Synovial sarcoma of the pleura: A clinical and pathologic study of three cases

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Synovial sarcomas are rare soft tissue malignancies that most commonly affect the extremities in the vicinity of large joints. These malignancies typically occur in adolescents and young adults between the ages of 15 and 40 years.^{1,2} Historically they are believed to originate from primitive pluripotent mesenchyme capable of synovial differentiation. This belief is consistent with the malignancy's origin from sites devoid of normal synovium, such as the pleural cavity. A variety of pleural cavity sarcomas have been described, including liposarcoma,³ chondrosarcoma,⁴ osteosarcoma,⁵ and malignant schwannoma.⁶ Pleural synovial sarcoma, however, is a much rarer entity. In fact, pleural synovial sarcoma was first described only 6 years ago⁷ and has not yet been reported in the surgical literature.

Because of its rarity, pleural synovial sarcoma is often mistaken for the histologically similar malignant mesothelioma, the most common of the pleural neoplasms. This is a critical distinction, because synovial sarcoma may be extremely aggressive. Studies in the last 10 years have shown it to be extremely sensitive to ifosfamide-based chemotherapy, and survival of patients with synovial sarcoma has recently increased with chemotherapy, with 5-year survivals now as high as 57%.⁸⁻¹⁰

In this report, we describe 3 cases of synovial sarcoma of the pleura. Clinical findings are correlated with pathologic features, including immunohistochemical stains and fluorescence in situ hybridization (FISH) for the identification of the diagnostic chromosomal translocation, t(X;18)(p11.2;q11.2). This delineation of the clinical and pathologic aspects of this rare, newly recognized tumor should increase awareness among the surgical community.

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Received for publication Jan 29, 2002; accepted for publication Feb 16, 2002.

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J Thorac Cardiovasc Surg 2002;124:828-32

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0022-5223/2002 \$35.00+0 12/54/124242

doi:10.1067/mtc.2002.124242

Methods

Patients and specimens. Institutional review board approval was obtained for our study. To identify potential cases of monophasic or biphasic synovial sarcoma of the pleura, we searched the primary and consultation files of the department of pathology at Fairview-University Medical Center in Minneapolis. All pertinent clinical, radiologic, and pathologic data, including hematoxylin and eosin-stained slides, were reviewed in all cases.

Immunohistochemical methods. For identified cases of synovial sarcoma, we performed immunohistochemical studies on representative tissue from paraffin sections. We used the avidin-biotin complex method and commercially available antibodies as follows: pankeratin (monoclonal MNF-116, at a dilution of 1:50; DAKO Corporation, Carpinteria, Calif), S100 protein (polyclonal, at a dilution of 1:600; DAKO); and epithelial membrane antigen (monoclonal E29, at a dilution of 1:10; DAKO). Negative and positive control preparations were stained in parallel.

Fluorescence in situ hybridization. For identified cases of synovial sarcoma, we performed FISH analysis on interphase nuclei isolated from formalin-fixed, paraffin-embedded tissue. Nuclei were extracted from paraffin-embedded 50- μ m tissue sections as described by Kuchinka and colleagues.¹¹ In brief, the sections were deparaffinized in xylene twice for 5 minutes each time and in ethanol twice for 5 minutes each time. Digestion was performed with collagenase XI (Sigma Chemical Co, St Louis, Mo) for 2 hours, followed by 0.05% trypsin and ethylenediaminetetraacetic acid (Life Technologies, Inc, Rockville, Md) for 30

TABLE 1. Clinical and pathological findings

Patient (age, sex)	Histology	Pankeratin	EMA	S100	t(X;18) by FISH	Status and length of follow-up
1, (39 y, M)	Monophasic	Positive	Positive	Negative	Negative	Dead, 8 y
2, (23 y, F)	Monophasic	Positive	Positive	Negative	Positive	Dead, 4 y
3, (33 y, M)	Biphasic	Positive	Positive	Negative	Indeterminate	Alive, 5 y

minutes at 37°C. The cells were spread on positively charged slides, baked for 2 hours at 50°C, and treated with 30% sodium bisulfite pretreatment solution (Oncor, Gaithersburg, Md) for 10 minutes, followed by digestion in 250-μg/mL proteinase K (Oncor) for 10 to 15 minutes at 45°C.

For the detection of t(X;18), we used FISH probes for the chromosome X pericentromeric region and for a region within 1 megabase telomeric to the *SYT* locus on chromosome 18. The chromosome X probe was obtained commercially from Vysis (CEPX; Vysis Inc, Downers Grove, Ill) and was composed of α satellite DNA sequences from the pericentromeric region directly labeled with Spectrum Orange. The chromosome 18 probe was CEPH YAC clone 770c4 (Research Genetics, Huntsville, Ala) that was biotinylated by random octamer priming. Probes and extracted nuclei were denatured simultaneously on a HYBrite slide warmer (Vysis), followed by hybridization at 37°C and stringency washing in 50% formamide and 2× SSC* for 15 minutes and 2× SSC for 8 minutes at 42°C. Detection of the biotinylated probe was with fluorescein isothiocyanate-conjugated avidin (Oncor).

At least 30 cells with strong, discrete FISH signals were analyzed per case. A structural rearrangement between chromosomes X and 18 was defined as colocalization of the YAC770c4 (fluorescein isothiocyanate conjugate) and CEPX (spectrum orange) signals no further than a probe signal diameter away from each other in most cells analyzed.

Results

Clinical data. Clinical data are summarized briefly in Table 1.

PATIENT 1. This patient was a 39-year-old man who was seen with progressive dyspnea and a pleurally based mass thought to be clinically consistent with diffuse malignant mesothelioma (Figure 1). Thoracoscopic biopsy was interpreted as malignant mesothelioma, sarcomatous type. The patient subsequently underwent an uncomplicated left extrapleural pneumonectomy. At the time of surgery, the pleural tumor was noted to peel off the chest wall surface with ease, as opposed to the usual tenacious adherence that sarcomatous mesotheliomas exhibit. After the operation, the patient received full hemithoracic and mediastinal irradiation.

Four years later, the patient noted a rapidly enlarging left lumbar paraspinal muscle mass. Computed tomography (CT) revealed a mass within the left paraspinal muscle, contiguous with nearby ribs but without involvement of the vertebral body or transverse process. After negative results of bone scan, the mass (along with associated muscle, skin, and ribs) was resected. The final pathologic diagnosis of the mass was read as synovial cell sarcoma, prompting review of the original pleural tumor. After this review, it was determined in retrospect that the patient indeed had

a pleural synovial cell sarcoma and that the muscle mass represented metastatic disease.

One year after resection of the muscle mass (5 years after the extrapleural pneumonectomy), routine chest CT revealed 30 new discrete nodules in the remaining right lung and thickened soft tissue projecting from the chest wall into the left thoracic cavity. CT-guided biopsy of a right middle lobe nodule was performed, revealing pathologic findings identical to those of the primary tumor. Treatment with doxorubicin chemotherapy led to dramatic reduction in the number of pulmonary nodules, from 30 to 6. However, a colopleural fistula to the left pleural space (pneumonectomy side) developed. Despite successful surgical repair, the patient died of the debilitating effects of chemotherapy and surgery.

PATIENT 2. This patient was a previously healthy 23-year-old woman whose initial evaluation was for a symptomatic left chest wall lesion. After biopsy, she underwent surgical resection of this chest wall mass (3 × 9 cm); the pathologic findings were consistent with synovial sarcoma. Two years after this resection, dyspnea and a left pleural effusion developed. Evaluation identified a left pleural mass, which was then widely resected through a left thoracotomy. Pathologic analysis of this specimen identified this tumor as mesothelioma (not synovial sarcoma). After the operation, the patient received a course of doxorubicin (Adriamycin) adjuvant chemotherapy. She also received tumor cell immunotherapy (rejection with neuraminidase-treated primary tumor cells after bacille Calmette-Guérin vaccination). One year later, she underwent her second thoracotomy because of a left pleural recurrence. The tumor was resected, and the pathologic findings were consistent with synovial sarcoma. Her next chemotherapy regimen included dacarbazine, vincristine, and cyclophosphamide. One year later, she returned with a third recurrence. This was locally advanced disease involving the diaphragm and the left lobe of the liver. Because this disease was unresectable, the patient underwent multiple rounds of chemotherapy. She died 4 years after her initial evaluation.

PATIENT 3. This patient was a previously healthy 33-year-old man with right-sided pleuritic pain after an upper respiratory infection. A chest radiograph demonstrated irregularities at the surface of the right hemidiaphragm. Chest CT demonstrated a large, complex, 10-cm mass in the right infrahilar region, extending inferiorly to the level of the diaphragm. Right thoracotomy with en bloc resection of the pleurally based mass and reconstruction of the right hemidiaphragm with Marlex mesh (Phillips Petroleum Company, Bartlesville, Okla) were performed. The patient had an uneventful postoperative course and received no adjuvant therapy. Currently, he is alive and doing well, without evidence of recurrent disease at 5 years.

Pathologic data

* Saline sodium citrate.

Figure 1. Pleural monophasic synovial sarcoma. Selected sections of conventional CT scan of chest from patient 1 showing large peripheral homogeneous soft tissue mass growing within pleural cavity.

Figure 2. Synovial sarcoma, monophasic type. Hematoxylin and eosin–stained section from patient 1 depicting monophasic synovial sarcoma (original magnification $\times 40$). Tumor cells are plump, spindle-shaped, and arranged in short fascicles, typical of classic monophasic variant.

GROSS EXAMINATION. In case 1, an extrapleural pneumonectomy showed a multifocal tumor between the visceral and parietal pleura. The largest nodule, near the diaphragm, measured 16 cm in greatest dimension. In case 2, the tumor resection was piecemeal, precluding precise measurement. In case 3, the gross specimen consisted of a 16-cm multilobular, solid, pale tan tumor densely adherent to the diaphragm.

HISTOLOGIC EXAMINATION. In both patients 1 and 2, the tumors had a monophasic histologic appearance. In patient 1, the tumor cells were plump, spindle-shaped, and arranged in short fascicles, typical of the classic monophasic variant (Figure 2). In patient 2, the tumor cells were round, with a high nucleus-to-cytoplasm ratio, and the fascicular architecture was not prominent (Figure 3); thus the tumor would be classified as a poorly differentiated variant.¹² In patient 3, the tumor was biphasic, with glandular epithelium interspersed among the spindle-shaped cells (Figure 4).

IMMUNOHISTOCHEMICAL ANALYSIS. In patients 1 and 3, pankeratin and epithelial membrane antigen showed diffuse immunoreactivity. In patient 2, there was rare focal immunoreactivity. S100 staining was negative in all cases.

FLUORESCENCE IN SITU HYBRIDIZATION. In patient 1, the tumor was negative for t(X;18). In patient 2, it was positive (Figure 5). The probes did not hybridize in patient 3, precluding FISH analysis.

Discussion

Synovial sarcoma involving the pleura was initially recognized only 6 years ago.⁷ More cases will no doubt be diagnosed in the future, thanks to increasing awareness of this entity and increasing application of adjunctive diagnostic tools. Clearly, surgeons must be able to recognize pleural synovial sarcoma. The 3 cases reported here represent the first series of pleural synovial sarcomas reported in the surgical literature.

Because of the rarity of pleural synovial sarcoma and its similarity (clinical and histologic) to other pleural neoplasms, particularly sarcomatous mesothelioma, diagnosis is often difficult. In the series of 5 primary pleural synovial sarcomas reported by Gaertner and associates,⁷ the original diagnoses were malignant mesothelioma, fibrosarcoma, and pulmonary blastoma. In our series, cases 1 and 2 were diagnosed at one point as malignant mesothelioma. After resection, both tumors recurred. In retrospect, the misdiagnosis of malignant sarcomatous mesothelioma in case 1 should have been suspected during follow-up. The patient's relatively young age and prolonged clinical course (8 years), makes the diagnosis of sarcomatous mesothelioma most unlikely. Sarcomatous mesothelioma typically presents at a later age (40–70 years old) with diffuse pleural thickening, and the median survival is 4 to 12 months after diagnosis.¹³ Patients with synovial sarcoma also have an aggressive clinical course but tend to survive longer than those with mesothelioma.⁷ As evidenced by patient 1, synovial sarcoma typically recurs after resection and is diagnosed by combining the clinical presentation with pathologic analysis.

Histologically, synovial sarcomas are either monophasic (consisting entirely of spindle cells) or biphasic (both epithelial and spindle cells). The biphasic tumors are more distinctive and thus more easily distinguished from other pleural sarcomas. In our series, case 3 represented a biphasic synovial sarcoma for which a definitive diagnosis was made on the initial biopsy. The monophasic variant is composed of spindle cells histologically similar to sarcoma and sarcomatous mesothelioma. Ancillary tests, such as

Figure 3. Synovial sarcoma, monophasic type. Hematoxylin and eosin–stained section from patient 2 depicting poorly differentiated monophasic synovial sarcoma with round cells showing high nucleus-to-cytoplasm ratio and absence of fascicular growth (original magnification $\times 40$).

Figure 4. Synovial sarcoma, biphasic type. Hematoxylin and eosin–stained section from patient 3. Tumor is biphasic and shows glandular epithelium interspersed among spindle-shaped cells (original magnification $\times 40$).

immunohistochemical or cytogenetic studies are helpful to confirm diagnosis.

Immunohistochemical findings that distinguish synovial sarcoma from other pleural sarcomas include positive staining for

Figure 5. FISH analysis. A, Patient 1, interphase nucleus with normal hybridization pattern for CEPX (orange) and YAC770c4 (green). B, Patient 2, interphase nucleus with abnormal hybridization pattern of colocalized YAC770c4 (green) and CEPX (orange) signals indicating 5(X;18).

cytokeratin and epithelial membrane antigen. Synovial sarcomas lack staining for neural (S100) and smooth muscle (desmin, smooth muscle actin) markers.¹⁴ This staining pattern is similar to that of sarcomatous mesothelioma, limiting its usefulness. The epithelial marker BerEp4 may help to distinguish biphasic synovial sarcoma from malignant mesothelioma, because it consistently stains biphasic synovial sarcoma, but is only focally positive in

some mesotheliomas. However, it is less useful for distinguishing between mesothelioma and monophasic synovial sarcoma, which also stains variably with BerEp4.¹⁴

The chromosomal translocation t(X;18)(p11.2;q11.2) has been found in more than 90% of synovial sarcomas, regardless of histologic subtype.^{12,15-17} This translocation results in the fusion of the *SYT* gene on chromosome 18 to either the *SSX1* or *SSX2* gene on chromosome X.¹⁸ Several techniques can be used to identify the translocation or fusion transcript, including conventional cytogenetic analysis, molecular cytogenetic analysis (FISH), and reverse transcriptase-polymerase chain reaction assay.¹⁷⁻²⁰ Recently, Aubry and colleagues²¹ reported 5 cases of pleural synovial sarcoma with this confirmed genetic rearrangement. In our series, case 2 represents a poorly differentiated tumor in which diagnosis was significantly aided by the positive FISH findings.

Optimal treatment for pleural synovial sarcoma has not been defined. Multimodal therapy of surgery, chemotherapy, and radiation has been used.⁷ Recurrences are likely and may be treated with further resections. In the extremities, synovial sarcoma has a notable sensitivity to chemotherapy, especially ifosfamide and doxorubicin.²² In our series, patient 1 showed a dramatic response to doxorubicin, with a reduction in the number of pulmonary nodules from 30 to 6. Thus if diagnosed correctly, synovial sarcoma may respond to specific chemotherapeutic agents.

As our 3 cases of pleural synovial sarcoma demonstrate, correct, timely diagnosis of this exceptionally uncommon tumor is essential for optimal therapy and survival.

We thank Drs Christopher D. M. Fletcher and Joseph M. Corson for contributing their expertise to the histologic analyses. We give special thanks to Drs Carlos Manivel and Theresa Perrone for help with identification of specimens. Ms Cathy Quigley is thanked for her assistance with immunostains. Finally, we are grateful for the expert editorial remarks provided by Dr Mary E. Knatterud.

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