Primary Pulmonary Synovial Sarcoma Showing a Prolonged Survival with Multimodality Therapy

Hirokazu Ogino 1, Masaki Hanibuchi 1, Hiromitsu Takizawa 2, Shoji Sakiyama 2, Hiroyuki Sumitomo 2, Seiji Iwamoto 3, Hitoshi Ikushima 3, Kohei Nakajima 4, Shinji Nagahiro 4, Taito Yamago 1, Yuko Toyoda 1, Yoshimi Bando 5 and Yasuhiko Nishioka 1

Abstract

A 54-year-old man was referred to our hospital due to a mass shadow noted on a chest X-ray. Thoracoscopic lobectomy yielded a diagnosis of primary pulmonary synovial sarcoma according to the histology and SYT-SSX1 gene analyses. Five months after the thoracic surgery, he developed brain metastasis; therefore, we performed resection of the brain metastatic focus followed by radiotherapy. As a local recurrence in the thoracic cavity concurrently emerged, systemic chemotherapy was also administered. These observations indicated that a multidisciplinary approach may be useful against primary pulmonary synovial sarcoma, although there is presently no established therapeutic strategy due to its rarity and highly aggressive nature.

Key words: primary pulmonary synovial sarcoma, spontaneous regression, brain metastasis, multimodality therapy

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Introduction

Synovial sarcoma is a distinct soft tissue neoplasm which occurs mainly in the extremities and limb girdle, and it represents 7-10% of all human soft tissue sarcomas (1, 2). It often metastasizes to the lung; however, primary pulmonary synovial sarcoma is extremely rare and has been reported to comprise less than 0.5% of pulmonary neoplasms (3, 4). Primary pulmonary synovial sarcomas have been increasingly reported as a result of growing awareness and improved diagnostic capabilities (5-9). This tumor is thought to be more locally aggressive and associated with a poorer prognosis than soft tissue synovial sarcoma (9); however, precise clinical data, such as on the prevalence rate, prognosis, and metastatic pattern, as well as on the therapeutic strategy, are still unclear due to its rarity.

We herein report a rare case of primary pulmonary synovial sarcoma successfully treated with multimodality therapy.

Case Report

A 54-year-old man was referred to our hospital for the further examination of an abnormality noted on a chest radiograph. The patient had a smoking history of 3 pack-years and was undergoing treatment for hypertension. He had intermittent left chest pain; however, no abnormality was noted on a physical examination. Blood tests showed slight elevation of inflammatory reactions; however, tumor markers for lung cancer and markers for mycotic infection were negative. An interferon-gamma release assay (QuantiFERON®) was positive (Table). A chest X-ray showed a mass shadow in the left lower lung field (Fig. 1), and computed

**Figure 1.** The chest X-ray on admission. A mass shadow was seen in the left lower lung field.

tomography (CT) showed a nodule which was 23 mm in diameter in the left lower lobe (S8) (Fig. 2A).

Positron emission tomography (PET)-CT showed a slightly increased fluorodeoxyglucose (FDG) uptake [standardized uptake values (SUVs) of the nodule was 1.4] (Fig. 3A). No evidence of distant metastases was found on PET-CT or contrast-enhanced brain magnetic resonance imaging (MRI) (data not shown). A transbronchial biopsy with bronchoscopy yielded no definitive diagnosis. No acid fast bacilli were detected in the sputum or bronchial lavage fluid, which suggested a latent tuberculosis infection (LTBI) that did not require treatment, rather than active tuberculosis. During the examination period, the nodule regressed spontaneously (from 23 to 18 mm in diameter) (Fig. 2B); therefore, we adopted a wait-and-see approach.

Two months later, the nodule showed regrowth (from 18 mm to 32 mm in diameter) (Fig. 2C, D), and the SUV-max of the nodule was elevated from 1.4 to 7.6 on follow-up PET-CT (Fig. 3B). Because a CT-guided percutaneous lung biopsy failed to establish a definitive diagnosis, we proceeded with thoracoscopic left lower lobectomy. A histologic examination of the specimens revealed the active proliferation of malignant tumor cells with a high nuclear cytoplasmic ratio (N/C ratio) and oval or short spindle nucleus (Fig. 4A). Immunohistochemistry (IHC) showed positive reactivity for Bcl-2, AE1/3, CD56, and vimentin (Fig. 4B-E), indicating a strong possibility of monophasic synovial sarcoma. Fluorescence in situ hybridization (FISH) showed that the SYT split-signal was positive in 96% of the tumor cells (Fig. 5A), indicating the existence of a chromosome translocation of the SYT gene (10). Finally, we performed reverse transcription-polymerase chain reaction (RT-PCR) and sequencing of the PCR product, and the results showed the existence of the SYT-SSX1 gene (Fig. 5B, C), which led to a diagnosis of primary pulmonary synovial sarcoma.

Five months after the operation, the patient showed the gradual development of visual field disturbance. A visual field test showed right homonymous hemianopia, and contrast-enhanced brain MRI showed a large ring-enhanced tumor with intratumoral hemorrhage and peripheral edema in the left occipital lobe (Fig. 6A). Because radiotherapy alone is thought to be insufficient to control brain metastasis of synovial sarcoma (11), we initially performed brain tumor resection followed by radiotherapy. A histologic examination of the brain tumor showed the proliferation of spindle-shaped malignant cells, which was similar to the findings in the primary lung tumor (Fig. 4F); therefore, we diagnosed it as a brain metastatic focus of primary pulmonary synovial sarcoma. After brain tumor resection, intensity-modulated radiation therapy (IMRT) was performed with 50, 40, and 30 Gy to the parietal region, occipital region, and whole brain, respectively. The combined therapy with craniotomy and radiation successfully eliminated the tumor (Fig. 6B) and no recurrence of the brain tumor has been observed up to this time. Although the results of objective tests, such as the visual field test, were not improved, his subjective symptoms, such as visual acuity, partially improved after the combined treatment.

**Table. Laboratory Data on Initial Visit.**

<table>
<thead>
<tr>
<th>Hematology</th>
<th>Biochemistry</th>
<th>Serology</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC 10,000 /µL</td>
<td>TP 7.9 g/dL</td>
<td>MPO-ANCA (-)</td>
</tr>
<tr>
<td>Neutrophils 76.0 %</td>
<td>ALB 4.2 g/dL</td>
<td>PR3-ANCA (-)</td>
</tr>
<tr>
<td>Eosinophils 1.0 %</td>
<td>BUN 15 mg/dL</td>
<td></td>
</tr>
<tr>
<td>Basophils 1.0 %</td>
<td>Cr 0.83 mg/dL</td>
<td></td>
</tr>
<tr>
<td>Lymphocytes 17.0 %</td>
<td>T-bil 0.6 mg/dL</td>
<td></td>
</tr>
<tr>
<td>Monocytes 5.0 %</td>
<td>AST 33 IU/L</td>
<td>CEA 2.3 ng/mL</td>
</tr>
<tr>
<td>RBC 505 × 10⁶ /µL</td>
<td>ALT 53 IU/L</td>
<td>Cyfra &lt;1.0 ng/mL</td>
</tr>
<tr>
<td>Hb 16.0 g/dL</td>
<td>LDH 213 IU/L</td>
<td>Pro GRP 36.2 pg/mL</td>
</tr>
<tr>
<td>Hct 47.0 %</td>
<td>ALP 321 IU/L</td>
<td></td>
</tr>
<tr>
<td>PLT 29.0 × 10⁴ /µL</td>
<td>γ-GTP 33 IU/L</td>
<td>Infection marker</td>
</tr>
<tr>
<td>Coagulation</td>
<td>Na 140 mEq/L</td>
<td></td>
</tr>
<tr>
<td>PT-INR 0.89</td>
<td>K 4.1 mEq/L</td>
<td>β-D glucan &lt;4.8 pg/mL</td>
</tr>
<tr>
<td>APTT 30.8 sec</td>
<td>CL 104 mEq/L</td>
<td>Aspergillus antigen (-)</td>
</tr>
<tr>
<td></td>
<td>CRP 0.71 mg/dL</td>
<td>Cryptococcus antigen (-)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>QuantiFERON® (+)</td>
</tr>
</tbody>
</table>
At the same time of the appearance of brain metastasis, tumor recurrence in the left thoracic cavity was seen on chest CT (data not shown); therefore, we initiated chemotherapy with doxorubicin (30 mg/m² per day, days 1 to 2) plus ifosfamide (2 g/m² per day, days 1 to 5 with mesna and pegfilgrastim) every 21 days after IMRT for brain metastasis. Because grade 3 leukopenia emerged, these drugs were administered every 35 days thereafter. After two cycles of chemotherapy, the nodule in the thoracic cavity slightly decreased (from 33 to 30 mm in diameter). Although the best overall response was stable disease (SD) according to the Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1), we judged it was clinically effective and continued therapy for a total of four cycles.
Discussion

Synovial sarcoma is a highly malignant tumor, and it easily develops into local recurrence and/or distant metastasis, especially to the lung, which results in a poor prognosis. Several reports showed that the 5-year survival rates were approximately 60% despite aggressive treatment (12, 13). Primary pulmonary synovial sarcoma is thought to be more aggressive than that of soft tissue origin, and in a retrospective study, 46% of pulmonary and mediastinal synovial sarcoma patients died within 5 years, and only 26% of them were alive with no evidence of disease after several treatments (9). In the present case, the tumor rapidly progressed and led to a large brain metastasis and local recurrence during the short follow-up period. This medical history with rapid tumor progression was consistent with the previous reports.

In the present case, small cell lung cancer was suspected after the first CT-guided percutaneous lung biopsy due to the observation of the aggregation of small oval cells with round bare nuclei. However, there was no evidence of metastasis to the lymph nodes and distant organs at that time, and IHC revealed that both chromogranin A and synaptophysin were negative (data not shown), which was incompatible with small cell lung cancer. Therefore, we performed lobectomy, which successfully yielded a diagnosis of primary pulmonary synovial sarcoma. Primary pulmonary synovial sarcoma is generally diagnosed in patients with unusual clinical or histological features, such as lung cancer (9), and thus we should aggressively proceed with diagnostic studies including a surgical approach, detailed IHC, or genomic testing.

Brain metastasis of primary pulmonary synovial sarcomas is extremely rare and has been reported in only a few cases (7, 14). Moreover, to the best of our knowledge, this is the first reported case of primary pulmonary synovial sarcoma with brain metastatic focus treated by brain tumor resection. While there was no evidence of any brain metastasis before thoracic surgery, a large brain metastatic focus in the occipital lobe developed five months postoperatively. Given the aggressive nature of the disease, as observed in the present case, close follow-up should be conducted for the early detection of local recurrence and/or distant metastasis even after curative surgical resection.

In general, the combination of surgery and radiation therapy is more effective than radiation monotherapy for soft tissue sarcoma. Indeed, radiotherapy combined with surgery was reported to achieve better local control than either modality alone for the majority of soft tissue sarcomas (11, 15), and pre- and postoperative approaches could achieve acceptable local control (16). Therefore, we performed craniotomy for brain tumor resection followed by radiotherapy. As a result, we have not observed the recurrence of the brain tumor up to this time. Although the results of objective tests, such as visual field test, were not improved, the patient’s subjective symptoms, such as visual acuity, partially improved.

A phase 3 trial which assessed the efficacy of the first-line treatment of doxorubicin with ifosfamide for advanced or metastatic soft tissue sarcoma showed that the response rate, median progression-free survival and median overall

![Histopathology and immunohistochemistry of the tumors (×40). Bar indicates 100 μm.](image-url)
Figure 5. A chromosome translocation of the SYT gene was detected in the thoracic tumor. (A) Fluorescence in situ hybridization (FISH) showed that the SYT split-signal was positive in 96% of tumor cells, which indicated that the tumor cells had the chromosome translocation of the SYT gene. (B) Reverse transcription-polymerase chain reaction (RT-PCR) showed the existence of the SYT-SSX1 gene in the tumor of the present case. The primers for SYT-SSX1 were as follows: F-primer: 5’-CAACAGCAAGATGCACTACCA-3’ and R-primer: 5’-GGTGCAGTTTCCCATCG-3’. The detection of a PCR product of 331 base pair size indicated the existence of the SYT-SSX1 gene. (C) The sequential analysis of SYT-SSX1. The resulting PCR product of SYT-SSX1 was purified, followed by direct sequencing. This revealed the break points of the SYT gene and SSX1 genes.

Figure 6. Contrast-enhanced brain MRI findings. (A) A large ring-enhanced tumor with intratumoral hemorrhage and peripheral edema in the left occipital lobe was seen at the time of the development of visual field disturbance. (B) The brain tumor disappeared after brain tumor resection and radiotherapy.
platelet-derived growth factor receptor-
hibitor with activity against VEGF receptor-1, -2, and -3 and showed that pazopanib, a multitargeted tyrosine kinase in-
genic factors, such as vascular endothelial growth factor (VEGF) (19-21). In 2012, a phase 3, placebo-controlled trial showed that pazopanib, a multitargeted tyrosine kinase in-
hibitor with activity against VEGF receptor-1, -2, and -3 and platelet-derived growth factor receptor-\(\alpha\), \(\beta\), significantly in-
creased the median progression-free survival (4.6 months with pazopanib versus 1.6 months with placebo) in patients who had at least one regimen containing anthracycline (22); as a result, it was approved for the treatment of soft tissue sarcoma in Japan and the U.S. Although the efficacy of pa-
zopanib against primary pulmonary synovial sarcoma re-
ains unclear, it may be a useful therapeutic option in the present case in the near future.

Interestingly, the primary tumor spontaneously regressed during the initial course of the disease in the present case. Spontaneous regression of a malignant tumor is defined as “the partial or complete disappearance of a malignant tumor in the absence of all treatment or in the presence of therapy which is considered inadequate to exert a significant influence on neoplastic disease” (23). The incidence of spontane-
ous regression has been estimated to be no more than 1 in 60,000-100,000 cases (24), and there appear to be no reports of spontaneous regression of synovial sarcoma. Immune sys-
tems and hormonal effects are thought to play important roles (25); however, the precise mechanisms are still un-
known.

In summary, we encountered a rare case of primary pul-
monary synovial sarcoma that developed a large brain me-
tastatic focus with visual field disturbance. This case high-
lights the importance of an intensive diagnostic approach and an awareness of the aggressive metastatic potential of this rare tumor. The combined modality treatment success-
fully controlled the disease, indicating that a multidiscipli-
nary approach may be a useful therapeutic strategy against primary pulmonary synovial sarcoma.

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

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