Treatment Of An Exposed Achilles Tendon Within A Refractory Mixed Arterial Venous Leg Ulcer With The Novel Use Of Pericardium Allograft In Combination With Amniotic Allografting, Synthetic Extracellular Matrix, And Acellular Dermis Allografting: A Case Report

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Abstract

Xenografts, commonly from porcine or bovine sources, have decades long documented use in reconstructive surgery, including the repair of Achilles Tendons. Despite decellularization processes, the risk of antigenicity with xenografts still poses a threat for graft failure. Allograft tissues reduce the risk of immune response and provide greater likelihood of successful grafting. BoneBank ™ Allografts SteriGraft® Pericardium (BSP) (San Antonio, Texas, USA) is a lyophilized allograft obtained from the pericardial sac that has undergone sterilization and processing for use in the surgical repair. The aim of this case study was to highlight the novel use of human pericardium allograft in the repair of an exposed Achilles tendon within a vascular ulceration with the concomitant use of synthetic extracellular matrix, amniotic allografting, dermal allografting and negative pressure wound therapy to achieve healing of the wound and restoration of limb function.

Introduction

Tissue grafts are commonly used in regenerative medicine and include xenografts, autografts, and allografts. Xenografts are grafts that are trans- planted between different species, often bovine or porcine.1 Autografts are harvested from one area of the patient's body and implanted into the same patient to replace an injured tissue. Autografts have drawbacks including limited supply of donor tissue available, morbidity, pain, and requiring a "secondary" surgery, although in many cases they are the ideal option. Tissue allografts are harvested from donor tissue and implanted in different patients. Allograft tissues are usually obtained from cadaveric donors and are commonly stored frozen or cryopreserved.

Tissue allografts have a long history of use and have overcome the obstacles of immunologic rejection through various processing techniques including the use of formaldehyde, glutaraldehyde, deep freezing, cryopreservation with cryoprotectants, freeze-drying, and irradiation.2 Allograft tissues undergo a "decellularization" process which removes cellular byproducts and genetic material using detergents and digesting enzymes leaving only mechanically intact but biologically inert extracellular matrix scaffolds which can then be repopulated with the patient's own cells.3-5 Preserved animal and human pericardium has been used in a wide variety of surgical and clinical applications.2

Pericardium is a sac-like membranous tissue surrounding the heart and roots of the major blood vessels that serve a protective and mechanical function.6,7 It con- sists of two layers of tissue, the outer fibrous pericardium (parietal) and the inner serous pericardium which is in con- tact with the myocardium (epicardium).7 The parietal pericardium is a collagen-rich biological tissue containing glycoproteins and glycoaminoglycans, including hyaluraonic acid, in an amorphous matrix which acts as a reservoir for signaling molecules such as cytokines and growth factors.7,8 The parietal pericardium con- sists of a loose arrangement of collagen and elastic fibers (elastin and fibrillin), and it is primarily composed of collagen type I.7 Pericardium allograft has also been shown to have the preservation of biochemical and biomechanical properties and the histioarchitecture of the pericardial scaffold following decellularization processing.6

The Achilles is the strongest and largest tendinous structure in the body.9 The Achilles tendon tissue contains fibroblasts (tenocytes) that are interspersed between collagen fiber bundles which synthesize and maintain the extra-cellular matrix of the tendon and facilitate healing. The Achilles tendon is comprised of 90% collagen type I and the remainder is primarily glycosaminoglycans and structural proteins such as elastin connect adjacent fibrils.9,10

Loss of the posterior skin over the distal aspect of the lower extremity exposing the Achilles tendon presents a difficult wound to heal that often does not heal spontaneously.11 These ulcerations can originate from many sources including vascular disease, diabetic ulcerations, radiation exposure, trauma, pressure sores, and collagen disorders.12 Exposed tendon wounds are difficult to heal due to poor local blood supply, lack of local growth factors, and high susceptibility of infection.13 The loss of extracellular matrix in combination with the exposure of tendinous structures slows and may ultimately prevent closure of the wound.14 The exposed avascular tendon in the wound base complicates management, and achieving coverage of the Achilles tendon is difficult due to the tightness of the skin in the area.11 Reconstruction and repair of the wound must be durable enough to withstand weight bearing but thin enough to allow use of footwear.15 Part of the difficulty in treating exposed tendons in ulceration is that the lack of blood flow to the tendon itself leads to tendon necroses after prolonged exposure, and at the same time, the lack of local granulation tissue growth around the tendon leads to necrosis of dermal grafts.13 Replacement of the extracellular matrix has been shown to significantly increase the chances of healing since, with revascularization of the matrix, a wound bed is created that may either heal by secondary intention or via the application of a graft.14 If granulation tissue can be stimulated to cover the vascularly deficient region, reepithelization can occur.11

BSP is a lyophilized (freeze-dried) allograft obtained from the pericardial sac that has undergone sterilization and processing for use in the surgical repair. It undergoes proprietary processing called GraftCleanse™ (Bone Bank Allografts, San Antonio, Texas) and is sterilized using gamma radiation.

SimpliDerm® Acelluar Dermal Matrix (ADM) (Aziyo Biologics, Silver Spring, Maryland) is a pre-hydrated human acellular dermal matrix which enhances and supports the angiogenic process, provides a pliable matrix, and has been shown to promote fast integration and rapid revascularization.16,17

Negative pressure wound therapy (NPWT) is an effective treatment modality used to promote granulation tissue formation and perfusion while providing a closed, moist wound healing environment.18 NPWT is especially effective with vascular ulcerations as it has been shown to help reduce edema and remove exudate from the wound.18 V.A.C White- Foam™ Dressing (WFD) (3M, Saint Paul, Minnesota) is a white polyvinyl alcohol foam which is dense, open-pore, and hydrophilic, with high tensile strength. Its non-adherent properties help to protect delicate structures such as grafts.

PalinGen® XPlus Hydromembrane (PXH) (Amnio Technology, Phoenix, Arizona) is chemically cross-linked with extracellular matrix fibers to give it strength, shape, and slower resorption in vivo.1 PalinGen® Flow (PF) (Amnio Technology, Phoenix, Arizona) is a cryopreserved suspension amniotic allograft.19,20

These amniotic allografts contain collagen types I, III, IV, V, and VII, cytokines, hyaluronic acid, fibronectin, laminin, fibrinogen, amino acids, proteoglycans, tis- sue inhibitors of metalloproteinases (TIMPs), extracellular matrix proteins, and mesenchymal stem cells, which are all recognized as part of the complex wound healing process.9 Amniotic allografts also include key growth factors such as fibroblast growth factor (FGF), epidermal growth factor (EGF), platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), and transforming growth factor beta (TGF-β).21 When applied to a wound, however, the amniotic stem cells contained in amniotic allografts can experience rapid cell death and clearance. The ultrafine fibers of electro- spun synthetic extracellular matrices have been shown to promote stem cell survival and proliferation.22-33 Anthem™ Wound Matrix is a three-dimensional electrospun synthetic polymer matrix (3D ESPM) which mimics the native extracellular matrix and facilitates pro-regenerative cellular adhesion, infiltration, and proliferation.34-36

In this case, we demonstrate the use of amniotic allografts in combination with synthetic extracellular matrix to stimulate granulation tissue within a vascular ulceration with an exposed Achilles tendon. This is followed by the novel use of a pericardium allograft to repair the Achilles tendon. The grafting of a dermal allograft in conjunction with NPWT can achieve healing and closure of the wound.

Case Report

We present the case of a 76-year-old male patient with a past medical history of adult-onset diabetes mellitus, hyper- tension, hyperlipidemia, and peripheral vascular disease. The patient had a mixed arterial and venous leg ulceration (MAVLU) of the left posterior ankle that had been present for several months and was refractory to conservative wound care efforts. The patient had undergone left femoral endarterectomy and patch angioplasty, left common iliac artery stenting, left lower extremity angiogram, and wide debridement of the left posterior ankle ulceration which fully exposed the distal Achilles tendon. Following the successful revascularization of the left lower extremity and debridement of the wound by our colleagues in vascular surgery, the patient's care was transferred to our team in podiatric surgery for management of the wound.

During the initial visit, a thorough his- tory was obtained which was comprised of their past medical history, current medications, allergies, surgical history, and social history. A complete review of systems was performed, and a lower extremity focused exam was conducted which included vascular, dermatologic, neurologic, and musculoskeletal. Radiographs were obtained of the lower extremity and blood tests were performed including glycosylated hemoglobin levels. A wound swab was then collected from the wound and sent for culture/sensitivity testing.

The patient had no known drug allergies and was on long-term anticoagulation therapy. The patient was a former heavy smoker with a 32-year pack history. Physical exam demonstrated palpable pedal pulses, intact protective sensation, and no gross deformity of the foot or lower extremity.

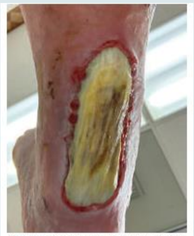

Figure 1. Initial presentation of a wound with an exposed and devitalized Achilles tendon.

The ulceration was located on the posterior aspect of the left ankle. The patient reported intense pain from the ulceration. The Achilles tendon was fully exposed from its insertion on the calcaneus, about 10cm proximally. The Achilles tendon was desiccated and the paratenon was friable. Deep to the Achilles tendon, the tibia was exposed. Additionally, the periwound skin was erythematous and fragile. The wound was malodorous and had sanguinopurulent drainage. The lower leg and foot were edematous. The exposed Achilles tendon comprised >90% of the wound bed, the remainder of which was primarily granular tissue. Radiographs revealed no concerning findings for osteomyelitis. Glycosylated hemoglobin had a reported value of 6.6. A wound swab was obtained and sent for culture and sensitivity testing which showed group B streptococcus and pseudomonas aeruginosa. The patient was started on oral antibiotic therapy which was continued throughout the duration of treatment.

The planned treatment protocol was decided at the initial visit to be appropriate debridement and a combination of amniotic allografting with synthetic extracellular matrix to granularize the wound and promote wound healing. This would be followed by repair of the Achilles tendon with a pericardium allograft and negative pressure wound therapy. Following successful integration of the pericardium allograft, a skin substitute allograft would be grafted overtop to close the wound and negative pressure wound therapy would be continued until the graft was fully incorporated.

At the initial visit and the subsequent seven visits afterward, the following treatment protocol was performed. The left lower leg was scrubbed with provodone-iodine using a sponge brush, rinsed clean with sterile saline, and allowed to air dry (Fig. 2a). Local anesthesia was obtained at about the left lower leg using 1:1 2% lidocaine plain and 0.5% bupivacaine plain in a ring block fashion proximal to the ulceration

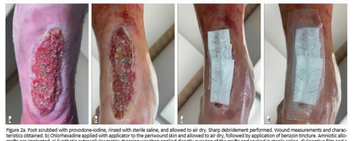

Figure 2a. Foot scrubbed with provodone-iodine, rinsed with sterile saline, and allowed to air dry. Sharp debridement performed. Wound measurements and characteristics obtained. b) Chlorhexidine applied with applicator to the periwound skin and allowed to air dry, followed by application of benzoin tincture. Amniotic allografts are implanted. c) Synthetic extracellular matrix dressing was then applied directly over top of the grafts and soaked in sterile saline. d) Coaptive film and a non-adherent dressing were used to secure the grafts and synthetic extracellular matrix in place.

Sharp debridement was performed removing all non-viable tissue. Wound size measurements were recorded at each visit. Wound size was calculated as the product of the length, width, and depth in cubic centimeters (cm3).

Chlorhexidine was then applied with an applicator to the peri-wound skin and allowed to air dry. This was followed by the application of benzoin tincture to the periwound skin. PXH and PF were applied directly to the wound bed (Fig. 2b). 3D ESPM was then applied directly over top of the grafts after being soaked in sterile saline (Fig. 2c). Utilizing coaptive film and a non-adherent dressing, the grafts and syn- thetic extracellular matrix were secured in place (Fig. 2d). This was followed by a secondary dressing which included an inner absorptive and outer protective layer. The left lower extremity was then offloaded using total contact casting.

Figure 3a. Preparation of Achilles tendon for grafting. b) Circumferential wrapping of BSP around Achilles tendon. c) Repair of Achilles tendon with BSP followed by application of PXH and PF.

Following two months of combination therapy using PXH, PF, and 3D ESPM, granulation tissue had sufficiently filled the wound bed, and it was decided to proceed with repair of the Achilles tendon using the pericardium allograft (Fig. 3a). The left Achilles tendon was debrided of all nonviable tissue and repaired with 80mm x 80mm BSP allograft which was wrapped circumferentially about the Achilles tendon and sutured in place (Fig. 3b). The PXH and PF were applied directly to the wound bed (Fig. 3c).

A hydrocolloid ring was applied around the wound perimeter (Fig. 4a), and WFD was used to protect the pericardium graft (Fig. 4b). Negative pressure wound therapy was then applied (Fig. 4c). The left lower leg and foot were wrapped with a cotton roll and a com- pression wrap just distal to the knee. The patient was placed in a pneumatic below- knee offloading boot with foam cutouts to offload and protect the ulceration.

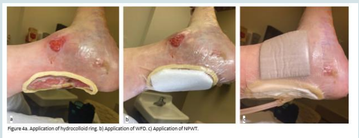

Figure 4a. Application of hydrocolloid ring. b) Application of WFD. c) Application of NPWT.

After four weeks of NPWT, the pericardium allograft had fully incorporated into the Achilles tendon and the wound bed was ready for closure with skin grafting (Fig. 5a). SimpliDerm™ (Elutia Inc., Silver Spring, Maryland) was fenestrated and sutured in place over top of the wound (Fig. 5b). Negative pressure wound therapy was continued and the patient continued to be offloaded in a pneumatic below-knee boot.

Subsequent visits saw continued incorporation of the dermal allograft and healing of the wound. The dermal allograft completely incorporated and granular tissue fully covered the Achilles tendon. The patient reported minimal pain from the wound and was able to resume normal activates of daily living with full weightbearing.

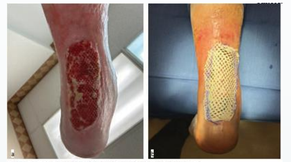

Figure 5a. BSP fully incorporated into Achilles tendon. b) Application of ADM.

Discussion

Eight weeks of combination therapy using amniotic allografts and synthetic extracellular matrix prepared the wound bed for repair of the Achilles tendon which was accomplished with the novel use of human pericardium.

After 10 weeks of treatment using negative pressure wound therapy and dermal allografting, the patient's functional use of the lower extremity was restored, the wound pain level was reduced, and healthy granular tissue formed, which completely covered the previously exposed Achilles tendon.
The similarity of human pericardium with tendonous tissues in the foot and ankle in regard to biomechanical properties and the histioarchitecture hints at the potential for pericardium allografts to be used in other podiatric surgical applications such as interpositional arthroplasties, acute tendon repairs, ten- don augmentation and transfers, and many others.

It is important to note that this case was performed at the Southern Arizona Veteran Affairs Health Care System; there- fore, cost and reimbursement were not factors in determining treatment. Pericardial allografts, dermal allografts, amniotic allografts, and synthetic extracellular matrices are all reimbursable through Medicare and private insurance and have their own designated HCPCS codes. The cost to benefit ratio would need to be assessed on an individual provider and patient basis. All pricing of the wound care products used in this case are available to the public through the Department of Veteran Affairs Federal Supply Schedule.

Conclusion

When presented with this case, our goals of therapy were to prevent progression of the ulceration through limb salvage, achieve tissue coverage over the exposed Achilles tendon, restore function of the Achilles tendon, minimize patient discomfort, and improve patient quality of life. The outcome of this case report sup- ports the use of human pericardium allograft in Achilles tendon repair.

Additionally, it demonstrates the clinical value of combination therapy using syn- thetic extracellular matrices and amniotic allografting in wound care. Furthermore, this case report illustrates the value of employing multiple wound care modalities, including negative pressure wound therapy and dermal allografting, in the treatment of lower extremity ulcerations. This case demonstrates the novel use of pericardium allografting in the repair of an Achilles tendon and suggests potential indications for use in the repair of tendinous structures in the foot.

Conflict of Interest Statement

The authors of this article declare no conflict of interest. The companies involved had no role in the design of the study; in the collection, analyses, or interpretation of date; in the writing of the manuscript, or in the decision to publish the results.

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