The Journal of Foot & Ankle Surgery 58 (2019) 1281–1284

Contents lists available at ScienceDirect

The Journal of Foot & Ankle Surgery

journal homepage: www.jfas.org

The Effects of Collagenase *Clostridium histolyticum* on Plantar Fibromatosis: A Case Study

Jeffrey D. Lehrman, DPM, FASPS, MAPWCA, CPC[1,2], Amy L.L. Miceli, DPM, FAPWCA[3], Simon G. Tabchi, DPM, AACFAS[4,5], Mark A. Kaplan, MD, PhD[6]

[1] *Private Practice, A Step Ahead Foot & Ankle Center Fort Collins, CO*
[2] *Teaching Panel, Crozer-Keystone Health System Podiatric Surgical Residency, Springfield, PA*
[3] *Camp Hill, PA*
[4] *Associate, PA Foot and Ankle Associates, Allentown, PA*
[5] *Teaching Panel, St. Luke's University Health Network Podiatric Surgical Residency, Allentown, PA*
[6] *Pathologist, Crozer Keystone Health System, Upland, PA*

ARTICLE INFO

Level of Clinical Evidence: 4

Key Words:
Dupuytren's contracture
Ledderhose's disease
Peyronie's disease
plantar fibroma
XIAFLEX

ABSTRACT

Plantar fibromatosis, also known as Ledderhose's disease, is a rare disorder of benign fibroblast proliferation involving the plantar aponeurosis (i.e., plantar fascia). Traditionally, surgical intervention has been the most common treatment for plantar fibromatosis. However, numerous studies have reported high recurrence rates of plantar fibromatosis after surgical intervention, as well as wound healing difficulties and nerve injury. Plantar fibromatosis often coexists with other superficial fibrous diseases such as Dupuytren's contracture and Peyronie's disease; immunohistochemical and ultrastructural analyses suggest a relationship between Ledderhose's disease and Dupuytren's contracture. The US Food and Drug Administration approved collagenase *Clostridium histolyticum* for the treatment of Dupuytren's contracture in 2010 and Peyronie's disease in 2013. This case study presents the successful treatment of Ledderhose's disease almost 4 years (45.5 months) after off-label use of collagenase *C. histolyticum* injection in a 22-year-old white female who had recurrent plantar fibromatosis after surgical intervention.

Plantar fibromatosis (PF), also known as Ledderhose's disease (LD), is a rare benign hyperproliferative disorder involving the plantar aponeurosis (i.e., plantar fascia) with an unknown etiology, affecting <200,000 people in the United States (1). Although PF may occur at any age, the greatest prevalence of PF occurs in middle-aged or older individuals (1). Men are affected twice as often as women, and 25% of patients have bilateral foot involvement (1,2). PF commonly manifests as either one or multiple nodules (fibromas) in the medial or central bands of the plantar fascia (1). Typically presenting with an insidious onset and a slowly progressing course, PF normally becomes locally aggressive with invasion of the fibromas into the overlying skin or deep structures, which often prompts patients to seek treatment (3). Patients typically present with a complaint of swelling or pain in the sole of the affected feet as a result of the aggressively growing fibromas (4). The diagnosis of PF is clinical, but often magnetic resonance imaging (MRI)—considered by some to be the gold standard of diagnostic imaging for PF—is used to attain additional information concerning the extent of involvement and location of the fibromas (5). Conservative treatment such as nonsteroidal anti-inflammatory drugs, shoe gear modifications, orthotics, physical therapy, intralesional corticosteroid injections, chemotherapy, or radiotherapy may be initially attempted, but the conservative treatment options often fail to alleviate the patient's symptoms long term, at which time surgical intervention may be considered (1). Typically surgical management of PF includes 1 of 3 operative methods: (1) local excision, (2) wide excision, or (3) total plantar fasciectomy with or without skin grafting (6). However, surgical intervention of PF is associated with numerous complications, of which the most common and notorious is recurrence. Depending on the surgical procedure performed, recurrence rates of PF have been reported to be as high as 100% after surgery, causing one to question the validity of this treatment option (2,6).

PF sometimes coexists with other superficial fibromatoses such as Dupuytren's contracture (DC) (or palmar fibromatosis) and Peyronie's disease (PD) (or penile fibromatosis); immunohistochemical and ultrastructural analyses suggest a relationship between LD and DC (2). The US Food and Drug Administration (FDA) approved collagenase *Clostridium histolyticum* for the treatment of DC in 2010 and PD in 2013 (7). Although there has been substantial evidence reported in the literature demonstrating the efficacy of collagenase *C. histolyticum* injection in the treatment of DC and PD, the authors are aware of only 1 published case report detailing the attempt to treat recurrent PF with the off-label

Financial Disclosure: None reported.
Conflict of Interest: None reported.
Address correspondence to: Amy Miceli, P.O. Box #291, Camp Hill, PA 17001.
E-mail address: allmiceli57@gmail.com (A.L.L. Miceli).

1067-2516/$ - see front matter © 2019 by the American College of Foot and Ankle Surgeons. All rights reserved.
https://doi.org/10.1053/j.jfas.2019.04.006

use of collagenase *C. histolyticum* injection (7), an unsuccessful treatment in a 72-year-old white male. However, the current case study presents the successful treatment of PF 7 years (84 months) after off-label use of collagenase *C. histolyticum* injection in a 22-year-old white female with recurrent PF after surgical intervention.

Case Report

A 20-year-old white female initially presented in May 2012 with a chief complaint of left foot pain. The patient related that the pain in her left foot had gradually developed over the prior month, over which time she had also noticed a lump on the bottom of her left foot. Weightbearing activities at her jobs as a pharmacy technician and professional dancer made the pain in her left foot worse; non-weightbearing alleviated the pain. She had been diagnosed with depression, for which she was taking 20 mg of escitalopram by mouth daily, and she denied any known allergies to drugs or food.

On physical examination, skin was intact to the left foot without signs of infection, and there was a mobile soft tissue mass to the plantar medial midfoot. Pain was elicited on palpation of the soft tissue mass. Clinically, the patient's signs and symptoms were consistent with PF.

Initial treatment included offloading, steroid injections, and physical therapy. The patient had no relief of symptoms after 2 months of these conservative treatments, and she was sent for an MRI with and without contrast of her left foot, to further investigate the extent of the soft tissue mass. The MRI revealed mild nonspecific fat stranding and edema within the soft tissues of the heel, greater on the medial side (Fig. 1).

Three months after the initial conservative treatment failed to alleviate symptoms, the patient underwent surgery consisting of local excision of the soft tissue mass to her plantar medial left foot; a <1 cm margin of plantar fascia was excised along with the soft tissue mass. The pathology report of the soft tissue mass removed showed nodular collagenous thickening of the membranous aponeurosis dense connective tissue and adjacent fibroadipose tissue (Fig. 2). After surgery, the patient was initially non-weightbearing for several weeks and then gradually transitioned to full weightbearing. Although the patient's symptoms initially had improved after surgery, the pain to her left foot on weightbearing eventually returned a few months after her operation.

Fig. 1. T1-weighted spin-echo image in coronal preparation and axial preparation shows mild nonspecific fat stranding and edema within the soft tissue of the medial heel.

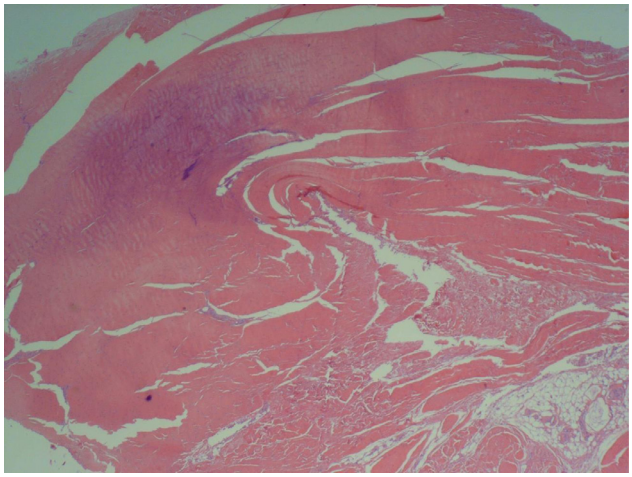

Fig. 2. Nodular collagenous thickening of the normally flat membranous aponeurosis dense connective tissue and adjacent fibroadipose tissue.

Five months after the surgical excision of the soft tissue mass, at age 21 years, the patient underwent an endoscopic plantar fasciotomy (EPF) of her left foot in an effort to alleviate her pain. Once again, her symptoms improved for several months, but eventually returned. A second EPF was performed on the patient's left foot in July 2013, but it too proved unsuccessful because the pain in her left foot on weightbearing returned a few months after surgery, as did another palpable, moveable mass along the plantar medial aspect of her left heel.

A fourth surgery to excise the recurrent plantar fibroma to the bottom of the left foot was discussed with the patient 6 months after the second EPF failed to alleviate her symptoms. The off-label use of collagenase *C. histolyticum* injection, brand name XIAFLEX (Endo Pharmaceuticals, Malvern, PA), was also presented as a possible alternative treatment option. We discussed the paucity of literature regarding the use of collagenase *C. histolyticum* injection for the treatment of PF, and we explained that collagenase *C. histolyticum* injection was approved by the FDA for the treatment of a similar superficial fibromatosis disorder, DC. The patient gave her written consent to undergo collagenase *C. histolyticum* injection for the treatment of the recurrent plantar fibroma to the bottom of her left foot. An office procedure was then performed to inject collagenase *C. histolyticum* into the plantar fibroma. Using a 1-mL syringe and 25-gauge, 1.5-inch-long needle, 0.25 mL of reconstituted solution containing 0.58 mg of collagenase *C. histolyticum* was injected into the patient's plantar fibroma after the skin was properly cleansed with an alcohol swab. One-third of the dose of collagenase *C. histolyticum* reconstituted solution was injected into the center of the fibroma. The needle was partially withdrawn and repositioned several millimeters proximal to the initially injected dose, and an additional one-third of the collagenase *C. histolyticum* dose was injected into the fibroma. Once again the needle was partially withdrawn and repositioned several millimeters distal to the initially injected dose. and the remaining one-third dose was injected into the fibroma. The needle was withdrawn. A small rectangular-bordered adhesive bandage was applied to the injection site, and the patient was instructed to bear weight as tolerated in a supportive athletic shoe even though she related some discomfort to her left foot after the injection. The patient returned to the office the next day complaining of significant pain to

Fig. 3. Image of the patient's left foot illustrating the swelling and bruising sustained by the patient the day after injection of collagenase *Clostridium histolyticum*.

the injection site. The small rectangular bordered adhesive bandage was removed; the plantar fibroma was no longer palpable, but the plantar left foot was swollen and ecchymotic (Fig. 3). Extension of the toes and massaging of the plantar left foot was performed as described in the prescribing Information on the Endo Pharmaceuticals website (8) for the treatment of DC and PD with collagenase *C. histolyticum* injection. The patient was instructed to perform her daily activities as tolerated and to follow up in the office in 1 month.

When the patient returned a month later for her 30-day follow up appointment, she related that she had resumed all of her normal activities and no longer had pain in her left foot. On exam, the ecchymosis had resolved to the plantar left foot, and only mild edema remained. At both her 60-day (Fig. 4) and 90-day (Fig. 5) follow-up appointments, the patient reported that she was continuing to enjoy pain-free activity; on physical examination, the mild edema had resolved, and there were no findings to suggest recurrence of the plantar fibroma such as an antalgic gait or any palpable soft tissue mass to the sole of the foot.

When the patient was last seen in our office 33.5 months after collagenase *C. histolyticum* injection, she was still pain free, and there were no signs on physical examination of recurrence of the plantar fibroma. We last spoke with the patient regarding her foot 84 months postinjection, and she reported that she remains symptom free. She never had any repeat imaging after the collagenase *C. histolyticum* injection.

Fig. 4. Image of the patient's left foot 60 days after injection of collagenase *Clostridium histolyticum*.

Discussion

PF is a rare connective tissue proliferative disorder of unknown etiology that results in the formation of nodules within the plantar fascia. These nodules often cause swelling and pain within the soles of the affected feet, and these symptoms often prompt patients to seek care. Conservative treatment of PF often fails, and patients may resort to surgical intervention to find relief of symptoms. However, multiple studies have reported a high recurrence of PF after surgical excision. In a study by Aluisio et al (6), 17 patients underwent surgical excision of PF; 10 patients underwent local excision, 3 patients had wide excision of the nodule defined as removal of the nodule along with at least a 1-cm margin, 2 patients had subtotal fasciectomy, and 2 patients had subtotal fasciectomy with skin grafting. Recurrence of PF was more common in those patients who had local excision (4 of 10 patients; 40%) than in those who underwent wide excision (1 of 3 patients; 33%). Both patients who underwent subtotal fasciectomy with skin grafting had recurrence (100%), whereas neither of the patients who had subtotal fasciectomy without skin grafting had recurrence of PF (6). In a study by Durr et al (4), 13 primary lesions were treated with local excision of the nodule, wide excision of the nodule defined as removal of the nodule with a 2- to 3-cm margin, or complete plantar fasciectomy. Of the nodules surgically removed by local excision, 100% recurred, and 80% of the nodules removed by wide excision recurred, but none of the nodules removed with complete plantar fasciectomy recurred (4). Although they include small sample sizes, the trends in the studies by Aluisio et al (6) and Durr et al (4) are consistent with other reports in the literature and support the conclusion that if surgery is performed, the

Fig. 5. Image of the patient's left foot 90 days after injection of collagenase *Clostridium histolyticum*.

procedure with the lowest recurrence rate of PF is plantar fasciectomy followed by wide excision, and local excision of PF commonly results in recurrence of disease (2,5,9,10,11).

Given the high recurrence rate associated with surgical intervention of PF, there remains a need for a more efficacious treatment modality. The gold standard for treatment of DC is surgery; however, with the FDA approval of collagenase *C. histolyticum* in 2010, several studies have shown that collagenase *C. histolyticum* injection is a safe and effective treatment alternative to surgical intervention for DC (12). Immunohistochemical and ultrastructural analyses suggest a relationship between LD and DC; therefore, collagenase *C. histolyticum* injection may also be a possible safe and effective treatment option for PF.

In 2014, Hammoudeh (7) reported a case study in which he treated a 72-year-old white male with collagenase *C. histolyticum* injection for recurrent PF after failed conservative treatment and partial plantar fasciectomy. Hammoudeh injected the recurrent fibroma on 3 separate occasions >1 month apart with 0.58 mg collagenase *C. histolyticum* in 0.25 mL of reconstituted solution, but he admitted in his case study that he failed to perform the manufacturer-recommended 24-hour postinjection extension of the contracted digits of the foot, citing the lack of a palpable plantar cord as the reason (7). Unfortunately, the patient's final outcome was no relief of pain or softening of the plantar fibroma after the collagenase *C. histolyticum* injection series (7).

In our study, we injected our patient's plantar fibroma with the same dose of collagenase *C. histolyticum* reconstituted solution as Hammoudeh did. However, we injected the patient's plantar fibroma on only 1 occasion, and the patient did return the next day after injection, at which time both extension of the toes and massaging of her plantar left foot was performed. Our patient did have successful treatment of her recurrent PF after collagenase *C. histolyticum* injection, and at her final follow-up appointment 33.5 months after injection, the patient had no signs, symptoms, or complaints of recurrence of PF.

With conflicting case report outcomes, more research regarding the off-label use of collagenase *C. histolyticum* for the treatment of PF needs to be performed. Perhaps the reason Hammoudeh's case study (7) did not achieve successful treatment of PF was the lack of toe extension or massaging of the foot within 24 to 72 hours after injection of collagenase *C. histolyticum*.

Although successful, our case study did have a couple of drawbacks. As with any case study, future studies with a larger sample size would be more conclusive. In retrospect, we could have instructed the patient to remain non-weightbearing and to elevate her foot before her first postinjection appointment, as is recommended by the manufacturer for the treatment of DC with collagenase *C. histolyticum*, to help reduce the intensity of pain and swelling after injection. However, we think that having our patient bear weight immediately after injection of collagenase *C. histolyticum* perhaps helped to manipulate the tissue, thus degrading the plantar fibroma faster.

In conclusion, although PF is a rare disorder, traditional conservative measures often fail, causing patients to undergo surgical intervention, which is notoriously associated with recurrence. The off-label use of collagenase *C. histolyticum* injection for PF appears to be a safe and effective alternative treatment to surgery; however, there is a need for additional investigation into this emerging treatment option.

Acknowledgments

Endo Pharmaceuticals donated the vial of XIAFLEX used in this case study.

References

1. Fausto De Souza D, Micaelo L, Cuzzi T, Ramos-e-Silva M. Ledderhose disease: an unusual presentation. J Clin Anesth Dermatol 2010;3:45–47.
2. Veith NT, Tschernig T, Histing T, Madry H. Plantar fibromatosis—topical review. Foot Ankle Int 2013;34:1742–1746.
3. De Bree E, Zoetmulder FA, Keus RB, Peterse HL, Van Coevorden F. Incidence and treatment of recurrent plantar fibromatosis by surgery and postoperative radiotherapy. Am J Surg 2004;187:33–38.
4. Durr HR, Krodel A, Trouillier H, Lienemann A, Refior HJ. Fibromatosis of the plantar fascia: diagnosis and indications for surgical treatment. Foot Ankle Int 1999;20:13–17.
5. Zgonis T, Jolly GP, Polyzois V, Kanuck DM, Stamatis ED. Plantarfibromatosis. Clin Podiatr Med Surg 2005;22:11–18.
6. Aluisio FV, Mair SD, Hall RL. Plantar fibromatosis: treatment of primary and recurrent lesions and factors associated with recurrence. Foot Ankle Int 1996;17:672–678.
7. Hammoudeh ZS. Collagenase *Clostridium histolyticum* injection for plantar fibromatosis (Ledderhose disease). Plast Reconstr Surg 2014;143:497e–498e.
8. XIAFLEX® Full Prescribing Information. Endo Pharmaceuticals Inc. Website. August 2016. Available at: http://www.endo.com/File%20Library/Products/Prescribing%20Information/Xiaflex_prescribing_information.html. Accessed November 11, 2016.
9. Carroll P, Henshaw RM, Garwood C, Raspovic K, Kumar D. Plantar fibromatosis: pathophysiology, surgical and nonsurgical therapies: an evidence-based review. Foot Ankle Spec 2018;11:168–176.
10. Young JR, Sternbach S, Willinger M, Hutchinson ID, Rosenbaum AJ. The etiology, evaluation, and management of plantar fibromatosis. Orthopedic Research and Reviews 2019;11:1–7.
11. Fuiano M, et al., Current concepts about treatment options of plantar fibromatosis: A systematic review of the literature, Foot Ankle Surg 2018; https://doi.org/10.1016/j.fas.2018.06.001.
12. Thomas A, Bayat A. The emerging role of *Clostridium histolyticum* collagenase in the treatment of Dupuytren disease. Therapeut Clini Risk Manage 2010;6:557–572.