Jpn J Clin Oncol 2005;35(5)274–279
doi:10.1093/jjco/hyi073

Primary Pulmonary Synovial Sarcoma Confirmed by Molecular Detection of *SYT–SSX1* Fusion Gene Transcripts: a Case Report and Review of the Literature

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Received August 12, 2004; accepted November 20, 2004; published online May 6, 2005

This is a case report of a rare patient with primary pulmonary synovial sarcoma. The patient was a 58-year-old woman who presented with a well-defined giant mass in the right lower field on a chest radiograph. A malignant pulmonary tumor was suspected and consequently a right middle and lower lobectomy was performed. Grossly, the tumor measured $10 \times 8 \times 7$ cm, was whitish-yellow in color and friable with hemorrhage. Histologically, the tumor showed a dense proliferation of spindle cells. In some areas, a herringbone-like pattern with coagulation necrosis of large size was noted. Immunohistochemically, the tumor cells were focally positive for cytokeratin and epithelial membrane antigen (EMA). As these features suggested a monophasic synovial sarcoma, we looked for the presence of *SYT–SSX* fusion gene transcripts using RNA samples from the paraffin-embedded tissue. A reverse transcription–polymerase chain reaction (RT–PCR) amplified a single 118 bp fragment characteristic of the *SYT–SSX1* fusion gene transcripts. As no tumor was found at other sites, it was diagnosed as primary pulmonary synovial sarcoma. Molecular testing proved to be very helpful or necessary when monophasic spindle cell synovial sarcoma was recognized in uncommon/unexpected sites. In our review of primary pulmonary synovial sarcomas confirmed by molecular detection of *SYT–SSX* fusion gene transcripts, the *SYT–SSX2* fusion protein expression correlates with poorer prognosis. This is in contrast to the association between the *SYT–SSX1* fusion protein expression and poorer prognosis in soft tissue synovial sarcomas.

Key words: primary pulmonary synovial sarcoma – spindle cell tumor – immunohistochemistry – SYT–SSX fusion gene transcripts

INTRODUCTION

Pulmonary sarcomas are rare, and most malignant mesenchymal tumors of the lung are metastases of a primary tumor from elsewhere (1). Primary pulmonary sarcomas account for <0.5% of lung cancers (2). The diagnosis can be established only after clinical and imaging investigations have failed to identify an alternative primary source. In addition, only detailed immunohistochemistry allows exclusion of other primary spindle cell neoplasms. Leiomyosarcomas, fibrosarcomas and hemangiopericytomas are the most common types of primary pulmonary sarcomas (1).

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Synovial sarcoma is a morphologically well-defined neoplasm that most commonly occurs in soft tissue. This type of tumor accounts for ~10% of all soft tissue sarcomas (3). Histologically, it is classified into four subtypes: biphasic, monophasic fibrous, monophasic epithelial and poorly differentiated. However, the monophasic epithelial subtype is extremely rare (4). Synovial sarcoma occurs predominantly in the extremities, where it tends to arise in the vicinity of large joints, especially the knee region. The tumor is intimately related to tendons, tendon sheaths and bursal structures, usually just beyond the confines of the joint capsule. It is rare within the joint cavity itself. Its existence and microscopic resemblance to normal synovium have been described in early reports (3). However, normal synovial tissues do not stain for epithelial markers such as cytokeratin or epithelial membrane antigen (EMA), whereas synovial sarcomas stain for these markers with high frequency. Also, this tumor has been described in numerous locations unrelated to joint

structures, including the head and neck, chest and abdominal wall (4). On the basis of these findings, it is currently thought that the origin of this tumor is unrelated to normal synovial tissues and thus synovial sarcoma is placed among the miscellaneous soft tissue tumors (5).

Primary pulmonary synovial sarcoma is extremely rare, but recently the occurrence of this tumor is being increasingly recognized (6–17). Here we present a case of this tumor occurring in a 58-year-old woman, the diagnosis being proven by *SYT–SSX* fusion gene transcripts using reverse transcription–polymerase chain reaction (RT–PCR), with a review of the English language literature.

CASE REPORT

A 58-year-old woman without a smoking history was admitted to our hospital because of a giant mass in the right lower field on a routine chest radiograph (Fig. 1). She had no complaint. On admission, her height was 151 cm, body weight 48.8 kg, and body temperature 36.5°C. Physical and neurological examinations were unremarkable.

Her complete blood count revealed slight anemia. Lactate dehydrogenase (LDH) was elevated, at 532 mU/ml (normal, 215–410). Alanine aminotransferase was normal at 12 mU/ml (normal, 4–30). Arterial blood gas analysis and tumor markers were normal.

A computed tomography (CT) scan of the chest revealed a well-defined giant mass occupying the right middle lobe which displayed heterogeneous enhancement using intravenous contrast materials (Fig. 2). We failed to collect a transbronchial biopsied specimen, because we could not guide a forceps to the tumor under X-ray fluoroscopy. An ultrasonically guided transthoracic needle biopsy was performed, and the biopsied specimen revealed a spindle cell tumor with large areas of coagulation necrosis. Numerous mitotic figures were seen. Immunohistochemically, the tumor cells were positive for vimentin, but negative for desmin, S-100 and CD34. A diagnosis of focal mesothelioma or synovial sarcoma was made. A general work-up of the patient was performed to search for a possible primary lesion, but none was found. As a primary pulmonary tumor was suspected clinically, a right middle and lower lobectomy with radical lymph node dissection was performed.

Pathological Findings

Grossly, the tumor measured 10 × 8 × 7 cm, and occupied the right middle lobe. It was well circumscribed, whitish-yellow in color and friable with hemorrhage. There was no calcification in the tumor. Histologically, the tumor showed a dense proliferation of spindle cells. In some areas, a herringbone-like pattern and large areas of coagulation necrosis were noted (Fig. 3). Numerous mitotic figures were seen. Immunohistochemically, the tumor cells were diffusely positive for vimentin (Fig. 4). Epithelial markers such as cytokeratin (KL-1) (Fig. 5) and EMA (Fig. 6) were focally positive in the tumor. As these features suggested a monophasic synovial sarcoma, we tried to look for the presence of *SYT–SSX* fusion gene transcripts.

RT–PCR findings

Total RNA was isolated from a 4 μm paraffin-embedded tissue section according to the Pinpoint Slide RNA Isolation

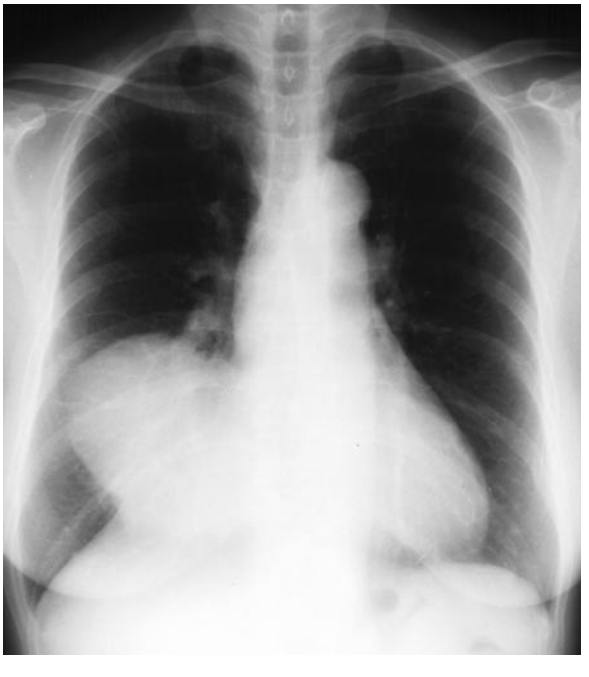

Figure 1. Chest radiograph on admission showing a giant mass in the right lower field.

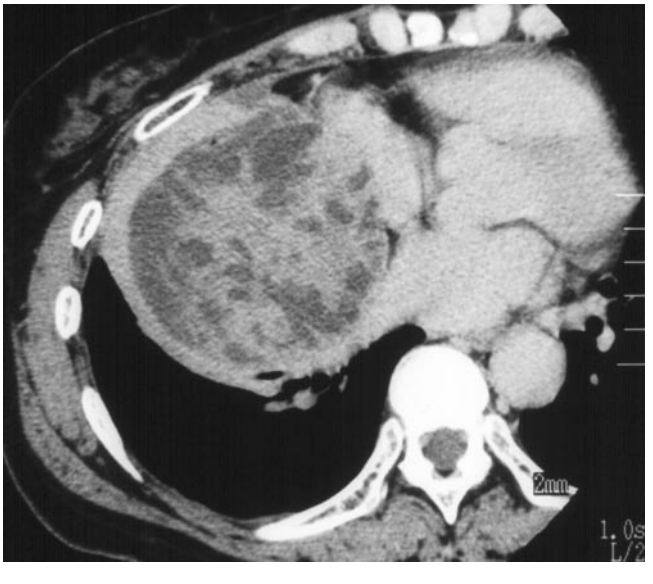

Figure 2. A CT scan of the chest revealing a well-defined giant mass occupying the right middle lobe, which displayed heterogeneous enhancement with intravenous contrast materials.

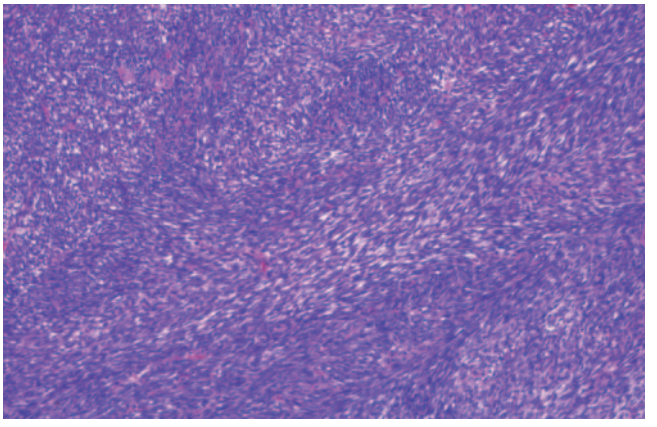

Figure 3. Microscopic findings showing a dense proliferation of spindle cells. In some areas, a herringbone-like pattern and large coagulation necroses were noted. Numerous mitotic figures were seen.

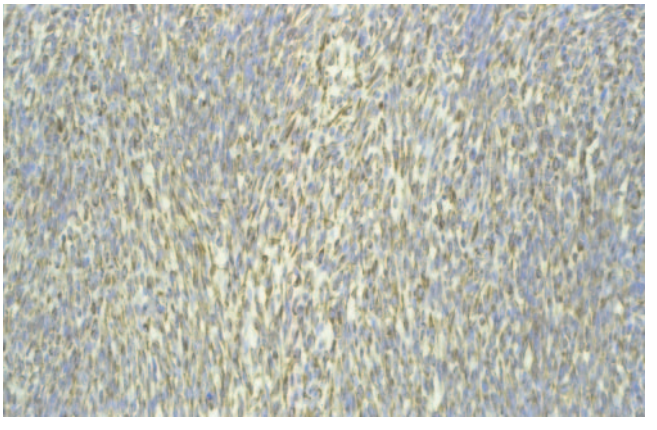

Figure 4. Immunohistochemically, the tumor cells were diffuse positive for vimentin.

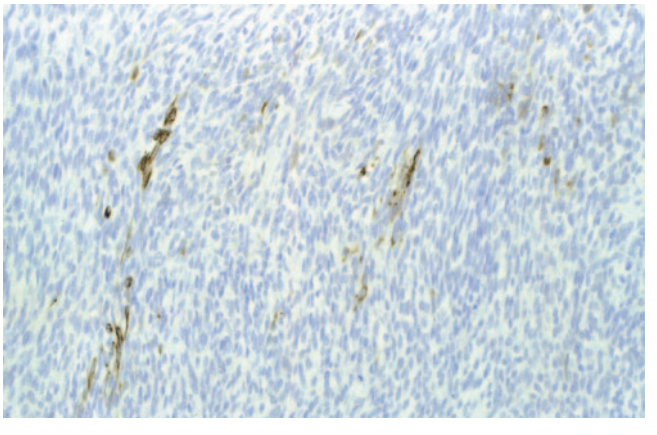

Figure 5. Epithelial markers such as cytokeratin (KL-1) were focal positive in the tumor.

System II protocol (Zymo Rearch, USA). The cDNA was synthesized with SuperScript II RNase Reverse Transcriptase (GIBCO BRL Life Technologies, USA) in the presence of random primers for 1 h at 42°C. The PCR product was amplified with both *SYT–SSX1* and *SYT–SSX2* fusion gene

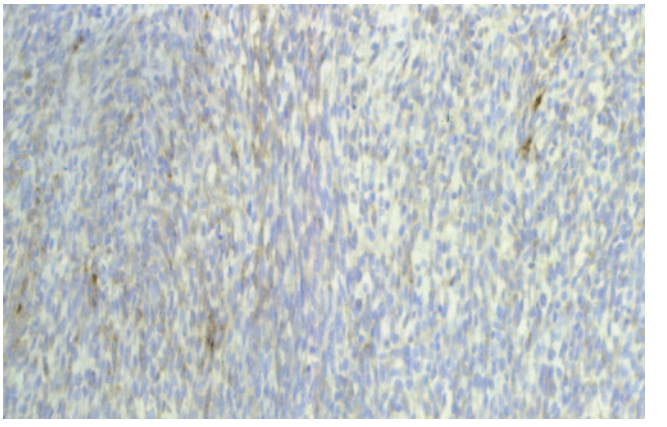

Figure 6. EMA were focal positive in the tumor.

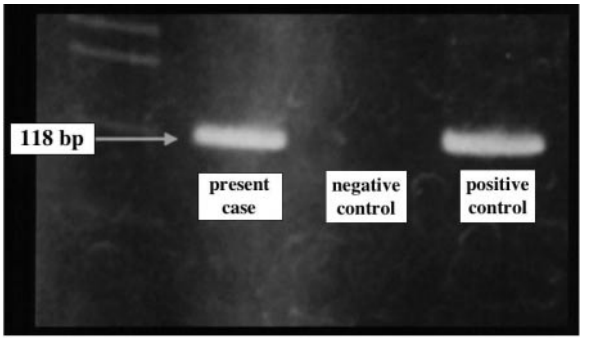

Figure 7. RT–PCR amplified a single 118 bp fragment characteristic of the *SYT–SSX1* fusion gene transcripts.

Table 1. Primer sequences of the oligonucleotides used in the study

SYT1	5′-AGA CCA ACA CAG CCT GGA CCA-3′
SYT2	5′-CAG CAG AGG CCT TAT GA-3′
SSX1	5′-GGT GCA GTT GTT TCC CAT CG-3′
SSX2	5′-TCT CGT GAA TCT TCT CAG AGG-3′

transcripts, using the following thermocycling conditions: an initial denaturation at 94°C for 5 min was followed by 35 step cycles of denaturation at 94°C for 30 s, annealing at 61°C for 30 s, and elongation at 72°C for 30 s, with a final extension at 72°C for 5 min. Semi-nested PCRs were performed with *SYT–SSX1* and *SYT–SSX2* fusion gene transcripts, using the same thermocycling conditions (18,19). The amplified products were electrophoresed on 8% polyacrylamide gels and visualized with ethidium bromide. Each product size was 118 bp for *SYT–SSX1* and 157 bp for *SYT–SSX2* fusion gene transcripts. As an internal control for PCR and for quality assessment of the tumor RNAs, a 247 bp portion of the ubiquitously expressed phosphoglycerate kinase transcript was amplified with primers 5′-CAT TTT GGA GCT CCT GGA AAG-3′ and 5′-TGC AAA TCC AGG GTG CAG TG-3′ (Table 1). RT–PCR amplified a single 118 bp fragment characteristic of the *SYT–SSX1* fusion gene transcripts (Fig. 7).

Table 2. Primary pulmonary synovial sarcoma with molecular confirmation showing characteristic translocation

Reference	Age	Sex	Race	Symptoms	Location	Maximum size (cm)	Histological subtype	Immunohistochemical findings		Cytogenetics	Prognosis
								Positive	Negative		
6	62	F	Black	Chest pain (myocardial infarction)	RUL	4	Monophasic	vim, EMA, ker	syn, chr, S-100, des, SMA	46, X, t(X;18)	20 months NED
7	12	F	NA	Cough, fever (pneumonia)	LLL	3.7	Monophasic	vim, EMA, S-100	ker, CD34, des, SMA	46, X, t(X;18)	9 months NED
8	44	F	Japanese	Cough, fever, weight loss	RML	NA	Monophasic	vim, ker, S-100, bcl-2	CD34, des, SMA, MSA	SYT–SSX2	6 months DOD
8	50	F	NA	Cough, backache	RUL	15.5	Monophasic	vim, EMA, ker, S-100, bcl-2	CD34, des, SMA, MSA	SYT–SSX1	4 years AWD
9	35	F	NA	Back pain, dyspnea, cough, hemosputum	RMLL	8	NA	ker, CD99	S-100	t(X;18)	NA
10	49	F	NA	Productive cough	LUL	5	Monophasic	EMA, ker, syn, NCAM, bcl-2	vim, S-100, chr	SYT–SSX1	1 year NED
11	29	F	NA	No symptoms	LULL	8	Poorly differentiated	vim, EMA, CD99, syn, NSE, NF	ker, CD34, chr, S-100, des, SMA, MSA, LCA	t(X;18)	11 months NED
12	72	M	white	No symptoms	LUL	2	Poorly differentiated	vim, NSE	EMA, ker, chr, des, CD99, HMB-45, LCA	t(X;18)	12 months NED
13	50	M	Japanese	No symptoms	RUL	5	Poorly differentiated, monophasic	vim, EMA, ker, bcl-2, CD34, cal	syn, chr, S-100, des, SMA, CD99, TTF-1, HMB45, LCA	SYT–SSX1	NA
14	45	F	NA	Chest pain	LLL	9	Monophasic	vim, EMA, ker, bcl-2, CD99, CD117	S-100, des, SMA, TTF-1	SYT–SSX2	6 months DOD
15	42	F	Japanese	Hemosputum	lt main bronchus	2.5	Monophasic	vim, EMA, ker, bcl-2	chr, S-100, CD34, SMA, NSE, CD117, TTF-1	SYT–SSX1	3 years AWD
Present case	58	F	Japanese	No symptoms	RML	10	Monophasic	vim, EMA, ker, S-100, des	CD34, SMA, p53	SYT–SSX1	10 months DOD

NA, not available; NED, no evidence of disease; DOD, died of disease; AWD, alive with disease; vim, vimentin; EMA, epithelial membrane antigen; ker, keratin; syn, synaptophysin; chr, chromogranin; des, desmin; SMA, smooth muscle actin; MSA, muscle-specific actin; NCAM, neural cell adhesion molecule; NSE, neuron-specific enolase; NF, neurofilament; cal, calretinin; LCA, leukocyte common antigen; TTF-1, thyroid transcription factor-1.

The final diagnosis was primary pulmonary synovial sarcoma of the monophasic fibrous type.

Clinical Outcome

The patient was discharged 19 days after the operation without any complications, but local relapse and metastasis to thoracic vertebrae occurred 3 months after resection. Because her paraplegia had not improved despite the irradiation to thoracic vertebrae and because hematochezia had occurred due to rectal ulcer without tumor, we discontinued the treatment with chemotherapy. She was discharged to a hospice facility, where she died 8 months after resection.

DISCUSSION

Primary pulmonary synovial sarcomas are very rare tumors, and their clinical course is largely unknown. Approximately 60 cases of synovial sarcomas of the lung have been reported in the English literature to date. A large series of monophasic synovial sarcomas of the lung have been confirmed by clinicopathological, immunohistochemical and ultrastructural studies but without molecular detection of *SYT–SSX* fusion gene transcripts. The tumor had an almost equal gender distribution and a mortality rate of 55% in 18 of the 25 patients who had follow-up from 1 to 20 years (17). Six of the 10 patients who died had metastatic disease, and four died of unrelated causes and had no evidence of disease at death. Four of the patients who were alive had either recurrence or metastasis between 1 and 7 years after diagnosis, and four were well without evidence of disease from 2 to 20 years after diagnosis. To the best of our knowledge, 11 cases of primary pulmonary synovial sarcoma have been reported to be confirmed by molecular detection of *SYT–SSX* fusion gene transcripts in the English language literature (Table 2) (6–15). The patients were relatively older than those with its soft tissue counterpart, ranged in age from 12 to 72 years (mean age, 46; median age, 47), and 83% were female, contrary to the previous report. Four patients including the present one had no symptoms and the tumor was found on a routine chest radiograph. Macroscopically, the tumors ranged from 2 to 15.5 cm in size (mean size, 6.6) with no predilection of tumor location. Okamoto et al. reported that pulmonary synovial sarcoma tended to occur in older patients and showed an aggressive behavior probably due to its anatomical location and a large tumor, often resulting in incomplete resection and high proliferative activity (16).

Synovial sarcoma is a morphologically distinct entity. Of the two histological types, the biphasic type is easily diagnosed based on the presence of both epithelial and spindle cell components. The monophasic type is difficult to diagnose, because it has a uniform spindle cell pattern and thus may be confused with other malignant spindle cell neoplasms, such as fibrosarcoma, hemangiopericytoma, leiomyosarcoma and spindle cell carcinoma or carcinosarcoma. Immunohistochemical studies have been extremely useful in the diagnosis of this tumor. In our review, eight cases were monophasic tumors and three cases were poorly differentiated tumors. Epithelial markers such as cytokeratin and/or EMA stained positive in most of the cases, but only one case with poorly differentiated tumor was negative for both epithelial markers. Four monophasic tumors (33%) including the present case were positive for S-100 protein. Okamoto et al. reported a potential pitfall of immunohistochemical evaluation, especially S-100 protein in the diagnosis of synovial sarcoma (16). Hummel et al. also pointed out a pitfall in the cytological diagnosis because of the positivity for neural and nerve sheath markers in poorly differentiated tumors (11). Coindre et al. reported a prospective study of 204 cases of possible synovial sarcoma to investigate the utility of molecular testing (22). They concluded that molecular testing was not required if the diagnosis of synovial sarcoma was certain or probable on the basis of clinical, histological and immunohistochemical evaluation. However, they also concluded that molecular testing proved to be very helpful or necessary when the diagnosis of synovial sarcoma was only possible or monophasic spindle cell synovial sarcoma was recognized in uncommon/unexpected sites, such as the lung, pleura, mediastinum and retroperitoneum. Therefore, we examined *SYT–SSX* fusion gene transcripts in the present case.

Molecular diagnosis has been successfully performed by RT–PCR analysis, using RNA extracted from frozen materials and archival paraffin-embedded specimens (18–21). The t(X;18) (p11.2;q11.2) translocation commonly found in synovial sarcomas results from fusion of the *SYT* gene on chromosome 18 to either of the two closely related genes, *SSX1* or *SSX2*, on chromosome X. The function of the fusion protein remains uncertain; the *SYT* protein appears to function as a transcriptional activator, whereas the *SSX* protein appears to function as a transcriptional co-repressor. It is not known if one or both functions persist in the fusion protein. In our review, *SYT–SSX1* fusion gene transcripts were detected in five cases, and *SYT–SSX2* fusion gene transcripts were detected in two cases, but unfortunately we did not confirm the type of *SYT–SSX* fusion gene transcripts in the other five cases. This gene expression pattern is of interest not only in diagnosing synovial sarcoma, but also in predicting the prognosis. Soft tissue synovial sarcomas that express the *SYT–SSX1* fusion protein (irrespective of the histological type) have a poorer prognosis than those expressing the *SYT–SSX2* fusion protein, with respective 5-year progression-free survival rates of 42 versus 89% (23,24). However, only one of five patients with *SYT–SSX1* fusion gene transcripts (the present case) and both patients with *SYT–SSX2* fusion gene transcripts died of the disease in the follow-up period in our review. In other series of pulmonary synovial sarcomas, the association between the type of *SYT–SSX* fusion gene transcripts and clinical outcomes have been discussed. Further studies are needed to determine whether the *SYT–SSX2* fusion protein expression correlates with poorer prognosis in primary pulmonary synovial sarcomas, in contrast to the association between the *SYT–SSX1* fusion protein expression and poorer prognosis in soft tissue synovial sarcomas.

References

1. Etienne-Mastroianni B, Falchero L, Chalabreysse L, Loire R, Ranchere D, Souquet PJ, et al. Primary sarcomas of the lung: a clinicopathologic study of 12 cases. *Lung Cancer* 2002;38:283–9.
2. Travis WD, Travis LB, Devesa SS. Lung cancer. *Cancer* 1995;75:191–202.
3. Cadman NL, Soule EH, Kelly PJ. Synovial sarcoma: an analysis of 134 tumors. *Cancer* 1965;18:613–27.
4. Enzinger FM, Weiss SW. Soft Tissue Tumors, 3rd edn. Mosby Year Book, Inc., St Louis;1995:757–86.
5. Weiss SW. Histological Typing of Soft Tissue Tumors. International Histological Classification of Tumors, 2nd edn. World Health Organization, Berlin;1994.
6. Roberts CA, Seemayer TA, Neff JR, Alonso A, Nelson M, Bridge JA. Translocation (X; 18) in primary synovial sarcoma of the lung. *Cancer Genet Cytogenet* 1996;88:49–52.
7. Kaplan MA, Goodman MD, Satish J, Bhagavan BS, Travis WD. Primary pulmonary sarcoma with morphologic features of monophasic synovial sarcoma and chromosome translocation t(X; 18). *Am J Clin Pathol* 1996;105:195–9.
8. Hisaoka M, Hashimoto H, Iwamasa T, Ishikawa K, Aoki T. Primary synovial sarcoma of the lung: report of two cases confirmed by molecular detection of *SYT–SSX* fusion gene transcripts. *Histopathology* 1999;34:205–10.
9. Sekeres M, Vasconcelles MJ, McMenamin M, Rosenfeld-Darling M, Bueno R. Two patients with sarcoma. Case 1. Synovial cell sarcoma of the lung. *J Clin Oncol* 2000;18:2341–2.
10. Terasaki H, Niki T, Hasegawa T, Yamada T, Suzuki K, Kusumoto M, et al. Primary synovial sarcoma of the lung: a case report confirmed by molecular detection of *SYT–SSX* fusion gene transcripts. *Jpn J Clin Oncol* 2001;31:212–6.
11. Hummel P, Yang GC, Kumar A, Cohen JM, Winkler B, Melamed J, et al. PNET-like features of synovial sarcoma of the lung: a pitfall in the cytologic diagnosis of soft-tissue tumors. *Diagn Cytopathol* 2001;24:283–8.
12. Fadare O, Ciesielski T. Pathologic quiz case: a pulmonary mass. *Arch Pathol Lab Med* 2003;127:e160–2.
13. Mikami Y, Nakajima M, Hashimoto H, Kuwabara K, Sasao Y, Manabe T. Primary poorly differentiated monophasic synovial sarcoma of the lung. A case report with immunohistochemical and genetic studies. *Pathol Res Pract* 2003;199:827–33.
14. Boroumand N, Raja V, Jones DV, Haque AK. *SYT–SSX2* variant of primary pulmonary synovial sarcoma with focal expression of CD117 (c-Kit) protein and a poor clinical outcome. *Arch Pathol Lab Med* 2003;127:201–4.
15. Niwa H, Masuda S, Kobayashi C, Oda Y. Pulmonary synovial sarcoma with polypoid endobronchial growth: a case report, immunohistochemical and cytogenetic study. *Pathol Int* 2004;54:611–5.
16. Okamoto S, Hisaoka M, Daa T, Hatakeyama K, Iwamasa T, Hashimoto H. Primary pulmonary synovial sarcoma: a clinicopathologic, immunohistochemical, and molecular study of 11 cases. *Hum Pathol* 2004;35:850–6.
17. Zeren H, Moran CA, Suster S, Fishback NF, Koss MN. Primary pulmonary sarcoma with features of monophasic synovial sarcoma: a clinicopathological, immunohistochemical, and ultrastructural study of 25 cases. *Hum Pathol* 1995:26:474–80.
18. Guillou L, Coindre JM, Gallagher G, Terrier P, Gebhard S, de Saint Aubain Somerhausen N, et al. Detection of the synovial sarcoma translocation t(X;18) (SYT;SSX) in paraffin-embedded tissues using reverse transcriptase–polymerase chain reaction: a reliable and powerful diagnostic tool for pathologists. A molecular analysis of 221 mesenchymal tumors fixed in different fixatives. *Hum Pathol* 2001;32:105–12.
19. Yang K, Lui WO, Xie Y, Zhang A, Skytting B, Mandahl N, et al. Co-existence of *SYT–SSX1* and *SYT–SSX2* fusions in synovial sarcomas. *Oncogene* 2002;21:4181–90.
20. Tsuji S, Hisaoka M, Morimitsu Y, Hashimoto H, Shimajiri S, Komiya S, et al. Detection of *SYT–SSX* fusion transcripts in synovial sarcoma by reverse transcription–polymerase chain reaction using archival paraffin-embedded tissues. *Am J Pathol* 1998;153:1807–12.
21. Hill DA, Riedley SE, Patel AR, Shurtleff SA, Hyer J, Cain AM, et al. Real-time polymerase chain reaction as an aid for the detection of *SYT–SSX1* and *SYT–SSX2* transcripts in fresh and archival pediatric synovial sarcoma specimens: report of 25 cases from St. Jude Children's Research Hospital. *Pediatr Dev Pathol* 2002;6:24–34.
22. Coindre JM, Pelmus M, Hostein I, Lussan C, Bui BN, Guillou L. Should molecular testing be required for diagnosing synovial sarcoma? A prospective study of 204 cases. *Cancer* 2003;98:2700–7.
23. Kawai A, Woodruff J, Healey JH, Brennan MF, Antonescu CR, Ladanyi M. *SYT–SSX* gene fusion as a determinant of morphology and prognosis in synovial sarcoma. *N Engl J Med* 1998;338:153–60.
24. Nilsson G, Skytting B, Xie Y, Brodin B, Perfect R, Mandahl N, et al. The *SYT–SSX1* variant of synovial sarcoma is associated with a high rate of tumor cell proliferation and poor clinical outcome. *Cancer Res* 1999;59:3180–4.