

Primary Mediastinal Synovial Sarcoma

We report a rare case of a primary mediastinal synovial sarcoma. A 44-year-old man had a well-defined tumor in the left posterior mediastinum involving the left lower lobe of the lung, as detected on chest computed tomography, and underwent an *en bloc* excision and a left lower lobectomy. Grossly, the tumor measured 8.0 cm in the greatest diameter, with a solid and tan-white cut surface. Histologically, the tumor was mainly composed of spindle-shaped cells with a few foci of epithelial differentiation. Immunohistochemical studies were focally positive for cytokeratin, and diffusely positive for vimentin and bcl-2. Epithelial membrane antigen, S-100 protein, desmin, smooth muscle actin, calretinin, and CD34 were all negative. The SYT-SSX1 gene fusion transcript was detected by a reverse transcription- polymerase chain reaction, which was diagnostic of primary synovial sarcoma of the mediastinum. We also reviewed the literature with regard to the clinicopathologic, immunohistochemical, and molecular studies of primary intrathoracic synovial sarcoma. (**J Lung Cancer 2008;7(1):29–33**)

Key Words: Synovial sarcoma, Mediastinum

Hyun Ju Lee, M.D.¹
Jin-Haeng Chung, M.D.¹
Joon Sung Joh, M.D.²
Jae-Ho Lee, M.D.²
Tae Jeong Kim, M.D.³
Sanghoon Jheon, M.D.⁴
Soo-Mee Bang, M.D.² and
Jae-Sung Kim, M.D.⁵

Departments of ¹Pathology, ²Internal Medicine, ³Radiology, ⁴Thoracic Surgery and ⁵Radiation Oncology, Seoul National University Bundang Hospital, Seongnam, Korea

Received: May 14, 2008
Accepted: May 28, 2008

Address for correspondence

Jin-Haeng Chung, M.D.
Department of Pathology, Seoul National University Bundang Hospital, 300, Gumi-dong, Bundang-gu, Seongnam 463-707, Korea.
Tel: 82-31-787-7713
Fax: 82-31-787-4012
E-mail: chungjh@snu.ac.kr

Synovial sarcomas (SSs) are aggressive neoplasms accounting for up to 14% of soft tissue sarcomas. The majority of SSs develop in the vicinity of the large joints of the extremities, especially around the knee and thigh. These tumors rarely occur in the mediastinum(1). The histologic hallmark of SSs is the biphasic morphology of the tumor cells. SSs are divided into biphasic, monophasic fibrous, and poorly differentiated subtypes according to conventional morphologic criteria, as defined by Weiss and Goldblum(2). Classic biphasic SSs are usually easy to recognize by light microscopy, whereas the monophasic spindle cell and the poorly differentiated forms are still a challenge in the differential diagnosis of spindle and small round cell neoplasms. Intrathoracic SSs may cause diagnostic challenges because of its unusual location and predominant monophasic fibrous histologic appearance. In this unusual location, the detection of SYT-SSX fusion transcripts is a valuable diagnostic adjunct. Herein, we describe a rare case of

a primary mediastinal SS with SYT-SSX fusion transcripts, and review the relevant literature.

CASE REPORT

A 44-year-old man presented with a cough, dyspnea, and chest pain, which had been present for 6 months. His medical history was non-contributory. Computed tomography (CT) images showed a lobulated soft tissue mass in the left posterior mediastinum. The mass was bulky, 12×10 cm in size, and mainly located in the posterior mediastinum involving the left lower lobe of the lung (Fig. 1). Meticulous examination ruled out the possibility of metastasis from contralateral side. CT-guided gun biopsy was done for pathologic diagnosis. The biopsy specimen showed neoplastic spindle-shaped cells of uniform appearance with small amounts of indistinct cytoplasm and oval dark-staining nuclei. The tumor cells were indis-

tinguishable from those of a fibrosarcoma. However, a transition between a pale-staining, vaguely epithelioid area and dark-staining spindle cell elements was suspected. Immunohistochemical staining, including cytokeratin, epithelial membrane antigen (EMA), vimentin, bcl-2, and β -catenin was done. The tumor cells were strongly positive for vimentin, bcl-2, and β -catenin, and focally positive for cytokeratin in the pale-staining, vaguely epithelioid area. Pathologic diagnosis of "spindle cell neoplasm with vimentin, bcl-2, and β -catenin expression, most likely synovial sarcoma" was made based on histologic and immunohistochemical findings. At that time, the result of a reverse transcription-polymerase chain reaction (RT-PCR) for the SYT-SSX1 fusion transcript was negative. After showing a partial response to six cycles of neoadjuvant chemotherapy

(adriamycin/dacarbazine), *en bloc* excision, and left lower lobectomy of the lung was performed. Grossly, the tumor was relatively well-circumscribed, 8.0×6.0×5.5 cm in size, and showed expansile growth to the lung. The tumor was round-to-oval, a more or less lobulated mass, and the cut surface was fleshy, light yellow to gray-white in appearance with focal hemorrhage (Fig. 2). Histologically, the tumor consisted of a solid proliferation of spindle cells with small, indistinct nucleoli (Fig. 3A). Focal areas of transition between epithelial and dark-staining spindle cells were identified (Fig. 3B). Mitotic counts were >20 per 10 high-power fields. Focal necrosis, hemorrhage, hyalinization, and myxoid change were present; neither calcification nor osseous metaplasia was identified. On the immunohistochemical staining, tumor cells showed focal



Fig. 1. Computed tomography (CT) images showed a soft tissue mass in the left posterior mediastinum.

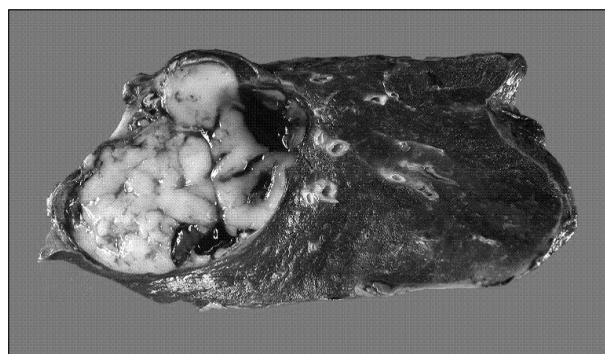


Fig. 2. Gross photograph of the resected synovial sarcoma. The mass was relatively well-demarcated and showed expansile growth to the lung.

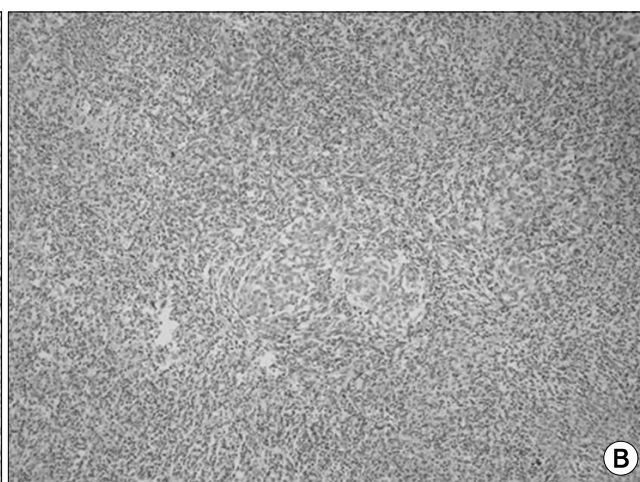
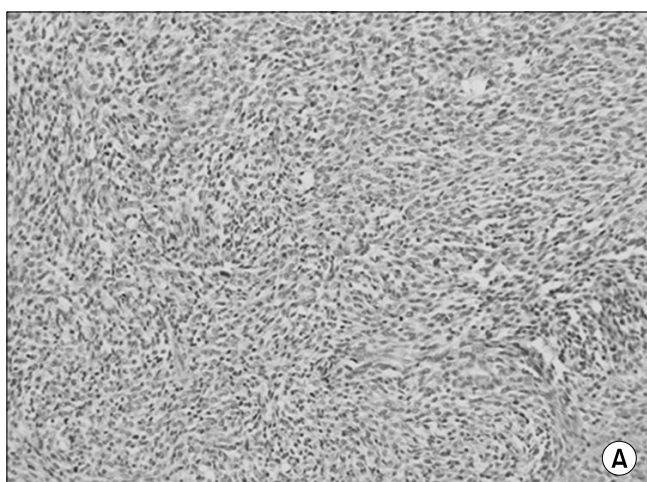


Fig. 3. Histologic features of synovial sarcoma; most areas consisted of monophasic fibrous type (x200) (A), A transition between pale staining epithelial and dark staining spindle cells is identified (x100) (B).

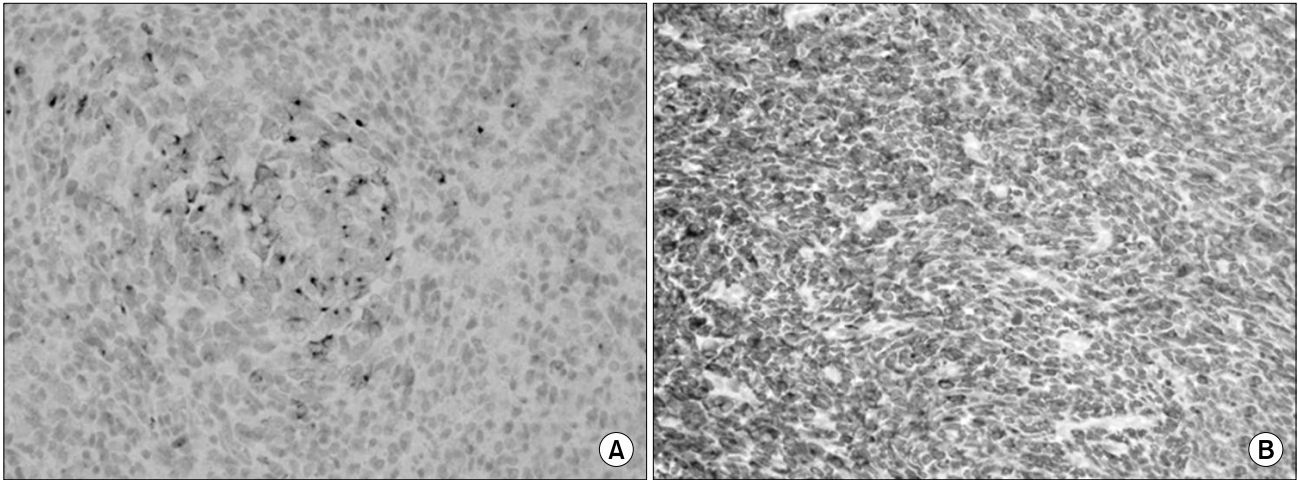


Fig. 4. Immunohistochemical findings; focal positivity for cytokeratin in the vaguely epithelial area (x400) (A), and diffuse positivity for bcl-2 (x400) (B).

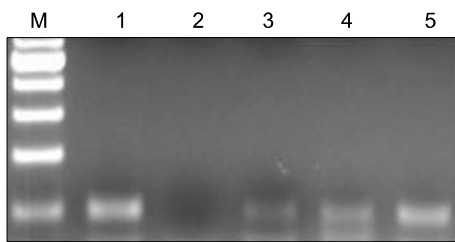


Fig. 5. The result of RT-PCR for the SYT-SSX1 fusion transcript in the resected tumor cells was positive. Sample 1: PC (positive control), 2: NC (negative control), 3, 4, 5: this case.

positivity for cytokeratin in the vaguely epithelioid area (Fig. 4A), and diffuse positivity for vimentin, β -catenin, and bcl-2 (Fig. 4B). Tumor cells were negative for epithelial membrane antigen (EMA), S-100 protein, desmin, smooth muscle actin (SMA), CD31, CD34, calretinin, TTF-1, and chromogranin. The result of RT-PCR for the SYT-SSX1 fusion transcript using a resected sample was positive (Fig. 5). Our final pathologic diagnosis was primary mediastinal SS of the monophasic fibrous type. The patient received adjuvant postoperative radiotherapy (59.4 Gy in 33 fractions) due to the intraoperative finding of adjacent organ invasion (aorta, esophagus, and pericardium) by the primary mass. Three months after finishing radiotherapy, multiple metastatic nodules were found in both lungs on follow-up CT. Then, he underwent six cycles of salvage chemotherapy, followed by metastasectomy twice. He is currently stable receiving salvage chemotherapy.

DISCUSSION

Primary mediastinal SSs are rare, reported in the literature either as single observations or small series(1,3-9). According to the recent paper of Keel et al.(4), malignant fibrous histiocytomas and SSs might be the most frequent primary sarcomas of the lung. There is growing evidence based on immunohistochemical and molecular approaches, including detection of tumor-specific fusion genes, that SSs may develop as a primary tumor, not only in the lung, but also in the pleura and the mediastinum(1,3-7). The lung is the most frequently involved site in intrathoracic SS, followed by the pleura and mediastinum. Such patients are significantly older (median age, 47 years) than those presenting with a soft tissue (non-intrathoracic) SS (median age, 34.5 years)(10). Intrathoracic SSs are almost exclusively monophasic, with a large proportion of poorly differentiated features and a high histologic grade. The diagnosis of intrathoracic SSs often requires molecular analysis(8). In >90% of cases of SS, the classic translocation, t(X;18)(p11;q11), can be identified(3-7). This involves the SYT gene on chromosome 18q11 and 2 genes, SSX1 and SSX2, on Xp11.2. The SSX1 and SSX2 genes are closely related. Guillou et al.(8) reported that the presence of SYT-SSX chimeric RNA transcripts within a tumor, as detected by RT-PCR, is considered the gold standard (in combination with morphology and immunohistochemistry) for a positive diagnosis of SS. Begueret et al.(9) documented a series of primary intrathoracic SSs in which the location initially obscured the diagnosis and led to

confusion, but was finally confirmed as t(X;18)-positive.

In our case, it was very difficult to diagnose SS in the small gun biopsy specimen with negative RT-PCR results for the SYT-SSX1 translocation. The RT-PCR results could be negative on a small biopsy specimen. The biopsy specimen was composed mainly of spindle cells of the monophasic fibrous type. Generally, pathologists can not identify spindle cell sarcomas based on histologic features alone. It is important that this should be distinguished from other spindle cell neoplasms, such as leiomyosarcomas, malignant peripheral nerve sheath tumors, fibrosarcomas, mesotheliomas, sarcomatoid carcinomas, and solitary fibrous tumors of the pleura.

Under these circumstances, immunohistochemical findings are of great help in diagnosing SSs. According to the recent paper of Okamoto et al.(5), nearly all SSs showed high rates of staining for the epithelial markers, AE1/AE3 (67%), CAM5.2 (72%), and EMA (72%), and all of the cases had focal areas with tumor cells positively immunoreactive to at least one epithelial marker. Such expression of epithelial markers is characteristic of SSs and is very useful in the differential diagnosis. Immunoreactivity for bcl-2 protein can be particularly helpful in separating SSs from other possibilities in the differential diagnosis, including leiomyosarcomas, malignant peripheral nerve sheath tumors, and fibrosarcomas(11,12). Hirakawa et al.(11) examined 19 cases of SS and 29 additional soft tissue spindle cell sarcomas and identified bcl-2 protein positivity in 79% of the SSs and negative immunohistochemical staining for bcl-2 protein in all leiomyosarcomas, malignant peripheral nerve sheath tumors, and fibrosarcomas examined. They further suggested that bcl-2 positivity might be linked to the classic chromosomal translocation associated with SSs, as they both involve chromosome 18. Although it was already known that bcl-2 protein expression is also non-specific, its positive reaction may support the diagnosis of SS. Recently, Saito et al.(13) reported that aberrant expression of β -catenin was also observed in most of the SS cases and could contribute to the progression of SS and correlates with poor survival.

In conclusion, we have described a case of primary mediastinal SS, of the monophasic fibrous type, which disguised itself, thereby causing a diagnostic challenge in the gun biopsy specimen. Immunohistochemical findings of a positive reaction with bcl-2 and epithelial markers and RT-PCR for SYT-SSX chimeric RNA transcripts would be of great help for the

diagnosis of SS. Primary SS should be considered in the differential diagnosis of spindle cell neoplasms of the thoracic cavity. Finally, in considering a diagnosis of primary mediastinal SS, metastases from tumors of origin in the extremities should be ruled out. Synovial sarcomas may metastasize to the lung, and a complete medical examination should be performed to exclude this possibility.

REFERENCES

1. Witkin GB, Miettinen M, Rosai J. A biphasic tumor of the mediastinum with feature of synovial sarcoma: a report of four cases. *Am J Surg Pathol* 1989;13:490-499.
2. Weiss SW, Goldblum JR. *Enzinger and Weiss's Soft Tissue Tumors*. 4th ed. St Louis, MO: Mosby, 2001:1487-1503.
3. Essary LR, Vargas SO, Fletcher CD. Primary pleuropulmonary synovial sarcoma: reappraisal of a recently described anatomic subset. *Cancer* 2002;94:459-469.
4. Keel SB, Bacha E, Mark EJ, Nielsen GP, Rosenberg AE. Primary pulmonary sarcoma: a clinicopathologic study of 26 cases. *Mod Pathol* 1999;12:1124-1131.
5. 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;35:850-856.
6. Zeren H, Moran CA, Suster S, Fishback NF, Koss MN. Primary pulmonary sarcomas with features of monophasic synovial sarcoma: a clinicopathological, immunohistochemical, and ultrastructural study of 25 cases. *Hum Pathol* 1995;26:474-480.
7. 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;34:205-210.
8. Guillou L, Coindre JM, Gallagher G, et al. Detection of the synovial sarcoma translocation t(X;18)(SYT;SXX) in paraffin-embedded tissues using reverse transcriptase-polymerase chain reaction: a reliable and powerful diagnostic tool for the pathologists. A molecular analysis of 221 mesenchymal tumors fixed in different fixatives. *Hum Pathol* 2001;32:105-112.
9. Begueret H, Galateau-Salle F, Guillou L, et al. Primary intrathoracic synovial sarcoma: a clinicopathologic study of 40 t(X;18)-positive cases from the French Sarcoma Group and the Mesopath group. *Am J Surg Pathol* 2005;29:339-346.
10. Guillou L, Benhattar J, Bonichon F, et al. Histologic grade, but not SYT-SSX fusion type, is an important prognostic factor in patients with synovial sarcoma: a multicenter, retrospective analysis. *J Clin Oncol* 2004;22:4040-4050.
11. Hirakawa N, Naka T, Yamamoto I, Fukuda T, Tsuneyoshi M. Overexpression of bcl-2 protein in synovial sarcoma: a comparative study of other soft tissue spindle cell sarcomas and an additional analysis by fluorescence in situ hybridization.

- zation. Hum Pathol 1996;27:1060-1065.
12. Suster S, Fisher C, Moran CA. Expression of bcl-2 oncoprotein in benign and malignant spindle cell tumors of soft tissue, skin, serosal surface, and gastrointestinal tract. Am J Surg Pathol 1998;22:863-872.
 13. Saito T, Oda Y, Sakamoto A, et al. Prognostic value of the preserved expression of the E-cadherin and catenin families of adhesion molecules and of beta-catenin mutations in synovial sarcoma. J Pathol 2000;192:342-350.
-