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Pathogenetic and clinical significance of fungal infection of the palmar aponeurosis in Dupuytren's contracture

T.A. Stupina✉, N.A. Shchudlo, T.N. Varsegova, D.A. Ostanina

Ilizarov National Medical Research Centre for Traumatology and Orthopedics, Kurgan, Russian Federation

Corresponding author: Tatyana A. Stupina, StupinaSTA@mail.ru

Abstract

Introduction Among the generally accepted theories of the etiology and pathogenesis of palmar fascial fibromatosis, the role of infectious factors has not been considered; however, there are references to fungal skin lesions in patients with advanced contractures and several studies that identified fungal infection in surgical material from such patients.

The purpose of the work was to assess the pathogenetic and clinical significance of fungal infection of the palmar fascia in Dupuytren's contracture.

Materials and methods We studied 41 medical records of patients operated on for Dupuytren's contracture in stages II-IV. The surgical material was examined at the light-optical level (hematoxylin-eosin and methenamine-silver PASM stains) and with scanning electron microscopy.

Results Fungal infection of the palmar aponeurosis was detected in 20 out of 41 patients; various types of tissue reaction to the introduction of fungi into the palmar aponeurosis and the blood vessels perforating it were found. Groups of patients without signs of fungal invasion (n = 21) and with signs of fungal infection of the palmar aponeurosis (n = 20) were comparable in clinical and demographic characteristics, but significantly differed in the rate of early relapses, 0 versus 25 % in the group with fungal infection (p = 0.02).

Discussion The immunogenetic characteristics of patients with palmar fascial fibromatosis and characteristic skin lesions create general and local conditions for the introduction of fungal flora.

Conclusion Histological detection of pseudohyphae of the genus Candida in the palmar aponeurosis and the lumens of blood vessels in patients with Dupuytren's contracture verifies invasive candidiasis; the relationship between fungal infection of the aponeurosis and an increased rate of early relapses of contracture has been statistically proven. To increase the duration of the relapse-free period and potentially the life expectancy of patients, consultations with infectious disease mycologists and correction of modifiable risk factors for candidiasis are necessary.

Keywords: palmar fascial fibromatosis, Dupuytren's contracture, mycoses, relapses

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INTRODUCTION

Dupuytren's disease or palmar fascial fibromatosis (PFF) refers to fibroproliferative diseases of connective tissue which is characterized by an increased content of myofibroblasts, hyperproduction of collagen types III and I, thickening and contraction of the palmar-digital fascia and dermis of the skin [1]. Changes in fascial structures and integumentary tissues lead to restrictions in finger extension, and then to contractures and fixed deformity of the metacarpophalangeal and interphalangeal joints, and a decrease in hand grip strength [2]. These changes inevitably reduce the quality of life of patients, disrupting professional skills, daily activities and social contacts [3]. Despite the development of many methods for conservative, surgical and minimally invasive treatment of Dupuytren's contracture [4], fascial fibromatosis is considered incurable, since it has infiltrative growth and recurs [5].

Among the generally accepted theories of the etiology and pathogenesis of Dupuytren's disease, the main ones are genetic, microtraumatic, immunological, toxic, ischemic [6], and metabolic [7]. Fibromatous nodes are characterized by microvascular changes, primarily occlusion of capillaries and proliferation of pericytes, and presence of macrophages, the number of which correlates with the number of myofibroblasts; lymphocytes are localized around the nodes [8].

Despite the identification of inflammatory cells in most patients, the role of infectious factors in the development of fascial fibromatosis is not traditionally considered. However, a case of phlegmonous infection in the first stage of the disease was described [9], and the development of skin mycoses was mentioned in severe contractures [10]. Skin retractions that form in some patients in the early stages of the disease [11] can facilitate deeper penetration of the infectious agent [12]. Using scanning electron microscopy in patients with Dupuytren's contracture, budding fungal flora was established in the areas of the pathologically altered aponeurosis excised during fasciectomy [13]. Diagnosis of mycoses is critical not only for full postoperative rehabilitation, but also for the future life of patients; however, the pathogenetic and clinical significance of mycotic invasion into the fascial structures of the hand remains unclear.

Purpose: to evaluate the pathogenetic and clinical significance of fungal infection of the palmar fascia in Dupuytren's contracture.

MATERIALS AND METHODS

In the period from 2017 to 2020, interventions were performed in 153 patients with Dupuytren's contracture at the Ilizarov National Medical Research Center for Traumatology and Orthopaedics. Using a random selection method, a sample of 41 patients with contracture of the Tubiana degrees II-IV [14] was formed who underwent partial fasciectomy. Among them there were 39 men and 2 women aged from 39 to 77 years.

Inclusion criteria were clinically evident and histologically confirmed palmar fascial fibromatosis. Exclusion criteria were hand contractures of another etiology.

For histological examination, tissue samples, after fixation in a 10 % neutral formaldehyde solution, were embedded in paraffin according to standard methods. Paraffin sections (5-7 μm thick) were prepared using an HM 450 Thermo Scientific microtome (USA) and were stained with hematoxylin and eosin; PASM methenamine-silver staining was used to identify fungal mycelium. Light-optical study and digitization of images of histological sections were carried out using an AxioScope.A1 microscope with an AxioCam digital camera and Zen Blue Edition software (Carl Zeiss MicroImaging GmbH, Germany).

Tissue samples (size, 3 × 5 mm) fixed in formalin for examination in a scanning electron microscope (SEM) "JSM-840" (Jeol, Japan) were washed in distilled water, then dehydrated in ethanol (from 70 to 96 %) and soaked in 3 ,3-dimethyl-2-methylenebicyclo[2,2,1]heptane (camphene) [15]. The samples were dried in a thermostat at 37 °C, then mounted on polished clean aluminum disks

using conductive glue and sputtered with silver in an IB-6 ion sputter (Eiko, Japan). The conductive paste was used to remove the charge from the sputtered surface of the sample.

The patients were divided into two groups for subsequent clinical and statistical analysis, based on the results of studying the surgical material at the light-optical level and SEM: Dupuytren's contracture without signs of mycotic invasion (group 1, n = 21) and Dupuytren's contracture with signs of mycotic lesions of the palmar aponeurosis (group 2, n = 20). For the comparative analysis, the following parameters were used: age at the start of PFF, the male-to-female ratio, age at the time of surgery, PFF imcidene in both hands, degree of contracture, number of fingers with impaired function, frequency of primary operations and operations for relapses, frequency of visits for relapses.

Statistical processing of quantitative data was carried out in the Attestat software (version 9.3.1, developer I.P. Gaidyshev, Rospatent certificate No. 2002611109). Hypotheses about the normality of distribution were tested using the Shapiro–Wilk test. For some samples, the hypothesis of normality was rejected; table data are presented in the form of medians and quartiles, as well as minimum and maximum values (Me (Q1÷Q3)) (min-max). To test hypotheses about differences between the compared groups, the Mann–Whitney test and Fisher's exact test were used.

RESULTS

Light microscopy of paraffin sections revealed signs of mycotic lesions of palmar aponeurosis in four out of 41 patients (9.76 %). Pseudomycellar structures (budding yeast cells and pseudohyphae) were located in foci of chronic inflammation with signs of activation of lymphocytes and macrophages, as well as deposits of amorphous eosinophilic substance (Fig. 1 a, b). PASM stain revealed silver-positive yeast cells and pseudohyphae in the perivascular spaces and in the lumens of blood vessels (Fig. 1 c, d). In one patient out of four, giant multinucleated macrophages of the foreign body type cells and degenerative eosinophils were found in the foci of chronic inflammation, along with lymphocytes and macrophages (Fig. 1 e).

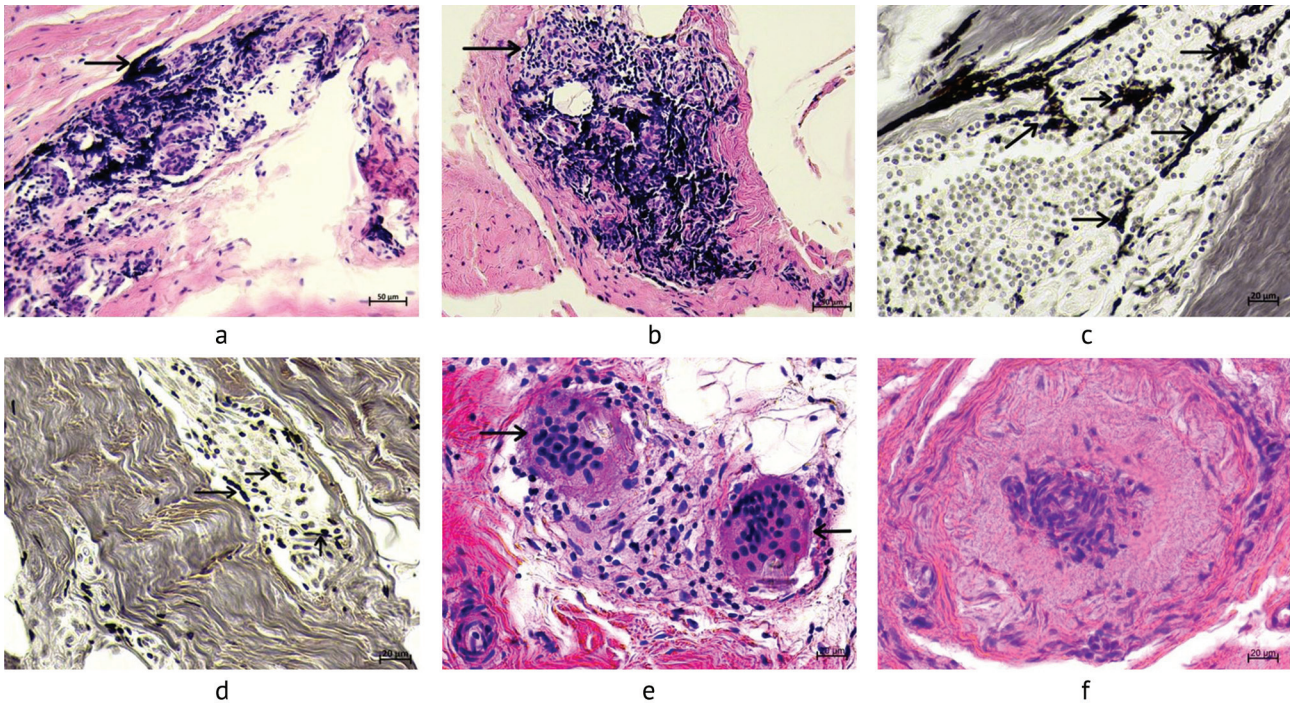

Fig. 1 Fragments of the palmar aponeurosis in Dupuytren's contracture with signs of fungal invasion: *a* pseudomicellar structures (arrow); *b* focus of chronic inflammation (arrow); *c, d* pseudohyphae in the lumen of blood vessels (arrows); *e* giant multinucleated macrophages of the foreign body cell type (arrows); *f* obliterated arteriole. Paraffin sections, stained with hematoxylin and eosin (*a, b, e, f*), methenamine-silver PASM (*c, d*). Magnification 200× (*a, b*) and 400× (*c, d, e, f*)

Few yeast cells and short pseudohyphae along with crystalline inclusions were located in the cytoplasm of giant multinucleated macrophages, such as foreign body cells. There were obliterated arterioles (Fig. f), in which degenerating yeast cells were detected along with dying cells of the vascular wall and inflammatory cells.

The SEM method detected fungal flora (Fig. 2 a-d) in 20 patients out of 41 (43.9 %). In 18 out of those 20 patients, budding yeast cells and pseudohyphae were found (Fig. 2 a, b, c), and pseudohyphae with blastospores were detected in two patients (Fig. 2 d).

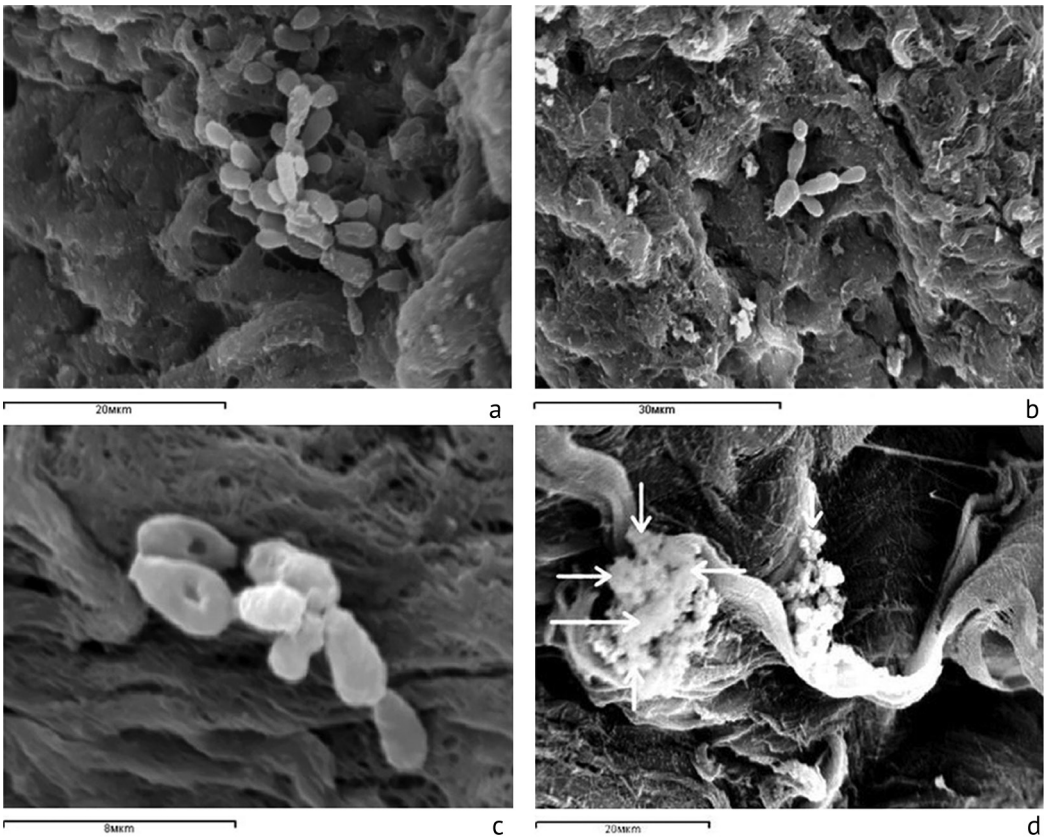

Fig. 2 Fragments of a pathologically altered palmar aponeurosis. SEM: *a* single and budding yeast cells; *b* pseudohypha; *c* pseudohypha and blastospores; *d* yeast cells (horizontal arrows) forming blastospores (vertical arrows). ×2300 (*a*), ×1700 (*b*), ×6000 (*c*), ×1800 (*d*)

Yeast cells had a round, round-oval, pear-like or slightly elongated shape; their sizes varied from 2 to 7 μm. Along with separately lying yeast cells, budding cells were also found. Some cells had a brightly contrasted depression in the center (Fig. 2 c). Both in intact and destroyed intercellular contacts, a ring-shaped girdle was evident at one end of the cell and a bud at the other. The thickness of the intercellular contact zone was no more than 0.5 μm. Blastospores were located on the surface of yeast cells in the form of clusters, immersed in the intercellular matrix in some places (Fig. 2 d), had a spherical shape, and were heterogeneous in size. Cavities were formed around the budding yeast cells as the connective tissue fibers loosened, exfoliated and lysed (Fig. 2 a-c).

Comparison of clinical and statistical indicators of patients (Table 1), divided into groups based on the absence or presence of fungal flora, found that the groups were comparable in age, gender composition, duration of fascial fibromatosis and the frequency of damage to both hands, degree of contracture, number of fingers with impaired function, the ratio of primary operations and operations for relapses, as well as the frequency of visits for late relapses (11-18 years after the primary operation) – $p > 0.05$.

Table 1

Clinical and statistical indicators of patients with Dupyuitren's contracture

Parameter	Group 1, *n* = 21		Group 2, *n* = 20		*P*[1,2]
	Me (Q1÷Q3)	(min-max)	Me (Q1÷Q3)	(min-max)	
Age at the onset of PFF, years	51 (40÷55)	(39-66)	48 (42÷59)	(38-69)	0.92[1]
Males:Females	21:1		19:1		0.74[2]
Age at surgery, years	57 (54.5÷63.5)	(45-71)	59 (55÷65)	(39-77)	0.57[1]
Duration of fascial fibromatosis	5 (3÷7.5)	(1-15)	6 (2.25÷10)	(1.5-18)	0.67[1]
Rate of fascial fibromatosis in both hands, %	57.14		50.0		0.76[2]
Contracture severity	3 (2.75÷3)	(1-4)	3 (2.5÷3.75)	(2-4)	0.52[1]
Number of finger with functional disorders	2 (1÷3)	(1-6)	2 (1÷3.5)	(1-7)	0.99[1]
Ratio of the studied material from primary operations and operations for relapse	19:2		16:4		0.41[2]
Rates of contracture recurrence at long term (11-18 years), %	9.52		5.00		0.52[2]
Rate of early recurrence (4-15 months after primary operation), %	0		25		0.02[2]*

[1] – Mann – Whitney test; [2] – Fisher's exact test; * – differences are significant $p < 0.05$

However, there were no complaints about early recurrence (4-15 months after the primary operation) in group 1, and in group 2 their rate was 25 % ($p < 0.05$).

DISCUSSION

Invasive fungal infections remain an underestimated cause of morbidity and mortality to this day [16], even in immunocompetent carriers [17].

We previously established the presence of fungal flora in the surgical material of patients with Dupuytren's contracture; we showed a higher resolution of SEM compared to light microscopy in detecting fungi and determining their taxonomic affiliation [13].

This study, carried out on a larger material, not only confirmed the difficulty of detecting fungal flora at the light-optical level and the frequent occurrence of fungal flora in the palmar aponeurosis with Dupuytren's contracture, but also could identify various options for tissue reactions to the introduction of fungi into the palmar aponeurosis, as well as the penetration of yeast cells and pseudohyphae into vessels perforating the palmar aponeurosis. The penetration of fungal flora through the epithelial and endothelial barriers may be facilitated by impaired blood supply [18, 19].

The lymphocytic-histiocytic chronic inflammatory infiltrate that forms in the invasion zone, giant multinucleated cells, degenerating eosinophils, crystal formation and damage to blood vessels are characteristic, but nonspecific for fungal infections, as they can occur with bacterial and parasitic lesions [20].

Pseudohyphae, dimorphism (yeast cells and blastospores), as well as features of the ultrastructure of intercellular contacts of fungal cells [21] are characteristic of Candida albicans, the most common representative of the opportunistic fungal flora, the various stages of morphogenesis of which have different effects on immune recognition [22]. Cutaneous candidiasis caused by other species of the genus Candida is rare in the clinic, as it is unusual for humans [23]. Since other species of the genus Candida may exhibit increased resistance to drugs, in recent years there has been intensive development of molecular and genetic methods for species identification, which have higher sensitivity and specificity compared to traditional microbiological methods [24].

The role of histological examination in the diagnosis of mycoses is great, since the presence of fungi, as well as signs of their invasion into tissues and blood vessels in histological preparations, is reliable evidence of a deep fungal infection [25]. If the presence of fungal flora is suspected and even with clinical manifestations of mycoses, microbiological methods frequently show false-negative results and do not allow differentiating contamination, colonization and infection, and polymerase chain reaction (PCR) methods and immunohistochemical reactions are not available in all laboratories, therefore scanning electron microscopy is regarded as an important diagnostic method [26], which can detect fungal lesions [27].

The work contains a comparative clinical and statistical analysis of two groups of patients with Dupuytren's contracture for the first time: without signs of fungal invasion and with damage to the palmar aponeurosis by fungi of the genus Candida. The groups are comparable in clinical and demographic characteristics, but significantly differ in the frequency of early Dupuytren's contracture recurrence, which indicates the pathogenetically significant role of fungal invasion as a damaging factor initiating the activity of fascial fibromatosis. The immunogenetic features that are characteristic of Dupuytren's disease [28] form general (systemic) risk factors for fungal invasion. Involvement of the skin in the fibromatous process [29] violates its barrier properties and creates local conditions for the introduction of infectious agents into deeper tissues. On the other hand, first of all, in the study of Candida albicans, and then other species of this genus of fungi, different authors identified the peptide toxin candidalysin, which perforates cell membranes and inhibits the complement system [30].

Candida fungi are known as representatives of the normal microbiota of the mucous membranes and skin of most healthy people; however, commensals are transformed into pathogens under the influence of general and local factors. Cutaneous candidiasis is characterized by superficial localization; lesions of the dermis and subcutaneous tissue are rare [31]. Our study revealed the introduction of Candida pseudohyphae into deep tissues (palmar aponeurosis), as well as into the bloodstream, which refers to the criteria for invasive candidiasis, which, as a rule, develops as a result of increased colonization in combination with impaired factors of general and local defense of the patient's body [32]. Candida fungi that have entered the bloodstream can be successfully eliminated from the body of a healthy person; however, in elderly patients with chronic diseases, candidemia frequently leads to hematogenous dissemination of the pathogen and fatal complications [33].

The limitations of the study are its monocenter nature and the average sample size.

Further comprehensive studies using immunohistochemical analysis, PCR, microbiological cultures of blood and wound fluid would be promising for the development of rational antimycotic therapy and anti-relapse therapy for fascial fibromatosis. Consultation of patients with Dupuytren's contracture by an infectious disease mycologist and the prescription of etiotropic therapy does not eliminate the need to correct modifiable risk factors for candidiasis, which include malnutrition and micronutrient deficiency, obesity, diabetes mellitus, irrational antibiotic therapy and corticosteroids [34].

CONCLUSION

Histological detection of pseudohyphae of the genus Candida in the palmar aponeurosis and the lumens of blood vessels in patients with Dupuytren's contracture verifies invasive candidiasis; the relationship between fungal infection in the aponeurosis and an increased rate of early relapses of contracture has been statistically proven. To increase the duration of the relapse-free period and, potentially, the life expectancy of patients, consultations with infectious disease mycologists and correction of modifiable risk factors for candidiasis are necessary.

Conflict of interest *Not declared.*

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Ethical expertise *The study was performed in accordance with the ethical standards of the Declaration of Helsinki (revised in October 2013) and was approved by the ethics committee (protocol No. 4 (68) of 11/11/2020).*

Informed consent *Patients gave voluntary informed consent to publish the study results without disclosing their identity.*

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Information about the authors:

Tatyana A. Stupina – Doctor of Biological Sciences, leading researcher, StupinaSTA@mail.ru, https://orcid.org/0000-0003-3434-0372;

Natalia A. Shchudlo – Doctor of Medical Sciences, leading researcher, nshchudlo@mail.ru;

Tatyana N. Varsegova – Candidate of Biological Sciences, senior researcher, varstn@mail.ru, https://orcid.org/0000-0001-5430-2045;

Daria A. Ostanina – orthopedic traumatologist, https://orcid.org/0000-0002-4399-2973.

Contribution of the authors:

Stupina T.A. – development of the concept and design of the study; collection, analysis and interpretation of data, writing the text;

Shchudlo N.A. – development of the concept and design of the study, writing the text;

Varsegova T.N. – collection, analysis and interpretation of data, writing the text;

Ostanina D.A. – data collection, writing a fragment of the text.