A Mechanically Powered Negative Pressure Device Used in Conjunction with a Bioengineered Cell-based Product for the Treatment of Pyoderma Gangrenosum: A Case Report

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Abstract
Pyoderma gangrenosum (PG), an uncommon inflammatory and ulcerative skin disease, typically is treated medically with a combination of immunosuppression and local wound care, but evidence to guide care is limited. PG wounds can be difficult to heal. A 76-year-old male patient presented with a history of rheumatoid arthritis and recalcitrant PG. After 9 months of treatment with local wound care, steroids, and topical tacrolimus, the wound had increased in size from 1.8 cm x 1.5 cm to 7.2 cm x 5.6 cm. At that time, he was started on a regimen of five applications of a bioengineered cell-based product (one application every 2 weeks for a total of five applications) with twice-weekly mechanically powered negative pressure device changes. The latter was started at 75 mm Hg and changed to 125 mm Hg after 4 weeks. Oral corticosteroid therapy was initially started at 40 mg of prednisone, then slowly tapered to 20 mg, but could not be completely discontinued due to a flare in the patient’s rheumatoid symptoms. The wound was completely healed after 16 weeks. Research to ascertain the effectiveness of protocols of PG care, including the combination treatment described, is needed to help clinicians provide evidence-based care for these challenging wounds.

Keywords: case report, pyoderma gangrenosum, negative-pressure wound therapy, artificial skin, wounds

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Pyoderma gangrenosum (PG) is an uncommon inflammatory and ulcerative skin disease.1 The disease is classified as a neutrophilic dermatosis; approximately 50% of patients who develop PG have systemic diseases, including inflammatory bowel disease, hematologic malignancies, and arthritis.2 Typical PG lesions begin with folliculocentric pustules or fluctuant nodules with an inflammatory halo that expands peripherally to form an ulcer with sharply circumscribed violaceous raised edges, usually affecting the lower extremities and trunk.2 These lesions are typically painful and tender because the patient usually does not have neuropathy.2 Diagnosis is based on a clinical-histological approach to exclude other ulcerative processes involving dermal neutrophilia.3

The current mainstay of PG empirical treatment is long-term immunosuppression with high doses of corticosteroids or low doses of cyclosporine.4,5 Surgical management of PG is controversial because of the phenomenon of pathergy, which results in the emergence of new PG lesions or the rapid expansion of existing ulcerative PG in response to any type of trauma, such as surgery. When pathergy occurs, PG can mimic postsurgical wound ulceration or spontaneous dehiscence.6

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Negative Pressure in Wound Healing

Negative pressure wound therapy (NPWT) is now commonly used in the management of large, complex, acute, and chronic skin ulcers from a wide variety of causes. At least three randomized controlled trials demonstrate the efficacy of NPWT as a primary treatment for nonhealing skin ulcers. In 1997, Argenta and Morykwas reported that 300 chronic, subacute, and acute wounds treated, 296 responded “favorably to subatmospheric pressure” and had increased granulation tissue. Armstrong and Lavery’s randomized controlled trial of 162 partial diabetic foot amputations reported that 43 (56%) of NPWT and 33 (39%) of wounds managed with standard moist wound care were healed after 112 days of treatment (P = 0.040). In a multicenter, randomized controlled trial conducted among 362 patients with diabetes and foot ulcers, Blume et al found NPWT to be safe and more efficacious than advanced moist wound therapy alone, achieving complete closure within the 112-day treatment phase (P = 0.007). In 2006, Vuerstek et al compared NPWT to conventional wound care in the form of multilayer, short, stretch bandages in 60 hospitalized patients. They found the median time to healing was significantly less (P = 0.0001) in the NPWT treated patients compared to the conventional wound care patients with chronic leg ulcers (29 days versus 45 days). Based on their randomized controlled trial, they suggested NPWT should be considered “the treatment of choice for chronic leg ulcers owing to its significant advantages in the time to complete healing and wound bed preparation time compared with conventional wound care.”

Animal and human studies and randomized controlled trials have demonstrated the benefits of NPWT, which include increased tissue perfusion, increased granulation tissue formation, reduced bacterial load, and removal of excess interstitial edema compared to standard wound care alone. Genevoc et al used both porcine and human models and found that split-thickness skin donor graft sites treated with NPWT epithelialized at a “much faster rate” than those treated with standard occlusive dressing.

The SNaP (Smart Negative Pressure) Wound Care System (Spiracur, Inc, Sunnyvale, CA) is a single-use, mechanically powered NPWT device that utilizes specialized springs (instead of an electric pump) to generate pre-set continuous subatmospheric pressure levels (125 mm Hg, 100 mm Hg, or 75 mm Hg) to the wound bed. Each canister maintains its preselected, continuous setting and once filled with exudate is discarded. By eliminating the electric pump, this device helps solve many of the constraints associated with traditional NPWT device use in the ambulatory setting.

Armstrong et al conducted a randomized controlled trial enrolling 132 patients with noninfected, nonischemic, nonplantar lower extremity wounds who were managed with the mechanically powered single use device or a battery-powered negative pressure system (V.A.C. Therapy, KCI, San Antonio, TX). No differences in healing time, rates of healing, or number of adverse events were observed, but patient ease of use and quality of life were rated higher by subjects using the SNaP. For the primary end point (percent decrease in wound area) SNaP was found to be noninferior to NPWT at weeks 4, 8, 12, and 16 (P = 0.0030, 0.0130, 0.0051, and 0.0044, respectively). The authors also found no difference in the proportion of wounds that healed over time (P = 0.9620), an indication that SNaP worked as effectively as the comparator. The proportion of subjects experiencing device-related adverse events was similar between groups (SNaP, n = 64, comparator, n = 68) with maceration being the most common in both groups. What was significantly better in the SNaP subjects was a variety of quality-of-life indicators such as sleep disruption (P = 0.0019), comfort of wear (P < 0.001), and overall satisfaction (P = 0.0009).

Bioengineered Cell-based Therapy

Bioengineered cell-based skin substitute (Apligraf, Organogenesis, Inc., Canton, MA) is a living cell-based product consisting of both dermal and epidermal layers. It is generated in vitro from neonatal foreskin and is free of contaminating cells or those that cause rejections. The dermal layer provides structural and additional matrix proteins and the epidermal layer is comprised of human keratinocytes but lacks human skin structures such as hair follicles and blood vessels.

Initial safety studies were performed on mice to investigate the human allogeneic response. Briscoe et al engrafted the genetically altered mice with both human skin and human skin equivalent and found the human skin equivalent engrafted while the human skin was rejected. The bioengineered skin substitute was examined for safety and efficacy by Falanga et al in a prospective, randomized study of 293 patients with venous leg ulcers. This study compared compression therapy alone versus compression plus human skin equivalent and found that venous ulcers treated with human skin equivalent in addition to standard compression therapy healed more quickly. At the 6-month point of the
study, 92 out of 146 ulcers treated with human skin equivalent versus 63 out of 129 treated with compression alone had 100% wound closure (p = 0.02).

Human skin equivalent also has been studied for effectiveness in diabetic foot ulcerations. In a prospective randomized, multicenter clinical trial (N = 208) of Graftskin (the previous name for Apligraf) versus saline-moistened gauze for the treatment of noninfected, nonischemic, chronic, plantar diabetic foot ulcers, significantly more Graftskin-treated patients achieved complete wound healing than the control group at the 12-week follow-up visit (P = 0.0042).

Both NPWT and bioengineered skin substitute have shown to be beneficial in more standard wounds, but there is only case study documenting their use in treating PG and they have never been used synchronously. The purpose of this case study is to add to the literature by describing how using a bioengineered cell-based product along with NPWT may be a viable adjunctive modality for the treatment of recalcitrant PG.

Case Report

Mr. X is a 76-year-old man with a history of severe destructive rheumatoid arthritis, coronary artery disease, osteoporosis, gastroesophageal reflux, hyperlipidemia, and seborrheic dermatitis. He is allergic to cephalexin and clindamycin. He presented to the VA wound clinic with a slightly painful ulcer on his anterior left leg that had been present for approximately 3 months. He had been seen by his rheumatologist 1 month before, at which time the wound measured 1.8 cm x 1.5 cm; no lymphadenopathy, fever, or other constitutional symptoms were noted. The rheumatologist believed the wound was a venous stasis ulcer and treated it with local wound care consisting of moistened gauze. By the time Mr. X presented to the wound clinic, his ulcer had increased in size to 4.5 cm x 5.0 cm. The majority of the wound was approximately 0.5 cm deep. Small areas of pitting measured approximately 1 cm in depth with elevated ridges between them. The wound had a white fibrotic base with a purple rubrous border and displayed moderate periwound erythema. A tissue biopsy was taken from the periphery of the wound because this area has the most consistent dermatopathologic findings and also surrounding normal tissue for comparison. The biopsy was read as having lymphohistocytic superficial perivascular infiltrate and numerous multinucleate giant cells with neutrophils within the dermis near the ulcer base. There was no evidence of vasculitis, and fungal and acid-fast results were negative for micro-organisms. These findings are compatible with PG.

Once diagnosed, the rheumatologist started Mr. X on 40 mg of prednisone and topical application of tacrolimus covered with a multilayered lightly compressive dressing. Tacrolimus is an immunosuppressant that inhibits T-lymphocyte activation that is considered 100 times more potent than cyclosporine. Mr. X’s wound continued to increase in size to 7.2 cm x 5.6 cm after a total of 9 months of treatment, while his prednisone was tapered to 20 mg (see Figure 1).

Due to lack of healing progression using the above treatment, other options were explored. Because of other successful case reports and evidence of success healing chronic wounds, a bioengineered cell-based product was applied according to manufacturer’s instructions for use with an application every 2 weeks for a total of five applications. In addition, NPWT was applied to help manage exudate and aid in graft adherence according to manufacturer’s directions for use, and the dressing was changed twice per week (see Figure 2). The ultra-portable device was chosen due to the patient’s fraility. The 75-mm Hg mechanical device was initially utilized for 4 weeks due to the patient’s fragile skin and to see if he could tolerate the negative pressure from a pain perspective. Because a small amount of leakage oc-
curred at 75 mm Hg and because the patient had no symptoms of increased pain with application and treatment, pressure was increased using the 125 mm Hg device for the remainder of the treatment period in order to better control the volume of exudate.

Using this treatment regimen, wound size decreased to 2.9 cm x 2.5 cm after 12 weeks. Mr. X was able to taper his prednisone by 1 mg every 2 weeks; he had to remain on prednisone due to a flare up in his rheumatoid arthritis symptoms. No peri-wound maceration was noted, and Mr. X reported his pain greatly decreased while the NPWT device was applied and active on his leg. Mr. X’s wound reached full epithelialization 13 months after initial presentation and 16 weeks after commencing with NPWT and the bioengineered cell-based product applications (see Figures 3 and 4).

Discussion

The predominant mode of therapy for PG is immunomodulatory and immunosuppressive medical therapy and management of possible underlying associated disease. Nearly all of the literature consists of retrospective chart reviews or case studies or series of successful types of treatment, many of which consist of a combination of therapies. Initially, topical tacrolimus was selected for use based on both a review that suggested topical tacrolimus could represent the first-line treatment for PG and a case report by Lé Cleach et al in which a 32-year-old woman had complete closure of her wound with topical tacrolimus after failure with other topical corticosteroid.

When Mr. X’s wound did not show clinical improvement, treatment was changed based on case studies where the same bioengineered cell-based product was used. Duchini presented the case of a 76-year-old man with a suspected PG recalcitrant to systemic corticosteroids and triamcinolone acetonide injected into the lesion. After increasing systemic corticosteroids and adding three doses of infliximab, the bioengineered cell-based product was applied. The corticosteroid dose was decreased and the patient was discharged home; the wound ultimately healed in 4 months. de Imus et al utilized cyclosporine, systemic steroids, and bioengineered cell-based product to achieve healing in 6 weeks in a wound in a 26-year-old woman; the authors of the report postulated the product “prevented severe wound contracture.”

Geller and Longton first described NPWT for the management of PG in 2005 in a case report. An otherwise healthy 82-year-old woman presented with a progressively enlarging lower extremity wound with severe edema from knees to toes. After treatment with several antibiotics including cephalexin, ciprofloxacin, and metronidazole by other clinicians, the authors assessed the patient and obtained a biopsy that confirmed a diagnosis of PG. The authors began treatment with 1 week of four-layer compression followed by negative pressure and achieved substantial wound closure after 7 months. Another case by Ghersi et al described the use of NPWT to treat a 57-year-old woman with a 2-year history of nonhealing PG; both the Geller and Longton case and the Ghersi et al case had successful outcomes as measured by successful healing in this challenging diagnosis.

Only one randomized controlled trial conducted by Brooklyn et al addresses treatment of PG; 30 patients were randomized to either infliximab (a monoclonal antibody against tumor necrosis factor alpha) or placebo. The patients received a 5 mg/kg infusion at week 0, and then were reassessed for the primary endpoint 2 weeks later. The authors noted (but did not define) “clinical improvement” in six of the 13 patients receiving infliximab versus improvement in only one of 13 receiving placebo. These findings, while not statistically significant, can serve as a pilot to further studies. This single small, randomized controlled trial, unrelated to the current study, shows the scant amount of literature available to help guide treatment of PG.

Conclusion

Invasive modalities such as surgery are contraindicated as the primary or sole treatment of active PG due to high occurrence of the pathergy phenomenon. Some authors have described surgical management as an adjunctive therapy, where skin grafts, muscle flaps, and cultured autografts concomitant with or before immunopharmacologic therapy in noninfected and controlled PG ulcers are used. In this case study, the wound increased in size for almost 6 months and healed after 16 weeks of treatment using a bioengineered cell-based product and application of mechanically powered NPWT while titrating parenteral immunosuppression. The wound in this patient with rheumatoid arthritis showed consistent improvement only after
this combination therapy was provided. Further research on optimal strategies of care for patients with PG, including the approach described, is needed.

References