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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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 × 8 × 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).

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 trans-thoracic 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
System II protocol (Zymo Research, 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 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 CCA-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 1. Primer sequences of the oligonucleotides used in the study

<table>
<thead>
<tr>
<th>Primer</th>
<th>Sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>SYT1</td>
<td>5’-AGA CCA ACA CAG CCT GGA CCA-3’</td>
</tr>
<tr>
<td>SYT2</td>
<td>5’-CAG CAG AGG CCT TAT GA-3’</td>
</tr>
<tr>
<td>SSX1</td>
<td>5’-GGT GCA GTT GTT CCA CAT CG-3’</td>
</tr>
<tr>
<td>SSX2</td>
<td>5’-TCT CGT GAA TCT TCT CAG AGG-3’</td>
</tr>
</tbody>
</table>

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.

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

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

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 clinical, histopathological, 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, hemangioepicytoma, 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


