Primary Pleural Synovial Sarcoma Treated with Pazopanib

Arata Sugitani 1,2, Kazuhisa Asai 1, Kazuya Kojima 1,3, Yosuke Eguchi 1,2, Tomoya Kawaguchi 1, Masahiko Ohsawa 4 and Kazuto Hirata 1

Abstract

A 42-year-old woman presented with chest pain and breathlessness with a nodule measuring 2×2 cm in size at the base of the right lung. A bronchoscopic examination did not reveal any malignancy. However, the patient developed difficulty in breathing, enlargement of the nodule, and right pleural effusion 14 days later. A video-assisted thoracic surgical biopsy specimen revealed the presence of pleural synovial sarcoma. The patient was treated with doxorubicin-ifosfamide combination chemotherapy because of metastasis to the pelvis. However, after a transient partial clinical response, there was a relapse of refractory disease. Although treated with pazopanib as second-line chemotherapy, the patient died eight months after the initial presentation.

Key words: primary synovial sarcoma of the pleura, doxorubicin, ifosfamide, pazopanib

(DOI: 10.2169/internalmedicine.54.3570)

Introduction

A synovial sarcoma is a soft tissue tumor that most commonly affects the extremities near large joints in young and middle-aged adults. However, synovial sarcomas are also reported to occur in other parts of the body, such as the head and neck, mediastinum, heart, lungs, pleura, mesentery, and retroperitoneal space. Primary synovial sarcoma of the pleura is rare, and its prognosis and treatment are not well defined. The benefits of chemotherapy for primary synovial sarcoma of the pleura are unclear, but an improvement in survival has been reported with doxorubicin-ifosfamide combination chemotherapy. We herein report a case of rapidly progressing primary pleural synovial sarcoma treated with doxorubicin and ifosfamide in combination, as a first-line chemotherapy, and pazopanib (a tyrosine-kinase inhibitor) as a second-line chemotherapy.

Case Report

A 42-year-old woman presented at the outpatient clinic of the Osaka City University Hospital with a history of chest pain and breathlessness. Initial computed tomography (CT) of the chest demonstrated a nodule measuring 2×2 cm in size at the base of the right lung (Fig. 1). A bronchoscopic examination did not reveal any malignancy. Unexpectedly, the patient presented at the emergency department of the hospital 14 days later complaining of difficulty in breathing. On auscultation, there were diminished breath sounds on the right side. A CT scan revealed an enlargement of the tumor and the occurrence of a right pleural effusion (Fig. 2). The results of a laboratory analysis of the peripheral blood were normal, except for increased levels of lactate dehydrogenase (LDH) and C-reactive protein (CRP) (Table). Although the pleural effusion was exudative in nature and of lymphocytic predominance, a cytological examination of the pleural effusion was negative for the presence of malignant cells (Table). Subsequently, video-assisted thoracic surgery (VATS) from the fourth intercostal of the right axilla showed a giant mass in the right lower lobe, hemorrhagic pleural effusion and pleural dissemination. The pathological analyses of the biopsy specimen from the pleural dissemination revealed tumor cells with hyperchromatic large nuclei and little cytoplasm. In addition, this biopsy specimen showed the presence of both an epithelial component with high cellularity
Figure 1. Initial computed tomography of the chest. A small tumor measuring 2×2 cm can be seen at the right lung base.

Figure 2. Enlargement of the tumor and the appearance of right pleural effusion.

Table. Findings from Laboratory Analyses of Peripheral Blood and Pleural Effusion.

<table>
<thead>
<tr>
<th>Hematology</th>
<th>Biochemistry</th>
<th>Pleural Effusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC 8,000 /μL</td>
<td>T-Bil 0.7 mg/dL</td>
<td>Total cell count 592 /μL</td>
</tr>
<tr>
<td>Neu 75.8 %</td>
<td>BUN 12 mg/dL</td>
<td>Neu 4 %</td>
</tr>
<tr>
<td>Ly 15.2 %</td>
<td>Cr 0.64 mg/dL</td>
<td>Ly 59 %</td>
</tr>
<tr>
<td>RBC 404×10⁴ /μL</td>
<td>TP 7.2 g/dL</td>
<td>Rivalta +</td>
</tr>
<tr>
<td>Hb 10.5 g/dL</td>
<td>ALB 3.9 g/dL</td>
<td>Protein 4450 mg/dL</td>
</tr>
<tr>
<td>Ht 33.5 %</td>
<td>Na 140 mEq/L</td>
<td>LDH 830 IU/L</td>
</tr>
<tr>
<td>PLT 21.2×10⁴ /μL</td>
<td>K 4.2 mEq/L</td>
<td>Glucose 72 mg/dL</td>
</tr>
<tr>
<td>Cl 106 mEq/L</td>
<td>ADA 20.0 U/L</td>
<td></td>
</tr>
<tr>
<td>Serology</td>
<td>Ca 8.8 mg/dL</td>
<td>CEA 3.6 ng/mL</td>
</tr>
<tr>
<td>CRP 3.36 mg/dL</td>
<td>AST 16 IU/L</td>
<td>Hyaluronic acid 12200 ng/mL</td>
</tr>
<tr>
<td>CEA 2.7 ng/mL</td>
<td>ALT 9 IU/L</td>
<td></td>
</tr>
<tr>
<td>CYFRA 2.5 ng/mL</td>
<td>CK 60 IU/L</td>
<td>Cytology Class II</td>
</tr>
<tr>
<td>ProGRP 17.9 pg/mL</td>
<td>LDH 367 IU/L</td>
<td></td>
</tr>
</tbody>
</table>

Peripheral blood findings were normal, except the increased lactate dehydrogenase (LDH) and C-reactive protein (CRP). Pleural effusion was exudative in nature but pleural fluid cytology was negative for malignant cells.
and short spindle cells with fibrous proliferation, thus indicating a biphasic type (Fig. 3). Immunohistochemical analyses revealed positive staining for CD99 and vimentin and focal staining for B-cell lymphoma 2 (Bcl-2) and cytokeratins (Fig. 3). However, the mesothelium markers (e.g., thrombomodulin and HBME1), markers of lung cancer (e.g., TTF1 and Napsin A) and neuroendocrine markers (e.g., NSE and Chromogranin A) were negative. The SYT-SSX fusion gene is characteristic of synovial sarcoma and results from the chromosomal translocation t(X;18)(p11.2;q11.2). Although a chimeric mRNA qualitative analysis by reverse transcription polymerase chain reaction (RT-PCR) assays was performed on RNA extracted from the paraffin block, the product of the SYT-SSX fusion gene was not detected. According to the immunohistochemical analyses by a pathologist, we diagnosed the tumor to be pleural synovial sarcoma (biphasic type).

The patient was treated with a combination of doxorubicin (60 mg/m²) and ifosfamide (10 g/m²) as first-line chemotherapy because of the detection of systemic metastasis to the pelvis on positron emission tomography (PET) before starting therapy. Doxorubicin-ifosfamide combination chemotherapy achieved a transient decrease in the tumor size; however, an increase in the tumor size was later observed (Fig. 4). The patient was treated with the tyrosine-kinase inhibitor, pazopanib, which has been recently approved in Japan for the treatment of soft tissue sarcoma, as second-line chemotherapy. However, pazopanib had little therapeutic ef-
fect, and the pleural synovial sarcoma progressed up until the patient’s death.

**Discussion**

Pleural synovial sarcoma is a rare tumor, which was first reported by Gaertner et al. in 1996 (1). Most pleural synovial sarcoma patients are young or middle-aged adults, and there is no sex bias (2). The typical symptoms include chest pain, dyspnea, and cough. However, 40% of pleural synovial sarcomas have been incidentally observed by using chest radiography without symptoms (3). On the chest CT scans, a pleural synovial sarcoma is commonly characterized as a well-circumscribed mass with pleural effusion. Although the histogenesis of pleural synovial sarcomas is unclear, it is believed that they arise from pluripotent mesenchymal cells capable of epithelial differentiation.

The SYT-SSX fusion gene, resulting from the chromosomal translocation t(X;18)(p11.2;q11.2), is found in approximately 90% of synovial sarcomas of the extremities by fluorescence in situ hybridization (4) or RT-PCR analysis of the gene transcript. Although some papers have reported the presence of the SYT-SSX fusion gene in pleural synovial sarcoma (5, 6), its true frequency in pleural synovial sarcoma is unknown. Even if molecular testing for SYT-SSX fusion gene was negative, the diagnosis of synovial sarcoma is made by immunohistochemistry. The biphasic type is easily diagnosed based on the presence of both epithelial and spindle cell components and its immunohistochemical characteristics (7). Immunohistochemically, epithelial markers, such as cytokeratins (75%) and CAM5.2 (72%), were found to be positive in synovial sarcoma. The mesenchymal marker vimentin (100%) was highly positive, and Bcl-2 (72%), CD99 (50%) and S-100 (83%) were also found to be positive in synovial sarcoma (8, 9). In the present case, while the product of the SYT-SSX fusion gene was not detected, the tumor was positive for vimentin, cytokeratins, Bcl-2, and CD99 and negative for S-100. Additionally, the biopsy specimen showed a biphasic type (the presence of both epithelial-like cells with high cellularity and short spindle cells with fibrous proliferation). Therefore, we made a final diagnosis of synovial sarcoma.

In the present case, the tumor was well-circumscribed and not large enough to be reached by endobronchial forceps; moreover, a biopsy sample from the bronchoscopic examination had given a false negative initial indication of nonmalignancy. Diagnosing sarcoma from a small sample is usually difficult, and others have reported that even a CT-guided Tru-Cut needle biopsy sample is not enough to confirm the diagnosis of a sarcoma (5). After 14 days, the patient’s tumor increased in size and massive pleural effusion occurred. According to previous reports, synovial sarcomas characteristically demonstrate a slower progression. In the total or extended resected post-operative state, time to recurrence extended to several years and some patients did not demonstrate recurrence. However, in some post-operative cases, recurrence occurred one month after resection. Rapid growth within two weeks, such as in our case, may sometimes occur (10, 11). In the present case, a [18F] fluorodeoxyglucose (FDG)-PET examination revealed an abnormal uptake of FDG in the pelvis. The diagnosis of pleural synovial sarcoma may be established by the exclusion of histologically sarcoma-like primary lung malignancies and metastatic extrathoracic sarcoma. The pelvic lesion was very
small compared to the intrathoracic lesion, and our final diagnosis of the tumor in the present case was primary pleural synovial sarcoma, not pulmonary metastasis of an extrathoracic synovial sarcoma.

There is no gold standard of therapy for pleural synovial sarcoma because it is a rare malignancy. However, other groups have applied similar treatment to that used in the present study in synovial sarcomas occurring at other sites (12). Primary pleural synovial sarcoma has a high recurrence rate compared to other sarcomas. A five-year disease-free period after radical multidisciplinary therapy has been reported in 20.9% of cases (13). A multidisciplinary approach to treatment, including surgery, chemotherapy, and radiotherapy, has been suggested. Radical resection is the first-line treatment for synovial sarcoma. In the present case, because of metastasis to the pelvis revealed by PET and pleural dissemination via massive tumor and pleural effusion, systemic chemotherapy was administered without surgical resection. An improvement in survival has been described with doxorubicin-ifosfamide combination chemotherapy (14). In the present case, although the combination of doxorubicin and ifosfamide initially resulted in a significant reduction in the tumor size and decrease in the serum LDH value, the tumor size and the LDH value increased again. Therefore, we initiated second-line chemotherapy with pazopanib. As synovial sarcoma is a rare malignancy, a specific tumor marker has never been established. However, LDH is known to reflect the progression of sarcomas and is suggested to be a prognostic factor of sarcoma (15). In the present case, the LDH value reflected both the tumor size and progression.

To the best of our knowledge, this is the first report of pazopanib administration for pleural synovial sarcoma. Pazopanib is a potent and selective multi-targeted receptor tyrosine-kinase inhibitor which blocks tumor growth and inhibits angiogenesis. It has been approved in Japan for soft tissue sarcoma and renal cell carcinoma therapy, but is not recommended for use in cytotoxic chemotherapy-naïve patients. The major adverse effects are liver disorder and failure, hypertension and hypertensive crisis, cardiac dysfunction, and nephrotic syndrome. We gradually increased the dose of pazopanib by 200 mg/day to 800 mg/day, and it was well tolerated with the minor adverse effect of hair discoloration. Although pazopanib showed a transient anti-tumor effect with stable tumor size, tumor progression was later observed. Thus, further development of this therapy is warranted.

In conclusion, we herein reported a case of pazopanib-treated pleural synovial sarcoma. Although the pazopanib treatment was tolerable, it was ultimately not successful. For the improvement of pleural synovial sarcoma treatment, further data regarding its natural history, diagnosis, and treatment are needed.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement

We would like to thank Dr. Katsuhito Takahashi, Representative Cure Sarcoma Center at Osaka Medical Center for Cancer and Cardiovascular Disease, for his expertise regarding the sarcoma diagnosis and the treatment and the molecular analysis of the SYT-SSX fusion gene.

References