wound Matrix™, Integra Lifesciences, Plainsboro, NJ), while a silicone free collagen-glycosaminoglycan based product (Integra™ Wound Dressing) was placed over remaining areas of exposed tendon on the medial ankle wound only. All wounds were then covered with nonfenestrated equine pericardium (Unite® Biomatrix, Synovis Life Technologies, St. Paul, MN), which extended approximately 2 cm–3 cm beyond the wound margins. The collagen-glycosaminoglycan was applied in an attempt to expedite cell migration into defects where contact between the xenograft and the underlying tissue was not possible. The collagen-glycosaminoglycan matrix is designed as a temporary matrix allowing for cell integration and eventual replacement by host cells. Data in favor or against the use of combined therapies as implemented in this patient are not currently available. The decision to use this combination of products was based on wound evaluation and clinical judgment at the time of surgery. The equine pericardium was the primary graft material used for all of the wounds, including the medial ankle. The xenograft was held in place with either staples or Steri-Strips™ (3M Healthcare, St. Paul, MN) depending on the status of the periwound tissue and the location of the wound. Where periwound inflammation was still present or where the skin appeared fragile, the Steri-Strips were used in place of the staples. The xenograft was then covered with a single layer of petrolatum gauze, multiple layers of bolstered 4-in x 4-in gauze pads, Kerlix, and a Coban™ wrap (3M Healthcare, St. Paul, MN). The patient tolerated both the procedure and anesthesia exceptionally well, and there were no complications or difficulties. The patient was readmitted to the Medicine Service postoperatively for ongoing care and observation. The patient was continued on his preoperative antibiotics and kept in the hospital nonweight-bearing for the initial week, followed by crutch training and nonweight-bearing on the left lower extremity. A removable splint had been placed on the left lower extremity postoperatively for immobilization of exposed tendon. Due to his home and insurance situation, discharge did not occur until postoperative day 11 (Figure 3).

Subsequent to the surgery, the dressings were left intact for 1 week. Drainage was not evident at the time of dressing change and all underlying xenograft appeared intact with no drainage from the xenograft margins.

The patient stated that he had significantly less pain and was able to decrease his pain medication intake. Staples and retention materials were removed at week 1, and the wound was redressed in a manner similar to how it was applied in the operating theater.

Dressings were again changed at postoperative day 12 at which time the xenograft appeared to be desiccating externally with “lifting” on the material at the wound margins. Re-epithelialization had occurred at the wound edges. All wounds appeared to be progressing toward closure. Clinical signs of periwound inflammation were absent as were edema, erythema, and heavy drainage.

The patient was discharged home and presented for a follow up visit 1 week following discharge to the outpatient Wound Clinic at UCSD Medical Center. At the time of his outpatient presentation, wounds were continuing to close with displacement of the xenograft following underlying wound closure.

Figures 4, 5, and 6 illustrate the wounds 8 weeks following surgery. At this time the patient was ambulating successfully with the use of a cane.

All but the largest of the wounds had fully closed without complications. The patient was subsequently discharged and had left the country to get married following his last visit. He subsequently stopped by the clinic 3 weeks later to thank the staff, confirm that all his wounds were closed, and to inform the clinic that he was no longer ambulating with a cane.

**Discussion**

Wounds associated with scleroderma are multifactorial and traditionally treated with a variety of modalities combined with local wound care such as debridement, topical antimicrobials, and dressing changes. Some authors have reported successful treatment of wounds of ischemic etiology by improving blood flow and tissue perfusion using hyperbaric oxygen therapy, vasodilator drugs, platelets inhibitor, and fibrinolytic agents. In
severe cases, surgical intervention such as arterial bypass, skin grafting, and below knee amputation were reported.\textsuperscript{3,9,10} Yoon et al\textsuperscript{11} reported successful treatment of vasculitic wounds without ischemia in the lower extremities in a 62-year-old woman using becaplermin gel (recombinant human platelet-derived growth factor) supplemented by oral immunosuppressive agents. Wounds were closed by 22 weeks.\textsuperscript{11} The patient in the present case had excellent arterial blood flow and the wounds were not ischemic, but were secondary to vasculitis and severe inflammation with extensive necrotic tissue. The pain reduction in the first week of treatment and wound closure by 8 weeks made the benefits of the xenograft evident.

The mechanism of action of equine pericardium on the repair process is not clearly understood at this time, although studies are underway to determine its mechanism of action, particularly at the cellular level. A recent study by Winter et al\textsuperscript{12} suggests that an allograft acts as an implant, which allows cellular infiltration and eventual allograft incorporation into the wound defect. The authors allowed different treatments on the wounds thereby not enabling the effect of the allograft to be differentiated from that of other modalities. Since the study was neither randomized nor well controlled, a conclusion as to its mechanism of action and clinical value of the allograft cannot be made.

In the present case, only the xenograft was used as treatment from initial application through complete wound closure. This case study illustrates the potential benefits of a xenograft in a case of an inflammatory wound. Although it can be hypothesized that the effect of the xenograft is one that allows for optimal cellular activity through modulation of inflammatory levels and cytokine activity, a conclusion cannot be made without randomized, controlled clinical trials that include histological and gene array analyses. Neither allografts nor xenografts are true grafts or implants in the chronic wound setting, rather they appear to be biological modulators of the intrinsic cells present during the repair process.

Unite Biomatrix is used as a wound dressing for a variety of chronic wounds including diabetic ulcers. These products are equine pericardia based, which go through a decellularization process followed by stabilization (flexible cross-linking) and sterilization with EDC (non-toxic, water soluble chemical). This results in a flexible cross-linked tissue that is biocompatible, pliable, has a natural texture and feel, and is highly resistant to prote-
olytic enzymes degradation. The final product retains the native structural attributes of collagen (Figure 7).13

Regardless of etiology, once an ulcer develops and does not proceed to healing, the chronic wound environment develops unique characteristics, which include excessive proteases, increased cellular senescence, and an increase in bacterial bioburden.14 At a cellular level, evidence suggests that higher levels of MMP production by fibroblasts is one of many factors that contributes to delayed healing.15 Some of the noncollagen degrading proteases are also known to impair anchoring of the remodeling cells entering chronic wounds.16

Conclusion

Lower extremity ulcerations are associated with severe inflammation, high levels of pain, tissue necrosis, and fail to respond to conservative or surgical intervention, particularly when the underlying etiology is related to systemic scleroderma. Conventional skin grafts may not always be an option due to the wound presentation, location, and rapid skin graft breakdown associated with the ongoing underlying inflammatory response and high levels of proteases in the wound. The authors presented a case of limb-threatening bilateral lower extremity ulcerations associated with scleroderma, which healed subsequent to a single surgery involving the application of acellular tissue substitutes. At this time, the mechanism of action is not known although it may be postulated that the xenograft affects the level of activity of inflammatory and other cells. Animal and clinical trials are underway to determine the mechanism of action. It is also of important note that xenografts (as well as human allografts) do not function as true grafts; rather they are more correctly classified as biological dressings, when used on chronic and problematic wounds. These products should be considered as viable treatment options, as well as biological covers, in difficult to heal wounds.

References

4. Systemic sclerosis (scleroderma) and related disorders.
15. Ballsam CB, Davidson JM. Delayed wound healing in aged rats is associated with increased collagen gel remodeling and contraction by skin fibroblast, not with differences in apoptotic or myofibroblast cell populations. Wound Repair Regen. 2001;9(3):223–237.