Tepecik Eğit. ve Araşt. Hast. Dergisi 2016; 26(1):46-52
doi:10.5222/terh.2016.046

Klinik Araştırma

Comparison of ER-α, ER-β, β-catenin, EGFR, CD117, p53, Ki-67 expressions and mitotic rate between superficial and deep fibromatoses

Yüzeyel ve derin fibromatozislerde ER-α, ER-β, β-katenin, EGFR, CD117, p53, Ki-67 ekspresyonları ve mitotik oranların karşılaştırılması

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ABSTRACT

Objective: Despite of their similar microscopic findings. Fibromatoses are divided into two groups as superficial fibromatoses and deep fibromatoses, which have different immunohistochemical profiles and clinical characteristics Our aim was to evaluate the expressions of ER-a, ER-b, b-catenin, EGFR, CD117, p53, Ki-67 and mitotic rate in superficial and deep fibromatoses.
Methods: Thirty-seven cases consisting of 15 superficial and 22 deep fibromatoses were reevaluated as regards ER-α, ER-β, β-catenin, EGFR, CD117, p53 expressions, Ki-67 proliferative index and the mitotic rate. Two groups were compared statistically and discussed.
Results: ER-a expression was not observed in any case. ER-b and b-catenin expressions were more intense in the deep fibromatoses group. The ER-b intensity, b-catenin expression, Ki-67 proliferation index and mitotic rates were statistically significantly higher in the deep fibromatoses group (p=0.04, 0.01, 0.001, 0.001 respectively). There was no statistically significant difference in CD117, EGFR, and p53 expressions between groups.
Conclusion: ER-β intensity, β-catenin and Ki-67 expression rates and the mitotic index were statistically significantly higher in the deep fibromatoses group in our study. We suggest that these markers may have predictive value in determining the course of the lesions.

Key words: Fibromatoses, estrogen receptor beta, beta-catenin, Ki67 index, mitotic rate

ÖZ

Amaç: Fibromatozisler benzer mikroskobik bulgulara sahip olmasına rağmen, farklı immünohistokimyasal profileri ve klinik özellikleri nedeniyle yüzeyel ve derin fibromatozisler olmak üzere iki gruba ayrılırlar. Amacımız yüzeyel fibromatozisler ve derin fibromatozislerde ER-α, ER-β, β-katenin, EGFR, CD117, p53, Ki-67 ekspresyonlarını ve mitotik oranlarını değerlendirmek.
Yöntemler: ER-α, ER-β, β-katenin, EGFR, CD117, p53, Ki-67 ekspresyonları ve mitotik oranları 15 yüzeyel, 22 derin fibromatozisi içeren 37 olguda yeniden değerlendirildi, iki grup istatiksel olarak karşılaştırıldı ve tartışıldı.
Bulgular: ER-α ekspresyonu hiçbir olguda izlenmedi. ER-β ve β-katenin ekspresyon şiddeti derin fibromatozis grubunda daha yüksek idi. ER-β ekspresyon şiddeti, β-katenin ekspresyonu, Ki-67 proliferasyon indeksi ve mitotik oranlar derin fibromatozis grubunda istatistiksel olarak anlamlı düzeyde yüksekti (sırasıyla; p=0,04, 0,01, 0,001, 0,001). Yüzeyel ve derin fibromatozis grupları arasında CD117, EGFR ve p53 ekspresyonlarında istatiksel olarak anlamlı fark saptanmadı.
Sonuç: Çalışmamızda ER-β ekspresyon şiddeti, β-katenin ekspresyonu, Ki-67 proliferasyon indeksi ve mitotik oranı derin fibromatozis grupunda anlamlı olarak yüksek bulundu. Biz bu belirteçlerin, hastalığın gidişatını belirlemede bir öngörü değeri olabileceğini düşünmekteyiz.

Anahtar kelimeler: Fibromatozis, östrojen reseptör beta, beta-katenin, ki67 indeks, mitotik hız

Alındığı tarih: 01.12.2015
Kabul tarihi: 17.12.2015

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INTRODUCTION

Fibromatoses make up a broad group of fibroblastic/myofibroblastic proliferations with similar gross and microscopic appearances. Their biologic behavior is between that of benign fibroblastic lesions and fibrosarcoma [1,2]. They tend to have an infiltrative growth pattern without metastasis but high recurrence risk and are therefore classified as an intermediate (locally aggressive) group of fibroblastic/myofibroblastic tumors according to the World Health Organization (WHO) 2013 criteria [2].

Fibromatoses are divided into two major subgroups as superficial (SF) and deep fibromatoses (DF). Both have several subtypes with different clinical characteristics despite similar microscopic findings [2]. SFs are small and slowly growing lesions arising from the fascia and aponeurosis of the hand (palmar fibromatosis), foot (plantar fibromatosis), penis or phalangeal joints [1]. They rarely involve deep structures. On the other hand, DFs are large, rapidly growing tumors. They involve deep structures and can be located in the abdominal wall (abdominal fibromatoses) or intraabdominal (pelvic and mesenteric fibromatoses) or extraabdominal (extraabdominal fibromatoses) regions [1,3].

Fibromatoses have a high recurrence risk after surgery. Systemic treatment modalities including anti-fibrotic agents such as non-steroidal anti-inflammatory drugs, sex hormone-receptor blockers, tyrosine kinase inhibitors, and low-dose metronomic chemotherapy have been tried to decrease the recurrence risk. Recurrence has also been observed after treatment with anti-fibrotic agents and/or targeted treatment modalities that have become popular recently. Modalities targeting oncogenic factors such as C-kit, APC and β-catenin gene mutations and abnormal p53 and Rb expressions have been found to be effective in previous studies [4,5].

Hormonal factors may also be effective in the proliferative activity of fibromatoses as ER-α and ER-β expressions have been reported in these lesions. It has been also shown that cases with ER-β expression respond to antiestrogenic therapy [6].

Beta-catenin is an oncoprotein with transcription activity downstream the Wnt signal pathway. Nuclear accumulation of β-catenin has been shown in tumors with β-catenin mutations. Many sporadic DF cases show β-catenin mutation leading to β-catenin overexpression that can be screened by using immunohistochemical methods [7].

Epidermal growth factor (EGF) binds to EGFR with a high affinity. EGF stimulates the intrinsic tyrosine kinase activity of the receptor, leading to the activation of cell proliferation. Some studies have reported overexpression of EGFR in the fibromatoses [5,8-10].

CD117 is the immunohistochemical hallmark of the C-kit oncogene. It is a transmembrane tyrosine kinase receptor that activates signals playing a role in cell proliferation. Few data about CD117 expression have been reported in cases with fibromatoses [11-14].

p53, encoded by the TP53 gene, is a tumor supressor protein that regulates the cell cycle. p53 overexpression is suggested to have a predictive value in fibromatoses [4,9].

Ki-67 is a nuclear marker and plays a role in the active phase of the cell cycle [15].

Our aim was to evaluate the immunohistochemical expression rates and patterns of ER-α, ER-β, β-catenin, EGFR, CD117, p53, Ki-67 and mitotic rate in SF and DF cases.

MATERIAL and METHOD

Thirty-seven cases (15 SF and 22 DF) diagnosed between 2000 and 2012 were included in our study. Information about clinical parameters such as age, and sex of the patients, and location of the lesion(s) were obtained from pathology reports. Hematoxylin-eosin-stained sections were reviewed according to the World Health Organization (WHO) 2013 classification system for fibromatoses. Four μm-thick sections were taken from the best representative areas of tumor tissues and placed on lysinated slides for immunohistochemical analysis. Staining procedures were performed on an automated immunohistochemical staining processor (Autostainer Link 48, Dako,

Denmark). Procedures appropriate for the device and En Vision Flex ready-to-use kits were used. The immunohistochemical antibody panel, dilutions and clones employed are shown in Table 1.

Table 1. Characteristics of immunohistochemical antibodies.

Antibody	Clone	Dilution	Manufacturer
ER-α	EP1	Ready to use	Dako
ER-β	PPG5/10	Dilution (1/20)	Dako
β-catenin	β-catenin-1	Ready to use	Dako
EGFR	E30	Dilution (1/25)	Dako
CD117	104D2	Dilution (1/500)	Dako
p53	DO-7	Ready to use	Dako
Ki-67	MIB-1	Ready to use	Dako

Nuclear staining of ER-α, ER-β, β-catenin, p53 or Ki-67 was evaluated as a positive result. Cytoplasmic staining for CD117, membranous or cytoplasmic staining for EGFR were considered as positive. The intensity of ER-β and β-catenin staining was also evaluated and subgrouped as follows: (weakly 1+ / moderately 2+ / strongly 3+ staining). The mitotic index was counted per 20 high power fields.

Statistical analysis

The Statistical Package for the Social Sciences (SPSS) for Windows 16.0 program was used (SPSS Inc., IBM, Somers, New York, USA) for statistical analysis. In addition to descriptive statistical methods (mean, percentage), the chi-square test was used for qualitative, and the Mann-Whitney U / t-test was used for quantitative data. P<0.05 were considered as statistically significant.

RESULTS

Demographic data

The median age for all cases with fibromatoses was 43.16 years (range:4-79 yrs), while it was 53.3 for the SF, and 36.2 for the DF groups. The difference between the two groups as for age was statistically significant (p=0.002).

Seventeen (77.3%) DF cases were female, whereas 12 (80%) SF cases were male. The intergroup difference regarding sex distribution was also statistically significant (p=0.001).

SF lesions were located on the palmar (n=13) and plantar (n=2) regions. DF lesions were localized on the abdominal wall (n=9), trunk/extremity (n=9) and in the intraabdominal cavity (n=4).

Immunohistochemical Features

None of the cases showed ER-α expression.

ER-β expression was observed in 13 SF (86.6%), and 21 DF(95.4%) cases (p=0.86). The mean expression rate of ER-β was 47.3% in the SF , and . 49.9% in the DF groups and the difference between the two groups was not statistically significant (p=0.93). However, there was a significant difference between the groups for ER-β expression intensity (p=0.04). Most of the positive cases (n=10) showed (2+) inten-

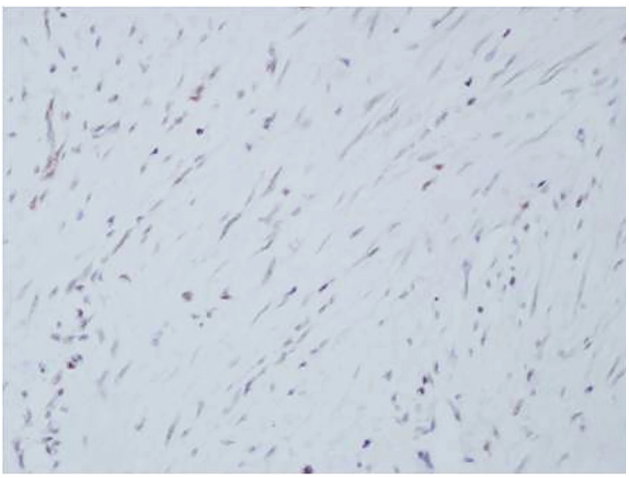

Figure 1. Weak (+1) ER-β expression in SF (x400).

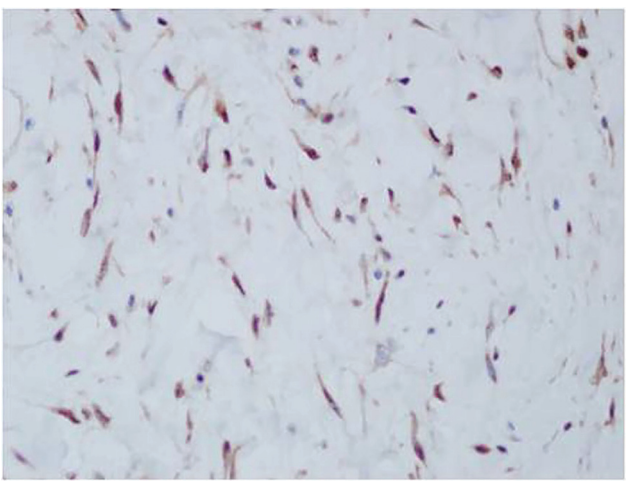

Figure 2. Strong (+3) ER-β expression in DF (x400).

sity in the SF, and (3+) intensity in the DF group (n=9) (Figure 1,2).

Twelve DF cases (54.5%) showed β-catenin expression whereas there was no β-catenin expression in the SF group. The difference between the groups was statistically significant (p=0.01). Beta-catenin expression intensity was (3+) in 8, (2+) 2, and (1+) 2 DF cases (Figure 3,4).

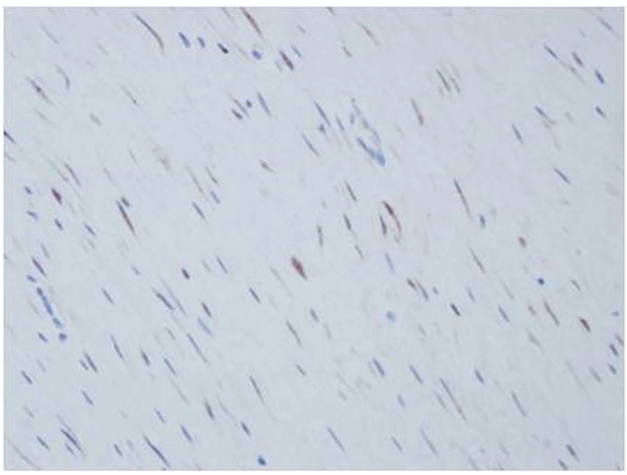

Figure 3. Weak (+1) β-catenin expression in DF (x400).

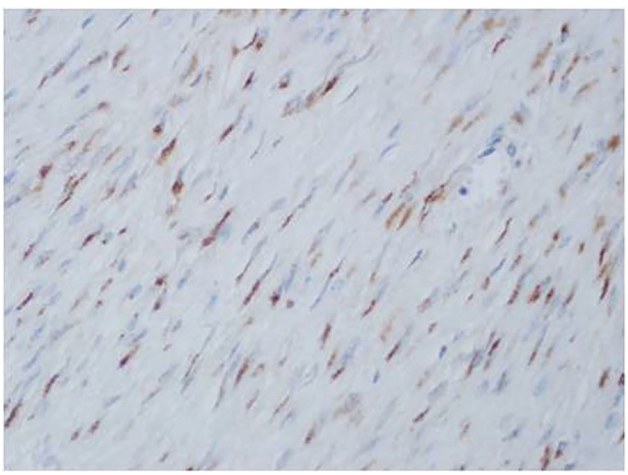

Figure 4. Strong (+3) β-catenin expression in DF (x400).

CD117 expression was noted in one SF and two DF cases. There was no statistically significant difference between the two groups in terms of CD117 expression (p=0.68).

EGFR expression was detected only in one SF, (6.6%) and three (13.6%) DF cases. There was no statistically significant difference between the two groups (p=0.5).

Eight (54.5%) SF, and seven (31.8%) DF cases showed p53 positivity without any statistically significant difference between the groups (p=0.19).

The mean Ki-67 proliferation index for the whole cases was 3.45 % (range: 1-10%). There was a statistically significant difference between the two groups (2.17% in the SF group vs. 4.36% in the DF group, p=0 .001) (Figure 5,6).

The mean number of mitoses per 20 high power fields were 0.73 in the SF and 1.72 in the DF group. The difference was statistically significant (p=0.001).

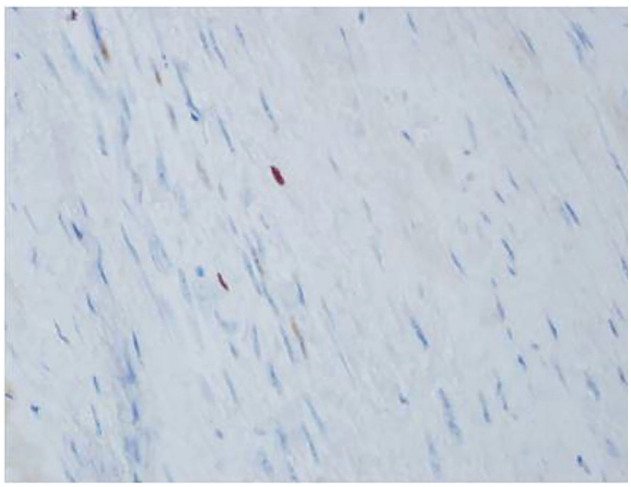

Figure 5. Ki-67 proliferation index 1% in SF (x400).

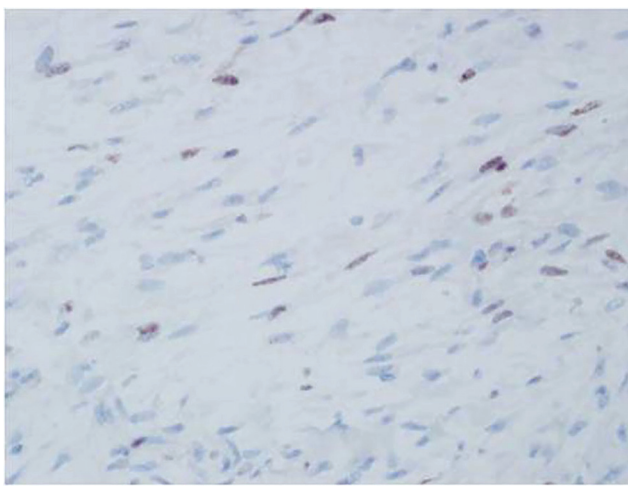

Figure 6. Ki-67 proliferation index 10 % in DF (x400).

A detailed comparison of the SF and DF groups is given in Table 2.

Table 2. Comparison of age, sex and immunohistochemical characteristics of SF and DF.

	SF	DF	P
Mean age	53.3	36.2	0.002
Sex (female/male)	3/12 (20/80)	17/5 (77.2/22.8)	0.001
ER-β positivity N (%)	13 (86.6)	21 (95.4)	0.86
ER-β intensity N (%)			
+1	1 (7.6)	6 (28.5)	
+2	10 (76.9)	6 (28.5)	0.04
+3	2 (15.3)	9 (42.8)	
β-catenin positivity N (%)	0 (0)	12 (54.5)	0.01
β-catenin intensity N (%)			
+1	-	2 (16.6)	
+2	-	2 (16.6)	0.04
+3	-	8 (66.6)	
CD117 positivity N (%)	1 (6.6)	2 (9.09)	0.68
EGFR positivity N (%)	1 (6.6)	4 (18.1)	0.5
p53 positivity N (%)	8 (53.3)	7 (31.8)	0.19
Mean Ki-67 expression rate	2.1 (1-5)	4.4 (1-10)	0.001

DISCUSSION

Fibromatosis is an adult-onset disease. SF is more frequent in males in their middle and advanced ages [1,2] whereas DF is seen between the ages of 16-60 years and is more frequent in females [1,4,12,16]. The median ages of the SF and DF groups in this study were 53.3 and 36.2 years respectively. Furthermore SF was four times more frequent in males than females. Our results are consistent with literature data.

ER-α expression of fibromatoses is a controversial issue. ER-α positivity in fibromatoses has been shown in a few studies using ligand binding, fluorescent hormone binding and immunohistochemical techniques [6] however, ER-α has been reported to be negative in fibromatoses in recent studies [17]. Deyrup et al. [18] suggested that the positivities reported in the initial studies might be due to the cross-reactivity of ER-α with ER-β, depending on the method and antibody clone. We used ER-α (EP1 clone) on autostainer and ER-α was negative in all our cases, consistent with the current literature data.

Though previous studies have reported ER-β positivity in DF [11,12,17], we could not reach any literature data on ER-β expression in SF. We found ER-β positivity both in the DF (95.45%) and SF (86.6%) groups. ER-β expression intensities were significantly higher in the DF group that might be due to the female predominance of this group. Etiopathogenetic factors should be further analysed to clarify the reason of the different ER-β expressions in SF and DF.

Several studies have demonstrated β-catenin immunoreactivity and gene mutations in cases with DF [5,19]. Beta-catenin positivity has been shown in cases with SF by immunohistochemistry but no mutation was detected with gene analyses [5,19]. Furthermore, Degreef et al. [20] reported β-catenin positivity only in the involution phase of 23 fibromatoses. We used a different antibody clone (β-catenin-1) than the clones used in previous studies. We also did not group the lesions according to their phases. While none of the SF cases showed β-catenin immunoreactivity, we found β-catenin positivity in 54.5% of the DF cases. This finding indicates that DFs are associated with nuclear accumulation of β-catenin that leads to an aggressive course [18].

Literature data regarding CD117 expression in fibromatoses is controversial. Some studies have shown CD117 negativity [9,11,12] whereas others reported CD117 positivity ranging from 77-100% in cases with DF [21,22] Hornick&Fletcher [22] and Miettinen [23] stated that these could be false positivities due to inappropriate CD117 antibody dilutions. There is no data on CD117 expression in SF. We used the '104D2 clone' (1/500 dilution) on an automatic system in our study. We found CD117 positivity in only 3 cases (1 SF, 2 DF) (p=0.68). Such small numbers prevented further analysis between the groups.

Though neither SF nor DF express EGFR immunoreactivity in general [4,10], Magro et al. [8] found EGFR expression in hypercellular areas by RT-PCR and immunohistochemical methods. We used a different antibody clone (E30) and dilution rate (1/25) than Margo et al. [8] and noted 3 positive cases [one SF (6.6%) and three (13.6%) DF] and the difference between EGFR expressions of SF and DF was not statistically significant in our study. It appears that controlled analyses on larger case series are needed to arrive at a conclusion.

p53 positivity in fibromatoses is another controversial issue. Mofatt et al. [4] found p53 positivity in

2 of 47 SF cases while Muller et al. [24] reported that all of their 6 cases were negative. Gebert et al. [9] found p53 positivity in 12 of 37 DF cases, but all 13 DF cases of Muller et al. [24] demonstrated p53 negativity. We found p53 positivity in 8 (54.5%) SF, and 7 (31.8%) DF cases. Though the controverseries of the studies may be related with the antibody clones, p53 expression alone seems to be a useful tool both in SF and DF.

There is no recent data on Ki-67 expression in SF and the data regarding DF is conflicting. Leithner et al. [11] found Ki-67 positivity in 20 and Mofatt [4] in 47 DF cases with a threshold value of 5% and 1%, respectively. However Hoos [16] found all DF cases to be negative with a 20% threshold value. Gebert [9] reported a Ki-67 index <2% in 36 DF cases and >5% in 1 case without defining any threshold value. We evaluated the Ki-67 proliferation index in all cases (n=37) without defining any threshold value and found statistically significantly higher Ki-67 expression rates in DF (4.36%) compared with SF (2.17%) (p=0.001). This finding supports the more aggressive course of DF.

Fibromatoses are not actively mitotic lesions [1,2,25]. There is no previous study on the number of mitoses in SF and relevant data on DF is limited. Huang and Tzen [26] found less than 2 mitoses in most of their cases. The number of mitoses in our study ranged from 0 to 5 per 20 high power fields in both groups and the mean number of mitoses was significantly higher in the DF group (0.73/20 HPF in the SF, 1.72/20 HPF in DF p=0.018). This finding also indicates a more aggressive course in DF.

CONCLUSION

ER-β intensity, β-catenin and Ki-67 expression rates and the mitotic index were statistically significantly higher in the DF group in our study. Our findings suggest that these markers have functional role in the development of fibromatoses. And they might have a predictive value in determining aggressive course of these lesions. Furthermore these parameters may be the targets of treatment modalities.

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