Review

Plantar Fibromatosis: Pathophysiology, Surgical and Nonsurgical Therapies

An Evidence-Based Review

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Abstract: *Plantar fibromatosis (morbus Ledderhose), an extra-abdominal desmoid tumor of the plantar foot, is a rare benign hyperproliferative disorder of the plantar fascia with an unknown etiology. The main clinical characteristics include slow growing nodules on the medial and central bands of the plantar fascia, which may become painful and negatively affect ambulation. Most established conservative therapies today target symptomatic relief. As symptoms progress, therapies such as injections, shockwave ablation, radiation, and/or surgery may be required. This review aims to provide insight into the pathophysiology of this condition in addition to detailing current and investigational therapies for this disorder. Many therapies have been proven in similar conditions, which could lead to promising treatment options for plantar fibromatosis.*

Levels of Evidence: *Level V: Expert opinion*

Keywords: fasciectomy; hyperproliferative; myofibroblasts; nodule; plantar fascia; verapamil topical

Plantar fibromatosis or morbus Ledderhose disease was first described in 1897 by Georg Ledderhose.[1] It is characterized by slow growing benign extra-abdominal desmoid nodules on the plantar aponeurosis (Figure 1). It has been hypothesized that these nodules form as a result of hyperactivity of mature fibroblasts.[2-4] However, the exact etiology is unknown.[3,5] Ledderhose disease has been associated with several other conditions such as Dupuytren's, Peyronies's, frozen shoulder, alcohol addiction, diabetes, epilepsy, smoking, repeated trauma, long-term phenobarbital use and possible genetic inheritance.[2,3,6,7] Men are twice as likely to be affected as females most common seen between the ages of 20 and 40 years.[2-4,6,8] In roughly 25% of the cases, it occurs bilaterally.[3,8] The aim of this study is to review the current literature regarding the pathophysiology, presentation, as well conservative and surgical treatment options for plantar fibromatosis.

> "Plantar fibromatosis is most commonly seen on the medial and central bands of the plantar apeuneurosis."

Presentation

Plantar fibromas are well encapsulated and firm (Figure 2). Symptoms include painful ambulation, large nodules on the plantar foot as well as toe flexure

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Figure 1.

A 48-year-old woman with a large plantar fibroma.

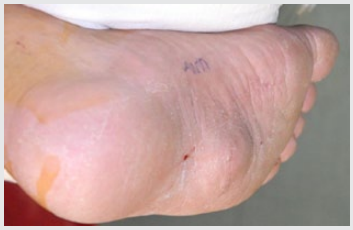
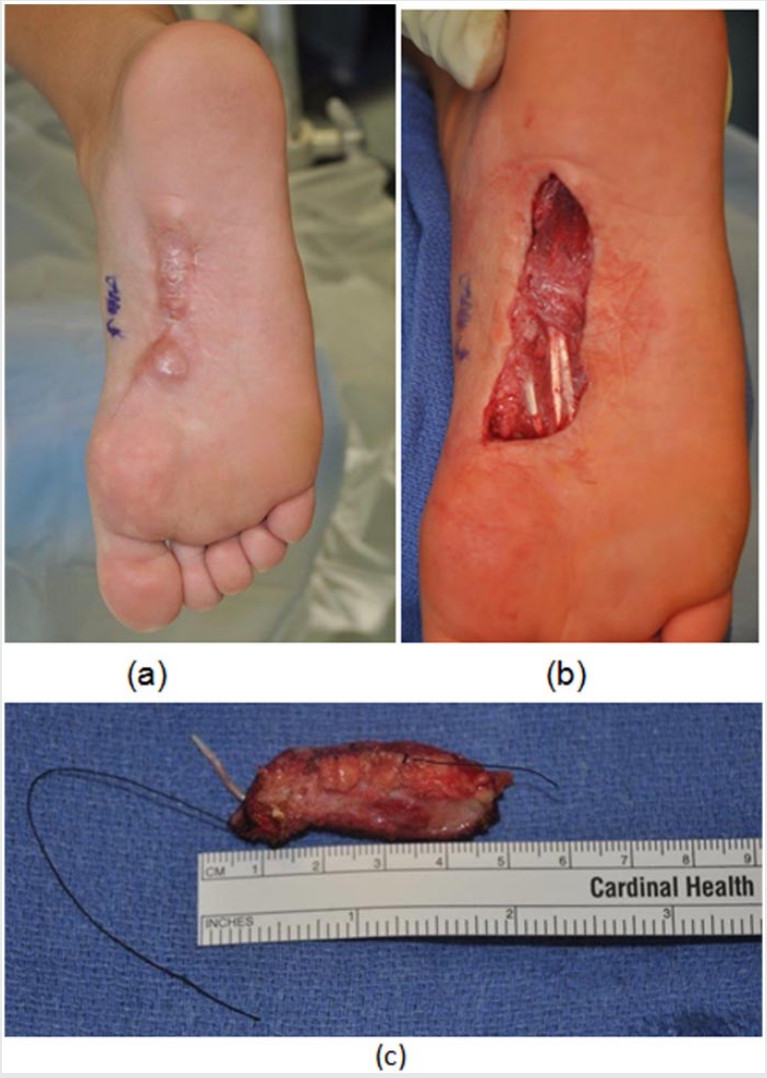


Figure 2.

Plantar fibromas are well-encapsulated, firm structures. In some occasions fibromas have extension to skin. In these cases, the skin needs to be removed with the lesion and a skin graft may be required.

Figure 3.

A case of recurrence juvenile aponeurotic fibromatosis (a). Wide excision of the lesion (b). Resected fibroma (c).



contractures in more advanced lesions. These nodules are most commonly found on the medial and central bands of the plantar aponeurosis.[2,6,8,9] Two forms of the disease have been described, juvenile aponeurotic fibromatosis and adult fibromatosis.[10] The juvenile form is more aggressive, forming intermuscular septae and flexor tendon sheath infiltration (Figure 3). The adult form is slower growing and less likely to infiltrate the flexor tendon sheath.[10] Diagnosis is usually clinical, based on presentation and symptoms. Benign differential diagnosis includes ganglion cysts, inclusion cysts, keloids, lipomas, and in one reported case, pigmented villonodular synovitis (PVNS) and extraskeletal myxoid chondrosarcoma.[2,11,12] In a letter to the editor in the *Journal of Joint Bone Spine*, 2 cases of patients developing rapidly growing plantar fibromas while undergoing anti–tumor necrosis factor α (anti-TNFα) therapy for spondyloarthritis have been reported.[13] Biopsies may be useful for differentiating fibromas from malignancies such as fibrosarcoma, synovial sarcoma, and liposarcoma as well as directing treatment.[2] Advanced imaging such magnetic resonance imaging (MRI) and ultrasound are also useful in identifying fibromas from malignancies.[2,3,10]

Pathophysiology

Plantar fibromatosis is most commonly seen on the medial and central bands of the plantar apeuneurosis.[2,8] Some studies have reported growth factors to play a role in increasing fibroblastic activity causing the formation of the fibromas. Some of these growth factors that have been identified include platelet-derived

Figure 4.

Plantar fibromatosis: Low-power view showing a typical multinodular growth pattern within the fibrous tissue of the fascia (hematoxylin and eosin, ×40).

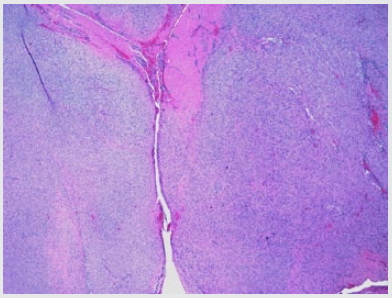


Figure 5.

Plantar fibromatosis: Medium-power view in proliferative phase showing hypercellular fibroblastic/myofibroblastic cells (hematoxylin and eosin, ×100).

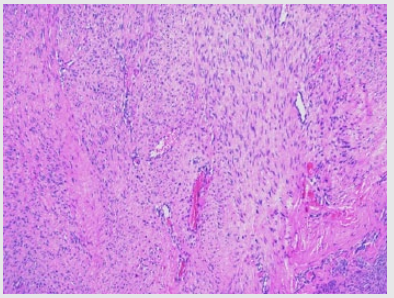
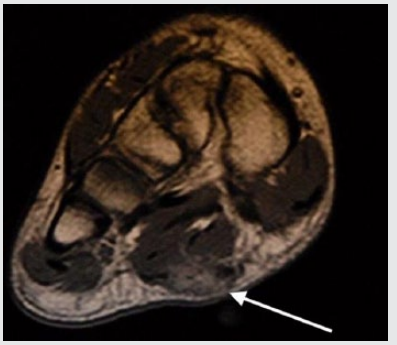


Figure 7.

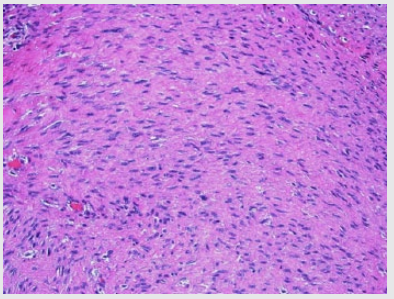
T1-weighted magnetic resonance imaging demonstrating low intensity of a plantar fibroma.



growth factor, transforming growth factor–β (TGF-β), free oxidized radicals, and interleukin-1α and -1β.[3,10,14,15] Histologically, Ledderhose disease appears similar to Duyptren's disease.[4,6,10,16] Ledderhose disease can be broken down into 3 histological phases: phase I, or proliferation phase, is characterized by a cellular, multinodular proliferation of plump, immature-appearing spindle cells in a background of fascial fibrous tissue with low production of intracellular substance (Figure 4).[2-4,8-10,17] These cells do not vary in size and shape and have bland appearing nuclei with small pinpoint nucleoli (Figure 5). Mitotic figures are rare. Cells are separated by moderate amounts of stromal collagen and elongated blood vessels (Figure 6). In phase II, the active phase, production of predominately type III collagen fibers, is at its highest and the nodule is formed. Fibroblasts, typically look similar to smooth muscle cells because they contain large amounts of actin and myosin microfilaments. However, it appears different in phase III because they contain abundant amounts of rough endoplastic reticulum and golgi apparatus.[4] Older lesions are less cellular and more densely collagenized. In 1972, Gabbiani and Majno[4] called these cells "myofibroblasts," in recognition of their

Figure 6.

Plantar fibromatosis: High-power view of cytologically bland cells separated by collagen (hematoxylin and eosin, ×200).



altered appearance. Phase III is the maturation or residual phase, which is characterized by the reduction in myofibroblasts and collagen formation with contracture of the tissue potentially leading to flexor contractures.[3,4,9] Fibromas become symptomatic as they mature in the later phases of II and III.

Imaging

The diagnosis of plantar fibromatosis can often be made without the use of diagnostic imaging; however, cross-sectional imaging can be useful to rule out other diagnoses or for surgical planning. Plain radiography is very limited in aiding with the diagnosis of plantar fibromatomosis, but is frequently done as an initial evaluation. Computed tomography (CT) is also limited because of the fact that the appearance of the plantar fibroma is very non-specific on CT scan.[18] Currently, MRI is the best modality available for assessment of a plantar fibroma. MRI is useful for evaluating extension of the mass into surrounding tissue.[9,10,17] On T1-weighted sequence, areas of dense collagen within the fibroma appears to have a low signal intensity and on T2-weighted sequence it appears with low-to-intermediate signal intensity (Figure 7).[9,17,18] If the lesion appears with low signal intensity on T2, the lesion is most likely in its residual phase.[18] If it is in the active phase it will appear with intermediate intensity.[18] Despite cost, MRI is influential in surgical planning. MRI can help define the margins of the lesion allowing for better surgical resection. There is debate about the use of ultrasound in assessing and diagnosis fibromas. However, ultrasound is inexpensive and may prove useful for performing intralesional injections.[17] On ultrasound, fibromatosis nodules appear as fusiform nodules within the plantar fascia away from the insertion at the

Table 1.

Conservative Therapies.

Treatment	Mechanism of Action	Results
Offloading pads	Offloads fibroma with use of orthotics and cut-outs	Does not affect size or progression of fibroma. Provides symptomatic relief
Radiation	Ionizing radiation disrupts TGF-β produced by myofibroblasts during proliferation phase	Requires multiple sessions of radiation during several week periods. 50% of patients report decrease in size of lesion
Extracorporeal shock wave	Exact mechanism of action unknown, possibly directly damages lesion resulting in removal by macrophages	Pain reduction and softening of lesions have been reported as early as 2 weeks after initiation of treatment
Steroids	Decreases expression of VCAM-1 and alters production of TGF-β and bFGF	Reduces size and pain of lesion, however, lesion can reoccur after several years
Anti-estrogen	Decreases contraction rates of myofibroblasts	Currently there are no in vivo studies evaluating its efficacy
Verapamil	Inhibits collagen production and increases collagenase activity	No reported studies published in plantar fibromas, but has been shown to decrease plaque size in Peyronie's disease
Collagenase	Contains 2 types of collagenase AUX-1 and AUX-2, which degrade collagen	Has been shown to decrease contractions in Peyronie's and Duyuptren's. In one case study in plantar fibromas did not show improve of lesion size
Colchicine	Inhibits microtubule polymerization by binding to tubulin	Has not been proven effective, more studies are needed to evaluate efficacy[18-20]

Abbreviations: bFGF, basic fibroblast growth factor; TGF-β, transforming growth factor–β; VCAM-1, vascular cell adhesion molecule–1.

calcaneus. Most nodules appear hypoechoic to isoechoic, without intrinsic vascularity.[17]

Conservative Therapies

Table 1 list the conservative therapies for plantar fibromatosis.

Offloading Pads

Simple offloading pads can be used to offload smaller fibroma. Materials such as foam or gel inserts with proper cutouts are useful for offloading lesions. For larger fibromas, custom orthotics with a cutout can provide relief. Offloading pads decrease the tension on the plantar fascia, which has the potential to decrease symptoms.[2,3,10,18,21]

Radiation

There exist very little published data on the use of radiation on plantar fibromas. However, radiation therapy has been shown to be effective in early stages of the disease. In comparison, radiotherapy has been a treatment option with patients suffering from Dupuytren's disease for years. Ionizing radiation interacts with myofibroblasts by disrupting TGF-β seen in the proliferation phase of the disease.[8,14] Current treatment regimens consist of a 5-week regimen of weekly doses of 3.0 Gy repeated for one additional session after 6 weeks for a total of 30.0 Gy.[3,8,9] Seegenschmiedt and Attasi[16] in 2003 found that 50% of patients had improved gait and 50% experienced an improvement in visual analog scale (VAS) after a 38-month follow-up. Heyd et al[8] in 2010 reported 33.3% of patients had complete remission and 54.4% had partial remission of nodes. Pain remission was achieved in 68% and gait improved in 70%. Negative side effects of treatment include: short-term erythema and dry skin. Seegenschmiedt[22] in 2008 reported in the hand and foot there is a 0.5% to 1% theoretical risk of soft tissue sarcoma or skin cancer after radiotherapy after latency periods of 8 to 30 years, with patients under 30 being the most at risk.

Extracorporeal Shock Wave Therapy

Shockwave therapy has been an effective treatment option for Peyronie's

and Dupuytren's disease; however, there is limited literature for use in plantar fibromatosis.[23,24] The exact mechanism of action is unknown, however, there are two theories. One theory is that extrcorporeal shock wave therapy (ESWT) causes direct damage to the lesion triggering a healing response, while the other theory is that it increases vascularity to the lesion, lysing the lesion, which results in macrophage removal.[25] In 2012, Knobloch and Vogt[23] recruited 8 patients who underwent ESWT for plantar fibroma treatment. Lesion size was not reported pre- or posttreatment. The regimen consisted of 2000 cycles at a frequency 3 Hz with an energy flux density of 1.24 mJ/mm^2 for 2 sessions with a 1-week interval between sessions. All eight patients observed softening of the nodules after 14 days. At 3 months, pain remained minimal; however, lesion size and reoccurrence was not reported.[23] No adverse side effects were reported.

Intralesional Steroids

Steroid injections in Dupuytren's nodules have shown to decrease expression of vascular cell adhesion molecule–1 (VCAM-1).[15] VCAM-1 is associated with the transendothelial migration of inflammatory cells from the blood stream to tissues. These cells produce growth factors and cytokines such as TGF-β, basic fibroblast growth factor (bFGF), and interleukins, which contribute to the proliferation of myofibroblast and collagen production.[15] Intralesional steroids also have been found to alter production of growth factors and cytokines such as TGF-β.[15] Pentland and Anderson[26] reported very good results with intralesional steroids of plantar fibromas in a runner. They injected 0.5 to 10.mL of triamcinolone acetonide, 40 mg/mL (Aristocort), diluted 3:1 with 1% lidocaine hydrochloride to a final concentration of 30 mg/mL for 5 consecutive weeks into bilateral plantar foot nodules; 4 months after final injection, lesions were smaller, and the patient was able to jog.[26] There is some promise in the hand literature. In 2000, Ketchum and Donahue[27] injected Dupuytren's nodules with 60 to 120 mg/injection in a series of 3 injections 6 weeks apart with a 50% reoccurrence rate of nodules in the first 3 years. This regimen may be promising in treatment of plantar fibromatosis. Currently, recommendations for intralesional injections of triamcinolone actonide include a total of 3 to 5 injections with each injection given 4 to 6 weeks apart at a concentration of 15 to 30 mg per nodule. While sufficient for therapy, optimal dosage has not been determined.[18] Hyperkerotic scars and fibromas are similar as they both are influenced by bFGF and TGF-β. This has led to hypertrophic scar treatments to be experimented on fibromas.[28] Ahuja and Chatterjee[28] compared triamcinolone against verapamil in treatment of hypertrophic scars. In the triamcinolone group, 20 of 22 scars were completely flat after 3 weekly injections compared with 22 of 26 in verapamil group after 5 weekly injections.[28] What was suggested in this study was a combination of both compounds may have a synergistic affect and have better results than each compound separately.

Antiestrogen

Currently, there are no in vivo studies evaluating the efficacy of antiestrogen therapy in the use of plantar fibromatosis. Tamoxifen has been used in vitro studies regarding fibroblast activity. Kuhn et al[29] isolated fibroblasts from patients with and without Dupuytren's and treated the cells with tamoxifen. What was found was that the Dupuytren's fibroblasts treated with tamoxifen had decreased contracture rates after 5 days compared with those not treated with tamoxifen.[29] It was also reported that fibroblasts from Dupuytren's patients released larger amounts of TGF-β than fibroblast's isolated from patients without Dupuytren's.[29] Tamoxifen may be potential treatment option in plantar fibromatosis as the fibroblasts also produce an excessive amount of TGF-β. Tamoxifen has shown promise in other extra-abdominal desmoid tumors, demonstrating size regression in 15% to 20% of patients and stabilizing tumor size in 25% to 30% of patients.[30]

Verapamil

Off-label use of verapamil 15% transdermal cream is occasionally used in the treatment of plantar fibromas. It is most commonly applied 2 times a day for about 9 months. To our knowledge, there is no published literature assessing its efficacy. However, topical verapamil 15% cream and intralesional verapamil have been explored as a standard for the treatment of Peyronie's disease.[24] Verapamil plays a role in the metabolism of the extracellular matrix by inhibiting collagen production and increasing collagenase activity.[31] It also alters the release of cytokines, interleukins 6 and 8, and plaque growth factor. Furthermore, it decreases inflammation.[31] Intralesional verapamil was shown to decrease plaque size from 1.42 to 0.63 mL in a study conducted by Rehman et al.[31] This was in stark contrast to the marginal increase in plaque size (1.37 to 1.39 mL) noted by the authors in the control group.

In 2010, Heidari et al[32] reported results from a study that enrolled 25 patients with Peyronie's disease. The patients received intralesional injections of verapamil (10 mg/cm^2) every 2 weeks for a total of 6 weeks. At the conclusion of the study, those enrolled showed an approximately 30% decrease in plaque size and curvature.[32] Current recommendations for treatment include 1 injection every other week or twice weekly for several weeks to months.[24] In a study conducted by Fitch et al,[33] 18 patients with Peyronie's disease who were instructed to use verapamil 15% gel twice daily demonstrated decreases in plaque size of 55% and 84.7% at 3 and 9 months, respectively. It was also reported that contact dermatitis was the most common side effect of topical verapamil.

Collagenase

While collagenase injections are currently used to treat Peyronie's and Dupuytren's disease, the injections have

Table 2.

Sammarco and Mangone Classification.

Tumor Grade	No. of Lesions	Propagation	Soft Tissue Infiltration
I	Focal	Isolated to medial/central plantar fascia	No extension to skin or flexor sheath
II	Multifocal	Possible proximal or distal extension	No extension to skin or flexor sheath
III	Multifocal	Possible proximal or distal extension	Either extension to skin or flexor sheath
IV	Multifocal	Possible proximal or distal extension	Extension to skin and flexor sheath

not been established for the treatment of Ledderhose disease.[18] Collagense *Clostridium histolyticum* (CCH) is a mixture of 2 collagenases, AUX-1 and AUX-2.[24,34] These enzymes dissolve interstitial collagens. The protocol to treat Peyronie's disease includes 2 injections of 10 000 units (0.58 mg) given 24 to 72 hours apart repeated every 6 weeks for 4 treatment cycles.[24,34] Jordan[34] reported a decrease of 32% in penal curvature after 9 months. In a study consisting of 120 patients with Dupuytren's contractures injected with CCH, Arora et al[35] found that 71% of patients completed release and 26% experienced partial release of the contracture. A case study examining CCH for plantar fibromas (injected with 0.58 mg in 0.25 mL for a period of 3 injections with 1-month intervals) failed to show improvement in nodule size, softening or painful ambulation.[42] Side effects of CCH injections include erythema, ecchymosis, and pain at the injection site.

Classification

In 2000, Sammarco and Mangone[21] developed a pre- and intraoperative staging system (Table 2). This system is a tool for predicting patients who are at risk for both wound dehiscence and recurrence. In this study, it was found that 3 out of 6 (50%) patients with stage III and 7 out of 8 (88%) with stage IV developed necrotic skin edges and delayed wound healing.[3,21]

Surgical Treatment

Surgical treatment is required for patients who have failed conservative treatments and who continue to experience discomfort. A large incision for greater exposure is needed to evaluate any extension of the lesion to surrounding tissues (Figure 8). Care must be taken with incision planning as these surgeries have a high incidence of wound complications. If the nodule extends into the skin, a skin graft may be required. The most common incision is a longitudinal straight or lazy "S" incision near the medial arch to minimize vascular compromise.[37,38] Of the several surgical options, total fasicectomy has the lowest recurrence rate.[36,39] The first procedure, local excision, involves removing just the nodule. Recurrence rates with local excision of primary lesions are 57% to 100%.[36,39] Wide excision of the lesion involves removing a 2 to 3 cm margin of uninvolved tissue. For treatment of primary lesions, recurrence rates have been reported to be as low as 8% to as high as 80%.[36,39,40] de Bree et al[40] reported that wide excision with radiotherapy has recurrence rates below 50%. The most radical of the procedures described is the complete plantar fasciectomy. Recurrence rates are the lowest for primary lesions at around 0% to 50%.[39] Endoscopic plantar fasciectomy has been described in literature; however, the evidence is very limited.[41] Meticulous wound closure is critical to minimize complications (Figures 9 and 10). Potential complications of surgery include painful scar, wound dehiscence, recurrence of lesion, nerve entrapment, and loss of arch height.

Figure 8.

Larger plantar incision gives the best exposure of the lesion. Adjacent structures need to be examined for infiltration of lesion.

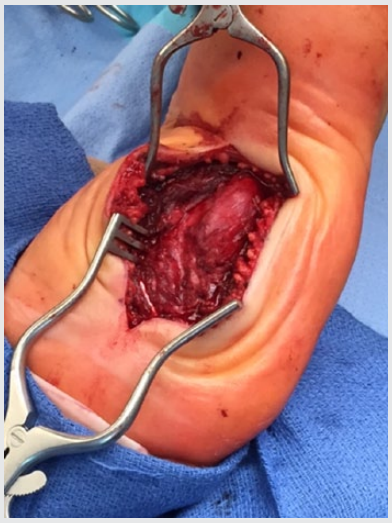


Figure 9.

Excised large desmoid tumor/ fibromatosis.

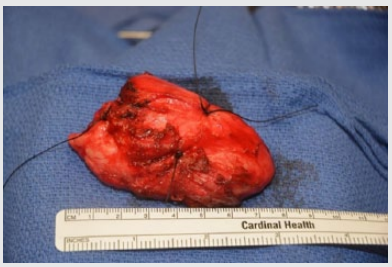


Figure 10.

Meticulous wound closure and protection from weight bearing is needed to minimize the risk of wound complications.

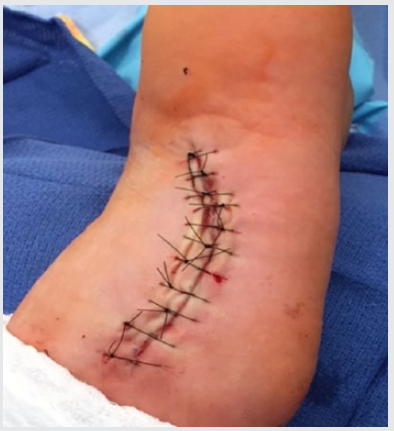


Figure 11.

Healed incision 19 months after surgery and external beam radiation.

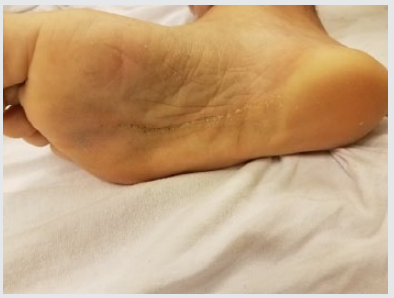
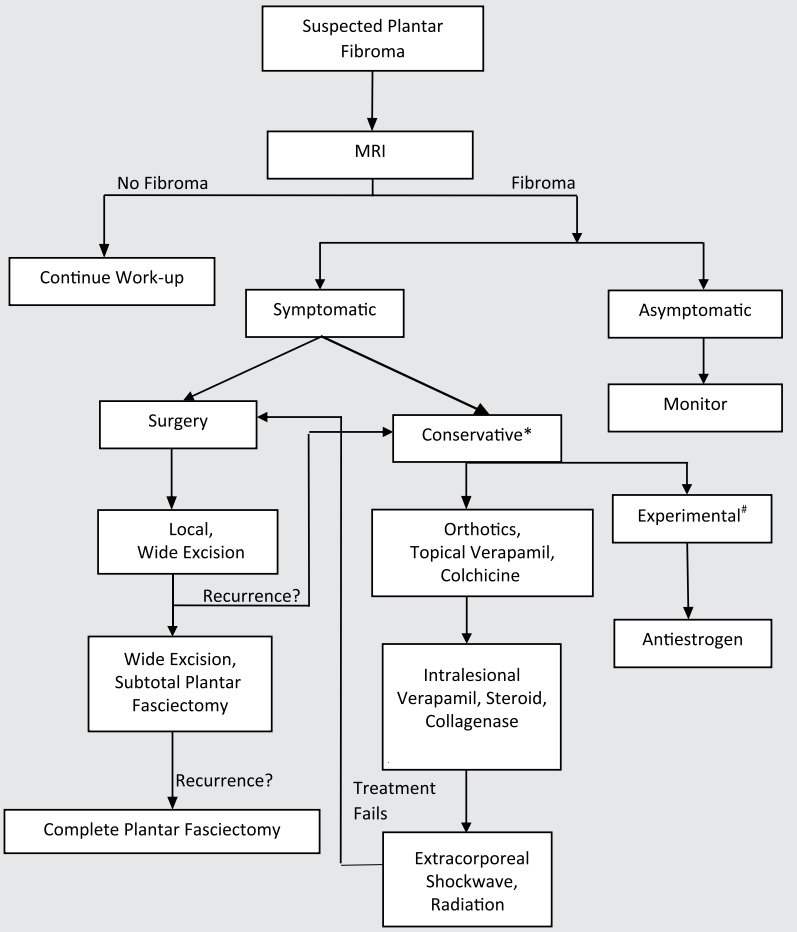


Figure 12.

Suggested treatment algorithm. *Conservative treatments have low-level evidence and some treatments are anecdotal. There are no current guidelines; however, each subsequent treatment is more invasive than previous treatment. #In vitro study only.



Case-Study

A 37-year-old man was referred to the senior author (RMH) for treatment of a recurrent desmoid tumor/fibromatosis of his plantar right foot. The patient had undergone 6 prior surgeries for removal of the mass, all through a dorsal approach. Since the last surgery 2 years prior, the mass has grown and become more symptomatic. An MRI at the time of referral showed a large deep plantar mass with extensions between the second and third metatarsals. On physical exam, a palpable 5 cm firm fixed mass was present on the plantar foot. The remaining physical exam was unremarkable. Treatment options included surgical excision with or without radiation and enrollment into a clinical trial for desmoid tumors using sorafenib. The patient elected for surgical excision followed by radiation. The patient successfully underwent soft tissue mass excision through a plantar approach (Figures 8-10). After uneventful healing of the wound, he underwent 25 external beam radiation treatments. Nineteen months after surgery, the patient reports mild pain and neuropathy, no functional limitations, and no evidence of recurrence (Figure 11).

Conclusion

The exact etiology of plantar fibromatosis is unknown. Treatment with steroids, ESWT, and radiation therapies does provide some relief of symptoms. Many of these treatment options are promising, but require further studies. Further investigation of verapamil (intralesional or topical), collagenase, and tamoxifen may provide promising treatment options. We recommend starting treatment conservatively and progressing as needed (Figure 12). Current best practice surgical intervention for painful nodules that are unresponsive to conservative options is total plantar

fasciectomy. However, this procedure does have its own complications. Further investigation of the disease is necessary for the development of optimal treatment.

Declaration of Conflicting Interests

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Ethical Approval

Not applicable, because this article does not contain any studies with human or animal subjects.

Informed Consent

Not applicable, because this article does not contain any studies with human or animal subjects.

Trial Registration

Not applicable, because this article does not contain any clinical trials.FAS

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