

Research article

Ledderhose Disease: a synthetic overview of a rare medical condition and the role of physical therapy in a clinical case presentation

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Citation: Andone I., Cocolos A., Elisei I., Spînu A., Popescu C., Ciocoi A., Daia C., Onose G. - Ledderhose Disease: a synthetic overview of a rare medical condition and the role of physical therapy in a clinical case presentation

Balneo and PRM Research Journal
2024, 15(1): 669

Academic Editor(s):
Constantin Munteanu

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Viorela Bembea

Production Officer:
Camil Filimon

Received: 19.02.2024
Published: 31.03.2024

Reviewers:
Carmen Nistor Cseppento
Sinziana Călina Silisteanu

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Abstract: Introduction: Ledderhose disease (LD), a rare and benign pathology, manifests in the thickening of the plantar aponeurosis, leading to the development of nodules on the plantar surfaces. First stages typically feature painless nodules, but progression may result in discomfort or pain attributed to inflammatory and irritating processes. Also known as plantar fibromatosis (PF), this condition is part of a spectrum of pathologies characterized by hyperproliferation of fibrous connective tissue, similar to Dupuytren contracture (palmar fibromatosis).

Given that this pathology is relatively unknown but potentially disabling, we consider it important to review this condition in order to manage possible complications and to expand the rehabilitation treatment, currently limited to a few physiotherapy procedures.

Materials and methods: This paper presents the case of a 66-year-old patient known to have Ledderhose disease diagnosed in 2003, Dupuytren contracture of bilateral hands, osteopenia, invasive ductal carcinoma surgically treated and followed by chemotherapy and radiotherapy (2018). The patient presented to our clinic complaining of bilateral plantar pain, with the left side exhibiting greater severity, accompanied by paresthesia in a sock-like distribution and difficulty with ambulation. On clinical examination, bilateral flatfoot deformity, stage 1 Dupuytren contracture of the bilateral palmar aponeurosis, mildly reduced distal muscle strength in both upper and lower extremities and plantar synovial cysts were noted, findings that were subsequently confirmed via MRI imaging. The physiotherapeutic plan was designed to reduce symptomatic manifestations, attenuate the inflammatory cascade and optimize gait pattern. However, considering the patient's medical history, we were limited in prescribing physiotherapy procedures.

The patient was dynamically evaluated using the following scales: Visual analogue scale (VAS), Life Quality Assessment (QOL), The Functional Ambulation Categories (FAC), Index of Independence in Activities of Daily Living (ADL) and Medical Research Council Scale for muscle strength (MRC).

Results: Considering the associated oncological pathology, our ability to prescribe physiotherapy procedures was constrained. However, the patient benefited from an individualized rehabilitation program specific to the pathology with a favorable evolution and a promising prognosis. The program included physical therapy sessions targeting stretching, toning and enhancing muscle strength for the plantar and palmar muscle groups, alongside paraffin applications, low-frequency current (Transcutaneous Electrical Nerve Stimulation - TENS) and Deep oscillation applications.

Conclusions: The complex rehabilitation approach in a patient with a rare medical condition, complicated with degenerative diseases, though limited in variety due to associated oncological pathology contributed in the end to a significant improvement of the patient's quality of life.

Keywords: rehabilitation program, Ledderhose disease, plantar fibromatosis, rare disease

1. Introduction

Ledderhose disease (LD) is a rare disorder, also known as plantar fibromatosis (PF), which was first described in 1875 by Madelung [1] and later, in 1987, reported by a German doctor named Georg Ledderhose, as a Dupuytren-like disease of the foot [2, 3].

This condition represents a benign and hyperproliferative disorder of the plantar aponeurosis, with an unknown etiology (although some research suggests microtraumas as potential causative factors) [4], resulting in its hypertrophy and the development of plantar nodules.

Subcutaneous nodules are usually painless in the early stages, grow progressively slowly and do not metastasize [5,6], causing discomfort, pain symptoms through inflammatory and irritating phenomena, increased tension of the fascia and increased sensitivity to pressure on the affected leg. The lesion has a high recurrence rate and local aggressiveness extending into the adipose and fibrous tissue. It may also be adherent to the skin and muscles in the vicinity, but does not invade adjacent nerves or blood vessels. In the advanced stages, retractions of the plantar fascia may appear. LD is often present on the medial and central bands of the plantar aponeurosis [7].

The exact incidence rate of LD remains uncertain [8]. Though the number of people affected has not been precisely assessed, the disease continues to appear on the National Institute of Health's list of rare diseases affecting <200,000 people [9]. However, there are authors who report LD a rather common disease with plantar contraction developed in approximately 25% of middle-aged or elderly individuals (1 of every 4 with Dupuytren contracture) [10]. Pickren et al. describe a prevalence of 1.75/100,000 [11] and Bree et al. found a prevalence of 1/100,000 [6]. A recent study conducted by Akdag et al. reported a frequency about 1–1.75/100 000 [12].

Although LD affects primarily those in their middle age, several cases have been described in children <16 years of age and even as young as 9 months [13]. Men are more often affected than women [14], and it appears that PF impact white people more than other groups [15]. It is frequently associated with palmar fibromatosis (Dupuytren disease) and Peyronie disease (penile fibromatosis), but the nodules can be observed elsewhere in the body [16]. Lanting et al. found in a systematic review and meta-analysis on the prevalence of Dupuytren disease in the general population of Western countries, that LD had a prevalence rate of 1.4 percent [17]. In a recent study, Mohede et al. found Ledderhose disease prevalence rates of 16.1 percent respectively 22.0 percent in their cohort of patients affected by Dupuytren disease [18], results similar to a study conducted by Degreef et al. [19].

Also, the etiology is incompletely understood, but plantar fibromatosis has been characterized as most prevalent in patients with hepatic dysfunction, prolonged phenobarbital usage, alcoholism, diabetes mellitus, low body mass index, recurrent trauma, epilepsy, adhesive capsulitis, and smoking [2].

Stuart Kim et al. conducted a genome-wide association study to identify genetic loci linked to plantar fascial disorders. The study proposed a potential genetic predisposition to plantar fascial disorders, encompassing PF [20].

The clinical manifestations of LD may exhibit interindividual variability and encompass a spectrum of presentations including arthralgia, paresthesia, subcutaneous nodules in PF, lack of skin elasticity, peripheral neuropathy [16]. Contracture of the toes, including the great toe, has been reported in severe proliferation and infiltration of the nodule [16]. Additionally, the severity of symptomatology may fluctuate, encompassing a spectrum from localized pressure and distention to painless nodules, and extending to tender, erythematous lesions that can affect the patient's weight-bearing capacity [16].

The characteristic nodule can be approximately 0.5–3.0 cm in diameter, slow-growing and located in the medial or central plantar aponeurosis [16]. Although subcutaneous nodules are usually painless in the early stages, the slowly and progressive growth cause discomfort and pain. Certain circumstances such as using constrictive footwear, direct

compression on the mass, walking barefoot, or prolonged periods of orthostasis, may exacerbate the pain. Furthermore, a negative prognostic is influenced by the presence of multiple fibromas that may proliferate over time [16].

LD diagnosis can be made based on clinical symptoms alone [16]. Ultrasonography-assisted biopsy can also be conducted for diagnostic confirmation and is the most economically efficient method used to validate clinical suspicion [2,3]. During ultrasound investigation we can find a single isoechoic nodule, having about 1 cm in diameter, with a heterogeneous structure and thin hyperechoic septae [3]. It does not invade adjacent tissues, has well-defined margins, without any fluid collection or calcifications within its internal structure [3]. Doppler examination reveals absence of vascularity within the nodule. [3]. The use of MRI will facilitate the determination of the size and malignant characteristics of the nodular lesion [16]. Diagnostic imaging aids in establishing a comprehensive differential diagnosis by discerning between benign pathologies from malignant tumors [3]. It also facilitates the assessment of local extension and invasion into adjacent tissues, thereby playing a significant role in surgical planning [21,22,23].

In the context of histopathological examination, the evolution of this rare disease can be described through three distinct phases: the proliferative phase, characterized by minimal collagen deposition and a large number of fibroblasts; the active phase, marked by increased collagen production and the maturation of fibroblasts; and the maturation phase, distinguished by the formation of larger bundles of collagen fibers [24]. There is an absence of abnormal cells or aberrant mitotic proliferation and frequently all three phases can coexist together [25].

The treatment comprises a multifaceted approach integrating pharmacotherapy, physiotherapy, kinesiotherapy and surgical interventions. Pharmacological management entails the administration of analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), vitamins, muscle relaxants, and topical agents. Among conservative modalities, commonly used are rest, including wearing orthotic devices (for reducing tension within the plantar fascia), cryotherapy, plantar fascia stretching exercises, physical therapies, and local corticosteroid injections (a combination of corticosteroid and local anesthetic can be intradermally administered into the plantar fibroma), resulting in pain and inflammation reduction, along with a gradual decrease in nodule size. These local infiltrations are recommended, especially in the early stages of plantar fascial fibromatosis [26,27,28].

Cryosurgery presents an excellent alternative to conventional surgical or conservative modalities in medical management. Clinical investigations indicate an approximately 80% efficacy rate [29].

Flanagan et al. present two instances of intralesional fenestration and corticosteroid injection for symptomatic plantar fibromatosis utilizing a blend of triamcinolone acetonide and mepivacaine hydrochloride, administered via intralesional fenestration [30]. Significant diminishment in both size and rigidity was observed in both cases. It seems that local steroid injections reduce fibroblast proliferation and augment apoptosis rate [31]. There are other methods of conservative treatment described in the specialized literature. Verapamil is a calcium channel antagonist, primarily prescribed for hypertension management. Studies suggest that it enhances the activity of collagenase while concurrently inhibits collagen synthesis [2,32]. Transdermal and intralesional administration of verapamil gel has demonstrated reductions in fibroma size ranging from 55% to 85% [2,32].

In 2010, the US Food and Drug Administration granted approval for the utilization of collagenase *Clostridium histolyticum* in the management of Dupuytren contracture, followed by its approval for Peyronie disease in 2013. In 2019 Lehrman et al. reported a case study in which they injected a 22-year-old white female with a plantar fibroma with 0.58 mg collagenase *C. histolyticum* in 0.25 mL of reconstituted solution, one time [33]. At the patient's ultimate follow-up consultation, 33.5 months post-injection, there were no

indications, clinical manifestations, or complaints of relapse of PF [33]. However more future studies with a greater sample size would be more decisive.

Isolated from *Streptomyces caespitosus*, Mitomycin C is an antineoplastic antibiotic that has anti-fibroblastic properties, inhibiting the proliferation of fibroblasts [34]. In a study conducted by Amer et al. [35], following the surgical removal of plantar nodules, topical administration of Mitomycin C (6cc, 0.4 mg/mL) was applied to the tumor bed for a duration of five minutes. The findings provided an unexpected outcome: a notable absence of recurrence in plantar nodules when Mitomycin C was combined with surgical excision, as opposed to surgical intervention alone [35]. These findings suggest that Mitomycin C exerts inhibitory effects on tumor growth by blocking fibroblastic activity [35]. Furthermore, the study demonstrates the safety of topical Mitomycin C application, as documented by the absence of wound toxicity or delayed wound healing [35].

The management of plantar fibroma typically involves physical therapy interventions such as ultrasound or shockwave therapy. These modalities aim to disrupt adhesions and diminish the dimensions of plantar fibroma nodules. It usually necessitates 3-4 sessions of either ultrasound or shockwave therapy to observe improvement in pain levels or fibroma size. Additionally, LASER therapy may be used to reduce the pain due to its vasculobiotrophic effects. A comprehensive physiotherapy program typically comprises approximately 10 sessions of therapeutic procedures.

Knobloch and Vogt considered high-energy extracorporeal shock wave treatment in 5 patients with plantar fibromatosis [36]. Extracorporeal shock waves (number of shockwaves: 2000 impulses, frequency: 3 Hertz, energy flux density 1.24 mJ/mm²) were applied in 2 therapeutic sessions [36]. All patients reported an improvement in pain (assessed on the VAS scale) and noted a decrease in nodule stiffness [36].

Strengthening exercises can be performed for toes to help support the arch and stretches can help to improve foot flexibility [37, 38]. The optimal exercises for plantar fibromatosis involve elongating and fortifying the plantar fascia alongside adjacent soft tissues, the gastrocnemius and soleus muscles, as well as the Achilles tendon. These exercises play a pivotal role in diminishing tension across the plantar fascia, consequently alleviating the irritation associated with plantar fibromas. These exercises are thereby recognized as efficacious modalities in the management and treatment of LD [39].

Orthoses are beneficial in the management of plantar fibroma. These contribute to the redistribution of biomechanical forces, alleviating the load on the calcaneus and reducing tension within the plantar fascia. Orthotic devices enhance the comfort of weight-bearing activities and footwear use thereby improving quality of life [40]. Custom-made orthoses are favored due to their ability to conform closely to foot morphology. However, this method does not prevent the progression of the lesion [40].

In recent decades, radiotherapy has emerged as a novel therapeutic modality for LD, demonstrating encouraging outcomes [41]. The mechanism underlying radiotherapy's efficacy remains partially elucidated; however, it is theorized that radiotherapy slows the proliferation of mitotic fibroblasts and myofibroblasts while inducing the generation of free radicals, thereby inhibiting proliferative activity and interfering with growth factors and cytokines [32]. Radiotherapy seems to be very efficient during the active phase of the disease process, when it is the peak of cellular proliferation [32]. Between 2003 and 2022, the effect of radiotherapy as the primary treatment for patients with Ledderhose disease was investigated in only four retrospective studies [42]. These investigations have demonstrated analgesia with negligible toxicities. Nevertheless, the incremental benefit of radiotherapy remains unexplored in a randomized controlled trial [42,43].

The surgical excision of the nodule can be performed to alleviate symptoms and prevent progression of the disease [16]. Surgical resection is typically used as a final option in cases in which conservative modalities were ineffective, in progressive lesions, late-stage pathology, intolerable pain, ambulatory or equilibrium impairments [3]. This procedure may be executed via conventional or endoscopic methods [3]. A comprehensive removal

of the lesion, ensuring the absence of residual pathological tissue, with partial or complete fasciectomy is imperative to minimize recurrence rates, from 0-50% [3]. However, plantar fibromatosis frequently tends to be recurrent following local excision (only the nodules) with a rate from 57–100% [44,45].

Ledderhose's disease does not affect life expectancy. However, the disease's active phase may diminish the quality of life due to heightened symptomatology, manifesting as intense pressure pain upon weight-bearing on the plantar surfaces of the feet.

CASE REPORT

On 13.03.2023, a 66-year-old female patient presented to our clinic with complaints of mechanical pain localized at the left plantar and left calcaneus regions, exacerbated during ambulation. She also reported bilateral paresthesia with in sock-like distribution, predominantly affecting the left side, accompanied by a moderate restriction in bilateral lower limb mobility. Consequently, a personalized physiotherapy and kinesiotherapy program was initiated.

The patient's familial medical history revealed no significant contributions to her current condition. Her personal medical history included Ledderhose disease (diagnosed in 2010), bilateral Dupuytren disease (diagnosed in 2019), invasive breast ductal carcinoma (managed surgically with chemotherapy and radiotherapy in 2018), chronic hepatitis B infection and osteopenia.



Figure 1 - Dupuytren disease on both hands stage 1
(Kinesiomed Rehabilitation Clinic Division,

PATIENT'S EXAMINATION

Upon admission, the patient exhibited consciousness, cooperation, and temporal-spatial orientation with a nonspecific facial expression. The patient displayed mildly diminished muscle strength in the distal lower extremities (graded 4/5 on the MRC scale).



Figure 2 - bilateral hallux valgus and subcutaneous nodules on the left leg with slight local edema (Kinesiomed Rehabilitation Clinic Division casuistry)



Figure 3 - significant flatfoot
(Kinesiomed Rehabilitation Clinic Division casuistry)

Dynamometer assessment revealed a slight reduction in motor strength in the right hand (9kg) compared to the left hand (11kg). Bilateral plantar paresthesia was noted, more pronounced on the left side. Osteotendinous reflexes remained within normal limits. Dupuytren contracture with minimal palmar aponeurosis retraction (stage one of Dupuytren disease) was evident bilaterally. Examination of the lower limbs revealed significant bilateral flatfoot, bilateral hallux valgus and subcutaneous nodules with slight local edema on the left leg.

From a functional point of view, the patient was able to walk medium distances within tolerance. The following parameters were assessed on the first day and after 10 sessions of physiotherapy and kinesiotherapy (day 10):

1. Visual analogue scale (VAS) which highlights 10 stages of pain from 0 (no pain) to 10 points (the highest intensity for pain) [46].
2. Life Quality Assessment (QOL) which comprises 16 items and a 7-point satisfaction scale ranging from "very satisfied" to "very dissatisfied" to assess quality of life from the perspective of the patient [47]. Scores can range from 16 to 112.
3. The Functional Ambulation Categories (FAC): the 6-point functional walking test is a clinical assessment tool aiming to evaluate ambulatory capacity. It assesses the level of human assistance needed by the patient during ambulation, whether or not he/she utilizes a personal assistive device [48].
4. Index of Independence in Activities of Daily Living (ADL). The scale evaluates the functional status by quantifying the patient's capacity to execute activities of daily living independently. The Index evaluates the adequacy of performance across six functions: bathing, dressing, toileting, transferring, continence, and feeding. Patients are assessed for independence in each function, resulting in a binary scoring system of yes/no. A score of 6 signifies complete functionality, while 4 denotes moderate impairment and 2 or below indicates severe functional deficiency [49].
5. Medical Research Council Scale for muscle strength (MRC): the muscle scale assesses muscle strength using a grading system ranging from 0 to 5 in relation to the anticipated maximum strength for the specific muscle being evaluated [50].

PARACLINICAL ASSESSMENTS

Plantar X-ray did not reveal radiographically focused bone lesions in the examined sequences. A left calcaneal osteophyte was described.

MRI of the right plant native and with contrast substance revealed:

- Focal space-replacing process in the subcutaneous cellular tissue at the level of the middle 1/3 of the plant, adjacent to the plantar fascia, without change in thickness or signal. It presented a blurred contour, moderate contact socket, without adjacent edema - possibly inflammatory substrate.



Figures 4 and 5 - Plantar X-ray - left calcaneal osteophyte, no radiographically focused bone lesions (Kinesiomed Rehabilitation Clinic Division, casuistry)

MRI of the left sole native and with contrast substance revealed:

- Focal space-replacing process in the subcutaneous cellular tissue at the 1/3 level of the plant, adjacent to the plantar fascia, anteroposterior dimensions 20mm, thickness 8mm, imprecisely delimited.
- The underlying plantar fascia thickened on a 32mm anteroposterior portion with a heterogeneous signal, suggesting a degenerative aspect.
- In the vicinity of the insertion on the calcaneus, there was a portion of fusiform thickening of the plantar fascia, over a length of 26mm, without edema, without interruption of the path or insertion.

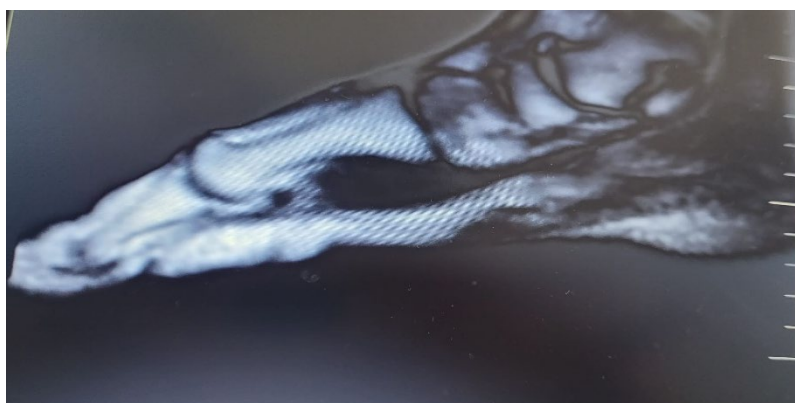


Figure 6 - MRI of the left sole native (Kinesiomed Rehabilitation Clinic Division, casuistry)

Considering the bilateral changes, the appearance may correspond to regions of plantar fibrosis juxtaposed with areas of overutilization and intrinsic rupture/degeneration of the plantar fascia on the left side (exhibiting features of Ledderhose disease), whereas the integrity, thickness, trajectory, and insertion points of the right plantar fascia remain unaffected.

A comprehensive assessment was conducted, considering potential differential diagnoses, including benign neoplasms such as lipoma and synovial cyst, malignant tumors like fibrosarcoma and giant cell fibroblastoma, plantar fasciitis, limb deformities such as flat foot and equine clubfoot and degenerative conditions like metatarsal arthrosis.

THE REHABILITATION PROGRAM

The objectives of our rehabilitation program aimed to decrease pain, combat contractures, enhance muscular strength, optimize functionality and mobility, rectify static and dynamic dysfunctions through gait retraining and augment overall quality of life.

Considering the concomitant oncological pathology, it was imperative to restrict the implemented physiotherapeutic interventions.

Transcutaneous electrical nerve stimulation (TENS) is a non-pharmacological modality that induces analgesia by stimulating a complex neuronal network, triggering descending inhibitory pathways within the central nervous system to reduce hyperalgesia [51]. TENS is considered safe for the patients with cancer [52].

Deep oscillation is a low-intensity and frequency pulsating electrostatic field, established between the manual applicator and the targeted tissue of the patient. As a result, rhythmic frictions occur as the applicator is moved repeatedly and swiftly in the same direction. This process induces oscillations in the local tissue, including the skin, subcutaneous tissue, muscles, blood vessels and lymphatic vessels, potentially leading to enhanced local vascular circulation [53]. It can be safely utilized in patients with oncological history [54].

The patient underwent ten sessions of each physiotherapy procedure:

- Paraffin applied bilaterally on hands

- TENS: bilateral heel, frequency 150 imp/sec, I for pleasant tingling, duration 30 min
- Deep oscillation: bilateral palmar and plantar frequency 100Hz, DI: DP=1:1, 15 minutes
- Lymphatic drainage with medium pressure for 20 minutes time for reducing the plantar edema



Figures 9 and 10 - Deep oscillation application (Kinesiomed Rehabilitation Clinic Division casuistry)

The patient also followed 10 sessions of ergotherapy.



Figure 7 - paraffin (Kinesiomed Rehabilitation Clinic Division casuistry)



Figure 8 - Tens application on heels (Kinesiomed Rehabilitation Clinic Division casuistry)

The patient's personalized kinesiotherapy program consisted of:

- Strengthening exercises targeting the leg stabilizer muscles
- Improving/increasing leg flexibility
- Stretching exercises for the Achilles tendon
- Improvement of walking scheme/correction of gait

The patient performed bicycle exercises, pedal exerciser routines, wooden stick exercises, toe curls with a resistance band, toe extensions, standing gastrocnemius stretch, standing soleus muscle stretch, calf stretch on an elevated surface, plantar fascia massage, and supervised ambulation under the guidance of the physical therapist.



Figure 11 - Lymphatic drainage on lower limbs (KinesioMed Rehabilitation Clinic Division casuistry)

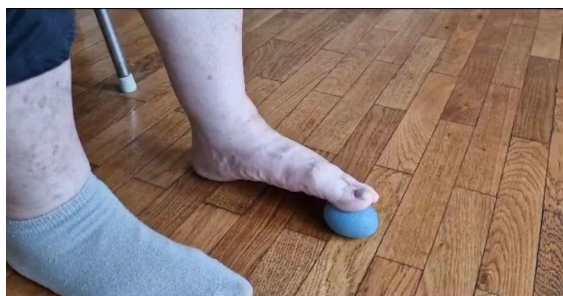




Figure 12 - Kinesiotherapy on lower limbs (Kinesiomed Rehabilitation Clinic Division casuistry)

RESULTS

After undergoing the personalized rehabilitation program, the patient experienced improvements in pain symptoms, enhanced muscular strength, optimized gait pattern, and ultimately achieved a progressive enhancement in overall quality of life (table 1).

Table 1 The modification of parameters after 10 days of treatment

	Day 1	Day 10
Visual analogue scale (VAS)	4-5/10	1/10
Life Quality Assessment (QOL)	84/112	104/112
The Functional Ambulation Categories (FAC)	5	6
Index of Independence in Activities of Daily Living (ADL)	8/10	9/10
Medical Research Council Scale for muscle strength (MRC)	4/5 upper limb 4/5 lower limb	4/5 upper limb 4+/5 lower limb

DISCUSSION

Currently, we have not found any rehabilitative treatment options in the medical literature for a patient diagnosed with Ledderhose disease and known to have oncological pathology. Additionally, articles discussing applied physiotherapy procedures are limited, with most focusing solely on the use of Ultrasound and Shock Wave therapy. In our case, we were unable to use these two physiotherapy procedures, as they are contraindicated in patients with a history of cancer. Therefore, we could only utilize TENS and Deep Oscillation therapy.

The prognosis ad vitam was favorable and life expectancy remained unrestricted despite the slow progression of the disease. Applying conservative therapeutic measures, avoiding exacerbating factors, adhering to hygiene protocols and embracing a lifestyle tailored to the disease's characteristics are crucial for the evolution of LD, potentially leading to favorable outcomes.

This prognosis can only be influenced by the potential complications arising from underlying pathologies, necessitating the patient to undergo periodic reassessments.

The *ad laborum prognosis* indicated that the patient was already retired and capable of performing most of her daily activities autonomously.

The *ad functionem prognosis* proved gratifying, considering the patient's adherence to the rehabilitation program, provided she persists continuing kinesiotherapy.

The particularity of our case lies in the concomitance of plantar and palmar fibromatosis in a female patient in her sixth decade of life, presenting with an associated oncologic condition and a pre-existing hepatic pathology commonly linked with Ledderhose disease. Additionally, we mention the reduced number of cases discovered from this pathology, categorizing it as a rare disease and the favorable progression of the patient following conservative treatment, even after a decade.

CONCLUSIONS

LD is a rare medical condition characterized by its benign nature yet posing challenges in treatment modalities. The quest for the most efficacious treatment protocol remains ongoing. Conservative therapies continue to be first-line alternatives for symptomatic cases.

The complex rehabilitation approach even if limited in diversity by the associated oncological pathology, in a patient with a rare medical condition, complicated with degenerative diseases, determined in our clinical experience an improvement in the patient's quality of life.

In treating patients with Ledderhose disease, it is necessary to form a multidisciplinary team composed of physical medicine and rehabilitation physicians, orthopedists, physiotherapy assistants, physiotherapists, orthotists, and psychologists.

We believe that implementing physiotherapy procedures such as TENS and Deep Oscillation can serve as a treatment alternative for patients who experience pain due to the PF. However, in the future, a larger number of patients and more studies will be needed to confirm these findings.

Ethics approval and consent to participate: This paper has the approval from THEBA Bioethics Committee.

Author Contributions: All authors have an equal contribution to the publication. All authors have

read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Informed Consent Statement: Written informed consent was obtained from the patient.

Data Availability Statement: Not applicable.

Acknowledgments: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

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