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Original Article

Recurrence of Solitary Fibrous Tumor/Hemangiopericytoma Could Be Predicted by Ki-67 Regardless of Its Origin

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Since the discovery of the *NAB2-STAT6* gene fusion in 2013, solitary fibrous tumor (SFT) and hemangiopericytoma (HPC) have been considered the same disease. STAT6 nuclear stain is approved as a highly sensitive and specific marker to diagnose SFT/HPC from other tumors with similar histology. As the next step, detection of fusion variants that may predict clinical malignancy of SFT/HPC has been attempted. However, no fusion variants with a clear relation to malignancy have been identified. In this study, the clinical and histological backgrounds of 23 Japanese patients diagnosed with SFT/HPC from 2000 to 2019 at Kochi University Hospital were examined to identify factors potentially related to recurrence. A significant relationship to recurrence was detected for mitosis ≥ 1/10 HPF (400×), necrosis, and Ki-67 > 5%. These findings indicate that a deliberate investigation of histological features such as mitosis and necrosis is crucial for the clinical observation of SFT/HPC patients. In addition, Ki-67 was revealed to be a useful parameter to predict recurrence in SFT/HPC patients.

Key words: solitary fibrous tumor, hemangiopericytoma, Ki-67, *NAB2-STAT6*, WHO classification, WHO grading criteria, Marseille Grading System

Solitary fibrous tumor (SFT) and hemangiopericytoma (HPC) are rare mesenchymal neoplasms. They occur approximately equally in each sex and are most commonly reported in individuals between the ages of 30 to 70 years. There are several reports of children under the age of 10 and younger patients tend to have more malignant prognosis [1-8]. In the last decade, the definition, classification, and diagnostic techniques for these 2 tumors have undergone interesting transformations [9].

In 1931, Klemperer and Robin made the first report of primary mesenchymal tumors of the pleura [10]. In 1942, Stout and Murray also reported 9 cases of skin tumor. They hypothesized that these tumors derived from the capillary pericytes and suggested that they should be called "hemangiopericytoma" [11]. Ten years later, in 1951, Stout and Himadi reported 8 cases of pleural neoplasms, similar to the tumors reported by Klemperer and Robin, which they called "solitary (localized) mesothelioma" of the pleura [7]. The 2013 World Health Organization (WHO) Classification of Tumors of Soft Tissue and Bone removed the term "hemangiopericytoma" as a synonym for SFT and combined these tumors as SFT under the category of fibroblastic/myofibroblastic tumors [3, 12-15]. In the same year, 3 different groups discovered that SFT/HPC had a common gene fusion between *NAB2* and *STAT6* [16-18], which has been confirmed in multiple studies and is generally accepted at present [1, 3, 13-15, 19, 20]. The

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2016 WHO Classification of Tumors of the Central Nervous System (CNS) designated these tumors, characterized by the *NAB2-STAT6* gene fusion, as SFT/HPC in mesenchymal/non-mesenchymal tumors [1,9,19,21]. After the detection of the *NAB2-STAT6* gene fusion in 2013, STAT6, which has dual function as a signal transducer and an activator of transcription in SFT/HPC, was recognized as a highly sensitive and specific immunohistochemical marker for SFT/HPC [1,3,14,15,19,22-25].

Clinically, each case of SFT/HPC might have a different course from the one that was diagnosed accidentally and treated completely by a successful surgical resection, to the one that relapsed with local recurrence or multiple distant metastases after many years in spite of surgical treatment followed by radiotherapy and/or intensive chemotherapy [2,3,16,19,23,26-30]. Researchers have attempted to detect fusion variants that might predict clinical malignancy through polymerase chain reaction to investigate *NAB2-STAT6* gene fusions [23,31-33]; however, no fusion variants with a clear relation to malignancy have been identified [24,32,33]. Recently, classical gradings of SFT/HPC with histopathological molecular backgrounds such as mitosis and necrosis have been reevaluated to detect factors that may be associated with a malignant prognosis [26,27,34]. In regard to SFT/HPC of the CNS, the WHO Grading Criteria and the Marseille Grade Score (MGS) were appraised (Table 1) [1,21,33]. Other immunohistochemical approaches, such as aldehyde dehydrogenases, telomerase reverse transcriptase, and Ki-67, have also been attempted [3,4,26,27,33,35-42]. Several groups have already reported that Ki-67 was statistically related to recurrence in SFT derived from the pleura and the CNS [1,26,27]. However, until now, no report has investigated the value of Ki-67 for predicting recurrences in SFT/HPC originated from locations other than the pleura or CNS.

Objective of the study. The purpose of this study was to detect factors related to a malignant prognosis in Japanese patients diagnosed with SFT/HPC at Kochi University Hospital. First, we used nuclear staining for STAT6 to confirm the previous diagnoses of SFT/HPC. Then, we statistically analyzed the clinical and immunohistochemical backgrounds of patients to detect factors related to malignancy.

Materials and Methods

Patients. Twenty-three Japanese patients previously diagnosed with SFT or HPC at Kochi University Hospital between 2000 to 2019 were included in this study. Table 2 shows the clinical backgrounds and immunohistochemical characteristics of these patients. All patients underwent tumor resection surgery once, and some patients with recurrence underwent an additional resection. Surgically obtained tissues were embedded in paraffin blocks after formalin fixation and preserved. All patients were observed at Kochi University Hospital after the surgery. Each case had a unique clinical course. Two patients (Cases 3 and 8) died due to the disease.

Table 1 Definitions of WHO Grading Criteria and the Marseille Grading System

	WHO Grading Criteria	Updated MGS
Grade I	SFT phenotype Alternation of hypo-and hypercellular areas Abundant collagen Mitotic activity $<5/10$ HPF*	Mitotic activity $<5/10$ HPF* (independent of necrosis)
Grade II	HPC phenotype Mitotic activity $<5/10$ HPF	Mitotic activity $\geq 5/10$ HPF No necrosis
Grade III	Mitotic activity $\geq 5/10$ HPF	Mitotic activity $\geq 5/10$ HPF and necrosis

*10 HPF (MGS): containing of 10 adjacent field with total magnification of 400× (total surface 2.2 mm^2) in the most proliferative areas as asessed in a Hematoxylin & Eosin stained slide or guided by Ki-67 stain if available. The 2016 WHO classification does not provide a definition for hypercellularity and "10 HPF" (Macagno, et al. [25]).

Table 2 Clinical Backgrounds of 23 patients

Case	Sex	Age	Tumor origin	Size (cm)	mitosis ≧1/10 HPF	necrosis	Ki-67 (%)	Ki-67 >5%	Recurrene	Recurrence-free period (Mo)	TNM classification	WHO Scoring Grade†	Marseille Grading System†
1	F	80s	Bone & Soft tissue	3.5	−	−	5	−	−		T1N0M0	−	−
2	F	50s		10.5	−	−	5	−	−		T3N0M0	−	−
3	M	50s		12.5	+	−	10	+	+	89	T3N0M0	−	−
4	M	70s		10.0	+	+	8	+	+	0	T2N0M1	−	−
5	F	70s		9.0	+	−	9	+	−		T2N0M0	−	−
6	M	60s		15.0	−	−	1	−	−		T3N0M0	−	−
7	M	30s		11.0	−	−	1	−	−		T3N0M0	−	−
8	F	70s		10.0	+	+	10	+	+	4	T2N0M0	−	−
9	F	50s		12.5	−	−	3	−	−		T1N0M0	−	−
10	F	60s		9.0	−	−	3	−	−		T2N0M0	−	−
11	F	40s	Head & Neck	1.6	−	−	2	−	−		T1orT2N0M0	−	−
12	F	50s		1.7	−	−	9	+	−		T1N0M0	−	−
13	F	70s		3.5	−	−	4	−	−		T2N0M0	−	−
14	F	60s	Lung & Pleura	4.0	−	−	5	−	−		T2aN0M0	−	−
15	M	70s		6.0	+	+	56	+	+	6	T3N0M0	−	−
16	M	30s		14.0	−	−	0.4	−	−		T4N0M0	−	−
17	F	50s		8.0	−	−	2	−	−		T4N0M1	−	−
18	F	30s	CNS	1.0	+	−	3	−	+	24	−	I	I
19	M	60s		5.0	−	−	5	−	−		−	I	I
20	F	50s		2.0	−	−	4	−	−		−	I	I
21	F	60s		1.0	+	−	10	+	+	119	−	II	I
22	F	30s		5.5	+	−	8	+	+	49	−	II	I
23	F	60s		1.5	+	−	5	−	−		−	I	I

Immunohistochemical analysis. Formalin-fixed paraffin-embedded tissue samples, which had been preserved from the previous surgery, were sliced at 4 μm thickness and heat-treated with ULTRA cell conditioning 1 retrieval solution (CC1; Ventana Automated Systems, Tucson, AZ, USA). Immunohistochemical examination was performed for this study using a Ventana automated system with the following antibodies: CD-34 (QBEnd10, dilution 1 : 50; DAKO, Glostrup, Denmark), Ki-67 (MIB-1, dilution 1 : 50; DAKO), and STAT6 (D-1, sc-374021, dilution 1 : 50; Santa Cruz Biotechnology, Santa Cruz, CA, USA). Immunochemical expression was evaluated in the cytoplasm with CD34 and in the nucleus with Ki-67 and STAT6. It was graded as negative, weak, moderate, or strong and defined as "positive" when the detected expression was moderate or strong. To investigate the proportion of positive Ki-67, a total of 100 tumor cells were counted at 5 different hot spot fields. The mean value of positive cells was then calculated and input as a percentage for statistical analysis. Independent evaluation of immunostaining was performed by 2 different expert pathologists.

Statistical analysis. Pearson correlation coefficient analysis was conducted between recurrence and each of the following factors: sex, age, tumor origin,

tumor size, mitosis ≥ 1/10 HPF (400×), and necrosis. To detect the relationship between Ki-67 and recurrence, a cutoff value was examined by ROC curve analysis. According to the gained cutoff value of Ki-67 (5%), all cases were divided into 2 groups, and the Pearson correlation coefficient was examined between Ki-67 and recurrence. Kaplan-Meier analysis was conducted to analyze the recurrence-free survival distributions among the factors with a significant relationship to recurrence by Pearson correlation coefficient. The recurrence-free survival rate of all patients was also examined by Kaplan-Meier analysis.

This study was reviewed and approved by the Ethics Committee for Clinical Research of the School of Medicine, Kochi University (ERB-105384). All procedures were carried out with the adequate understanding and written consent of each subject.

Results

Positive nuclear staining for STAT6 was observed in all cases. Table 2 shows the clinical backgrounds of the 23 cases. The average tumor size was 6.9 (1.0-14.0) cm. Mitosis ≥ 1/10 HPF (400×) and necrosis were detected in 9 and 3 cases, respectively. The average Ki-67 was 7.3 (0.4-56)% at the initial surgery. Eight cases had Ki-67 greater than 5%. Seven cases developed recurrence at 0 to 119 months after the first surgery. TNM classification was shown with tumors originating from the bone, soft tissue, head, neck, lung and pleura. The WHO Scoring Grade and the MGS were also shown with tumors from the CNS.

Table 3 shows the results of the Pearson correlation coefficient analysis between recurrence and each factor: sex, age, tumor origin, tumor size, mitosis ≥ 1/10 HPF (400×), necrosis and Ki-67 > 5%. A significant relationship to recurrence was detected for mitosis ≥ 1/10 HPF

Table 3 Correlation (*p*-value) between each clinical factor and recurrence

		Total n	Recurrence n	*p*-value
Sex	male	7	3	ns
	female	16	4	
Age (y.o.)	31–40	4	2	ns
	41–50	2	0	
	51–60	5	1	
	61–70	6	1	
	71–	6	3	
Tumor origin	CNS	6	3	ns
	Bone & Soft tissue	10	3	
	Lung	4	1	
	Head & Neck	3	0	
Tumor size	–3 cm	6	2	ns
	–5 cm	3	0	
	–10 cm	6	2	
	10 cm–	8	3	
Mitosis ≧ 1/10 HPF	+	9	7	<0.01
	–	14	0	
Necrosis	+	3	3	<0.01
	–	20	4	
Ki-67 > 5%	+	8	6	<0.001
	–	15	1	

(400×) and necrosis ($p<0.01$). Sex, age, tumor origin, and tumor size were not related to recurrence. However, Ki-67 > 5% showed a very strong relationship to recurrence ($p<0.001$).

Figures 1-3 show the recurrence-free survival rates of mitosis, necrosis, and Ki-67 by Kaplan-Meier curves. Figure 4 shows the recurrence-free survival rates of all 23 patients. The 1-, 5-, and 10-year recurrence-free survival rates were 86.1%, 76.3%, and 61.2%, respectively. Five case reports are summarized below.

Case Reports

Case 5. A woman in her late 70s underwent colon cancer surgery. At her follow-up examination the next year, a tumor was detected in the dorsal area. SFT was diagnosed by a needle biopsy, and a complete resection of the tumor with posterior spinal fusion from Th12 to L1 was performed. She has had no recurrence or distant metastasis for 8 years.

Case 8. A woman in her 70s underwent surgery for SFT in the right retroperitoneum. The following year she had an additional surgery for a tumor recurrence. Ki-67 was increased from 10% at the initial surgery to 40% at the second surgery (Fig. 5). Shortly after her second surgery, she developed a metastasis on the lung. Pazopanib hydrochloride at a dose of 400 mg/day was prescribed, which was effective on the lung metastasis, but the local recurrence continued to grow. She passed away due to pneumothorax within 2 years of the first surgery.

Case 15. A man in his late 70s had an abnormal shadow detected during his annual chest x-ray screening. Non-small cell lung cancer was diagnosed by a needle biopsy and surgical treatment was performed. The pathological diagnosis was SFT with squamous cell carcinoma. Over the next year, multiple metastases on the lungs, cervical spine, and costa were observed. He was referred to a terminal care institution due to aggravation of the systemic condition at 2 years after the surgery.

Case 18. A woman in her 50s underwent surgery

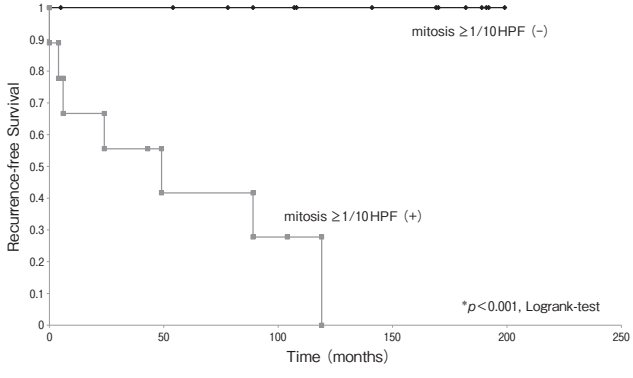

Fig. 1 Kaplan-Meier curves of mitosis ≥1/10 HPF (×400) (+) or (−).

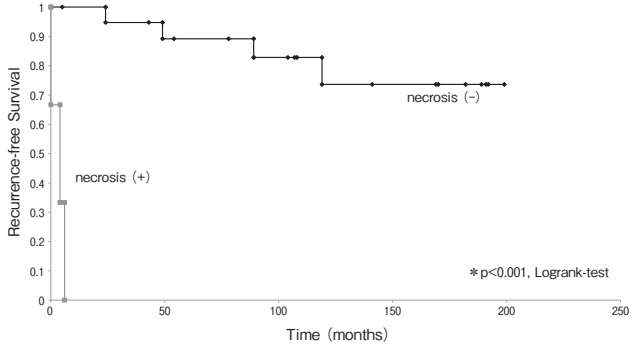

Fig. 2 Kaplan-Meier curves of necrosis (+) or (−).

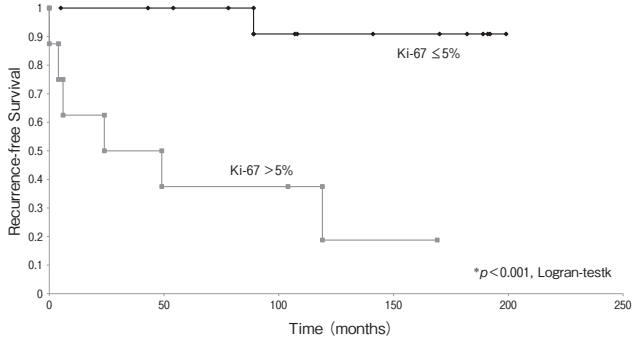

Fig. 3 Kaplan-Meier curves of Ki-67 > 5% or less.

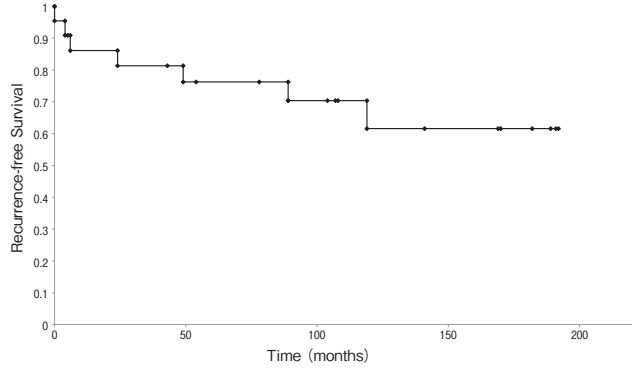

Fig. 4 Kaplan-Meier curve of all twenty-three patients.

for SFT at the lower thoracic spine. In spite of two additional surgeries for local recurrence performed in the following 5 years, the tumor spread to the spinal cord with an invasion of the cauda equina nerve roots. Ki-67 was increased from 3% at the first surgery to 20% at the third surgery. Pazopanib hydrochloride was prescribed at an initial dose of 200 mg/day, and was later increased to 400 mg/day. Nineteen years after the first surgery she remains free of distant metastasis. Her systemic condition has not deteriorated, with the exception of neuropathy at the bilateral lower extremities.

Case 22. A woman in her late 30s underwent craniotomy for the total resection of a brain tumor. The diagnosis was hemangiopericytoma (Fig. 6, 7). Four

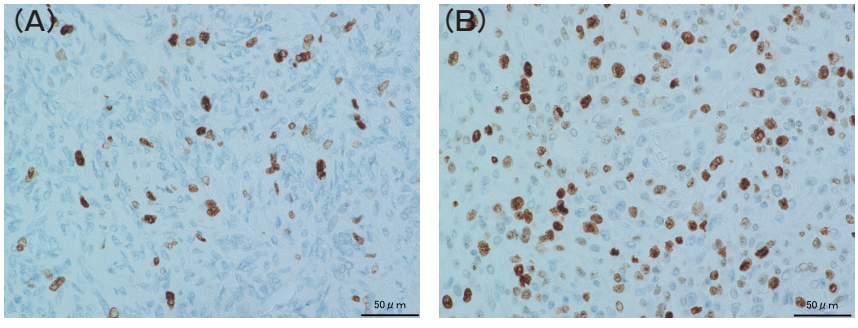

Fig. 5 Ki-67 stain in Case 8. (**A**) at the first surgery and (**B**) at recurrence. Ki-67 increased from 10% to 40% (×200).

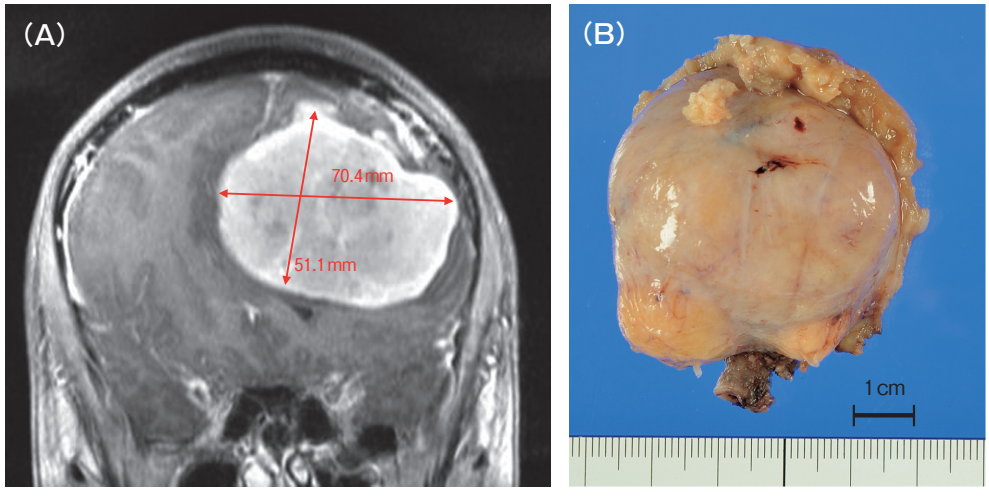

Fig. 6 Brain MRI and the largest resected tissue of Case 22. (**A**) Contrasted-enhanced MRI (coronal T1-weighted) revealed a large mass lesion with nodular contours and perilesional edema. (**B**) The mass composed of several nodules with the smooth surface and vessel invasion. The diameter of the largest nodule was about 3.5 cm.

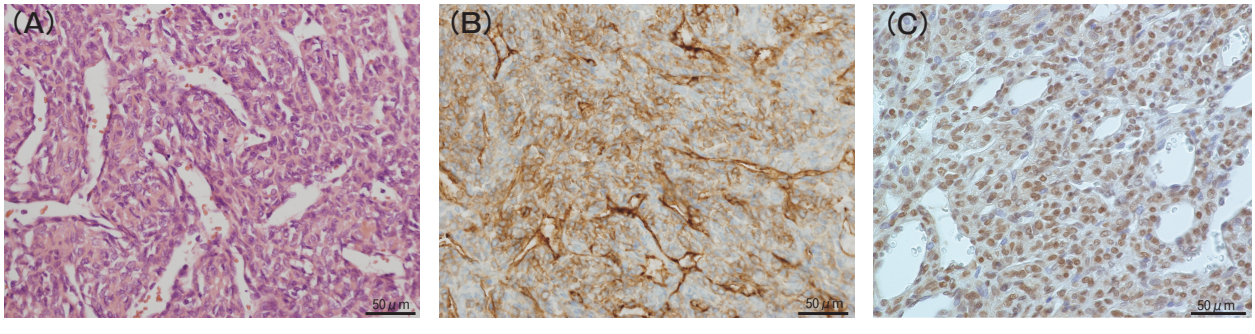

Fig. 7 Histopathology of the tumor in Case 22. (**A**) The tumor was densely composed of polygonal or spindle-shaped cells surrounding vascular abundant spaces with enlarged slit-like or 'stag-horn' appearance vessels (Hematoxylin-Eosin). (**B**) The tumor cells were immunoreactive for CD34. (**C**) Specific staining in the nuclear was detected (STAT6).

years later multiple distant metastases were detected in the brain, cervical spine, liver and pelvis. After surgery of posterior spinal fusion from C4 to Th2, proton therapy was performed on the cervical region. Pazopanib hydrochloride at a dose of 400 mg/day and denosumab subcutaneous injection at a dose of 120 mg/month were started following the surgery. Five years after the first surgery, this treatment continues to effectively suppress the tumor growth.

Discussion

In this study, we evaluated the rate of recurrence in 23 Japanese patients with SFT/HPC. A total of 30.4% of patients (7/23) experienced recurrence, 21.7% (5/23) had distant metastasis, and 9% (2/23) died due to the disease. Shukla *et al.* reported a recurrence rate of 31% in 13 patients diagnosed with intracranial and spinal SFT/HPC, and none of their 13 patients showed distant metastasis [1]. Diebold *et al.* reported a recurrence or related death rate of 11% in 78 patients diagnosed with SFT of the pleura [30]. The recurrence rates detected in our study were 50.0% (3/6) and 23.5% (4/17) with cases diagnosed in the CNS and outside of the CNS, respectively. The increased recurrence rates in our study may have resulted from the relatively longer observation period of 19 years compared to the observation periods of 11 and 15 years in the studies mentioned above. Case 21 in this study developed recurrence at 119 months, showing that SFT/HPC can recur even after 10 years. In addition, Diebold's patients were limited to SFT of the pleura. In our study, SFT/HPC outside of the CNS was derived from various areas of the body, such as the pleura, peritoneum, lung, muscle, soft tissue and oral cavity. SFT/HPC originating from areas with abundant blood flow may have increased chances of malignancy. Further, Diebold *et al.* found that tumor size larger than 10 cm was independently associated with recurrence [27], but in our study tumor size was not associated with recurrence. Tumor origin was also not statistically associated with recurrence, either. These results could be related to the relatively low number of patients included in our study, which in turn was due to the rarity of SFT/HPC. Further studies with larger numbers of cases will be needed in the future.

Mitosis ≥ 1/10 HPF (400×), necrosis, and Ki-67 > 5% were all significantly related to recurrence. Because both necrosis and mitosis were included as essential factors to evaluate malignancy of SFT/HPC of the CNS in the WHO Grading Criteria and the MGS, their careful observation is definitely important to predict a possible recurrence of SFT/HPC, as Vogel [33] and Macagno [21] wrote. Several papers had detected the relationship between recurrence and Ki-67 in SFTs of the pleura and CNS [1, 26, 27]. Other studies on brain tumors reported that 5% Ki-67 was a cutoff value to relate to survival rate or the grades of the WHO criteria [41-43]. In this study, 5% was also the cutoff value of Ki-67, and a very strong relationship to recurrence was detected in cases with Ki-67 > 5% ($p < 0.001$). As detailed above for case 8, the Ki-67 increased from 10% at the first surgery to 40% at recurrence. Similarly, in case 18, the Ki-67 was 3% at the first surgery, but the patient developed recurrence at 24 months and the Ki-67 increased to 20%. We suggest this phenomenon may also imply an association between Ki-67 and recurrence of SFT/HPC. The 2016 WHO CNS Classification (Table 1) defines tumor cellularity, classifying HPC into Grades I or II/III. However, in this study, only 6 of the 23 cases had tumors originating from the CNS. Tumors occurring in the other 17 cases originated from various parts of the body (Table 2). As such, we did not carry out a statistical analysis of tumor cellularity in the entire sample set of 23 cases.

Surgical resection is the first strategy of treatment for SFT/HPC; however, complete resection is not always feasible, and recurrence or metastasis may occur even after a long period of postoperative follow-ups. These cases may require additional radiotherapy or chemotherapy. Unfortunately, there is no therapy that directly targets the *NAB2-STAT6* gene fusion. Pazopanib hydrochloride, a broad spectrum tyrosine kinase inhibitor, has been approved for the treatment of soft tissue sarcoma since 2012 in Japan, and its effectiveness was reported in several papers [44, 45]. In our study, cases 8, 18, and 22 were treated with pazopanib hydrochloride. However, the periods of pazopanib hydrochloride treatment were not long enough to evaluate the efficacy of the treatment. In case 8, pazopanib hydrochloride could not suppress the original tumor growth, and the patient died within six months after pazopanib hydrochloride treatment started. The development of new treatments that directly target the *NAB2-STAT6* gene fusion will be greatly beneficial for SFT/HPC patients in the future.

Positive nuclear staining for STAT6 was confirmed

in all 23 cases included in this study. This may indicate that our initial diagnoses of SFT/HPC—performed in the past using conventional immunohistochemical methods—were correct. STAT6 staining can make a definitive diagnosis of SFT/HPC easier for cases that do not show the typical expression by conventional methods. However, there have been reports of SFTs with negative or weakly positive STAT6 staining [46, 47], and STAT6 is not 100% positive in all cases of SFT/HPC. Such cases could easily be diagnosed incorrectly, and thus it is important to use conventional immunohistochemical methods to make a definitive diagnosis of SFT/HPC.

In conclusion, discovery of the *NAB2-STAT6* gene fusion greatly increased the accuracy of SFT/HPC diagnosis through STAT6 nuclear staining. Evaluation of patient data over the past 19 years revealed the value of Ki-67 as an additional tool to predict the recurrence of SFT/HPC, regardless of its origin.

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