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Original Article

Immunohistochemical evaluation of stem cell markers and signal transducer and activator of transcription 6 (STAT6) in solitary fibrous tumors

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Abstract: Solitary fibrous tumors (SFT) are fibroblastic, ubiquitous mesenchymal tumors. Although several SFT studies have been conducted, the cell of origin of SFT remains controversial and reliable diagnostic markers are needed for SFT identification for proper prognosis and therapeutics. To analyze the immunophenotype of SFT for the identification of specific diagnostic markers and the cell of origin of this tumor, we performed an immunohistochemical study of stem cell markers [aldehyde dehydrogenase 1 (ALDH1), CD29, CD44, CD133, and nestin] and signal transducer and activator of transcription 6 (STAT6) in 18 cases of SFT. The results demonstrated that ALDH1 was present in 16 cases (16/18), STAT6 in 13 cases (13/18), CD44 in 8 cases (8/18), and CD29 in 1 case (1/18), whereas CD133 and nestin were absent in all cases (0/18). Our results indicate that combination with ALDH1 and STAT6 can improve the diagnostic value of CD34 for SFT. The immunohistochemical findings for stem cell surface markers indicate that SFT may originate from stem cells and that ALDH1 plays an important role in the development of SFT.

Keywords: Solitary fibrous tumor, STAT6, ALDH1, stem cell markers, immunohistochemistry

Introduction

Solitary fibrous tumors (SFT) are rare mesenchymal tumors that were first described as primary pleural tumors in 1931 by Klemperer [1]. Initially, SFTs were found in the pleural cavity, but recently they have been discovered in every part of the body [2]. Although SFTs can form at all ages, they are more commonly found in people aged 50-70 years. SFTs are characterized by several histopathological features, such as a hemangiopericytomatous vascular pattern, a patternless architecture of alternating hypo- and hyper-cellular areas, and a hyalinized vascular wall [3].

SFTs are frequent misdiagnosed as other spindle cell lesions, most notably when they are found in an unusual location. The standard diagnosis of SFT is based on histopathological and immunohistochemical features. Although SFT cells have various immunoreactive markers, such as CD34, CD99, BCL-2, and vimentin [4-7], these markers are non-specific and non-constant, revealing a need for more reliable diagnostic markers for SFT patients. Recently, several studies have demonstrated that ALDH1 and STAT6 could be highly sensitive immunohistochemical markers for the identification of SFT [8-11].

In addition to the diagnostic problems of SFT identification, the cell of origin of this neoplasm is still ambiguous. Originally, SFTs were found in the pleural cavity, and England *et al.* suggested that they arose from immature mesenchymal stem cells [12]. However, Sawada *et al.* used immunohistochemistry to indicate that most SFTs may be derived from vascular or lymphatic endothelial cells [13]. In recent years, further studies based on electron microscopy showed considerable cellular heterogeneity in SFTs that

Table 1. Informations for primary antibodies

Specificity	Dilution	Pretreatment	Immunostaining	Clone	Manufacturer	Positive control
CD34	1:400	PCA-CB	Envision	QBEnd/10	Immunotech, Marseille Cedex, France	Vascular endothelium
Vimentin	1:200	PCA-CB	Envision	V9	DAKO, Glostrup, Denmark	Tonsilar lymphoma
Bcl-2	1:1200	PCA-CB	Envision	124	DAKO, Glostrup, Denmark	Human tonsil
CD99	1:400	PCA-CB	Envision	12E7	DAKO, Glostrup, Denmark	Ewing's sarcoma
Ki-67	1:600	PCA-CB	Envision	BIM-1	DAKO, Glostrup, Denmark	Burkitt lymphoma
STAT6	1:600	PCA-EDTA	Envision	YE361	Abcam, Epitomics, USA	Human skin carcinoma
ALDH1	1:200	PCA-CB	Envision	EP1933Y	Abcam, Cambridge, UK	Human liver tissue
CD29	1:1500	PCA-CB	Envision	EP1041Y	Abcam, Cambridge, UK	Human breast carcinoma
CD44	1:200	PCA-CB	Envision	DF1485	DAKO, Glostrup, Denmark	Human urinary bladder tissue
CD133	1:200	PCA-CB	Envision	Polyclonal	ARP, Waltham, America	Pancreatic tissue
Nestin	1:200	PCA-CB	Envision	SP103	Abcam, Cambridge, UK	Human kidney tissue

PCA-CB, pressure cooker heating in citrate buffer (0.01 M, pH 6.0); PCA-EDTA, pressure cooker heating in EDTA (pH 9.0).

possibly originating from perivascular undifferentiated mesenchymal stem cells [14-16]. In this study, we applied an immunohistochemical analysis of several stem cell markers (ALDH1, CD29, CD44, CD133, and nestin) to SFT specimens to explore the cell of origin of this tumor and the expression of STAT6. In addition, possible relevant clinical markers (CD34, vimentin, BCL-2, CD99, and Ki-67) for the diagnosis of SFT were examined.

Materials and methods

Materials

Eighteen SFT specimens were collected from the Department of Pathology, Shihezi University School of Medicine, Xinjiang China and People's Hospital of Xinjiang Autonomous Region between 2008 and 2015. Clinical information was obtained from the medical records. Each tumor was diagnosed according to the 4th edition WHO Classification of Tumors of Soft Tissue and Bone. All cases were reviewed based on histopathology with hematoxylin and eosin staining and immunohistochemical analysis. In total, 18 formalin-fixed, paraffin-embedded samples of primary SFT from each specimen were prepared for immunohistochemistry. Clinical outcome was evaluated according to the history of disease recurrence or metastasis. This study was approved by the institutional ethics committee at the First Affiliated Hospital of Shihezi University School of Medicine.

Immunohistochemistry

In total, 18 SFT samples were paraffin-embedded, sectioned at 4 μm, and used for the immunohistochemical analysis. The immunohistochemical procedures, including antibodies and positive controls for primary antibodies, used in our study are summarized in **Table 1**. The EnVision™ Systems two-step immunohistochemical kit (Dako System, Glostrup, Denmark) was used to detect specific target proteins. Phosphate-buffered saline (PBS) was used rather than the primary antibody as a negative control. Briefly, slides were baked at 60°C for 2 h, deparaffinized with xylene, rehydrated using graded alcohol solutions, and then quenched with 3% hydrogen peroxide. Heat-induced antigen retrieval was performed for all primary antibodies except anti-STAT6 in citrate buffer (pH 6.0), or in EDTA (pH 9.0) for STAT6. The sections were incubated with the primary antibodies at 4°C overnight. The samples were then washed with PBS and subsequently incubated with secondary antibodies at 37°C. A peroxidase substrate, 3,3'-diaminobenzidine (DAB), was used as a chromogen. Slides were counterstained with hematoxylin and dehydrated, and a coverslip was used to seal the samples.

Results

Clinical findings

The clinical findings of the current study corresponded approximately with the World Health Organization classifications. The clinicopathological data and representative histology of the 18 primary tumors are presented in **Table 2** and **Figure 1**. Tumor specimens were acquired from female patients aged 32 to 76 years (mean, 50.5 years; median, 50 years). All specimens were completely resected, including primary tumors from the pleura (2 cases) and

Table 2. The clinicopathological data for 18 pramary tumor

Case	Age	Sex	Greatest dimension (cm)	Site	Tumor border	Mitoses/ 10 HPF	Necrosis	Atypia	Follow-up (months)	Outcom
1	35	M	4.5	lung	Pushing	Absent	Absent	Absent	74	Survival
2	69	M	11	liver	Pushing	5-7	Absent	Absent	NA	NA
3	38	F	12.5	abdomen	Pushing	4-7	Absent	Absent	NA	NA
4	46	M	2.7	neck	Pushing	Absent	Absent	Absent	57	Survival
5	42	F	0.5	auricula	Pushing	Absent	Absent	Absent	NA	NA
6	56	F	13.5	enterocoelia	Pushing	Absent	Absent	Absent	NA	NA
7	69	F	10.5	mediastinum	Pushing	Absent	Absent	Absent	44	Survival
8	76	F	9.5	pleura	Pushing	Absent	Absent	Absent	42	Survival
9	42	F	6.5	pleura	Pushing	Absent	Absent	Absent	41	Survival
10	38	M	3.5	lung	Pushing	Absent	Absent	Absent	NA	NA
11	43	M	4	back	Pushing	Absent	Absent	Absent	29	Survival
12	51	F	5	groin	Pushing	Absent	Absent	Absent	29	Survival
13	55	M	2.5	meninges	Pushing	Absent	Absent	Absent	28	Survival
14	56	M	2.9	mediastinum	Pushing	Absent	Absent	Absent	24	Survival
15	58	F	3	breast	Pushing	Absent	Absent	Absent	20	Survival
16	32	F	5.5	nasopharynx	Pushing	Absent	Absent	Absent	17	Survival
17	54	F	7	groin	Pushing	Absent	Absent	Absent	NA	NA
18	49	F	5	forehead	Pushing	Absent	Absent	Absent	3	Survival

F = female; M = male; NA = not available.

extra-pleura (16 cases from lung, liver, and mediastinum, among other locations). All cases were benign except for two cases. The available post-operative information for 12 of the 18 cases, with follow-up times ranging from 3 to 74 months (median of 29 months) after surgery, indicated that each patient was still alive, and no metastasis or recurrence was documented.

Pathological findings

Overall, the tumors measured 0.5-13.5 cm (mean of 5 cm; median of 6.1 cm) at the greatest dimension with the appearance of clearly defined borders. Notably, hemorrhage was discovered in the specimens resected from case 7 and case 10. Histological observations revealed that the tumor cells were ovoid to spindle-shaped and enclosed limited, pale cytoplasm with indistinct borders. All specimens exhibited a patternless architecture (**Figure 1A**) with alternating hypo- and hyper-cellular regions (**Figure 1B**). Five specimens contained areas with a hemangiopericytoma-like pattern with thin-walled, branching, dilated blood vessels, and all but one of them had hyalinization of the vessels (**Figure 1C** and **1D**). In addition, individual tumor cells were separated by a collagenous stroma, composed of thick bands with foci of keloid-like hyalinization (**Figure 1E**). Artificial fracture was found in six cases. Atypical mitoses, necrosis, pleomorphism, or other signs of malignant SFT were not observed in any of the benign tumor samples, but mitoses (>4 mitoses/10 HPF) was observed in the 2 malignant cases (**Figure 1F**).

Expression of relevant markers for clinical diagnosis of SFT

The immunohistochemical staining results are summarized in **Table 3** and **Figures 2**-**4**. Cytoplasmic immunoreactivity for CD34 (15/18), CD99 (16/18), and BCL-2 (15/18) was observed in tumor cells. In addition, CD34 reactivity was observed in the endothelial cells of tumor vessels. Vimentin reactivity was common to all tumor cytoplasmic fractions (18/18). Moreover, in the 2 malignant cases, the Ki-67 labeling index was 40% and 45%, whereas it was 8% in the other cases. STAT6, which was recently determined to be a diagnostic marker for SFT, was positively stained in the nucleus in 13 specimens (13/18).

Stem cell marker expression in SFT

Every tested SFT specimen exhibited diffuse cytoplasmic immunoreactivity for ALDH1,

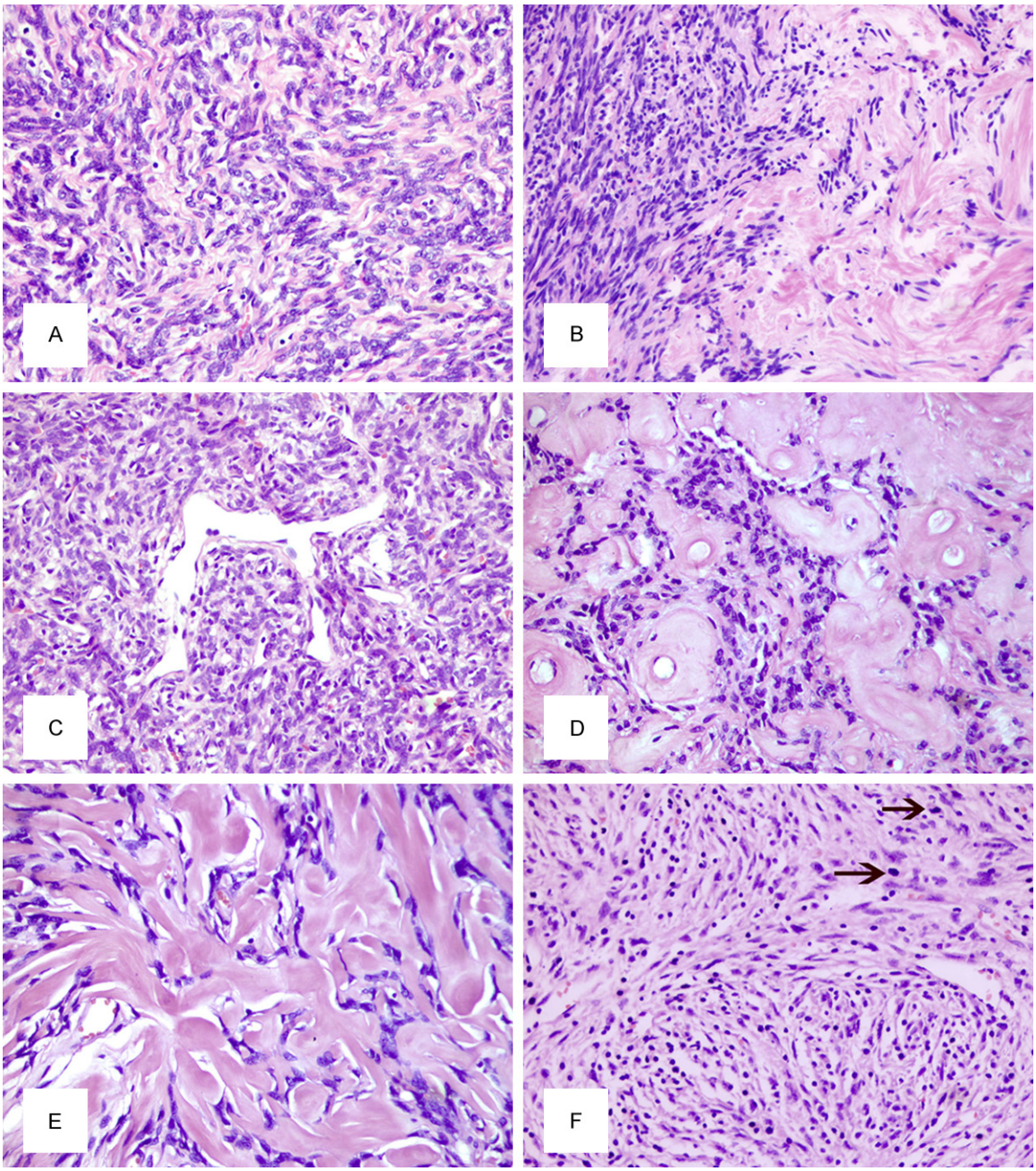

Figure 1. Histological features of SFT (× 200). A: Patternless architecture; B: Areas of hyper- and hypo-cellularity; C: Hemangiopericytoma-like and staghorn-like blood vessels; D: Stromal and perivascular hyalinization; E: Keloidal-type deposition of collagen; F: Mitoses.

except for the 2 malignant cases, which stained negative (16/18). CD44 displayed focal immunoreactivity in tumor cells in 8 of 18 cases, and in every case, it was detected only in macrophages infiltrating the SFT (8/18). CD29 also exhibited focal immunoreactivity in the tumor cells of one specimen (1/18), but was observed in the vascular endothelial cells within the tumor in all cases. No immunoreactivity for CD133 was found in any specimen (0/18). Similarly, in all cases, nestin was only observed in the endothelial cells of tumor vessels (0/18).

Discussion

SFTs are uncommon spindle cell neoplasms that can form virtually anywhere in the body [2], and are characteristically immunoreactive for

Table 3. Immunohistochemical findings

Case	ALDH1	STAT6	CD34	Vimentin	CD99	Bcl-2	CD29	CD44	Nestin	CD133	Ki-67
1	+	-	+	+	+	+	+†	-	+†	-	1%
2	-	-	+	+	+	-	+†	+	+†	-	40%
3	-	-	-	+	+	+	-	-	+†	-	45%
4	+	+	+	+	+	+	-	+	+†	-	8%
5	+	+	+†	+	+	-	-	+‡	+†	-	1%
6	+	+	+†	+	+	+	+†	+‡	+†	-	<1%
7	+	+	+	+	+	+	+†	+	+†	-	5%
8	+	+	+	+	-	+	+†	+	+†	-	2%
9	+	+	+	+	-	+	+†	+‡	+†	-	3%
10	+	-	+	+	+	+	-	+	+†	-	1%
11	+	+	+	+	+	-	-	-	+†	-	3%
12	+	+	+	+	+	+	+†	+	+†	-	3%
13	+	+	+	+	+	+	-	-	+†	-	2%
14	+	-	+	+	+	+	-	+‡	+†	-	5%
15	+	+	+	+	+	+	-	+	+†	-	8%
16	+	+	+	+	+	+	-	+	+†	-	3%
17	+	+	+	+	+	+	+	+‡	+†	-	2%
18	+	+	+	+	+	+	+†	+‡	+†	-	2%

+†CD34, +†CD29, +†Nestin staining was only positive in the endothelial cells of tumor vessels. +‡CD44 staining was only positive in infiltrated macrophages.

CD34 (90-95%) [3]. However, CD34 expression is also common in other tumors that may mimic SFT traits. In addition, SFTs show cytoplasmic staining for CD99 and vimentin in approximately 70% of cases [4]. Positive immunoreactivity for BCL-2 is observed in nearly all SFTs, but the reaction is non-specific, as expression is also observed in a variety of other mesenchymal neoplasms [7].

Although the diagnosis of most SFT cases is usually straightforward, in atypical types that mimic other mesenchymal tumors or lack expression of CD34, improper identification of these tumors can occur. Recently, Bertucci and Bouvier demonstrated that the stem cell marker ALDH1 could be used as an accurate diagnostic tool for SFT [8, 11]. Comparably, several studies have shown that STAT6 is a highly sensitive immunohistochemical marker for SFT [9, 10]. In addition, several recent studies have detected a recurrent fusion NAB2-STAT6 in SFT and have found that it enables cytosolic STAT6 to relocate to the nucleus [17-20]. In this study, 16 samples were diffusely positive for ALDH1; only the 2 malignant cases were negative. Moreover, in 13 SFT cases, intense immunoreactivity revealed diffuse nuclear expression of STAT6. The 2 malignant cases were negative for both ALDH1 and STAT6. Our results confirmed those from previous studies and indicated that combination with ALDH1 and STAT6 can improve the diagnostic value of CD34 for SFT. Moreover, the lack of expression of ALDH1 and STAT6 may be associated with malignant SFT, and the pathogenesis of benign and malignant SFT may be different. More malignant SFT cases and NAB2-STAT6 gene fusion studies are need to further confirm the utility of ALDH1 and STAT6 as constructive tools in the diagnosis of SFT, and to determine whether the pathogenesis is different between benign and malignant SFT.

The SFT cell of origin remains controversial. As discussed above, SFTs were initially found in the pleural cavity and thought to arise from immature mesenchymal stem cells [12]. In addition, Sawada *et al.* detected the expression of the vascular endothelial cell markers VEGFR-1, VEGFR-2, Tie-2, and c-Met in SFTs by immunohistochemistry and suggested that most SFTs may be derived from to vascular or lymphatic endothelial cells [14]. Nielsen hypothesized that SFTs could be mesenchymal neoplasms that originate from ubiquitous mesen-

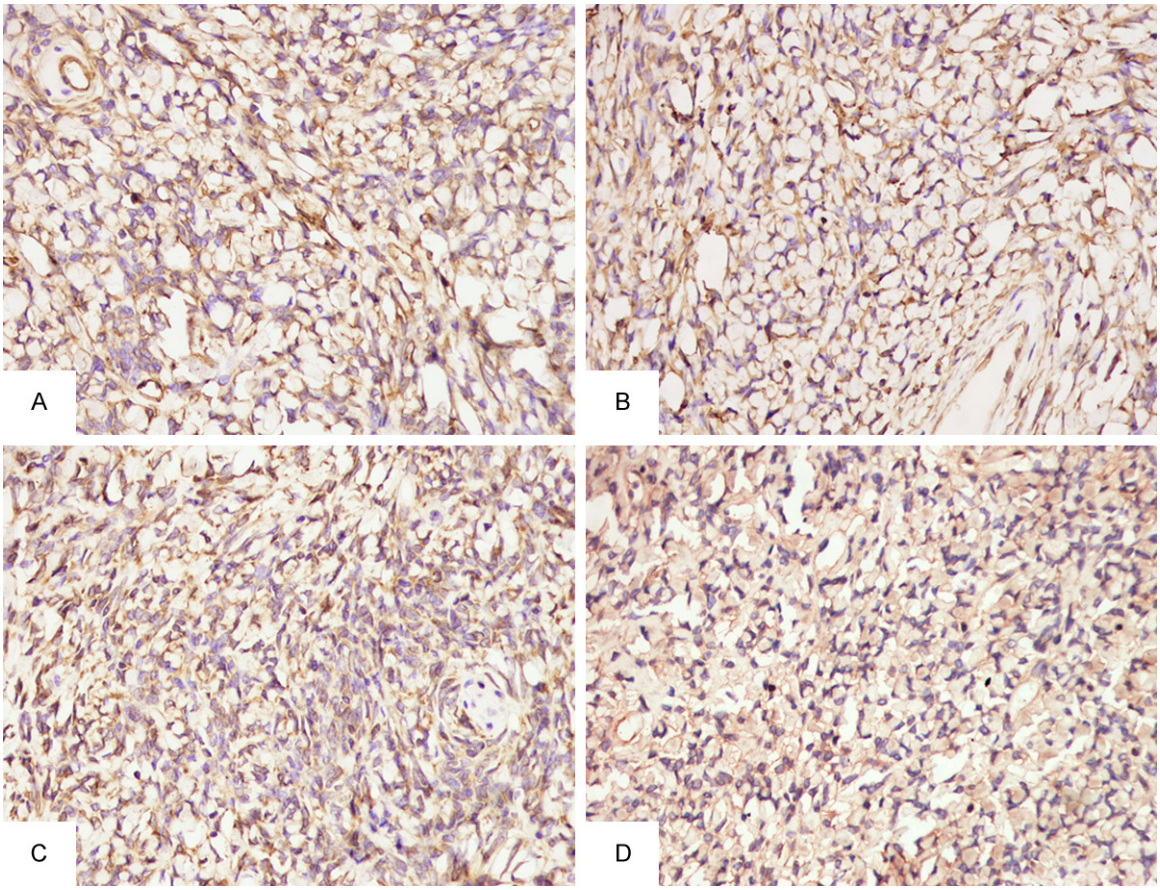

Figure 2. Immunohistochemical findings of relevant clinical diagnostic markers (× 200). 15/18 cases showed diffuse staining for CD34 and the other two cases were vascular positive. All cases showed diffuse staining for vimentin; 15/18 cases were BCL-2 positive; 16/18 cases were focally positive for CD99.

chymal stem cells in various human tissues [16]. Rodriguez-Gil *et al.* proposed that the perivascular undifferentiated cells of SFT may represent a quiescent stage of adult mesenchymal stem cells and may be the target of genetic mutations that eventually result in neoplastic growth [21]. Although these studies proposed that SFT may be derived from mesenchymal stem cells, to date, there has been no examination of the expression of various mesenchymal stem cell markers in SFT.

Recently, many specific mesenchymal stem cell markers have been found. In 2011, Mafi *et al.* summarized the available information for the characterization of the cell surface of adult human mesenchymal stem cells and noted that CD29 and CD44 were demonstrated to be positive markers for mesenchymal stem cells [22]. In addition to these specific markers, Méndez-Ferrer *et al.* suggested that nestin-positive cells have the characteristics of mesenchymal stem cells [23]. Furthermore, Yuan *et al.* proposed that mesenchymal stem cells in the perivascular region also express CD133 [24]. In the present study, these markers were expressed as follows: CD44 (8/18), CD29 (1/18), CD133 (0/18), and nestin (0/18). CD44 was expressed in 8 cases, whereas CD29, CD133 and nestin were almost negative in all cases. There are many specific mesenchymal stem cell markers, and different tissue-derived mesenchymal stem cells express different markers [22]. Thus, the set of mesenchymal stem cell markers that we choose may not have been the appropriate markers to confirm that SFT is derived from mesenchymal stem cells. In addition, in another study of perivascular epithelioid cell tumors by our group (data unpublished), these markers were highly expressed, suggesting that these two types of mesenchymal tumors may not have originated from the same type of stem cell.

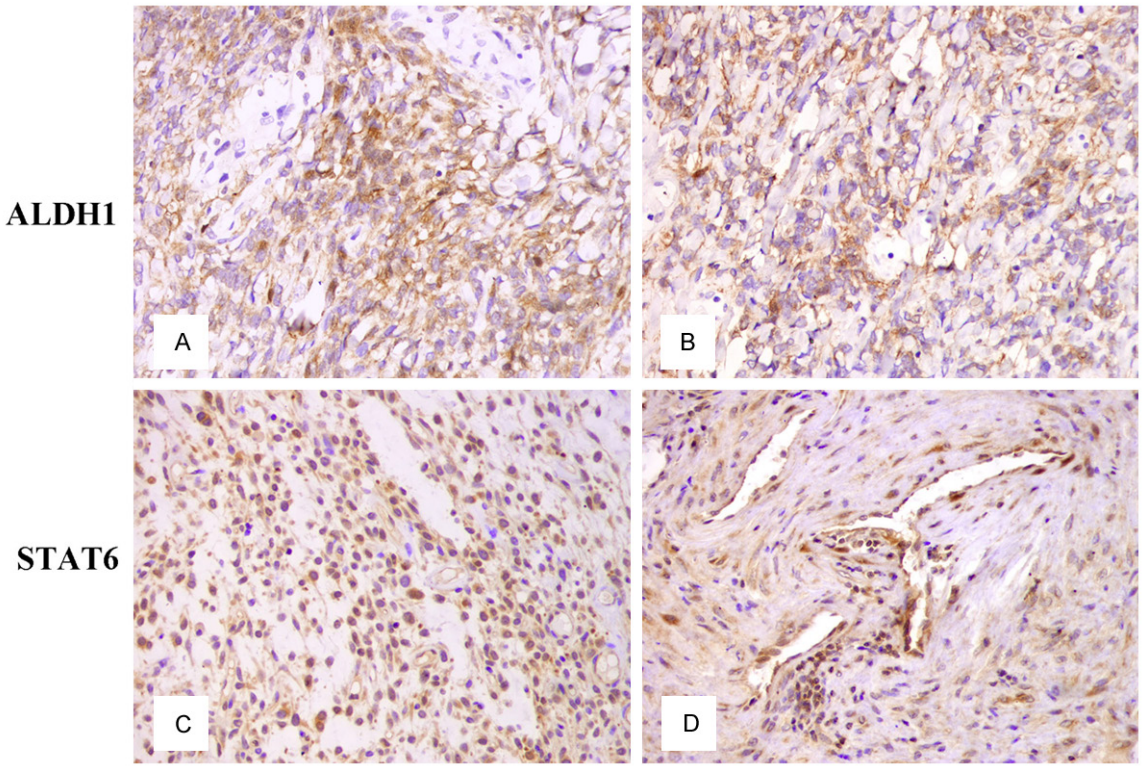

Figure 3. Immunohistochemical findings of ALDH1 and STAT6 (× 200). 16/18 cases stained diffusely positive for ALDH1 except for 2 malignant cases; 13/18 cases showed nuclear staining for STAT6.

However, it is interesting that the most consistent diagnostic markers for SFT, i.e., CD34 and ALDH1, are stem cell markers. These data could have cell-of-origin significance. CD34 is a transmembrane protein that is detected in hematopoietic stem cells, endothelial progenitor cells, and endothelial cells in blood vessels [25]. ALDH1 is a member of the ALDH enzyme family and plays a major role in early differentiation of stem cells [26]. Recently, Honoki *et al.* found that subpopulations with elevated ALDH1 expression were present in human sarcoma cell lines [27, 28]. Bertucci *et al.* found that several genes previously identified in mesenchymal stem cells were overexpressed in SFT [29]. In addition, mesenchymal cells have been reported to originate from ALDH1-positive cells that display properties of stem cells [30]. Combined with the expression of CD34, the expression of ALDH1 may suggest that SFTs are derived from stem cells and the ALDH1 plays an important role in the development of SFTs.

ALDH1 is not only important for the diagnosis and the cell-of-origin of SFT but also could be a cancer stem cell (CSC) marker for SFT. ALDH1, CD133, and nestin are commonly used as CSC markers for a variety of tumors [31-33]. Our study showed that only ALDH1 had diffuse expression in 16 cases; the other CSC markers were nearly all negative. In addition, ALDH1 can metabolize and detoxify chemotherapeutic agents, and adjuvant chemotherapies have no significant effect on SFT [34, 35], which suggests that specific inhibitors of ALDH1 could be new therapeutic targets for SFT.

The aim of the present study was to explore possible diagnostic markers and the cell of origin of SFT. For this purpose, we performed an immunohistochemical study of stem cell markers (ALDH1, CD29, CD44, CD133, and nestin) and STAT6 in 18 SFT cases. Our results indicate that combination of ALDH1 and STAT6 can improve the diagnostic value of CD34 for SFT. The immunohistochemical findings for the stem cell surface markers indicated that SFT may have originated from stem cells and that ALDH1 plays important role in the development of SFTs. Further investigation using cultured cells from SFTs and more case studies are neces-

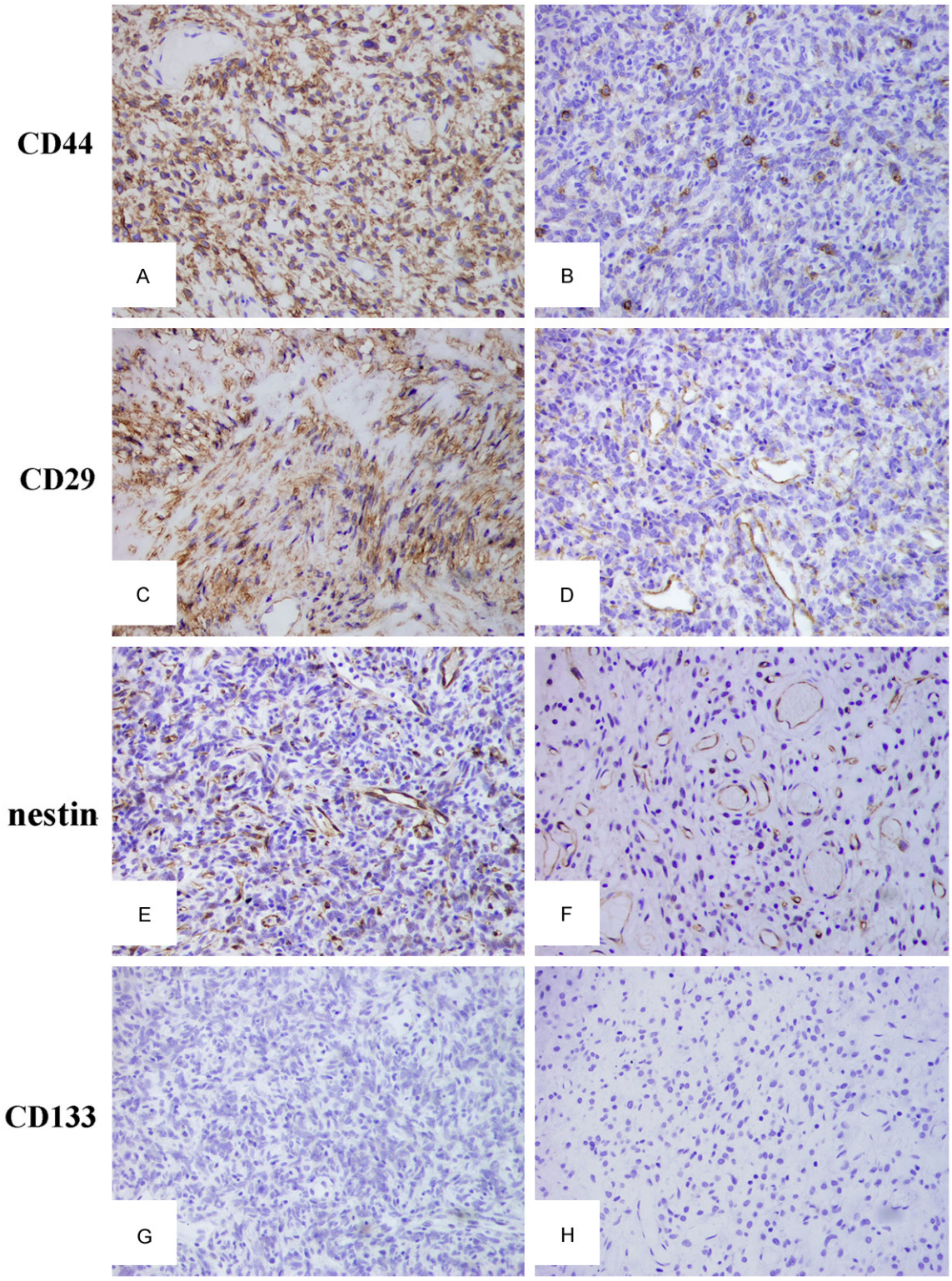

Figure 4. Immunohistochemical findings of CSCs markers (× 200). CD44 was focally positive in 8 of 18 cases and was only observed in infiltrating macrophages in the all cases; all cases showed CD29 vascular positive and only 1 case showed CD29 focally positive in tumor tissue. All cases were negative for CD133. Nestin was only observed in endothelial cells of tumor vessels.

sary to examine the utility of these stem markers for accurate diagnosis and to identify the cell of origin of SFT.

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Disclosure of conflict of interest

None.

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