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Original Article

Transducer-like enhancer of split 1 (TLE1) as a novel biomarker for diagnosis of synovial sarcoma correlates with translocation t(X;18): a study of 155 cases in China

Yingxue Li[1,2], Xuedong Zhang[2], Aichun Wang[3], Shanshan Ding[4], Ying Li[5], Hongqun Wang[1], Yali Lv[1], Huaiyin Shi[1]

[1]Department of Pathology, Chinese PLA General Hospital, Beijing 100853, China; [2]Department of Pathology, Liaocheng People's Hospital, Liaocheng 252000, Shandong, China; [3]Department of Pathology, Haidian Maternal and Children Health Hospital, Beijing 100080, China; [4]Department of Pathology, The General Hospital of The PLA Rocket Force, Beijing 100032, China; [5]Department of Pathology, The First Affiliated Hospital of Jiamusi University, Jiamusi 154000, Heilongjiang, China

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Abstract: Synovial sarcoma (SS) is a mesenchymal tumor of uncertain histogenesis which is defined by the translocation t(X;18). Transducer-like enhancer of split 1 (TLE1) as a new immunomarker for SS has offered an alternative to pathologists in distinguishing synovial sarcoma from other mesenchymal neoplasms, especially in limited molecular facilities. The main aim was to study the expression and diagnostic specificity and sensitivity of TLE1 in SS. We performed this immunohistochemical study on 155 SS (107 monophasic, 35 biphasic, and 10 poorly differentiated), 10 fibrosarcomas, 10 angiosarcomas, 10 epithelioid sarcomas, 10 Ewing sarcoma/PNETs and 8 malignant peripheral nerve sheath tumors (MPNST) using TLE1 immunomarker. Furthermore, in problematic cases (n=43), molecular confirmation was performed by fluorescent in situ hybridization (FISH) to detect the t(X;18) translocation. We correlated the TLE1 overexpression with the t(X;18) and other established biomarkers (CD117, CD56, cytokeratin AE1/AE3, EMA, CD99, BCL2, VIM, CD34, S100, Ki67, SMA). TLE1 expression was observed in 76.19% (112/147) of the SS, including 75.96% (79/104) of monophasic, 78.79% (26/33) of biphasic, and 70% (7/10) of poorly differentiated type. 65.99% (97/147) of SS cases showed a strong to moderate staining of TLE1. Other mesenchymal tumors showed very low or absent staining of TLE1 ($P < 0.001$). The overall sensitivity and specificity of TLE1 expression for the diagnosis of SS were 86.21% and 78.57%, respectively. Further molecular analysis showed that t(X;18) was clearly correlated with TLE1 expression ($P=0.000$). TLE1 is a specific and sensitive diagnostic immunomarker for SS and can be helpful to distinguish SS from other mesenchymal neoplasms.

Keywords: Synovial sarcoma, TLE1, immunohistochemistry, t(X;18) translocation, FISH

Introduction

Synovial sarcoma (SS) is a translation-associated mesenchymal malignant tumor that accounts for approximately 10% of all soft tissue sarcomas [1, 2]. Three main histological variant of SS have been recognized the monophasic, biphasic, and poorly differentiated subtypes. Approximately 70% of synovial sarcomas are of the monophasic fibrous subtype and 30% are biphasic, showing both epithelial and spindle cell components [3]. Poorly differentiated synovial sarcomas, showing a round cell pattern, account for < 5% of synovial sarcoma, and many arise from either monophasic or biphasic synovial sarcomas [4-6]. Diagnosing biphasic synovial sarcoma is generally straight forward, owing to distinctive histologic features. However, the differential diagnosis of monophasic and poor differentiated synovial sarcoma may be more challenging. Although the typical immunohistochemical panel consists of CK AE1/AE3, CK7, EMA, Bcl-2, CD99 and CD34 to aid in differentiating synovial sarcoma from other sarcoma, there is overlap in the immunophenotypes of these various tumors, and does not always yield a definitive diagnosis with immunohistochemistry alone [7-9]. Molecular

Table 1. Anatomic location of synovial sarcoma cases

Anatomic location	No. of synovial sarcoma cases
Head & neck	16 (10.32%)
Neck	5
Pharynx	5
Tongue	1
Other	5
Trunk	24 (15.48%)
Chest	1
Abdominal well	3
Mediastinum	2
Lung mass	3
Other	15
Upper extremities	31 (20%)
Forearm-wrist	9
Shoulder	10
Elbow-upper arm	9
Hand	3
Lower extremities	79 (50.64%)
Thigh-knee	46
Foot	7
Lower leg-ankle	12
Hip-groin	14
Other[a]	5 (3.23%)
Total	155 (100%)

[a]Anatomic location unknown.

diagnostic tools such as fluorescent in situ hybridization (FISH) or reverse transcriptase polymerase chain reaction (RT-PCR) to detect the specific translocation t(X;18) (SS18-SSX1/2) are increasing used for the definitive diagnosis of synovial sarcoma [10]. However, such techniques are limited in many laboratories, and require well-preserved genetic material [11-13]. Therefore, there is a necessary to investigate novel immunohistochemistry markers that are not only highly sensitive and specific for synovial sarcoma, but also cheaper than molecular testing.

A Groucho homolog, the Transducin-like Enhancer of Split 1 (TLE1), is a Groucho/TLE/Grg family of corepressors that involve many signaling pathways [14]. Human TLE1 operates with some critical transcription factors that regulate the hematopoiesis, survival and differentiation of normal cells [15-17]. TLE1 is expressed in synovial sarcomas, which is a unique factor that is barely expressed in other mesenchymal neoplasms. Some pathologists suggest that TLE1 staining should be used to differentiate synovial sarcoma from others [18, 19].

Here, we investigate TLE1 immunoreactivity in synovial sarcomas and other mesenchymal tumors commonly considered in their differential diagnosis, to assess the value of TLE1 as a diagnosis marker for this sarcoma.

Materials and methods

Tumor samples

Tissue samples of soft tissue tumors were retrieved from the surgical pathology archives of the Department of Pathology, Medical School of Chinese PLA in Beijing. A total of 241 mesenchymal neoplasms were evaluated and included the following: 155 synovial sarcomas (107 monophasic, 35 biphasic, and 10 poorly differentiated), 22 fibrosarcomas, 21 angiosarcomas, 16 epithelioid sarcomas, 19 Ewing sarcoma/PNETs and 8 malignant peripheral nerve sheath tumors (MPNST).The synovial sarcoma tumor collective and the anatomic location are summarised in **Table 1**. The age at presentation of the synovial sarcomas ranged from 10 to 82 years (median age 35 y, female n=74, male n=79). Tumor size ranged from 1.5 to 23 cm with a median size of 6 cm. Immunohistochemical analysis was performed according to standard procedures to confirm the diagnosis (CD117, CD56, cytokeratin AE1/AE3, EMA, CD99, BCL2, Vimentin, CD34, S100, Ki67, SMA, Desmin). In problematic cases (n=43), molecular confirmation was performed by FISH to detect the t(X;18) translocation. From the available slides in the archive (n=198) immunohistochemical analysis of TLE1 was performed. We correlated the TLE1 overexpression with the t(X;18) and other established biomarkers(CD117, CD56, cytokeratin AE1/AE3, EMA, CD99, BCL2, VIM, CD34, S100, Ki67, SMA, Desmin).

Immunohistochemistry

Immunohistochemical staining was performed for CD117, CD56, cytokeratin AE1/AE3, EMA, CD99, BCL2, Vimentin, CD34, S100, Ki67, SMA and TLE1. Four-μm sections of formalin-fixed paraffin-embedded material were used according to standard laboratory procedures. Details of the antibodies used are given in **Table 2**. Immunohistochemical staining for TLE1 was

Table 2. Antibodies for immunohistochemistry

Antibody	Supplier	Clone	Dilution	Subcellular distribution
TLE1	Origene	T13C9	1:100	Nucleus
CD117	MAB	YR145	1:200	Cytoplasm/Membrane
CD56	MAB	56C04	1:200	Membrane
CKAE1/AE3	DAKO	AE1/AE3	1:200	Cytoplasm/Membrane
EMA	DAKO	E29	1:100	Cytoplasm/Membrane
CD99	DAKO	12E7	1:100	Membrane
BCL2	DAKO	124	1:200	Membrane
Vimentin	DAKO	Vim3B4	1:400	Cytoplasm
CD34	DAKO	QBEnd 10	1:300	Cytoplasm
S100	DAKO	Policolnal	1:400	Cytoplasm
Ki67	DAKO	M2B-1	1:100	Nucleus
SMA	Origene	1A4	1:200	Cytoplasm
Desmin	Origene	0TI4G1	1:150	Cytoplasm

performed following pressure cooker antigen retrieval (citrate buffer; pH 6.0), using a mouse polyclonal antibody (1:100 dilution; Origene, USA) and the EnVision Plus detection system (DAKO, USA).

For TLE1, nuclear staining was considered positive. The intensity of the TLE1 immunostaining in tumor cells was evaluated by two independent pathologists and scored semiquantitatively as -, negative; 1+, mild; 2+, moderate; and 3+, strong positive [20]. For each of the antibodies, we performed positive and negative controls on full histological sections using tissues recommended by the manufacturer. The index of Ki-67 ≥ 10% was considered high.

Fluorescence in situ hybridization (FISH)

In problematic cases (n=43), molecular confirmation was performed by FISH to detect the t(X;18) translocation. FISH was performed on 4 μm paraffin-embedded tissue sections using a commercially available LSI SYT (18q11.2) Dual Color Break Apart Probe (Abbott Molecular Inc., USA) according to the manufacturer-provided protocol. The sections were deparaffinized in xylene (3 times, 5 min each), and dehydrated in 100% ethanol (2 times, 3min each). The sections were then pretreated with boiled water for 30 minutes followed by protease digestion for another 10 minutes. After the probes were applied, the sections were denatured at 83°C for 5 min and hybridized overnight at 42°C in a HYBrite. After washing, the slides were counterstained with DAPI and visualized using a fluorescence microscope (Olympus BX61). The FISH slides were scored separately by two investigators in 100 cells in each case. A break-apart signal pattern was considered positive when it showed at least one green and one red split nuclear signal. A case was interpreted positive for gene rearrangement if at least 10% of the nuclei showed break-apart signals [21-25].

Statistical analysis

Statistical analysis was performed using SPSS 17.0 (SPSS Inc., Chicago). The count date was expressed as rate and was analyzed with the X^2 test or Fisher's exact test. The *P* value was used to indicate the significance the test was a=0.05, and *P*-value < 0.05 was considered statistically significant. Multivariate analysis was performed with a logistic regression and stepwise conditional forward procedures. For assessing and comparing the variables, a significance level of 0.05 was used for inclusion and 0.1 for exclusion of variables.

Results

Immunohistochemistry

The summary of immunohistochemistry results for TLE1 in synovial sarcomas and other mesenchymal tumors in the differential diagnosis is listed in **Table 3**. Expression of TLE1 was observed in 61.54% of all evaluated cases (any positive +, 120/195). In synovial sarcomas, positive staining was found in 76.19% (112/147), including 79 (75.96%) of 104 of the monophasic type (**Figure 1**), 26 (78.79%) of 33 of the biphasic type (**Figure 2**), and 7 (70%) of 10 of the poorly differentiated type (**Figure 3**) (X^2=0.337, *P*=0.845). 97 of 147 (65.99%) of SS cases showed a strong to moderate staining (score 3+/2+) and 10.20% showed a weak staining (score 1+) (**Table 3**). In biphasic synovial sarcomas, the glandular elements generally showed stronger staining than did the spindle cell component (**Figure 2**).

In contrast to synovial sarcoma, TLE1 staining was low to absent in other mesenchymal tumors, such as 10% (1/10) fibrosarcomas, 50%

Table 3. Summary of TLE1 immunohistochemistry results

Tumor type	n	Negative	1+	2+	3+	Any positive (%)	Positive 2+, 3+ (%)	X^2	*P*
SS	147	39	15	52	45	112 (76.19)	97 (65.99)		
Monophasic	104	25	10	35	34	79 (75.96)	69 (66.35)	0.337	0.845
Biphasic	33	7	4	14	8	26 (78.79)	22 (66.67)		
Poorly differentiated	10	3	1	3	3	7 (70.00)	6 (60.00)		
Fibrosarcomas	10	9	1	0	0	1 (10.00)	0 (0.00)	42.716	0.000
Angiosarcomas	10	5	2	2	1	5 (50.00)	3 (30.00)		
Epithelioid sarcomas	10	9	1	0	0	1 (10.00)	0 (0.00)		
Ewing sarcoma/PNETs and	10	8	1	1	0	2 (20.00)	1 (10)		
MPNST	8	5	0	2	1	3 (37.50)	3 (37.50)		
Total	195	75	20	57	47	120 (61.54)	100 (51.28)		

Synovial sarcoma (SS), Malignant peripheral nerve sheath tumors (MPNST).

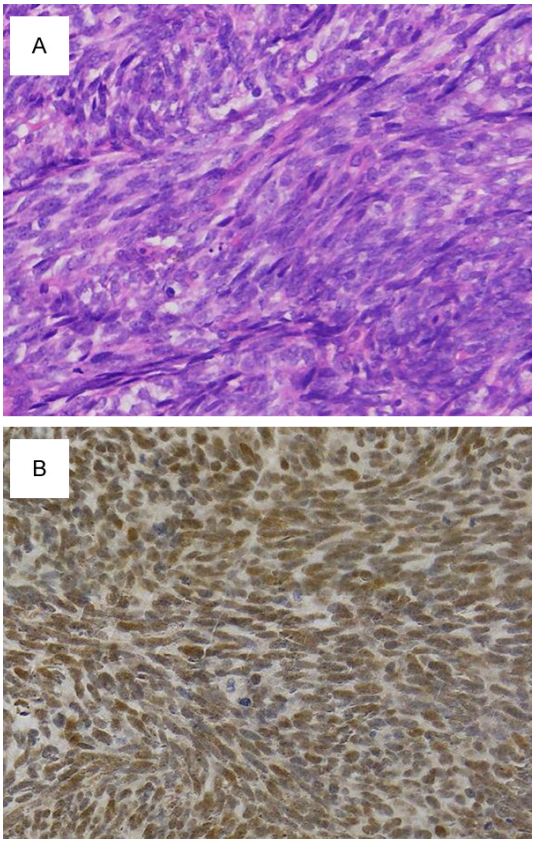

Figure 1. Monophasic synovial sarcoma composed of highly cellular short fascicles of uniform spindle cells (A, H&E, ×200). Neoplastic cells show diffuse and strong nuclear reactivity for TLE1 (B, ×200).

(5/10) angiosarcomas, 10% (1/10) epithelioid sarcomas, 20% (2/10) Ewing sarcoma/PNETs and 37.5% (3/8) malignant peripheral nerve sheath tumors (MPNST) (X^2=42.716, *P*=0.000) (**Table 3**). TLE1 was significantly more commonly expressed by SS (76.19%) compared with non-SS (25%) cases (X^2=52.002, *P*=0.000) (**Table 4**).

Furthermore, BCL2 was positive in 89.05% (122/137) of the synovial sarcomas, CD99 in 88.89% (112/126), Vimentin in 88.06% (118/134), Ki67 in 75.63% (90/119), cytokeratin AE1/AE3 in 56.41% (66/117), EMA in 53.57% (60/112), CD56 in 52.78% (19/36), S100 in 23.85% (26/109), SMA in 12.64% (11/87), CD117 in 4.44% (2/45) and CD34 in 6.20% (8/123) (**Table 4**). From the immunohistochemistry panel available, BCL2 (*P*=0.001), cytokeratin AE1/AE3 (*P*=0.023) and CD34 (*P*=0.000) were significantly more commonly expressed by SS compared with non-SS cases. There were no significant difference in expression of CD117, CD56, EMA, CD99, Vimentin, S100, Ki67 and SMA in both SS and non-SS cases. On the other hand, Desmin expression was completely negative in both SS and non-SS cases (**Table 4**).

Molecular confirmation of synovial sarcoma cases

We investigated 43 cases for translocation t(X;18). The translocation was found in 29 cases (67.44%) with a positive result in FISH (all these tumors were classified as synovial sarcoma: 19 monophasic and 10 biphasic) and 14 (32.56%) showed a negative result (**Figure 4**). These specimens were additionally stained with TLE1 translocation t(X;18)-positive cases (n=29) showed TLE1 expression in 25 cases (86.21%, *P*=0.000), translocation t(X;18)-negative cases (n=14) showed TLE1 expression in 3 cases (**Table 5**).

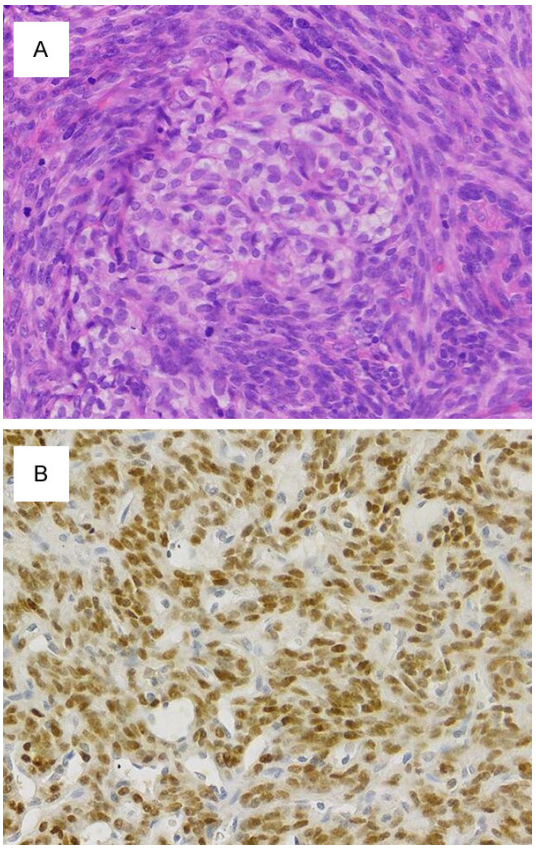

Figure 2. Biphasic synovial sarcoma (A, H&E, ×200) with 3+ TLE1 expression in glandular epithelium (B, ×200), TLE1 expression is much less frequent in the spindled component of this biphasic tumor.

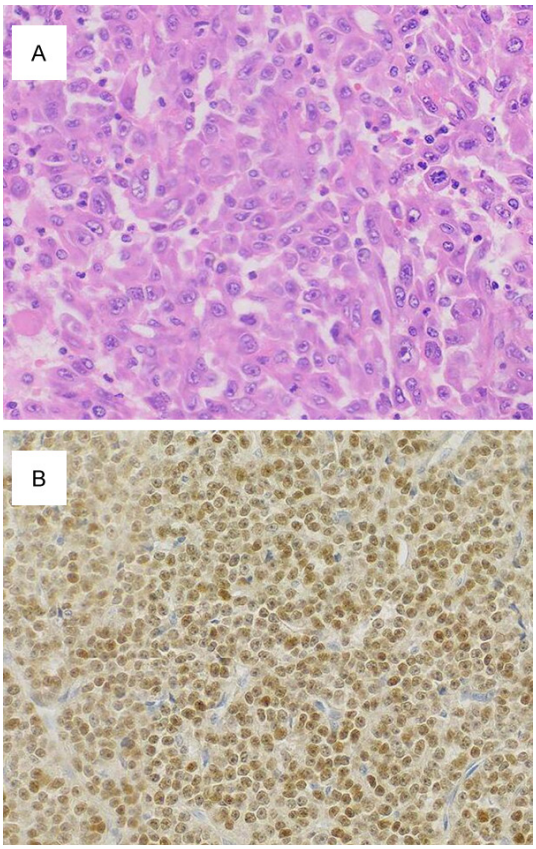

Figure 3. Poorly differentiated synovial sarcoma (A, H&E, ×200) with 3+ TLE1 expression (B, ×200).

The overall sensitivity and specificity of TLE1 expression for the diagnosis of synovial sarcoma were 86.21% and 78.57%, respectively.

Discussion

Synovial sarcomas include biphasic, monophasic, and poorly differentiated variants. Distinguishing monophasic synovial sarcoma from other spindle cell tumors can present a diagnostic challenge, particularly in those cases that do not exhibit biphasic histology. Poorly differentiated synovial sarcoma can be difficult to distinguish from other round cell sarcomas, especially Ewing sarcoma/PNET [1-3]. In these situations, immunohistochemical analysis plays an important role in confirming the diagnosis of synovial sarcoma. Although an extensive panel of IHC markers is available for diagnosing a synovial sarcoma, there has been no single, fairly sensitive and specific marker. For example, commonly used IHC markers, such as bcl-2, EMA, and CK, are neither specific nor sensitive for synovial sarcoma. Moreover, IHC markers of other tumor types in the differential diagnosis, including CD99 and S-100, are often expressed by synovial sarcoma as well. Gene expression profiling studies have shown consistent overexpression of the TLE family of genes in synovial sarcoma. Subsequently, in several recent studies, TLE1 protein was detected by immunohistochemical analysis in most synovial sarcomas and, more rarely, in other mesenchymal neoplasms [7-9].

TLE1 is one of four Transducin-Like Enhancer of split (TLE) genes that encode human homologues of the Drosophila transcriptional corepressor Groucho. The TLE family proteins are required for embryogenesis, including hematopoiesis, body patterning, and neurogenesis. As corepressors, Gro/TLE family proteins do not bind to DNA directly, but are rather recruited to the template by DNA-bound repressor proteins. The repressive effect of Groucho and TLE1 is dependent on phosphorylation status and involves histone deacetylase (HDAC) activity. The HDAC inhibitor FK228 has recently been

Table 4. Summary of all immunohistochemistry results

Tumor type Antibody	SS	Fibrosarcomas	Angiosarcomas	Epithelioid sarcomas	Ewing sarcoma/PNETs	MPNST	non-SS Total	X^2	*P*
TLE1	112/147 (76.19)	1/10 (10.00)	5/10 (50.00)	1/10 (10.00)	2/10 (20.00)	3/8 (37.50)	12/48 (25.00)	52.002	0.000
CD117	2/45 (4.44)	1/6 (16.67)	1/7 (14.29)	0/1 (0.00)	1/1 (100.00)	0/2 (0.00)	3/17 (17.65)	2.901	0.089
CD56	19/36 (52.78)	0/1 (0.00)	0/0 (0.00)	0/0 (0.00)	11/14 (78.57)	1/1 (100.00)	12/15 (80.00)	3.292	0.070
CKAE1/AE3	66/117 (56.41)	2/12 (16.67)	4/17 (23.53)	15/15 (100.00)	2/16 (12.50)	0/0 (0.00)	23/60 (38.33)	5.184	0.023
EMA	60/112 (53.57)	1/3 (33.33)	1/9 (11.11)	11/11 (100.00)	0/4 (0.00)	0/3 (0.00)	13/30 (43.33)	0.993	0.319
CD99	112/126 (88.89)	4/10 (40.00)	4/5 (80.00)	8/8 (100.00)	19/19 (100.00)	2/2 (100.00)	37/44 (84.09)	0.693	0.405
BCL2	122/137 (89.05)	12/19 (63.16)	8/10 (80.00)	2/7 (28.57)	10/11 (90.91)	3/4 (75.00)	35/51 (68.63)	11.258	0.001
Vimentin	118/134 (88.06)	15/15 (100.00)	18/19 (94.74)	15/16 (93.75)	7/12 (58.33)	4/5 (80.00)	59/67 (88.06)	0.000	1.000
CD34	8/123 (6.20)	21/22 (95.45)	19/21 (90.48)	11/16 (68.75)	0/7 (0.00)	1/6 (16.67)	52/72 (72.22)	92.078	0.000
S100	26/109 (23.85)	0/19 (0.00)	4/14 (28.57)	3/10 (30.00)	6/13 (46.15)	6/7 (85.71)	19/63 (30.16)	0.822	0.365
Ki67	90/119 (75.63)	13/20 (65.00)	16/19 (84.21)	13/13 (100.00)	12/13 (92.31)	5/6 (83.33)	59/71 (83.10)	1.466	0.226
SMA	11/87 (12.64)	4/17 (23.53)	3/12 (25.00)	2/8 (25.00)	1/5 (20.00)	0/4 (0.00)	10/46 (21.74)	1.872	0.171

Synovial sarcoma (SS), Malignant peripheral nerve sheath tumors (MPNST).

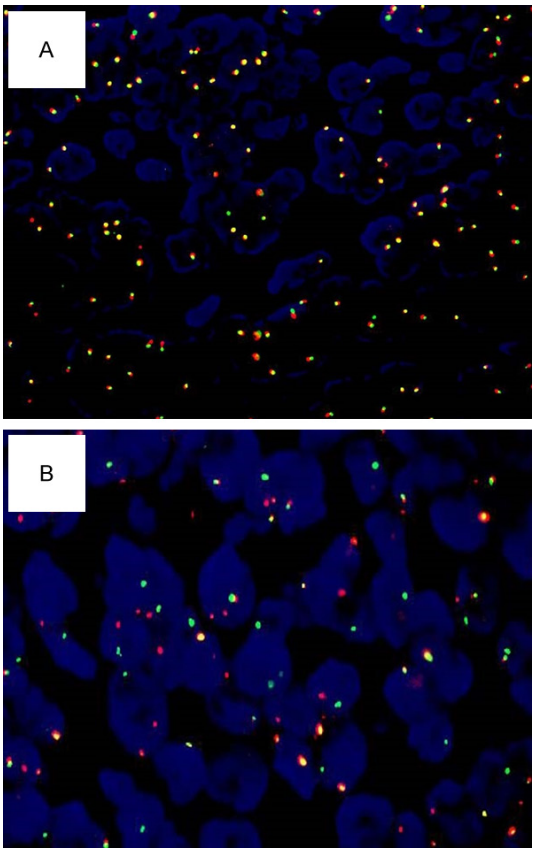

Figure 4. A. An example of undifferentiated high-grade sarcoma by SS18 gene break-apart FISH assay, which shows 2 or 3 pairs of intact SS18 signals (overlapped green and red signals) (×1000). B. An example of poorly differentiated synovial sarcoma by SS18 gene break-apart FISH assay, which shows 1 pair of intact and 2 or 3 break-apart SS18 signals (separated green and red signals) (×1000).

shown to inhibit proliferation of synovial sarcoma, supporting the idea that TLE1 overexpression may play an important role in synovial sarcoma pathobiology and identifying TLE1 as a potential therapeutic target. The TLE family proteins are also involved in the Wnt signaling pathway, which has previously been associated with synovial sarcoma [14-16, 19, 21].

In this study, we examined the usefulness of TLE1 as a diagnostic immunomarker for distinguishing synovial sarcoma from tumors most commonly considered in the differential diagnosis. We performed this immunohistochemical study on 155 synovial sarcomas (107 monophasic, 35 biphasic, and 10 poorly differentiated), 10 fibrosarcomas, 10 angiosarcomas, 10 epithelioid sarcomas, 10 Ewing sarcoma/PNETs and 8 malignant peripheral nerve sheath tumors (MPNST) using TLE1 immunomarker. In synovial sarcomas positive staining was found in 76.19%, including 75.96% of the monophasic type, 78.79% of the biphasic type, and 70% of the poorly differentiated type, whereas the sensitivity of TLE1 for synovial sarcoma in previous studies ranged from 70% to 90% [8, 9, 22, 26]. 65.99% of SS cases showed strong to moderate staining (score 3+/2+) and 10.20% showed weak staining (score 1+). This finding was similar to that of Foo et.al who found that only 60% of synovial sarcoma were positive for TLE1, if 2+ and 3+ nuclear staining were considered to be the positive criteria [26].

In contrast to synovial sarcoma, TLE1 staining was low to absent in other mesenchymal tumors, such as 10% of fibrosarcomas, 50% angiosarcomas, 10% epithelioid sarcomas, 20% Ewing sarcoma/PNETs and 37.5% malignant peripheral nerve sheath tumotumourrs

Table 5. Summary of TLE1 immunohistochemistry results in molecular confirmation of synovial sarcoma cases

Tumor type	n	Negative	1+	2+	3+	Any positive (%)	Positive 2+, 3+ (%)	χ^2	*P*
SS (Translocation t(X;18)-positive cases)	29	4	5	10	10	25 (86.21)	20 (68.97)	17.442	0.000
SS (Translocation t(X;18)-negative cases)	14	11	0	3	0	3 (21.43)	3 (21.43)		
Total	195	75	20	57	47	120 (61.54)	100 (51.28)		

Synovial sarcoma (SS).

(MPNST). These findings are similar to previous studies [7, 21].

TLE1 was significantly more commonly expressed by SS (65.31%) compared with non-SS (25%) cases. We investigated 43 problematic cases for translocation t(X;18). 29 translocation t(X;18)-positive cases showed TLE1 expression in 24 cases (82.76%), 14 translocation t(X;18)-negative cases showed TLE1 expression in 3 cases. The sensitivity and specificity of TLE1 expression for the diagnosis of synovial sarcoma were 82.76% and 78.57% respectively. Our findings are quite similar to those in the recent study by Atef et al. and Knösel et al. [7, 21].

In our multivariate analysis TLE1 staining was an independent predictor, including PanCK and BCL2 as positive biomarkers and CD34 as a negative biomarker of synovial sarcomas indicating a high value of sensitivity and specificity which was confirmed in univariate analysis [9, 21, 22]. Additionally, TLE1 expression was significantly correlated with the translocation t(X;18) which may be of interest to laboratories that do not have the experience, manpower or equipment to do molecular translocation analysis on a routine basis.

In conclusion, TLE1 is a specific and sensitive diagnostic immunomarker for synovial sarcoma and can be helpful to distinguish synovial sarcoma from other mesenchymal neoplasms, particularly if moderate or strong staining is observed. Although, molecular testing remains the "gold standard" for a synovial sarcoma, immunohistochemistry is much faster and, more cost effective than molecular testing. Its inclusion in an optimal IHC panel formed by CK, BCL2 and CD34, for substantiating a histopathological diagnosis of a synovial sarcoma in cases occurring at unusual sites and with variable histopathological features, could reduce further requests for molecular testing. TLE1 staining should be used as a screening method prior to molecular testing.

The biomarker TLE1 will significantly aid in the pathologic diagnosis of synovial sarcoma, and may have implications for understanding its biology and for developing new anticancer-targeted therapies.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Huaiyin Shi, Department of Pathology, Chinese PLA General Hospital, Beijing 100853, China. Tel: 00 86 010-66887329; Fax: 00 86 010-66887329; E-mail: shihuaiyin@sina.com

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