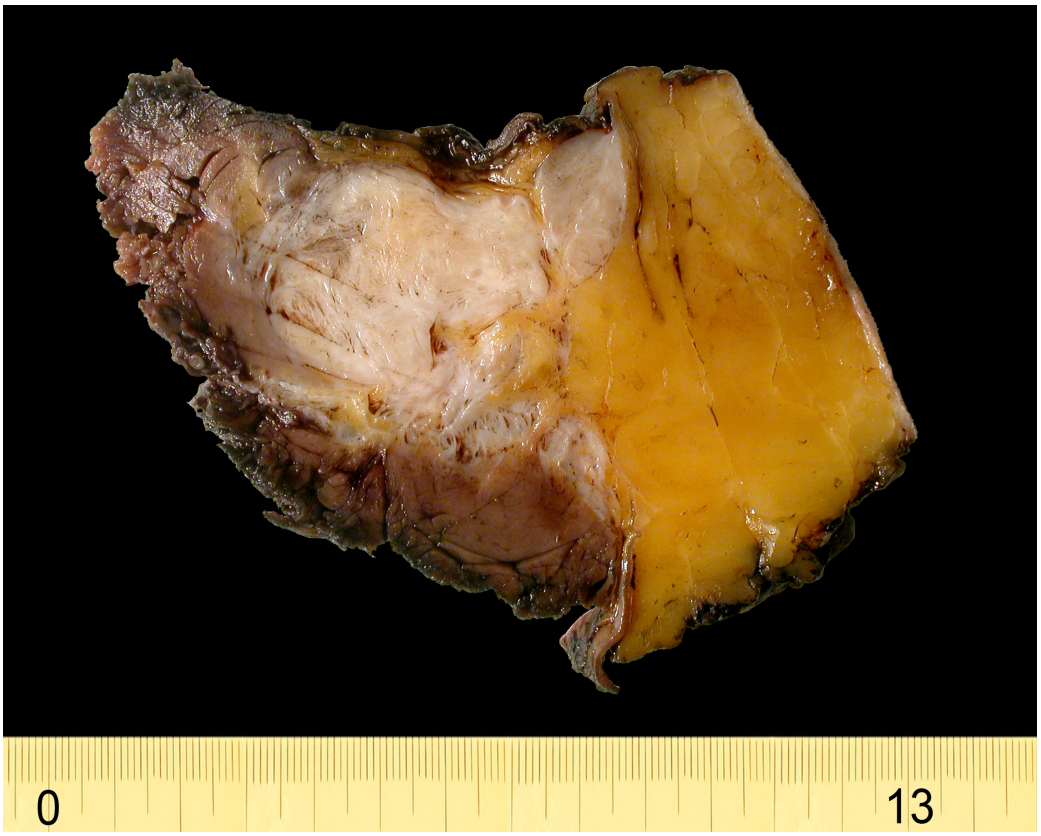

Therapy of infantile digital fibromatoses and desmoid tumors in children and adolescents

Lukas Fraissler

Diplomarbeit

Therapy of infantile digital fibromatoses and desmoid tumors in children and adolescents

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Graz, im Juni 2009 *Lukas Fraissler*

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Zusammenfassung

Titel: Therapie der infantilen digitalen Fibromatose und der Desmoidtumore bei Kindern und Jugendlichen

Hintergrund: Kindliche Fibromatosen können sich verschiedenartig präsentieren. Auf Grund ihrer hohen Rezidivrate von bis zu 60% und 88%, stellen die infantile digitale Fibromatose (IDF) und die Fibromatose vom Desmoid-Typ oder auch aggressive Fibromatose (AF) eine besondere Herausforderung dar. Einige Autoren empfehlen eine abwartende Haltung in der Therapie der IDF, andere die chirurgische Entfernung. Trotz verschiedener Therapieansätze bleibt die Neigung zu lokalen Rezidiven. Andere Publikationen machten auf den möglichen Zusammenhang immunhistochemischer Marker und Therapieerfolg aufmerksam.

Ziel: Ziel dieser Arbeit ist das klinische Verhalten kindlicher Fibromatosen zu untersuchen und mittels immunhistochemischer Marker potentielle Angriffspunkte einer pharmakologischen Therapie zu evaluieren.

Patienten und Methoden: Insgesamt wurden neunzehn Patienten mit AF und drei Patienten mit IDF in die Studie inkludiert. Die Altersgrenze wurde bei 20 Jahren festgelegt. Das durchschnittliche Alter bei Diagnose betrug 6.3 Jahre (Range 0 bis 17 Jahre). Wir evaluierten Resektionsränder, pharmakologische Therapie, Rezidive und immunhistochemische Marker (Östrogenrezeptoren α und β, Progesteron- und Androgenrezeptoren, Somatostatin, Ki-67, c-kit, PDGF-Rezeptoren α und β und β-catenin).

Ergebnisse: Das durchschnittliche Follow-up betrug 112 Monate (Range 2 bis 251 Monate). Zwei der drei Patienten mit IDF und vier der 19 Patienten mit AF zeigten ein Rezidiv nach einem durchschnittlichen krankheitsfreien Intervall von 21 bzw. 55 Monaten. Wir fanden keinen Zusammenhang zwischen Markern und Rezidiven.

Diskussion: Obwohl die Fibromatosen vom infantil-digitalen Typ primär eine hohe Rezidivrate aufwiesen, traten trotz R1/2-Resektionen keine weiteren Rezidive auf. Auch schien die Art der Resektion (R0 oder R1/2) der Desmoidtumore in dieser

Altersgruppe im Gegensatz zu Desmoidtumoren bei Erwachsenen keinen Einfluss auf die Rezidivrate zu nehmen. Auf Grund der Heterogenität des Therapiemanagements ist eine Aussage betreffend Vorgehen nicht möglich. Wir empfehlen eine weite Exzision des Primärtumors. Ist dies nicht möglich ist ein „wait-and-see“ Management das Vorgehen der Wahl.

Abstract

Title: Therapy of infantile digital fibromatoses and desmoid tumors in children and adolescents

Background: Several types of fibromatoses can occur in children and adolescents. Because of their high recurrence rates of up to 60% and 88%, infantile digital fibromatosis (IDF) and desmoid-type fibromatosis (AF) especially pose a challenge to the attending physician. While some authors suggest a “wait and see” policy for IDF, others recommend surgical excision. First choice treatment of AF still remains wide or radical resection whereas little is known about non-surgical treatment. Despite non-cytotoxic and cytotoxic therapy there’s still a tendency toward local recurrence.
Other publications showed possible correlations between immunohistochemical markers and therapy of IDF and AF.

Objective: To analyse clinical appearance and immunohistochemical patterns of infantile fibromatoses and to evaluate possible pharmacological treatment.

Patients and Methods: Nineteen patients with AF and three patients with IDF were included. The age limit was set at 20 years. Mean age at diagnosis was 6.3 years (range 0 to 17 years). We evaluated margins at resection, medical treatment, time of recurrence, as well as immunohistochemical markers (estrogen receptor α and β, progesterone and androgen receptors, somatostatin, Ki-67, c-kit, platelet-derived growth factor α and β and β-catenin).

Results: The mean follow up was 112 months (range 2 to 251 months). Two of three patients with IDF and four of 19 patients with desmoid-type fibromatosis showed recurrences after a mean time of 21 and 55 months. There was no correlation between positive immunohistochemical markers and tumor recurrences detectable.

Conclusion: Despite high primary recurrence rates and R1/2 resections, infantile digital fibromatoses showed no more recurrences. Type of resection (R0, R1/2) of desmoid tumors did not influence recurrence rate. In conclusion desmoids seem to behave in a different way in children and adolescents than in adult patients.

The heterogeneity of treatment made it impossible to give a statement about therapy management. Therefore, we again state that only a large, prospective, randomized trial could really provide an answer for the efficacy of any adjuvant treatment.
Nevertheless we recommend wide excision of primary desmoid tumors as treatment of choice. If an appropriate resection is not possible or associated with a high morbidity a wait-and-see policy might be indicated.

Contents

1. Introduction

1.1 Fibromatoses

Fibromatoses are a group of benign and intermediate (locally aggressive) fibrous tumors with similar microscopic features and a variable behavior between benign fibrous lesions and fibrosarcoma. Characteristics are infiltrative growth, a tendency to local recurrence and their inability to metastasize. Fibrous tumors occur predominantly in adults as firm, non-encapsulated, poorly circumscribed nodules, appear solitary or multiple and have a predilection for certain anatomical regions [1, 2]. Superficial fibromatoses arise from the fascia or aponeurosis. They grow slowly and are small of size. In contrast deep (desmoid-type) fibromatoses are rapidly growing and can attain a large size. In comparison to their superficial counterpart they involve deeper structures, tend to be more aggressive and have a higher recurrence rate [3, 4]. According to Enzinger and Weiss these major groups of fibrous tumors are classified as shown in table 1 [1]. However, this classification is not helpful regarding tumors in children and adolescents, because these superficial entities usually do not occur in this age group while deep fibromatoses equate to the infantile desmoid tumors.

Classification of fibromatoses
I. Superficial (fascial) fibromatosis
A. Palmar fibromatosis (Dupuytren's disease)
B. Plantar fibromatosis (Ledderhose's disease)
C. Penile fibromatosis (Peyronie's disease)
D. Knuckle pads
II. Deep (musculoaponeurotic) fibromatosis
A. Extraabdominal fibromatosis
B. Abdominal fibromatosis
C. Intraabdominal fibromatosis
1. Pelvic fibromatosis
2. Mesenteric fibromatosis
3. Mesenteric fibromatosis in Gardner's syndrome

Table 1. Classification of fibromatoses [1]

1.2 Fibrous tumors of infancy and childhood

Non-malignant fibrosing tumors and fibromatoses in pediatrics are clinically challenging because of their infrequent occurrence and variety of names associated with these conditions. Weiss et al. classified these entities of fibrous tumors of infancy and childhood as shown in table 2 [5]. According to the World Health Organization (WHO) Classification of tumors of soft tissue and bone these entities are belonging to the group of fibroblastic/ myofibroblastic tumors [2].

	Age	Location	Rec	Reg
Fibrous hamartoma	B – 2	Axillary and inguinal region	Rare	-
Myofibromatosis	B – A	Soft tissue, bone, viscera		+
Fibromatosis colli	B – 2	Sternocleidomastoid muscle		+
Digital fibromatosis	B – 2	Fingers and toes	Common	+
Infantile (desmoid-type) fibromatosis	B – 4	Musculature		-
Calcifying aponeurotic fibroma	2 – A	Hands and feet		+
Hyaline fibromatosis	2 – A	Dermis and subcutis	-	-

Table 2. Fibrous tumors of infancy and childhood [5]

1.2.1 Fibrous hamartoma

Fibrous hamartoma (FH) is a rare, benign, subcutaneous fibrous lesion usually detected during the first 2 years of life. About 15 to 20% of the cases of FH are present at birth. FH is a solitary condition, characterized by initial rapid growth, occurring with a predilection for certain anatomical sites as limbs, trunk, the sacral region and scrotum. This tumor does not cause pain and is usually treated by complete local excision with a low recurrence rate of less than 15% [6, 7].

1.2.2 Myofibromatosis

Myofibromatosis affects particularly infants and younger children. Chung et al reported that 88% of cases were diagnosed before the age of 2 years, and 60%

were recognized at birth or shortly thereafter [8]. This fibrous tumor may manifest as a solitary or multicentric lesion. The solitary form arises predominantly in soft tissues of the head-neck region and the trunk. In contrast, the multicentric type was found not only in soft tissues but also in bones and viscera. Prognosis ranges from spontaneous regression to recurrences and even death of disease due to extensive involvement of multiple viscera. Treatment varies from observing a possible regression of a solitary tumor to surgical excision, radiotherapy, and chemotherapy, especially for unresectable, progressive, or symptomatic lesions [8-11].

1.2.3 Fibromatosis colli

Fibromatosis colli is an infrequent fibrous condition that manifests in the sternocleidomastoid muscle during the first 2 months of life. Chiefly affected by this rapidly growing mass is the lower part of the sternocleidomastoid muscle. The tumor then becomes stationary and finally regresses. Occasionally some patients develop torticollis by reason of tumor growth, others evolve muscle contraction when the mass already has disappeared. Surgical treatment is only used in few patients [1, 12].

1.2.4 Calcifying aponeurotic fibroma

Calcifying (juvenile) aponeurotic fibroma (CAF) is a rare benign type of fibrous tumors and occurs mainly in young patients under 20 years of age. Clinical presentation is a hard and painless tumor of the palm or sole. CAF shows histological features of a malignant fibroblastic proliferation, with areas of calcification and chondroid differentiation, as well as a recurring and aggressive growth pattern. State-of-the-art treatment is wide excision of the mass with function preservation. Radical surgery is mainly not necessary even for recurrences [13-15].

1.2.5 Hyaline fibromatosis

Last entities discussed are the hyaline fibromatosis syndromes. The etiology is unknown. Accumulation of amorphous hyaline material leads to two clinically distinct syndromes: infantile systemic hyalinosis (ISH) and juvenile hyaline fibromatosis (JHF). Characteristics of ISH and JHF are papular and nodular skin lesions, gingival hyperplasia, joint contracture and various degrees of bone lesions. In both lesions the skin is thick and stiff and indurations are specifically evident over joints. While motor development usually is affected, mental development is normal. ISH additional involve viscera (intestinal, cardiac, hepatic, splenic, thyroidal) and patients affected die in early childhood [16-18].

1.3 Infantile digital fibromatosis

1.3.1 Definition

Infantile digital fibromatosis (IDF) also called inclusion body fibromatosis, was first described by Reye in 1965 [19]. It is a fibrous tumor of infancy and childhood which exclusively occurs in fingers and toes. Characteristics of IDF are inclusion bodies within the cytoplasm of the proliferated fibroblasts, the tendency to recur locally and the inability to metastasize [5, 20].

1.3.2 Epidemiology

IDF is a very rare, non-malignant condition, representing 0,1% of the fibromatoses in children [21]. In 1995 approximately 100 case reports of this entity were described in literature [22]. Recently in 2009, Laskin et al. presented a study of 57 patients with IDF [23].

1.3.3 Etiology

The etiology of IDF still remains unclear. Some authors suggested a viral genesis [21]. A study looking for human papilloma virus DNA (HPV types 6, 11, 16, 18) and herpes simplex virus DNA (types 1 and 2), however, describes no association with IDF [24].

Few authors hypothesized that in some cases of patients with digital fibromas, metatarsal and metacarpal defects, and facial pigmentary abnormalities (digitocutaneous dysplasia syndrome) a genetically transmittable syndrome is present [25-29].

1.3.4 Clinical findings

The myofibroblastic nodules, which develop exclusively in the digits of hands and feet, are hemispherical with a smooth glistening, pale red or skin colored surface. They are more often found in fingers than in toes and in all cases thumbs and

great toes are spared. Although they are usually small and rarely exceed 2 cm in greatest diameter, the nodules are nearly always noted during the first year of live. The tumor occurs as a single lesion or multiple, often affecting more than one digit of the same hand or foot. Sometimes fingers and toes of the same patient are involved, but they are very rare outside the hands and feet [5, 30].
Usually the nodules do not cause discomfort or pain, even if they have been present for several months prior to excision. In some cases associated functional impairment and joint deformities were noted [5].

1.3.5 Histopathological findings

This intradermal non-encapsulated tumor is composed of spindle cells arranged in whorls or interdigitating sheets (see figure 1). The characteristic eosinophilic intracytoplasmic inclusion bodies distinguish IDF from other fibromatosis, though they are not found in each case [23, 31]. They are described as round or ovoid and granular about 3-10 µm in size. The inclusion bodies stain pink with hematoxylin and eosin, red with Masson's trichrome, and purple with phosphotungstic acid hematoxylin. Recent immunohistochemical and ultrastructural studies suggest that they are composed of actin and viment [32-35]. Pathologic features vary from haphazard arrangement of spindle cells with few inclusion bodies and numerous lymphocytes to well-organized arrangement of spindle cells with abundant inclusion bodies and rare lymphocytes. Grenier et al. suggest that in a well organized arrangement of spindle cells the inclusion bodies become more prevalent, while the amount of inflammation decreases [33].

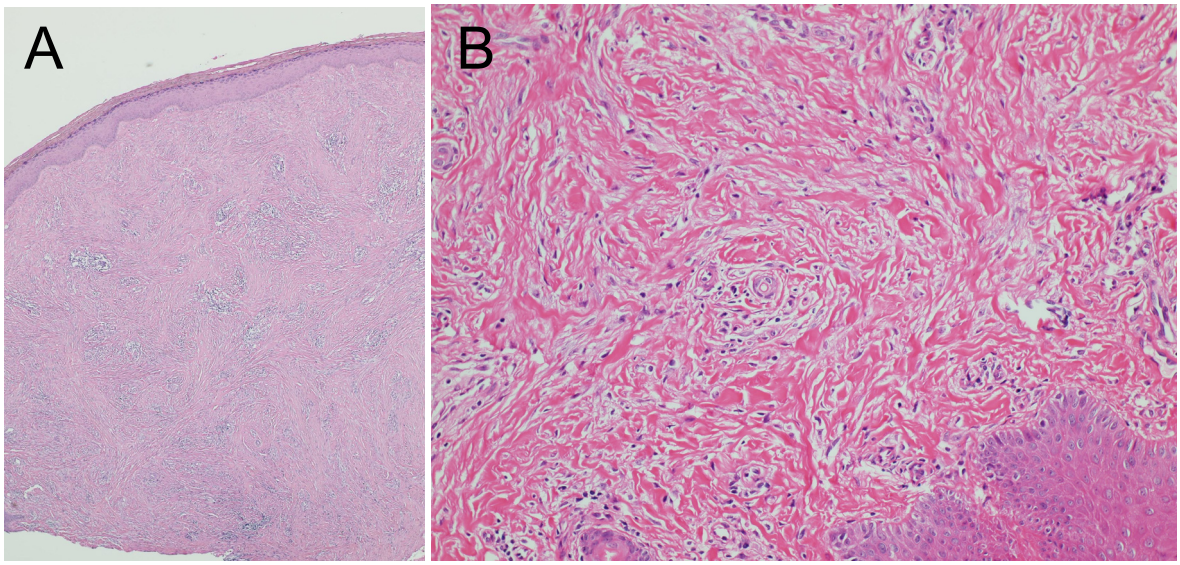

Figure 1. IDF of a three-year-old girl (Pat. 22). Low magnification demonstrates well-organized interlacing fascicles of spindle cells (hematoxylin and eosin staining; original magnification, x5). (B) High magnification shows spindle cells arranged in whorls (hematoxylin and eosin staining; original magnification, x20).

1.3.6 Differential diagnoses

As differential diagnoses of IDF some disorders should be considered. The most common differential diagnosis is the keloid or hypertrophic scar. The keloid develops after a few weeks or months from a wound and outgrows the boundaries of the original scar. The lesion may causes itching and contractures. Moreover, hypertrophic scars show a familial tendency [36].

Other disorders that should be mentioned in this context are juvenile aponeurotic fibroma, pachydermodactylia, or the recently described terminal osseous dysplasia [36, 37]. The juvenile aponeurotic fibroma is an invasive calcifying tumor mainly occurring on palm and sole. The neoplasm appears firm and fixed but is not adherent to the overlaying skin and may be painful. Calcium deposits can be seen on radiographs [36]. Characteristic for pachydermodactylia is the symmetrical and diffuse swelling of the dorsal aspect and side of the proximal phalanges of the digits. Repeated rubbing or injuries of the fingers may play a part in genesis of this lesion [36]. Terminal osseous dysplasia with pigmentary defects (TODPD) is an early childhood disease with an x-linked inheritance, concerning girls only. This

condition is characterized by pigmentary anomalies of the skin, skeletal abnormalities of the limbs and recurring digital fibromatosis of hands and feet [37].

1.3.7 Treatment

Caused by the low incidence of IDF and the still high recurrence rate there is no standardized therapy scheme. Several authors recommend surgical excision of the tumor as an appropriate therapy [20, 21], although some reports of spontaneous regression exist [34, 36, 38]. Surgical excision remains an appropriate recommendation for therapy of these tumors, because regression does not occur in every case and these lesions may cause mobility dysfunction.

1.4 Infantile (desmoid-type) fibromatosis

1.4.1 Definition

Desmoid fibromatosis, also known as aggressive fibromatosis (AF), is a fibroblastic neoplasm, arising from musculoaponeurotic elements. The name derives from the greek word “desmos” meaning aponeurosis, tendon. Desmoids are characterized by infiltrative growth, a tendency to recur locally and the inability to metastasize [2].

1.4.2 Epidemiology

Desmoid tumors are soft tissue lesions with an incidence of about 3 to 4 per million [39]. Although aggressive fibromatosis may be observed at any age, it is more common in children older than 6 years of age and in adolescents. There is also a slight predilection for the male gender reported [40].

1.4.3 Etiology

The pathogenesis of desmoid tumors is multifactorial and includes genetic and endocrine as well as physical factors [1]. They can occur sporadically but are often associated with hereditary diseases. The sporadic (idiopathic) desmoid is most likely caused by somatic mutations of the APC and/ or the β-catenin gene [41]. The inherited type of aggressive fibromatosis includes familial adenomatous polyposis (FAP), familial infiltrative fibromatosis (FIF) and the hereditary desmoid disease (HDD). These syndromes are caused by diverse germline mutations of the APC gene [42-44].

1.4.4 Clinical findings

Extra-abdominal fibromatoses occur in diverse locations such as shoulder, chest wall and back, thigh and head and neck. Figure 2 shows an aggressive fibromatosis of the submandibular region. Abdominal desmoids also emerge from

musculoaponeurotic structures, especially the rectus and internal oblique muscles and their fascial coverings. Intra-abdominal tumors arise in the mesentery.
Depending on their site of appearance these tumors can present asymptomatic as well as cause pain, decreased joint mobility, neurological symptoms, gastrointestinal bleeding or an acute abdomen secondary to bowel perforation [1].

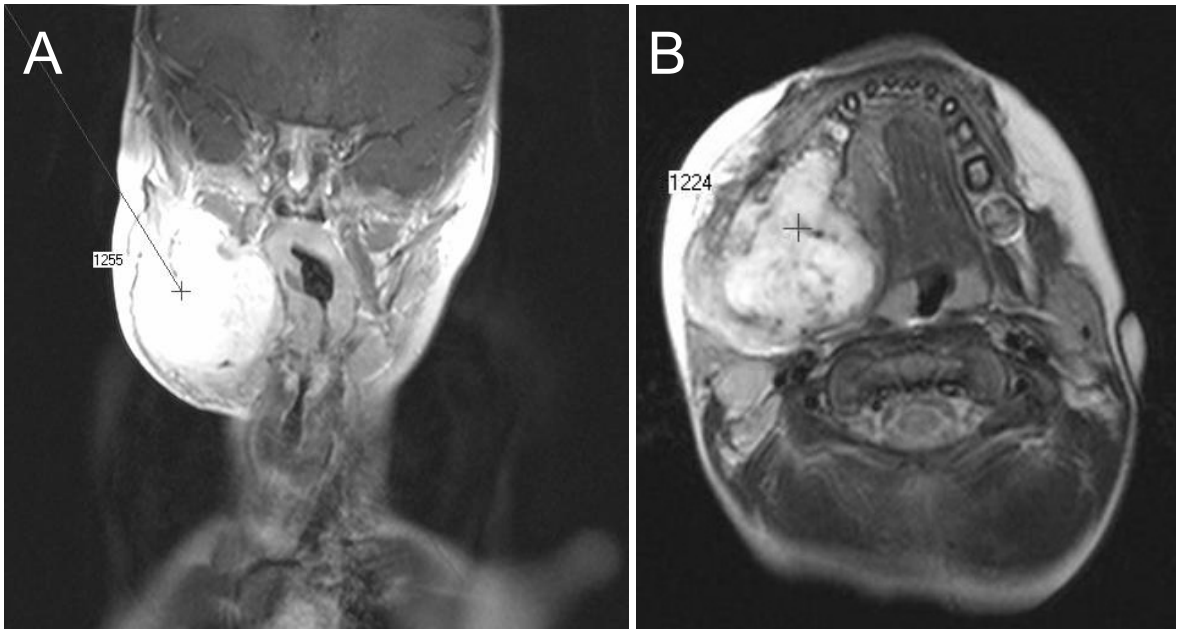

Figure 2. MRI (T2-weighted) of a submandibular desmoid tumor (Pat. 6). (A) Coronal and (B) axial plane.

1.4.5 Histopathological findings

These lesions are described as heterogeneous, typically poorly circumscribed, infiltrating masses (see figure 3). Histological characteristics are uniform elongated, slender spindle-shaped cells (fibroblasts-like) arranged in sweeping bundles, which are surrounded by collagen fibers (see figure 4). There is a lack of hyperchromasia or atypia but variation in cellularity when multiple sections are examined. The nuclei are small, pale staining and sharply defined. As in other fibrous proliferations intracytoplasmatic bundles of actin-type microfilaments, often condensed in certain areas (dense bodies). Cellular boundaries can only be discerned in cases with small amounts of collagen. At the periphery of the tumor muscle fibers undergo atrophy or assemble multinucleated giant cells. These cells could be mistakenly considered as an evidence for malignancy. Aggregates of

lymphocytes and microhemorrhages are common. Rarely calcification or chondroid or osseous metaplasia can be seen [1].

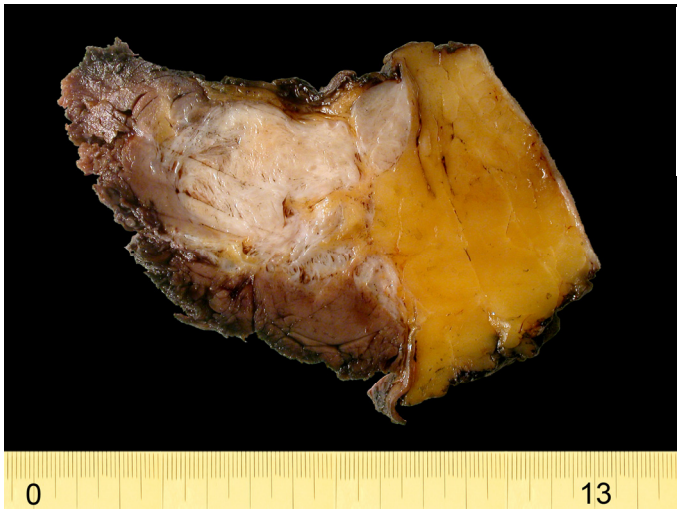

Figure 3. Macroscopic aspect of an adult desmoid tumor.

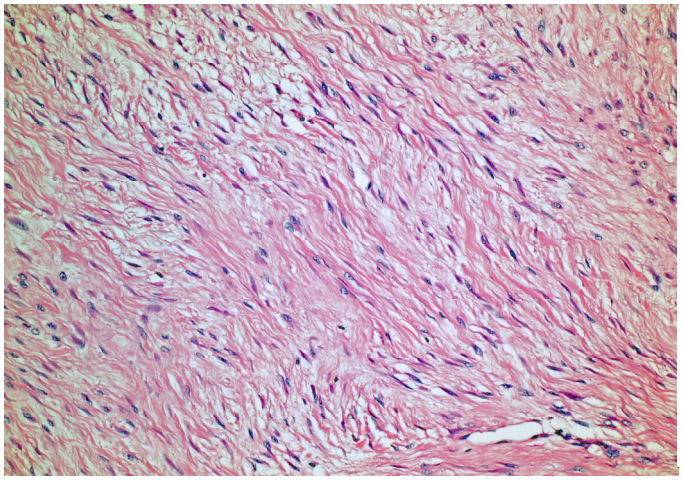

Figure 4. Sample of an abdominal desmoid (Pat. 15). Typical uniform elongated, slender spindle-shaped cells arranged in sweeping bundles (hematoxylin and eosin staining; original magnification, x20).

1.4.6 Differential diagnoses

Fibrosarcoma and reactive fibrosis must be primarily considered in differential diagnosis. Aspects against fibrosarcoma are the uniform growth pattern, absence of mitotic figures and the paradoxically more prominent infiltrative growth pattern of desmoids in small tumors. Mitotic figures can be found occasionally, but one or more mitotic figures per high-power field or atypical figures are an indication of malignancy. Transformation of aggressive fibromatosis to fibrosarcoma is very rare. We found only one report of a fibrosarcoma arising in an extra-abdominal desmoid tumor [45]. Reactive fibroses following trauma, minor muscle tear or intramuscular injection can imitate desmoid-type fibromatosis. They are very

similar except for their more variable growth pattern and the existence of focal microhemorrhages. Other rather uncommon lesions are desmoplastic fibroma of bone, and myxoma or nodular fasciitis. [1].

1.4.7 Treatment

Surgery

Excision of desmoid tumors still remains the most important therapy of aggressive fibromatosis. Wide or radical excision was found to be the most successful primary treatment modality [46] and a significant prognostic factor [47]. Leithner et al. compared a group of 152 patients with wide or radical microscopic surgical margins with a group of 260 patients with marginal or intralesional excision [47]. In the first group 41 patients (27%) and in the second one 187 patients (72%) developed a recurrence. But there are also studies which arrive at the conclusion that there is no relevant difference in outcome compared to positive margins [48, 49]. Stoeckle et al. recommend direct surgery only in primary lower trunk wall/girdle locations. In other types of presentation they suggest medical treatment and a “Wait-and-see” policy [50].

Adjuvant therapy

There are no publications with a large patient collective about adjuvant treatment of desmoid tumors in children and adolescents. Therefore further prospective studies including higher patient numbers are needed to identify the best medical treatment.

Adjuvant therapy is graduated in non-cytotoxic and cytotoxic drugs as summarized and shown in table 3.

Janinis et al. suggest to start therapy with non-steroidal anti-inflammatory drugs (NSAIDs) like indomethacin or sulindac (a long-acting analog of indomethacin), followed by anti-estrogens like tamoxifen, and afterwards, if needed, a treatment with cytotoxic drugs [51].

In the group of non-steroidal anti-inflammatory drugs, both COX-2 selective and COX-2 non-selective agents resulted in the same decrease of cell proliferation. Blockade of COX-2 decreases tumor growth, but does not play a role in tumor initiation [52].

Endocrine treatment with anti-estrogens is effective despite the absence of estrogen receptor (ER) α [53, 54]. Recent reports suggest mediation by ER β [55], but an ER-independent pathway of reducing tumor growth factor β 1 (TGFβ1) which inhibits matrix metalloproteinases (MMP) through tissue inhibitors of matrix metalloproteinases (TIMPs) has also been evidenced [56].

Interferon α (IFN-α) is also suggested as an adjuvant treatment for patients with resected desmoids to prevent further tumor growth [57], but the number of patients in published studies [57-60] is too small to make conclusive statements.

In patients with progressive or unresectable AF cytotoxic treatment with vinblastine, methotrexate and liposomal doxorubicin can promote tumor regression or at least block tumor growth in most children [61-63].

Imatinib mesylate, a tyrosine kinase inhibitor, is reported to be a potential therapy. The activity seems to be mediated by platelet-derived growth factor receptors α and β and not by c-kit [53, 64-67].

Radiotherapy

Although publications report the effectiveness of adjuvant radiotherapy in treating desmoid tumors with positive margins at resection [68, 69], it is still not recommended as a therapy-option in skeletally immature patients because of the risk of growth disturbance, pathologic fracture, fibrosis, edema, skin ulceration, paresthesia and paresis, cellulitis and secondary malignancies [70].

Non-cytotoxic drugs			
NSAIDs	Indomethacin		COX inhibitor
	Sulindac		COX inhibitor
	Diclofenac	Voltaren®	COX inhibitor
	DFU		COX-2 selective inhibitor
	MF-tricyclic		COX-2 selective inhibitor
SERMs	Tamoxifen	Nolvadex®, Toremifen®	Estrogen receptor antagonist
Biological agents	Interferon α		Cytokine
Cytotoxic drugs			
Antimetabolits	Methotrexate		Antifolate drug
Vinca alkaloids	Vinblastine	Velbe®	Anti-mitotic drug
Anthracyclines	Liposomal doxorubicin		DNA intercalating drug
Tyrosine kinase inhibitors	Imatinib	Glivec®	Tyrosine kinase inhibitor

Table 3. Adjuvant treatment options of desmoid-type fibromatosis; NSAIDs – non-steroidal anti-inflammatory drugs; COX – cyclooxygenase; DFU - 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulphonyl)phenyl-2(5H)-furanone; MF-tricyclic - Merck Frosst Tricyclic; SERMs – selective estrogen receptor modulators.

2. Aims

2.1 Hypotheses

The aim of this study is to analyse clinical appearance, biological behaviour and immunohistochemical patterns of infantile fibromatoses and to evaluate possible pharmacological treatment

Hypotheses:

- Infantile digital fibromatosis and desmoid-type fibromatosis have a different immunohistochemical pattern
- The course of disease is more aggressive in desmoid-type fibromatosis than in infantile digital fibromatosis
- Both entities show a preference towards typical anatomical sites
- The treatment should be adapted to the patient's age
- There is a high recurrence rate after R1/2 resection

2.2 Objective

The aim of this survey is to investigate possible correlations of recurrence rate, diverse immunohistochemical markers and location of tumor genesis between IDF and desmoid-type fibromatosis in young patients to evaluate possible pharmacological treatment. Correlating to current immunohistochemical studies about these types of fibrous tumors, markers were chosen and examined: Estrogen receptors α and β (ER α, ER β), progesterone receptor (PR), androgen receptor (AR), somatostatin (SOM), Ki-67, c-kit (CD117), platelet-derived growth factor receptors α and β (PDGFR α, PDGFR β) and β – catenin.

3. Patients and Methods

3.1 Patients

The patients were recruited from the central patient database of the Institute for Medical Informatics, Statistics and Documentation, Medical University Graz with the documentation system AURA. Selection criteria were diagnosis “desmoid-type fibromatosis”, “infantile digital fibromatosis” and age <21 years.

Nineteen patients with desmoid-type fibromatosis and three patients with IDF were identified. In all patients age at diagnosis, sex, tumor location, surgery, pharmacological treatment and recurrences were evaluated.

Sixteen patients have already been included in previous studies by Leithner, Liegl and Lackner [47, 53, 57, 61, 65, 71]. Four of these publications did not evaluate immunohistochemical markers [47, 57, 61, 71]. The two immunohistochemical studies did not include all markers and/or all patients evaluated in the present investigation [53, 65].

3.2 Location

Most tumors evolved on typical anatomical sites as shown in table 4 and figure 5. Despite the fact that desmoid-type fibromatoses are rare on hands and feet, two of nineteen desmoids developed in the plantar region. Two IDF were located in the digits of the feet and one IDF emerged from a digit of the hand. Manifestations of desmoid fibromatoses: Head-Neck: Six tumors; trunk: six tumors; upper extremity: two tumors; lower extremity: five tumors. In conclusion, all tumors arose in expected or accordant anatomical locations.

Location		Total	Desmoid	IDF
Abdominal		3	3	0
Extra-abdominal	Head/Neck	6	6	0
	Limbs	10	7	3
	Thoracal	3	3	0

Table 4. Tumor location

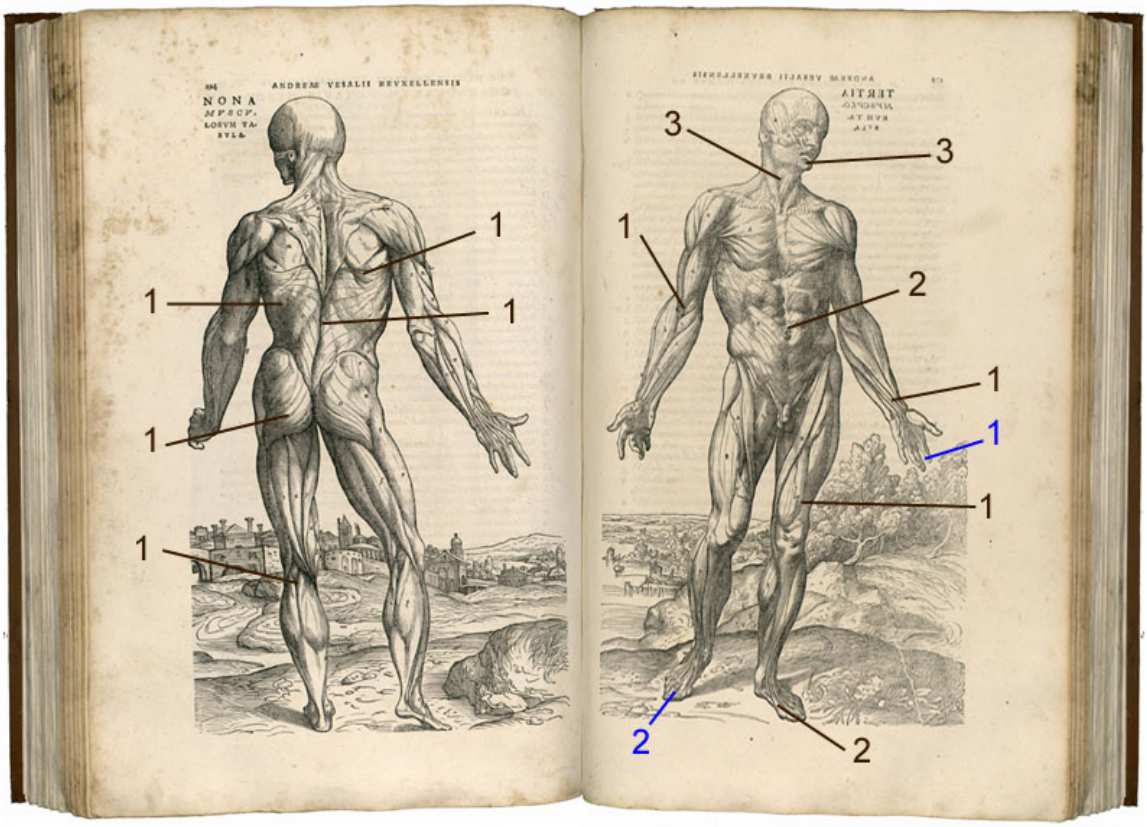

Figure 5. Tumor location; black - desmoid, blue – IDF (Andreas Vesalius *"De humani corporis fabrica",* 1543)

3.3 Study design

The present study is a retrospective 22–year evaluation of all pediatric patients diagnosed with "infantile digital fibromatosis" and "desmoid-type fibromatosis" by the Institute of Pathology, Medical University Graz. Included were patients with first diagnosis of one of the entities mentioned above between 1987 and 2008. Data considered date of birth, age at diagnosis, location, margins at resection, recurrences, pharmaceutical treatment and time of follow-up. Additional immunohistochemical staining and data analysis were performed by the Institute of Pathology, Medical University Graz.

3.4 Immunohistochemistry

All specimens were fixed in 4% natural buffered formalin, routinely processed, and paraffin embedded. Four-micron thick sections were stained with hematoxylin and eosin.

Immunohistochemical studies were performed using streptavidin-biotin peroxidase complex method. A detailed summary of the used antibodies is provided in Table 5.

Antibody/ Antigen	Company	Clonality	Type	Clone	Code	Dilution
ER α	Ventana	monoclonal	Mouse	6F11	760-2596	Kit confirm
ER β	Abcam	monoclonal	Mouse	14C8	ab288	1/50
PR	Dako	monoclonal	Mouse	PGR 636	760-2547	Ready to use
AR	Dako	monoclonal	Mouse	AR441	M3562	1/50
SOM	Dako	polyclonal	Rabbit		A0566	1/2000
Ki-67	Dako	monoclonal	Mouse	MIB-1	M7240	1/200
c-kit	Dako	polyclonal	Rabbit		A4502	1/1000
PDGFR α	Neomarker	polyclonal	Rabbit		RB 1691	1/100
PDGFR β	Neomarker	polyclonal	Rabbit		RB 1692	1/100
β-catenin	Transduction		Mouse	14	610154	1/1000

Table 5. Antibody details: ER α - estrogen receptor α; ER β - estrogen receptor β; PR - progesterone receptor; AR - androgen receptor; SOM - somatostatin; PDGFR α - platelet-derived growth factor receptor α; PDGFR β - platelet-derived growth factor receptor β.

Abcam, Cambridge, UK ; Dako Cytomation, Vienna, Austria; Neomarker, Fremont, CA; Transduction, Lexington, KY; Ventana Medical Systems, Illkirch, France.

The tissue sections were processed according to manufacturer guidelines or standard protocols. All slides were evaluated independently by three different persons. Appropriate positive and negative controls were included. Normal human soft tissue served as an internal negative control. As positive control following specimens were stained: lymph nodes for Ki-67; prostate cancer for androgen

receptor and PDGFR α; breast cancer for estrogen receptors α and β, progesterone receptor and PDGFR β; pancreas for somatostatin. Scoring of staining pattern was done according to manufacturer guidelines or internationally accepted standards: at least 10% of the tumor cells had to be positive for estrogen receptors α and β and progesterone receptor; a minimum of 5% for androgen receptor and Ki-67; and more than 1% for somatostatin.

4. Results

4.1 Patients collective

Eleven male and eight female patients with aggressive fibromatosis and three female patients with IDF were identified (see table 6). Desmoid tumors showed a slight tendency towards male sex (M:F=11:8). In contrast we found just female patients with IDF. Mean age at diagnosis was 6.6 years in desmoid tumors and 4 years in IDF. Overall, mean follow-up was 112 months (desmoid tumors 114 and IDF 97).

	Total	Desmoid	IDF
Patients	22	19	3
Male : Female	11:11	11:8	0:3
Mean age at diagnosis [years]	6,3 (0-17)	6,6 (0-17)	4 (3-6)
Mean follow-up [months]	112 (2-251)	114 (2-251)	97 (90-106)
Patients with recurrences	6	4	2
Mean time to recurrence [months]	41	55	21
Max. recurrences/patient	3	2	3

Table 6. Patient collective

4.2 Recurrence rate

Dormans et al. reported recurrence rates of up to 75% in desmoid-type fibromatosis [70]. In comparison, about 60% of the cases of IDF recur locally [22]. Against expectation this patient collective brought different results as shown in table 7. Twenty-one percent (4/19) of desmoid tumors and two of three IDF recurred at least once. Sixteen percent (3/19) of infantile and one digital fibromatosis recurred twice. One IDF recurred a third time.

Few authors described the need of amputation of digits by reason of aggressive growth pattern and high recurrence rate of IDF [20, 23, 72]. In our patient collective an amputation of digits was not necessary.

Recurrences	Desmoid		IDF	
1	4/19	21%	2/3	66%
2	3/19	16%	1/3	33%
3	0/19	0%	1/3	33%

Table 7. Recurrence rate

4.3 Margins at resection

Being a retrospective analysis, only the histological margin status (R0, R1/2) could be determined, the surgical margin status according to Enneking (wide/radical/intralesional) could not be defined. In the group of 19 patients with desmoid-type fibromatosis three of 13 patients with margin status R1/2 at first resection had recurrences and one of four patients with R0 excision. In one case margins could not be evaluated and in another patient the desmoid was not resected. The four recurrences were again treated with surgical resection. One recurrence showed margin status R0, two had margin status R1/2 and in one patient status could not be evaluated. The patient with R0 resection and the one with unknown margin status had a second recurrence and were again treated with surgical resection. In one case margin status was R1/2 in the other sample status was not evaluable. In the three patients with IDF, margin status (first resection and excision of recurrences) was R1/2 in each case.

Patients with desmoid-type fibromatosis								
Pat.-Nr.	M/F	Age at diagnosis (years)	Location	Margins at first resection	Non-surgical Treatment	Number of recurrences	Follow-up (months)	Status
1	M	9	Plantar	R0	Diclofenac, Tamoxifen	None	54	NED
2	F	1	Submandibular	ND	Diclofenac, Tamoxifen	None	142	NED
3	F	1	Paravertebral	R1/2		None	142	NED
4	F	7	Cubital	NA		None	225	NED
5	M	6	Pretracheal	R1/2	Diclofenac, Tamoxifen, MTX, VBL	1	98	NED
6	F	1	Submandibular	R1/2	Diclofenac, Tamoxifen, MTX, VBL	None	82	NED
7	M	14	Antebrachial	R1/2	Diclofenac	None	80	NED
8	M	5	Gluteal	R0		None	251	NED
9	F	6	Subscapular	R1/2	Diclofenac, Tamoxifen	None	84	NED
10	M	0	Collar	R1/2		None	140	NED
11	M	2	Plantar	R1/2	Diclofenac, Tamoxifen	2	87	NED
12	F	17	Femoral	R1/2		None	232	NED
13	M	2	Abdominal	R0		None	192	NED
14	F	0	Thoracal	R1/2	Diclofenac, Tamoxifen, Carboplatin, VCR	1	212	NED
15	F	16	Abdominal	R1/2		None	6	NED
16	M	8	Hypoglossal	R1/2	Diclofenac, Tamoxifen	None	2	NED
17	M	14	Abdominal	R1/2		None	11	NED
18	M	0	Collar	R1/2		None	3	NED
19	M	17	Popliteal	R0	Celecoxib, Interferon-α, XRT	2	124	NED

Table 8a Patients with desmoid-type fibromatosis

Patients with infantile digital fibromatosis								
Pat.-Nr.	M/F	Age at diagnosis (years)	Location	Margins at resection	Non-surgical Treatment	Number of recurrences	Follow-Up (months)	Status
20	F	6	4th toe	R1/2		3	90	NED
21	F	3	5th toe	R1/2		none	106	NED
22	F	3	3rd finger	R1/2		1	95	NED

Table 8b Patients with infantile digital fibromatosis

Legend: NED – No evidence of disease; ND – Not Done; NA – Not Available; R0 – negative margins; R1/2 – positive margins; MTX – methotrexate; XRT – radiation therapy; VBL – vinblastine; VCR -vincristine

4.4 Immunohistochemistry

4.4.1 Estrogen receptors α and β

All samples were tested negative for estrogen receptor (ER) α. Staining for ER β was positive in one (male) case in desmoids and in one (female) sample of IDF. Table 9 summarizes the results of the immunohistochemical staining.

4.4.2 Platelet-derived growth factor receptors α and β

All samples, desmoid-type fibromatosis (nine male, three female) as well as IDF (two female), showed a positive reaction with antibodies to platelet-derived growth factor receptors (PDGFR) α and β. Figure 6 shows positive samples of a desmoid tumor.

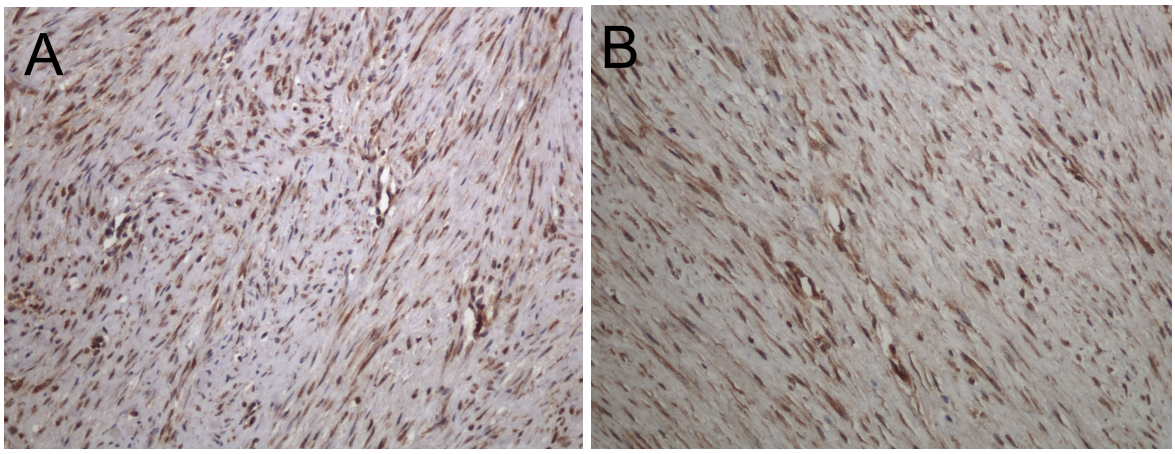

Figure 6. Staining for PDGFR α and β. (A) PDGFR α and (B) PDGFR β positive desmoid tumor (original magnification, x40).

4.4.3 Somatostatin

Staining for somatostatin (SOM) was positive in one (female) of the two (female) cases of IDF. All samples of desmoid-type fibromatosis were tested negative.

4.4.4 Androgen receptor

Positive staining for androgen receptor (AR) was found in only one (male) of 13 desmoid cases. None of the two samples of IDF showed a positive reaction with antibodies to androgen receptors.

4.4.5 Progesterone receptor

Staining for progesterone receptor (PR) was negative in all cases. We found neither in desmoid samples nor in IDF positive reactions.

4.4.6 Ki-67

Staining for Ki-67 was positive in one (male) of 13 cases of desmoid-type fibromatosis and in one (female) of the two samples of IDF.

4.4.7 C-kit (CD117)

All samples, desmoid tumors as well as IDF, showed a negative reaction with antibodies to c-kit (CD117).

4.4.8 β-catenin

Staining for β-catenin was positive in eight of nine (seven male, one female) samples of desmoid tumors and in one (female) of the two cases of IDF. Figure 7 shows positive cell reaction.

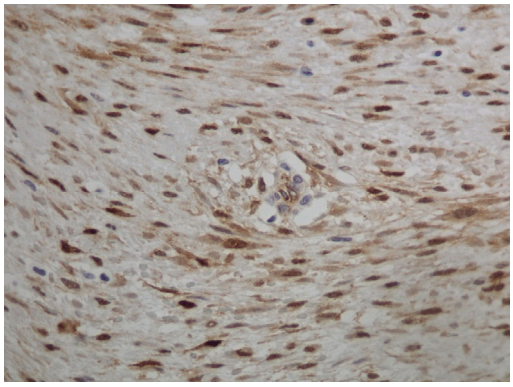

Figure 7. β-catenin positive desmoid-type fibromatosis (original magnification, x40).

Antibody	Desmoid (positive/ tested)	IDF (positive/ tested)
ER α	0/14	0/2
ER β	1/14	1/2
PDGFR α	12/12	2/2
PDGFR β	12/12	2/2
SOM	0/13	1/2
AR	1/13	0/2
PR	0/14	0/2
Ki-67	1/13	1/2
c-kit (CD117)	0/14	0/2
β-catenin	8/9	1/2

Table 9. Immunohistochemical results; IDF – infantile digital fibromatosis; ER – estrogen receptor; PDGFR – platelet-derived growth factor receptor; SOM – somatostatin; AR – androgen receptor; PR – progesterone receptor

5. Discussion

Desmoid-type fibromatosis and IDF are rare neoplasms and present a therapeutic challenge. A significant number of patients develop disease recurrence after surgical treatment or systemic therapies with non-steroidal anti-inflammatory drugs and anti-estrogen.

The aim of this study was to investigate possible correlations of recurrence rate, location of tumor genesis and specific immunohistochemical patterns for IDF and desmoid-type fibromatosis in children and adolescents and develop a specific therapeutic recommendation.

5.1 Tumor characteristics

As supposed most tumors arose in typical anatomical sites. IDF always occurred on the digits of hands and feet. In two of 19 cases of desmoid-type fibromatosis the tumor was located in the plantar region, which is a rare, but not uncommon site of origin. All other desmoid tumors emerged from more common abdominal and extra-abdominal locations.

Interestingly, tumor recurrence did not correlate with margins at resection. In the group of 19 patients with desmoid-type fibromatosis three of 13 patients with margin status R1/2 at first resection had recurrences and one of 4 patients with R0 excision. The four recurrences were again treated with surgical resection. One recurrence showed margin status R0, two margin status R1/2 and in one patient margins could not be evaluated. The patient with R0 resection and the one with unknown margin status had a second recurrence and were again treated with surgical resection. In one case margin status was R1/2 in the other sample status was not evaluable. Both patients showed no more recurrences.

In the three patients with IDF, in each case margin status (first resection and excision of recurrences) was R1/2. Despite high primary recurrence rates and R1/2 resections, IDF showed no more recurrences and patients are disease-free.

These results do not correlate with previous studies with older patient collectives [46, 47]. Desmoid fibromatoses seem do behave in a different way in children and adolescents than in adult patients.

5.2 Immunohistochemistry

5.2.1 Estrogen receptors α and β

Desmoid-type fibromatoses and IDF should be regarded as ER α negative. The use of anti-estrogens is in dispute. Therapy is based on studies reporting positive ER α [39, 73-78]. In contrast, there are also large studies with a greater patient collective and no positive staining [40, 54, 79]. Authors report successful treatment [80] as well as lack of benefit [40, 81]. But ER negativity does not necessarily mean that the tumor is insensitive to estrogen and is not affected by anti-estrogens [82]. Some patients with ER negative breast cancer are known to respond to anti-estrogens, although the response is much lower than that seen in ER positive patients [83].

In our patient collective staining for ER β was positive in just one case in desmoids and in one sample of IDF. Deyrup et al. found in their group of 40 patients with extra-abdominal desmoid-type fibromatosis in every case at least focally positive ER β [55]. They suggest that anti-estrogens may have a role via this ER β way. Leithner et al. found positive reaction to ER β in seven of 80 cases [53]. In comparison, pediatric desmoid-type fibromatoses seem to have a lower rate of ER β positive tumors.

5.2.2 Progesterone receptor

We found five studies with partial positive results for progesterone receptor [73, 74, 76, 78, 84] and four studies with negative results [53, 79, 85, 86]. Laskin et al. also report negative reaction to progesterone receptors in IDF [23]. In our study staining for this receptor was negative in all cases.

5.2.3 Androgen receptor

Results for androgen receptors are differing. Ishizuka et al. described a positive reaction in fourteen of 27 cases [84]. In disagreement, Leithner et al. found a weak signal in six of 46 cases [53]. In our patient collective, staining for androgen

receptor was positive in one of 13 cases of desmoid-type fibromatosis. There was no positive reaction with IDF.

5.2.4 Somatostatin

Two studies analyzed somatostatin receptors in desmoid-type fibromatosis. De Pas et al. found a positive reaction in two of ten patients [87]. Leithner et al. had nine positive samples in a larger collective of 80 patients [53]. In our series of desmoid tumors staining was negative in all cases. In one of two samples of IDF we found a positive reaction with somatostatin receptor.
The advantage of therapy of desmoid tumors with peptide receptor radiotherapy using a somatostatin analogue, as proposed by De Pas et al. still remains uncertain [87].

5.2.5 Ki-67

Contrary to two studies reporting negative results in a total of 42 patients [88, 89], other authors report positive staining for Ki-67 in desmoid tumors [53, 90-92]. A positive reaction was found in ten of 25 cases [90], 20 of 80 samples [53], 13 of 50 cases [92] and in one case report [91]. This divergence might result from different cut-off values used: positive results with a cut-off value of 5% [53, 90] and 10% [92], negative results with a cut-off value of 20% [88] or not stated [89]. In our series one of 13 cases of desmoid-type fibromatosis was positive (cut-off at 5%).
There are no papers about staining for Ki-67 in IDF. In our patients one of two samples was positive (cut-off at 5%).

5.2.6 C-kit (CD117)

Although there are publications of positive results [66, 93], desmoid-type fibromatosis can be regarded as c-kit negative. Several authors report negative staining in a total of 52 patients [91, 94-96]. Two other papers each found only one focal weak staining in a total of 100 samples [53, 97]. Moreover, Miettinen [98] and

Hornick and Fletcher [97] doubt about the positive results of Yantiss and colleagues [93]. In our series of 13 samples of desmoid tumors we found no positive reaction. Lucas et al. demonstrated that these different results may be caused in part by the use of variant antibodies and different dilutions [94].
Laskin et al. found in six of eight cases of IDF a positive reaction with antibodies to CD117 [23]. Our two samples tested were both c-kit negative. In both studies the same polyclonal CD117/c-kit antibodies by Dako (A4502) were utilized. The different results might be partially explained by the different dilutions used – e.g. Laskin et al used a dilution of 1:100 while our study was executed using the same antibody with a dilution of 1:1000 (according to standard protocol of the Institute of Pathology).

5.2.7 Platelet-derived growth factor receptors α and β

Platelet-derived growth factors and their receptors play a crucial role in pathways involved in the regulation of cell proliferation, growth and function in a wide range of solid tumors. Several authors report staining of PDGFR α and β in desmoid-type fibromatosis, but with varying results. In a recent report by Signoroni et al. PDGFR α and β were found to be immunoreactive in all 14 cases [67]. Expression and activation status of PDGFR β was higher than that of PDGFR α. Mace et al. report nine tumors positive to PDGFR α and β [66]. However, Heinrich et al. are in doubt about the PDGFR α antibody used by Mace [64]. They concluded that all their desmoid tumor samples expressed minimal to zero levels PDGFR α, but expressed levels of PDGFR β that are comparable with normal fibroblasts. Another author found increased expression in thirteen of 17 pediatric fibromatoses [99]. In the analysis of Liegl et al. immunohistochemical results showed strong positivity with antibodies to PDGFR α, but there was no immunoreactivity of tumor cells with antibodies to PDGFR β [65]. In our series, all of the 12 cases of desmoid-type fibromatosis and both of the two IDF samples were positive to PDGFR α and β.
Results seem to vary due to the choice of antibody as proposed by Heinrich and colleagues. However, our results indicate that both, PDGFR α and β are activated,

and imatinib mesylate may be effective in treatment of desmoid-type fibromatosis and IDF.

5.2.8 β–catenin

Nuclear immunoreactivity for β-catenin is useful in diagnosing adult desmoid-type fibromatoses. Many of them exhibit mutations within the APC/ β-catenin (Wnt) pathway. Recent studies showed the importance of β-catenin. Ferenc et al. did not find a statistically significant correlation between expression of β-catenin and tumor size but expression and patient age [100]. The percentage of β-catenin positive cells decreased with age. Gebert and colleagues concluded that a nuclear overexpression of β-catenin (>20% positive nuclei) is associated with a decreased event-free survival [101]. Thway et al. found high-level expression in pediatric desmoid-type fibromatosis in 21 of 50 cases but not in other myo-/ fibroblastic tumors of childhood [102]. Another publication about IDF found weak positive results in nine and >5% in two of 11 cases [23]. In our series eight of nine desmoid-type samples and one of two IDF cases were positive for β-catenin.

6. Conclusion

1. According to our results in pediatric and in accordance to most previous studies on adults concerning immunohistochemical markers, desmoid-type fibromatoses can be seen as β-catenin and PDGFR α and β positive and ER α, c-kit and somatostatin negative tumors [53, 55, 64, 65, 67, 99]. Pediatric desmoid-type fibromatoses seem to have a lower rate of ER β positive tumors [53, 55]. Staining for other immunohistochemical markers was inconclusive. IDF showed a tendency towards the same immunohistochemical pattern as desmoid tumors. Interestingly, our CD117/ c-kit results did not correlate with the analysis of Laskin et al. [23].
2. The heterogeneity of treatment made it impossible to give a statement about therapy management. Therefore, we again state that only a large, prospective, randomized trial could really provide an answer for the efficacy of any adjuvant treatment.
3. Desmoid fibromatoses also seem to behave in a different way in children and adolescents than in adult patients. Our results showed that negative margins at resection have no influence on recurrence rate.
4. Nevertheless we recommend wide excision of primary desmoid tumors as treatment of choice. If an appropriate resection is not possible or associated with a high morbidity a wait-and-see policy might be indicated.

7. Index

7.1 Figures

7.2 Tables

7.3 Abbreviations

A	adults
AF	aggressive fibromatosis
APC	adenomatous polyposis coli
AR	androgen receptor
B	birth
CAF	calcifying aponeurotic fibroma
COX	cyclooxygenase
DFU	5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulphonyl)phenyl-2(5H)-furanone
ER	estrogen receptor
FAP	familial adenomatous polyposis
FH	fibrous hamartoma
FIF	familial infiltrative fibromatosis
HDD	hereditary desmoid disease
HPV	human papilloma virus
IDF	infantile digital fibromatosis
IFN α	interferon α
ISH	infantile systemic hyalinosis
JHF	juvenile hyaline fibromatosis
MMP	matrix metalloproteinases
MTX	methotrexate
NA	not available
ND	not done
NOD	no evidence of disease
NSAIDs	non-steroidal anti-inflammatory drugs
PDGFR	platelet-derived growth factor receptor
PR	progesterone receptor
Reg.	regression
SERMs	selective estrogen receptor modulators
SOM	somatostatin
TGFβ1	tumor growth factor β1

TIMPs	tissue inhibitors of matrix metalloproteinases
TODPD	terminal osseus dysplasia with pigmentary defects
VBL	vinblastine
VCR	vincristine
WHO	World Health Organization
XRT	radiation therapy

7.4 References

[1] Weiss SW, Goldblum JR. Fibromatoses. In: Weiss SW, Goldblum JR, eds. Enzinger and Weiss's soft tissue tumors. 4th ed. St. Louis Baltimore Berlin: Mosby 2001:309-46.

[2] Fletcher CDM, Unni KK, Mertens F, eds. World Health Organization classification of tumours. Pathology and genetics of tumours of soft tissue and bone. Lyon: IARC Press 2002.

[3] Goldblum JR, Fletcher JA. Desmoid-type fibromatoses. In: Fletcher CDM, Unni KK, Mertens F, eds. World Health Organization classification of tumours. Pathology and genetics of tumours of soft tissue and bone. Lyon: IARC Press 2002:83-4.

[4] Goldblum JR, Fletcher JA. Superficial fibromatoses. In: Fletcher CDM, Unni KK, Mertens F, eds. World Health Organization classification of tumours. Pathology and genetics of tumours of soft tissue and bone. Lyon: IARC Press 2002:81-2.

[5] Weiss SW, Goldblum JR. Fibrous tumors of infancy and childhood. In: Weiss SW, Goldblum JR, eds. Enzinger and Weiss's soft tissue tumors. 4th ed. St. Louis Baltimore Berlin: Mosby 2001:347-408.

[6] Carretto E, Dall'Igna P, Alaggio R, Siracusa F, Granata C, Ferrari A, et al. Fibrous hamartoma of infancy: an Italian multi-institutional experience. J Am Acad Dermatol. 2006;54(5):800-3.

[7] Hashimoto H. Fibrous harmatoma of infancy. In: Fletcher CDM, Unni KK, Mertens F, eds. World Health Organization classification of tumours. Pathology and genetics of tumours of soft tissue and bone. Lyon: IARC Press 2002:58-9.

[8] Chung EB, Enzinger FM. Infantile myofibromatosis. Cancer. 1981;48(8):1807-18.

[9] Ebert CS, Jr., Zdanski C, Ardeshirpour F, Patel M, Hart CF, Drake AF. Recurrent infantile myofibromatosis: a report of conservative management and discussion of treatment strategies. Ear Nose Throat J. 2008;87(12):E4.

[10] Hausbrandt P, Leithner A, Beham A, Bodo K, Raith J, Windhager R. A rare case of infantile myofibromatosis and review of literature. J Pediatr Orthop B. 2009 [in press].

[11] Rubin BP, Bridge JA. Myofibroma / Myofibromatosis. In: Fletcher CDM, Unni KK, Mertens F, eds. World Health Organization classification of tumours. Pathology and genetics of tumours of soft tissue and bone. Lyon: IARC Press 2002:59-61.

[12] O'Connell J. Fibromatosis colli. In: Fletcher CDM, Unni KK, Mertens F, eds. World Health Organization classification of tumours. Pathology and genetics of tumours of soft tissue and bone. Lyon: IARC Press 2002:61-2.

[13] Lu FH, Tzen CY, Chen BF, Chang PY. Calcifying aponeurotic fibroma: a report of three cases. Zhonghua Yi Xue Za Zhi (Taipei). 1995;56(2):139-42.

[14] Rahmi M, Chakkouri K, Cohen D, Hassoun J, Trafeh M. Fibrome aponevrotique juvenile. A propos d'un cas, avec revue de la litterature. Chir Main. 2002;21(1):33-5.

[15] Farshid G. Calcifying aponeurotic fibroma. In: Fletcher CDM, Unni KK, Mertens F, eds. World Health Organization classification of tumours. Pathology and genetics of tumours of soft tissue and bone. Lyon: IARC Press 2002:69-70.

[16] Mancini GM, Stojanov L, Willemsen R, Kleijer WJ, Huijmans JG, van Diggelen OP, et al. Juvenile hyaline fibromatosis: clinical heterogeneity in three patients. Dermatology. 1999;198(1):18-25.

[17] Larralde M, Santos-Munoz A, Calb I, Magarinos C. Juvenile hyaline fibromatosis. Pediatr Dermatol. 2001;18(5):400-2.

[18] O'Connell J. Juvenile hyaline fibromatosis. In: Fletcher CDM, Unni KK, Mertens F, eds. World Health Organization classification of tumours. Pathology and genetics of tumours of soft tissue and bone. Lyon: IARC Press 2002:63-4.

[19] Reye RD. Recurring digital fibrous tumors of childhood. Arch Pathol. 1965;80:228-31.

[20] Talbot C, Khan T, Smith M. Infantile digital fibromatosis. J Pediatr Orthop B. 2007;16(2):110-2.

[21] Rimareix F, Bardot J, Andrac L, Vasse D, Galinier P, Magalon G. Infantile digital fibroma--report on eleven cases. Eur J Pediatr Surg. 1997;7(6):345-8.

[22] Azam SH, Nicholas JL. Recurring infantile digital fibromatosis: report of two cases. J Pediatr Surg. 1995;30(1):89-90.

[23] Laskin WB, Miettinen M, Fetsch JF. Infantile digital fibroma/fibromatosis: a clinicopathologic and immunohistochemical study of 69 tumors from 57 patients with long-term follow-up. Am J Surg Pathol. 2009;33(1):1-13.

[24] Zhu WY, Xia MY, Huang YF, Leonardi C, Penneys NS. Infantile digital fibromatosis: ultrastructural human papillomavirus and herpes simplex virus DNA observation. Pediatr Dermatol. 1991;8(2):137-9.

[25] Bacino CA, Stockton DW, Sierra RA, Heilstedt HA, Lewandowski R, Van den Veyver IB. Terminal osseous dysplasia and pigmentary defects: clinical characterization of a novel male lethal X-linked syndrome. Am J Med Genet. 2000;94(2):102-12.

[26] Bloem JJ, Vuzevski VD, Huffstadt AJ. Recurring digital fibroma of infancy. J Bone Joint Surg Br. 1974;56-B(4):746-51.

[27] Breuning MH, Oranje AP, Langemeijer RA, Hovius SE, Diepstraten AF, den Hollander JC, et al. Recurrent digital fibroma, focal dermal hypoplasia, and limb malformations. Am J Med Genet. 2000;94(2):91-101.

[28] Horii E, Sugiura Y, Nakamura R. A syndrome of digital fibromas, facial pigmentary dysplasia, and metacarpal and metatarsal disorganization. Am J Med Genet. 1998;80(1):1-5.

[29] Izadpanah A, Hogeling M, Buka RL, Eichenfield LF, Bird LM. Digitocutaneous dysplasia. J Am Acad Dermatol. 2007;56(2 Suppl):S6-9.

[30] Canioni D, Richard S, Rambaud C, Manach Y, Nezelof C. Lingual localization of an inclusion body fibromatosis (Reye's tumor). Pathol Res Pract. 1991;187(7):886-9; discussion 9-91.

[31] O'Connell J. Inclusion body fibromatosis. In: Fletcher CDM, Unni KK, Mertens F, eds. World Health Organization classification of tumours. Pathology and genetics of tumours of soft tissue and bone. Lyon: IARC Press 2002:64-5.

[32] Choi KC, Hashimoto K, Setoyama M, Kagetsu N, Tronnier M, Sturman S. Infantile digital fibromatosis. Immunohistochemical and immunoelectron microscopic studies. J Cutan Pathol. 1990;17(4):225-32.

[33] Grenier N, Liang C, Capaldi L, Ney A, Lapidus C, Schappell D, et al. A range of histologic findings in infantile digital fibromatosis. Pediatr Dermatol. 2008;25(1):72-5.

[34] Ishii N, Matsui K, Ichiyama S, Takahashi Y, Nakajima H. A case of infantile digital fibromatosis showing spontaneous regression. Br J Dermatol. 1989;121(1):129-33.

[35] Iwasaki H, Kikuchi M, Mori R, Miyazono J, Enjoji M, Shinohara N, et al. Infantile digital fibromatosis. Ultrastructural, histochemical, and tissue culture observations. Cancer. 1980;46(10):2238-47.

[36] Niamba P, Leaute-Labreze C, Boralevi F, Lepreux S, Chamaillard M, Vergnes P, et al. Further documentation of spontaneous regression of infantile digital fibromatosis. Pediatr Dermatol. 2007;24(3):280-4.

[37] Kokitsu-Nakata NM, Antunes LF, Guion-Almeida ML. Terminal osseous dysplasia and pigmentary defects in a Brazilian girl. Am J Med Genet A. 2008;146A(20):2698-700.

[38] Kawaguchi M, Mitsuhashi Y, Hozumi Y, Kondo S. A case of infantile digital fibromatosis with spontaneous regression. J Dermatol. 1998;25(8):523-6.

[39] Reitamo JJ, Scheinin TM, Hayry P. The desmoid syndrome. New aspects in the cause, pathogenesis and treatment of the desmoid tumor. Am J Surg. 1986;151(2):230-7.

[40] Pignatti G, Barbanti-Brodano G, Ferrari D, Gherlinzoni F, Bertoni F, Bacchini P, et al. Extraabdominal desmoid tumor. A study of 83 cases. Clin Orthop Relat Res. 2000;(375):207-13.

[41] Lips DJ, Barker N, Clevers H, Hennipman A. The role of APC and beta-catenin in the etiology of aggressive fibromatosis (desmoid tumors). Eur J Surg Oncol. 2008.

[42] Bertario L, Russo A, Sala P, Eboli M, Giarola M, D'Amico F, et al. Genotype and phenotype factors as determinants of desmoid tumors in patients with familial adenomatous polyposis. Int J Cancer. 2001;95(2):102-7.

[43] Eccles DM, van der Luijt R, Breukel C, Bullman H, Bunyan D, Fisher A, et al. Hereditary desmoid disease due to a frameshift mutation at codon 1924 of the APC gene. Am J Hum Genet. 1996;59(6):1193-201.

[44] Scott RJ, Froggatt NJ, Trembath RC, Evans DG, Hodgson SV, Maher ER. Familial infiltrative fibromatosis (desmoid tumours) (MIM135290) caused by a recurrent 3' APC gene mutation. Hum Mol Genet. 1996;5(12):1921-4.

[45] Soule EH, Scanlon PW. Fibrosarcoma arising in an extraabdominal desmoid tumor: report of case. Proc Staff Meet Mayo Clin. 1962;37:443-51.

[46] Buitendijk S, van de Ven CP, Dumans TG, den Hollander JC, Nowak PJ, Tissing WJ, et al. Pediatric aggressive fibromatosis: a retrospective analysis of 13 patients and review of literature. Cancer. 2005;104(5):1090-9.

[47] Leithner A, Gapp M, Leithner K, Radl R, Krippl P, Beham A, et al. Margins in extra-abdominal desmoid tumors: a comparative analysis. J Surg Oncol. 2004;86(3):152-6.

[48] Gronchi A, Casali PG, Mariani L, Lo Vullo S, Colecchia M, Lozza L, et al. Quality of surgery and outcome in extra-abdominal aggressive fibromatosis: a series of patients surgically treated at a single institution. J Clin Oncol. 2003;21(7):1390-7.

[49] Merchant NB, Lewis JJ, Woodruff JM, Leung DH, Brennan MF. Extremity and trunk desmoid tumors: a multifactorial analysis of outcome. Cancer. 1999;86(10):2045-52.

[50] Stoeckle E, Coindre JM, Longy M, Bui Nguyen Binh M, Kantor G, Kind M, et al. A critical analysis of treatment strategies in desmoid tumours: a review of a series of 106 cases. Eur J Surg Oncol. 2009;35(2):129-34.

[51] Janinis J, Patriki M, Vini L, Aravantinos G, Whelan JS. The pharmacological treatment of aggressive fibromatosis: a systematic review. Ann Oncol. 2003;14(2):181-90.

[52] Poon R, Smits R, Li C, Jagmohan-Changur S, Kong M, Cheon S, et al. Cyclooxygenase-two (COX-2) modulates proliferation in aggressive fibromatosis (desmoid tumor). Oncogene. 2001;20(4):451-60.

[53] Leithner A, Gapp M, Radl R, Pascher A, Krippl P, Leithner K, et al. Immunohistochemical analysis of desmoid tumours. J Clin Pathol. 2005;58(11):1152-6.

[54] Sorensen A, Keller J, Nielsen OS, Jensen OM. Treatment of aggressive fibromatosis: a retrospective study of 72 patients followed for 1-27 years. Acta Orthop Scand. 2002;73(2):213-9.

[55] Deyrup AT, Tretiakova M, Montag AG. Estrogen receptor-beta expression in extraabdominal fibromatoses: an analysis of 40 cases. Cancer. 2006;106(1):208-13.

[56] Balducci C, Lilli C, Stabellini G, Marinucci L, Giustozzi G, Becchetti A, et al. Human desmoid fibroblasts: matrix metalloproteinases, their inhibitors and modulation by Toremifene. BMC Cancer. 2005;5:22.

[57] Leithner A, Schnack B, Katterschafka T, Wiltschke C, Amann G, Windhager R, et al. Treatment of extra-abdominal desmoid tumors with interferon-alpha with or without tretinoin. J Surg Oncol. 2000;73(1):21-5.

[58] Acker JC, Bossen EH, Halperin EC. The management of desmoid tumors. Int J Radiat Oncol Biol Phys. 1993;26(5):851-8.

[59] Fernberg JO, Brosjo O, Larsson O, Soderlund V, Strander H. Interferon-induced remission in aggressive fibromatosis of the lower extremity. Acta Oncol. 1999;38(7):971-2.

[60] Geurs F, Kok TC. Regression of a great abdominal desmoid tumor by interferon alpha. J Clin Gastroenterol. 1993;16(3):264-5.

[61] Lackner H, Urban C, Benesch M, Raith J, Moser A, Sovinz P, et al. Multimodal treatment of children with unresectable or recurrent desmoid tumors: an 11-year longitudinal observational study. J Pediatr Hematol Oncol. 2004;26(8):518-22.

[62] Skapek SX, Ferguson WS, Granowetter L, Devidas M, Perez-Atayde AR, Dehner LP, et al. Vinblastine and methotrexate for desmoid fibromatosis in children: results of a Pediatric Oncology Group Phase II Trial. J Clin Oncol. 2007;25(5):501-6.

[63] Wehl G, Rossler J, Otten JE, Boehm N, Uhl M, Kontny U, et al. Response of progressive fibromatosis to therapy with liposomal doxorubicin. Onkologie. 2004;27(6):552-6.

[64] Heinrich MC, McArthur GA, Demetri GD, Joensuu H, Bono P, Herrmann R, et al. Clinical and molecular studies of the effect of imatinib on advanced aggressive fibromatosis (desmoid tumor). J Clin Oncol. 2006;24(7):1195-203.

[65] Liegl B, Leithner A, Bauernhofer T, Windhager R, Guelly C, Regauer S, et al. Immunohistochemical and mutational analysis of PDGF and PDGFR in desmoid tumours: is there a role for tyrosine kinase inhibitors in c-kit-negative desmoid tumours? Histopathology. 2006;49(6):576-81.

[66] Mace J, Sybil Biermann J, Sondak V, McGinn C, Hayes C, Thomas D, et al. Response of extraabdominal desmoid tumors to therapy with imatinib mesylate. Cancer. 2002;95(11):2373-9.

[67] Signoroni S, Frattini M, Negri T, Pastore E, Tamborini E, Casieri P, et al. Cyclooxygenase-2 and platelet-derived growth factor receptors as potential targets in treating aggressive fibromatosis. Clin Cancer Res. 2007;13(17):5034-40.

[68] Ballo MT, Zagars GK, Pollack A. Radiation therapy in the management of desmoid tumors. Int J Radiat Oncol Biol Phys. 1998;42(5):1007-14.

[69] Goy BW, Lee SP, Eilber F, Dorey F, Eckardt J, Fu YS, et al. The role of adjuvant radiotherapy in the treatment of resectable desmoid tumors. Int J Radiat Oncol Biol Phys. 1997;39(3):659-65.

[70] Dormans JP, Spiegel D, Meyer J, Asada N, Alman BA, Pill SG, et al. Fibromatoses in childhood: the desmoid/fibromatosis complex. Med Pediatr Oncol. 2001;37(2):126-31.

[71] Lackner H, Urban C, Kerbl R, Schwinger W, Beham A. Noncytotoxic drug therapy in children with unresectable desmoid tumors. Cancer. 1997;80(2):334-40.

[72] Dabney KW, MacEwen GD, Davis NE. Recurring digital fibrous tumor of childhood: case report with long-term follow-up and review of the literature. J Pediatr Orthop. 1986;6(5):612-7.

[73] Alman BA, Goldberg MJ, Naber SP, Galanopoulous T, Antoniades HN, Wolfe HJ. Aggressive fibromatosis. J Pediatr Orthop. 1992;12(1):1-10.

[74] Hayry P, Reitamo JJ, Vihko R, Janne O, Scheinin TM, Totterman S, et al. The desmoid tumor. III. A biochemical and genetic analysis. Am J Clin Pathol. 1982;77(6):681-5.

[75] Lim CL, Walker MJ, Mehta RR, Das Gupta TK. Estrogen and antiestrogen binding sites in desmoid tumors. Eur J Cancer Clin Oncol. 1986;22(5):583-7.

[76] Maddalozzo J, Tenta LT, Hutchinson LR, Crawford SE, Morse DS. Juvenile fibromatosis: hormonal receptors. Int J Pediatr Otorhinolaryngol. 1993;25(1-3):191-9.

[77] McDougall A, McGarrity G. Extra-abdominal desmoid tumours. J Bone Joint Surg Br. 1979;61-B(3):373-7.

[78] Reis-Filho JS, Milanezi F, Pope LZ, Fillus-Neto J, Schmitt FC. Primary fibromatosis of the breast in a patient with multiple desmoid tumors--report of a case with evaluation of estrogen and progesterone receptors. Pathol Res Pract. 2001;197(11):775-9.

[79] Serpell JW, Tang HS, Donnovan M. Factors predicting local recurrence of desmoid tumours including proliferating cell nuclear antigen. Aust N Z J Surg. 1999;69(11):782-9.

[80] Hansmann A, Adolph C, Vogel T, Unger A, Moeslein G. High-dose tamoxifen and sulindac as first-line treatment for desmoid tumors. Cancer. 2004;100(3):612-20.

[81] Easter DW, Halasz NA. Recent trends in the management of desmoid tumors. Summary of 19 cases and review of the literature. Ann Surg. 1989;210(6):765-9.

[82] Fong Y, Rosen PP, Brennan MF. Multifocal desmoids. Surgery. 1993;114(5):902-6.

[83] Early Breast Cancer Trialists' Collaborative Group. Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy. 133 randomised trials involving 31,000 recurrences and 24,000 deaths among 75,000 women. Lancet. 1992;339(8784):1-15.

[84] Ishizuka M, Hatori M, Dohi O, Suzuki T, Miki Y, Tazawa C, et al. Expression profiles of sex steroid receptors in desmoid tumors. Tohoku J Exp Med. 2006;210(3):189-98.

[85] Biermann JS. Desmoid tumors. Curr Treat Options Oncol. 2000;1(3):262-6.

[86] Chaudhuri PK, Walker MJ, Beattie CW, Das Gupta TK. Presence of steroid receptors in human soft tissue sarcomas of diverse histological origin. Cancer Res. 1980;40(3):861-5.

[87] De Pas T, Bodei L, Pelosi G, De Braud F, Villa G, Capanna R, et al. Peptide receptor radiotherapy: a new option for the management of aggressive fibromatosis on behalf of the Italian Sarcoma Group. Br J Cancer. 2003;88(5):645-7.

[88] Hoos A, Lewis JJ, Antonescu CR, Dudas ME, Leon L, Woodruff JM, et al. Characterization of molecular abnormalities in human fibroblastic neoplasms: a model for genotype-phenotype association in soft tissue tumors. Cancer Res. 2001;61(7):3171-5.

[89] Kouho H, Aoki T, Hisaoka M, Hashimoto H. Clinicopathological and interphase cytogenetic analysis of desmoid tumours. Histopathology. 1997;31(4):336-41.

[90] Brueckl WM, Preuss JM, Wein A, Jung A, Brabletz T, Pfluger R, et al. Ki-67 expression and residual tumour (R) classification are associated with disease-free survival in desmoid tumour patients. Anticancer Res. 2001;21(5):3615-20.

[91] Heidemann J, Ogawa H, Otterson MF, Shidham VB, Binion DG. Antiangiogenic treatment of mesenteric desmoid tumors with toremifene and interferon alfa-2b: report of two cases. Dis Colon Rectum. 2004;47(1):118-22.

[92] Stalinska L, Turant M, Tosik D, Sygut J, Kulig A, Kopczynski J, et al. Analysis of pRb, p16INK4A proteins and proliferating antigens: PCNA, Ki-67 and MCM5 expression in aggressive fibromatosis (desmoid tumor). Histol Histopathol. 2009;24(3):299-308.

[93] Yantiss RK, Spiro IJ, Compton CC, Rosenberg AE. Gastrointestinal stromal tumor versus intra-abdominal fibromatosis of the bowel wall: a clinically important differential diagnosis. Am J Surg Pathol. 2000;24(7):947-57.

[94] Lucas DR, al-Abbadi M, Tabaczka P, Hamre MR, Weaver DW, Mott MJ. c-Kit expression in desmoid fibromatosis. Comparative immunohistochemical evaluation of two commercial antibodies. Am J Clin Pathol. 2003;119(3):339-45.

[95] Miettinen M, Sobin LH, Sarlomo-Rikala M. Immunohistochemical spectrum of GISTs at different sites and their differential diagnosis with a reference to CD117 (KIT). Mod Pathol. 2000;13(10):1134-42.

[96] Yamaguchi U, Hasegawa T, Masuda T, Sekine S, Kawai A, Chuman H, et al. Differential diagnosis of gastrointestinal stromal tumor and other spindle cell tumors in the gastrointestinal tract based on immunohistochemical analysis. Virchows Arch. 2004;445(2):142-50.

[97] Hornick JL, Fletcher CD. Immunohistochemical staining for KIT (CD117) in soft tissue sarcomas is very limited in distribution. Am J Clin Pathol. 2002;117(2):188-93.

[98] Miettinen M. Are desmoid tumors kit positive? Am J Surg Pathol. 2001;25(4):549-50.

[99] Gibson S, Sebire NJ, Anderson J. Platelet-derived growth factor receptors and ligands are up-regulated in paediatric fibromatoses. Histopathology. 2007;51(6):752-7.

[100] Ferenc T, Wronski JW, Kopczynski J, Kulig A, Sidor M, Stalinska L, et al. Analysis of APC, alpha-, beta-catenins, and N-cadherin protein expression in aggressive fibromatosis (desmoid tumor). Pathol Res Pract. 2009;205(5):311-24.

[101] Gebert C, Hardes J, Kersting C, August C, Supper H, Winkelmann W, et al. Expression of beta-catenin and p53 are prognostic factors in deep aggressive fibromatosis. Histopathology. 2007;50(4):491-7.

[102] Thway K, Gibson S, Ramsay A, Sebire NJ. Beta-Catenin expression in pediatric fibroblastic and myofibroblastic lesions: A study of 100 cases. Pediatr Dev Pathol. 2008:1 [Epub ahead of print].

8. Appendix

Curriculum Vitae

Persönliche Daten

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Staatsbürgerschaft:	Österreich
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Ausbildung

1990-1994 VS Webling/ Jägergrund

1994-2002 Bischöfliches Gymnasium Graz

2002 Matura am Bischöflichen Gymnasium Graz

2003 Präsenzdienst Kaserne St. Michael/ 18. Jägerbataillon

2003 Inskription an der Medizinischen Universität Graz

2004 Abschluss des 1. Studienabschnittes

Seit 2004 regelmäßige ehrenamtliche Tätigkeiten für das Österreichische Rote Kreuz

2005 Abschluss der Ausbildung zum Rettungssanitäter

2007 Abschluss der Ausbildung zum Einsatzfahrer

2008 Abschluss des 2. Studienabschnittes

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Wissenschaftliche Arbeiten

Vortrag:

Therapy of superficial (infantile) and deep (desmoid-type) fibromatosis in children and adolescents. Fraissler L, Leithner A, Lackner H, Benesch M, Urban C, Beham A, Windhager R. 21st EMSOS meeting, May 15th, 2008, Warsaw, Poland.

Persönliche Interessen

Mountainbike, Snowboard, Tuba (Trachtenkapelle Graz-Wetzelsdorf)