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*Case Report*

# A case of dedifferentiated solitary fibrous tumor of the thoracic cavity

Yoshio Masuda[1], Aiko Kurisaki-Arakawa[1], Kieko Hara[1], Atsushi Arakawa[1], Shiaki Oh[2], Kenji Suzuki[2], Takashi Yao[1], Tsuyoshi Saito[1]

*[1]Department of Human Pathology, Juntendo University School of Medicine, 2-1-1, Hongo, Bunkyo-ku, Tokyo, Japan; [2]Department of General Thoracic Surgery, Juntendo University School of Medicine, 2-1-1, Hongo, Bunkyo-ku, Tokyo, Japan*

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**Abstract:** Solitary fibrous tumors (SFTs), initially observed in the pleura, were later found to develop in almost any extrapleural site. Dedifferentiation within SFTs, a rare phenomenon, was characterized only recently, although it was previously described in soft tissue and bone tumors. We report a case of dedifferentiated SFT arising in the right pleura of a 69-year-old man. Computed tomography revealed a huge mass in the thoracic cavity. The tumor contained an area with a high degree of calcification and was heterogeneously enhanced. Macroscopically, the resected tumor was 175 × 145 × 135 mm in size. Morphologically and immunohistochemically, this was comprised of a typical SFT juxtaposed to a high-grade component including an osteosarcomatous component. These were sharply demarcated by thin fibrous septa. Furthermore, NAB2-STAT6 fusion transcripts were detected by reverse-transcriptase polymerase chain reaction in both conventional and high-grade components, supporting the concept of a dedifferentiation process in this tumor.

**Keywords:** Solitary fibrous tumor, dedifferentiation, NAB2-STAT6

## Introduction

Solitary fibrous tumors (SFTs), initially observed in the pleura [1], were later reported to develop in almost any extrapleural site [2-4]. The biology of SFT is somewhat unpredictable, and as a large majority of cases are morphologically and clinically benign, approximately 5% of cases show aggressive behavior in the form of recurrent or metastatic disease. Some morphologic features that are known to be associated with aggressive clinical behavior include the presence of more than 4 mitoses/10 HPF, pleomorphism, increased cellularity in either the pleural or extrapleural SFT, size greater than 10 cm, and necrosis/hemorrhage in the pleural SFT [5, 6]. In addition, positive surgical margins and tumor size >10 cm have been shown to be associated with a poorer metastasis-free survival [5].

Next-generation sequencing of RNA and DNA from SFTs recently resulted in the identification of a *NAB2/STAT6* fusion gene in the majority of cases [7-9]. Reverse-transcriptase polymerase chain reaction (RT-PCR) analysis identified a *NAB2/STAT6* fusion in 37 out of 41 cases in a recent study [9]. Therefore, this fusion is considered to be involved in the pathogenesis of SFT.

Dedifferentiation is a phenomenon that is well described in soft tissue and bone tumors such as well-differentiated liposarcoma [10-13], chondrosarcoma [14, 15], chordoma [16], and osteosarcoma [17, 18]. Dedifferentiation can arise de novo (combined with a well-differentiated tumor) or develop in a recurrence of a prior well-differentiated malignancy. Morphologically, dedifferentiation is characterized most often by abrupt transition between the well-differentiated component and high-grade areas of the tumor, and it confers more aggressive biological behavior.

Dedifferentiation within SFTs is a rare phenomenon that was characterized only recently [19-21]. Dedifferentiated SFT differs from malig-

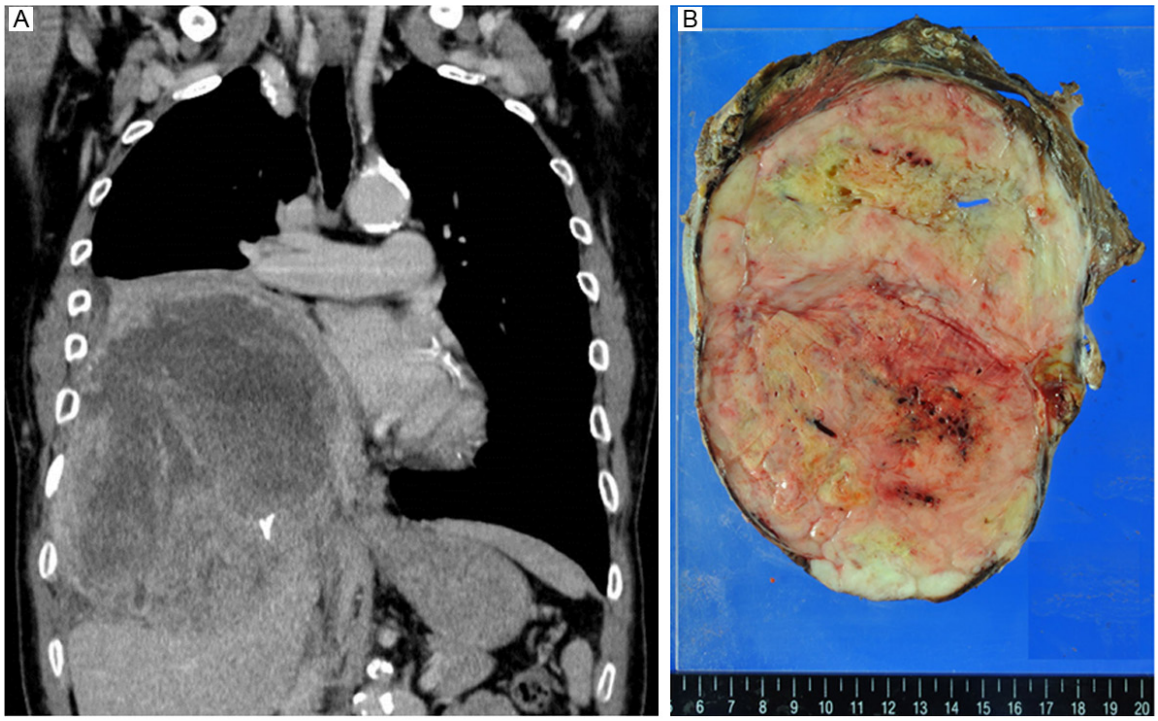


**Figure 1.** A: Computed tomography of the thoracic cavity revealed a huge heterogeneously enhanced mass with a high degree of calcification. B: A cut surface revealed a solid tumor with focal necrosis and bleeding. Focal calcification was also noted.

nant SFT in that there is an abrupt transition between conventional SFT and the dedifferentiated component. The latter is a high-grade sarcoma, which can exhibit a number of morphologies including heterologous differentiation such as rhabdomyosarcomatous or osteosarcomatous component.

We report a case of dedifferentiated SFT, with a heterologous osteosarcomatous component, arising in the right pleura of a 69-year-old man. This was comprised of morphologically and immunohistochemically typical SFT, juxtaposed with a high-grade component including an osteosarcomatous component, which were sharply demarcated by thin fibrous septa. Furthermore, NAB2-STAT6 fusion transcripts were detected in both conventional and high-grade components, supporting the concept of a dedifferentiation process in this tumor.

## Case report

A 69-year-old man had received a bare metal stent implantation in the left anterior descending coronary artery upon diagnosis of acute myocardial infarction in January 2012. Plain radiography at this time revealed a thoracic tumor. In addition, he had experienced shortness of breath, difficulty in breathing, and weight loss since April 2012. Detailed radiological examination of the thoracic mass led to a suspicion of the presence of a solitary fibrous tumor. Therefore, he was transferred to the Department of General Thoracic Surgery, Juntendo University Hospital and was hospitalized in February 2013. Computed tomography of the thoracic cavity revealed a huge mass (177 × 166 × 129 mm) in the thoracic cavity between the right lower lung and the right lobe of the liver. The tumor contained an area with a high degree of calcification and was heterogeneously enhanced (**Figure 1A**). Angiography revealed that the tumor had feeder arteries from the inferior phrenic artery, intercostal artery, and right bronchial artery. Embolization of these arteries was performed before surgery. At the time of the surgery, the tumor was found to infiltrate into the chest wall, the right middle and lower lobes of the lung, and the right diaphragm. A rapid diagnosis of conventional SFT was made during the surgery. Although the tumor macroscopically contained some necrotic areas with stromal bleeding,

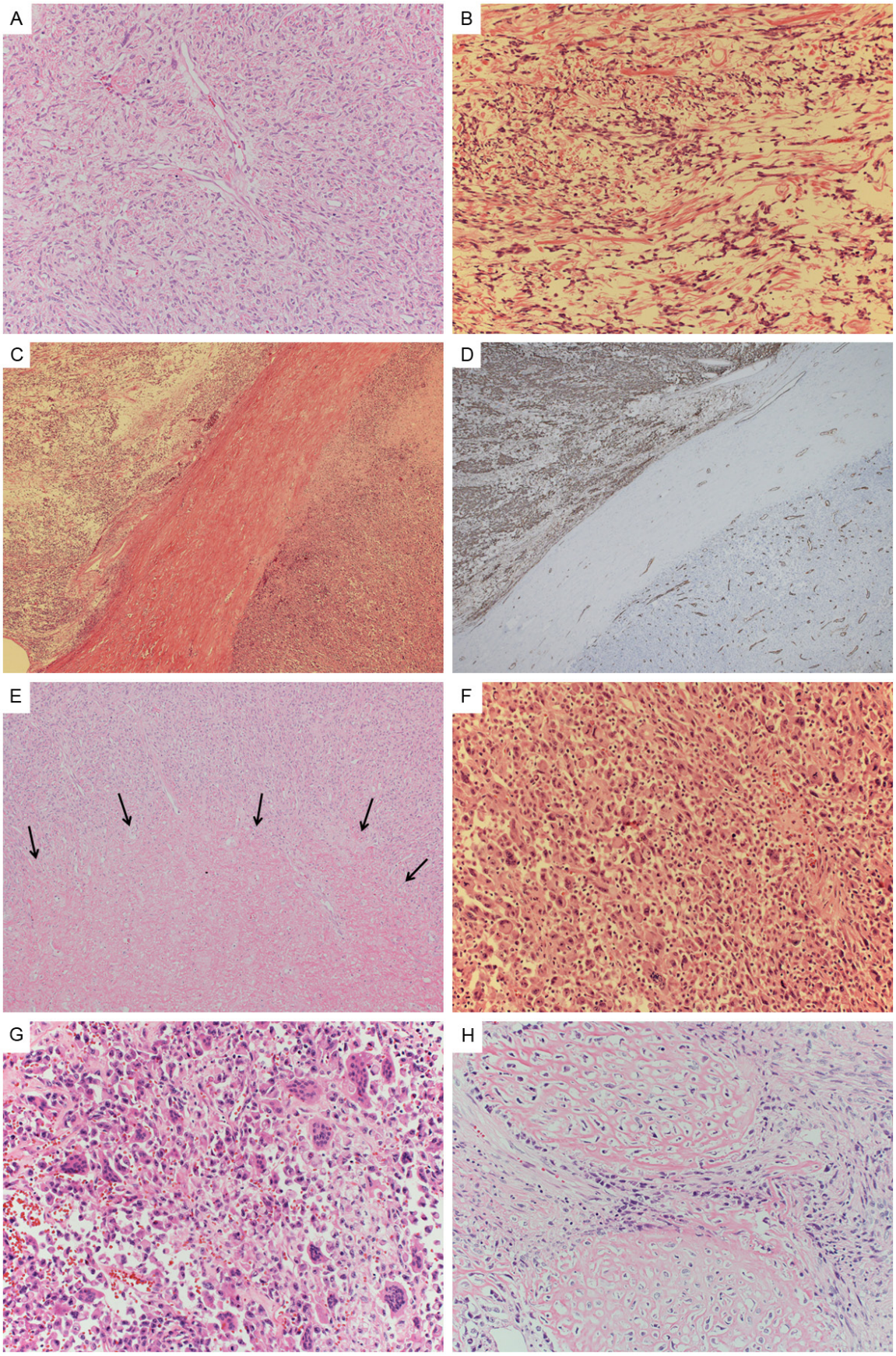
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**Figure 2.** Histologic feature of dedifferentiated SFT. A: The tumor was comprised of a proliferation of spindle-shaped cells in a patternless or partial storiform fashion with thin-walled branching; B: Focally, myxoid edematous stroma was noted. C: High-grade areas (lower right) separated by fibrous septa consisting of pleomorphic cells were also observed adjacent to the conventional SFT area (upper left); D: High-grade area (lower right) lacked immunohistochemically CD34 expression; E: Coagulative necrosis was also noted (area surrounded by arrows); F: Rhabdoid cells were frequently seen in the high-grade area; G: Tumor giant-cells were scattered between the in-cohesive rhabdoid cells. H: Race-like tumor osteoid formation in the high-grade area.

these were thought to be due to the therapeutic effects of the preoperative embolization.

Macroscopically, the resected tumor was 175 × 145 × 135 mm in diameter with a fibrous capsule. A cut surface revealed a solid tumor with focal necrosis and bleeding (**Figure 1B**). Focal calcification was also noted. Histologically, the periphery of the tumor showed characteristic features of a conventional SFT, and it was comprised of a proliferation of spindle-shaped cells in a patternless or partial storiform fashion with thin-walled branching vessels and sometimes with myxoid edematous stroma (**Figure 2A** and **2B**). However, high-grade areas separated by fibrous septa consisting of pleomorphic cells with high-mitotic rate (>4/10 HPF) were also observed adjacent to the conventional SFT area (**Figure 2C**). The high-grade area lacked immunohistochemically CD34 expression (**Figure 2D**). The high-grade area of the tumor lacked characteristic features of SFT, and the tumor showed solid proliferation of pleomorphic cells within a less collagenous background. Spindle-shaped pleomorphic cells were proliferating in a fascicular fashion. Necrosis and high mitotic activity were also observed (>10/10 HPF) (**Figure 2E**). Occasional rhabdoid cells and giant cells were also noted (**Figure 2F** and **2G**). At the macroscopically calcified area, tumor osteoid was observed surrounding the pleomorphic tumor cells, suggesting osteosarcomatous component (**Figure 2H**). By immunohistochemistry, the well-differentiated conventional SFT area showed immunoreactivities for CD34, bcl-2, and CD99, but not for S-100 protein, SMA, or AE1/3. The MIB-1 labeling index (LI) was approximately 10% (**Figure 3A**) in conventional SFT area, though it was nearly 80% in high-grade area (**Figure 3B**). Tumor cells showed scattered tumor cells with weakly positive staining for p53 (**Figure 3C**). The high-grade component showed negative staining for CD34 but stronger immunoreactivities for p53 than the conventional SFT area (**Figure 3D**). Immunohistochemistry for p16 was also interesting, diffuse staining was observed in the conventional SFT area, whereas only focal expression was seen in the dedifferentiated area (**Figure 3E** and **3F**). The final diagnosis was dedifferentiated SFT comprised of conventional SFT and undifferentiated high-grade sarcoma with an osteosarcomatous component. The patient has no evidence of recurrence or metastasis 6 months after surgery.

*RNA extraction and RT-PCR*

RNA extraction was performed on paraffin-embedded tissue obtained from each component of the conventional and dedifferentiated high-grade areas as previously described [22]. The primer sequences used in this study were also described previously [7-9]. An aliquot of the PCR product was electrophoresed on 2% agarose gel and stained with ethidium bromide. The PCR product at the appropriate anticipated size was cut from the gel and sequenced. A fusion gene of NAB2(exon4)-STAT6(exon2) (described as variant 1 by Chmielecki et al.) was confirmed in both the conventional SFT and dedifferentiated high-grade components, further confirming the diagnosis (**Figure 4A** and **4B**).

*Mutational analysis of the p53 gene and PDGFRβ*

Mutations in *p53 and PDGFRβ* have been previously reported to occur in SFT [21, 23, 24], albeit rarely. To test for these, genomic DNA was extracted from formalin-fixed and paraffin-embedded blocks. Mutations in the *p53* (exon5-9) and *PDGFRβ* (exon12, 14, 18-20) genes were examined using PCR, followed by direct sequencing. The primer sequences used in this study were described previously [23, 25, 26]. No mutations of these genes were detected in any of the tested tissue components.

## Discussion

SFT is a borderline malignancy, whose biological behavior is difficult to predict. Unlike malig-

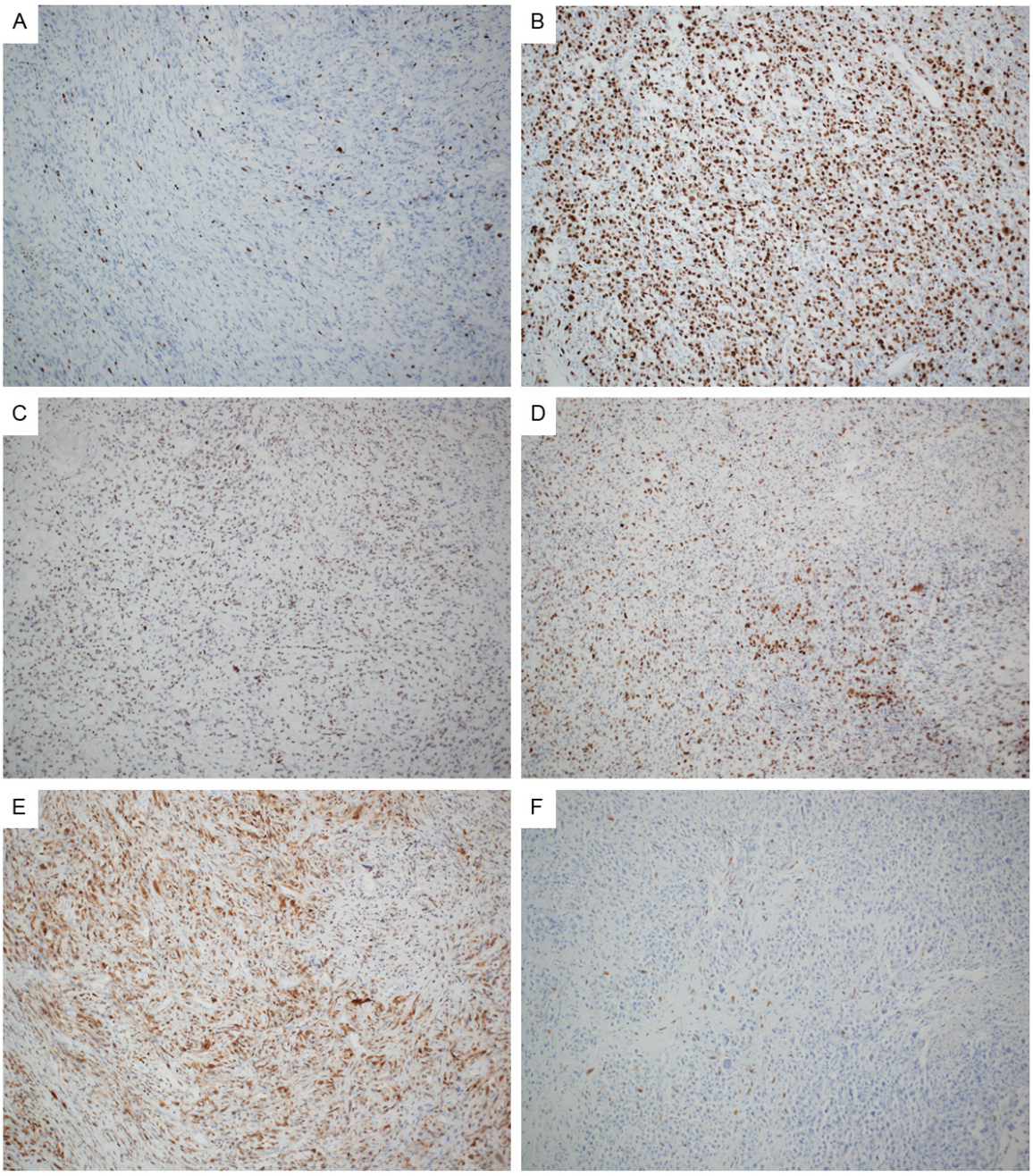


**Figure 3.** Immunohistochemistry. (A, B) MIB-1 LI was extremely higher in the dedifferentiated area (B) compared to the conventional SFT area (A); (C, D) Proportion of p53 positive cells in dedifferentiated area (D) was slightly higher than that of conventional SFT area (C) and intensity was also stronger in the high-grade area; (E, F) Expression of p16 was diffusely observed in the conventional SFT area (E), though only focal expression was seen in the dedifferentiated area (F).

nant SFT, which usually shows malignant features throughout the tumor, dedifferentiation within a SFT is a rare phenomenon that was characterized only recently [19-21]. There is an abrupt transition between the area of classical SFT and the dedifferentiated component. The latter is a high-grade sarcoma, which can exhibit a number of morphologies including heterologous differentiation. In such cases, it may be difficult to make an accurate diagnosis using small samples during intraoperative rapid diagnosis. This case was unfortunately diagnosed

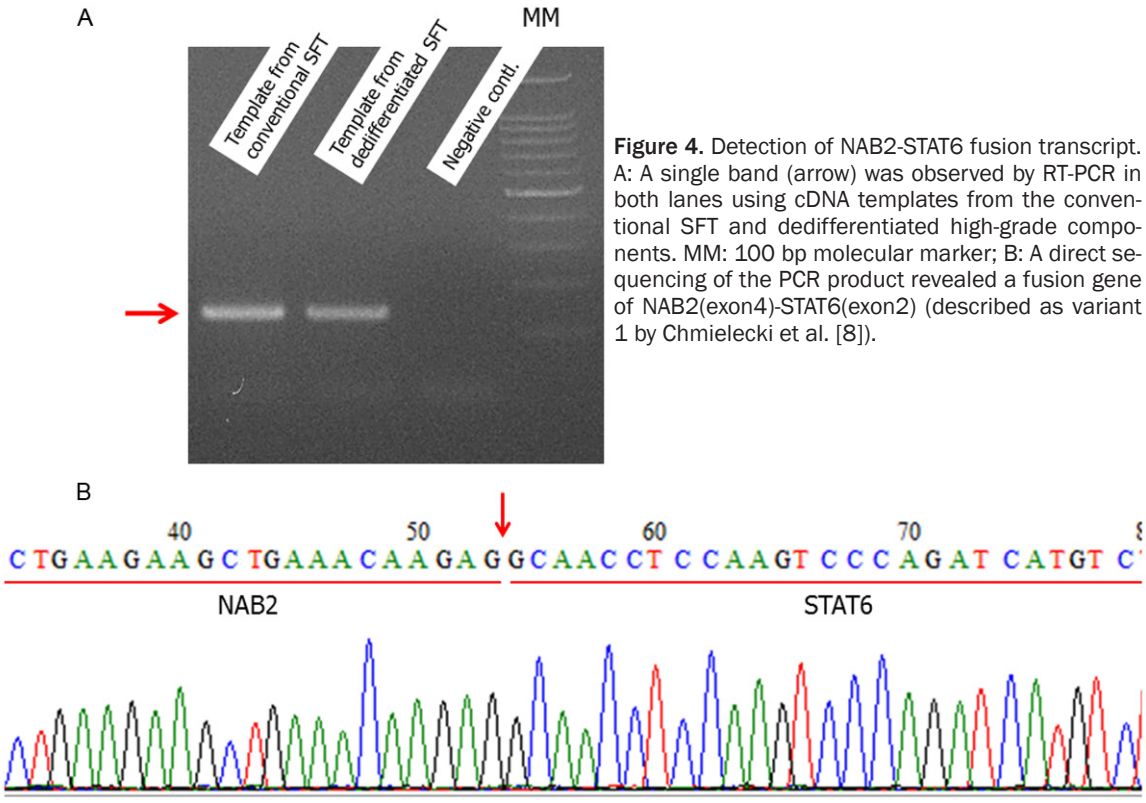


**Figure 4.** Detection of NAB2-STAT6 fusion transcript. A: A single band (arrow) was observed by RT-PCR in both lanes using cDNA templates from the conventional SFT and dedifferentiated high-grade components. MM: 100 bp molecular marker; B: A direct sequencing of the PCR product revealed a fusion gene of NAB2(exon4)-STAT6(exon2) (described as variant 1 by Chmielecki et al. [8]).

as conventional SFT at the intraoperative rapid diagnosis. Although, macroscopically, the tumor contained some necrotic areas with stromal bleeding, these were thought to be as the therapeutic effects of the preoperative embolization, especially because SFT can spontaneously exhibit these kinds of degenerative changes upon gross sectioning.

This case is a morphologically typical case of dedifferentiated SFT, in which both a conventional SFT area and a high-grade area were sharply demarcated by thin fibrous septa. Distinctive immunohistochemical differences between the components were observed, including the presence/absence of CD34, p16 and MIB-1. However, the same type of *NAB2-STAT6* fusion transcript was detected in both the conventional and the high-grade components, suggesting that the formation of the fusion gene is an early event in the tumorigenesis of this dedifferentiated SFT. This supports the concept of a dedifferentiation process in this tumor.

The prognostic value of the detection of p53 overexpression or mutation in SFT has been reported previously [23, 24, 27]. In addition, high p53 expression was significantly related to conventional clinicopathologic prognostic features as well as overall survival and disease-free survival [23]. In dedifferentiated SFT, it has been shown that p53 expression was either negative or present only in scattered positive cells in the well-differentiated SFT areas, in contrast to positive or else stronger and more diffuse staining in the high-grade component [20]. In this case, p53 expression was relatively strongly observed in the dedifferentiated component and weaker expression was seen in the conventional area, in line with the previous findings. Mutations of *p53* were not detected.

In this case, immunohistochemical expression of CD34 in the dedifferentiated component was absent but positive in the conventional SFT. Positive immunoreactivity for CD34 has been used as a diagnostic marker for SFT, and loss of CD34 immunoreactivity in high-grade tumors following the malignant transformation of SFT has been also described (27), in line with our case findings. Recently, *NAB2-STAT6* was identified as a recurrent gene fusion in SFTs [7-9]. *CD34* is expected to be one of the down-

stream targets of the NAB2/STAT6 fusion protein; thus, the expression of these downstream genes could be affected by various secondary genetic alterations. Although secondary genetic alterations are reported to be rare in SFTs [23, 24], for purposes of the diagnosis of SFT, it is well to keep in mind that CD34 expression may sometimes be lost in SFTs, especially in malignant cases.

It has been demonstrated that p16 expression was significantly associated with tumor recurrence in SFT [28]. Furthermore, a study comprised of 8 cases of dedifferentiated SFT also demonstrated that immunohistochemistry of p16 showed either negative or scattered positive cells in well differentiated SFT areas, in contrast to positive or stronger and more diffuse staining in the high-grade component [20]. Thus, p16 expression seems to be associated with aggressive behavior in SFT. This case, nonetheless, diffuse p16 expression was observed only in the conventional SFT component, and only scattered positive cells were seen in the dedifferentiated area.

In conclusion, this case report provides evidence that the general concept of dedifferentiation process in bone and soft tissue sarcoma can be also adapted to SFT.

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## Disclosure of conflict of interest

We declare that there is no conflict of interest.

**Address correspondence to:** Dr. Tsuyoshi Saito, Department of Human Pathology, Juntendo University School of Medicine, 2-1-1, Hongo, Bunkyo-ku, Tokyo, Japan. Tel: +81-3-3813-3111; Fax: +81-3-3813-3428; E-mail: tysaitou@juntendo.ac.jp

## References

[1] Klemperer P, Rabin C. Primary neoplasms of the pleura: a report of five cases. Arch Pathol 1931; 11: 385-412.

[2] Chan JK. Solitary fibrous tumour—everywhere, and a diagnosis in vogue. Histopathology 1997; 31: 568-576.

[3] Goodlad JR, Fletcher CD. Solitary fibrous tumour arising at unusual sites: analysis of a series. Histopathology 1991; 19: 515-522.

[4] Hasegawa T, Matsuno Y, Shimoda T, Hasegawa F, Sano T, Hirohashi S. Extrathoracic solitary fibrous tumors: their histological variability and potentially aggressive behavior. Hum Pathol 1999; 30: 1464-1473.

[5] Gold JS, Antonescu CR, Hajdu C, Ferrone CR, Hussain M, Lewis JJ, Brennan MF, Coit DG. Clinicopathologic correlates of solitary fibrous tumors. Cancer 2002; 94: 1057-1068.

[6] Vallat-Decouvelaere AV, Dry SM, Fletcher CD. Atypical and malignant solitary fibrous tumors in extrathoracic locations: evidence of their comparability to intra-thoracic tumors. Am J Surg Pathol 1998; 22: 1501-1511.

[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, Chinnaiyan AM. Identification of recurrent NAB2-STAT6 gene fusions in solitary fibrous tumor by integrative sequencing. Nat Genet 2013; 45: 180-185.

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

[9] 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, 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 Oct; 52: 873-86. doi:10.1002/gcc.22083.

[10] Evans HL. Liposarcoma: a study of 55 cases with a reassessment of its classification. Am J Surg Pathol 1979; 3: 507-523.

[11] Evans HL. Atypical lipomatous tumor, its variants, and its combined forms: a study of 61 cases, with a minimum follow-up of 10 years. Am J Surg Pathol 2007; 31: 1-14.

[12] Henricks WH, Chu YC, Goldblum JR, Weiss SW. Dedifferentiated liposarcoma: a clinicopathological analysis of 155 cases with a proposal for an expanded definition of dedifferentiation. Am J Surg Pathol 1997; 21: 271-281.

[13] McCormick D, Mentzel T, Beham A, Fletcher CD. Dedifferentiated liposarcoma. Clinicopathologic analysis of 32 cases suggesting a better prognostic subgroup among pleomorphic sar-

comas. Am J Surg Pathol 1994; 18: 1213-1223.
[14] Dahlin DC, Beabout JW. Dedifferentiation of low-grade chondrosarcomas. Cancer 1971; 28: 461-466.
[15] Frassica FJ, Unni KK, Beabout JW, Sim FH. Dedifferentiated chondrosarcoma. A report of the clinicopathological features and treatment of seventy-eight cases. J Bone Joint Surg Am 1986; 68: 1197-1205.
[16] Meis JM, Raymond AK, Evans HL, Charles RE, Giraldo AA. "Dedifferentiated" chordoma. A clinicopathologic and immunohistochemical study of three cases. Am J Surg Pathol 1987; 11: 516-525.
[17] Sheth DS, Yasko AW, Raymond AK, Ayala AG, Carrasco CH, Benjamin RS, Jaffe N, Murray JA. Conventional and dedifferentiated parosteal osteosarcoma. Diagnosis, treatment, and outcome. Cancer 1996; 78: 2136-2145.
[18] Wold LE, Unni KK, Beabout JW, Sim FH, Dahlin DC. Dedifferentiated parosteal osteosarcoma. J Bone Joint Surg Am 1984; 66: 53-59.
[19] Collini P, Negri T, Barisella M, Palassini E, Tarantino E, Pastorino U, Gronchi A, Stacchiotti S, Pilotti S. High-grade sarcomatous overgrowth in solitary fibrous tumors: a clinicopathologic study of 10 cases. Am J Surg Pathol 2012; 36: 1202-1215.
[20] Mosquera JM, Fletcher CDM. Expanding the spectrum of malignant progression in solitary fibrous tumors: A study of 8 cases with a discrete anaplastic component—Is this dedifferentiated SFT? Am J Surg Pathol 2009; 33: 1314-1321.
[21] Subramaniam MM, Lim XY, Venkateswaran K, Shuen CS, Soong R, Petersson F. Dedifferentiated solitary fibrous tumour of the nasal cavity: the first case reported with molecular characterization of a TP53 mutation. Histopathology 2011; 59: 1269-1274.
[22] Tsuji S, Hisaoka M, Morimitsu Y, Hashimoto H, Shimajiri S, Komiya S, Ushijima M, Nakamura T. Detection of SYT-SSX fusion transcripts in synovial sarcoma by reverse transcription-polymerase chain reaction using archival paraffin-embedded tissues. Am J Pathol 1998; 153: 1807-1812.
[23] Schirosi L, Lantuejoul S, Cavazza A, Murer B, Brichon PY, Migaldi M, Sartori G, Sgambato A, Rossi G. Pleuro-pulmonary solitary fibrous tumors: a clinicopathologic, immunohistochemical, and molecular study of 88 cases confirming the prognostic value of de Perrot staging system and p53 expression, and evaluating the role of c-kit, BRAF, PDGFRs (α/β), c-met, and EGFR. Am J Surg Pathol 2008; 32: 1627-1642.
[24] Morimitsu Y, Nakajima M, Hisaoka M, Hashimoto H. Extrapleural solitary fibrous tumor: clinicopathologic study of 17 cases and molecular analysis of the p53 pathway. APMIS 2000; 108: 617-625.
[25] Saito T, Mitomi H, Izumi H, Suehara Y, Okubo T, Torigoe T, Takagi T, Kaneko K, Sato K, Matsumoto T, Yao T. A case of secondary malignant giant-cell tumor of bone with p53 mutation after long-term follow-up. Hum Pathol 2011; 42: 727-733.
[26] Saito T, Mitomi H, Suehara Y, Okubo T, Torigoe T, Takagi T, Kaneko K, Yao T. A case of de novo secondary malignant giant-cell tumor of bone with loss of heterozygosity of p53 gene that transformed within a short-term follow-up. Pathol Res Pract 2011; 207: 664-669.
[27] Yokoi T, Tsuzuki T, Yatabe Y, Suzuki M, Kurumaya H, Koshikawa T, Kuhara H, Kuroda M, Nakamura N, Nakatani Y, Kakudo K. Solitary fibrous tumour: significance of p53 and CD34 immunoreactivity in its malignant transformation. Histopathology 1998; 32: 423-432.
[28] Liu CC, Wang HW, Li FY, Hsu PK, Huang MH, Hsu WH, Hsu HS, Wang LS. Solitary fibrous tumors of the pleura: clinicopathological characteristics, immunohistochemical profiles, and surgical outcomes with long-term follow-up. Thorac Cardiovasc Surg 2008; 56: 291-297.