Human Pathology Reports 26 (2021) 300564

Contents lists available at ScienceDirect

Human Pathology Reports

journal homepage: www.journals.elsevier.com/human-pathology-reports

Case Report

Transmission electron microscopy of Ledderhose disease in a patient with bilateral presentation

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ARTICLE INFO

Keywords
Ledderhose disease
Foot
Myofibroblast
Transmission electron microscopy

ABSTRACT

The plantar fibromatosis of the foot, also known as Ledderhose Disease, presents itself as one or more rounded, firm, hard nodules, typically located on the medial side of the plantar vault. The etiology is unknown but Ledderhose Disease is correlated with the Dupytren contracture and Peyronie's Disease, as they are all fibroproliferative disorders. The lack of significant literature for Transmission Electron Microscopy (TEM) of Ledderhose Disease, prompted us to perform an extensive TEM analysis in a case of bilateral presentation, in a Caucasian male of 31 years of age. We confirmed the morphological similarities among these three diseases. A highly disordered assembly of collagen fibers was documented together with the morphological characters of myofibroblasts for the cell population. Presence of giant cells and possibly mast-cells was notable, but their role and relevance are matter for speculation because of the allergic diathesis of the patient. The specific history of the patient seems to exclude that a recurrent external mechanical stress was the causative action, because it was applied only on one side in an otherwise bilateral presentation. A recommendation is made to every clinician to be aware of Ledderhose Disease and to provide an early diagnosis. In case surgery is required, it should be an accurate micro-surgical excision to be performed in a qualified center.

Introduction

The plantar fibromatosis of the foot, also known as Ledderhose Disease (LD), was described by the german surgeon Georg Ledderhose in the paper "Zur Pathologie der Aponeurose des Fusses und der Hand" (Pathology of the aponeuroses of the feet and hand) published in the Langebecks Archives in 1897. LD is a rare benign hyperproliferative disorder of the plantar aponeurosis [2,5,12]. It presents itself as one or more rounded, firm, hard nodules, typically located on the medial side of the plantar vault, which develop in the context of the medial and central bands of the plantar fascia. The etiology is unknown but LD is correlated with the Dupytren contracture (DC) and Peyronie's Disease (PD), as they are all fibroproliferative disorders characterized by abnormalities in the connective tissue of the palm of the hand (DC), the tunica albuginea of the penis (PD), and the sole of the foot (LD) respectively. Patients have been described with combined presentation of DC and LD, DC and PD and even all three conditions [1,3,8,11,15].

While the Transmission Electron Microscopy (TEM) of DC [6] and PD [7,10,14] has been published with details, TEM of LD seems reduced to a mere three published TEM photomicrographs in two publications [4,6]. This lack of TEM images for LD prompted us to plan and perform a TEM analysis on a case of LD bilateral presentation in a man of 31 years of age. To the best of our knowledge, this is the third paper on LD TEM and the first to provide a set of high magnification images, in the past fifty years. A comparison of our LD TEM images with the literature on DC TEM and PD TEM confirms the morphological similarities among LD, DC and PD at the ultrastructural level.

Materials and methods

Patient history

A 31 years old white Caucasian male came to our attention for what he defined as a right foot plantar "cyst". He reported that the "cyst" was tentatively excised in another hospital, but it has recurred and worsened. The patient worked as a cargo-loader in a major international

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https://doi.org/10.1016/j.hpr.2021.300564
Received 23 July 2021; Received in revised form 4 October 2021; Accepted 5 October 2021
Available online 25 October 2021

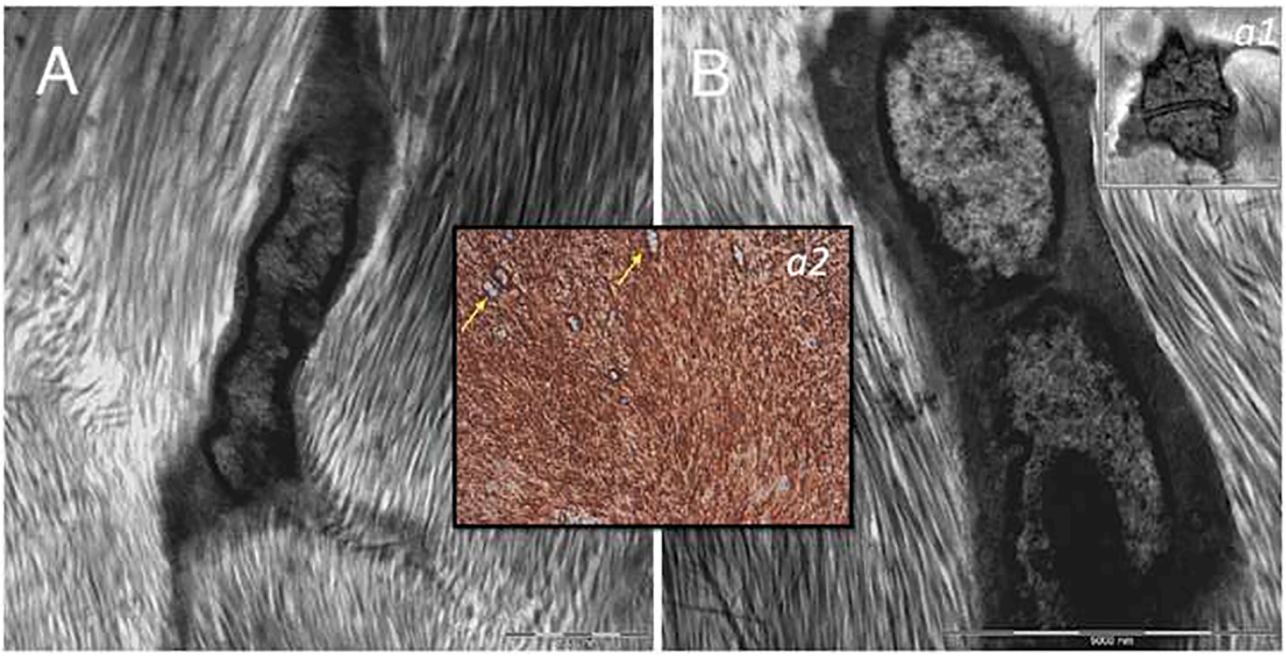

Fig. 1. A)-an elongated cell with very little cytoplasm and slightly indented nucleus, immersed in bundles of parallel collagen fibers (mag 11000X; scale bar = 2000 nm). B)-more deeply indented nucleus with a transverse constriction (inset a1) that, according to the plane of section, let the nucleus appears like divided into two parts (mag 11000X; scale bar = 5000 nm). Cells stained intensely with alpha-smooth-muscle actin antibody (brown color); giant cells (yellow arrows) were present (inset a2). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

airport. He reported that a common practice to loads luggage on planes required him to hit a lever hard with the sole of the right foot. He did not report any smoking habit. He suffered from allergy to pollen and grass and he treated a topical allergic dermatitis by anti-histaminic drugs.

Physical examination

The sole of the right foot presented a modest lump on the medial side and the scar from the previous surgical operation. A hard-elastic multi-nodular formation could be appreciated upon palpation. The patients referred that the "cyst" has become painful and is limiting his ability to work and walk. Upon inspection of the contralateral left foot, we noted a similar formation which presented with the same hard-elastic multi-nodular characters upon palpation. Surprisingly, the patient was not aware of this contralateral formation. He was asked whether he performed a hard hit with his left sole similar to what he reported to the right, and the answer was negative. He stated that his left sole was not solicited neither by work nor leisure activities and he never experienced pain on the left sole. It was possible for us to elicit a moderate dull pain by compressing the formation on the left foot. During the following weeks, the patient started to appreciate a discomfort on the left foot.

Surgical treatment

We planned two surgeries: the first was aimed at removing the formation from its right foot and the scar from the previous operation. The second was aimed at excising the newly-discovered formation on the left foot. TEM was planned in association with the second procedure. Both operations were performed under local anesthesia (wide-awaken surgery), without local ischemia (tourniquet), and with the assistance of optical magnification (microsurgery). A curvilinear incision along the medial side was performed (similar to the Tubiana's approach for DC) and a smooth dissection followed. A careful microsurgical dissection of subcutaneous tissue was performed; control of bleeding relied on compressive gauzes and avoided the use of electrocauterization. A rounded white nodular formation was identified as a fusiform thickening of the plantar aponeurosis. The formation was not easy to cleave; so, we proceeded with a wide surgical incision all around the nodule, then dissected the aponeurotic plane from the deeper structures. We remove the entire lump "en bloc". At this point, a small bipolar forcep was used to cauterize larger bleeding vessels. A moderate bleeding was allowed following the procedure. Skin was closed by single-stitch monofilament not-resorbable suture. A lightly compressive bandage of the plantar vault completed the surgical procedure. The explant was immersed in abundant 4% Formalin solution immediately after removal, under an aspiration hood adjacent to the operating room. It was then sent to the processing for light microscopy and TEM.

Histopathology

Light microscopy

Explant was fixed in buffered formalin, routinely processed and embedded in paraffin. Five-micron sections were stained with Hematoxyln&Eosin. Immunohistochemical analysis was performed with a Dako AutostainerLink 48 (Dako, Carpinteria, CA, USA) according to the manufacturers' instructions. The following primary antibodies were used: alpha-smooth muscle actin (clone 1A4; Dako; 1:100).

Transmission electron microscopy

Samples were fixed in 1% (v/v) glutaraldehyde in 0.1 M cacodylate buffer (pH 7.4) and stored at 4 °C until processed. Samples were post-fixed with a solution of 1.0% osmium tetroxide in cacodylate buffer for 2 h. After postfixation, samples were dehydrated in ethanol and embedded in an epoxydic resin. Ultrathin sections (80–90 nm) were obtained with a diamond knife using a Reichert ultramicrotome, and mounted in copper grids. Observations were made with a Zeiss EM10 electron microscope operating at 80 kV.

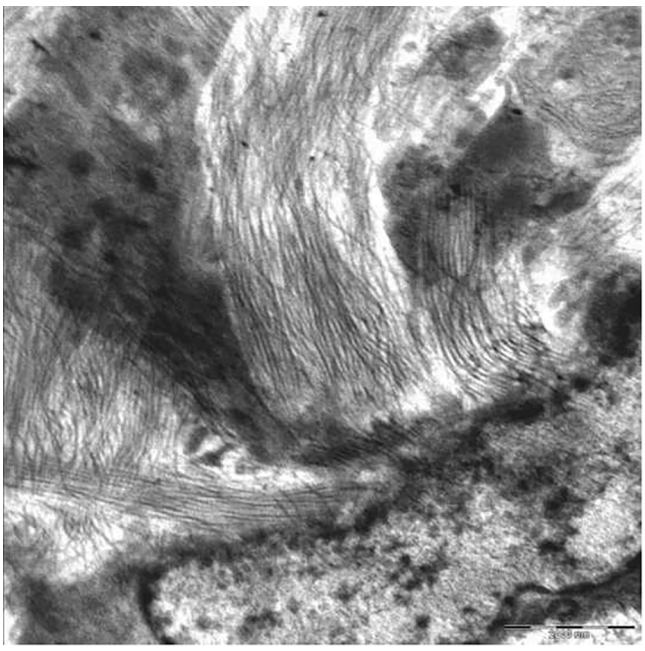

Fig. 2. Large bundles of parallel collagen fibers stem from an elongated cell body (mag 11000X; scale bar = 2000 nm).

Results

Follow-up

The patient was gradually allowed to weight bear on the operated limb in a period of two months, with bi-weekly outpatient ward control. A long-term follow-up of five years after both operations showed no recurrence.

Light microscopy

There was an hyperproliferation of mostly monomorphic cells, with no atypia. They were elongated/spindle-shaped cells in an abundant collagen stroma. They presented elongated nuclei, most of them cross-banded, resembling the morphological characters typical of myofibroblasts. These cells stained intensely with alpha-SMA (smooth-muscle actin) antibody, denoting them as myofibroblasts (Fig. 1 inset a2). Giant cells, with more rounded nuclei, were also present (Fig. 1). Mast-cells were not specifically searched for in light microscopy.

Electron microscopy

There was a population of elongated cells with very little cytoplasm and slightly indented nuclei, immersed in bundles of parallel collagen fibers (Fig. 1A). The deeply indented nuclei showed a transverse constriction that, according to the plane of section, let them appear like divided into two parts (Fig. 1B and inset a1). Large bundles of parallel collagen fibers stem from these cells to reach far away anchorage (Fig. 2). All these characters, and the presence of abundant rough endoplasmic reticulum, denoted a population of myofibroblasts. Overall, there was a highly disordered collagen stroma with fibers intersecting in every direction (Fig. 3). Few cells, with cytoplasmic granules of variable electrondensity, remind the characters of mast cells (Fig. 4).

Discussion

The prognosis for LD (as well as for DC), seems to be related above all to the quality of surgical ablation. LD may have a high recurrence rate [2,13]. We suspect, however, that there is the possibility that a wrong early diagnosis can lead to LD recurrences if a less than accurate excision procedure follows. In our case, for example, LD was probably misdiagnosed as a subcutaneous cyst and treated accordingly in another hospital. We suggest that a greater care should be given in providing the general practitioners with a better knowledge about LD. At the same time, when a LD diagnosis is made, the patient should be addressed to a surgeon qualified for a microsurgical aponeurectomy.

Our histopathological analysis showed the morphological character of myofibroblasts for the cellularity of the sample [9]. This finding confirms what reported in the literature regarding the commonality between LD, DC and PD [6,8,11]. We report the presence of giant cells in light microscopy and possibly of mast-cells in TEM. We have no data to discuss further on a possible correlation of both giant cells and mast-cells with the allergic diathesis affecting the patient. For this reason, we cannot speculate on the possible correlation between the allergic diathesis and the insurgence of LD. To answer this question, we suggest that a routine search for giant cells and mast-cells should be performed in any case of LD.

While a history of recurrent mechanical stress, a well-known promoter of myofibroblasts differentiation [9], was reported for the right foot, this was absent for the left foot. This specific history seems to exclude the recurrent external mechanical stress as a causative action,

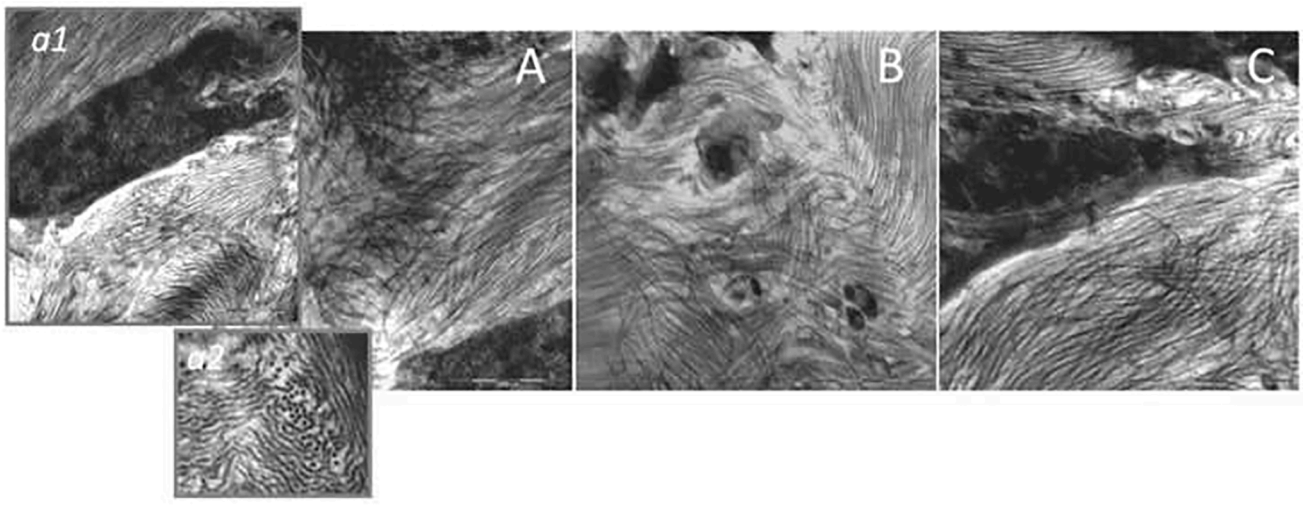

Fig. 3. Representative images of the abundant rough endoplasmic reticulum (inset a1) and the overall disordered collagen stroma, with fibers intersecting in every direction (fibers at right angle are clearly visible in the inset a2) (mag 11000X; scale bar = 2000 nm).

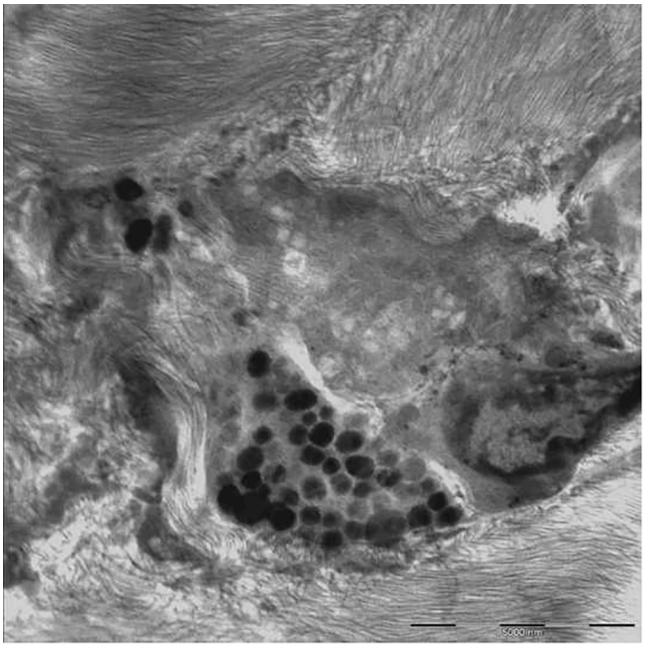

Fig. 4. A cell with cytoplasmic granules of variable electrondensity; its morphological characters remind of a mast cell (mag 11000X; scale bar = 5000 nm).

because it was applied only on one side in an otherwise bilateral presentation. Smoking habit is associated with DC but was absent in our LD patient.

This study has the limitation, typical of a case report on a rare disease, that only one patient was observed. Another limitation may be in the quality of the retrieved explant, which reflects the condition to operate in a real clinical environment and not in the best conditions of a laboratory setting (as is possible, for example, during animal studies). It is likely that this same limitation was encountered by other investigators, and this may explain why literature is so poor on TEM analysis of LD. We described an impressive disarray of interwoven collagen fibers, but we are aware that another limitation in our study was the lack of the analysis of collagen type.

In conclusions: an extensive TEM analysis of a case of LD was performed for the first time, which documented the morphological similarities of this rare disease with Dupuytren's Contracture and Peyronie's Disease. A highly disordered assembly of collagen fibers was documented, so it was the morphological characters of myofibroblasts for the cell population. Presence of giant cells and possibly mast-cells was notable, but their role and relevance are matter for speculation, because of the allergic diathesis of the patient. The history of the patient seems to exclude a recurrent mechanical stress as a causative action. A recommendation is made to every clinician to be aware of LD and to provide an early diagnosis. In case surgery is required, it should be an accurate micro-surgical excision to be performed in a qualified center.

Patient consent statement

The authors comply with the HPCR guideline that "Formal consents are not required for the use of entirely anonymised images from which the individual cannot be identified- for example, xrays, ultrasound images, pathology slides or laparoscopic images, provided that these do not contain any identifying marks and are not accompanied by text that might identify the individual concerned."

None of the images or other data reported in the paper can allow the identification of the patient.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Authors acknowledge the dedication of Prof. Marco De Spirito and Mr. Mario Amici, from the Central Laboratory for Microscopy, for providing technical assistance in TEM; Prof. Libero Lauriola and Dr. Antonella Coli, from the Service for Histopathology, for performing histopathological light microscopy analysis; Dr. Claudio Proietti, Orthopedic and Trauma Surgery, for contributing in the gathering of clinical data. There were no other funding sources apart from institutional funds.

Funding informations

No specific funding was associated with this work, which was performed under the institutional duties of the Authors.

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