Dehydrated Human Amnion/Chorion Membrane as Adjunctive Therapy in the Multidisciplinary Treatment of Pyoderma Gangrenosum: A Case Report

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Abstract

Pyoderma gangrenosum (PG) is an uncommon chronic and progressive skin disorder that can lead to severe tissue necrosis, pathergy, horrendous pain, and disfigurement if not properly and promptly diagnosed and treated. Systemic treatment traditionally consists of long-term immunosuppression. Topical care of the painful wound often represents a clinical challenge. A 77-year-old woman with multiple comorbidities including venous insufficiency and diabetes mellitus was diagnosed through exclusion with refractory, painful PG. She was managed for 3 months by a multidisciplinary team comprised of an internist, 2 dermatologists, and a podiatric wound care specialist using immunosuppressive therapy, several local wound care modalities, and supportive bandages. During that time, severe wound pain continued unabated and the affected area changed from 3 separate wounds measuring 1.4 cm x 1.0 cm x .01 cm, 1.2 cm x 0.5 cm x 0.1 cm, and 0.6 cm x 0.5 cm x 0.1 cm to 1 wound measuring 8.0 cm x 10.3 cm x 0.1 cm. At that time, dehydrated human amnion/chorion membrane (dHACM) allograft, previously reported to facilitate healing venous leg and diabetic foot ulcers, was incorporated into the treatment plan. The patient reported wound pain decreased from 10 out of 10 to 5 out of 10 within hours following application. At the 4 day follow-up visit, she reported no pain; after 1 week, the wound decreased 6.4 cm x 9.4 cm x 0.1 cm in size and after 2 months (3 applications) the wound had reduced in area from 103 cm^2 to 57.96 cm^2 (reduced by more than half [56%]). In this patient, following the application of dHACM as an adjunct to immunosuppressive therapy, pain receded and wound healing commenced. Additional controlled studies are needed to ascertain the generalizability of this observation.

Keywords: case study, pyoderma gangrenosum, leg ulcer, amniotic membrane, autoimmune diseases

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Potential Conflicts of Interest: Dr. Snyder serves as a consultant for MiMedx Group, Inc, Marietta, GA.

Pyoderma gangrenosum (PG) is an uncommon, inflammatory, destructive neutrophilic dermatosis.[1] PG may be greatly debilitating and extremely painful and can lead to pathergy (ie, wound enlargement secondary to insidious trauma), severe tissue necrosis, and disfigurement if not properly diagnosed and treated.[2] The pathophysiology of this disease is not well understood but thought to be initiated by an inflammatory immune response leading to the nonspecific finding of neutrophilic infiltration.[1] Although the etiology is idiopathic, 50% of PG cases have been associated with other systemic autoimmune diseases such as ulcerative colitis, Crohn's disease, rheumatoid arthritis, and irritable bowel syndrome.[3]

Unfortunately, dermatopathologists have no pathognomonic markers to unequivocally diagnose this malady; therefore, it is a diagnosis of exclusion and usually based upon clinical presentation. According to a retrospective chart review,[4] many clinicians misdiagnose PG with other conditions

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that overlap in symptoms, such as venous leg ulcers, arterial insufficiencies, vasculitis, and various polymicrobial infections. In a review of 86 cases,[3] wound enlargement secondary to insidious trauma (pathergy) was shown to occur in approximately 25% to 50% of PG cases, leading to dramatic enlargement of wounds and often accompanied by severe pain.

PG may be chronic, lasting for months or even years. Although immunosuppression is the mainstay of treatment, literature reviews[5,6] show a variety of topical and systemic agents also are utilized in conjunction with local wound care. The hallmark of systemic treatment for PG remains corticosteroids and cyclosporine; however, several other regimens, used individually or in tandem, have been successful, including the use of various chimeric and human biologics.[5,6] Additionally, researchers[7] hypothesize treatment with mycophenolate mofetil in conjunction with prednisolone may be highly efficacious and even synergetic in cases of PG. Negative pressure wound therapy (NPWT) has been widely used on patients with various wound types and has been shown to improve the rate of healing in lower extremity ulcerations.[8] However, this modality has not been studied in PG; therefore, overall success rates as a treatment for PG are currently unknown. Other therapies, including low-dose tetracycline (for its anti-inflammatory effect) and diaminodiphenyl sulfone, also have been shown in retrospective studies[7] to facilitate healing. Because PG often is associated with other underlying systemic issues, a multidisciplinary team approach that includes internists, dermatologists, and podiatric wound care specialists is often necessary in order to correctly diagnose and treat the condition.

Human amniotic membrane comprised of both amnion and chorion layers has been used for a number of clinical applications for more than a century.[9] In scientific laboratory studies, the molecular fabric of this tissue has demonstrated many key functions: it provides a matrix for cellular migration and proliferation,[10] contains proteins shown to reduce inflammation[11-13] and development of scar tissue, [12,13] has antibacterial properties,[13] and reduces pain at the site of the wound from baseline pain levels.[12] Therapies such as dehydrated human amnion/chorion membrane (dHACM) allografts (EpiFix®, MiMedx Group, Inc, Marietta, GA) have been shown in observational studies and randomized controlled trials to enhance healing of diabetic, venous, and other wounds compared to standard wound care with debridement, moist wound dressing, and compression.[14-16]

Laboratory studies[17] show matrices such as dHACM induce angiogenesis due to the presence of multiple proangiogenic factors found within the dehydrated tissue that retain their molecular composition. To help elucidate the potential angiogenic properties of dHACM allografts *in vitro*, Koob et al[17] demonstrated dHACM grafts contain angiogenic growth factors that retain their biologic activity, promote amplification of angiogenic cues by inducing endothelial cell proliferation and migration, aid in upregulating production of endogenous angiogenic growth factors by endothelial cells, and support the formation of blood vessels *in vivo*. Additional laboratory studies[18] suggest these scaffolds may foster cell-mediated regeneration of extracellular matrix while acting as a magnet for mesenchymal stem cells. These properties suggest dHACM allografts may be an effective treatment for conditions such as PG.

The purpose of this case study is to describe the care of a patient with painful PG whose wound was managed with dHACM as part of her treatment plan. The patient has given written informed consent for publication of the details of her case.

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Key Points

- Pyoderma gangrenosum (PG) may be greatly debilitating and can cause a variety of complications, including very painful ulcerations.
- The author describes the case of a woman with PG who initially presented with a history of a painful lower leg wound, presumed to be caused by venous disease.
- Following 3 months of appropriate systemic treatments, topical wound care, and limited progress, a dehydrated human amnion/chorion membrane allograft was applied to the wound.
- Pain decreased within a few hours and after 2 months the wound was more than 50% healed.
- Studies are needed to help clinicians optimize care for patients with wounds secondary to PG.

Case Report

Presentation and medical history. Ms. J is a 77-year-old Caucasian woman with a medical history that includes diabetes mellitus, hypertension, hyperlipidemia, macular degeneration, microalbuminuria, venous insufficiency, and obesity. Her past surgical history includes a 3-vessel coronary artery bypass graft, right hip replacement, right femur fracture with internal fixation, a remote history of sternal wound infection, and left shoulder surgery. Her current medications include losartan, insulin (Lantus®, Sanofi-Aventis US, LLC, Bridgewater, NJ; and Novolog®, Novo Nordisk, Plainsboro, NJ), indapamide, metformin, Plavix (Sanofi-Aventis US, LLC), and metoprolol.

Ms. J presented with a chief complaint of severely painful lesions on her right anterior shin of 4 months' duration. During that time, Ms. J was told by her previous wound care specialist/podiatrist she had ulcers secondary to varicose veins. According to information obtained from the patient, previous treatments included local wound debridement, topical cadexamer iodine, foam dressings, and multilayer compression

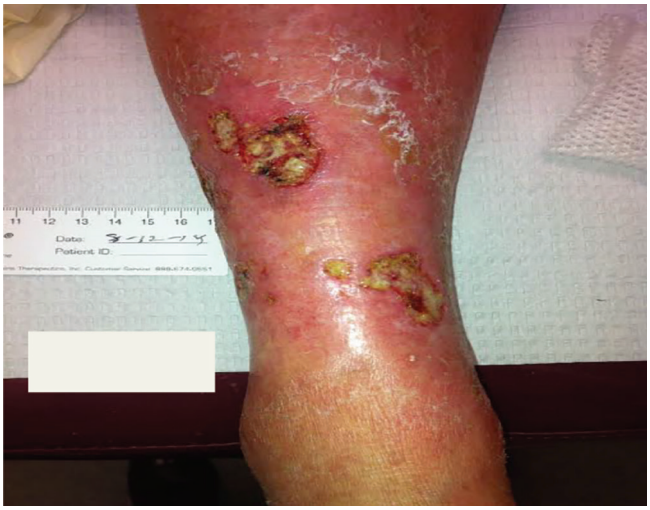

Figure 1. July 2014: Early stage of pyoderma gangrenosum at presentation with 3 separate wounds measuring 1.4 cm x 1.0 cm x .01 cm, 1.2 cm x 0.5 cm x 0.1 cm, and 0.6 cm x 0.5 cm x 0.1 cm.

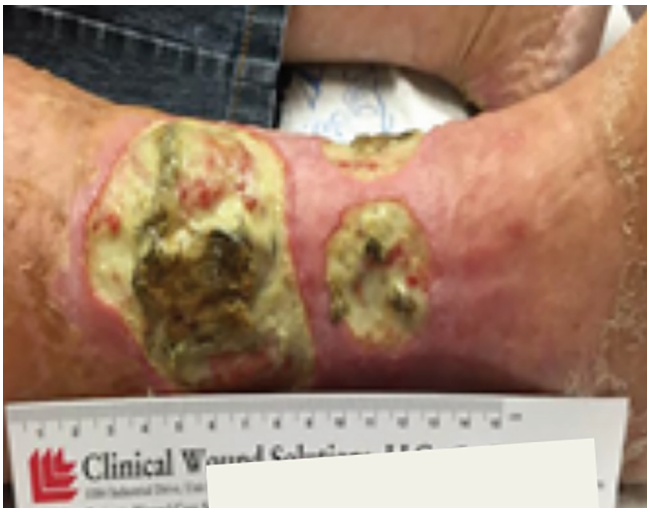

Figure 2. August 2014: 1 month later. The lesions increased in size to 8.5 cm x 6.0 cm x 0.1 cm (central proximal), 3.5 cm x 3.0 cm x 0.1 cm (lateral), 3.3 cm x 5.0 cm x 0.1 cm (medial) with increased necrotic tissue.

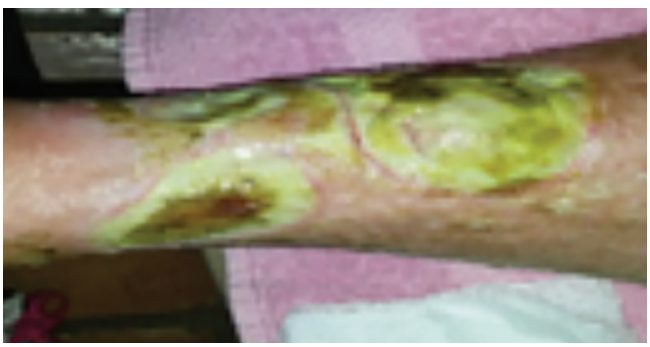

Figure 3. September 2014: Necrotic tissue became more apparent as the disease progressed. The 3 separate wounds started to bridge together. Wound size: 8.0 cm x 6.0 cm x 0.1 cm, 3.5 cm x 3.0 cm x 0.1, 3.3 cm x 5.0 cm x 0.1 cm.

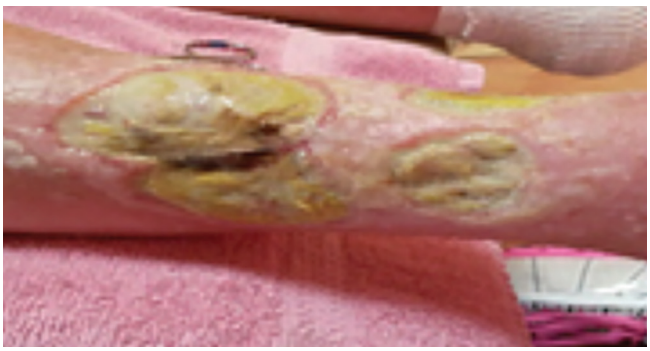

Figure 4. December 2014: The wound had coalesced with irregular violaceous borders, yellow slough, central necrotic tissue before application of the allograft. Wound size: 8.0 cm x 10.3 cm x 0.1 cm.

wraps. Ms. J stated the lesions initially started as "pimples" but within 1 week became open wounds. She said the pain was increasing and the wounds were enlarging despite treatment. Multiple biopsies had been performed several weeks before her first encounter with her wound care specialist/podiatrist who reported the results failed to reveal malignancy, vasculitis, or vasculopathy, although scattered neutrophillic infiltrates were observed throughout the specimens and special stains for bacteria and fungus proved negative. The fact that the wounds "grew larger" after the biopsies prompted Ms. J to seek a second opinion at the authors' clinic.

Physical examination. Physical examination revealed 3 open ulcerative lesions with blisters at the posterior aspect of the right anterior shin. The wounds showed no signs of infection and did not probe to bone, but they were copiously draining.

The 3 separate small lesions had irregular violaceous borders and minor yellowish slough, with isolated patches of necrotic tissue (see Figure 1). No significant pitting edema was observed. Vascular examination revealed weakly palpable pedal pulses on the left and nonpalpable pedal pulses on the right lower extremities. Ms. J's ankle brachial index was 1.3 bilaterally, typically observed in patients with diabetes mellitus with "pipe-stem" arteries and medial calcinosis.[19] Signs of venous insufficiency, including hemosiderosis, lipodermatosclerosis, and torturous varicosities, were noted in both lower legs. Capillary refill was delayed. Homan's sign was absent bilaterally. Neurological examination with Semmes-Weinstein monofilament revealed loss of protective sensation consistent with diabetic neuropathy.

Wound management. The authors initially treated Ms. J's wounds with an absorptive silver dressing prophylactically.

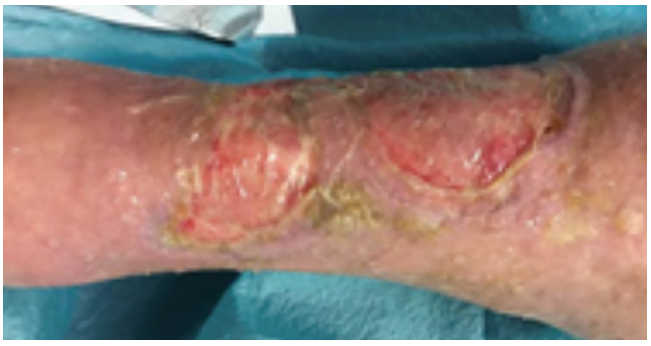

Figure 5. January 2015: 6 months after initial presentation and 1 week after dHACM application. Wound size: 6.4 cm x 9.4 cm x 0.1 cm.

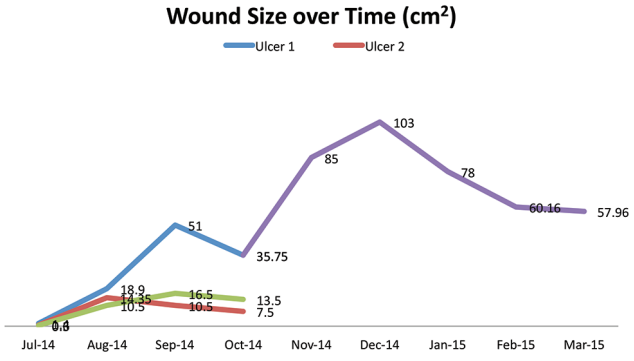

Figure 6. Progression of wounds during the course of treatment. Note that after application of the allograft on January 14, 2015 wound size decreased markedly. As of March 2015, a reduction of 56% from December was noted.

Due to concerns regarding arterial vascular disease, compression was deferred and Ms. J was urgently referred to an interventional vascular specialist who performed a CT angiogram. The right leg arteriogram demonstrated scattered moderate to severe stenosis along the distal superficial femoral artery and upper popliteal artery, which was successfully treated with angioplasty alone. Ms. J was started on clopidogrel 75 mg daily in combination with 81 mg of aspirin daily post procedure. Although vascularity improved, attempts at multilayered compression were followed by intense pain and therefore discontinued in favor of lower-level compression with Tubigrip™ (Mölnlycke Health Care, Marietta, GA). Local wound management with a silver-impregnated foam dressing and selective debridement failed to garner improvement. In weekly follow-up visits over the next month, the wounds were increasing in size (see Figure 2).

Over the next month, the ulcerations continued to enlarge (see Figure 3). Necrotic tissue/slough was treated with topical cadexomer iodine (Iodoflex, Smith & Nephew Inc, St. Petersburg, FL) and perilesional triamcinolone steroid ointment. The perilesional topical was subsequently changed to tacrolimus ointment (Protopic, Astellas Pharma US, Inc, Northbrook, IL). Low-dose doxycycline 20 mg was administered orally for its anti-inflammatory affect. Pentoxifylline (400 mg, 3 times daily) was prescribed for venous disease, and L-arginine (6 g daily) was dispensed as a final common pathway to nitric oxide. During this time, no aggressive debridement was performed due to concerns about potential pathergy. Ms. J reported severe, ongoing pain (10 out of 10).

Diagnosis of PG. Although Ms. J clearly exhibited symptoms of venous insufficiency, treatments failed to improve the lesions and her wounds continued to worsen. A working diagnosis of PG with pathergy was formulated by the multidisciplinary team, which included an internist, 2 dermatologists, and a podiatric wound care specialist. The diagnosis of PG was developed 1 month after her initial presentation at the authors' facility based on the following clinical picture:

1. The wounds did not respond to supportive bandaging, local wound care, and pentoxophylline.
2. The ulcers had elements of necrosis in the absence of ischemia.
3. The patient exhibited severe and unremitting pain in the absence of ischemia. Symptoms appeared to far exceed those accompanying venous disease.
4. The wounds exhibited pathergy, a symptom not observed in venous leg ulcers.
5. Biopsies were negative for malignancy, vasculitis, and vasculopathy. Special staining for bacterial or fungal infection was negative.
6. Behçet's Disease (another disease that can cause pathergy) was ruled out based on lack of recurrent oral lesions and ocular abnormalities.

As previously stated, multiple punch biopsies were procured by Ms. J's previous physician. The authors believe that due to the micro-trauma of the biopsies, pathergy occurred and the lesions continued to increase in size unabated. The diagnosis of PG was corroborated by multiple physicians on the multidisciplinary team.

Treatment of PG. Over the next 3 months, Ms. J received care for PG coordinated by her multidisciplinary team. Goals of care included wound healing, pain control (ie, using a fentanyl patch and hydrocodone for breakthrough pain), control of wound exudate and bioburden, and management of her diabetes and concomitant diseases. Ms. J was given a combination of systemic and local treatment for the lesions. When low-dose doxycycline proved ineffective, she was referred to a dermatologist who prescribed diaminodiphenyl sulfone, (25 mg twice daily) after it was determined Ms. J did not suffer from glucose-6-phosphate dehydrogenase deficiency (G-6-PD). Ms. J also was prescribed prednisolone (60 mg per day) initiated in divided doses with a plan to titrate the drug slowly as symptoms improved. Her blood sugars were monitored daily and determined to be under control by her internist. When the lesions failed to progress, Ms. J was referred to a tertiary medical center for

Table 1. Topical and systemic therapeutic regimens used throughout the course of patient care

Date	Topical	Systemic
August 2014	Triamcinolone topical cream 0.1% was applied 3 times a day with dry sterile dressing taped to the skin. Mild compression was also utilized with Tubigrip (Mölnlycke Health Care, Norcross, GA) with approximately 9 mm Hg	Pentoxifylline 400 mg L-arginine Doxycycline
September 2014	Silver foam was applied every other day or as needed with dry sterile dressing	Prednisone (40 mg) Diaminodiphenyl sulfone (25 mg) – twice daily
October 2014	Continued with Mepilex Ag (Mölnlycke Health Care, Norcross, GA); however, the wounds were flushed with normal saline and Allevyn (Allegro Medical, Bolingbrook, IL) was applied to all wounds along with dry sterile dressings taped to skin	Prednisone (20 mg) Diaminodiphenyl sulfone (25 mg) – twice daily
November 2014	Negative pressure wound therapy (75 mmHG) was ordered with GranuFoam (KCI, San Antonio, TX). Mepilex Ag was also utilized during this juncture	Prednisone (20 mg) Cyclosporin 100 mg twice daily
December 2014	Iodoflex (Smith & Nephew, Inc, Fort Worth, TX) and mild compression with tubigrip was applied to the wound. Negative pressure wound therapy was subsequently halted prior to graft treatment	Prednisone (20 mg) Cyclosporin (100 mg) twice daily
January 2015	dHACM allograft was applied to wounds then covered with Adaptic Touch (Systagenix, San Antonio, TX), foam, and dry sterile dressing taped to the skin	Prednisone (30 mg) Mycophenolate mofetil (500 mg) twice daily
February 2015	dHACM allograft was applied wounds then covered with Adaptic Touch, foam, and dry sterile dressing taped to the skin	Prednisone (30 mg)

pulse steroid therapy. To augment the steroids, she initially was treated with cyclosporine (100 mg, twice daily) but due to side effects (nausea and vomiting) was subsequently switched to 500 mg mycophenolate mofetil (Cellcept®, Genentech, San Francisco, CA) to further augment immunosuppressant therapy. However, this drug was discontinued as well due to untoward effects (abdominal pain and confusion). Topical and systemic therapies utilized during the course of treatment are listed in Table 1.

Debridement was contraindicated at this time due to concomitant pathergy. With a goal to improve granulation tissue formation, decrease periwound edema, increase local blood flow, and stimulate wound contraction, NPWT was initiated when deemed safe from a pathergic standpoint (ie, use of chronic immunosuppression). This therapy was used for <1 month and garnered some improvement but was painful and therefore discontinued at Ms. J's request.

After 3 months of treatment for PG, the wounds appeared to improve clinically (eg, drainage and periwound hyperemia decreased), but they had coalesced and continued to be extremely painful.

dHACM. At this time, to potentially help reduce inflammation and facilitate wound healing, the decision was made to incorporate advanced wound therapy in the form of a dHACM allograft, consisting of a bilayer matrix of amnion/chorion, into the treatment plan. Before initiation of dHACM, the wound measured 8.0 cm x 10.3 cm x 0.1 cm, with local necrosis and slough (see Figure 4). Because Ms. J had been receiving immunosuppressive medications, loose devitalized tissue was carefully debrided using an iris scissors and pick-up. The 7 cm x 7 cm allograft was carefully placed at the margins of the wound edge in order to promote epithelialization and keratinocyte migration while avoiding waste; the allograft was covered with an outer dressing consisting of foam, gauze, and Kerlix (Medtronic, Minneapolis, MN) that was changed daily. The inner nonadherent foam dressing and graft were left in place until Ms. J returned to the clinic 1 week later.

At the follow-up visit, Ms. J stated that within hours after graft placement her pain had reduced substantially to 5 out of 10 and within a few days disappeared (0/10). Within 1 week, wound size decreased 6.4 cm x 9.4 cm x 0.1 cm (approximately 27%). Over the next 3 weeks, a total of 3 dHACM allografts were utilized (see Figure 5). Over the course of 2 months, wound size decreased (56%) from 103 cm^2 to 57.96 cm^2 with continued absence of pain (see Figure 6).

Prognosis. The PG lesions continue to improve and although after 7 months Ms. J has not completely healed, wound size and pain severity have dramatically lessened. No adverse effects were observed related to dHACM. Ms. J currently is receiving 20 mg of prednisone daily; this will be titrated slowly over the next several months as symptoms further improve.

Discussion

In the case discussed, PG initially presented as pustules and wounds that rapidly enlarged secondary to pathergy and evolved into painful ulcers. A patient-centered, multidisciplinary team approach was utilized to effect a positive outcome. Despite appropriate diagnosis involving rule-out of conditions with symptoms similar to PG and treatment, the condition of her wound remained largely unchanged until dHACM was applied.

dHACM and wound healing. The dHACM allograft represents 1 of many treatment options for refractory chronic wounds. Theoretically, these tissue grafts may help reduce pain, in large part, due to their anti-inflammatory properties,[11-13] although the act of covering nerve endings and vital structures also may play a role. The level of near immediate pain reduction reported by Ms. J after the dHACM was applied was remarkable and seemed to represent a turning point in her recovery.

It is important to note molecular components contained in dHACM (cytokines, growth factors, cell signaling molecules, and defensins) are known to provide a framework for proper wound healing.[17,18] The authors believe these components may have helped facilitate healing in this case. Additionally, clinical studies[20] have shown the application of the amniotic membrane aids in providing a scaffold to properly regulate adequate levels of proteases within the wound environment. The mechanism behind this process can be deducted from corneal studies[20] that showed a reduction of metalloproteinase activity and an increase of tissue inhibitor of metalloproteinase with the application of amniotic membrane.

The use of amniotic membrane as a treatment for PG is not totally without precedent. In 1978, Gruss[21] reported the use of natural amniotic membrane in a large case series of 120 patients with wounds of diverse origin. In 1 patient with PG completely resistant to all forms of treatment for 18 months, pain was relieved after commencing treatment with amniotic membrane and within 6 weeks the wound reduced in size by 66%. The present report, the first on the contemporary use of dHACM in PG, showed similar results. Current results also are consistent with studies of other wound types. Previous clinical studies have shown application of dHACM is an effective treatment option in patients with diabetic foot ulcers and venous leg wounds. Zelen et al[15] conducted a prospective, randomized, single-center clinical trial to compare healing characteristics of diabetic foot ulcers treated with dHACM versus standard care including debridement, moist therapy, standardized use of Silvasorb gel (Medline Inc, Mundelien, IL)/Aquacel AG (deRoyal, Powel, TN) compression dressing, and offloading (N = 25). After 4 and 6 weeks of treatment, the overall healing rates for dHACM were 77% and 92%, respectively, while the control group healing rates were 0% and 8.0% (P <0.001). Pain reduction was not a study outcome. Serena et al[16] implemented an 84-patient multicenter randomized controlled clinical trial to evaluate the use of dHACM and multilayered compression therapy versus multilayered therapy alone (Coban™2, 3M™, St. Paul, MN) in the treatment of venous leg ulcers. In this study, 53 patients were randomized to receive the allograft and 31 were randomized into the control group. At 4 weeks, 62% in the allograft group and 32% in the control group demonstrated >40% wound closure (P = 0.005), a significant difference noted between the allograft-treated group and the control group at the 4-week surrogate endpoint. During the study period, 35 out of 44 patients (79.5%) in the dHACM group reported a reduction in pain from the randomization visit when dHACM was applied to the 4-week visit.

The results of these clinical trials show dHACM is an effective treatment for the management of diabetic foot and venous ulcers. In this case study, 3 applications of dHACM also facilitated healing of a PG ulcer.

Although reduction of pain after treatment with amniotic membrane has been previously reported,[12,16,21] the exact mechanism of action for pain reduction is unknown. However, anecdotal reports of similar events with cadaveric allograft are available. More research is required to explain this phenomena.[22]

Conclusion

PG is a difficult-to-diagnose, potentially serious malady that often is recalcitrant to recognized treatment regimens. In the case presented, utilization of dHACM allograft may have been the catalyst in fostering wound healing and mitigating pain. Because this is a report of 1 case, more research is required to determine the generalizability of this observation. ■

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