Desmoid-type fibromatosis is locally aggressive tumor rare in general population, although commonly present in patients with familial adenomatous polyposis, significantly contributing to the morbidity and mortality of patients. To optimize and individualize the management of patients it is necessary to better understand the biology of these tumors. Immunohistochemical analysis of β-catenin, VEGF, hormone receptors ERβ, ERα and PR, COX-2, APC protein, EGFR, c-kit (CD117), bcl-2 and HER2 expression, potential therapeutic targets, was carried out on 15 archival biopsy samples together with APC gene mutational screening. β-catenin expression was found in all samples, with over 73% showing high range positivity, however with no prognostic significance. Non-specific cytoplasmic localization of β-catenin was observed FAP-associated cases lacking CTNNB1 mutations. Hormone receptor status demonstrated expression of ERβ in 93% of lesions, without detectable ERα or PR. Distinct COX-2 expression of variable intensity was present in all but one desmoid-type fibromatosis case. All lesions demonstrated intense VEGF positivity. Immunoreactivity for the APC protein was found only in 4 cases associated with FAP. No EGFR, HER2, bcl-2 or c-kit expression was detected in any sample. Expression of β-catenin, VEGF, ERβ, COX-2 in high number of cases suggests a potential as future therapeutic targets in desmoid-type fibromatosis.

Key words: desmoid-type fibromatosis, APC, familial adenomatous polyposis, targeted therapy.

Introduction

Desmoid-type fibromatosis (DTF), also known as aggressive fibromatosis is a clonal fibroblastic/myofibroblastic proliferation. Although histologically benign, desmoids are locally invasive and associated with a high local recurrence rate, but lack metastatic potential [1]. Most DTFs occur in sporadic form and are rare in the general population. However more than 20% of patients with familial adenomatous polyposis (FAP) develop DTFs contributing significantly to the morbidity and mortality of mainly post-colectomy patients [2, 3]. Desmoid-type fibromatosis most commonly involves extra-abdominal locations in the general population whereas patients with FAP mostly present with intra-abdominal disease [4, 5].

Due to the variable and often unpredictable clinical course and the rarity of DTFs no established or evidence-based treatment approach is available as of today. An improved understanding of the biology of these tumors may help to individualize management...
Table I. Summary of patients’ clinical data

| PATIENT | GENDER/AGE | SITE |
|---------|------------|------|
| SPORADIC |            |      |
| 1       | M/30 years old | Retroperitoneum* |
| 2       | F/56 years old | Pelvis |
| 3       | M/24 years old | Interscapular |
| 4       | F/15 years old | Submandibular |
| 5       | F/26 years old | Pelvis |
| 6       | F/3 years old | Retroperitoneum |
| FAP-ASSOCIATED |         |      |
| 7       | F/14 years old | Intraabdominal |
| 8       | M/31 years old | Intraabdominal |
| 9       | M/28 years old | Intraabdominal |
| 10      | F/27 years old | Intraabdominal |
| 11      | F/21 years old | Intraabdominal |
| 12      | F/30 years old | Intraabdominal** |
| 13      | F/25 years old | Intraabdominal |
| 14      | F/37 years old | Intraabdominal |
| 15      | F/24 years old | Intraabdominal |

F – female, M – male
* recurrent DTF (rebiopsied 1 year after diagnosis)
** recurrent DTF (rebiopsied 2 years and again 5 years after diagnosis)

of the patients, improve risk stratification, and estimate disease recurrence.

The etiopathogenesis of DTF is not yet clear. Aggressive fibromatosis shows evidence of hormone dependency, since there is a higher incidence in fertile women, especially after pregnancy and also association with oral contraceptives [6]. A key molecule in the pathogenesis of DTF is believed to be β-catenin, which intracellular levels are regulated by the adenomatous polyposis coli (APC) gene and the Wnt pathway [7]. Disruption of the regulatory mechanism of β-catenin leads to its translocation to the nucleus and to the transcription of various target genes responsible for the promotion of tumorigenesis, one of them being cyclooxygenase-2 [8].

The presented study focused on the immunohistochemical expression analysis of supposed ethiopathogenetic targets (ERβ, β-catenin, APC protein, COX-2) together with the evaluation of well-established cancer therapy targets (c-kit - CD117, EGFR, HER2, VEGF) in biopsy samples of DTF.

Material and methods

15 cases of desmoid-type fibromatosis were studied. The diagnosis of DTF was revised according to current classification standards [9]. Patients were divided into sporadic group (n = 6) and FAP group (n = 9) (Table I). Inclusion into FAP group was based on positive family history, polyp count, colon cancer at young age and APC gene mutation status.

The FAP group was predominantly composed of young women (women n = 7; men n = 2) with 28 years median age at the time of diagnosis. Family history was positive in all patients in this group. All of these patients had intra-abdominal tumors. In 5 patients DTFs developed after proctocolectomy in a time range of 12 to 26 month. Only two women of this group have been pregnant before DTF development.

The sporadic group comprised of 6 patients (women n = 4; men n = 2) with 24.5 years median age at the time of diagnosis. All of these patients had a negative family history for DTFs and FAP. Tumor location in this group encompassed the pelvis (n = 2), retroperitoneum (n = 2), interscapular (n = 1) and submandibular (n = 1) region. Two patients had recurrent lesion which were repeatedly biopsied (Table I).

Immunohistochemistry

For immunohistochemistry 5 µm tissue sections of formalin-fixed and paraffin-embedded material were prepared on glass slides. Antibodies and dilutions used are listed in Table II. Briefly, after standard protocol deparaffinization the specimens assigned for EGFR detection were pretreated with proteinase K (Agilent, Santa Clara, California, USA) for 10 minutes at room temperature (RT). On samples assigned for adenomatous polyposis coli protein (APC) detection repeated heat-induced epitope retrieval with citrate (10mM, pH 6,0) in microwave (750W) was performed, first for 4,5 minutes and after a 10 minutes cooling break for 1 minute. All other specimens were revitalized in EnVision™ FLEX Target Retrieval Solution, pH 9 (Agilent, Santa Clara, California, USA) in a pressure cooker for 20 minutes. After rinsing, the slides were incubated with the particular primary antibody according to manufacturer’s instructions, followed by rinsing and incubation with dual (anti-mouse/anti-rabbit) secondary antibody conjugated with horseradish peroxidase (Envision HRP polymer, Agilent, Santa Clara, California, USA) for 30 minutes at RT. For visualization dianimobenzydizin (Dako Cytomation, Glostrup, Denmark) was used. Evaluation of HER2 expression was accomplished with the use of HercepTest™ (Agilent, Santa Clara, California, USA).

All slides were evaluated by light microscopy. Classification as positive was done according to standard protocols for the positive control. In negative control, primary antibody was replaced by buffer. The surrounding non-neoplastic tissue, including the skeletal muscle, fibrous vascularized connective tissue, mature adipose tissue and nerve fibers were evaluated.
as internal negative control to desmoid-type fibromatosis. Where it was applicable and the statistic calculation were valid, the differences between sporadic and the FAP group were compared using Fisher’s exact test.

### APC mutation screening

In all patients mutation screening of the complete coding region and exon-intron boundaries of the APC gene was performed using a combination of high resolution melting (HRM) and protein truncation test (PTT). For PTT analysis exon 15 was initially amplified from genomic DNA in four overlapping segments. The PTT test was performed using the TnT T7 Quick for PCR DNA system (Promega). Exons 1-14, 10A and 5’ part of the APC gene were analyzed using HRM. Primers for HRM analysis were designed to flank the coding regions and neighboring intronic sequences while avoiding benign variants within introns if possible. The minimum number of bases separating the 3’ end of the primers from the exon-intron boundaries was 10 bp. The HRM amplicons varied from 170 to 303 bp in length. HRM analysis was performed on the LightScanner instrument (Idaho

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**Table II. Summary of antibodies used in DTFs immunohistochemistry**

| Antibody                  | Company               | Clonality   | Type     | Dilution | Incubation Time |
|---------------------------|-----------------------|-------------|----------|----------|-----------------|
| EGFR                      | Dako                  | Monoclonal  | Mouse    | 1:50     | 1 h             |
| COX-2                     | Dako                  | Monoclonal  | Mouse    | 1:50     | 3 h             |
| Erβ                       | Dako                  | Monoclonal  | Mouse    | 1:20     | 1 h             |
| PR                        | Dako                  | Monoclonal  | Mouse    | prediluted | 1 h            |
| VEGF (subtype unspecific) | Thermo Fisher Scientific | Polyclonal  | Rabbit   | 1:1000   | 1 h             |
| c-kit (CD117)             | Dako                  | Polyclonal  | Rabbit   | 1:600    | 1 h             |
| APC (C terminal)          | AbCam                 | Polyclonal  | Rabbit   | 1:100    | 1 h             |
| bcl-2                     | Dako                  | Monoclonal  | Mouse    | 1:100    | 1 h             |
| β-catenin                 | Dako                  | Monoclonal  | Mouse    | 1:200    | 1 h             |
| HER2                      | Dako                  | HercepTestTM | -        | 1 h      |

EGFR – epidermal growth factor receptor; COX-2 – cyclooxygenase 2; ERβ – estrogen receptor β; ERα – estrogen receptor α; PR – progesterone receptor; VEGF – vascular endothelial growth factor; APC – adenomatous polyposis coli protein

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**Fig. 1. VEGF immunohistochemistry, recurrent DTF case.** A) Primary biopsy sample presenting cytoplasmic VEGF expression (brown color) of low intensity (+) in 60% of tumor cells; B) Rebiopsy after 1 year showing cytoplasmic VEGF expression (brown color) of high intensity (+++) in 90% of tumor cells. DAB, 100× (insert 200×)
Technology) with the DNA intercalating dye LC-Green (Idaho Technology).

All positive findings obtained by both screening methods were verified by sequencing analysis on the ABI PRISM 3130 Genetic Analyzer (Applied Biosystems). Sequencing reactions were performed in forward and reverse directions.

All patient samples that were found negative by these two methods were further screened for large genomic alterations in the APC gene by multiplex ligation-dependent probe amplification using the SALSA MLPA P043 APC kit (MRC-Holland).

**Results**

**Immunohistochemistry**

The β-catenin expression was found in all DTF samples. 11/15 cases (73.3%) showed high range nuclear positivity (> 25% of tumor cells). The remaining lesions demonstrated low range (< 25% of tumor cells) and/or cytoplasmic expression of β-catenin. In recurrent lesion both, increased and lowered β-catenin expression was observed. Low range and/or cytoplasmic positivity was more often found in FAP-associated desmoids, however the difference was not significant. The β-catenin specific nuclear expression was present only in desmoid-type fibromatosis and not in the surrounding non-neoplastic tissues.

VEGF showed diffuse cytoplasmic positivity in skeletal muscle cells and focal cytoplasmic expression in fibrous connective tissue, but no positivity was found in neural fibers or mature adipose tissue. Cytoplasmic positivity of VEGF in the tumor cells was noted in all DTF specimens with variations in intensity ranging from weak to strong (weak positivity n = 2, intermediate positivity n = 2, intense positivity n = 11) and number of positive tumor cells (50-100%). In repeatedly sampled patients, increase of VEGF expression in the later biopsy samples was observed (Fig. 1). Desmoid-type fibromatosis with excess of collagen and hyalinization showed higher range of VEGF expression in comparison with hypercellular forms. No significant differences of VEGF expression between sporadic and FAP DTFs was found. Cytoplasmic positivity of VEGF was also present in the endothelial cells of blood vessels.

Hormone receptor evaluation showed only expression of ERβ. Nuclear ERβ positivity was found in 14/15 samples. In the remaining case non-specific cytoplasmic ERβ expression was observed. In 12 of the 14 tumors ERβ positivity was graded as high range (25% of tumor cells). In recurrent lesions we noticed a decrease of the number of positive tumor cells (Fig. 2) or loss of ERβ expression in the later biopsies. DTFs were completely negative for ERα and PR. ERβ showed nuclear expression only in nerve fibers in surrounding non-neoplastic tissues.

Specific cytoplasmic cyclooxygenase-2 expression was observed in 14/15 DTF patients. The positivity

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*Fig. 2. ERβ immunohistochemistry, recurrent DTF case; A) Primary biopsy sample presenting nuclear ERβ expression (brown color) in 90% of tumor cells; B) Rebiopsy after 1 year showing nuclear ERβ expression (brown color) in 30% of tumor cells. DAB, 200× (insert 400×)*
varied from focal to diffuse and from weak to moderate. No significant differences of COX-2 expression between sporadic and FAP DTFs were found.

The APC protein showed membranous and/or cytoplasmic positivity, which was found in samples from 4/15 DTF patients all from the FAP group. In one of these patients 3 tumor samples from different biopsies (Fig. 3) were accessed; only the first sample showed APC protein expression. Later biopsies were APC protein negative.

No expression of EGFR, c-kit (CD117), bcl-2 and HER2 was found in any DTF sample. Results of DTF immunohistochemistry are summarized in Table III.

**APC mutation screening**

Mutation of the APC gene were detected in all FAP-associated cases of DTF except in one patient, who had a positive family history, multiple colon adenomas and a diagnosed colorectal carcinoma. All samples of DTF from the sporadic group were tested negative for APC mutations except from one patient, who was without a positive family history for FAP and without any clinical records of colon polyps or colorectal adenocarcinoma.

Results of APC gene mutation status are summarized in Table IV.

**Discussion**

Desmoid-type fibromatosis is a relatively rare disease and for that there are not many works evaluating the prognosis and factors indicating possible targeted therapy approaches [10]. The present work assesses expression of some proteins integrated in different signaling pathways activated in the tumor cells. Detection of these proteins may contribute to the therapeutic considerations of DTFs.

β-catenin is the most used immunohistochemical marker of DTFs, though not entirely specific [11, 12]. Its immunoreactivity has been reported in the range of 67-80% of DTF cases [13]. Normally, β-catenin is continuously phosphorylated and degraded. In DTFs Wnt signaling pathway activation or the alteration of β-catenin degradation, prevents β-catenin phosphorylation and leads to its accumulation first in the cytoplasm with subsequent translocation to the nucleus. β-catenin expression was found in all our DTF samples, of which 73.3% showed high range nuclear positivity. The remaining cases demonstrated only low range nuclear and/or cytoplasmic expression (Fig. 4). Signoroni et al. [8] proposed, that cytoplasmic localization of β-catenin is seen in patients lacking CTNNB1 mutations, although Mencaglia et al. [14] found no such correlation. Low range nuclear and/or cytoplasmic β-catenin staining in our set of samples was found only in FAP-associated cases with present APC mutation, and since CTNNB1 and APC mutations are mutually exclusive in desmoid tumors [15], our results seem to correlate with the findings of Signoroni et al. [8].

Later studies found, that not only CTNNB1 mutation state, but CTNNB1 mutational variant seems to be associated with β-catenin immunohistochemi-

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**Fig. 3. APC protein immunohistochemistry, recurrent DTF case; A) Primary biopsy sample presenting cytoplasmic APC protein expression (brown color). B) Rebiopsy showing no APC protein expression. DAB, 200× (insert 400×)**
Potential molecular targets of desmoid-type fibromatosis

The authors report mutational type dependent staining pattern of $\beta$-catenin in sporadic DTFs, with strong nuclear staining found significantly higher in cases with S45F and cytoplasmic staining in the cases with T41A. Mutational type dependent staining pattern might be caused by differences in phosphorylation of $\beta$-catenin regulatory proteins. The prognostic significance of $\beta$-catenin expression in desmoid-type fibromatosis has not yet been defined, though some data suggest that its over-expression is associated with an increased rate of local tumor recurrence [17] and that relapsed lesions show higher immunoreactivity for $\beta$-catenin [18]. Our study could not support these findings, for we observed variable expression of $\beta$-catenin in recurrent DTF cases.

Therapies targeting $\beta$-catenin or other elements of the Wnt signaling pathway are being developed and tested. Two emerging drugs targeting $\beta$-catenin are of major interest in DTF at present; tegatrabetan, which in cultures induces apoptosis of desmoid tumor cells and gamma-secretase inhibitors, which due to their anti-Notch activity, indirectly regulate the Wnt/APC/$\beta$-catenin pathway [19].

The $\beta$-catenin protein levels are upregulated in desmoid-type fibromatosis due to either APC mutations and defective $\beta$-catenin regulation, or CTN-NB1 ($\beta$-catenin) gene mutations resulting in uncontrolled activation [13]. In its active form, $\beta$-catenin stimulates cell proliferation through transcription of various target genes, such as the gene for cyclooxygenase-2 [8]. The overexpression of COX-2 was shown to contribute to tumorigenesis by apoptosis inhibition, stimulation of angiogenesis and cell proliferation. Overexpression of COX-2 has been linked in some malignant tumors, including mesenchymal lesions, with tumor progression, poor survival and increased risk of metastasis [18].

Expression of COX-2 was observed in 14/15 DTF samples. In patients with recurring lesions, no increased COX-2 positivity was observed by us. Up to date no direct association is known between COX-2 expression and DTF prognosis. However, COX-2

Table III. Results of desmoid-type fibromatosis immunohistochemistry

| PATIENT | EGFR | VEGF | ER$\beta$ | ER$\alpha$ | PR | COX-2 | c-KIT | $\beta$-CATENIN | BCL-2 | HER2 | APC |
|---------|------|------|---------|----------|----|-------|-------|--------------|-------|------|-----|
|         | (m)  | (c)  | (n)     | (n)      | (c) | (m/c) | (n)   | (c)          | (c)   | (m/c) | (n) |
| SPORADIC|      |      |         |          |     |       |       |              |       |       |     |
| 1       | –    | +    | h       | –        | –  | +/–   | –     | 1            | –     | –    | –   |
| 2       | –    | +    | h       | –        | –  | +/–   | –     | h            | –     | –    | –   |
| 3       | –    | ++   | h       | –        | +  | +     | –     | h            | –     | –    | –   |
| 4       | –    | +++  | h       | –        | ++ | h     | –     | –            | h     | –    | –   |
| 5       | –    | +++  | h       | –        | +  | –     | –     | h            | –     | –    | –   |
| 6       | –    | +++  | h       | –        | +  | –     | –     | h            | –     | –    | –   |
| FAP-ASSOCIATED| | | | | | | | | | | |
| 7       | –    | +++  | –       | –        | –  | –     | –     | 1            | +     | –    | –   |
| 8       | –    | +++  | 1       | –        | –  | –     | –     | 1            | +     | –    | –   |
| 9       | –    | +++  | h       | –        | ++ | h     | –     | –            | +     | –    | –   |
| 10      | –    | +++  | h       | –        | ++ | h     | –     | –            | –     | –    | –   |
| 11      | –    | +++  | h       | –        | +/–| h     | –     | –            | –     | +    | –   |
| 12      | –    | ++   | h       | –        | –  | +     | –     | 1            | +     | –    | –   |
| 13      | –    | ++   | l       | –        | –  | +/–   | –     | 1            | –     | –    | –   |
| 14      | –    | +++  | h       | –        | –  | –     | –     | h            | –     | –    | +   |
| 15      | –    | ++   | h       | –        | +/–| h     | –     | –            | h     | –    | –   |

(n) – nuclear positivity; (c) – cytoplasmic positivity; (m) – membranous positivity; – – negative staining; +/– – weak; focal staining; + – weak; diffuse staining; ++ – moderate positivity; +++ – intense positivity; h – high grade positivity (> 25% of positive tumor cells); l – low grade positivity (< 25% of positive tumor cells)

The staining intensity was evaluated only in markers with cytoplasmic staining pattern. In markers showing nuclear staining percentage of positive tumor cells was determined.
seems to play a role in DTF progression. Poon et al. [20] detected elevated COX-2 levels in aggressive fibromatoses together with reduced proliferation of tumor cells after COX-2 blockade resulting in smaller sized tumors in mice. COX-2 blockade is therefore a useful adjuvant therapy method to slow down tumor growth.

In general, DTFs are thought to be hormonally sensitive, because of their higher occurrence in women in their reproductive age. Recent studies are pointing toward the main role of ERβ, and not as believed earlier ERα in desmoid-type fibromatosis [21, 22]. Our results of hormone receptor immunohistochemistry show expression of ERβ in 93% of lesions, from which 73% were graded as high range (>25% of tumor cells) positivity. No expression of ERα nor PR were detected. Similar results were published by Santos et al. and Deyrup et al. [21, 23] showing 90% and 100% positivity of ERβ, respectively. Protein expression of ERβ was equal in sporadic and FAP-associated cases. No difference of ERβ expressions in relation to DTF location was identified.

Santti et al. [24] have found a trend in very high ERβ expression to predict a higher risk of relapse. In our recurrent cases primary biopsy samples demonstrated high range ERβ positivity, which decreased in the rebiopsy samples even to a complete loss of expression.

Data on the discordance of hormone receptor expression between primary and recurrent DTF are very limited, therefore the reasons of these phenomenon could only be hypothesized. In tumors, as breast cancer, possible mechanisms for the decrease or loss of hormone receptor expression in recurrent lesions are clonal selection or a genetic drift of tumor cells as well as treatment related effect. Our small number of recurrent DTF cases allow no clear conclusions, but these findings may point to a necessity of repeat-

| TABLE IV. Results of APC gene mutation screening |
|-----------------------------------------------|
| **PATIENT** | **APC GENE MUTATION** |
| **SPORADIC** | |
| 1 | Positive (c.637C>T, p.Arg213Ter) * |
| 2 | Negative |
| 3 | Negative |
| 4 | Negative |
| 5 | Negative |
| 6 | Negative |
| **FAP-ASSOCIATED** | |
| 7 | Positive (c.5803delc, p.Gln1935fs) |
| 8 | Positive (c.1620dupa, p.Gln541fs) |
| 9 | Positive |
| 10 | Positive |
| 11 | Positive (c.3183_3187delacaaa, p.Lys1061fs) |
| 12 | Positive |
| 13 | Positive (c.2621c>a, p.Ser874ter) |
| 14 | Negative ** |
| 15 | Positive (c.4390G>T, p.Glu1464ter) |

* patient without positive family history for FAP and without any clinical records of colon polyps
** patient with multiple colon adenomas and colorectal adenocarcinoma

![Fig. 4. β-catenin immunohistochemistry: A) nuclear positivity; B) cytoplasmic positivity. DAB, 200×](image-url)
ed biopsy and hormonal status evaluation in recurrent DTFs treated with hormonal therapy.

Hormonal therapy in DTF, which is non-selective for ERα and ERβ, is reported to be potentially useful, but so far not highly effective. However, the hormone expression profile of DTFs indicates to a potentially possible higher effectiveness of ERβ selective treatment.

About 80% of sporadic desmoid-type fibromatosis harbor mutations in the β-catenin gene (CTNNB1), while those occurring in the background of FAP often contain germ-line mutation in one allele and somatic mutation in the other allele of the adenomatous polyposis coli (APC) gene [25]. We found mutations of the APC gene in all DTFs from the FAP-associated group, except for one. This patient was diagnosed with Gardner syndrome and had multiple colon adenomas, a colorectal carcinoma, odontomas and multifocal DTFs. APC germline mutations can be found in the majority of FAP patients; however, there is a group of APC mutation negative patients who had an APC protein negative DTF. All other sporadic patients were missing APC gene mutations and had also APC protein negative DTFs.

Our results also show an intense expression of VEGF, the main signal protein of angiogenesis, well known for its role in the processes of metasizing and growth of different tumors. All DTF lesions demonstrated VEGF positivity in > 50% of tumor cells. DTFs with excess of collagen and hyalinization showed higher range of VEGF expression in comparison with hypercellular forms. In recurrent DTFs an increased VEGF expression was noted, but no difference between the sporadic and the FAP group was found. VEGF expression was also present in the endothelium of blood vessels, similarly, observed by Mills et al. [29], presenting this VEGF expression pattern as differing from non-neoplastic tissues. Matono et al. [30] demonstrated a correlation between widespread nuclear β-catenin expression and VEGF overexpression. Our findings did not confirm such correlation.

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