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Review

Atypical Fibroxanthoma - Histological Diagnosis, Immunohistochemical Markers and Concepts of Therapy

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Abstract. *Background: Atypical fibroxanthoma (AFX) is an uncommon, rapidly growing cutaneous neoplasm of uncertain histogenesis. Thus far, there are no guidelines for diagnosis and therapy of this tumor. Patients and Methods: We included 18 patients with 21 AFX, and 2,912 patients with a total of 2,939 AFX cited in the literature between 1962 and 2014. Results: In our cohort, excision with safety margin was performed in 100% of primary tumors. Local recurrences were observed in 25% of primary tumors and parotid metastases in 5%. Ten-year disease-specific survival was 100%. The literature research yielded 280 relevant publications. Over 90% of the reported cases were negative for cytokeratins, S100, desmin and human melanoma black 45 (HMB-45). Recurrent AFX was reported in 7.6% and metastasizing AFX in 2.75% cases. No significant differences in the recurrence and survival rates following wide local excision versus Mohs microsurgery were observed. Twenty-year disease-specific survival rate was 97.8%. Conclusion: A well-selected panel of immunohistochemical markers is necessary to establish AFX diagnosis with sufficient certainty. Adequately treated, AFX has an excellent prognosis, but long-term follow-up is recommended due to the potential for aggressive behavior.*

Atypical fibroxanthoma (AFX) is a rare primary mesenchymal skin tumor of presumable fibroblastic origin, but of uncertain histogenetic derivation. It comprises up to 0.2% of all skin tumors (1). AFX was initially described by Lund and Kraus in 1962 (2). The name 'atypical fibroxanthoma' reflects the tumor composition, containing mainly xanthomatous-looking cells and a varying proportion of fibrocytoid cells with variable, but usually marked cellular atypia (3).

According to previous reports, AFX chiefly occurs in the sun-exposed head-and-neck area, especially in elderly males (3). There are two disease peaks described: one within the 5th to 7th decade of life and another one between the 7th and 8th decade. The former disease peak is associated with lower tumor frequency (21.8%) and tumors that do not necessarily manifest on skin areas exposed to sunlight (4).

There are no common guidelines described regarding the diagnosis and the therapy of AFX. Histologically, AFX closely resembles undifferentiated pleomorphic sarcoma (UPS), formerly known as malignant fibrous histiocytoma (MFH) (5-7). In contrast to UPS, however, AFX is a dermal-based neoplasm (8, 9) which, according to the current World Health Organization (WHO) classification of tumors of soft tissue (10), is limited to the dermis with no more than minimal extension into adjacent subcutaneous fat. The presence of significant subcutaneous infiltration as well as of coagulative necrosis and vascular invasion warrant the diagnosis of 'pleomorphic dermal sarcoma'. Admittedly, the latter is histologically indistinguishable from AFX if only the most superficial part of the tumor is sampled. Furthermore, many authorities consider the two entities likely to represent a disease spectrum. According to the current WHO classification, when diagnosed strictly as defined above, AFX behave in a benign fashion after complete excision with free margins.

Clinically, AFX are usually described as exophytic, dome-shaped solid nodules of greyish-brown to red color, which can be oozing or bleeding (3, 11). The size of the tumor rarely exceeds 2 cm (3, 11). The center of the tumor is often ulcerated, which causes an epithelial collarette rising above skin level (8). The epidermis directly above the tumor is usually attenuated or atrophied by the pressure of the tumor (8, 12). Occasionally, a narrow zone of collagen (grenz zone) separating tumor from

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epidermis is observed (13). Even though AFX is non-encapsulated, it is usually well-delineated from the surrounding tissue. Electron microscopic studies were consistent with a fibrohistiocytic origin of AFX (14-16). Histology commonly shows marked cellular pleomorphism, hyperchromatic cells with prominent bizarre nuclei and atypical mitotic figures (7, 8, 11). A variety of different cell types are observed, including fibroblastic spindle cells, epithelioid cells, large histiocytoid cells and multi-nuclear giant cells (14, 17). Various degrees of aneuploidy have also been reported (18-21), whereby a study on DNA quantification in 10 AFX cases showed that larger histiocytic or giant cells were often aneuploid, while smaller spindle-like cells were diploid (21). Despite bizarre histological features suggesting malignancy, AFX usually has a benign clinical course, aggressive progression is rare (22-24). Accordingly, the old synonym "superficial MFH" or "MFH of skin" should be abandoned to avoid the risk of misinterpretation by clinicians and the hazard of overtreatment.

Several sub-types of AFX have been described in the literature, which show uncommon characteristics and can be mistaken for other tumor entities (25, 26). These unusual variants include pigmented AFX (which can resemble malignant melanoma) (27-29), osteoclastic (30-34), osteoid (35), myxoid (36, 37), keloidal (33, 38-41), clear-cell (42-51), granular cell (33, 52-56) and monomorphous AFX (33, 40, 57). Altogether, 201 cases of these variants were thus far reported, with keloidal (42 cases) and monomorphous [37 cases (33, 40, 57)] AFX being the most common sub-types encountered among the uncommon variants.

Because of the non-specific clinical features, correct diagnosis without histopathological and immunohistochemical examination is difficult (34, 58). Immunohistochemistry aims at excluding spindle cell cutaneous squamous cell carcinoma (SCC) and desmoplastic melanoma, *via* staining for cytokeratins and S100 protein/melanocytic markers, respectively (13). In addition, several other markers, such as smooth muscle actin (SMA), desmin, CD31 and others may be necessary to exclude leiomyogenic, myofibroblastic, endothelial and other uncommon entities (8, 13).

In this study, we aimed to provide a more detailed analysis of AFX, including diagnosis and therapy, on the basis of 18 patients from our clinic and of nearly 3,000 cases published in medical literature and cited in PubMed. Particular attention was given to the elaboration of a panel of immunohistochemical markers helpful for a fast and cost-effective diagnosis and to the recommendations of an adequate treatment strategy for this tumor entity.

Materials and Methods

Patient history and clinical investigations. Eighteen patients with 21 AFX, treated at the University Hospital Erlangen, were included in the study. The clinical history was focused on factors associated with this disease (Table I). The whole skin of the patients, especially the tumor region, was screened. The regional lymph nodes of the affected area were likewise examined, as for in all malignancies of the head and neck (59). Biopsies and excisions of the suspected area were investigated histologically and immunohistochemically by one experienced pathologist (A.A.) and one experienced dermatopathologist (F.K.). For immunohistochemical analysis, a total of 29 tissue samples originating from 21 tumors were fixed in formalin, embedded in paraffin and cut into 1-2 μm thick sections. Following deparaffinization, sections were rehydrated and stained using primary antibodies against α1-antitrypsin (A1AT), α1-antichymotrypsin (A1AC), CD31 (clone JC70A), CD34 (clone QBEnd10), CD68 (clone PG-M1), CD74 (clone LN2), CD99 (Clone 12E7), MAC387 (myeloid/histiocyte antigen), S-100, melan-A (melanoma antigen recognized by T-cells, clone A103), anti-human melanoma black 4 (HMB45), smooth muscle actin (SMA, clone 1A4), desmin (clone D33), Ki67 (clone MIB-1), p53 (clone DO-7, wild-type), vimentin (clone V9), pancytokeratin (clones KL1, MNF116, AE 1/3), cytokeratin HMW (Clone 34βE12), factor VIII/von Willebrand factor (clone F8/86), and epithelial membrane antigen (EMA, clone E29) from Dako Cytomation (Glostrup, Denmark); cathepsin B (clone CB131) from Acris Antibodies GmbH (Herford, Germany); stromelysin-3 (MMP-11, clone SL3.05/3F268) from Lab Vision (Fremont, CA, USA), melanoma-associated antigen (NK1/C3) from Zymed Laboratories Inc. (San Francisco, CA, USA), and CD10 (clone 56C6) from Novocastra Laboratories Ltd. (Newcastle upon Tyne, UK).

Therapy. All of our patients were presented and discussed in our interdisciplinary tumor boards. Surgery (local excision with safety margin) was indicated as treatment of choice and performed in all cases. Wound closure was performed primarily (after fresh frozen sections) or secondary depending on the final histopathological results and the size of the defect. One patient with recurrent AFX received adjuvant percutaneous fractionated radiotherapy as recommended by the interdisciplinary tumor boards.

According to the routine procedures at our University, follow-up started 2 months after finishing the treatment and included assessment of local situation (light damaged skin, scar after surgery) and regional lymph nodes (clinical palpation, ultrasound examination).

Literature search. The MEDLINE bibliographic database (registry of all publications in English language, compiled by the United States National Library of Medicine http://www.ncbi.nlm.nih.gov/pubmed/), served as the source for our literature search. Additionally, the reference lists of the published articles were screened for further relevant publications.

The search for the term "atypical fibroxanthoma" produced in total 570 publications that appeared between 1962 and October 2014, out of which those were selected which matched the first-line inclusion criteria: confirmed and proved diagnosis of AFX including histological and immunohistological data. Information on epidemiology and etiology, therapy, outcome and follow-up were the second-line criteria. It must be noted that due to the definite data availability for each specific variable, not all analyses could be performed in all cases. This type of patient selection represents a form of unavoidable bias.

Statistics. We analyzed and compared our collective with patients with AFX reported in literature. For each variable, the analyses were

Table I. *Patient collective: Age, sex, atypical fibroxanthoma (AFX) localization, risk factors, primary diagnosis, therapy, as well as the data regarding relapse occurrence, follow-up duration and status are listed.*

Patient no.	Age (years)/ gender	Localization	Increased UV exposure	Other tumors/ other risk factors	Primary/differential diagnosis	Therapy	Recurrence/ metastasis	Follow-up (months)/status
1	81/M	Helix, right	Yes		BCC /SCC	Excision + amputation of right auricle after relapse	2/1 (Parotid)	89/AND
2	87/M	Nose/medial canthus, right	Yes		BCC	Excision	0	19/AND
3	81/F	Temple, right	No		Fibrosarcoma/ BCC	Excision	0	6/DAD
4	73/F	Cheek, left	Unknown	Unknown	SCC	Biopsy, excision only	Unknown	Not possible
5	71/M	Parietal, central-left	No	Multiple SCC	Unknown	Excision	1/0	51/AND
6	86/M	Ear, right	Yes	Mycosis fungoides, multiple BCC, two SCC, Bowen disease	BCC	Excision + auricle-reduction plastic	1/0	59 /AND
7	92/F	Forehead, right	Yes	Lentigo malignant melanoma	Bowen carcinoma	Excision	0	42 /AND
8	83/M	Helix left	No	SCC/frostbite of both ears	Undifferentiated pleomorphic sarcoma	Excision	0	56/DAD
9 (a)	83/M	Occipital	Yes	SCC, Bowen disease, prostate cancer/PDT	AFX	Excision	0	21/DAD
(b)	83/M	Parietal, left	Yes	SCC, Bowen disease, prostate cancer/PDT	AFX	Excision	0	13/DAD
10	68/M	Auricle, left	No	Tick bite	AFX	Excision	0	94/AND
11 (a)	49/M	Helix, left	Yes	Frostbite of both ears	BCC	Excision	0	171/AND
11 (b)	53/M	Parietooccipital, right	Yes	Frostbite of both ears	AFX	Excision + RT after relapses	5/0	122/AND
12	72/M	Scalp, lateral left	No	Bowen disease/ immunosuppression,	Actinic keratosis	Excision	0	19/AND
13	89/M	Recurrent AFX: Parietal, left	No	BCC, SCC	BCC/SCC	Excision	1/0	46/DAD
14	81/M	Parietal, left	No	BCC	SCC	Excision	0	20/AND
15	77/M	Collarbone, right	Yes	Colorectal cancer, multiple BCC, SCC	BCC	Excision	0	65/AND
16 (a)	77/M	Scalp	Yes		SCC	Excision	0	37/AND
16 (b)	77/M	Scalp	Yes		Actinic keratosis	Excision	0	29/AND
17	54/M	Occipital, left	Yes		BCC/irritated nevus cell nevus	Excision	0	23/AND
18	74/M	Temple	No		SCC/seborrhoic keratosis	Excision	0	35/AND

M: Male; F: female; a: first primary tumor; b: second primary tumor; BCC: basal cell carcinoma; SCC: squamous cell carcinoma; PDT: photodynamic therapy; RT: radiotherapy; AND: alive with no disease; DAD: died of another disease.

performed separately for our patients and for the previously reported AFX cases, with the exception of survival analysis, in which our collective was included. Data were expressed as average±SEM (median, range) unless stated otherwise. Distribution of variables was tested by Kolmogorov test. Proportions were calculated using Fisher exact test or chi-square test. Patient survival was calculated according to the Kaplan–Meier estimation product. Log-rank test was used for comparison between the groups. A value of $p<0.05$ was considered statistically significant.

Results

Patients and cases. Our cohort included 18 patients suffering from AFX. As three patients presented with two AFX each, the total number of tumors investigated was 21. From the literature, 280 publications fulfilled the criteria and a total of 2,912 patients with AFX were derived (1, 3-5, 7, 11, 12, 14-18, 24-27, 29-45, 48-57, 60-257), (258-286).

Multiple AFX was reported in 27 patients, resulting in 2,939 tumors that were included in the analyses. A case report regarding one of our patients had been published before (23), this patient was, therefore, excluded from the subsequent literature analyses. Altogether, our 18 patients *versus* 2,912 patients from the literature were compared in this study.

Epidemiology, history and etiology. The mean age of our patients was 75.8 years (median=77 years, range=49-92 years), and the male to female ratio was 5:1. The exact location of all 21 tumors, as well as detailed data regarding the time of tumor development and individual risk factors are shown in Table I.

Analysis of the previously reported cases of AFX revealed 828 patients with the detailed information regarding age, which was 70.4±15.8 years (median=74 years, range=3-107 years). Even though AFX usually occurs during the 7-9th decades of life (76.7% of affected patients; Figure 1A), there were cases of very young patients described (71, 82, 87, 146, 160, 177, 281). However, these occurrences were mostly associated with other comorbidities, as in the case of a 3-year-old patient suffering from xeroderma pigmentosum who developed AFX (146). In 2298 cases, the information about patient gender was available: The male (75.4%) to female (24.6%) ratio was approximately 3:1 (Table II). These data are in good concordance with those for our patient collective (Tables I and II).

AFX develops predominantly in the head and neck area, and rarely affects the trunk and limbs regions (186, 202, 249, 287). Our collective showed a similar distribution of tumor localization, with 95.2% of AFX detected within the head and neck region. In 2228 cases described in literature, the data concerning AFX localization was available: The head and neck area was affected in 84.4%, whereas the limbs and trunk area in 15.6% (detailed localizations of AFX reported in the literature are shown in Table III). AFX of the trunk and extremities most commonly affected younger patients (58.6±18.9 years, median=64 years, range=18-93 years; n=104 patients; Figure 1B).

Risk factors for AFX for both patient cohorts are high UV exposure, trauma and scarring in the area of tumor, exposure to radiation, immunosuppressive therapy and the history of other skin cancer. This was especially recognizable regarding UV exposure, which represents the highest risk according to our data (58.8%, 10 out of 17 patients) and those obtained by literature search (61.9%, Table II). Interestingly, the collected data also support the notion that immunosuppression may constitute an additional risk factor for AFX, being reported in 5% of our patients and in 3.3% of published cases (90, 97, 101, 108, 115, 145, 147, 209, 223).

Out of our patients presenting with external initial diagnosis, only four tumors were correctly diagnosed as AFX

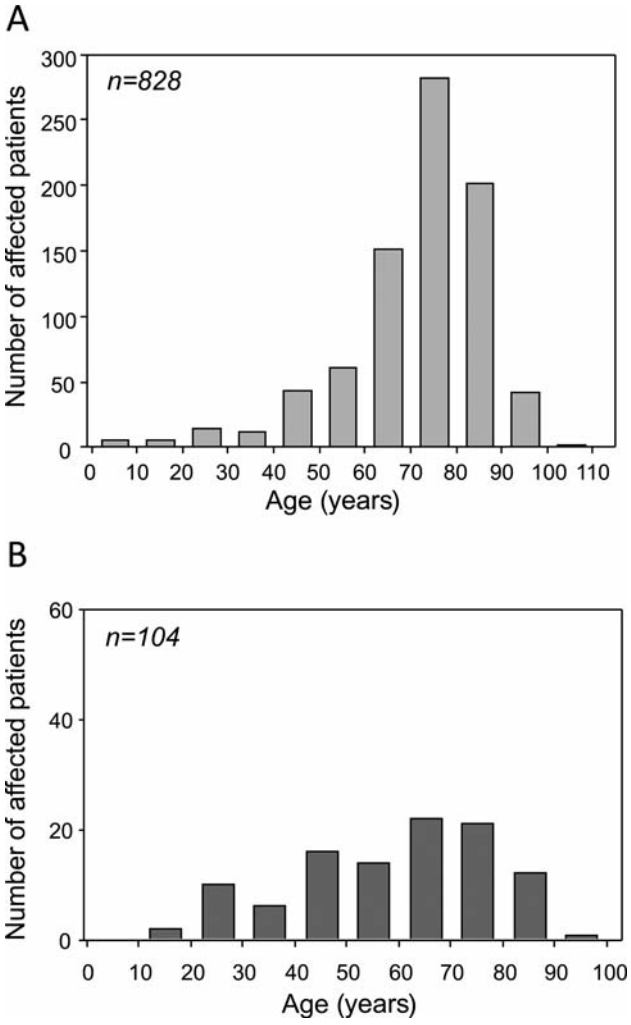

Figure 1. *The occurrence of atypical fibroxanthoma (AFX) in relation to patients' age. a: Age of AFX patients, n=828 reported cases. b: Age of the patients with AFX occurrences in the limbs and trunk region, n=104 reported cases.*

(Table I). The most common suspected diagnosis of 17 other tumors was basal cell carcinoma (BCC, seven cases) and SCC (four cases). In the literature, information regarding the initial clinical diagnosis was reported in 411 cases. AFX was correctly diagnosed in only 43% (Table IV).

Clinical presentation. Rapid development of the tumor was observed in our cohort (median=4 months; range=week-4 years) and in 245 cases reported in the literature, for which this information was available (median time to development=6 months, range=2 weeks-20 years). In most cases, the rapid progression of tumor growth within the weeks preceding medical consultation was given as the main reason for visiting a doctor (164).

Table II. *Occurrence and outcomes of atypical fibroxanthoma (AFX). Data reported in literature are compared to the present study collective. Statistical differences were assessed using Mann–Whitney's U-test. Proportions were calculated using Chi-square test or Fisher's exact test for sample number lower than 5. A value of p<0.05 was considered statistically significant.*

AFX occurrence and outcome	Data from literature, n (%) or median (range)	Total, n	Our collective, n (%) or median (range)	Total, n
Age, years	74 (3-107)	828	77 (49-92)	18
Gender, M/F (ratio)	1732/566 (3:1)	2298	15/3 (5:1)	18
Localization				
Head/neck	1880 (84.4%)	2228	20 (95.2%)	21
Trunk/limbs	348 (15.6%)	2228	2 (4.8%)	21
Risk factors				
UV exposure	490 (61.9%)	791	10 (58.8%)	17
Trauma/scarring	28 (3.5%)	791	2 (11.7%)	17
Immunosuppression	26 (3.3%)	791	1 (5.1%)	17
Other cancer	222 (40.8%)	544	9 (52.9%)	17
Size, cm	1.2 (0.02-8.5)	820	1.35 (0.6-3)	15
Multiple AFX	27 (0.9%)	2912	3/18 (16.7%)	18
Time of development, months	6 (0.5-240)	245	4 (0.25-48)	21
Therapy				
WLE	1031 (97.3)	1289	20 (100)	20
MMS	222 (17.2)	1289	0 (0)	20
Other excision	1 (0.1)	1289	0 (0)	20
Non-resectional	31 (2.4)	1289	0 (0)	20
Radiotherapy	4 (0.3)	1289	0 (0)	20
Recurrences	113 (7.6)	1488	5 (25)	20
Time to first recurrence <2 years	58 (89.2)	65	5 (100)	5
Metastases	41 (2.75)	1488	1 (5)	20
Follow-up in months, median	24 (0.25-456)	729	39.5 (6-171)*	20
AFX deaths	10 (0.7)	1488	0 (0)	17

*p=0.04, all other comparisons p>0.05.

The mean tumor size in our collective was 1.77±0.94 cm (median=1.35 cm, range=0.6-3 cm). In the literature, the tumor size was reported for 820 cases with a mean size of 1.45±0.96 cm (median=1.2 cm, Table II). In general, the clinical gross appearance of AFX was oval to round, or semi-nodular to nodular. Macroscopic tumor appearance in our patients was in line with the observations reported in the literature (see above).

Histopathology. Histopathological results did not differ from those reported in the literature (see above). Tumor cells were variably, but usually highly, pleomorphic with heterochromatic and hyperchromatic nuclei, prominent nucleoli, clear-cut nuclear atypia and atypical mitoses, as well as a shift of the nuclear:cytoplasmic ratio (Figure 2). Furthermore, 15 out of 21 primary tumors (71.4%) had a high rate of mitotic activity.

AFX infiltration in surrounding tissues with or without destruction of cartilage is rare and was observed in one recurrent AFX in our series. In the literature, it was thus far described in 39 cases (39/2939, 1.3%), with a dominant number infiltrating into the subcutaneous fatty tissue. However, large areas of necrosis were observed in 4 out of 21 tumors (19%) in our collective, whereby only one of these tumors was primary and three were recurrent AFX. Admittedly, some of these cases predated the current definition of AFX and might overlap with pleomorphic dermal sarcoma. In the literature, intratumoral areas of necrosis were rarely described (20, 33, 96, 229). Among the 2,912 patients included in our analyses, 10 cases with necrosis were mentioned, but in the largest collective reported thus far, by Beer *et al*. (33), necrosis was noted in 6/171 cases (3.5%).

Satellite tumors in the vicinity of the primary AFX were thus far described in two patients (24, 56), however, secondary satellites developing near (*i.e.* <1 cm) recurrent tumors are more common – altogether eight such occurrences were reported (3, 15, 91, 106, 107, 202), including one of our patients (23) shown in Figure 3.

Immunohistochemical findings. Immunohistochemical analyses of the excised specimens showed >90% positive rates for the following markers: A1AT, CD10, CD68, CD74, CD99, melanoma-associated antigen (NK1/C3), vimentin, SMA, stromelysin-3 and cathepsin B (Figure 2, Table V). The majority of cases (>90%) were negative for antibodies against

Table III. *Detailed localization of atypical fibroxanthoma (AFX) cases reported in the literature.*

AFX localization	Tumors	%
Head and neck	1880	84.38
Scalp	379	17.01
Ear	254	11.40
Cheek, mandible	137	11.68
Face (undefined)	132	11.25
Forehead	88	3.95
Temple	57	2.56
Nose	56	2.51
Neck	50	2.24
Lip	15	0.67
Eye/eyelid	5	0.22
Head/neck unspecified	707	31.73
Limbs and trunk	348	15.62
Arm	110	4.94
Leg	70	3.14
Trunk	55	2.47
Limbs/trunk unspecified	113	5.07
Total	2228	

Table IV. *Initial clinical diagnosis in the reported atypical fibroxanthoma (AFX) cases.*

Initial diagnosis	Reported cases	%
AFX	177	43.07
Squamous cell carcinoma	71	17.27
Sarcoma	48	11.68
Melanoma	26	6.33
Basal cell carcinoma	20	4.87
Pseudosarcomatous dermatofibroma	18	4.38
Pyogenic granuloma	7	1.70
Pseudosarcomatous reticulohistiocytoma	6	1.46
Dermatofibrosarcoma	5	1.22
Keratoacanthoma	4	0.97
Undifferentiated pleomorphic sarcoma	3	0.73
Rhabdomyosarcoma	3	0.73
Granuloma	2	0.49
Epithelioma (unspecified)	2	0.49
Naevus cell naevus	2	0.49
Actinic keratosis	1	0.24
Angioma	1	0.24
Neurofibroma	1	0.24
Unknown/unspecified	14	3.41
Total	411	

cytokeratins, S100 protein, desmin, melan-A/ melanoma antigen recognized by T-cells 1 (MART1) and epithelial membrane antigen (EMA), and >85% negative for CD34 and CD31 (Table III).

In the literature, there exist 200 reports that included the information about immunohistochemistry encompassing over 60 different markers. However, more than 20 of these markers were investigated on patient collectives smaller than 15 individuals. According to the literature, markers that are most often used for immunohistochemistry in context of AFX include cytokeratins and S100, smooth muscle actin, vimentin, CD68 and desmin (≥400 cases each). Positive reaction in >90% was demonstrated for vimentin, procollagen 1, CD1a, fascin, and in >85% for CD68 and CD10. Negative results in >90% were obtained for cytokeratins, S100, desmin, HMB-45, melan-A/MART1, as well as p63, nerve growth factor receptor (NGFR), CD15, and in >85% for EMA and CD31 (Table III).

Regarding positive staining, differences between our samples and published cases were observable in SMA (90.5% *vs*. 51.1% positive), A1AT (95.2% *vs*. 78.5%), CD99 (90.5% *vs*. 57.5%)), NK1/C3 (100% *vs*. 68.5%), cathepsin B (100% *vs*. 64.7%) and CD74 (100% *vs*. 36.6%, Table III), as well as in stromelysin-3 (Figure 2F), which was positive in 100% of our samples and 40% in a single report published so far with five AFX cases (283).

AFX therapy. Following diagnosis, one of the patients was not treated at the University Hospital Erlangen and was lost to follow-up (Table I). Therapy of the remaining 17 patients was by resection with a safety margin. In 11 cases, the tissue defects were covered primarily and in seven patients, a secondary coverage was necessary. Only one patient received adjuvant radiotherapy after recurrent tumors were resected for the fourth time. The tumor area was irradiated in 22 sessions over a period of five weeks with 10 MeV electrons at a reference dose of 37.5 Gy, following 6 MeV photons at a reference dose of 16.1 Gy. Another patient, who developed two recurrences and regional lymph node metastasis in the parotid gland, underwent sub-total ablation of the auricle, parotidectomy and neck dissection. He refused to continue the irradiation after 22 Gy had been applied (Table I, case no. 1) (23).

In the literature, we found information regarding therapy for 1289 AFX cases (Table II). Surgical excision was performed in 1254 out of 1289 cases (97.3%) representing the most common therapy of this tumor (Table II). Within this group, 1031 (82.2%) of the primary tumors were excised with particular focus on a safety margin (WLE) and 222 (17.7%) were treated using MMS. WLE with adjuvant therapy was performed in 12 cases. In only 35 of 1289 cases (2.7%) was tumor removal by means of non-resecting techniques reported: These included curettage and electrodesiccation (35, 117), diathermia (3, 27, 127) cryosurgery (26, 117) and radiotherapy (114, 123, 161).

Follow-up. Follow-up data were available for 17 out of our 18 patients (Table I), with a mean follow-up of 50.8±41.2 months

Table V. *Immunohistochemical (IHC) markers useful for differential diagnosis of atypical fibroxanthoma (AFX). Literature data: IHC markers investigated on patients cohorts larger than 15 patients are listed; Our collective: A total of 29 tissue samples originating from 21 tumors were investigated.*

IHC Marker	Reported cases, n	Positive cases		Total samples (own study), n	Positive samples	
		n	%		n	%
Cytokeratins	1,924	32	1.66	19	1	5.3
S100	1,328	53	4.0	20	1	5.0
Smooth muscle actin	540	276	51.1	21	19	90.5
Vimentin	484	481	99.4	20	19	95.0
CD68	459	391	85.2	21	20	95.2
Desmin	425	5	1.2	23	0	0
Human melanoma black 45	383	9	2.3	4	0	0
CD10	342	291	85.1	21	19	90.5
p63	282	21	7.4	ND	-	-
CD34	223	8	3.6	22	3	13.6
Melan-A/MART1	222	1	0.5	10	0	0
Procollagen 1	183	166	90.7	ND	-	-
α1-Antitrypsin/-antichymotrypsin	135	106	78.5	21	20	95.2
CD99	134	77	57.5	21	19	90.5
Epithelial membrane antigen	128	14	10.9	18	0	0
CD31	121	13	10.7	7	1	14.3
CD163	104	44	42.3	ND	-	-
CD117	100	34	34.0	ND	-	-
Lysozyme	94	49	52.1	ND	-	-
Factor XIIIa	94	42	44.7	ND	-	-
Podoplanin (D2-40)	90	37	41.1	ND	-	-
Peanut agglutinin	59	10	17.0	ND	-	-
Melanoma-associated antigen	57	39	68.5	17	17	100
Nerve growth factor receptor	52	1	1.9	ND	-	-
p53	47	27	57.5	19	19	100
CD74	41	15	36.6	21	21	100
Microphthalmia-associated transcription factor	41	12	29.3	ND	-	-
Ki67	40	40	100	22	18	81.8
Ferritin	38	19	50.0	ND	-	-
CD15	39	0	0	ND	-	-
Neuron specific enolase	32	5	15.6	ND	-	-
Ubiquitin carboxy-terminal hydrolase L1 (neuronal marker)	30	9	30.0	ND	-	-
CD1a	28	27	96.4	ND	-	-
S100A9 (MAC387)	21	7	33.3	4	2	50.00
Fascin	17	17	100	ND	-	-
Cathepsin B	17	11	64.7	16	16	100
Bcl-2-associated X protein	17	6	35.3	ND	-	-

ND: Not determined.

(median=39.5 months, range in 6-171 months). Four of the patients died of unrelated diseases.

In the literature, we found 729 AFX cases with reference to the duration of follow-up (mean=41.7±57.3 months; median=24 months, range=0.25-456 months, Table II).

Regression, recurrences and metastases. In 30 reported cases, features of regression were noted (41, 201) and a spontaneous regression of AFX without therapeutic intervention was described in two patients (164, 215). Within our collective, 25% (5/20) of primary tumors developed recurrences that arose within 24 months after initial diagnosis (median=19 months, range=5-23 months). Three patients developed recurrences once, one patient twice, and one five times. In the patient with two recurrences, secondary satellite lesions of 0.5 and 0.7 cm were detected 11 months after the diagnosis of primary tumor, within 0.3 cm distance from the second recurrence of the tumor (Figure 3). At the same time, metastasis in the locoregional parotid region was detected in that patient, which was the only case of metastasizing AFX in our series (1/20; 5%, Table I, case no. 1).

In the literature search, we found 1,488 tumors for which the data on outcomes were available (Table II). Recurrent AFX was reported in 113/1488 cases (7.6%). Single relapse was

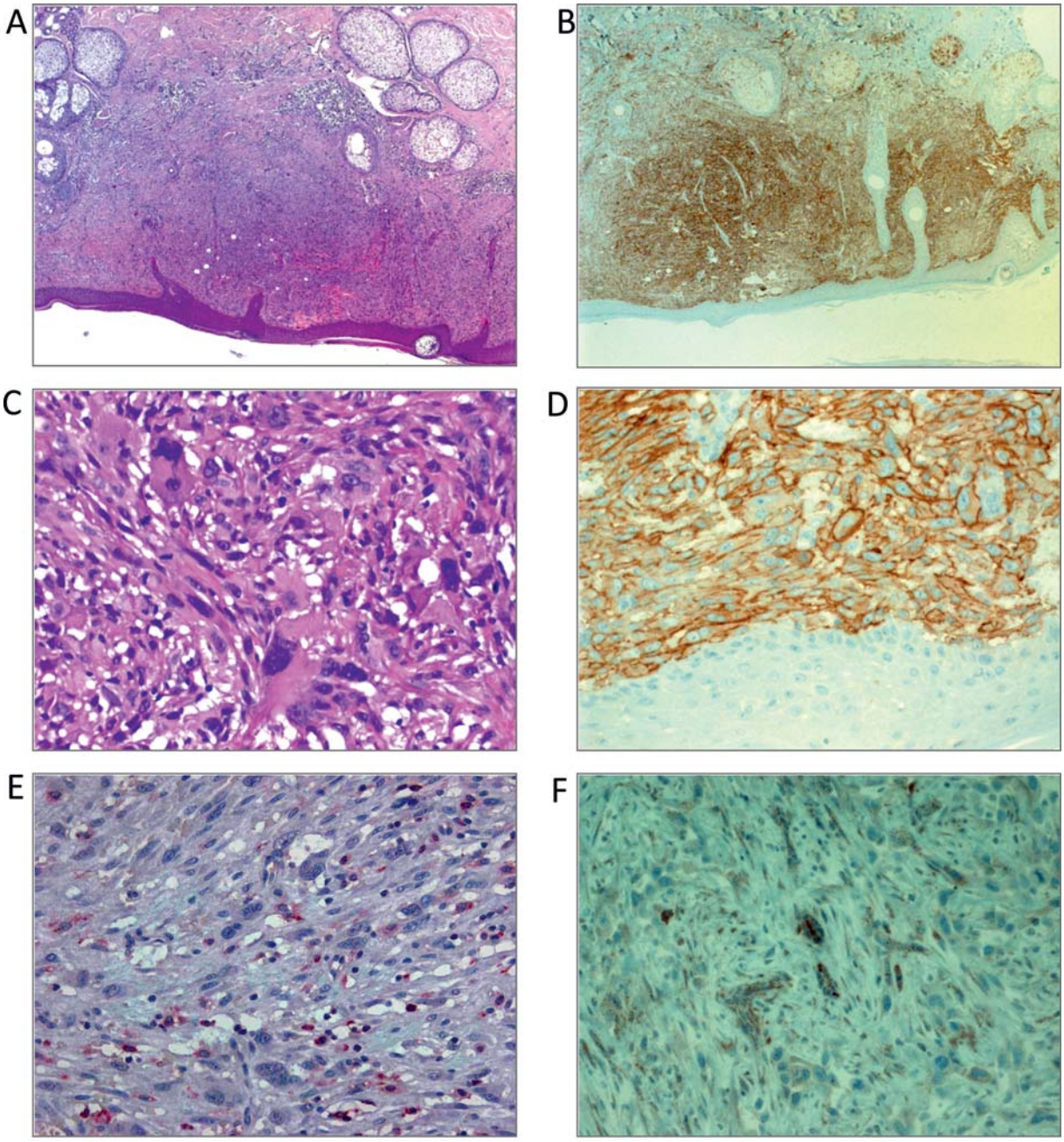

Figure 2. *Typical presentation of atypical fibroxanthoma (AFX). a: Overview of AFX showing a small dermal-based nodule immediately beneath the epidermis (×50). b: The lesion is limited to the dermis as highlighted by CD10 immunostain (×50). c: Higher magnification shows compact fascicles of highly atypical pleomorphic cells (×400). d: Characteristic diffuse and strong expression of CD10 (×400). e: CD74 expression (×200). f: Positivity for stromelysin-3 (×20).*

described in 99 patients (6.65%), whereas 14 patients (0.9%) developed multiple recurrences. For 65 patients with recurrent AFX, there was information available about the time to recurrence development. In 89.2% (58/65) of these patients, the first recurrence occurred within 24 months after primary tumor removal (5, 24, 57, 64, 76, 79, 94, 97, 106, 123, 150, 171).

For 101 out of 113 patients with recurrent AFX, we found data regarding the therapy of the primary tumor: 84 of these patients were treated with WLE, 16 patients with MMS and one patient with curettage. Regarding the total numbers of patients treated with WLE (n=898) and MMS (n=211) for whom the clinical data on outcomes were available, this

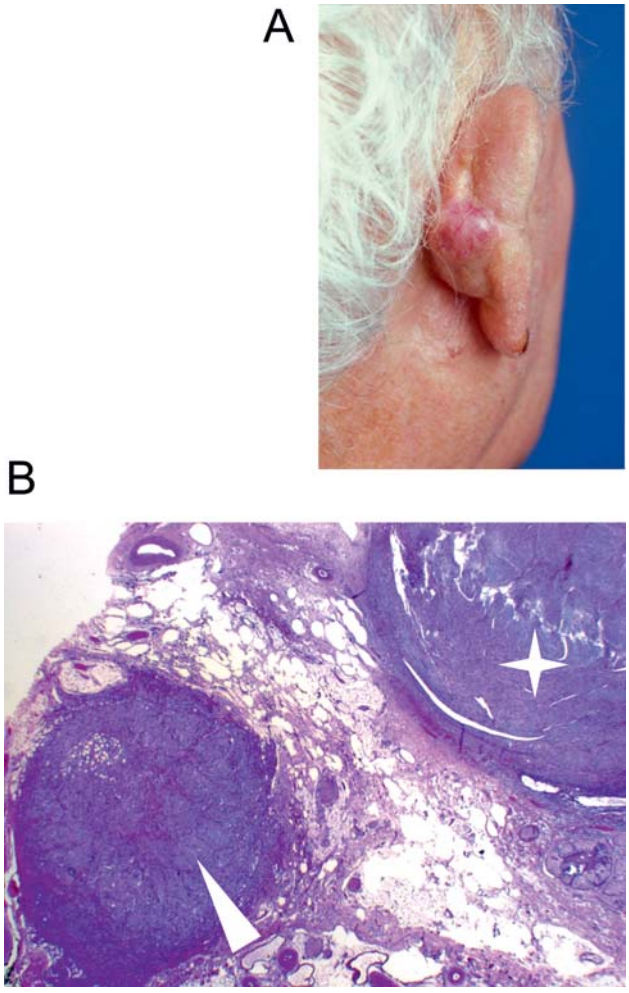

Figure 3. *Rare recurrent case of atypical fibroxanthoma (AFX). a: Multinodular mass of the ear. b: Overview image shows multinodular growth involving the deeper dermis and the subcutis (×125). Satellite tumor (white arrowhead) in a 0.3 cm distance from recurrent AFX (white star) is indicated.*

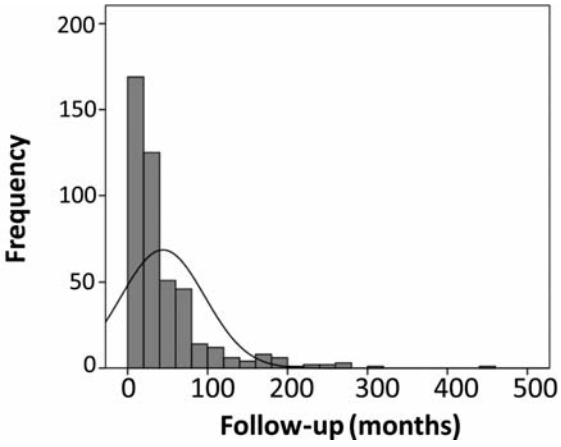

Figure 4. *Distribution of the follow-up duration in 451 analyzed patients with comparison to the normal curve of distribution.*

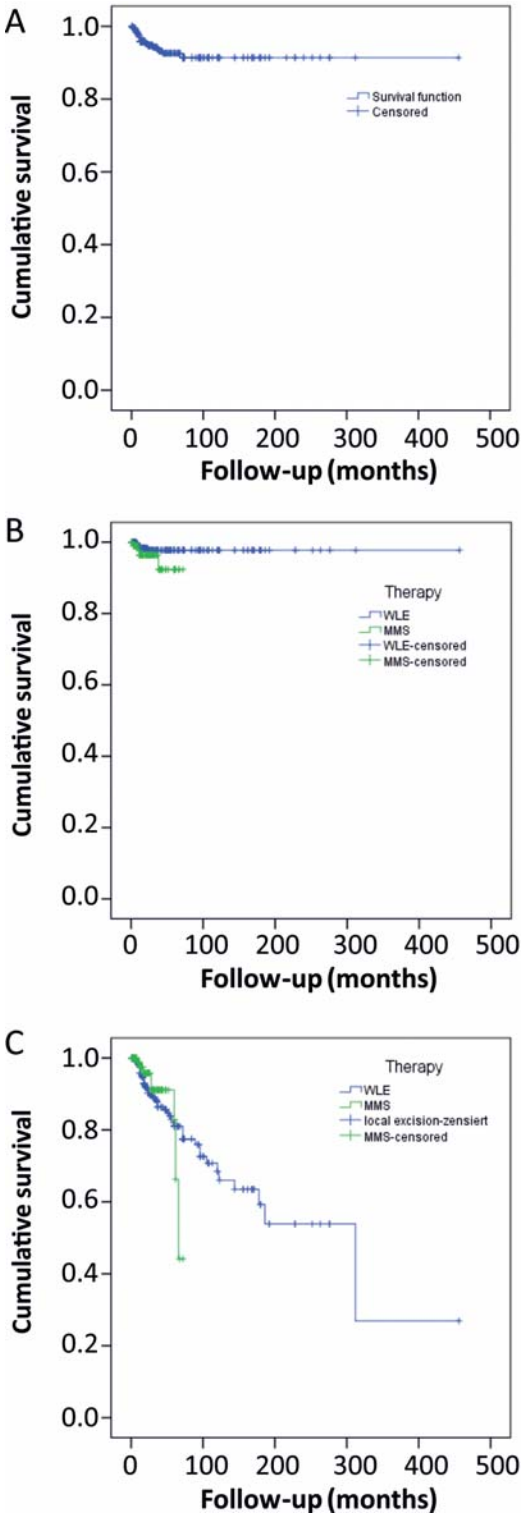

Figure 5. *Atypical fibroxanthoma-specific survival according to Kaplan–Meier analysis (n=451). a: Disease-specific survival. b: Disease-specific survival according to surgical treatment of the primary tumor. c: Recurrence-free survival according to surgical treatment method of the primary tumor. WLE: Wide local excision; MMS: Mohs micrographic surgery.*

corresponds to a relapse frequency ratio of 9.35% and 7.58%, respectively. Recurrent tumors were removed surgically. In 12 recurrent cases, adjuvant therapeutic measures were undertaken: adjuvant radiotherapy in 11 cases (61, 80, 102, 171, 181) and adjuvant topical therapy using fluorouracil and tretinoin ointment in one case (82).

Metastasizing AFX was reported in 41 out of 1,488 patients (2.75%). Twenty-three of these patients developed recurrences and metastases in parallel. Regional metastases were described in 13/41 cases and distant metastases in 18/41 cases. In 5/41 patients, both regional and distant metastases were reported. Data regarding the treatment of primary tumor was available for 32 of 41 AFX patients that developed metastases. Twenty-three of these patients were treated with excision with safety margin (2.56% of n=898 patients that underwent WLE) and nine were treated with MMS surgery, corresponding to 4.26% of n=211 patients undergoing MMS.

There were eight regional metastasizing cases initially treated with WLE and two MMS-treated cases that subsequently underwent neck dissection (24, 73, 78, 199, 223). Among these 10 patients, additional adjuvant therapy was described for nine cases [seven of radiotherapy, one of chemotherapy, and one of both radio- and chemotherapy; no information was available in one case (24)].

Survival. The AFX-related mortality was low: In total, only 10 deaths due to metastasizing AFX were described (0.3% of all cases and 1.4% of those with follow-up data) (24, 61, 78, 109, 152, 224, 288).

Among all the patients with AFX, the complete data we needed for survival analysis were available for 451 patients, including 17 patients from our collective for whom follow-up was available (Figure 4). For each of these patients, the most up-to-date information available was considered as the current status. As expected, overall survival was relatively low (5-year survival: 88.7%, 10-year survival: 86.9%, 20-year survival: 85.6%), mainly due to old age and existing co-morbidities. Disease-specific survival according to Kaplan–Meier analysis was 97.8% at 5, 10 and 20 years (Figure 5A). Among the 451 patients included in survival analyses, 64 recurrences and 36 metastases were noted, whereby deaths due to AFX were specifically related to the presence of distant metastases [nine out of 10 described cases, in one case with subcutaneous and regional lymph node metastases after MMS and radiotherapy, neck dissection was planned, but the patient died of the disease (288)]. Concerning the primary therapy, 326 patients in the analyzed group underwent WLE and in 97 patients, AFX was removed by MMS. Out of these 415 patients, those who had WLE developed recurrences more often (50/326, 15.3%, maximum follow-up time 326 months) than those treated with MMS (8/89, 6.4%, maximum follow-up time 97 months), but the patients who underwent MMS developed recurrences earlier. After a maximum of comparable follow-up time of 97 months, patients had a higher probability of being recurrence-free after WLE (94.7%) compared to MMS (44.2%). Growth of AFX in the primary tumor site was observed after more than 300 months after WLE (Figure 5C). 20-Year recurrence-free survival concerning these 415 patients was 84.7% for those treated with WLE and 91.8% for those treated with MMS (not significant), in the MMS cases, however, the recurrences tended to develop earlier after the surgery (Figure 5C). Comparing the disease-specific survival after WLE (98.2%) with that after MMS (95.9%) using the log-rank test revealed no statistical difference (p=0.146, Figure 5B and C).

Discussion

AFX is a relatively uncommon mesenchymal tumor that poses diagnostic difficulties due to the wide range of histological appearance and lack of specific immunohistochemical markers. In a very recent review by Hussein, histological features, as well as molecular pathology of this neoplasm were addressed in detail (289). However, dedicated analysis of the literature related to AFX was lacking.

Diagnosis and tumor markers. More than 55% of AFX cases have been primarily misdiagnosed, necessitating subsequent reclassification (Table IV). This is particularly true for several uncommon and potentially misleading histological subtypes of AFX (201 cases of nine different variants out of 2939 tumors) which can be mistaken for other tumor entities (25-56).

Although there are no immunohistochemical markers specific for AFX, immunostaining is essential for accurate diagnosis. Essentially, AFX still remains a diagnosis of exclusion. The most important immunomarkers for differential diagnoses are cytokeratins (to exclude sarcomatoid or spindle cell SCC), S-100 and melanogenesis markers (to exclude melanoma) and desmin, actin and H-caldesmon (to exclude leiomyosarcoma) (8, 13). Other markers useful for exclusion of melanoma are melan-A, HMB-45 and melanoma cocktail (negative in AFX), as well as p63 and p40 for exclusion of SCC. As staining for cytokeratins can occasionally be negative in spindle cell and sarcomatoid SCC, use of multiple markers is necessary for distinction (239, 242).

Overall, the immunohistochemical data obtained in our AFX samples are in good agreement with the results reported in the literature. In over 90% of our patients and the literature cases, negative tissue reaction was observed to markers of epithelial, melanocytic, leiomyogenic, endothelial and other specific lineages. Regarding the markers which were not determined in our series, over 90% of the literature cases were negative for NGFR and CD15, more than 85% were negative for NSE, and more than 90% were positive to procollagen-1, CD1a and fascin.

Our samples differed from the literature reports with regard to several markers including SMA, A1AT, CD99, CD74, NK1/C3, p53 and cathepsin B, all of which were positive in over 90% of our collective (Table V). In the case of CD74, the discrepancy was particularly notable: whereas in our collective, 100% of the investigated samples were positive for this marker, CD74 was reported as being positive in only 36% cases of the literature (Table V). Indeed, CD74 (LN-2) an antigen expressed by B-cells, macrophages, and Reed-Sternberg cells, was originally considered a potential marker useful for separation of AFX from UPS: Lazowa *et al*. demonstrated that 90% of cases of UPS showed strong staining for CD74, whereas 90% of AFX were negative or stained only weakly with CD74 antibodies (119). These data were not confirmed by Hollmig *et al*., who reported strong positive CD74 staining in three out of 14 AFX cases, two of which showed no aggressive behavior (230). In our collective, weak positive CD74 staining was detected in seven cases and strong positivity in 14 out of 21 analyzed samples, which was independent of tumor aggressiveness. Altogether the data suggest that CD74 is neither a marker for diagnosis, nor for aggressiveness of AFX.

An interesting finding among our collective was the strong staining for stromelysin-3 in all of 17 analyzed cases. Stromelysin-3 expression was previously investigated in five cases of AFX only, two of which were positive (168), which does not allow a conclusive statement about stromelysin-3 expression in AFX, but suggests that it may be an interesting novel marker to consider in AFX diagnosis.

Differences in positive staining may be caused by technical reasons, the use of different antibodies, or simply by different subtypes of AFX analyzed. Based on our cohort and the literature data, selection of immunohistochemical parameters proposed for diagnosis of AFX is shown in Table VI.

Table VI. *Panel of immunohistochemical markers for diagnosis of atypical fibroxanthoma (AFX).*

Positive markers	Negative markers
Vimentin	Cytokeratins
CD68	p63*
CD10	S100
Procollagen 1*	Desmin
CD1a*	Human melanoma black 45
Fascin*	Melan-A/MART1
A1AT**	Epithelial membrane antigen
	CD34
	CD31
	Nerve growth factor receptor*
	CD15*

*Previously published immunomarkers >90% positive or >90% negative in AFX, which were not investigated in our specimens (see Table V); **>80% positive in the literature cases and our collective.

Therapy. Concerning the therapy of AFX, excellent results are achieved with surgical removal of tumor, either by WLE or MMS. The frequency of MMS treatment increased over the last years. MMS is generally considered a technique superior to WLE, as the micrographic control allows precise, three-dimensional controlled removal of the cancerous tissue, reducing the risk of recurrence (79, 186). Furthermore, MMS ensures preservation of healthy tissue, which is of utmost importance in the facial region. However, MMS is expensive, time-consuming and the reported oncological outcomes are often not better than those after WLE (290, 291). Moreover, if tumor satellites are present, they may not be recognized and adequately removed by a surgical procedure such as MMS. Our present analyses did not confirm superiority of MMS over WLE in terms of the outcome. No significant differences between the recurrence and survival rates following WLE and MMS were observed (Figure 5B and C). When considering the cases with data regarding survival analysis (n=415), no significant difference in recurrence-free survival after MMS (91.8%, n=97) compared to WLE-treated patients (84.7%, n=326) was observable. But in the MMS cases, the recurrences tended to develop earlier after surgery. If the maximum number of data regarding frequency of recurrence is considered (n=1109, *i.e.* 898 WLE and 211 MMS), comparable recurrence rates were obtained after WLE and after MMS (9.3% *vs.* 7.6%). It seems important that most satellites and recurrences are observed in close vicinity of the primary tumor or scar, as it was in our case (<1 cm). The size of AFX at first presentation is less than 2 cm in the majority (>85%) of cases, although much larger tumors have also been reported (Table II). In the light of these data, WLE with a safety margin of at least 1 cm should be recommended for AFX which does not exceed a size of 2 cm. In the remaining cases of larger tumors, the safety margin should be adapted to the tumor size and may be extended above 1 cm.

Independently of treatment modality, strict follow-up according to the guidelines for malignant skin cancer is recommended. As the identification of patients with AFX at risk of recurrences or metastasis is extremely difficult due to the lack of markers of tumor aggressiveness, careful monitoring by clinical investigation and imaging is necessary.

Recommendations and Conclusion

Diagnosis of AFX remains essentially a diagnosis of exclusion, as no specific tumor markers of AFX exist and because several undifferentiated tumors can closely mimic AFX. A panel of immunohistochemical markers is necessary to differentiate AFX from other pleomorphic spindle cell tumors with similar clinical and pathological characteristics (Table VI).

If treated adequately, AFX has an excellent prognosis. Surgical removal of tumor is the treatment of choice. If defined according to current strict WHO criteria, AFX behaves in a benign fashion after complete excision (10). Tumors exhibiting adverse histological features or extending into subcutaneous fat possess a low to intermediate malignant potential and should rather be classified as pleomorphic dermal sarcomas. Examples of the latter are likely represented by cases of metastasizing AFX reported in the literature. Regular long-term follow-up is recommended after excision of AFX.

Conflicts of Interest

The Authors declare that there are no conflicts of interest.

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