Virchows Archiv (2019) 475:467–477
https://doi.org/10.1007/s00428-019-02622-9

ORIGINAL ARTICLE

Clinicopathological review of solitary fibrous tumors: dedifferentiation is a major cause of patient death

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Received: 5 February 2019 / Revised: 8 July 2019 / Accepted: 11 July 2019 / Published online: 7 August 2019

Abstract

Solitary fibrous tumor (SFT) is a soft-tissue neoplasm of intermediate malignant potential, presenting a wide histopathological spectrum. Poorer prognosis of hemangiopericytoma of the central nervous system (CNS), hypoglycemic SFT, and dedifferentiation are well-known characters of SFT, but their clinical significance were not demonstrated enough by large-sized study. Here, the clinicopathological features of SFTs are reviewed and the relationship between genetics and clinicopathological features is examined using 145 SFT cases. All cases were STAT6 IHC-positive and/or *NAB2-STAT6* fusion gene-positive. Tumor location was classified into three categories: 30 pleuropulmonary, 96 non-pleuropulmonary/non-central nervous system (CNS), and 18 CNS tumors. The tumor developed recurrence in 21 of 93 available cases (22.5%), metastasis in 11 of 93 (11.8%), and tumor death in 9 of 93 (9.6%). Hypoglycemia occurred in 2 primary tumors and 1 metastatic tumor among 63 reviewable cases, and dedifferentiation occurred in 10 cases (6.8%) including 6 primary tumors, 2 recurrent tumors, and 2 metastatic tumors. Recurrence was positively associated with CNS location ($p = 0.0109$) and hypoglycemia ($p = 0.001$); metastasis was positively associated with CNS location ($p = 0.0231$), hypoglycemia ($p < 0.0001$), and dedifferentiation ($p < 0.0001$), while metastasis was negatively correlated with pleural location ($p = 0.0471$). Tumor death was positively associated with male sex ($p = 0.0154$), larger size ($p = 0.0455$), hypoglycemia ($p < 0.0001$), and dedifferentiation ($p < 0.0001$). Multivariate analysis revealed independent statistical significance of dedifferentiation for overall survival ($p = 0.0467$). Exon variant of the fusion gene had no statistical correlation with clinical outcome. In conclusion, dedifferentiation is a major prognostic factor of SFT, and specific location such as cerebromeningeal and intra-abdominal site and hypoglycemia also had a high risk for unfavorable prognosis.

Keywords Solitary fibrous tumor · Hemangiopericytoma · SFT · STAT6 · Dedifferentiated · Hypoglycemia

Introduction

Solitary fibrous tumor (SFT) is a soft-tissue neoplasm of fibroblastic/myofibroblastic differentiation and intermediate-malignant potential, known to present a wide histopathological spectrum [1]. In 2013, *NAB2-STAT6* was discovered as a novel fusion gene of SFT [2, 3]. Recently, STAT6 immunostaining was established as a surrogate marker of *NAB2-STAT6* [4–8]. In addition to hemangiopericytoma (HPC), some historical lesions in the spectrum of giant-cell angiofibroma and a group of deep benign fibrous histiocytomas could be reclassified as SFT using STAT6 IHC and/or STAT6/NAB2 fusion testing. Eventually, SFT became a tumor category that was far more divergent histologically than it had been before the abovementioned discovery of the fusion gene.

During their course, approximately 10% and 5% of SFTs feature local recurrence and distant metastasis, respectively [1]. Unresectable SFT often shows a miserable clinical course because there is currently no alternative therapeutic strategy for it other than surgery. Although criteria for defining malignant SFT have been discussed in numerous investigations, for

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00428-019-02622-9) contains supplementary material, which is available to authorized users.

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example, the existence of necrosis, cellularity, hemorrhage, nuclear atypia, or nuclear pleomorphism, no definite determinant of malignancy has been established as being available for practical use [9–11]. In contrast, a poorer prognosis of SFT of the central nervous system (CNS) [12], hypoglycemic SFT [13–19], and, as a relatively new concept, dedifferentiation are well known [11]. Meanwhile, the biological behavior of SFT remains unclear, despite the abovementioned discovery of the fusion gene.

In this study, the authors reviewed the clinicopathological features of SFTs genetically confirmed by identification of the presence of the fusion gene, and statistically analyzed the relationship between genetics and clinicohistopathological features.

Materials and methods

Materials

A total of 145 cases, diagnosed with SFT, were retrieved from among the soft-tissue tumors registered in the files of the Department of Anatomic Pathology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan.

All current cases were histologically included in the spectrum of SFT described in the current WHO classification [1]. The diagnosis of each SFT case was confirmed by STAT6 immunostaining with a polyclonal antibody supplied by Santa Cruz Biotechnology (Delaware, CA, USA) or by RT-PCR for identification of the *NAB2-STAT6* fusion gene. All cases were STAT6 IHC-positive (Supplementary Fig. 1) and/or *NAB2-STAT6* fusion gene-positive. Cases that were STAT6-positive and MDM2 gene amplification-positive were excluded as dedifferentiated liposarcoma [20].

Clinicopathological and histopathological data

Clinical outcome was evaluated according to the history of local recurrence, distant metastasis, and tumor death. Positivity for dedifferentiated component of SFT was judged as a sarcomatous overgrowth of atypical mesenchymal cells with pleomorphic nuclei of primary, recurrent, and metastatic SFTs, as determined by histopathological review [11]. Mitotic activity was also evaluated; 4 or more mitotic counts per 10 HPFs was judged as "high mitotic activity." None of the 145 cases was treated by preoperative chemotherapy or irradiation therapy.

RT-PCR and direct sequencing

RT-PCR was performed for 121 available cases. Total RNA was extracted from frozen or paraffin-embedded samples using TRIzol reagent (Invitrogen, Carlsbad, CA, USA) and was reverse-transcribed using Superscript III reverse transcriptase (Invitrogen) to prepare the first-strand complementary DNA. *NAB2-STAT6* fusion assays were performed using primers (Supplementary Table 1) that specifically amplify the fusion gene transcripts. Each PCR product (5 μL) was loaded onto 2% agarose gel with ethidium bromide and visualized under UV illumination. The PCR products were also evaluated by direct sequence analysis using the Big-Dye terminator method (version 1.1; Applied Biosystems, Foster City, CA, USA) to confirm the breakpoints of the fusion transcripts.

The *NAB2-STAT6* fusion gene was divided into two subtypes by exon pattern according to the previous investigation of clinicopathological significance of the fusion gene variants [21]; type 1 includes *NAB2* (exon 4)-*STAT6* (exon 2) and *NAB2* (exon 4)-*STAT6* (exon 3), while type 2 consists of *NAB2* (exon 6)-*STAT6* (exon 16) and *NAB2* (exon 6)-*STAT6* (exon 17). The other exon variants of the *NAB2-STAT6* fusion gene were classified as "others."

Statistical analysis

Fisher's exact test was used to evaluate differences between pairs of populations. Thus, all of the clinicopathological and histopathological factors (age, size, location, hypoglycemia, local recurrence, distant metastasis, tumor death, dedifferentiation) were analyzed for their correlation to one another using Fisher's test for each 2 × 2 cells. The survival information was illustrated with Kaplan–Meier curves, and survival analyses were performed with the clinicopathological data by using the log-rank test. A two-sided P value of < 0.05 was considered to indicate statistical significance. Cox's proportional hazard model was adopted to validate the association between Kaplan–Meier curves and the items picked up in the above univariate analysis. The odds ratio (OR) was also determined. Data analysis was conducted with the JMP statistical software package (version 13.0.0; SAS Institute Inc.).

Results

Clinicopathological and histopathological findings

Survival data were available for 93 of the 145 cases (64%), with follow-up ranging from 2 to 340 months (mean 82.6, median 48.5). Clinicopathological findings are summarized in Supplementary Table 2. The age of the patients ranged from 3 to 79 years old (mean 52.4, median 55). There was a female predominance among the SFT cases (male/female = 58:86). Tumor size ranged from 1 to 27 cm in diameter (mean 7.2 cm, median 5.3 cm). The tumor developed local recurrence in 21 of 93 cases (22.5%), distant metastasis in 11 of 93 cases (11.8%), and tumor death in 9 of 93 cases (9.6%). Tumor location was classified into three categories (Table 1):

Table 1 Clinical impact of SFT location

Location	*N* (%)	Local recurrence	Distant metastasis	Tumor death	Hypoglycemia	Dedifferentiation
Pleuropulmonary	30 (20.8%)	3/22 (13.6%)	0/22 (0%)	1/22 (4.5%)	1/14 (7.1%)	0/30 (0%)
Pleural	20	3/15	0/15	1/15	1/8	0/20
Lung	10	0/7	0/7	0/7	0/6	0/10
Non-pleuropulmonary/non-CNS	96 (66.6%)	10/59 (16.9%)	5/59 (8.4%)	4/59 (6.7%)	1/41 (2.4%)	5/96 (5.2%)
Extremity	12	0/5	0/5	0/5	0/5	0/12
Trunk	30	0/20	1/20	0/20	0/14	2/30
Head and neck	10	2/7	0/7	0/7	0/4	0/10
Mediastinum	6	2/5	0/5	1/5	0/2	0/6
Intra-abdominal	30	4/15	4/15	3/15	1/10	3/30
Orbita	5	2/4	0/4	0/4	0/3	0/5
Others	3	0/3	0/3	0/3	0/3	0/3
CNS	18 (12.5%)	8/12 (66.6%)	6/12 (50.0%)	4/12 (33.3%)	0/8 (0%)	1/18 (5.5%)
Cerebrum/dura matter	7	3/5	5/5	2/5	0/4	1/7
Cerebellum/brain stem	4	3/4	0/4	1/4	0/2	0/4
Spinal cord	7	2/3	1/3	1/3	0/2	0/7

CNS central nervous system

30 pleuropulmonary tumors (20 pleural and 10 lung tumors), 96 non-pleuropulmonary/non-CNS tumors (30 trunk, 30 intra-abdominal, 12 extremities, 10 head and neck, 6 mediastinum, 5 orbita, 1 bone, 1 digestive tract, and 1 thyroid gland), and 18 CNS tumors (7 cerebrum and dura mater, 4 cerebellum and brain stem, and 7 spinal cord) were included. The subcategorization of tumor location was also shown in Table 1. One case was omitted from locational analysis because of ambiguous information on its location. In the SFTs of soft-tissue origin, 52 tumors were derived from superficial soft tissue such as subcutis of the extremities, trunk, and head and neck, while 36 tumors were located in deep soft tissue such as an intra-abdominal site and mediastinum.

The pleural tumors developed local recurrence in 3 of 22 cases, distant metastasis in 0 of 22 cases, and tumor death in 1 of 22 cases. The tumors also caused local recurrence in 10 of 59 cases, distant metastasis in 5 of 59 cases, and tumor death in 4 of 59 cases in the non-pleuropulmonary/non-CNS tumors. Moreover, local recurrence in 8 of 12 cases, distant metastasis in 6 of 12 cases, and tumor death in 4 of 12 cases were noted among the CNS tumors. Among the two cases with hypoglycemia associated with the primary tumor, both cases showed local recurrence, one showed distant metastasis, and both showed tumor death.

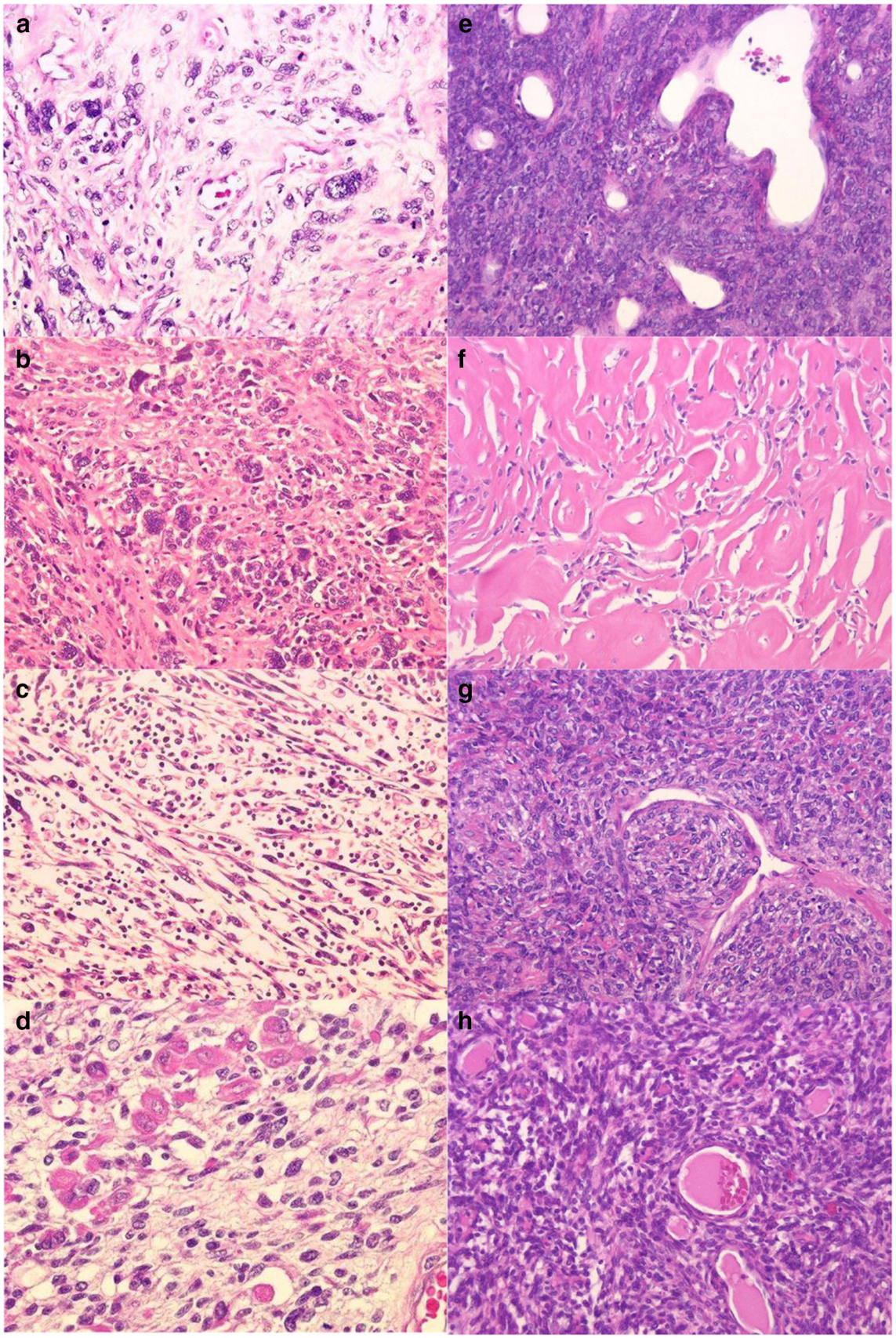
Data on the clinical symptom of hypoglycemia were available for 63 of 145 cases (43%). Hypoglycemia occurred in 3 cases; in 2 of these, it was caused by the primary tumor, while in the remaining 1 it was caused by a metastatic tumor. Dedifferentiation was observed in 10 cases, including 6 primary tumors, 2 recurrent tumors, and 2 metastatic tumors (Fig. 1). Among 6 primary cases with dedifferentiation, one case had no available clinical information, local recurrence developed in 1 of 5 available cases, distant metastasis in 3 of 5 cases, and tumor death in 3 of 5 cases. Moreover, all 4 local recurrence/ distant metastasis cases with dedifferentiation, including 2 LD and 2 distant metastasis, developed tumor death. Overall, 6 of 9 tumor death cases presented hypoglycemia and/or dedifferentiation: 1 showed hypoglycemia, 4 showed dedifferentiation, and the other 1 showed both hypoglycemia and dedifferentiation (Table 2). The primary tumors with high mitotic activity were 16 of 145 cases (11.0%).

RT-PCR

Representative results of the fusion gene analysis are shown in Fig. 2. Among all 121 available cases, 62 cases (51.2%) were fusion gene-positive. Thirty cases (24.7%) showed fusion gene type 1, 29 cases (23.9%) showed type 2, 3 cases (2.4%) showed others, and 59 were negative for the fusion gene. The pleuropulmonary tumors possessed the fusion gene type 1 in 17 (56.6%) and type 2 in 3 (10%) among all 30 pleural cases. Moreover, the 96 non-pleuropulmonary/non-CNS tumors included 9 (9.3%) cases with the type 1 fusion gene and 21 (21.8%) cases with type 2; CNS tumors carried type 1 in 4 (22.2%) of all 22 CNS cases and type 2 in 5 cases (27.7%).

Statistics

Survival curve (Kaplan–Meier curve) analysis was performed for each clinicopathological finding. Statistical data are shown in Table 3. Representative survival curves are presented in Fig. 3. Statistically significant results were as follows: local recurrence was positively associated with CNS location ($p =$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◀ **Fig. 1** Representative histology of dedifferentiated SFT. Dedifferentiation of **a** primary retroperitoneal SFT, **b** primary prostatic SFT, **c** primary SFT of back subcutis, and **d** metastatic SFT of abdominal cavity with rhabdomyosarcomatous differentiation; (e–h) images show the ordinary SFT component corresponding to the dedifferentiated SFTs above, respectively

0.0102), hypoglycemia with primary tumor alone ($p = 0.001$), and high mitotic activity ($p = 0.004$); distant metastasis was positively associated with CNS location ($p = 0.0076$), hypoglycemia with primary tumor alone ($p = 0.0009$), high mitotic activity ($p = 0.0001$), and dedifferentiation ($p < 0.0001$), while distant metastasis was negatively correlated with pleuropulmonary location ($p = 0.0471$); tumor death was positively associated with male sex ($p = 0.0154$), deep location ($p = 0.0247$), hypoglycemia with primary tumor alone ($p < 0.0001$), high mitotic activity ($p < 0.0001$), and dedifferentiation ($p < 0.0001$). When including hypoglycemia and dedifferentiation occurring in association with local recurrence and distant metastasis, tumor death was significantly associated with hypoglycemia ($p < 0.0001$) and dedifferentiation ($p < 0.0001$).

Multivariable analysis of the overall survival curve using the Cox proportional hazard model confirmed that dedifferentiation was an independently significant prognostic factor ($p = 0.0467$). As for local recurrence-free survival and distant metastasis-free survival, only hypoglycemia and dedifferentiation were independent prognostic factors for each analysis ($p = 0.0038$ and < 0.0001, respectively).

Additionally, Fisher's exact test was performed for each clinical and histological finding. The results with statistical significance were as follows: the test revealed associations between younger age and CNS location ($N = 143$, OR = 3.20, $p = 0.0214$), dedifferentiated SFT and size ($N = 110$, OR = not available, $p = 0.0052$), high mitotic activity and hypoglycemia ($N = 63$, OR = not available, $p = 0.0021$), and high mitotic activity and dedifferentiated SFT ($N = 145$, OR = 11.2, $p = 0.0016$). Moreover, in comparison of the tumors with fusion gene types 1 and 2, those in the former group were more prevalently located in pleuropulmonary ($N = 59$, OR = 3.71, $p = 0.0009$), while those in the latter group were larger in size ($N = 47$, OR = 3.96, $p = 0.0392$).

Risk stratification

From the above results, the authors established high-risk location (intraabdominal and cerebromeningeal site), hypoglycemia, and dedifferentiation as components of risk stratification of SFT. The scoring system for the risk stratification was as follows; when existence of each component of the risk stratification added one point, total score = 0 gave 2 tumor death cases (2/70, 2.8%), total score = 1 gave 2 tumor death cases (2/18, 11.1%), total score = 2 gave 3 tumor death cases (3/3, 100%), and total score = 3 gave 2 tumor death cases (2/2, 100%).

In addition, risk stratification model proposed by Demicco was adopted to the available 109 cases, according to the previous investigation; patient age was scored as 0 if < 55 years and 1 if ≥ 55 years. Mitotic activity was scored as 0 if < 1 mitotic figure/10 HPF, 1 if 1–3 mitotic figures/10 HPF, or 2 if ≥ 4/10 HPF. Tumor size was scored as 0 if < 5 cm, 1 if 5 to < 10 cm, 2 if 10 to < 15 cm, or 3 if ≥ 15 cm). Scores of 0–2 were considered low risk, 3–4 as intermediate risk, and 5–6 as high risk [22]. The cases were classified into low-risk (score 0: 11 cases, score 1: 38 cases, score 2: 33 cases), intermediate risk (score 3: 15 cases, score 4: 8 cases), and high-risk (score 5: 2 cases, score 6: 3 cases). Low-risk group included no metastatic and tumor death cases. Statistically, more than intermediate risk was correlated with distant metastasis ($p = 0.0089$) and

Table 2 Tumor death cases of SFT

Case	Age	Sex	Location	Local recurrence	Distant metastasis	Hypoglycemia	Dedifferentiation	Clinical course
1	5	F	Mediastinum	+	–	–	–	DOD 41mo
2	47	M	Cervical spine	+	+	–	–	DOD 11mo
3	28	M	Dura mater	+	+	–	–	DOD 290mo
4	65	M	Retroperitoneum	+	+	+	+	Hypoglycemia and dedifferentiation of the metastatic tumor, DOD 35mo
5	76	M	Pleura	+	–	+	–	Hypoglycemia of the primary tumor, DOD 54mo
6	60	F	Retroperitoneum	+	+	–	+	Dedifferentiation of the primary tumor, DOD 33mo
7	51	M	Dura mater	–	+	–	+	Dedifferentiation of the primary tumor, DOD 4mo
8	74	F	Cerebillum	+	–	–	+	Dedifferentiation of the recurrent tumor, DOD 41mo
9	58	M	Prostate	–	+	–	+	Dedifferentiaion of the primary tumor, DOD 35mo

DOD death of disease

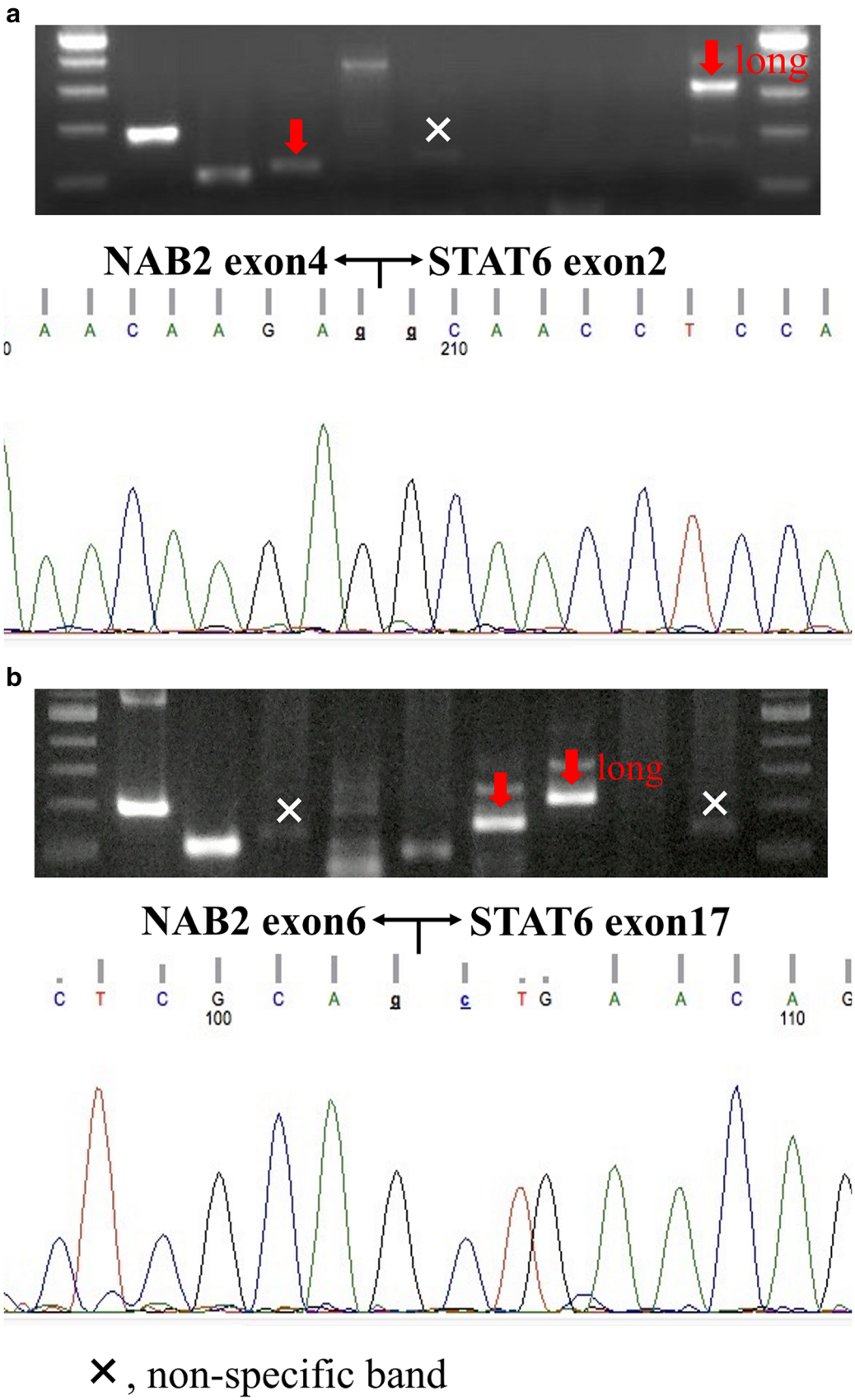

Fig. 2 The bands of NAB2-STAT6 fusion gene products and the results of direct sequencing are shown. **a** Variant type1 and **b** type 2 of the NAB2-STAT6 fusion gene were each detected in about a half of SFTs with informative results by RT-PCR analysis

Table 3 Statistical analysis by survival curves

			N (%)	Local recurrence*	Distant metastasis*	Tumor death*
Age	≥ 55 vs 55>	≥ 55	72	n.s.	n.s.	n.s.
		55>	71			
Sex	M vs F	M	58	n.s.	n.s.	0.0154[a]
		F	86			
Location	Pleuropulmonary vs others	Pleuropulmonary	30	n.s.	0.0471[a]	n.s.
		Non-pleuropulmonary	114			
	CNS vs others	CNS	23	0.0109[a]	0.0231[a]	n.s.
		Non-CNS	121			
	Superficial vs deep	Superficial	52	n.s.	n.s.	0.0247[a]
		Deep	36			
Size	≥ 5.2 vs 5.2>	≥ 5.2	57	n.s.	n.s.	0.0455[a]
		5.2>	53			
Fusion gene	Type 1 vs type 2	Type 1	30	n.s.	n.s.	n.s.
		Type 2	29			
Hypoglycemia	(Only primary tumor)	+	2	0.001[a]	0.0009[a]	< 0.0001[a]
		–	61			
Hypoglycemia	(Including LR/DM)	+	3			< 0.0001[a]
		–	60			
Mitotic activity	≥ 4/10 HPFs		16	0.004	0.0001	< 0.0001
	< 4/10 HPFs		129			
Dedifferentiation	(Only primary tumor)	+	6	n.s.	< 0.0001[a]	< 0.0001[a]
		–	139			
Dedifferentiation	(Including LR/DM)	+	9			< 0.0001[a]
		–	136			

n.s. not significant, *PP* pleuropulmonary, *CNS* central nervous system

**p* value, survival curve analysis

[a] *p* value < 0.05

tumor death ($p = 0.0041$). As the same, high-risk was correlated with local recurrence ($p = 0.0138$), distant metastasis ($p = 0.003$), and tumor death ($p < 0.0001$).

Discussion

Prognostic factors of SFT have been explored in numerous studies from clinical and histological perspectives [9–11, 22, 23]. However, no definite criteria for malignancy have been established yet. Hypoglycemia, CNS location, and dedifferentiation were previously proposed as prognostic factors [13–19], but clinical impact of the above three features have never been confirmed by large studies in which cases were confirmed on a genetic basis by the presence of the *NAB2-STAT6* fusion gene. In the current study, the authors statistically analyzed the clinicopathological findings from numerous SFT cases, confirming that hypoglycemia, CNS location, and dedifferentiation were statistically significant prognostic factors. CNS location was also proved to be a risk factor for local recurrence and distant metastasis distant metastasis, but not a statistically independent prognostic factor. Although the cause of the higher recurrence rate in cases with a CNS location could be associated with operative difficulty, CNS location may be associated with a specific mechanism for metastatic potential that is lacking in non-CNS cases. Further histopathological and genetic explorations of this issue are needed. The authors considered that histological risk stratification for SFT should be done except for cases with dedifferentiation as an independent prognostic factor for distant metastasis and tumor death because the different biological mechanisms, such as hypoglycemia and dedifferentiation, would contribute to unfavorable prognosis. Moreover, mitotic activity was also a risk factor of the primary SFTs, as demonstrated by the previous investigation [22, 23]. On the other hand, the primary tumors with high mitotic activity were not the same population as the dedifferentiated cases. Thus, the author considered that SFT showing poorer clinical course would not be the same as dedifferentiated cases and that SFT with high mitotic activity may represent non-dedifferentiated malignant SFT.

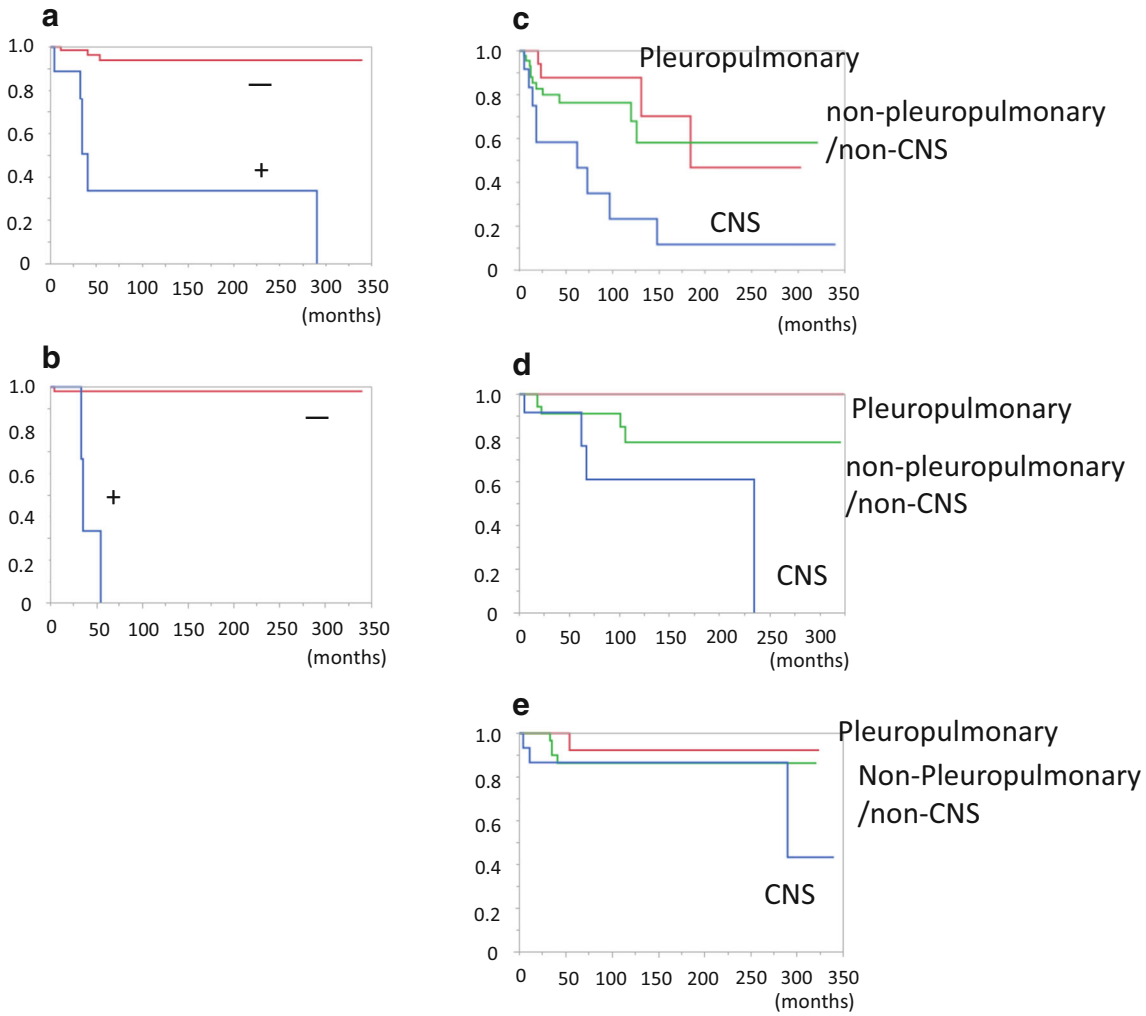

Fig. 3 Survival curve analysis. In **a**, **b**, +curve presents the group with dedifferentiation and hypoglycemia, respectively; −curve corresponds to the group without the above findings. **a**, **b** Overall survival curves of **a** dedifferentiation- and **b** hypoglycemia-positive cases. **c**–**e** Survival curves of three locational classifications of SFTs: pleuropulmonary, non-pleuropulmonary/non-CNS, and CNS. **c** The local recurrence-free survival curve showed a relatively high recurrence rate of CNS SFT. **d** The distant metastasis-free survival curve demonstrated low metastatic potential of pleuropulmonary SFT and high metastatic potential of CNS SFT. **e** The overall survival curves of SFTs showed no definite difference of clinical course to tumor death between them

The risk stratification model established by Domicco et al. was unavailable in the current investigation because of difficulty in size measure of specimen of CNS cases [22].

In SFT, it is known that metastasis rarely occurs, with a rate of approximately 5% being reported [1]. Our data also corresponded to the previously described clinical features of SFT; occasional local recurrence and rare cases of distant metastasis, hypoglycemia, and dedifferentiation were demonstrated in the current investigation. Interestingly, most of the tumor death cases showed hypoglycemia or dedifferentiation in primary, recurrent, or metastatic lesions. Moreover, although local recurrence and distant metastasis were significantly associated with tumor death, there were also cases with local recurrence or distant metastasis with long-term survival. Moreover, these cases with long-term survival did not exhibit any clinical symptoms of hypoglycemia and dedifferentiation (data not shown). SFT is generally known as a slow-growing tumor. Therefore, the authors considered that the feature of slow growth of SFT would cause a favorable clinical course despite metastasis, and that the occurrence of hypoglycemia and dedifferentiation in recurrent or metastatic cases may worsen the subsequent clinical course. The risk stratification established in the current investigation also proved that the specific location of intra-abdominal or cerebromeningeal site, hypoglycemia and dedifferentiation would increase the risk for tumor death, regardless of metastasis. It was proposed that long-term follow-up of SFT would require careful analysis of blood sugar level and that the histological features of recurrent/metastatic tumor should be explored by biopsy or surgical resection.

Fusion gene variants of *NAB2-STAT6* were identified as a potential candidate prognostic factor [21, 24–27]. The previous investigation reported that NAB2 exon 6-STAT6 exon 16/17 was associated with retroperitoneal, cellular, and recurrent tumors [21]. In the current investigation, the authors analyzed the genetic data and clinical outcomes of local recurrence, distant metastasis and tumor death, and finally considered that the fusion gene profile would not directly affect the clinical course. Moreover, the fusion gene profile was significantly associated with the tumor location. Specific tumor locations, such as an intra-abdominal or cerebromeningeal site, apparently contributed to a poorer clinical course. In contrast, there were no metastatic tumors in pleural SFT cases, except for one hypoglycemic case, although the fusion gene type 1 showed a tendency to be detected in pleural SFTs. Therefore, the authors concluded that the fusion gene variants of *NAB2-STAT6* of SFT occur in a manner dependent on the tumor location. The fusion gene variant may have some influence on the biological behavior of SFTs through the association of the fusion gene variants with the specific tumor location. It was proposed that the tendency for an exon variant of the *NAB2-STAT6* fusion gene to be present is more directly associated with the particular tumor location than the fusion gene variant. The detectability of NAB2-STAT6 was about 50%. The authors considered that relatively low detectability of the fusion gene in the current investigation may be due to the quality of old FFPE samples and insertion of non-exon area (data not shown).

As for the relationship between biological behavior and the location of SFT, the authors classified the SFTs into detailed locations, such as pleuropulmonary tumors into pulmonary and pleural ones; non-pleuropulmonary/non-CNS tumors into extremity, trunk, and intra-abdominal ones; and CNS tumors into cerebromeningeal and spinal cord ones. Interestingly, a poorer prognosis was detected for specific subcategories within each locational classification. In particular, intra-abdominal and cerebromeningeal locations showed a tendency to be associated with an aggressive clinical course. In contrast, pleuropulmonary SFTs showed less of a tendency for distant metastasis. Considering the finding that fusion gene variants were not associated with clinical outcome, it is suggested that the location of SFT would have a certain effect on the biological behavior, such as metastatic potential, due to microenvironmental or epigenetic factors.

Multivariable statistical analysis also validated the significance of dedifferentiation and hypoglycemia in SFT as a life-threatening risk factor in spite of scarcity of the cases with dedifferentiation and/or hypoglycemia. In the current investigation, the authors suggested dedifferentiation, hypoglycemia and the specific location as risk factors. However, these risk factors overlapped in some cases. Larger study including numerous high-risk cases with dedifferentiation, hypoglycemia, and the specific location is desired.

In the current investigation, the risk stratification by Demicco et al. [22, 23] was also validated. The risk stratification of Demicco et al. clearly divided the cases into three groups with or without distant metastasis or tumor death. The risk stratification of Demicco et al. included clinical and histological information of patient age, tumor size and mitotic count; thus, it was considered that one of precise method of risk evaluation such as preoperative biopsy.

In conclusion, hypoglycemia and dedifferentiation were found to be independent prognostic factors of *NAB2-STAT6*-positive/STAT6 IHC-positive SFTs for local recurrence, distant metastasis, and tumor death. In tumors with a CNS location, distant metastasis may frequently occur by a location-specific mechanism. Fusion gene variants of *NAB2-STAT6* had no definitive impact on the prognosis of SFT patients.

Acknowledgments Technical support for the experimental trials was provided by the following laboratory assistants: Motoko Tomita, Mami Nakamizo, Juri Godo, Miwako Ishii, Hisami Matsumoto, and Noriko Aoki. We also appreciate the technical assistance from staff at The Research Support Center, Kyushu University Graduate School of Medical Sciences.

Author contributions Yuichi Yamada performed the research and wrote the paper. Kenichi Kohashi, Izumi Kinoshita, Hidetaka Yamamoto and Takeshi Iwasaki contributed to the research design and slide review. Shin Ishihara, Yu Toda, Yoshihiro Itou, Yutaka Koga, Mikiko Hashisako, Yui Nozaki, Daisuke Kiyozawa, Daichi Kitahara, Takeshi Inoue, Munenori Mukai, Yumi Honda, Gouji Toyokawa, Kenji Tsuchihashi, Yoshifumi Matsushita, Fumiyoshi Fushimi, Kenichi Taguchi, Sadafumi Tamiya, Yumi Oshiro, Masutaka Furue, Yasuharu Nakashima, Satoshi Suzuki, and Toru Iwaki contributed to the sample collection and research design. Yoshinao Oda designed the research and gave final approval of the manuscript. All authors critically reviewed and approved the manuscript.

Funding This study was supported by a JSPS KAKEN Grant (No. 17K15645) and by funds from the Scholarship Program of the Takeda Science Foundation.

Compliance with ethical standards

This study was conducted in accordance with the principles embodied in the Declaration of Helsinki. The study was also approved by the Ethics Committee of Kyushu University (Nos. 25-111, 25-143). Informed consent was obtained from the subjects or guardians.

Conflict of interest The authors declare that they have no conflicts of interest.

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