Original Article
Diagnostic value of a monoclonal anti-STAT6 antibody for solitary fibrous tumors: immunohistochemical analyses

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Abstract: Solitary fibrous tumors (SFTs) have been shown to harbor the characteristic *NAB2-STAT6* gene fusion. Some recent studies have suggested that STAT6 is a useful marker for the diagnosis of SFTs. The aim of this study was to evaluate the diagnostic value of monoclonal anti-STAT6 in the distinction of SFTs from histologic mimics. The expression of STAT6 was evaluated in tissue microarrays and in whole sections of 407 tumors (including 63 SFTs and 344 nonSFTs) using a monoclonal anti-STAT6 antibody (clone: YE361). Only STAT6 nuclear staining was recorded as positive. All cases of SFTs (100%) exhibited nuclear STAT6 expression, and 45 cases displayed 3+ and strong staining intensity (72%), 7 cases displayed 3+ and moderate staining intensity (11%), 4 displayed 2+ and strong staining intensity (6%), 3 displayed 2+ and moderate staining intensity (5%) and 4 displayed 3+ and weak staining intensity (6%). The vast majority of the nonSFTs (343/344, 99.7%) were negative for STAT6. Only 0.3% (1/344) of the nonSFTs (one case of synovial sarcoma) showed 1+ and weak staining intensity of nuclear STAT6 expression. The sensitivity and specificity of nuclear STAT6 staining were 100% and 99.7%, respectively. In conclusion, the monoclonal anti-STAT6 antibody used in this study is highly sensitive and specific for the differential diagnosis of SFTs. In small biopsy specimens, negativity for STAT6 cannot completely exclude the diagnosis of SFT. Similarly, focal positivity for STAT6 cannot completely exclude the possibility of nonSFTs.

Keywords: Solitary fibrous tumor, STAT6, immunohistochemistry, tissue microarray

Introduction

Solitary fibrous tumors (SFTs) are mesenchymal tumors that belong to the fibroblastic/myofibroblastic family of tumors with a spectrum that ranges from benign to malignant [1]. Some SFTs were previously termed hemangiopericytomas (HPCs), and HPC is often used a synonym of SFT [1, 2].

Histologically, typical SFTs usually show patternless architecture of spindle to ovoid tumor cells with indistinct cytoplasmic borders. In addition, the stroma is usually composed of thick bands of hyalinized collagen and branching hemangiopericytoma-like vessels. Moreover, SFTs may be classified into several subtypes, such as cellular variants, fat-forming variants and malignant SFTs [1-3]. Traditionally, a panel of immunohistochemical markers, including CD34, Bcl-2, and CD99, has been

used to distinguish SFTs from their histologic mimics [4]. However, none of these markers is specific for the diagnosis of SFTs.

Recently, the *NAB2-STAT6* fusion gene has been identified in the vast majority of SFTs and has been described as a distinct molecular feature of SFTs [5-7]. The *NAB2-STAT6* fusion is due to an intra-chromosomal inversion that juxtaposes the 3' region of *NAB2* and the 5' region of *STAT6*, which encodes a fusion protein [5-7]. Therefore, the identification of the *NAB2-STAT6* fusion gene is helpful in the diagnosis of SFTs. However, molecular studies have not been widely used in all laboratories. Fortunately, Schweizer et al. [8] discovered that this fusion gene may be detected by immunohistochemistry for STAT6. Subsequently, some studies have detected the expression of STAT6 in SFTs using a polyclonal anti-STAT6 antibody (clone: S-20) [9-20]. A commercially available monoclonal

anti-STAT6 antibody (clone: YE361) has only recently emerged, and only 7 studies have used a monoclonal anti-STAT6 antibody to assess the diagnostic value of STAT6 in SFTs [21-27].

Here, we used the monoclonal anti-STAT6 antibody to investigate the expression of STAT6 in SFTs and in a large series of their histologic mimics to evaluate the diagnostic value of STAT6 in the diagnosis of SFTs.

Materials and methods

Study cases and tumor specimens

This study was approved by the West China Hospital Institutional Review Board. Formalin-fixed, paraffin-embedded (FFPE) tissue samples of SFTs and nonSFTs from January 2006 to January 2016 were retrieved from the archives of the Department of Pathology of the West China Hospital of Sichuan University. Pathology reports, histology sections, and immunohistochemically stained slides were reviewed by 3 experienced soft tissue pathologists (H.Z., H.C. and Z.Z.) and 1 general surgical pathologist (X.H.) according to the criteria of the fourth edition of World Health Organization Classification of Tumors of Soft Tissue and Bone and the sixth edition of Enzinger and Weiss's Soft Tissue Tumors [1, 3].

Tissue microarray (TMA) blocks were constructed. Briefly, routine hematoxylin- and eosin-stained sections were evaluated, and representative areas of the tissues were marked using a felt-tip pen for easy detection. One tissue cylinder with a diameter of 1.2 mm was punched from each morphologically representative area of each tissue block and placed in a recipient paraffin block (40 mm×30 mm×10 mm) using a homemade semiautomated tissue arrayer. To exclude bias due to possible tumor heterogeneity, 3 to 5 punches were obtained from each tumor specimen. A total of 375 tissue samples were selected from the TMA blocks including the following: 49 SFTs, 64 synovial sarcomas, 39 schwannomas, 35 neurofibromas, 32 malignant peripheral nerve sheath tumors (MPNSTs), 19 dermatofibrosarcoma protuberans (DFSPs), 18 rhabdomyosarcomas, 17 Ewing sarcomas, 15 desmoid-type fibromatoses, 15 epithelioid sarcomas, 14 clear cell sarcomas of the soft tissue, 12 leiomyosarcomas, 10 mesenchymal chondrosarcomas, 10 spindle cell carcinomas, 10 myxofibrosarcomas, 9 fibrosarcomas, and 7 myofibrosarcomas.

In addition, 32 cases were evaluated by means of conventional paraffin tissue blocks and included the following: 14 SFTs, 4 synovial sarcomas, 2 schwannomas, 2 MPNSTs, 2 DFSPs, 2 desmoid-type fibromatoses, 2 dedifferentiated liposarcomas, one spindle cell lipoma, one spindle cell liposarcoma, one cellular fibrous histiocytoma, and one undifferentiated pleomorphic sarcoma.

In summary, 407 cases were included in the present study: 63 SFTs and 344 histological mimics (68 synovial sarcomas, 41 schwannomas, 35 neurofibromas, 34 MPNSTs, 21 DFSPs, 18 rhabdomyosarcomas, 17 Ewing sarcomas, 17 desmoid-type fibromatoses, 15 epithelioid sarcomas, 14 clear cell sarcomas of the soft tissue, 12 leiomyosarcomas, 10 mesenchymal chondrosarcomas, 10 spindle cell carcinomas, 10 myxofibrosarcomas, 9 fibrosarcomas, 7 myofibrosarcomas, 2 dedifferentiated liposarcomas, one spindle cell lipoma, one spindle cell liposarcoma, one cellular fibrous histiocytoma, and one undifferentiated pleomorphic sarcoma). All SFTs were previously assessed via immunohistochemistry with CD34, Bcl-2 and CD99 antibodies. All synovial sarcomas were previously confirmed by fluorescence in situ hybridization (FISH) for t(X;18)(*SS18;SSX*).

Immunohistochemistry

Four-micrometer-thick sections were cut from TMA blocks and from conventional paraffin tissue blocks and were autoclaved in citrate buffer (pH 6.0) for antigen retrieval. Immunohistochemical staining for STAT6 was performed using a monoclonal antibody (YE361, 1:400 dilution; Abcam, Cambridge, UK) and the EnVision detection system (Dako, Carpinteria, CA, USA). 3,3'-diaminobenzidine (Dako, Carpinteria, CA, USA) was used as the chromogen, and the sections were counterstained with hematoxylin. Both positive and negative control sections were included.

In regards to the STAT6 staining, only nuclear staining was recorded as positive. The results of the STAT6 immunohistochemistry were semiquantitatively scored using a previously reported scoring system [21]. The extent of staining was graded as follows: 0 (no staining), 1+

Table 1. STAT6 Immunohistochemical staining of SFTs and histological mimics

Tumor Type	n[Δ]	Nuclear (%)	Cytoplasmic (%)
SFT	63 (17)	63 (100%)	0
Synovial sarcoma	68 (4)	1 (1%)	24 (35%)
Schwannoma	41 (2)	0	21 (51%)
Neurofibroma	35	0	5 (14%)
MPNST	34 (2)	0	0
DFSP	21 (2)	0	3 (14%)
Rhabdomyosarcoma	18	0	0
Ewing sarcoma	17	0	0
Desmoid-type fibromatosis	17 (2)	0	0
Epithelioid sarcoma	15	0	0
Clear cell sarcomas of the soft tissue	14	0	0
Leiomyosarcoma	12	0	0
Mesenchymal chondrosarcoma	10	0	0
Spindle cell carcinoma	10	0	0
Myxofibrosarcoma	10	0	0
Fibrosarcoma	9	0	0
Myofibrosarcoma	7	0	2 (29%)
Dedifferentiated liposarcoma	2 (2)	0	0
Spindle cell lipoma	1 (1)	0	0
Spindle cell liposarcoma	1 (1)	0	0
Cellular fibrous histiocytoma	1 (1)	0	0
Undifferentiated pleomorphic sarcoma	1 (1)	0	0

[Δ]Number in the parenthesis indicate immunohistochemical staining for STAT6 was performed on whole sections.

(1-25% staining), 2+ (26-50% staining), and 3+ (>50% staining). The staining intensity was graded as negative, weak, moderate, or strong.

Results

The 63 SFT specimens were acquired from 31 males and 32 females, and no gender predilection was observed. The age of the patients ranged from 18 to 78 years (mean: 41 years, median: 48 years). This series of SFTs arose from a wide variety of anatomical sites including the lung and pleura (32, 51%), head and neck (8, 13%), mediastinum (6, 9%), pelvic cavity (5, 8%), extremities (4, 6%), abdominal cavity (3, 5%), retroperitoneum (2, 3%), trunk (2, 3%), and inguinal region (1, 2%). The tumor size ranged from 2 to 23 cm (mean: 8.6 cm, median: 6.5 cm). The histological subtypes of the 63 SFTs included 37 (59%) conventional SFTs, 12 (19%) cellular SFTs, one (1%) fat-forming SFT and 13 (21%) malignant SFTs. CD34 immuno-

histochemical staining was performed in all cases of SFTs at the time of diagnosis. Sixty-two cases of SFTs (98%) were positive for CD34, whereas 1 malignant tumor was negative for this marker. Fifty-four cases were diffusely and strongly positive for CD34, and eight SFTs (seven conventional and one cellular) exhibited focal staining patterns of CD34 expression.

A summary of the STAT6 immunohistochemical staining results is provided in **Table 1**. All cases of SFTs (100%) exhibited nuclear positivity, regardless of the anatomic site and histological subtype (**Figure 1**). Among this series of SFTs, the rates of STAT6 positivity in TMAs and whole sections were 94% (46/49) and 100% (14/14), respectively. The three cases of STAT6-negative SFTs (two conventional and one cellular) from the TMAs were again subjected to STAT6 immunohistochemistry but as whole-sections. The results showed that one conventional SFT and one cellular SFT displayed 3+ and strong staining intensity, while one conventional SFT displayed 3+ and weak staining intensity. In summary, the distribution and the staining intensity were as follows: 45 cases (72%) displayed 3+ and strong staining intensity, 7 (11%) displayed 3+ and moderate staining intensity, 4 (6%) displayed 2+ and strong staining intensity, 3 (5%) displayed 2+ and moderate staining intensity and 4 (6%) displayed 3+ and weak staining intensity. The majority of SFTs (52/63, 83%) displayed diffuse staining (3+) and a pattern of moderate to strong staining intensity.

The vast majority of the nonSFTs (343/344, 99.7%) were negative for STAT6 expression (**Figure 2**). Only a single case of the nonSFTs (1/344, 0.3%) (one typical monophasic synovial sarcoma), showed 1+ and a weak intensity with respect to nuclear reactivity. However, this
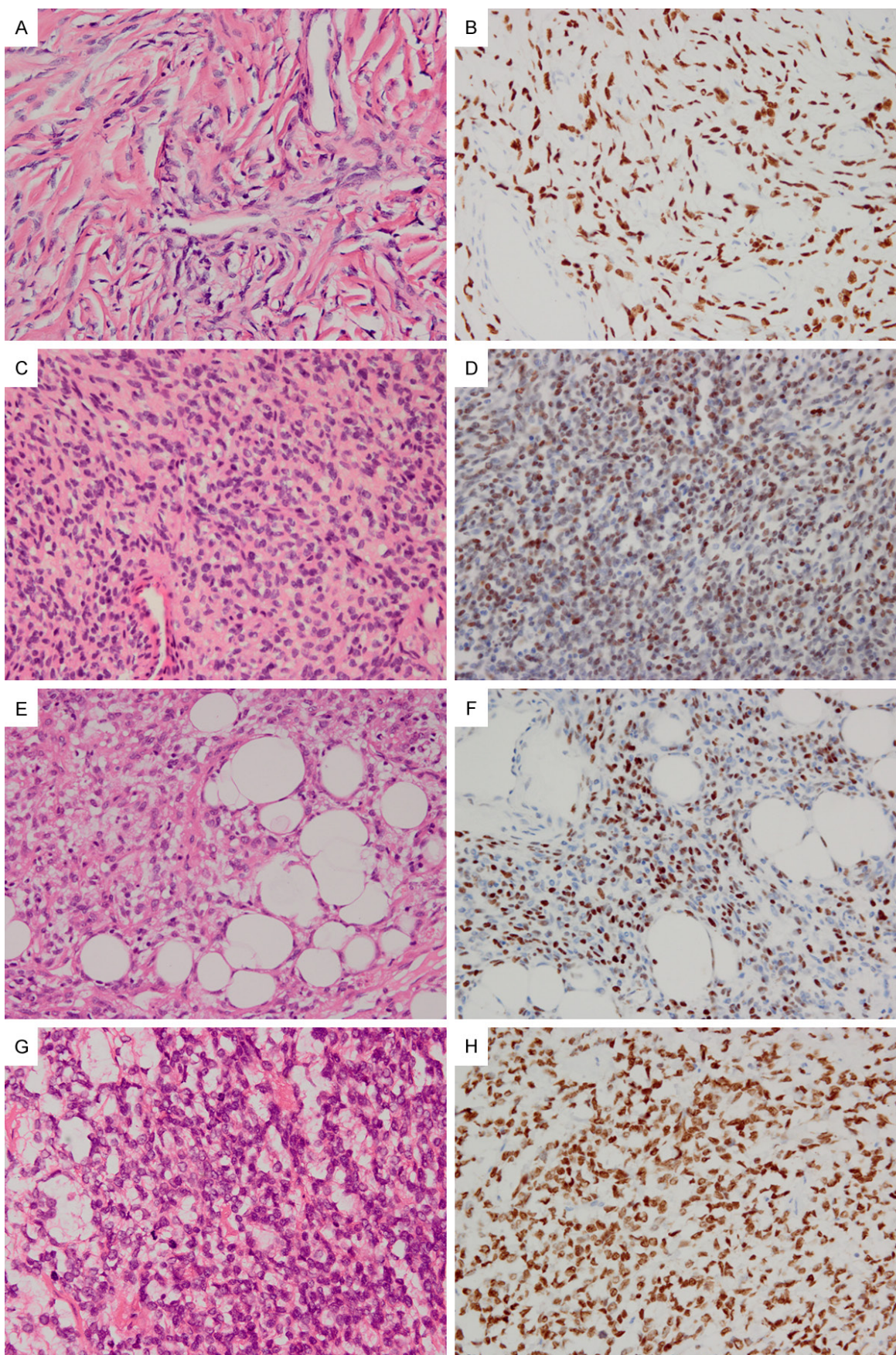
Figure 1. STAT6 immunohistochemical staining in different histologic subtypes of SFTs. A. A conventional SFT with spindle cells that are randomly arranged between collagen bundles. B. Diffuse and strong nuclear expression of STAT6 in a conventional SFT. Note the STAT6-negative endothelial cells. C. A cellular SFT composed of ovoid to slightly spindled cells with indistinct cytoplasmic borders. D. The tumor cells exhibit diffuse and strong nuclear staining for STAT6 in a cellular SFT. E. A fat-forming SFT composed of ovoid to spindled cells and mature adipocytes. F. The tumor cells exhibit diffuse and strong nuclear staining for STAT6 in a fat-forming SFT. G. A malignant SFT with conspicuous mitotic activity. H. The tumor cells exhibit diffuse and strong nuclear staining for STAT6 in a malignant SFT (original magnification 400×).

monophasic synovial sarcoma was positive for the expression of Transducin-like enhancer of split 1 (TLE1), epithelial membrane antigen, AE1/AE3, and CK7. More importantly, this tumor was found to harbor t(X; 18) (**Figure 3**).

In addition, 16% (55/344) of the nonSFTs, including 24 (35%) synovial sarcomas, 21 (51%) schwannomas, 5 (14%) neurofibromas, 3 (14%) DFSPs and 2 (29%) myofibrosarcomas, exhibited cytoplasmic STAT6 staining to various degrees and all of them exhibited focal or patchy distribution patterns with weak to moderate staining intensity (**Figure 4**).

In regards to the diagnosis of SFTs, the sensitivity and specificity of nuclear STAT6 staining were 100% and 99.7%, respectively.

Discussion

Most conventional SFTs can be diagnosed directly by a combination of morphologic features and the expression of traditional immunohistochemical markers including CD34, CD99 and Bcl-2. However, SFTs are sometimes difficult to distinguish from nonSFTs, especially when the tumors exhibit peculiar clinical findings or unusual morphologies. For example, SFT can be confused with other CD34-positive spindle cell neoplasms. Furthermore, negativity for CD34 cannot rule out the possibility of SFT. The *NAB2-STAT6* fusion gene is a novel molecular genetic discovery in SFTs [5-7]; this fusion gene may exist as several variants such as *NAB2ex4-STAT6ex2/3* and *NAB2ex6-STAT6ex16/17* [9, 17, 20, 22-24, 26, 28]. However, the C-terminus of STAT6 is present in all fusion proteins [5-7]. Therefore, an antibody that recognizes the C-terminus of STAT6 has been proposed as a surrogate marker for the *NAB2-STAT6* fusion gene in the diagnosis of SFTs [8]. Thus far, the majority of the previous studies used a polyclonal anti-STAT6 antibody [9-20], and the rates of STAT6 reactivity in SFTs ranged from 86% to 100% [9-20].

Prior studies on the use of monoclonal anti-STAT6 antibodies for SFTs are relatively scarce. In the present study, we used a monoclonal anti-STAT6 antibody to investigate the expression of STAT6 in SFTs and in a large series of histologic mimics. Nuclear STAT6 positivity was observed in 100% of the SFTs regardless of the anatomic site and histological subtype, and no cytoplasmic staining was observed; moreover, the sensitivity of this antibody was 100% for the diagnosis of SFTs. In addition, we noticed that STAT6 usually (83%) displays a diffuse staining pattern and moderate to strong staining intensity in the series of SFTs. In previous series, when monoclonal antibodies were used, the rates of STAT6 positivity in SFTs ranged from 72% to 100% [21-27].

Based on previous research and the present study, STAT6 is generally highly sensitive for SFTs, irrespective of whether a monoclonal or a polyclonal anti-STAT6 antibody is used. However, in the study by Macagno et al. [27], two negative cases that were stained with a monoclonal anti-STAT6 antibody exhibited a nuclear signal with a polyclonal anti-STAT6 antibody. Their results may indicate greater sensitivity of the polyclonal antibody for degraded antigen in older samples.

As is well known, CD34 seems to be one of the most important diagnostic markers for SFTs in clinical practice [1, 3]. However, approximately 5%-10% of SFTs are negative for CD34 [1], and CD34 expression is also common in spindle cell lipomas, DFSPs, epithelioid sarcomas and MPNSTs [29-32], which may be easily mistaken for SFTs, especially in small biopsy specimens. In our study, all SFTs were subjected to immunohistochemistry for CD34 at the time of diagnosis. One malignant SFT was negative for CD34, and 8 SFTs (seven conventional and one cellular) exhibited focal staining patterns of CD34 expression in whole sections; however, all of them exhibited STAT6 3+ and strong staining intensity in TMAs. Among the samples in
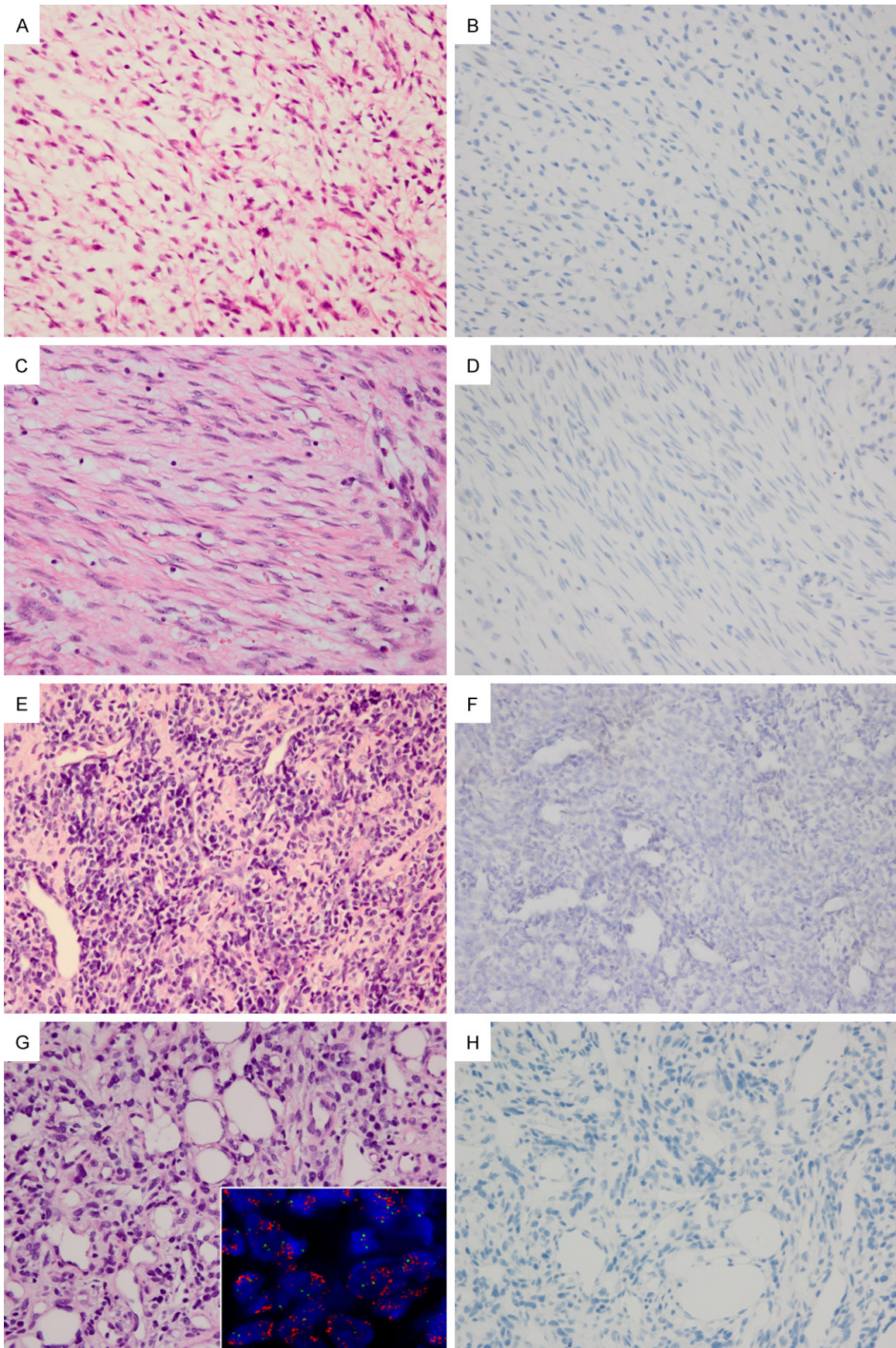
Figure 2. STAT6 negativity in nonSFTs. A. Myxoid area in an MPNST. B. STAT6 negativity in an MPNST. C. A desmoid-type fibromatosis composed of spindle-shaped cells arranged in long fascicles. D. STAT6 negativity in a desmoid-type fibromatosis. E. Small round cells surrounding hemangiopericytoma-like vessels in a mesenchymal chondrosarcoma. F. STAT6 negativity in a mesenchymal chondrosarcoma. G. A dedifferentiated liposarcoma with marked pleomorphism and showing positivity for amplification of *MDM2* gene (G inset: *MDM2*, red signals; CEP12, green signals, 1000×). H. STAT6 negativity in a dedifferentiated liposarcoma. (original magnification 400×).
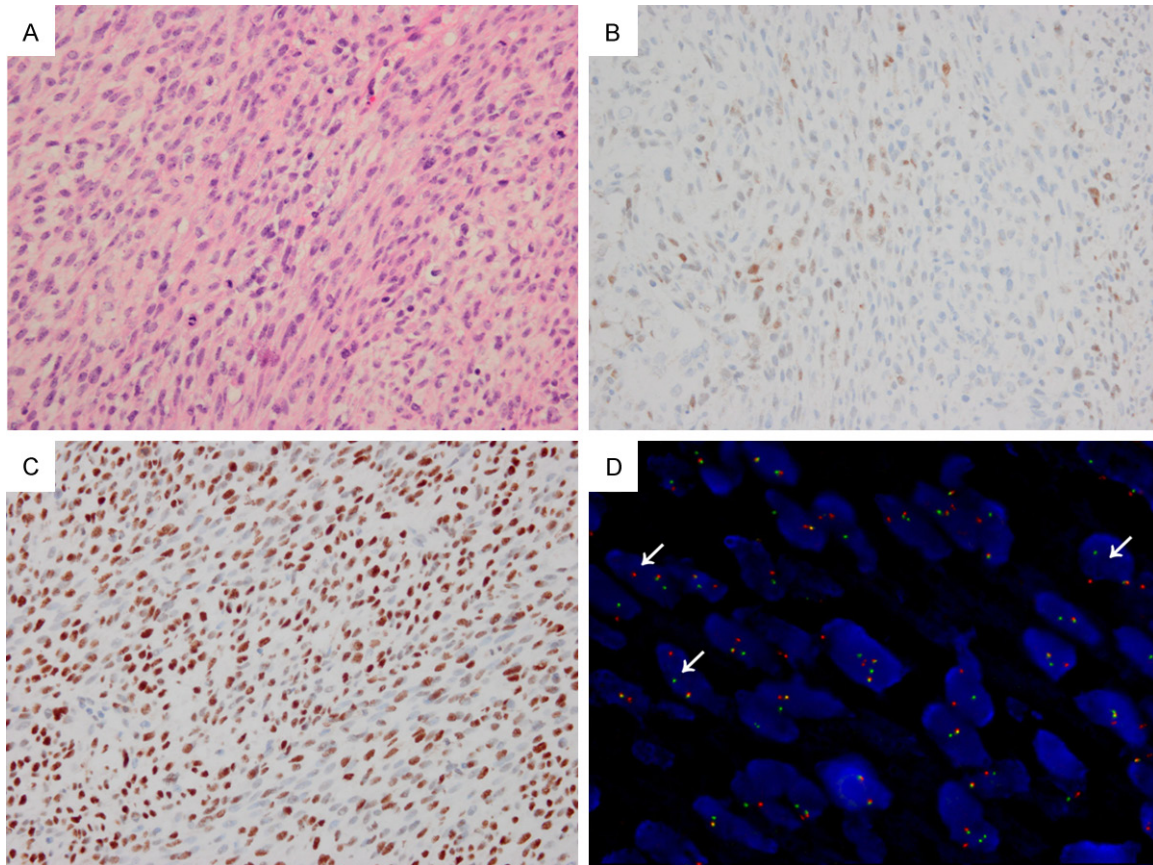

Figure 3. The results of immunohistochemistry and molecular tests on a synovial sarcoma. A. A monophasic synovial sarcoma with spindled cells arranged in fascicles. B. A small subset of tumor cells shows weak nuclear staining for STAT6. C. TLE1 positivity in a synovial sarcoma (original magnification 400×). D. Detection of the *SS18* rearrangement by FISH. The break-apart red and green signals indicated *SS18* rearrangement (arrow; 1000×).

this series, the rate of STAT6 positivity in TMAs was 94%. Interestingly, the tissue volumes used in TMAs are very small and are thus similar to biopsy specimens to some extent. These findings indicate that STAT6 is a sensitive and useful maker for the diagnosis of SFTs when the biopsy specimens are small. Cheah et al. [21] also suggested that STAT6 immunohisto-chemistry may be a valuable diagnostic adjunct in diagnostically challenging cases, particularly those where core needle biopsies were obtained. However, it should be noted that, in our study, the three cases of STAT6-negative SFTs in the TMAs were positive for STAT6 in

whole sections. This may imply that in small biopsy specimens, STAT6-negativity does not completely rule out the possibility of SFTs. In such situations, traditional immunohistochemical markers may be complementary, and surgically resected specimens are necessary for a definitive diagnosis.

In previous studies, when a monoclonal anti-STAT6 antibody was used, none of the nonSFTs showed nuclear positivity for STAT6 [21, 27]. In the present study, the specificity of this bio-marker for SFTs was 99.7%, which is similar to that in previous studies. However, in the pres-
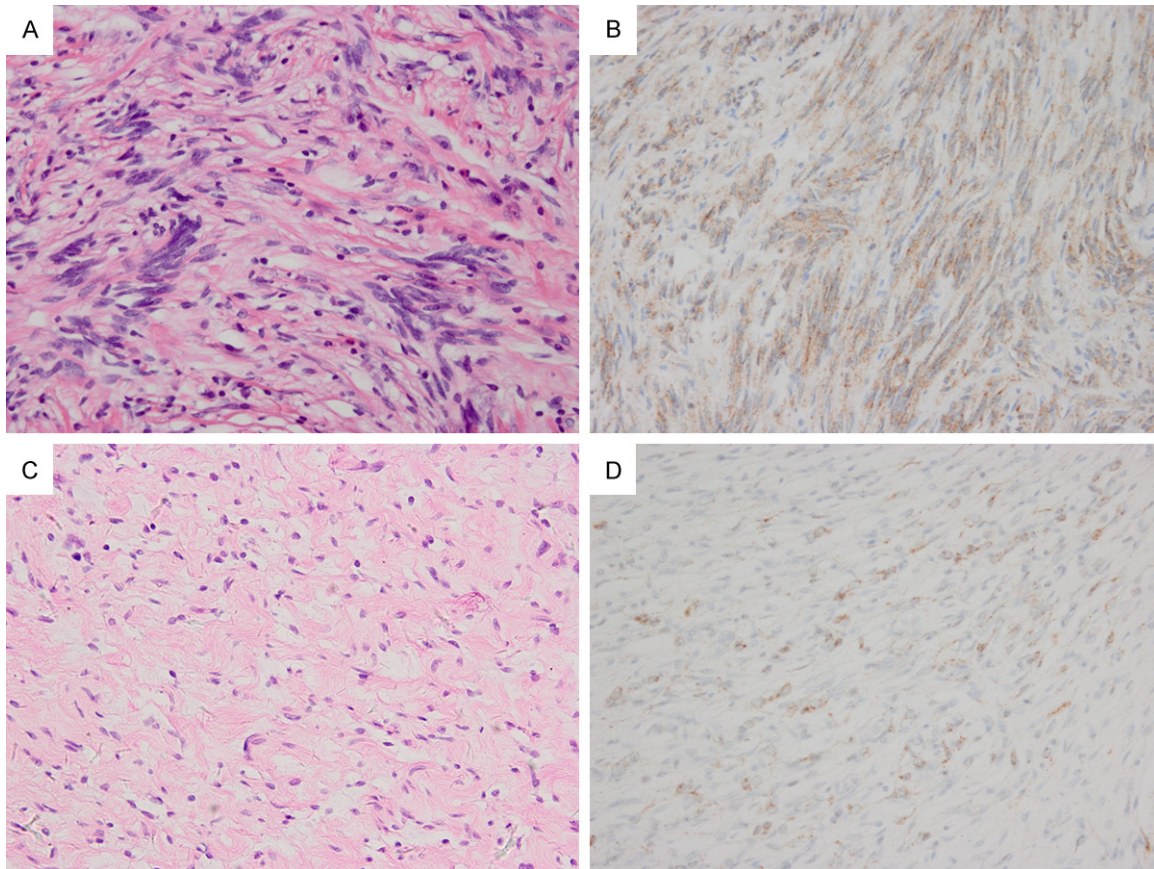
Figure 4. STAT6 immunohistochemistry in nonSFTs. A. Antoni A areas with short fascicles and focal nuclear palisading in a schwannoma. B. Weak to moderate granular cytoplasmic staining pattern of STAT6 in a schwannoma. C. A neurofibroma contains elongated cells with wavy and darkly stained nuclei. D. A small subset of tumor cells exhibits weak cytoplasmic staining for STAT6 in a neurofibroma (original magnification 400×).

ent study, nuclear STAT6 reactivity was observed in single case of monophasic synovial sarcoma, which demonstrated 1+ and weak staining intensity. Of course, further investigation is warranted to explain this phenomenon. This indicates that focal and weak nuclear STAT6 staining may not lead to a definitive diagnosis of SFTs. In contrast, diffuse and strong nuclear STAT6 staining with a monoclonal antibody may be highly suggestive of SFTs.

In previous studies, which used polyclonal anti-STAT6 antibodies, the positive rate of nonSFTs ranged from 1% to 4% [8, 11-15]. The nonSFTs comprised a wide variety of tumor types as follows: dedifferentiated liposarcoma (1.4%~14%) [11, 12, 14, 15, 33, 34], meningioma (3/90) [8], deep fibrous histiocytoma (1/10) [11], undifferentiated pleomorphic sarcoma (2/130, 2/173) [12, 14], nodular fasciitis (1/63) [12], low-grade fibromyxoid sarcoma (2/7), myxoid/

round cell liposarcoma (1/9), ovarian fibroma (1/2) [13], desmoid-type fibromatosis (14/184), unclassified spindle cell/epithelioid sarcoma (8/65) [14], well-differentiated liposarcoma (2/75) and synovial sarcoma (1/15) [15]. This may suggest that the specificity of polyclonal anti-STAT6 antibodies is slightly lower than that of monoclonal anti-STAT6 antibodies.

It should be noted that reactivity for polyclonal anti-STAT6 antibodies in a small subset of non-SFTs can pose potential pitfalls in the differential diagnosis of SFTs, especially for the variant subtype. Among the aforementioned nonSFTs, the most remarkable is dedifferentiated liposarcoma [11, 12, 14, 15, 33, 34]. It is difficult to distinguish dedifferentiated liposarcoma from fat-forming SFTs, especially when small biopsy samples are obtained. However, the majority of these dedifferentiated liposarcomas displayed weak to moderate, focal to mul-

tifocal nuclear STAT6 staining, but the STAT6 expression in SFTs is usually diffuse and strong [33]. Immunohistochemistry for MDM2 or CDK4 [35], especially FISH for *MDM2* amplification [36], is an invaluable diagnostic tool for dedifferentiated liposarcomas. Doyle et al. [33] demonstrated *STAT6* amplification by FISH in 4 cases that were positive for STAT6 by immunohistochemistry. *STAT6* (on 12q13) is close to *MDM2* (on 12q14.3-q15) and *CDK4* (on 12q14) on chromosome 12q. Therefore, the 12q amplification that includes the *STAT6* locus might be one of the reasons for *STAT6* amplification in a small subset of dedifferentiated liposarcomas [11, 12, 33]. However, the amplifications of 12q13-15 are frequent in dedifferentiated liposarcomas [37], whereas *STAT6* amplification is only a low-frequency event in dedifferentiated liposarcomas. Therefore, further investigation is warranted to explain this phenomenon. Synovial sarcomas may share some morphologic features with SFT and seem to be one of the most challenging tumor types in terms of the differential diagnosis of SFTs. However, synovial sarcomas usually show strong positivity for TLE1 [38-41] and do not show diffuse reactivity for STAT6 or CD34. The definitive diagnosis should be aided by molecular tests in extremely difficult cases.

STAT6 is a transcription factor that is involved in interleukin 4 signaling [42]. Normally, wild-type NAB2 protein localizes to the nucleus [43], whereas wild-type STAT6 protein is primarily localized to the cytoplasm and phosphorylated STAT6 translocates to the nucleus [42]. Therefore, the STAT6 positive signal is located in the nucleus due to the formation of NAB2-STAT6 fusion protein. In the present study, 16% (55/344) of the nonSFTs, including synovial sarcomas, schwannomas, neurofibromas, DFSPs and myofibrosarcomas, exhibited cytoplasmic staining. This result was similar to that of previous studies, especially those that used polyclonal anti-STAT6 antibodies [8, 13]. However, pathologists should consider that cytoplasmic staining must not be interpreted as positive in the differential diagnosis of SFTs. Therefore, the correct interpretation of the results of STAT6 immunohistochemistry is very important.

In summary, this study is a single-center, large-scale analysis of STAT6 immunohistochemical staining in SFTs and their histological mimics in Chinese patients using a monoclonal anti-STAT6 antibody. This antibody is highly sensitive and specific for the differential diagnosis of SFTs. It should be noted that negativity for STAT6 cannot completely rule out the diagnosis of SFTs in small biopsy specimens. Similarly, focal positivity for STAT6 cannot completely exclude the possibility of nonSFTs.

Disclosure of conflict of interest

None.

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References

[1] Fletcher CDM, Bridge JA and Lee JC. Extra-pleural solitary fibrous tumour. In: Fletcher CDM, Bridge JA, Hogendoorn PCW and Mertens F, editors. WHO classification of tumours of soft tissue and bone. 4th Edition. Lyon: IARC Press; 2013. pp. 80-82.

[2] Gengler C and Guillou L. Solitary fibrous tumour and haemangiopericytoma: evolution of a concept. Histopathology 2006; 48: 63-74.

[3] Goldblum JR, Folpe AL and Weiss SW. Solitary fibrous tumor (Hemangiopericytoma). In: Goldblum JR, Folpe AL and Weiss SW, editors. Enzinger and Weiss's Soft Tissue Tumors. 6th Edition. Philadelphia, Pa: Saunders; 2013. pp. 1002-1017.

[4] Rao N, Colby TV, Falconieri G, Cohen H, Moran CA and Suster S. Intrapulmonary solitary fibrous tumors: clinicopathologic and immunohistochemical study of 24 cases. Am J Surg Pathol 2013; 37: 155-166.

[5] Chmielecki J, Crago AM, Rosenberg M, O'Connor R, Walker SR, Ambrogio L, Auclair D, McKenna A, Heinrich MC, Frank DA and Meyerson M. Whole-exome sequencing identifies a recurrent NAB2-STAT6 fusion in solitary fibrous tumors. Nat Genet 2013; 45: 131-132.

[6] Mohajeri A, Tayebwa J, Collin A, Nilsson J, Magnusson L, von Steyern FV, Brosjo O, Domanski HA, Larsson O, Sciot R, Debiec-Rychter M, Hornick JL, Mandahl N, Nord KH

and Mertens F. Comprehensive genetic analysis identifies a pathognomonic NAB2/STAT6 fusion gene, nonrandom secondary genomic imbalances, and a characteristic gene expression profile in solitary fibrous tumor. Genes Chromosomes Cancer 2013; 52: 873-886.

[7]   Robinson DR, Wu YM, Kalyana-Sundaram S, Cao X, Lonigro RJ, Sung YS, Chen CL, Zhang L, Wang R, Su F, Iyer MK, Roychowdhury S, Siddiqui J, Pienta KJ, Kunju LP, Talpaz M, Mosquera JM, Singer S, Schuetze SM, Antonescu CR and Chinnaiyan AM. Identification of recurrent NAB2-STAT6 gene fusions in solitary fibrous tumor by integrative sequencing. Nat Genet 2013; 45: 180-185.

[8]   Schweizer L, Koelsche C, Sahm F, Piro RM, Capper D, Reuss DE, Pusch S, Habel A, Meyer J, Gock T, Jones DT, Mawrin C, Schittenhelm J, Becker A, Heim S, Simon M, Herold-Mende C, Mechtersheimer G, Paulus W, Konig R, Wiestler OD, Pfister SM and von Deimling A. Meningeal hemangiopericytoma and solitary fibrous tumors carry the NAB2-STAT6 fusion and can be diagnosed by nuclear expression of STAT6 protein. Acta Neuropathol 2013; 125: 651-658.

[9]   Agaimy A, Barthelmess S, Geddert H, Boltze C, Moskalev EA, Koch M, Wiemann S, Hartmann A and Haller F. Phenotypical and molecular distinctness of sinonasal haemangiopericytoma compared to solitary fibrous tumour of the sinonasal tract. Histopathology 2014; 65: 667-673.

[10] Creytens D and Ferdinande L. Diagnostic Utility of STAT6 Immunohistochemistry in the Diagnosis of Fat-forming Solitary Fibrous Tumors. Appl Immunohistochem Mol Morphol 2016; 24: e12-e13.

[11] Doyle LA, Vivero M, Fletcher CD, Mertens F and Hornick JL. Nuclear expression of STAT6 distinguishes solitary fibrous tumor from histologic mimics. Mod Pathol 2014; 27: 390-395.

[12] Koelsche C, Schweizer L, Renner M, Warth A, Jones DT, Sahm F, Reuss DE, Capper D, Knosel T, Schulz B, Petersen I, Ulrich A, Renker EK, Lehner B, Pfister SM, Schirmacher P, von Deimling A and Mechtersheimer G. Nuclear relocation of STAT6 reliably predicts NAB2-STAT6 fusion for the diagnosis of solitary fibrous tumour. Histopathology 2014; 65: 613-622.

[13] Yoshida A, Tsuta K, Ohno M, Yoshida M, Narita Y, Kawai A, Asamura H and Kushima R. STAT6 immunohistochemistry is helpful in the diagnosis of solitary fibrous tumors. Am J Surg Pathol 2014; 38: 552-559.

[14] Demicco EG, Harms PW, Patel RM, Smith SC, Ingram D, Torres K, Carskadon SL, Camelo-Piragua S, McHugh JB, Siddiqui J, Palanisamy N, Lucas DR, Lazar AJ and Wang WL. Extensive survey of STAT6 expression in a large series of

mesenchymal tumors. Am J Clin Pathol 2015; 143: 672-682.

[15] Ouladan S, Trautmann M, Orouji E, Hartmann W, Huss S, Buttner R and Wardelmann E. Differential diagnosis of solitary fibrous tumors: A study of 454 soft tissue tumors indicating the diagnostic value of nuclear STAT6 relocation and ALDH1 expression combined with in situ proximity ligation assay. Int J Oncol 2015; 46: 2595-2605.

[16] Petrovic A, Oberic A, Moulin A and Hamedani M. Ocular adnexal (orbital) solitary fibrous tumor: nuclear STAT6 expression and literature review. Graefes Arch Clin Exp Ophthalmol 2015; 253: 1609-1617.

[17] Barthelmess S, Geddert H, Boltze C, Moskalev EA, Bieg M, Sirbu H, Brors B, Wiemann S, Hartmann A, Agaimy A and Haller F. Solitary fibrous tumors/hemangiopericytomas with different variants of the NAB2-STAT6 gene fusion are characterized by specific histomorphology and distinct clinicopathological features. Am J Pathol 2014; 184: 1209-1218.

[18] Han Y, Zhang Q, Yu X, Han X, Wang H, Xu Y, Qiu X and Jin F. Immunohistochemical detection of STAT6, CD34, CD99 and BCL-2 for diagnosing solitary fibrous tumors/hemangiopericytomas. Int J Clin Exp Pathol 2015; 8: 13166-13175.

[19] Magro G, Angelico G, Leone G and Palazzo J. Solitary fibrous tumor of the breast: report of a case with emphasis on diagnostic role of STAT6 immunostaining. Pathol Res Pract 2016; 212: 463-7.

[20] Ishizawa K, Tsukamoto Y, Ikeda S, Suzuki T, Homma T, Mishima K, Nishikawa R and Sasaki A. 'Papillary' solitary fibrous tumor/hemangiopericytoma with nuclear STAT6 expression and NAB2-STAT6 fusion. Brain Tumor Pathol 2016; 33: 151-6.

[21] Cheah AL, Billings SD, Goldblum JR, Carver P, Tanas MZ and Rubin BP. STAT6 rabbit monoclonal antibody is a robust diagnostic tool for the distinction of solitary fibrous tumour from its mimics. Pathology 2014; 46: 389-395.

[22] Vogels RJ, Vlenterie M, Versleijen-Jonkers YM, Ruijter E, Bekers EM, Verdijk MA, Link MM, Bonenkamp JJ, van der Graaf WT, Slootweg PJ, Suurmeijer AJ, Groenen PJ and Flucke U. Solitary fibrous tumor - clinicopathologic, immunohistochemical and molecular analysis of 28 cases. Diagn Pathol 2014; 9: 224.

[23] Kao YC, Lin PC, Yen SL, Huang SC, Tsai JW, Li CF, Tai HC, Lan J, Chuang IC, Yu SC and Huang HY. Clinicopathological and genetic heterogeneity of the head and neck solitary fibrous tumours: a comparative histological, immunohistochemical and molecular study of 36 cases. Histopathology 2016; 68: 492-501.

[24] Tai HC, Chuang IC, Chen TC, Li CF, Huang SC, Kao YC, Lin PC, Tsai JW, Lan J, Yu SC, Yen SL,

Jung SM, Liao KC, Fang FM and Huang HY. NAB2-STAT6 fusion types account for clinicopathological variations in solitary fibrous tumors. Mod Pathol 2015; 28: 1324-1335.

[25] Wang C, Qi Y, Liu R, Lan J, Zhou Y, Ju X, Chen D, Zou H, Li S, Hu J, Zhao J, Shen Y, Sun Z, Pang L and Li F. Immunohistochemical evaluation of stem cell markers and signal transducer and activator of transcription 6 (STAT6) in solitary fibrous tumors. Int J Clin Exp Pathol 2015; 8: 10585-10594.

[26] Huang SC, Li CF, Kao YC, Chuang IC, Tai HC, Tsai JW, Yu SC, Huang HY, Lan J, Yen SL, Lin PC and Chen TC. The clinicopathological significance of NAB2-STAT6 gene fusions in 52 cases of intrathoracic solitary fibrous tumors. Cancer Med 2016; 5: 159-168.

[27] Macagno N, Figarella-Branger D, Mokthari K, Metellus P, Jouvet A, Vasiljevic A, Loundou A and Bouvier C. Differential Diagnosis of Meningeal SFT-HPC and Meningioma: Which Immunohistochemical Markers Should Be Used? Am J Surg Pathol 2016; 40: 270-278.

[28] Akaike K, Kurisaki-Arakawa A, Hara K, Suehara Y, Takagi T, Mitani K, Kaneko K, Yao T and Saito T. Distinct clinicopathological features of NAB2-STAT6 fusion gene variants in solitary fibrous tumor with emphasis on the acquisition of highly malignant potential. Hum Pathol 2015; 46: 347-356.

[29] Templeton SF and Solomon AR Jr. Spindle cell lipoma is strongly CD34 positive. An immunohistochemical study. J Cutan Pathol 1996; 23: 546-550.

[30] Goldblum JR and Tuthill RJ. CD34 and factor-XIIIa immunoreactivity in dermatofibrosarcoma protuberans and dermatofibroma. Am J Dermatopathol 1997; 19: 147-153.

[31] Miettinen M, Fanburg-Smith JC, Virolainen M, Shmookler BM and Fetsch JF. Epithelioid sarcoma: an immunohistochemical analysis of 112 classical and variant cases and a discussion of the differential diagnosis. Hum Pathol 1999; 30: 934-942.

[32] Zhou H, Coffin CM, Perkins SL, Tripp SR, Liew M and Viskochil DH. Malignant peripheral nerve sheath tumor: a comparison of grade, immunophenotype, and cell cycle/growth activation marker expression in sporadic and neurofibromatosis 1-related lesions. Am J Surg Pathol 2003; 27: 1337-1345.

[33] Doyle LA, Tao D and Marino-Enriquez A. STAT6 is amplified in a subset of dedifferentiated liposarcoma. Mod Pathol 2014; 27: 1231-1237.

[34] Creytens D, Libbrecht L and Ferdinande L. Nuclear expression of STAT6 in dedifferentiated liposarcomas with a solitary fibrous tumor-like morphology: a diagnostic pitfall. Appl Immunohistochem Mol Morphol 2015; 23: 462-463.

[35] Binh MB, Sastre-Garau X, Guillou L, de Pinieux G, Terrier P, Lagace R, Aurias A, Hostein I and Coindre JM. MDM2 and CDK4 immunostainings are useful adjuncts in diagnosing well-differentiated and dedifferentiated liposarcoma subtypes: a comparative analysis of 559 soft tissue neoplasms with genetic data. Am J Surg Pathol 2005; 29: 1340-1347.

[36] Weaver J, Downs-Kelly E, Goldblum JR, Turner S, Kulkarni S, Tubbs RR, Rubin BP and Skacel M. Fluorescence in situ hybridization for MDM2 gene amplification as a diagnostic tool in lipomatous neoplasms. Mod Pathol 2008; 21: 943-949.

[37] Rieker RJ, Weitz J, Lehner B, Egerer G, Mueller A, Kasper B, Schirmacher P, Joos S and Mechtersheimer G. Genomic profiling reveals subsets of dedifferentiated liposarcoma to follow separate molecular pathways. Virchows Archiv 2009; 456: 277-285.

[38] Knösel T, Heretsch S, Altendorf-Hofmann A, Richter P, Katenkamp K, Katenkamp D, Berndt A and Petersen I. TLE1 is a robust diagnostic biomarker for synovial sarcomas and correlates with t(X;18): Analysis of 319 cases. Eur J Cancer 2010; 46: 1170-1176.

[39] Rekhi B, Basak R, Desai SB and Jambhekar NA. Immunohistochemical validation of TLE1, a novel marker, for synovial sarcomas. Indian J Med Res 2012; 136: 766-775.

[40] Foo WC, Cruise MW, Wick MR and Hornick JL. Immunohistochemical staining for TLE1 distinguishes synovial sarcoma from histologic mimics. Am J Clin Pathol 2011; 135: 839-844.

[41] Terry J, Saito T, Subramanian S, Ruttan C, Antonescu CR, Goldblum JR, Downs-Kelly E, Corless CL, Rubin BP, van de Rijn M, Ladanyi M and Nielsen TO. TLE1 as a diagnostic immunohistochemical marker for synovial sarcoma emerging from gene expression profiling studies. Am J Surg Pathol 2007; 31: 240-246.

[42] Goenka S and Kaplan MH. Transcriptional regulation by STAT6. Immunol Res 2011; 50: 87-96.

[43] Svaren J, Sevetson BR, Apel ED, Zimonjic DB, Popescu NC and Milbrandt J. NAB2, a corepressor of NGFI-A (Egr-1) and Krox20, is induced by proliferative and differentiative stimuli. Mol Cell Biol 1996; 16: 3545-3553.