REVIEW

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Clinical, histological and therapeutic modern approach of Ledderhose disease

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Abstract

Ledderhose disease or plantar fibromatosis is a rare hyperproliferative disorder of the plantar aponeurosis, clinically characterized by nodules situated especially on the medial border of the foot. It is histopathologically associated with Dupuytren's disease. This disease has some risk factors, like old age, alcohol or nicotine abuse, liver dysfunction, trauma or exposure to vibrations and autoimmune disorders, but the exact etiology is still unknown. Even though it is benign, the local manifestations can be aggressive, leading to debilitating deformities and contractures of the toes. Ultrasound and magnetic resonance imaging are used to confirm the diagnosis and to eliminate other disorders. Whenever is possible, the conservative therapies are recommended. Having a high recurrence, Ledderhose disease can be hard to treat, needing multiple surgical interventions. This paper aims to cover all the important aspects of this disease for daily medical practice, from history to clinical manifestations, diagnostic methods and histopathological features, to conservative and surgical treatment modalities.

Keywords: Ledderhose disease, plantar fibromatosis, hyperproliferation, growth factors.

Introduction

Ledderhose disease is a benign hyperproliferative disorder of the superficial plantar aponeurosis [1], first reported in 1875 by Madelung [2] and 22 years later described by Georg Ledderhose as a Dupuytren-like disease of the foot [3]. It is characterized by slow growing nodules on the medial side of the foot arch [1]. Plantar fibromatosis is quite commonly associated with palmar fibromatosis (Dupuytren's disease), penile fibromatosis (Peyronie's disease), frozen shoulder and the risk of its occurrence is increased by other conditions such as alcoholic hepatic dysfunction [4], diabetes mellitus, epilepsy with long-term Phenobarbital treatment, nicotine abuse [5], repeated trauma, exposure to vibrations, vascular or autoimmune disorders and genetic inheritance [6]. Having an unknown etiology, there is no causal therapy available, the treatment being only symptomatic and functional [7]. There are some hypotheses about the fact that Ledderhose disease appear due to a hyperactivity of mature fibroblasts and some growth factors like platelet-derived growth factor, transforming growth factor-β (TGF-β), free oxidized radicals or interleukin (IL)-1α or IL-1β, but it is still in discuss [5].

Listed as a rare disease by the *Office of Rare Diseases of the National Institutes of Health* [5], it has a reported frequency about 1–1.75/100 000 [1]. Although it may appear unrelated to age, Ledderhose disease is rare in children, with the greatest prevalence in the sixth decade, especially affecting the male population [2] and being common in Caucasians in Northwestern Europe [6].

Even though it is benign, plantar fibromatosis can have aggressive local manifestations, progressively replacing the normal aponeurosis, causing pain, walking disability, problems of balance, debilitating contractures and deformities of the toes. It can be bilateral in almost 25% of patients [6, 8]. The same as plantar fasciitis, Ledderhose disease evolve especially on the central component of the fascia and so the nodules can be easily palpated [9].

Usually, the diagnosis is clinically established and does not require confirmation. In some specific cases, it is necessary to perform an incisional biopsy with histopathological analysis, in order to differentiate between benign or malignant lesions [10], such as epithelioid sarcoma, leiomyoma [11, 12], rhabdomyosarcoma and liposarcoma [13, 14]. Subcutaneous fat necrosis, keloids, ganglion cysts, lipomas, desmoid tumors and foreign-body reaction are the main differential diagnostics [9]. In a study from 2015, Omor *et al.* had reported that magnetic resonance imaging (MRI) can be successfully used to establish disease severity [2].

It is very important for Ledderhose disease to be promptly diagnosed and to determine a therapeutic plan in order to prevent its progression and to improve the patient's quality of life.

Usually, the clinical diagnosis and the therapeutic approach are easily established, but there are specific situations with unusual presentation, where little data are available.

This review aims to describe the clinical features, specific and misleading particularities in histological

assessment, as well as the available treatment options, making all the information easily accessible for the practical approach.

Clinical approach and diagnosis

Ledderhose disease is clinically defined by an insidious onset with slow growing and a mean symptomatic period between 6–72 months, characterized by the presence of firm nodules about 1–2 cm situated most often on the central and medial plantar fascia (Figure 1).

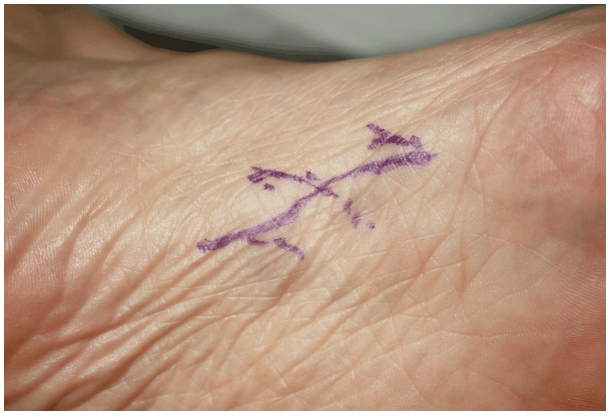

Figure 1 – ***Ledderhose disease: clinical aspect – firm nodules on the medial side of the foot.***

The normal aponeurosis is progressively replaced by abnormal thick collagen fibers leading to sclerosis of the entire plantar fascia [6]. Also, these nodules can form irregular masses of few centimeters that can be easily palpated. In many case, the nodules are fixed to the overlying skin. There can be few aggressive forms with the invasion of the adjacent tissues, especially the bone periosteum, leading to deformities and unpaired feet function that will need numerous surgical interventions and reconstructions [15, 16].

Couderc *et al.* reported two cases of rapidly growing plantar fibromatosis in two relatively young patients undergoing treatment for spondylarthrosis with anti-tumor necrosis factor-α (anti-TNF-α) [17] rising the suspicion that this therapeutic agent can play a role in the differentiation of fibroblasts into myofibroblast. Also, Vandersleyen *et al.* presented some cases of plantar fibromatosis developing in patients treated with the BRAF-inhibitor Vemurafenib for metastatic melanoma. It seems that it induces a paradoxical activation of the fibroblasts and, in combination with genetic predisposition, activate mutations in some components of the mitogen-activated protein kinases (MAPK) pathway ([18].

There are two forms of this disease described in literature: the juvenile form (the aggressive type with intermuscular septae formation and flexor tendon infiltration) and the adult form (the slow growing and less infiltrative type with a greatest prevalence in the sixth decade) [3, 19]. There is no standardized classification of Ledderhose disease.

From a clinical and pathological point of view, plantar fibromatosis can be classified as follows [7]:

- stage I: proliferative – increased fibroblastic activity – without clinical manifestations;
- stage II: involutional – typical nodule formation;
- stage III: residual – reduction in fibroblast activity, collagen maturation, late tissue contractures.

In the first stages of the disease, clinical manifestations can be absent. The usual symptoms include local pressure, pain and swelling leading to walking problems [20, 21], debilitating contractures of the toes leading to difficult ambulation [22, 23] and distension. Patients often describe the sensation like "a pea or a marble inside the shoe" [6]. Pain appearance is related to an inflammatory reaction of the tissues around the nodules or to an extension to the adjacent neurovascular or muscular tissues [7].

Ledderhose disease is often associated with palmar fibromatosis (Dupuytren's disease), penile fibromatosis (Peyronie's disease), frozen shoulder and there are some reported cases of oral manifestations (multiple nodules with variable sizes on the dorsal surface, borders or tip of the tongue) [24].

Ultrasound (US)-guided biopsy can be performed to establish the diagnosis [3].

Diagnosis of plantar fibromatosis is usually based on clinical examination and rarely requires further investigations for confirmation. Routine laboratory tests are performed in order to find an underlying pathology.

Because Ledderhose disease has an almost pathognomonic patter, frequently presenting as a single nodule on the medial border of the foot with an intimate relationship to the fascia, US investigation represents the most cost-efficient technique used to confirm the clinical suspicion. It is safe, quick and noninvasive. There can be seen a single isoechoic nodule, having about 1 cm in diameter, with a heterogeneous structure and thin hyperechoic septae. It does not invade adjacent tissues, has clear-cut margins, without any fluid collection or calcifications within the internal structure. If a Doppler technique is used, it shows no flow inside (lack of vascularity). US is also used for performing intralesional injections [25].

Diagnostic imaging helps to establish a differential diagnosis with benign pathologies, such as foreign-bodies reactions, plantar fasciitis, cysts, keloids, lipomas, lymph nodes inflammation, pigmented villonodular synovitis, vascular calcification on dialysis patients [26, 27], extra-skeletal myxoid chondrosarcoma, neurofibroma, leiomyoma [28, 29], as well as malignant disease – other space-occupying tumors like fibrosarcoma [30, 31] osteosarcoma, liposarcoma or synovial sarcoma [12, 21].

US and MRI are the most useful methods used to differentiate fibromatosis from malignant tumor, as well as to evaluate local extension and adjacent tissues invasion, being influential in surgical planning [32, 33].

MRI shows well-demarcated nodules with low-intensity signal on T1-weighted sequences (areas of dense collagen) and low-to-intermediate signal intensity on T2-weighted sequences [34]. If the nodule has low signal intensity on T2 it means that it is in the residual phase (stage III). It is used to measure the deep extension (in case of aggressive forms), allowing a better surgical resection, but because of the higher cost compared with US, it is not very used [35].

Plain radiography or computed tomography has limited utility since Ledderhose disease has non-specific signs outside the complications [3].

We consider that US is superior to MRI in the assessment of plantar fibromatosis because plantar fibromas can be small and difficult to differentiate from the plantar fascia (low signal intensity) on MRI and also it is cost and time spearing to examine both legs with US. Further, it is more facile to differentiate fiber interruption and tearing

from edema using US because plantar fibromas have an echotexture with poor reflection in contrast with fibrillar appearance of the normal plantar fascia.

Histopathological features

With certain clinical and radiological findings, histopathological and immunohistochemical (IHC) examinations confirm the diagnosis. Zgonis *et al.* carry out an ultrastructural and IHC study showing that Ledderhose disease has similar findings with those of Dupuytren's disease [12]. In contrast with palmar fibromatosis, this disorder is hypercellular with a specific gain in the collagen component.

Microscopic examinations show nodules-organized proliferation of non-atopic monomorphic cells (Figures 2 and 3). These cells have oval shaped nuclei with small nucleoli and fine chromatin with the preponderance of type III collagen and no identifiable mitosis [36].

Using the histological features, Ledderhose disease can be divided into three phases. The first phase – proliferation phase – is characterized by a typical multinodular proliferation of plump within the normal fibrous tissue of the plantar fascia. These cells have the same size and shape with bland nuclei and small nucleoli being separated by collagen fibers and elongated blood vessels [28] (Figures 4–6). In this early stage, there are no visible alterations in the plantar fascia. The second phase – active phase – type III collagen fibers are predominantly produced leading to nodule formation. The fibroblasts cells containing large amount of myosin and actin microfilaments, looks like smooth muscle cells [36]. The third phase – maturation or residual phase – is characterized by a reduction in collagen and myofibroblast production, with thick collagen fibers, the cells containing a high amount of Golgi apparatus and endoplasmic reticulum [5]. This is the moment when the tissues contract leading to flexor contractures [3].

Because histological features are non-specific, we recommend the use of immunohistochemistry in order to eliminate the differential diagnosis of this disease. Findings like atypical cells, nuclei with different shapes or bundles of spindle shaped fibroblast rule out fibrosarcoma due to the higher degree of differentiation and have a worse prognosis [12, 37, 38]. Therefore, the presence of anti-S100 marker suggest the proliferation of Schwann cells characteristic for neurofibroma or schwannoma, the proliferation of melanocytes is found in melanotic lesion and the anti-epithelial membrane antigen (EMA) marker suggest the presence of a perineurioma. When anti-caldesmon, anti-desmin and anti-myogenin markers are discovered they are typical for smooth or striated muscle proliferation. Fibroblast activity may be revealed using β-catenin staining of the nuclei (Figure 7), in contrast with epithelial cells where cytoplasmic β-catenin staining is also present. The proliferation of the epithelial cells is confirmed by the presence of anti-AE1/AE3 labeling. Another example is that fibromyxoid sarcoma or solitary fibrous tumor can be suggested by the presence of anti-CD34 and anti-MUC4 markers [38].

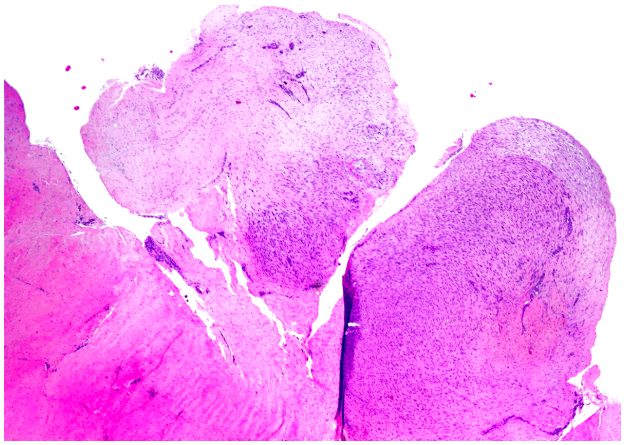

Figure 2 – ***Ledderhose disease: nodule of hypercellular proliferation of plump spindle cells (HE staining, ×25).***

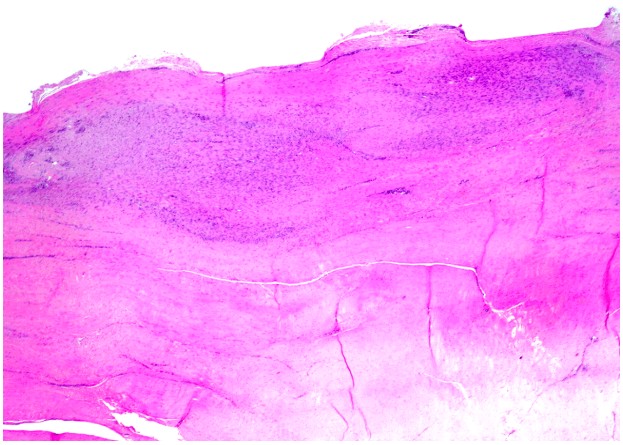

Figure 3 – ***Ledderhose disease: organized hypercellular proliferation of plump spindle cells (HE staining, ×25).***

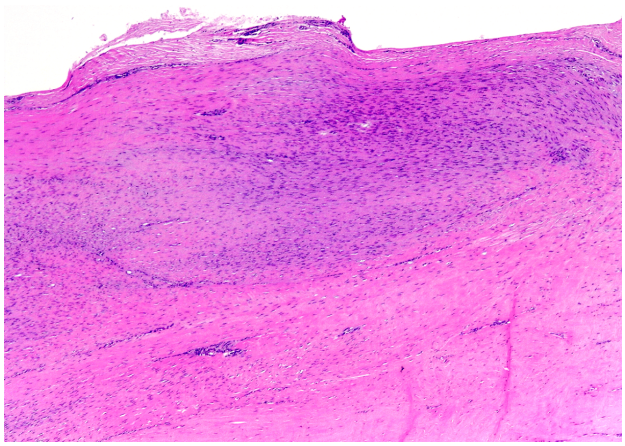

Figure 4 – ***Ledderhose disease: plump spindle cells (HE staining, ×50).***

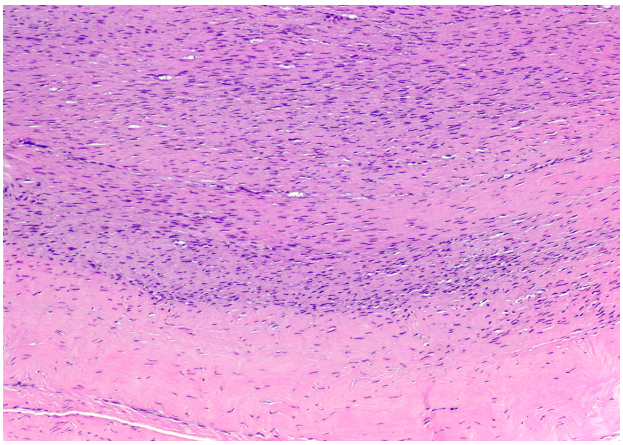

Figure 5 – ***Ledderhose disease: plump spindle cells (HE staining, ×100).***

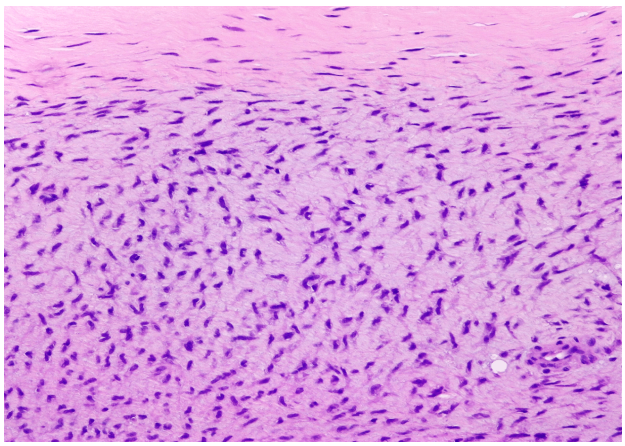

Figure 6 – ***Ledderhose disease: plump spindle cells with bland nuclei, indistinct nucleoli and no mitotic figures (HE staining, ×200).***

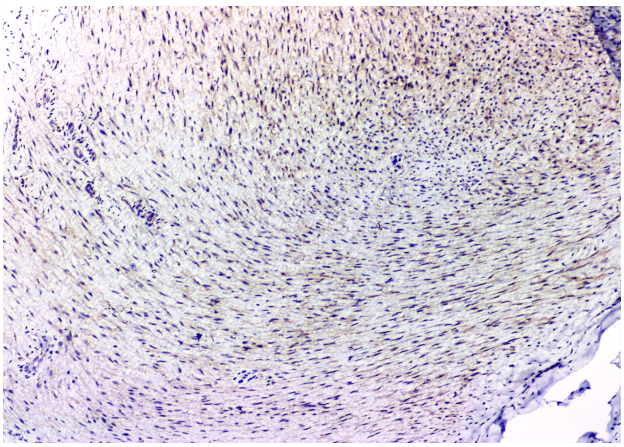

Figure 7 – ***Ledderhose disease: focal nuclear positive staining for β-catenin (Anti-β-catenin antibody immunostaining, ×100).***

Therapeutic management

Multiple therapeutic strategies are available, depending on the individual characteristics, presence and intensity of the symptoms, the stage of pathological modifications and on whether it is the first manifestation or a relapse. The most important aspect, like in any disease, is to relieve the pain and to get patient's comfort [39, 40] and to use therapeutic strategies, which do not activate or aggravate underlying chronic pathologies [41]. In current practice, one can choose between conservative treatment strategies and surgical interventions.

Conservative therapies can be applied in early stages of the disease, without pain, walking discomfort or balance problems. There should be consider from beginning that a new increase in nodules size or further relapse are inevitable, at some point, without surgical intervention [35].

The most non-invasive method is presented by the offloading pads with orthotics and cutouts that can be used in the first stage of the disease to decrease tension on the fascia providing pain-relief but does not prevent at all the lesion's progression [35].

Extracorporeal shock wave therapy was originally designed to treat Peyronie's and Dupuytren's disease, but Knobloch and Vogt presented a study in 2012 about the benefits of this therapy in reducing pain and softening of lesions of plantar fibromatosis [42]. It is indicated, like in other pathologies, to use systemic analgesics during the sessions [43].

It seems that shock therapy produces, on the one hand, direct trauma of the lesion unleashing an intensive healing response, and on the other hand produce the lesion lysing by increasing its vascularity [44].

Radiotherapy is effective in the first stages, targeting the disease progression and preservation of the feet function, but there are few studies that support this hypothesis. It is used for years as an option for treating Dupuytren's disease. Ionizing radiation reduces the proliferative activity of the fibroblasts and myofibroblasts by interacting with TGF-β production [3]. This therapy present acute side effects like lethargy, local edema and pain, local skin reaction. Late side effects are represented by fibrosis and skin modifications locally, but it can produce a decrease in patients' immunity status leading to general complications [45]. We do not recommend the use of this therapy in case of young patients due to the risk of promoting secondary malignancy like soft tissue sarcoma or skin cancer [46] (latency period between 8–30 years), although the risk is low because the irradiated area is usually small. Current regimen requires multiple session of radiation during five to 11 weeks [22].

Intralesional steroid injections, under US guidance, decreases expression of vascular cell adhesion molecule-1 (VCAM-1), thus dropping the production of TGF-β, basic fibroblast growth factor (bFGF) and IL-1α and IL-1β. In the end, the proliferation of fibroblasts and collagen production is decreased [47]. Intralesional steroids alter the production of grown factors and cytokines, reducing symptoms and also the size of lesions, however relapse is possible. Various studies have shown good results, decreasing the recurrence of the lesion with 50% in the first three years [48] and it can be useful in reducing the systemic inflammation level in those patients with chronic pathologies [49]. We think that the recommended three to five injections of Triamcinolone Acetonide in dose of 15–30 mg/nodule, given 4–6 weeks apart, is sufficient for treatment [50].

Antiestrogen therapy (Tamoxifen) was used *in vitro* to decrease fibroblasts activity, but there is no current recommendation for its use in Ledderhose disease [51].

Verapamil decrease collagen production and increasing collagenase activity, altering the release of cytokines, IL-6 and IL-8 and plague growth factor as well [52]. It can have synergistic effect in combination with steroid injections with better results [53].

Another conservative therapy is represented by collagenase *Clostridium histolyticum* (CCH) injections, containing two types of collagenase AUX-1 and AUX-2, which degrade collagen with good results in Peyronie's and Dupuytren's disease [54], but no study proves its benefits in treating Ledderhose disease [55].

Surgical excision is usually used as a last resort in cases with inefficient conservative therapies, progressive lesions, advanced stages of the disease, unsupportable pain, walking or balance problems. It can be performed classically or endoscopic.

We recommend the radical surgical treatment, with partial or complete fascia resection (Figure 8), due to its lowest recurrence rate, from 0–50%, along with meticulous wound closing to decrease the risk of complications (lesion recurrence, wound dehiscence, painful scar, nerve damage). Some surgeons prefer the local excision, removing only the nodules, but this method has a recurrence rate from 57–100% [56, 57]. For the primary lesion, it can be performed a wide excision (Figures 9 and 10), removing not only the nodules but also a safety margin of 2–3 cm, having a recurrence rate between 8–80% [58].

The endoscopic plantar fasciectomy has the benefit of reducing the wound size with better cosmetic, decreasing the incidence of painful hypertrophic scars, necrosis or infection. In case of lesions invading the muscle, plantar skin or neurovascular bundles, the technique is contra-indicated. Another impediment is that this approach is after all technically demanding and should be performed only be experienced arthroscopists [7].

Due to the fact that plantar fibromatosis progression is related especially with the quality of surgical inter-vention, the risk of local recurrence very low. According to the studies presented in the literature, the risk of this lesion recurrence is higher in patients with bilateral presentation, multiple manifestations, and family history in patients who develop post-operative neurinoma [59]. In addition to these, other comorbidities should be taken into consideration [60, 61].

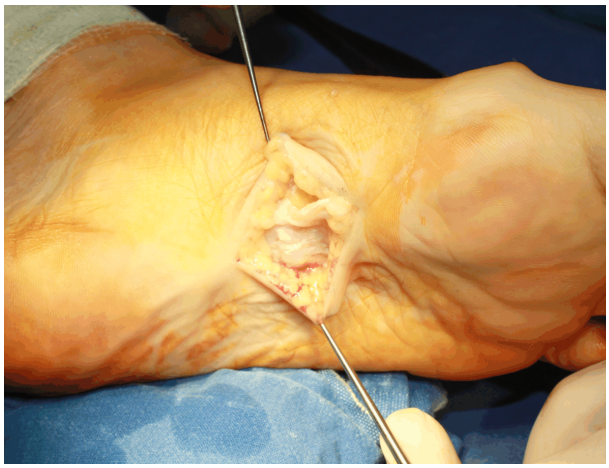

Figure 8 – ***Ledderhose disease: intraoperative aspect of the nodules and plantar aponeurosis.***

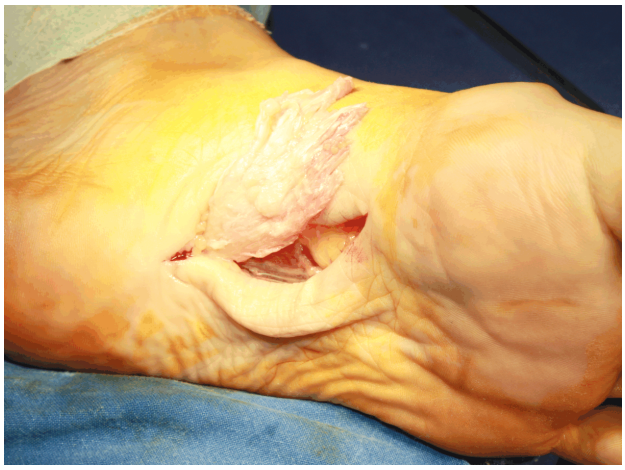

Figure 9 – ***Ledderhose disease: large resection of the plantar aponeurosis including the nodules.***

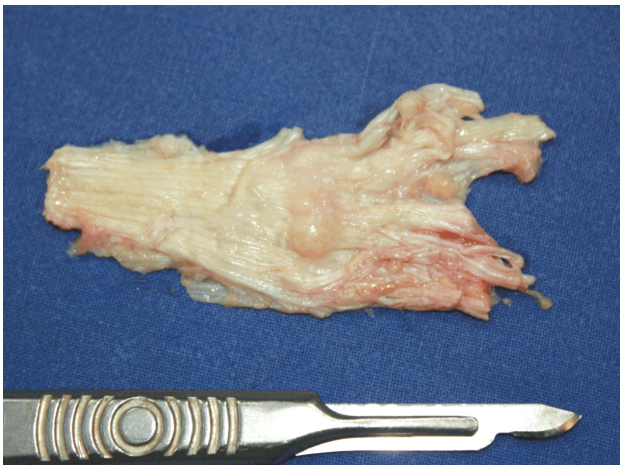

Figure 10 – ***Ledderhose disease: macroscopic aspect of the modified plantar aponeurosis revealing nodules of different dimensions.***

Conclusions

Ledderhose disease, a hyperproliferative disorder with unknown etiology and few determinant conditions, has a clinically based diagnosis and need US or MRI to exclude other conditions. IHC examinations may be performed in order to confirm the diagnosis since the histological aspect is non-specific. Even so, after the diagnosis has been established, choosing the right treatment may be a challenge, as there is no causal therapy available, the treatment being only symptomatic and functional. The recommended practical approach is starting with conser-vative therapies, progressing to partial or total plantar fasciectomy for painful, unresponsive forms of the disease. We consider that is very important to establish a perso-nalized therapeutic plan depending on the individual characteristics, presence and intensity of the symptoms, the stage of pathological modifications and on whether it is the first manifestation or a relapse.

Conflict of interests

The authors declare that they have no conflict of interests.

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