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Rewiev Article

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Aggressive Fibromatosis (Desmoid Tumors): Definition, Occurrence, Pathology, Diagnostic Problems, Clinical Behavior, Genetic Background

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Aggressive fibromatosis, usually called desmoid tumor develops from muscle connective tissue, fasciae and aponeuroses. This neoplasm is composed of spindle (fibrocyte-like) cells. As regards the site, aggressive fibromatoses can be divided into: extra-abdominal in the area of the shoulder and pelvic girdle or chest and neck wall; abdominal in abdominal wall muscles; intra-abdominal concerning pelvis, mesentery connective tissue or retroperitoneal space. Desmoid tumor is a neoplasm which rarely turns malignant and is non-metastasizing but demonstrates ability to local infiltration into tissue and is characterized by high risk of recurrence (25–65%) after surgical treatment. Desmoid tumor etiology is uncertain. This neoplasm occurs in sporadic (idiopathic) form and is also associated with some familial neoplastic syndromes. Most sporadic cases of aggressive fibromatosis contain a somatic mutation in either the adenomatous polyposis coli (*APC*) or -catenin genes. Sporadic tumors are more frequent in women than in men from 2 : 1 to 5 : 1. In about 10–15 per cent of patients with familial adenomatous polyposis (FAP), aggressive fibromatosis is a parenteral manifestation of this familial syndrome conditioned by *APC* gene mutation. Abdomen injury – most frequently due to surgery is said to play an important role in the initiation of fibrous tissue proliferative process in the cases of abdominal and intra abdominal forms. High cells growth potential with relatively high local malignancy is observed in about 10% of cases with sporadic tumors as well as in those FAP-associated.

Introduction

Fibromatosis is characterized by fibrous connective tissue proliferation. It is divided into superficial fibromatosis and aggressive fibromatosis (Table 1) [90].

Aggressive fibromatosis also called a desmoid tumor, is a mesenchymal neoplasm and develops from muscle connective tissue, fasciae and aponeuroses. Due to location, aggressive fibromatosis can be divided into several groups: **extra-abdominal** – in the area of shoulder and pelvic girdle, chest and neck muscles and in extremities; **abdominal** in abdominal wall muscles; **intra-abdominal** concerning small intestine mesentery connective tissue, pelvic or retroperitoneal space (Table 1). In addition, aggressive fibromatoses (deep) are further divided in accordance with the age of a patient into those that occur in infants and children under 5 (infantile fibromatosis) and those that occur in postpubertal individuals [38, 55, 90]. Aggressive fibromatosis (deep) is a neoplasm rarely presenting histological malignancy and lacks metastatic potential, but demonstrates the ability to local infiltration of tissues and is characterized by high risk of recurrence (25–65%) after surgical treatment [7, 41, 44, 57, 66, 70, 81, 84].

The risk of recurrence is governed less by the histological picture than by the anatomic location of the lesion, the patient's age, and the type of therapy [38, 70, 90]. The exact pathogenesis is unknown however, trauma, endocrine and genetic factors have been considered causative factors [2, 11, 16, 31, 41, 44, 46, 83, 88, 89]. This neoplasm

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TABLE 1
The classification of fibromatoses [90]

Fibromatosis
A. Superficial (fascial) fibromatoses
1. Palmar fibromatosis (Dupuytren's disease)
2. Plantar fibromatosis (Ledderhose's disease)
3. Penile fibromatosis (Peyronie's disease)
4. Knuckle pads
B. Deep (musculoaponeurotic) fibromatoses; aggressive fibromatosis
1. Extra-abdominal fibromatosis (extra-abdominal desmoid)
2. Abdominal fibromatosis (abdominal desmoid)
3. Intra-abdominal fibromatosis (intra-abdominal desmoid)
a) Pelvic fibromatosis
b) Mesenteric fibromatosis
c) Mesenteric fibromatosis in Gardner's syndrome

occurs sporadically, it is also associated with familial adenomatous polyposis (FAP). Sporadic desmoid tumors have been estimated to occur in 2–5 persons per 1,000,000 population per year. The female to male ratios of occurrence are from 2 : 1 to 5 : 1 [21, 22, 29, 31, 45, 53, 60].

Familial adenomatous polyposis is a hereditary neoplastic syndrome (numerous colorectal adenomatous polyps) which is conditioned by adenomatous polyposis coli (*APC*) gene mutation localized on chromosome 5 (5q21). The frequency of FAP is 1 : 7,500 and is autosomal dominantly inherited disease [14, 21, 29, 31, 60]. The data concerning the frequency of FAP-associated aggressive fibromatosis differ and are within the range from 10–15% [22, 70] to 8–38% [5]. In this group of patients aggressive fibromatosis is the second most frequent cause of death [22, 70]. The risk of developing desmoid tumors is 1,000 times higher in patients with FAP in comparison with the healthy population [22]. Aggressive fibromatosis also accompanies Gardner's syndrome in about 30% of cases. Gardner's syndrome with numerous colonic polyps and soft and hard tissue tumors, exhibits the incidence 1 : 14,000 and is inherited in autosomal dominating way [57, 79, 90].

Definition, Histogenesis of Aggressive Fibromatosis (Desmoid)

Aggressive fibromatosis, also called desmoid tumor, is a locally invasive but not metastasing soft tissue lesion composed of a clonal proliferation of spindle (fibrocyte-like) cells [3, 38, 55, 90]. Histologically it is composed of fibroblasts and myofibroblasts in a collagenous, often focally myxoid background. Aggressive fibromatosis is a mesenchymal neoplasm and develops from muscle connective tissue, fasciae and aponeuroses [38, 90, 92].

Initially described by McFarlane in 1832, the term desmoid (derived from the Greek *desmos* meaning tendon-like) was first introduced by Mueller in 1838. The term aggressive fibromatosis is sometimes employed to better describe the marked cellularity and aggressive local behavior of the lesions [81, 90].

Definition of Extra-Abdominal Fibromatosis

This is an infiltrating fibroproliferative process that develops in the soft tissues deep to the subcutaneous tissue and is composed of fibrocytes, fibroblasts, and myofibroblasts set within a collagenous to myxoid stroma that possesses uniformly bland nuclear features. Infiltration of skeletal muscle is so common as to be practically definitional [38]. Extra-abdominal fibromatoses are not infrequently multicentric [90]. The proliferations cannot be more than moderately cellular, and morphologically identical lesions arising in the abdominal wall, within the abdominal cavity, and in infants and children are excluded from the category [38].

Definition of Abdominal Fibromatosis

This is an infiltrating fibroproliferative process composed of fibroblasts and myofibroblasts with uniformly bland nuclear features, which develops deep to the subcutaneous tissue in the fascia and muscles of the abdominal wall, especially the rectus and internal oblique muscles and their fascial coverings [38, 90]. Infiltration of skeletal muscle is present in nearly all cases and the lesions cannot be more than moderately cellular. Identical tumors in extra-abdominal sites, within the abdominal cavity, and in infants and children are excluded [38].

Definition of Intra-Abdominal Fibromatosis

This category includes pelvic fibromatosis, mesenteric fibromatosis, and the fibromatosis of Gardner's syndrome [90].

Pelvic fibromatosis

Pelvic fibromatosis is a variant of abdominal fibromatosis, differing from the latter by its location in the iliac fossa and lower portion of the pelvis. As with fibromatosis of the abdominal wall, the tumor arises from the aponeurosis or muscle tissue. Grossly and microscopically the tumor is

indistinguishable from other forms of extra-abdominal or abdominal fibromatosis [90].

Mesenteric fibromatosis

Mesenteric fibromatosis is an infiltrating fibroproliferative process composed of fibroblasts and myofibroblasts with uniformly bland nuclear features [38]. Fibromatosis is the most common primary tumor of the mesentery. Most commonly, these tumors are located in the mesentery of the small bowel, but some originate from the ileocolic mesentery, gastrocolic ligament, omentum, or retroperitoneum [90]. Retroperitoneal fibromatosis may be located in the retroperitoneum, and then it is pathologically and clinically identical to pelvic and extra-abdominal fibromatosis. More commonly, fibromatosis in the retroperitoneum is an extension of mesenteric fibromatosis [38].

Mesenteric fibromatosis in Gardner's syndrome

Aggressive fibromatosis also accompanies Gardner's syndrome in about 30% of cases. The tumors arising in association with Gardner's syndrome were more likely to be multicentric, mesenteric, and smaller than those found in patients without polyposis [90]. Histologically this fibromatosis is virtually indistinguishable from those at other sites, and one cannot distinguish polyposis-related cases from sporadic cases by morphology alone. These tumors tend to have a prominent myxoid matrix [90].

Definition of Infantile Fibromatosis

Infantile desmoid fibromatosis is a fibrous proliferative process affecting individuals under the age of 10 years, in which the constituent cells vary from primitive mesenchymal cells to uniform fibroblasts/myofibroblasts set within a collagenous stroma. The process involves skeletal muscle and anatomically may be completely confined to that site [38].

Pathomorphology and Differential Diagnosis of Desmoid

Macroscopically desmoid tumors are hard fibrous lumps, typically infiltrating and adherent to the local tissue [38, 90]. Desmoid tumors also called aggressive fibromatosis are rare, slowly growing, histologically benign tumors. At a cellular level, they lack the nuclear and cytoplasmic features of malignancy and have no metastatic potential. Despite their benign appearance, they are locally aggressive and invade the surrounding structures, so sometimes they are classified as low-grade fibrosarcoma. The tumor infiltrates the surrounding tissue without forming a pseudocapsule. Histologically, desmoid tumors are composed of pale eosinophilic spindled, uniform fibroblasts and myofibroblasts with variably tapering or plump vesicular nuclei (Fig. 1). Cellularity and mitotic activity are extremely variable but rather scarce both within and between individual tumors. Some cases are remarkably hypocellular and hyalinized especially in children with a family history of FAP [38]. The growth pattern is characterized by broad elongated fascicles. The stroma is variably collagenous (keloid-like collagen foci and rich reticulin network) or focally myxoid (primarily abdominal form) and contains a varying number of thin-walled, elongated, compressed vessels [38]. Rarely, chondroosseus metaplasia or calcification may occur. Focal hemorrhages seen in fasciitis are not usual features of fibromatosis. At the advancing edge of the tumor, lymphoid aggregates and degenerated skeletal muscle are common. Tumor cells are generally actin positive and the extent of staining correlates positively with cellularity; desmin and S-100 protein also commonly stain a small minority of tumor cells [38, 90].

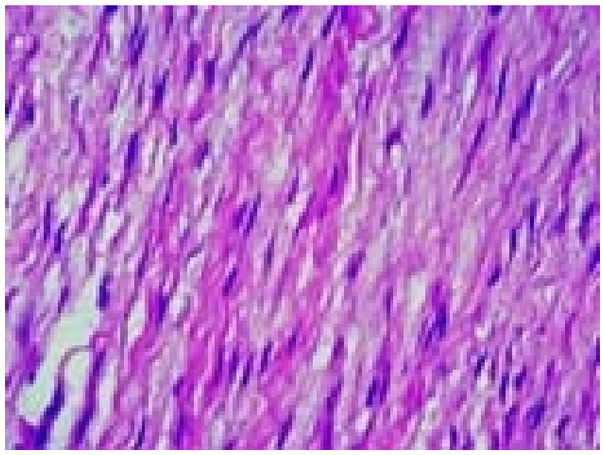

Fig. 1. Histological picture of desmoid. HE.

In the case of intra-abdominal location of desmoid, a group of gastrointestinal stromal tumors (GISTs) should be first of all considered in differential diagnostics (Table 2).

Moreover, differential diagnostics should include: fibrosarcoma, myxoma, nodular fasciitis as well as reactive proliferations of fibroblasts. Idiopathic retroperitoneal fibrosis (Ormond's disease) is a rare fibrosing reactive process that may be confused with mesenteric fibromatosis [32, 35, 90]. It is characterized by diffuse or localized fibroblastic proliferation and a chronic lymphoplasmacytic infiltrate in the retroperitoneum causing construction or obstruction of ureters, aorta, or other vascular structures [90]. Significant diagnostic problems may appear in case of evaluation of oligobiopsies of these tumors. Histoformativity and variable number of cells in various tumor regions may be the cause of diagnostic mistakes. Differentiation from fibrosarcoma may be particularly

TABLE 2
Selected elements from desmoid vs. GIST differential diagnostics [10, 47, 54, 56, 71, 90, 92]

Mean survival rate	DESMOID 5.3 years	GIST 2.2–5.4 years
Tumor biology	Local malignancy	Malignant
Macroscopic appearance		
consistency	hard	soft
structure	solid	lobar system
necrosis	no	yes
hemorrhages	no	yes
cystoid space	no	yes
Microscopic appearance		
growth type	infiltrating	expanding
histoformativity	alternating bundles	organoid
myxoid structures	no	yes
stroma structure	collagenous stroma	hyalinized stroma
Microscopic appearance (cytology)		
cells form	spindle	spindle and/or epithelioid
monomorphism/polymorphism	rather monomorphism	polymorphism
nuclear atypia	no	yes
Proliferation		
mitoses	4 mitoses/50 HPF*	15 mitoses/50 HPF*
Immunohistochemistry (antibodies)		
CD117	++/–	+++
CD34	–	++/–
S–100	–	+/–

* HPF – high power fields

difficult [10, 33, 51, 56, 62, 81, 95]. At present, attempts are undertaken to search for genetic markers helpful in diagnostics and prediction in regards to clinical course and prognosis of soft tissue tumors [65].

Aggressive Fibromatosis Problems

Basing on the survey of the cited literature [4, 8, 9, 21, 41, 44, 68, 70, 70–73, 78, 81] the following problems of aggressive fibromatosis have been noted:

– aggressive fibromatoses located in various parts of the body differ in biological behavior;
– there is individual variability in aggressive fibromatosis development dynamics and progression;
– in patients with aggressive fibromatosis, particularly in those with intra-abdominal forms concerning mesentery or retroperitoneal space there occur serious problems with early diagnostics as well as with surgical treatment and/or radiotherapy;
– patients with intra-abdominal location of neoplasms are characterized by relatively high local malignancy and high mortality;
– the histological examination alone does not permit accurate prediction of the clinical course. In practice prognostication is based on the tumor location, size and clinical course;
– there is lack of morphological features and biological markers e.g. immunohistochemical and cytogenetic (FISH), related to tumor cell growth potential and prognosis.

Tumor Location

Aggressive fibromatosis – sporadic tumor

Aggressive fibromatosis not associated with FAP (sporadic, idiopathic) occurs most frequently in the region of shoulder girdle, axilla, trunk muscles (chest wall, chest muscles), neck – mainly nape, pelvic girdle, thigh and knee joint. Tumors located in abdominal wall are most often perceptible in the vicinity of surgical scars. About 10–30% of cases of sporadic tumors located in abdomen could be associated with surgery (on average 4 years after the procedure) [1, 38, 41, 50, 55, 90]. In about 10% of cases aggressive fibromatosis is located in small intestine mesentery and retroperitoneal region [9, 44, 46, 70, 72, 73]. Intra-abdominal aggressive fibromatosis located in small intestine mesentery or retroperitoneal region is often of multifocal and tumor-like character [70, 90].

FAP-associated aggressive fibromatosis

About 50–70% of desmoid tumors associated with FAP have intra-abdominal location – most frequently in small intestine mesentery and retroperitoneum [9, 22, 53]. About 27–48% of tumors are located in abdominal wall, first of all in the direct vicinity of surgical scars. Only 2–9% of tumors have extra-abdominal location [4, 70, 72]. In patients with FAP, in about 25% of cases desmoid tumors were observed before surgery on bowels. In about 55–75% of these patients, tumor occurrence most frequently could have been associated with surgery, which had taken place 1–5 years (mean 2 years) earlier [21, 22, 70, 72]. About 10% of FAP-associated desmoid tumors demonstrate very aggressive growth [70].

Tumor Size

At the time of establishing the diagnosis desmoid tumors demonstrate very varied size. Tumors located in the chest wall, neck and extremities may be detected in natural way and subjected to early diagnostics and treatment, and thus they do not reach considerable size. A tumor with intra-abdominal location is often detected accidentally on laparotomy or on abdominal CT or MRI [70, 72]. The results of studies and descriptions of the cases presented in literature concerned desmoid tumors of different location and size from 5 to 25 cm [38, 70, 90]. Most examples of extra-abdominal fibromatosis are large, with an average size of 5 to 10 cm [38]. Abdominal fibromatosis tends to be smaller when discovered than extra-abdominal fibromatosis; with average size of 3–7 cm [38]. In majority of reports, the tumors located in mesentery or retroperitoneal region were 5–15 cm in diameter during the first diagnosis [38, 70].

Clinical Behavior

The process of aggressive fibromatosis (AF) development and progression is not homogeneous. The behavior of desmoid tumor cells growth is variable and comprises cases from macroscopically visible mesenteric lesions to accidentally detected sporadic and FAP-associated tumors exhibiting high cell growth potential with potentially high local malignancy and resulting high mortality [11, 70, 73].

Clinical problems concern evaluation at proper time of growth potential of tumor cells collected from each patient, or more seldom cells collected from several tumors occurring in the same patient. This may be difficult, as each desmoid tumor occurring in the same patient can exhibit different growth potential and can divergently react to therapy [70].

Extra-abdominal fibromatosis can occur at any non-abdominal site, but the most commonly involved areas are the shoulder girdle and upper arm, the thigh, the buttock, and the trunk. Around 10% occur in the head and neck area [38, 90]. The majority of patients are between the ages of 15 and 45 years at the time of diagnosis [38]. Children are sometimes affected. Childhood AF has an age distribution peak at approximately 8 years (range, 0–19 years) with a slight male predominance [19]. Women are more commonly affected than men [70, 90]. In abdominal fibromatosis approximately 70–90% of cases occur in women during the reproductive years; the majority of these patients are of 20–30 years [38]. Location inside the rectus muscle sheath is most common. Some abdominal desmoids develop in scars, for example, those after a cesarean section [55]. As with fibromatosis of the abdominal wall, the pelvic tumor arises from the aponeurosis or muscle tissue and occurs chiefly in young women, 20–35 years of age [90]. The age of patients with mesenteric fibromatosis varies from 10 to 80 years, with a mean of 40 years [38].

Although FAP-associated and sporadic aggressive fibromatoses concern subjects at any age, the highest incidence has been observed at the age of 28–34 years [22, 44, 72]. On the other hand, sporadic tumors located in the retroperitoneal region were more frequent in females at perimenopausal age [4, 11, 31]. Gender in correlation with age is one of the risk factors of tumor aggressive growth potential. The tumor aggressive growth was observed more frequently in women aged 55–59 years than in younger or older or in males [22, 70, 72]. Gardner's syndrome is more common in women than in men and is usually diagnosed in adults of 25–35 years [90]. Patients who have Gardner's syndrome have a higher risk of recurrence and complications including some tumor-related mortality, mainly due to intestinal obstruction or postsurgical short bowel syndrome [55].

In desmoid tumors, variety of clinical behavior is characterized by three most important features [70]:
– size (diameter) of the tumor as indicator of already present growth;
– degree of tumor diameter doubling (expansion), enabling to evaluate present biological growth potential;
– location, because clinical course dependently on location should be evaluated in different way.

In case of tumor progression, particularly of that with intra-abdominal location, increasing tumor mass and infiltrating character of tumor cells growth to surrounding tissues and organs lead to a number of complications e.g. intestinal obstruction, perforation, fistula formation, ureter obstruction or neural involvement. Dependently on the "initial point" and tumor growth rate in intra-abdominal location, infiltration of other organs may occur: kidneys, adrenal glands, pancreas, spleen, external gastric wall, liver hilus and lobes, retroperitoneal region vessels and pelvic minor organs [4, 9, 22, 53, 70, 85].

The suggested "DES classification" (Table 3) may be useful, similarly to TNM classification in case of malignant tumors, for the interpretation of the clinical course and undertaking various therapeutic options as well as for standardizing descriptions given by research teams [70]. For example, 8 cm abdominal wall tumor, which within the period of last 5 months doubled its size would be classified as D2E4S2 (Table 3).

Treatment

Unexplained etiology and different location make desmoid tumors treatment extremely difficult. At present, there is no a definite and effective method of treatment [9, 49, 66, 68–70, 73, 81, 85]. Current therapeutic methods in the management of aggressive fibromatosis are far from satisfying [3].

Surgery

Most frequently, wide surgical excision with the margin of clean tissues (2–3 cm), what sometimes is impossible, remains the principle therapeutic maneuver. There are also opinions that tumor excision should be less radical, only to improve functioning of the tumor affected organ [1, 8, 70, 73, 84]. High recurrence rate after surgery and observation of occurrence of intensified aggressiveness of growth after these procedures led to more conservative therapeutic management [21, 70, 84]. After operative treatment of sporadic desmoid tumors, the recurrence rate was 16–40%, while after FAP-associated aggressive fibromatosis, the rate was 57–85% [70, 91]. Total tumor resection is an optimal therapy in case of tumors (primary or recurrent) of extra-abdominal or abdominal wall location. In the case of intra-abdominal location – the authors emphasize that surgical procedures should be reserved to cases of complicated course, e.g. by intestinal or ureter obstructions [22, 41, 49, 70]. Total resection of mesenteric desmoids, infiltrating mesenteric vessels is associated with excessive blood loss during surgery and high postoperative mortality (10–60%) [22].

Other methods of treatment

Non-surgical methods, such as application of antiestrogenes nonsteroidal anti-inflammatory drugs, chemotherapeutic agents, do not have precise justification, as the results of these methods application are based on limited clinical material. However, it should be emphasized that in individual cases favorable response (complete or partial) to combined pharmacological treatment and/or radiotherapy was observed, manifesting itself with tumor progression inhibition [9, 43, 67, 69, 73, 91]. Sometimes beneficial "biologic behavior'' of the tumor is observed – idiopathic tumor regression [70]. It should be emphasized once more, that nearly after all kinds of therapy, marked recurrence rate is observed. All this proves that at presence there is no effective method of desmoid tumors treatment [9, 22, 70, 73].

TABLE 3
Suggested clinical classification of desmoid tumors (**DES**moid) [70]

Grade	**D** (diameter in cm)	**E** (expansion) Degree of tumour diameter doubling (months)	**S** (location)*
0	Minimal desmoid lesion	Unknown at first diagnosis	Unknown
1	< 5	> 24	E
2	5–10	12–24	AW
3	10–20	6–12	M1
4	> 20	1–6	M2

* Location: E – extra-abdominal; AW – abdominal wall; M1 – mesentery without obstruction; M2 – mesentery with obstruction

Radiotherapy

Radiotherapy in a dose 50 to 60 Gy fractions or brachytherapy were beneficial only in some cases – including those after partial resection of the tumor. The dose lower than 50 Gy prognosticates little efficacy [66, 68, 73]. Radiation is most frequently applied in case of tumor recurrence or in patients with R1 or R2 resection [70]. Radiotherapy of aggressive fibromatosis in intra-abdominal location is carried out only occasionally [7, 70, 73].

Drug therapy

As it has already been mentioned, there is a problem with the analysis of the effects of pharmacotherapy connected with desmoid tumor growth, resulting from small number of treated patients, therapy combined with various drugs and the difference in the natural course of tumor development in particular patients [8, 22, 41, 70]. Basic group of drugs applied in aggressive fibromatosis treatment includes [9, 67, 69, 73, 74, 80, 91]:

1. Cytostatic agents: e.g. doxorubicin, vincristine, vinblastine, methotrexate, cyclophosphamide, dactinomycin and others.
2. Hormonal drugs: toremifen, tamoxifen (nonsteroidal anti-estrogens), goserelin (agonist analog of gonadoliberin), medroxyprogesterone.
3. Non-steroid anti-inflammatory drugs: indomethacin, sulindac.
4. Anti-viral preparations: interferon- and - .

Genetics Background

Desmoid tumors are benign mesenchymal tumors characterized by monoclonal proliferation of spindle (fibroblast-like) cells [2, 41, 46, 55, 81]. These neoplasms rarely undergo histological malignant transformation – most frequently into fibrosarcomas [33, 61]. However, they demonstrate ability to aggressive infiltration of the surrounding tissues and are characterized by high risk of recurrence after surgical treatment [22, 57, 70]. Etiology of idiopathic aggressive fibromatosis, not FAP-associated is not well defined. Surgical trauma, radiation, hormonal stimulation (estrogens, progesteron) may be the factors initiating fibrous connective tissue cells growth process [4, 20, 44, 46, 70, 81]. Development of neoplastic process has been emphasized not to be connected with excessive proliferation of normal fibroblasts stimulated with endogenic factors e.g. TGF-beta [2, 3, 30].

Most sporadic cases of aggressive fibromatosis contain a somatic mutation in either the adenomatous polyposis coli (*APC*) or -catenin genes, resulting in -catenin protein stabilization [2, 46, 87, 89]. *APC* gene is located on chromosome 5q21 and consists of 15 exons [29, 48, 64]. The APC protein (312 kDa) is multifunctional (e.g., the cell migration and apoptosis) and its primary role appears to be linked to the breakdown of -catenin *via* ubiquitin degradation pathway [36, 37]. The APC plays an essential role in clearing unnecessary -catenin from the cytoplasm. -catenin acquires oncogenic activity when it is mutated or when it is up-regulated as a result of inactivation of APC. The APC competes with E-cadherin for binding to -catenin [13, 15, 34, 64, 86].

-catenin gene (*CTNNB1)* is located on chromosome 3p21 [37]. -catenin protein (92 kDa) has a nuclear function (binds transcription factors with the Tcl-Lef family) and a cell membrane function. -catenin can complex with other molecules and contains binding sites for -catenin, APC and E-cadherin [37, 39, 59, 82]. Cytoplasmic -catenin is an effector protein of the Wnt signaling cascade. In normal cells, intracellular -catenin is kept at low levels and is mainly regulated by degradation, which is probably initiated by interaction with APC protein [20, 87]. Abnormal nuclear localization of -catenin and its association with Tcl-Lef have been proposed as an important oncogenic step in various benign and malignant fibroblastic and myofibroblastic tumors [12, 20].

APC gene mutation in somatic cells is said to play an important role in the development of aggressive fibromatosis sporadic tumors [3, 31]. Thus, in case of sporadic tumors *APC* gene mutation is found only in tumor cells DNA. Alman et al. [3] searched for mutations in exon 15 of *APC* gene in sporadic tumor cells in 6 patients. In 3 of them somatic mutations were detected in exon 15 codons 1324, 1331 and 1493. Giarola et al. [31] found somatic mutations of *APC* gene (exon 15) in sporadic tumors in 2 of 16 examined patients.

As it has been mentioned earlier, genetic predisposition to aggressive fibromatosis is connected with *APC* gene germline mutation (FAP syndrome) and in Gardener's syndrome [4, 11, 21, 22, 29, 53]. In desmoid tumor cells in patients with FAP, mutation was found most frequently in both *APC* gene alleles. In this case, in accordance with Knudson's hypothesis the mutation is inherited in one allele and then there occurs somatic mutation in the second *APC* allele [3, 60].

Germline mutations of the *APC* gene in patients with FAP-associated aggressive fibromatosis were mainly found in exon 15 between codons 1444 and 1581 in the mutation cluster region (MCR) [29]. Mutations occurring in this region of *APC* gene result in truncated APC protein [3, 11, 22].

Immunohistochemical examinations with the use of antibodies against C-terminal of APC protein in 6 cases of desmoid tumors in extremities demonstrated: in 4 cases the presence and in 2 lack of positive reaction to APC protein [3]. In the studies of the same authors [3] the results of *APC* gene exon 15 sequencing exhibited mutations leading to preterm stop/codon in 3 of 6 cases. *Western blotting* analysis (reaction protein/antibody) demonstrated increased level of -catenin protein in the cells of all 6 cases of the analyzed tumors in comparison to adjacent to tumors normal fibrous tissue. However, *Northern blotting* analysis (reaction of hybridization cDNA/RNA) showed similar levels of mRNA for -catenin in tumor cells as well as in adjacent to tumors normal fibrous tissue. According to these authors increased level of -catenin in tumor cells without elevated mRNA level suggests decreased -catenin degradation in these cells as compared to normal cells [3]. Increased -catenin level may be also caused by -catenin gene mutations, which disturb normal structure and degradation of this protein [83].

With the help of immunohistochemical method the difference was observed in the site of -catenin localization in desmoid cells as compared to cells of normal fibrous tissue adjacent to the tumors. In tumor cells -catenin was localized in a dispersed form, while in normal fibrous tissue peripherally [3, 12]. Shitoh et al. [83] observed for the first time a case of -catenin gene mutation in codon 44 – change of ACC (Thr) to GCC (Ala) in desmoid tumor cells, which was located in subclavicular region. Immunohistochemical examination demonstrated -catenin location mainly in tumor cells nuclei.

Recent reports have demonstrated that E-cadherin and its cytoplasmic binding proteins: the catenins (,) and APC protein, are essential for intercellular junctions; their decreased expression correspond to poor prognosis associated with the dissemination of tumor cells and formation of metastases [15, 34, 76]. Alman et al. [3] concluded that the quantity and protein content of junctions differ between cell types, with fibrocytes having a smaller number as compared with colonocytes, containing N-cadherin rather than E-cadherin.

Muller et al. [63] investigated pRb and P53 expression on protein levels with immunohistochemical method in 13 cases of aggressive fibromatosis and in 6 cases of superficial fibromatosis in the palmar region. In superficial fibromatosis the presence of pRb was found in the nucleus while in aggressive fibromatosis nuclear localization of pRb was not observed. According to these authors [63] decreased pRb expression in aggressive fibromatosis may result from cell growth disturbances or from increased proliferation. P53 was not detectable in either of the fibromatoses [63].

Cyclin D1 protein (32 kDa) plays a major role in the control of the cell cycle, especially in G1 to S phase transition. The cyclin D1 gene (*CCND1/PRAD1*) was localized to chromosome 11q13, amplified or rearranged in several types of human neoplasms [27]. Saito et al. [77] stated with the use of immunohistochemical method positive correlation between -catenin nuclear expression and cyclin D1 overexpression in sporadic desmoid tumors. No significant difference was found between cyclin D1 gene amplification and overexpression of cyclin D1 protein in these cells [77].

The extracellular matrix environment plays an active role regulating cell proliferation and invasion during wound healing as well as in tumor progression. The accumulation and degradation of one extracellular matrix component, the polysaccharide hyaluronan (HA), regulate the extent of fibrosis in adult wounds, and enhance accumulation of HA. It is a part of connective tissue desmoplastic reaction that is associated with poor outcome in several human cancers [6, 26, 30, 89]. Overexpressing HA synthases, or adding purified HA *in vitro*, promotes tumor cell proliferation and invasive/metastatic properties, suggesting a role for this polysaccharide in neoplastic progression [89]. One of HA-binding proteins is Rhamm (receptor for hyaluronic acid-mediated motility) primarily associated with cell motility [26]. There are now several HA-binding proteins that resemble Rhamm/HMMR/IHABP/CD168 by commonly occurring within the intracellular, extracellular and cell surface compartments [89]. Tolg et al. [89] suggested that Rhamm regulates proliferation of cells with sparse cell-cell contact, such as occurs in aggressive fibromatosis. These authors found that the genetic deletion of *Rhamm* significantly reduces the number and size of fibromatosis, arising as a result of *APC* mutation, providing genetic evidence for a role of this HA-binding protein in tumor pathology [89].

Analysis of the chromosome aberrations in desmoid tumor

The identification of chromosomal aberrations in desmoid tumors is based on karyotype analysis, CGH (comparative genomic hybridization) and FISH (fluorescent *in situ* hybridization) methods. For the karyotype analysis the biopsy is taken, tissue cultures are harvested and slides containing metaphase cells are banded with GTG method. Desmoid tumors are rare therefore the analysis almost exclusively has to be performed on archival material. The big advantage of molecular cytogenetic methods such as CGH and FISH is the possibility to analyze chromosomal aberrations in non-dividing cells present in formalin fixed and paraffin-embedded tissue sections.

Many clonal chromosomal aberrations were observed in desmoid tumors short-term tissue cultures [52, 58], however trisomies of chromosome 8 [16, 24, 75] and chromo-

some 20 have been described as the most frequently found in the karyotype [52, 75].The presence of additional chromosome 8 has been associated with an increased risk of recurrence and more aggressive clinical behavior [28, 40]. Loss of chromosome Y was found in tumor cells from males [17]. Larramendy et al. [42] reported gain of band 1q21 as the most frequent aberration found by CGH method. In patients with Gardner's syndrome and familial adenomatous polyposis the abnormalities of 5q resulting in the deletion of the 5q21-22 region were reported in many cases [25, 93]. There is a discrepancy between classical cytogenetic and molecular cytogenetic studies of desmoid tumors concerning chromosome 8. In many published cases additional copy of chromosome 8 was not detectable by karyotype analysis or it was found only in the minority of the analyzed cells, while it was observed at much higher frequency using the FISH method [18, 24, 28]. This discrepancy has been explained by the presence of diploid cells (like fibroblasts, vascular elements or skeletal muscle) in the tumor tissue that grow preferentially in short-term culture and obscure the trisomy 8 population cells [28]. If it is only possible different cytogenetic methods should be combined. In the analysis methods like CGH array [85] should soon expand cytogenetic knowledge on desmoid tumors.

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