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Calponin and h-caldesmon expression in atypical fibroxanthoma and superficial leiomyosarcoma

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Abstract To evaluate smooth muscle differentiation, myogenic markers [desmin, alpha-smooth muscle actin (SMA), and muscle-specific actin (HHF35)] have been widely used. Calponin and h-caldesmon, which are cytoskeleton-associated actin-binding proteins, have been reported to be more specific myogenic markers, especially since myofibroblasts express a small amount of h-caldesmon. Atypical fibroxanthoma (AFX) occurs in the sun-exposed skin of the elderly and follows a benign clinical course. Histologically, AFX, which is a pleomorphic spindle cell tumor and considered to be a superficial variant of malignant fibrous histiocytoma, also mimics leiomyosarcoma. AFX has been thought to differentiate along pathways with fibrohistiocytic and myofibroblastic phenotypes. AFX (*n*=10), superficial leiomyosarcoma (S-LMS) (*n*=17) and benign fibrous histiocytoma (BFH) (*n*=17) were analyzed for myofibroblastic and smooth muscle differentiation immunohistochemically from the viewpoint of comparison. AFX and BFH showed immunoreactivities respectively for calponin (3/10, 11/17), desmin (3/10, 1/17), SMA (3/10, 13/17), and HHF35 (1/10, 5/17), but failed to express h-caldesmon (0/10, 0/17). S-LMS had a high immunoreactive rate of calponin (17/17), desmin (13/17), SMA (16/17), and HHF35 (16/17), while also expressing caldesmon (11/17). The results reveal that AFX and BFH have immunoreactivities for several myogenic markers, with myofibroblastic differentiation (calponin: ±, h-caldesmon: –), but without the smooth muscle differentiation seen in S-LMS (calponin:+, h-caldesmon: ±). In addition, calponin and h-caldesmon are considered to be useful markers for distinguishing AFX from S-LMS.

Keywords Atypical fibroxanthoma · Superficial leiomyosarcoma · Benign fibrous histiocytoma · Calponin · H-caldesmon

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Introduction

Calponin and h-caldesmon are cytoskeleton-associated proteins and both are expressed in smooth muscle and myoepithelial cells. Calponin is a calmodulin-, F-actin-, and tropomyosin-binding protein and is considered important in the regulation of smooth muscle contraction [7, 8, 24, 25]. Caldesmon has two isoforms, high-molecular-weight (h-caldesmon) and low-molecular-weight (l-caldesmon) [23, 26], and h-caldesmon has been reported to be specific for smooth muscle cells [14, 26]. It combines with calmodulin, tropomyosin, and actin and is thought to regulate cellular contraction [23]. In addition to smooth muscle cells, calponin, but not h-caldesmon, has been reported to be expressed in myofibroblastic lesions, such as desmoid and nodular fasciitis [17, 27]. Therefore, h-caldesmon is considered to be a useful marker for distinguishing smooth muscle tumors from myofibroblastic tumors [6, 17].

Helwig [11] initially designated the term “atypical fibroxanthoma” (AFX) in 1961. AFX is typically a nodu-

lar ulcerative lesion arising from the sun-exposed skin of the head and neck in the elderly. In its less common forms, the tumor occurs on the extremities and trunk [3, 5]. A report demonstrated UV-induced p53 mutations occurring at dipyrimidine sites in AFX, suggesting a central role for UV radiation in the pathogenesis of AFX [4].

AFX, which is a pleomorphic spindle cell tumor, is widely recognized as being a variant of malignant fibrous histiocytoma (MFH) occurring in the dermis [5, 28]. When AFX is less pleomorphic, it becomes indistinguishable from leiomyosarcoma [2]. Furthermore, AFX is known to express the myogenic markers mentioned above as well as histiocytic markers. Accordingly, it has been thought that AFX differentiates along multiple pathways with a bimodal pattern of fibrohistiocytic and myofibroblastic phenotypes [15].

To evaluate smooth muscle differentiation when making a diagnosis, alpha-smooth muscle actin (SMA) and muscle-specific actin are usually used immunohistochemically [21, 22]. However, these markers are not specific, since they have been identified not only in leiomyosarcoma, but also in AFX [15, 16, 19].

In order to evaluate myogenic differentiation in AFX in comparison with that in superficial leiomyosarcoma and benign fibrous histiocytoma, we examined calponin, h-caldesmon, and other myogenic markers [desmin, alpha-SMA, and muscle-specific actin (HHF35)] in these tumors. Ki-67 expression (cell-proliferation marker, MIB-1-LI) and some clinicopathological features were also compared.

Materials and methods

Specimens

Ten cases of AFX, 17 cases of superficial leiomyosarcoma (S-LMS), and 17 cases of benign fibrous histiocytoma (BFH) were collected from the histopathological files at our institute. In this study, we use the term “superficial” for leiomyosarcoma centered within the cutis or subcutis, in line with previous reports [9, 10]. In addition, the cases of benign fibrous histiocytoma were selected at random. Histopathological features were investigated and compared between AFX, S-LMS, and BFH using hematoxylin-eosin (H&E)-stained microscopic specimens. Formalin-fixed paraffin-embedded tissue blocks of these cases were used for immunohistochemical analysis.

We evaluated the frequency of mitotic figures, the presence of xanthoma cells, the degree of inflammatory elements, the involvement of appendages, and presence of giant cells in each case. The degree of inflammatory elements was assessed (absent, slight, mild, moderate, and dense).

Immunohistochemistry

Four-micron-thick histological sections of 10% formalin-fixed, paraffin-embedded materials were cut, mounted on glass slides coated by 3-aminopropyltriethoxysilane, and air dried overnight at room temperature. The sections were deparaffinized in xylene and rehydrated in ethanol. After dehydration, endogenous peroxidase was blocked by methanol containing 0.3% H_2O_2 for 30 min in the case of all of the above-mentioned antibodies. The sections were incubated with the primary antibody at 4°C overnight, followed by reaction with the streptavidin-biotin complex method using an SAB-PO kit (Nichirei, Tokyo, Japan). The sections were then finally reacted in a 3,3′ diaminobenzidine, peroxytrichloride substrate solution, counterstained with hematoxylin, and then mounted.

As for the antibodies for h-caldesmon and Ki-67, specimens were pretreated by heating in a microwave oven, while in the case of anti-calponin, specimens were preincubated in Trypsin (Sigma Chemical, St. Louis, MO, USA) in phosphate-buffered saline (PBS) for 30 min at 37°C. The antibodies used in this study were all mouse monoclonal antibodies and their dilutions were 1:200 for anti-calponin (CALP, Dako, Carpinteria, CA., USA), 1:400 for anti-h-caldesmon (h-CD, Dako, Carpinteria, CA, USA), 1:100 for anti-desmin (D33, Dako A/S, Glostrup, Denmark), 1:5,000 for anti-alpha-SMA (1A4, Sigma BioSciences, St. Louis, MO, USA), 1:200 for anti-muscle-specific actin (HHF35, Biomedia Corp, Foster City, CA, USA), and 1:100 for anti-Ki-67 (MIB-1, Immunotech, Marseilles, France).

Assessment of immunoreactivity

We evaluated the immunoreactivities of calponin, h-caldesmon, desmin, SMA, and HHF35 in the cytoplasm of tumor cells. The extent of staining in tumor cells was classed using a scoring system: 0 when <5% of tumor cells were stained; 1+ when ≥5% but <30% of the tumor cells were stained; 2+ when ≥30% but <80% of the tumor cells were stained; and 3+ when ≥80% of the tumor cells were stained. All scores greater than 1+ were interpreted as positive results, the others as negative results. Regarding Ki-67, in the selected areas containing the largest number of MIB-1-positive nuclei cells, the MIB-1-labeling index (MIB-1-LI) was estimated as the percentage of positive cells, counting at least 1,000 tumor cells.

Statistical analysis

The data regarding immunohistochemistry, clinicopathological features, and MIB-1-LI were evaluated using the Mann-Whitney *U*-test. A P value of <0.05 was considered to indicate statistical significance.

Results

Clinical features

The average ages (in years) of patients with these lesions were as follows; AFX (71.3; range, 46–92), S-LMS (55.9; 21–88), and BFH (27.0, 18–39) in descending order, with a significant difference between AFX or S-LMS and BFH (P<0.01). There was no significant difference between the average age of patients with AFX and S-LMS.

AFX showed a male-female predominance of 7 to 3 (M/F: 2.3/1), while S-LMS showed an 11 to 6 female predominance (M/F: 1/1.8). BFH showed no gender bias, occurring in 8 males and 9 females (M/F: 1/1.1). AFX occurred on the sun-exposed skin of the head, neck, and finger (9/10; 90%), except for one case on the leg (10%). AFX is known to occur in two clinical settings, on the head and neck of older people and on the extremities or trunk of younger people [3]. In this study, seven cases occurred on the head and neck (82, 84, 65, 71, 73, 92 and 86 years old). The other three AFX cases occurred

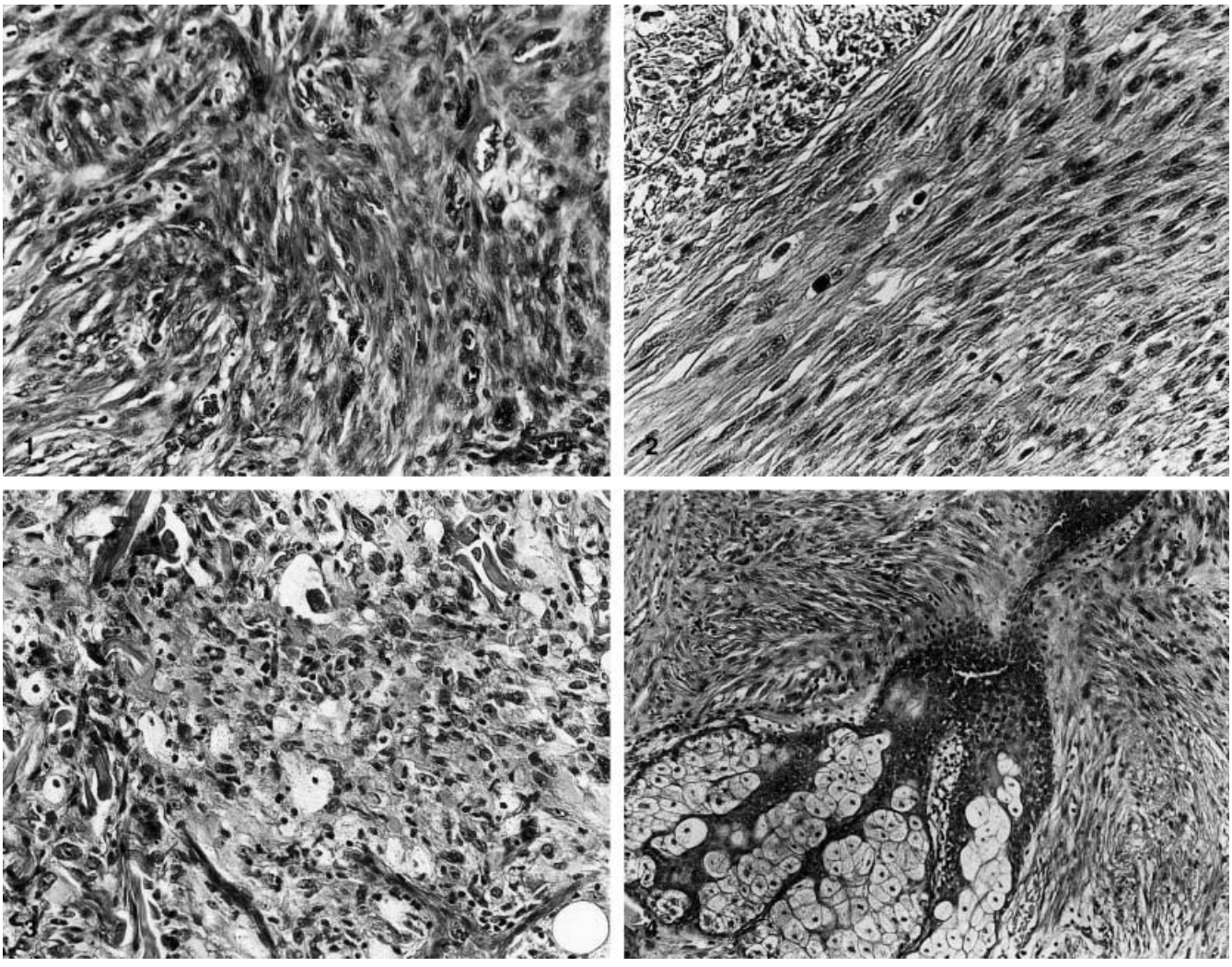

Fig. 1 Atypical fibroxanthoma, demonstrating proliferation of atypical spindle or epithelioid cells arranged in a haphazard or disorderly pattern, ×200

Fig. 2 Superficial leiomyosarcoma, which is composed of spindle cells with blunt-ended nuclei arranged in interlacing fascicles, ×250

Fig. 3 Atypical fibroxanthoma. Xanthoma cells can be frequently observed, some of which have enlarged nuclei suggesting neoplastic cells, ×200

Fig. 4 Atypical fibroxanthoma. Appendage involvement within the lesion can be observed, ×100

on the extremities. these in the three youngest patients in our series of AFX (50, 46, and 64 years old). Fifteen out of the 17 cases of S-LMS (89%) occurred on the trunk, lower extremities, or proximal upper extremities, all of which sites can be assumed to have been mostly shielded from sun exposure. In the other two cases of S-LMS, the lesions occurred on the wrists (12%). In contrast, BFH occurred at various sites without showing any special tendency. Furthermore, in our series, recurrence was recognized in six out of the 17 cases of S-LMS (35%), but not in any of the 10 AFX or 17 BFH) cases. The average size (in centimeters) of these lesions was as follows: S-LMS (4.7; range, 1.3–15.0), AFX (1.4; 1.0–3.0), and BFH (0.8; 0.5–1.3) in descending order, with a significant difference between S-LMS and AFX ($P<0.01$), between S-LMS and BFH ($P<0.01$), and between AFX and BFF ($P<0.01$).

Histological features

AFX is a nodular ulcerative lesion composed of various proportions of a mixture of spindle, pleomorphic, and epithelioid cells, arranged in a haphazard or disorderly pattern (Fig. 1). In this study, seven cases occurred on the head and neck and these were all of the pleomorphic type. Among the three AFX cases that occurred on the extremities, two were pleomorphic (one on the finger and one on the leg), while the other case was spindle cell/non-pleomorphic in type (on the finger). In a previous report, some of the AFX cases which occurred on the extremities were assumed to be examples of atypical benign fibrous histiocytoma [1]. However, the two AFX cases which occurred on the fingers in our series had UV-induced p53 mutations of C-T transitions at dipyri-

Table 1 Summary of immunohistochemical features of AFX and superficial leiomyosarcoma. *AFX* atypical fibroxanthoma, *S-LMS* superficial leiomyosarcoma, *BFH* benign fibrous histiocytoma, *SMA* smooth muscle actin, *HHF35* muscle-specific actin

Lesions	Calponin	h-Caldesmon	Desmin	SMA	HHF35
AFX	3/10 (30%)	0/10 (0%)	3/10 (30%)	3/10 (30%)	1/10 (10%)
S-LMS	17/17 (100%)	11/17 (65%)	13/17 (76%)	16/17 (94%)	16/17 (94%)
BFH[a]	11/17 (65%)	0/17 (0%)	1/17 (6%)	13/17 (76%)	5/17 (29%)

[a] BFHs were selected at random from our histological files

midine sites [20]. The BFH cases were located in the dermis or the superficial subcutis. BFH consisted of fibroblastic cells and histiocytic cells arranged in short interlacing fascicles or a vague storiform pattern. The tumor cells of BFH demonstrated no pleomorphism. Leiomyosarcoma was composed primarily of spindle cells with blunt-ended nuclei arranged in an interweaving and fascicular fashion (Fig. 2).

Mitotic figures were often seen (1–8/10 high-power fields, HPFs) in all (10/10) of the AFX cases as well as in 15 of 17 (88%) S-LMS cases, again commonly (1–10/10 HPFs). Atypical mitotic figures were also seen both in the AFX (5/10; 50%) and the S-LMS (6/17; 35%) cases. On the other hand, obvious mitotic figures including atypical types could not be recognized in our BFH cases (0/17). Xanthoma cells were seen in the AFX (3/10; 30%) (Fig. 3) and S-LMS (1/17; 6%) cases, but not in the BFH cases (0/17). Inflammatory elements (lymphocytes, plasma cells, and neutrophils) were present in all the AFX cases, being denser in the tumor borders and the ulceration sites than in the center of the lesions. AFX cases seemed to have a larger amount of inflammatory elements (moderate to dense) than BFH (mainly slight to mild) or S-LMS (mainly slight) cases.

Appendage involvement within the lesions, suggesting undestroyed adnexal structures, was frequently seen in the AFX cases (5/10; 50%) (Fig. 4) in contrast to the S-LMS (0/17) and BFH (0/17) cases; however. we cannot deny the influence of the superficial location of AFX. Osteoclast-type multinucleated giant cells were seen in AFX (3/10; 30%) and S-LMS (2/17; 12%) cases, while Touton-type giant cells were only seen in BHF cases (3/17; 18%).

Immunohistochemical findings

The immunohistochemical results are summarized in Table 1. AFX was immunoexpressed in calponin (3/10; 30%), desmin (3/10; 30%), alpha-SMA (3/10; 30%) and muscle-specific actin (1/10; 10%), while the expression of h-caldesmon was absent (0/10). Similar to AFX, BHF showed no h-caldesmon expression (0/17), although it showed expression of calponin (11/17; 65%), desmin (1/17; 6%), alpha-SMA (13/17; 76%), and muscle-specific actin (5/17; 29%). S-LMS showed a high positive immunoexpression rate for calponin (17/17; 100%), desmin (13/17; 76%), alpha-SMA (16/17; 94%), and muscle-specific actin (16/17; 94%), in addition to the expression of h-caldesmon (11/17; 65%) (Figs. 5 and 6).

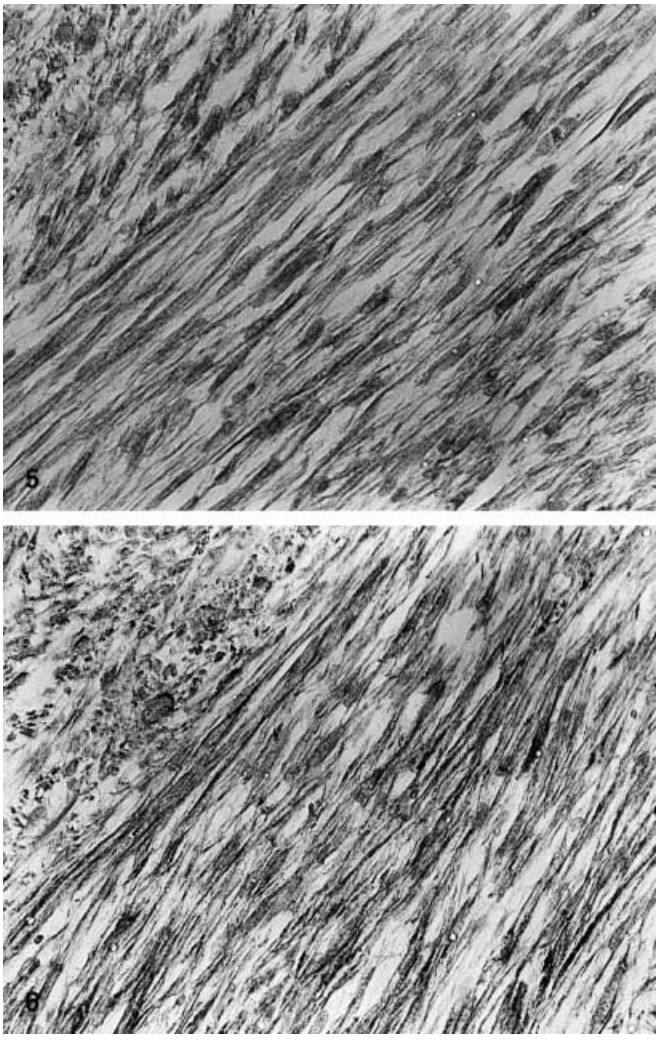

Fig. 5 Leiomyosarcoma, showing positive cytoplasmic immunoreaction for calponin, ×300

Fig. 6 Leiomyosarcoma, showing positive cytoplasmic immunoreaction for h-caldesmon, ×300

These features of positive/negative calponin and negative h-caldesmon immunoexpressions seen in both AFX and BFH seem to confirm that these tumors have myofibroblastic differentiation, in contrast to the reversed features of positive calponin and positive/negative h-caldesmon expressions suggesting smooth muscle differentiation, which were seen in S-LMS.

The average MIB-1-LIs in descending order are as follows: S-LMS, 18.8±3.5; AFX, 16.7±2.2; and BFH,

2.8±0.8; with a significant difference between both AFX and S-LMS and BFH ($P<0.01$). The difference in the MIB-1-LI between AFX and S-LMS was not significant.

Discussion

In this study, we evaluated the immunohistochemical reactivity of two actin-binding, cytoskeleton-associated proteins of calponin and h-caldesmon, as well as other myogenic markers of desmin, alpha-SMA, and muscle-specific actin (HHF35). In normal tissue, both calponin and h-caldesmon are consistently present in smooth muscle tissue and absent in skeletal muscle and other mesenchymal cell types [7]. In previous studies, the expressions of calponin and h-caldesmon in benign smooth muscle tumors have been consistent [17, 27]. In addition to being expressed in smooth muscle cells, calponin was also expressed in myofibroblastic lesions, such as desmoid and nodular fasciitis. On the other hand, h-caldesmon was only expressed to a very small degree in myofibroblastic lesions. Therefore, calponin and h-caldesmon are thought suitable for use as markers of myogenic differentiation in the evaluation of soft-tissue tumors, especially when attempting to distinguish smooth muscle differentiation from myofibroblastic differentiation [17, 27].

AFX is a pleomorphic spindle cell tumor. Since it remains difficult to distinguish AFX from MFH due to their close histological resemblance, AFX is widely recognized as being a variant of MFH that arises in the dermis [5, 28]. A less atypical variant of AFX has been reported, and in those cases leiomyosarcoma is also taken into consideration as a differential diagnosis [2]. AFX demonstrates multidirectional differentiation and morphologically heterogeneous features with a bimodal pattern of fibrohistiocytic and myofibroblastic phenotypes, on the basis that the expression of alpha-SMA has been described in 41% [15], while that of muscle-specific actin has also been described in 27–67% of AFX cases [15, 16, 19]. These actin-positive cells in AFX may reflect either the presence of reactive myofibroblasts or the differentiation of tumor cells into myofibroblasts. However, spindle, epithelioid, and bizarre atypical cells in AFX have been reported to express the above actins, although the cell type and the content of these positive cells varied from case to case [15]. In our study, three out of the ten cases of AFX (30%) showed staining for alpha-SMA, while one of them (10%) expressed muscle-specific actin. In addition, three of the ten cases of AFX (30%) showed staining for calponin, whereas none of them showed any reaction for h-caldesmon. On the other hand, all the cases of S-LMS expressed calponin (17/17; 100%) and approximately half of them expressed h-caldesmon (11/17; 65%). These results seemed to confirm that tumor cells of AFX, unlike S-LMS, have myofibroblastic differentiation but not smooth muscle differentiation. Furthermore, the immunoexpressions of calponin and h-caldesmon could possibly be useful markers in distinguishing AFX from S-LMS.

In a previous report, some uterine leiomyosarcomas showed h-caldesmon reactivity in the well-differentiated but not in the poorly differentiated areas. This led to the suggestion that there is a loss of h-caldesmon during tumor progression [13]. Accordingly, the reduced expression of h-caldesmon in our series of S-LMS might suggest a malignant character in leiomyosarcoma; however, there was no significant difference in the MIB-1-LI between the cases of S-LMS with h-caldesmon expression and those without.

Moreover, there was no significant difference between AFX and S-LMS with regard to the MIB-1-LI, as is also true for AFX and MFH [18]. However, despite rare reports of aggressive behavior, AFX almost always follows a benign clinical course [6]. Indeed, in this study, recurrence was recognized in S-LMS (6/17; 35%), but not in AFX cases (0/10). In addition to differences between their recurrent rates and tumor sites, AFX or S-LMS also differed in size (average size: AFX, 1.4 cm; S-LMS, 4.6 cm). Histologically, appendage involvement, suggesting an undestroyed appendage, was seen only in AFX (5/10; 50%), and not in S-LMS (0/17). A superficial location might contribute to the favorable clinical behavior [12] and the pathological differences noted between AFX and S-LMS; however, it is also possible that all these differences may simply be due to the peculiar pathogenesis of AFX.

In summary, we have evaluated, in addition to some clinicopathologic data in AFX, S-LMS, and BFH, the expression of calponin, h-caldesmon, and other myogenic markers. AFX shows myofibroblastic differentiation, on the basis of positive/negative calponin and negative h-caldesmon immunoexpressions. In contrast, S-LMS shows smooth muscle differentiation with positive calponin and positive/negative h-caldesmon. In addition, calponin and h-caldesmon are thought to be useful markers for distinguishing AFX from S-LMS.

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