



Palmar Fibromatosis: an Analysis of 25 Cases

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Abstract

Objective: Dupuytren's contracture (DC) is a benign tumor that results in nodular or fibrous band-like thickening of the palmar fascia and leads to palmar and digital contractures. Although they are benign lesions, post-operative recurrence is frequent. In the present study, we retrospectively analyzed clinicopathological findings of 25 cases that underwent surgery for DC. We also aimed to determine the relationship between relapse and Ki-67 proliferation index and smooth muscle actin (SMA) staining intensity in excision materials by immunohistochemical method.

Methods: The demographic characteristics, severity of contracture, treatment type, Ki-67 proliferation index, SMA staining intensity and recurrence were evaluated retrospectively in 25 patients who were operated with the diagnosis of DC at the Department of Orthopedics and Traumatology in Recep Tayyip Erdoğan University between 2009 and 2015.

Results: The age range of the patients was 42-75 years (mean age: 55 years), and 6 were female and 19 were male. Fifteen of the lesions were in the right hand, and 10 were in the left hand. All patients underwent extensive palmar fascia excision with regional intravenous anesthesia. Only one patient had recurrence. Ki-67 proliferation index was 1-2% in patients without recurrence, however, >5% nuclear positivity was detected in a patient with recurrence. In addition, strong positive staining for SMA was observed in this patient.

Conclusion: The use of Ki-67 proliferation index and SMA staining intensity to evaluate fibroblastic proliferation in the pathological examination of surgical DC specimens may be valuable in clinical follow-up in terms of recurrence.

Keywords: Dupuytren's contracture, Dupuytren's disease, fasciectomy, palmar contracture

INTRODUCTION

Dupuytren's contracture (DC) was first reported in 1777 by Henry Cline. It was described in detail by Baron Guillaume Dupuytren, a French surgeon, in 1834 (1, 2). DC is a tumor that results in nodular or fibrous band-like thickening of the palmar fascia in the palm and fingers. They are benign in character; however, they may also be locally aggressive. The clinical symptoms are seen in the palms and fingers. It is generally seen as a movement restriction and a painless mass (3, 4). DC can be associated with other fibromatoses including plantar fibromatosis (Ledderhose disease), penile fibromatosis (Peyronie disease), and fibromatosis of the dorsum of the proximal interphalangeal joints (Garrod's

nodules or knuckle pads) (5). The etiology is not clear. It extends from the palm towards the fingers in the form of myofibroblast-induced fibrous bands. Over time, palmar and digital flexion contractures occur. It disrupts hand function and affects quality of life (6). Even though it is widely seen among ethnic groups, its prevalence is high in North American men. Moreover, its prevalence increases with age (4). Despite recent research on different treatments (7), the surgical method commonly used in the treatment of contracture is incision and fasciectomy (8, 9). Post-operative recurrence has been reported to vary in a wide range from 0 and 70% (10). Despite different treatment modalities, the likelihood of recurrence is quite high (7). In the literature, there are studies investigating the relationship



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between the surgical method and the clinic in terms of determining the recurrence of DC (10, 11, 12). For this reason, it is very important to estimate in which cases the recurrence will be observed.

In the present study, it was aimed to investigate the relationship between recurrence and Ki-67 proliferation index, smooth muscle actin (SMA) staining intensity, and clinicopathological findings of cases who had been diagnosed with DC and undergone surgical intervention.

METHODS

After the approval of Recep Tayyip Erdoğan University Ethics Committee (no: 34, date: 12.23.2016), the clinical and pathological records of 25 cases diagnosed with DC in the Department of Pathology between 2009 and 2015 were documented. Written informed consent was obtained from the patients. The hematoxylin-eosin (HE) stained sections were retrospectively analyzed. Age, gender, localization, contracture level, treatment type, and recurrence were determined. In addition, Ki-67 proliferation index and SMA staining intensity were examined.

HE-stained preparations were fixed in formol. The 5 µm-thick cross-sections obtained from the selected paraffin blocks were taken on slides treated with HistoGrip™ (Zymed Laboratories, CA, USA). After deparaffinization, the cross-sections were boiled in citrate buffer (pH=6) in order to extract antigen. In immunohistochemical examination using the streptavidin-biotin method, Ki-67 (MM1, Cod: 801704, pre-prepared) primary antibody and SMA (MM1, Cod: 28330030, pre-prepared) were used, as well as aminoethyl carbazole chromogen used as chromogen. Mayer's hematoxylin was used in contrast staining. Mounting medium (Zymed) was used when closing the slide. Sections were analyzed by Olympus BX50 light microscope (Olympus America, Inc., NY, USA).

Randomly selected tumor sites were examined in Ki-67 scoring. The ratio of the number of positive stained cells to the total number of cells under 5 different magnification zones (40X) for each sample was determined as the labeling index (LI). Only the nuclei that were stained clearly were accepted as positive. The number of mitosis was determined at 10X magnification in a randomly selected microscopic region (x400). SMA staining intensity was divided into 3 groups as mild (+), moderate (++), and intense (+++).

Statistical Analysis

The SPSS 16.0 statistical software package (SPSS Inc, Chicago, Illinois, USA) was used for all calculations. Normality was tested using the Kolmogorov-Smirnov test. Data are presented as

median (inter-quartile range, IQR) for non-normally distributed continuous variables. Measurement of central tendency was given as a box-plot graphic. Difference between variables were evaluated by Kruskal-Wallis with post hoc Mann-Whitney U test. Group differences with p value <0.05 were accepted significant.

RESULTS

Twenty-five DC cases were examined. The patients' ages ranged from 42 and 75 years, with a mean age of 55 years. Twenty-four percent of the patients were female and 76% were male. All patients underwent extensive palmar fascia excision under regional intravenous anesthesia. The excised masses were in the form of cords. Fifteen cases (60%) were in the right hand and 10 (40%) were in the left hand. The most frequently observed contracture localization was the 4th and 5th fingers. Seven patients had type-II diabetes mellitus (DM) for more than five years. Table 1 shows the distribution of DC cases by age, gender, type of treatment, localization, Ki-67 proliferation index, and

Case no	Age	Gender	Recurrence	Side	Ki-67	SMA
1	49	Female	No	Right	0%	+
2	56	Male	No	Right	1%	+
3	42	Male	No	Left	1%	+
4	75	Female	No	Right	0%	+
5	42	Male	No	Left	1%	+
6	56	Male	No	Right	2%	++
7	62	Male	Yes	Right	5%	+++
8	54	Male	No	Left	1%	+
9	46	Male	No	Right	2%	+
10	46	Male	No	Right	1%	+
11	67	Male	No	Left	2%	+
12	75	Male	No	Left	2%	++
13	63	Male	No	Left	1%	+
14	49	Male	No	Right	1%	+
15	67	Male	No	Right	1%	+
16	75	Male	No	Right	1%	+
17	50	Female	No	Left	2%	+
18	60	Male	No	Left	1%	+
19	50	Male	No	Right	1%	+
20	58	Male	No	Right	1%	+
21	57	Female	No	Right	1%	+
22	45	Male	No	Right	2%	++
23	54	Male	No	Left	1%	+
24	52	Female	No	Left	2%	+
25	45	Female	No	Right	1%	+

SMA: Smooth muscle actin, Ki-67: Proliferation index

SMA staining intensity. The treatment was extensive excision for all contractures, and recurrence was observed only in one patient after approximately one year. All the patients admitted with a painless mass growing slowly on the hand and contracture of the fingers and metacarpophalangeal joint. Bone tissue was normal in the conventional radiological examination of the patients. Mass shadow was observed in soft tissues. In six cases with digital contracture, the clinical problem was trigger finger due to the compression in the A1 pulley. Nodules accompanied fibrous bands in 12 cases. On physical examination of all cases, there was a fibrous band that caused 20-30° flexion contracture in the metacarpophalangeal joint in the hand.

Pathological examination revealed irregularly shaped tissues with localized elastic nodules of different sizes and gray-white color. Microscopic examination revealed fibroblastic proliferation in fascial tissue samples (Figure 1). There was a severe increase in cellularity in four cases, moderate increase in eight cases, mild increase in seven cases, and no increase in six cases. In immunohistochemical analysis, Ki-67 proliferation rates of lesions were generally low (1-2%), but high in only one case (5%) (Figures 2 and 3). SMA staining was intense in one case (4%), moderate in three cases (12%), and mild in 21 cases (84%) (Figure 4). The relationship between Ki-67 proliferation rates and age and gender is presented in Figure 5.

DISCUSSION

Although the etiology of DC is not clear, it has been reported to be associated with age, genetic factors, gender, alcohol and smoking, as well as working (3, 4, 5, 9, 13). The most common site of the disease is palmar fascia. But, the involvement of body parts other than the palm can also be seen (5). Furthermore, it has

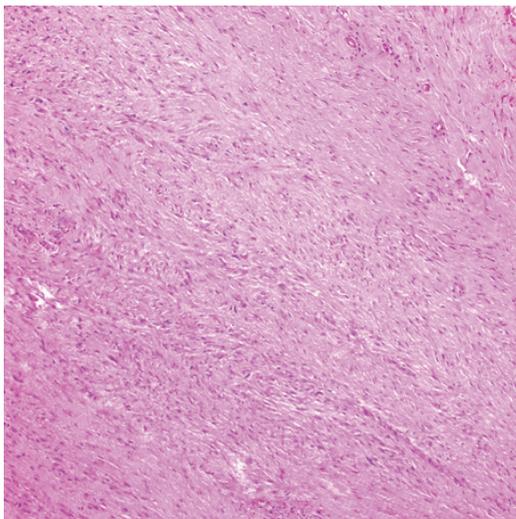


Figure 1. Lesion with proliferation of fibroblasts (H&E x100)

been reported to be associated with frozen shoulder syndrome due to its fibro-proliferative characteristics (11). However, no involvement was observed in other body regions in our cases.

In terms of gender, the prevalence of DC was 1.5-fold higher in males (14). It is more common especially among 40 year-old males (15). Palmar fascia is the target tissue for androgen activity. The higher number of androgen receptors in DC when compared to normal palmar fascia explains the higher frequency in male gender (16). In our patient group, the dominant gender was male with 76%. However, female/male ratio was higher than the literature. Moreover, the males had more severe contractures than females.

DC is a hand pathology that is frequently observed with DM. Its prevalence varies between 16% and 42% (17). The prevalence of DC increases with the duration of DM (18). The formation of contracture at hand is associated with smoking and free radical

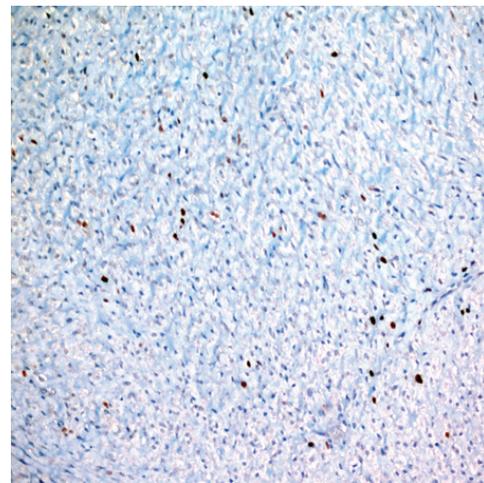


Figure 2. Low Ki-67 proliferation index (x200)

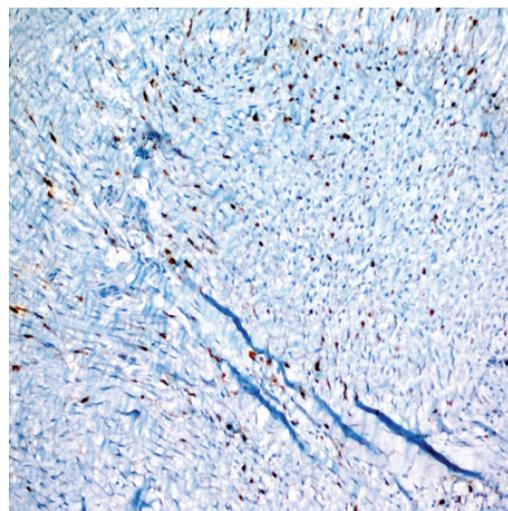


Figure 3. High Ki-67 proliferation index (x200)

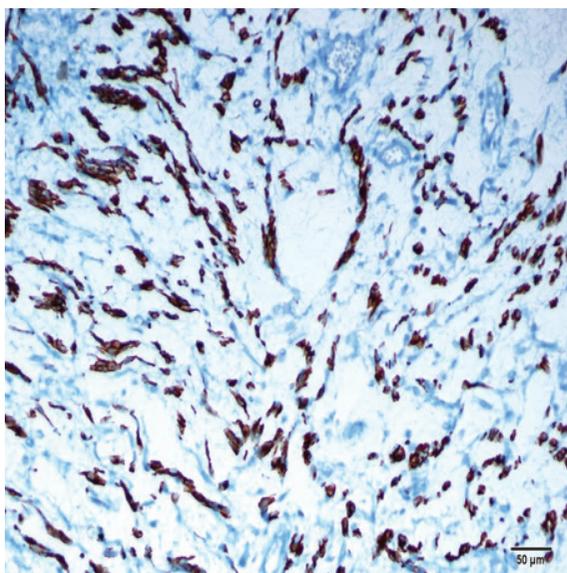


Figure 4. Strong smooth muscle actin positivity (x200) (in DM) and local ischemia (13). Twenty-eight percent of our cases had DM. The prevalence was consistent with the literature. However, in all cases, there were nodules accompanying the fibrous bands. But, there was no difference between the duration of DM and DC clinic.

In the histopathology of DC, there are proliferative, involutinal, and residual phases. In the proliferative phase, the number of fibroblasts increases. Due to various factors, fibroblasts form myofibroblasts. The myofibroblasts show the characteristics of both smooth muscle cell and fibroblasts. Thus, they have the ability to contract (19). The involutinal phase is characterized by cell loss and the number of myofibroblasts decreases (20). In residual phase, reductions are observed in the number of myofibroblasts. Together with mature fibroblasts, also the amount of collagen increases. At this phase, type III collagen increases (21, 22). Moreover, nodules form band-like structure from the mature scar tissue (23). Myofibroblasts play significant role in tissue contraction in DC (24).

DC nodules have a cell density of myofibroblasts that provides fibroblast and smooth muscle cell character. Compared with the cells derived from band, positive SMA staining was found to be higher in majority of nodule cell culture and it corroborates this conclusion (25).

Various factors have been proposed to play role in post-operative clinical recurrence (26, 27). One of these factors is the relationship between myofibroblasts and intracellular microtubules. The presence of myofibroblast in residual tissue can be used to predict the likelihood of recurrence. For this reason, radical excision of the palmar fascia and the involved skin zone with

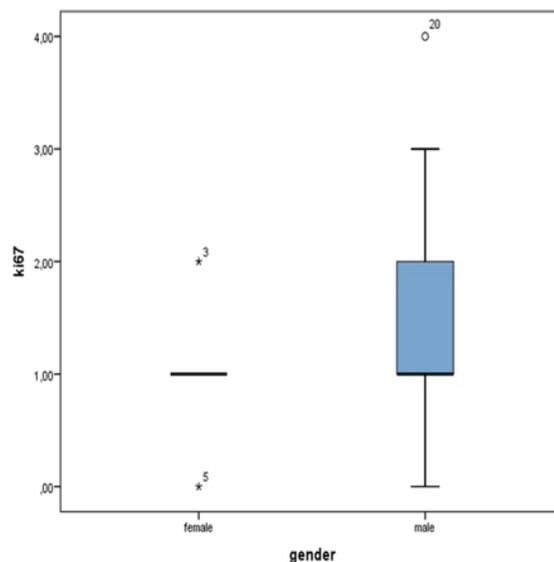


Figure 5. a) Relationship between Ki-67 proliferation rates and gender

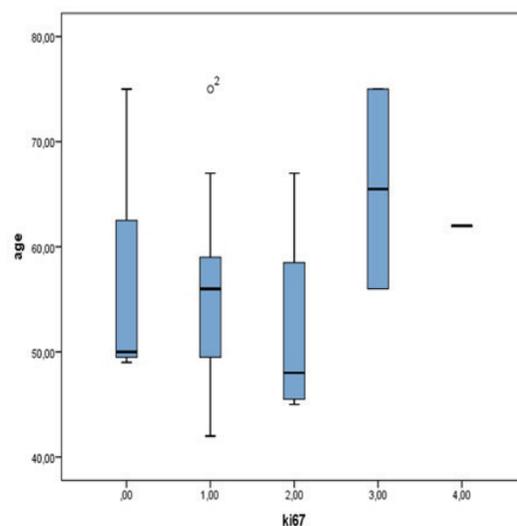


Figure 5. b) Relationship between Ki-67 proliferation rates and gender open surgery method and covering the surgery zone with full-thickness skin graft is useful in preventing the contracture (26).

Passive fibrous band fibroblasts may be reactivated as myofibroblasts with the effect of growth factors. This may be a major factor for high post-operative recurrence rates or for progression after injury (27).

Increased post-operative recurrence increased the importance of predicting the recurrence. Recurrence and aggressiveness can be estimated using a high level of increase in cellularity in DC, because the cellularity tends to decrease and the amount of type-III collagen tends to increase as the disease matures. Myofibroblasts decrease and the fibroblasts replace them in the residual phase (28). Significant increase in cellularity was

observed in four of our cases, but the recurrence was seen in only one of these cases.

If DC is aggressive and the proliferative phase is stronger, maturation is delayed. Recurrence of this disease is known to be associated with cellular diversity. The collagen rate is lower in aggressive cases (28). The presence of SMA in myofibroblasts is an indicator of disease activity. It is commonly found in aggressive surgical materials (29). Ki-67 proliferation index, which is a proliferative marker, can be frequently seen at high levels in aggressive cases (28). When our symptomatic cases were operated for 20-30° flexion contracture in the metacarpophalangeal joint, moderate-strong SMA positive staining was observed in three of four cases with high cellularity, and Ki-67 proliferation index was found to be at high level only in one case. The level of Ki-67 proliferation index was low in other cases. Despite the absence of benign lesions, the post-operative recurrence is common. Extensive surgical excision is very important because of the insufficient surgical excision (24). However, the recurrence was observed in our case with >5% Ki-67 proliferation index. Because of the recurrence despite the extensive excision of the palmar fascia, the use of Ki-67 proliferation index and SMA staining intensity in the analysis of the fibroblastic proliferation in the pathological examination of excised materials in DC may be beneficial in the clinical follow-up of the recurrence of the lesion.

The main limitation of the present study is limited number of cases. Moreover, no histopathological comparison could be made between different surgical samples, such as nodules and bands. However, despite all the limitations, we believe that it will contribute to further studies on recurrence in DC.

CONCLUSION

We believe that the use of Ki-67 proliferation index and SMA staining intensity with immunohistochemical staining method in surgical specimens in order to determine the clinical course of DC might be beneficial in estimating the recurrence.

Ethics

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Recep Tayyip Erdoğan University Ethics Committee (no: 34, date: 12.23.2016)

Informed Consent: Written informed consent was obtained from the patients.

Peer-review: External and internal peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.S.B., R.B., Concept: M.S.B., R.B., Design: M.S.B., R.B. Data Collection or Processing: M.S.B., R.B., Analysis or Interpretation: M.S.B., R.B., Literature Search: M.S.B., Writing: M.B.S.

Conflict of Interest: No conflict of interest was declared by the authors.

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