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Case Report

First Case of Severe Pain and Inflammation Reduction by Application of Purified Amniotic Fluid on Active Lesions of a Patient with Pyoderma Gangrenosum

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Abstract

We report the first case of severe pain and inflammation reduction by application of purified amniotic fluid on active lesions of a patient with pyoderma gangrenosum. We describe the impact of every third-day skin applications of a sterile fraction (4ml) from human purified amniotic fluid (ViX001) obtained from thoroughly screened volunteers at the time of planned c-section at the term of normal pregnancies. The product ViX001 was generated through a proprietary process and kept in frozen one or two milliliters cryovials (protein content was ~1mg/ml) and thawed just prior to applications. Pain improvement was recorded after each application, and inflammation suppression was confirmed by serial pictures of the lesions. While our findings need to be reproduced with a larger cohort of patients, preferably at an earlier stage of the disease, it is instructive that ViX001 reduced severe pain and inflammation for a patient with advanced pyoderma gangrenosum. Pyoderma gangrenosum is a dreadful skin condition consisting of noninfectious neutrophilic dermatosis that progresses to necrotic ulcers with a characteristic purple edge and extremely painful raw subdermal tissue exposure.

Keywords: Purified Amniotic Fluid; Perinatal Products; Pyoderma Gangrenosum; Inflammation, Extracellular Vesicles; Exosomes; Healing; Tissue Repair, Regenerative Medicine, Immunity.

Introduction

Pyoderma Gangrenosum (PG) is a noninfectious neutrophilic dermatosis which starts with a painful nodule or pustule that progresses to necrotic ulcers with a characteristic purple edge, usually located on lower limbs [1]. Pain associated with the ulcer lesions is excruciating and responds poorly to standard therapy. PG is a diagnosis of exclusion based on clinical and histological features. Up to 50% of the cases are associated with systemic disease, particularly inflammatory bowel disease (Crohn's and ulcerative colitis). Early lesions show neutrophilic folliculitis, and perifollicular inflammation with a dermal abscess, which may resemble a spider bite (a red bump).

PG is a rare disease, about 2,200 cases are diagnosed per year in the US. It affects women and men equally and is more frequent in individuals 50-70 years old. PG is an inflammatory skin disease

of unknown etiology, although approximately 25% of PG cases are caused by a limited injury or an external stimulus [2]. PG rapidly progresses after its onset and is classified into five types: ulcerative type (most frequent), bullous type, pustular type, vegetative type, and a type that develops around a stoma [3]. In ulcerative PG, the lesions expand to form raised ulcers with infiltration of their purple margins [4]. These ulcerations cause severe deterioration in patients' quality of life [5].

Case Presentation

The patient was a 78-year-old gentleman who had a complicated cardiovascular history with atrial fibrillation, blood clot in the right atrium, status post watchman device placement in left atrial appendage, pacemaker placement. He also had severe peripheral vascular disease, with left calf arterial occlusion and arterial thrombectomy. Further evidence of his thromboembolic proclivity was a history of deep vein thrombosis of the left leg complicated by saddle pulmonary embolism. He was treated with Eliquis to control his thrombotic diathesis. He also had severe coronary artery disease with a history of myocardial infarction, placement of five stents, two in his left anterior descending, and three in his circumflex, coronaries. He did have hypercholesterolemia and was treated for it with Evolocumab injections.

The patient had non-cardiovascular issues, including colon diverticulitis, status post-resection, and cholecystectomy. He had history of sleep apnea treated with Bipap device at night. He also demonstrated advanced signs of Alzheimer's disease when he developed Pyoderma Gangrenosum (PG). At that time, he did not have history of inflammatory bowel disease like Crohn's or ulcerative colitis. The patient received debridement of his left lower extremity to remove necrotic tissues. Right after the surgery to remove necrotic tissues, the lesions accelerated and began to spread. In a few weeks, the patient evolved from having what looked like a "spider bite" to severe and deep ulcers of his left leg below the knee, and one milder lesion behind his right calf. The lesions were treated by covering them with Systagenix Adaptic Non-Adhering Sterile Dressing 5"x9". He was receiving acetaminophen, tramadol, Percocet and Oxycontin for pain.

In late December the patient developed bright red rectal bleeding, his hemoglobin decreased from 15.1 g/dL to 12.1 g/dL. Urgent endoscopy and colonoscopy were performed. The colonoscopy did not reveal any inflammatory bowel disease. However, the upper endoscopy revealed three large bleeding ulcers in the antrum of his stomach. He was prescribed Dexilant, Carafate, and Pepcid.

In January 2023, we learned about the patient while he was in the hospital for the management of excruciating pain resulting from ulcers of his left leg, which were deep enough to expose the muscle layers, and the largest one covered an area of 15 x 7 centimeters. Because this was the single largest lesion of PG for the patient, it was the one illustrated by serial pictures (Figure 1). The patient was unable to leave the hospital because his pain was 10/10 and unmanageable at home.

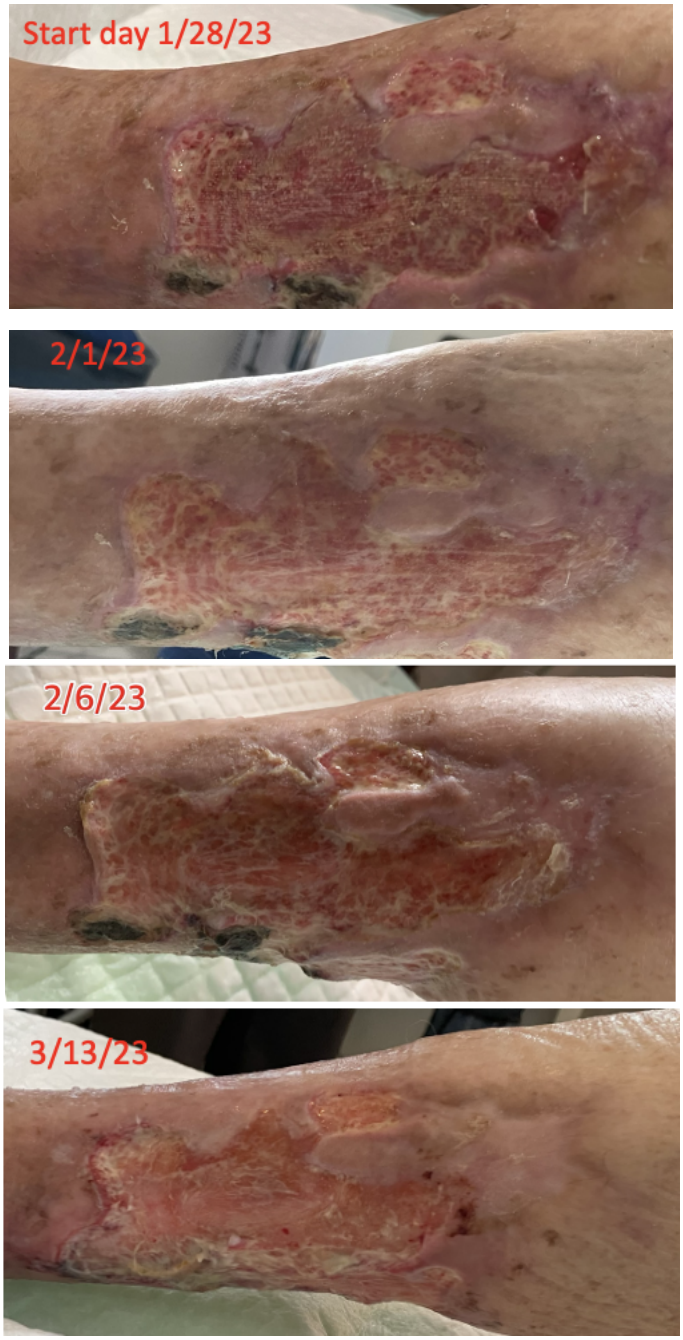

Figure 1: Sequential healing of pyoderma gangrenosum lesions with ViX001, a purified amniotic fluid fraction therapy. **(Top panel):** Ulcers surrounded by typical purple edges at the start

of treatment on January 28, 2023, showing extensive ulceration and inflammation. **(Next panels):** From top to bottom, matching lesions at various indicated time points, showing early signs of healing post treatments with ViX001. Note especially new skin recovery and contraction of the lesions, as well as reduction of the inflammatory swelling of the ankle.

Since the hospital staff was unable to control his pain, the family of the patient asked us to help with serial, every third-day applications of fraction ViX001 of purified amniotic fluid, which was generated through a proprietary process and kept in frozen one or two milliliter (1 ml or 2ml) cryovials (protein content was ~1mg/ml) thawed just before applications of ViX001 on the lesions. After signing an informed consent, we started topical application of ViX001 to the lesions on January 28, 2023. Each application consisted of 4 ml of undiluted ViX001 using a sterile leakproof atomizer (15 ml size) which was re-sterilized in-between treatments.

Within 30 minutes of the first application the pain was reduced from 8-10/10 to 0 to 2/10 and the patient was able to ambulate "all around the house" the next day, he did not need Percocet or other pain killers for the next few days. Ten days later, the pain was still well controlled, and some skin recovery was visible at the edge of lesions (Figure 1), edema of the leg was also reduced especially around the ankles. After the first ten days, on occasions, the patient needed a Percocet, especially right before the next application. On February 13, Humira injections (adalimumab, a fully human anti-TNFα monoclonal antibody) were started by his dermatologist, four shots initially, then administered every two weeks. Initially, the addition of Humira to ViX001 applications seemed to be well tolerated and resulted in further healing of the ulcers (Figure 1).

Complications

Despite of these early improvements, on March 22, 2023, the patient started complaining of left flank pain, followed by excruciating lower back pain which required his admission to the hospital for management, At this point, applications of ViX001 were discontinued. He had evidence of increased systemic inflammation indicated by elevation of his C-reactive protein and white blood cell counts. Due to the known risk of bacterial infection associated with Humira [6] and the patient's high white blood cell count, the Humira treatment was also discontinued. A CT-scan of the lumbar spine on the March 23, revealed multiple disk and other osteoarthritic issues and spinal stenosis. Next, on March 26, the patient developed severe ischemia of his toes, likely due to leukocytoclastic vasculitis, a known complication of Humira [7-11], according to the vascular surgeon. Amputation of the toes was not possible due to the patient's rapidly deteriorating general condition. In addition, the PG lesions expanded down from his legs to his ankles bilaterally, possibly as a result of abruptly stopping ViX001 and Humira. Immunoglobulin infusion was prescribed as an alternative to Humira. The patient developed proteinuria after receiving immunoglobins. He subsequently went into kidney failure. The patient was then switched to Hospice care to make him comfortable. He passed away a few days later.

Discussion

This case demonstrates the potential of a proprietary fraction of purified amniotic fluid (ViX001) in reducing pain and inflammation in PG lesions. The rapid pain relief and visible improvement in lesions were noteworthy, suggesting a promising avenue for PG treatment, especially if applied early in the disease progression. However, the patient's complex medical history and the emergence of new complications highlight the challenges in managing such complex cases. This case underscores the importance of holistic patient care and the need for comprehensive approaches to managing multifaceted medical conditions of such complexity. The interaction of ViX001 with other treatments, such as the use of Humira, the only Food and Drug Administration (FDA) approved treatment for PG, warrants further investigation.

Indeed, Humira was granted orphan drug designation by the FDA for the treatment of PG in 2019, which makes Humira the world's first drug indicated for the treatment of PG. This approval is based on the data from a Japanese phase III clinical trial conducted in Japanese patients with PG [6]. This study evaluated the efficacy and safety of Humira targeting patients with active ulcers in Japan who were diagnosed with PG and whose local treatment was not sufficiently effective. Humira was successful at PG ulcer area reduction after 26 weeks of administration, the trial's primary endpoint. The most common adverse drug reactions in patients receiving Humira were skin bacterial infection, and other complications as illustrated with our patient.

Conclusion

The application of ViX001 presents a novel and potentially effective local (and possibly systemic, to be tested) treatment for pain and inflammation associated with PG. However, the complexity of the patient's overall medical condition highlights the necessity for a more integrated approach in treating such multifaceted diseases and at an earlier stage of the disease. Further studies with larger cohorts are required to fully understand the efficacy and safety of ViX001 in the treatment of PG, especially considering the potential interactions with other medical conditions and treatments.

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Their dedication and commitment were admirable in supporting our patient, and beyond, the many future patients that may be helped by this novel technology.

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