INTERNAL MEDICINE

□ CASE REPORT □

Primary Pulmonary Synovial Sarcoma Showing a Prolonged Survival with Multimodality Therapy

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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

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Table. Laboratory Data on Initial Visit.

Hematology			Biochemistry			Serology		
WBC	10,000	/μL	TP	7.9	g/dL	MPO-ANCA	(-)	
Neutrophils	76.0	%	ALB	4.2	g/dL	PR3-ANCA	(-)	
Eosinophils	1.0	%	BUN	15	mg/dL			
Basophils	1.0	%	Cr	0.83	mg/dL	Tumor marker		
Lymphocytes	17.0	%	T-bil	0.6	mg/dL			
Monocytes	5.0	%	AST	33	IU/L	CEA	2.3	ng/mL
RBC	505×10^4	/μL	ALT	53	IU/L	Cyfra	<1.0	ng/mL
Hb	16.0	g/dL	LDH	213	IU/L	Pro GRP	36.2	pg/mL
Hct	47.0	%	ALP	321	IU/L			
PLT	29.0×10^4	/μL	γ-GTP	33	IU/L	Infection marker		
			Na	140	mEq/L			
Coagulation			K	4.1	mEq/L	β-D glucan	<4.8	pg/mL
			CL	104	mEq/L	*Aspergillus* antigen	(-)	
PT-INR	0.89		CRP	0.71	mg/dL			
APTT	30.8	sec				*Cryptococcus* antigen	(-)	
						QuantiFERON®	(+)	

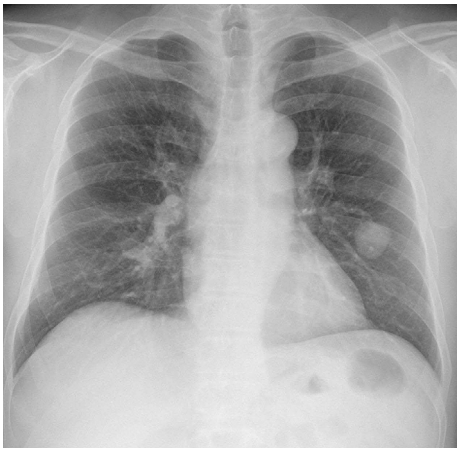

Figure 1. The chest X-ray on admission. A mass shadow was seen in the left lower lung field.

tomography (CT) showed a nodule which was 23 mm in diameter in the left lower lobe (S^8) (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.

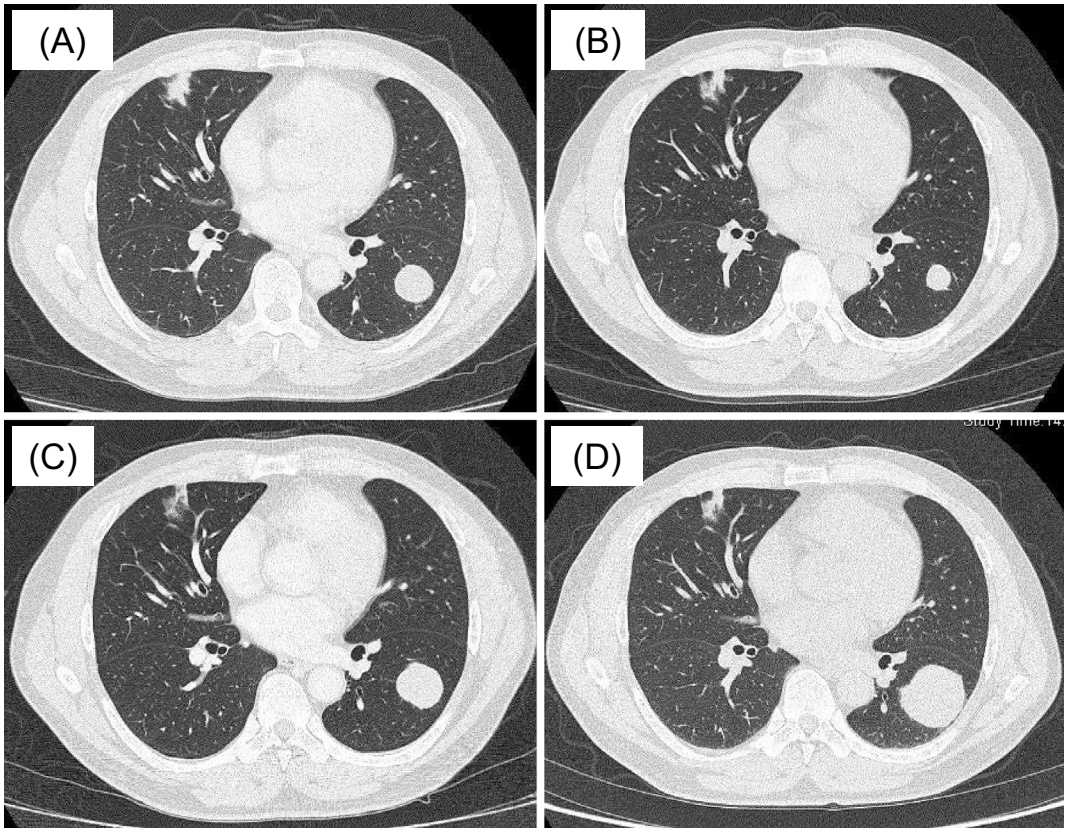

Figure 2. **Chest computed tomography findings. (A) At the initial visit. A nodule, which was 23 mm in diameter, was seen in the left lower lobe (S^8). (B) One month after the initial visit, the nodule spontaneously regressed (from 23 to 18 mm in diameter). (C) Two months later, the nodule showed regrowth (from 18 to 32 mm in diameter). (D) At the time of thoracic surgery, the nodule had further grown.**

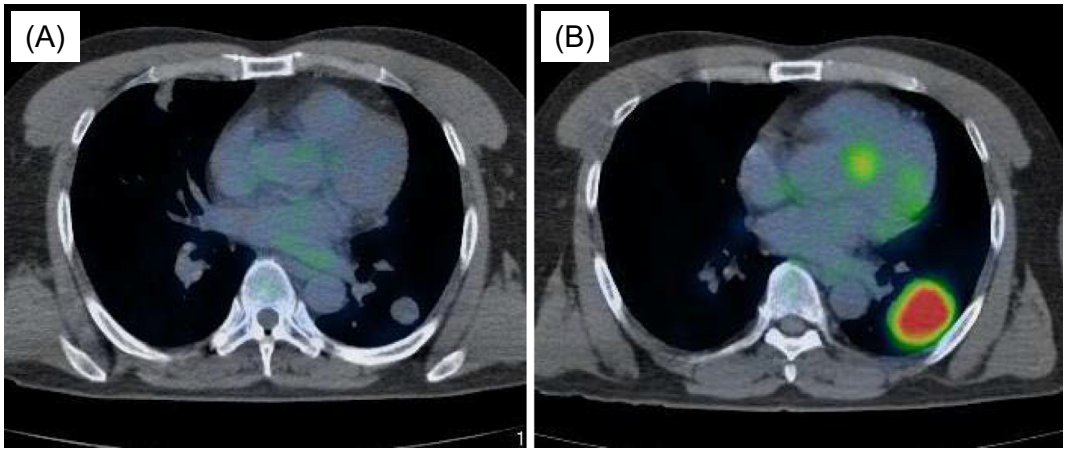

Figure 3. **PET-CT findings. (A) A slight increase of FDG uptake (SUV: 1.4) was observed in the nodule in the left lower lobe. (B) The SUV-max (7.6) of the nodule in the left lower lobe was further elevated during the follow-up period.**

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/m^2 per day, days 1 to 2) plus ifosfamide (2 g/m^2 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.

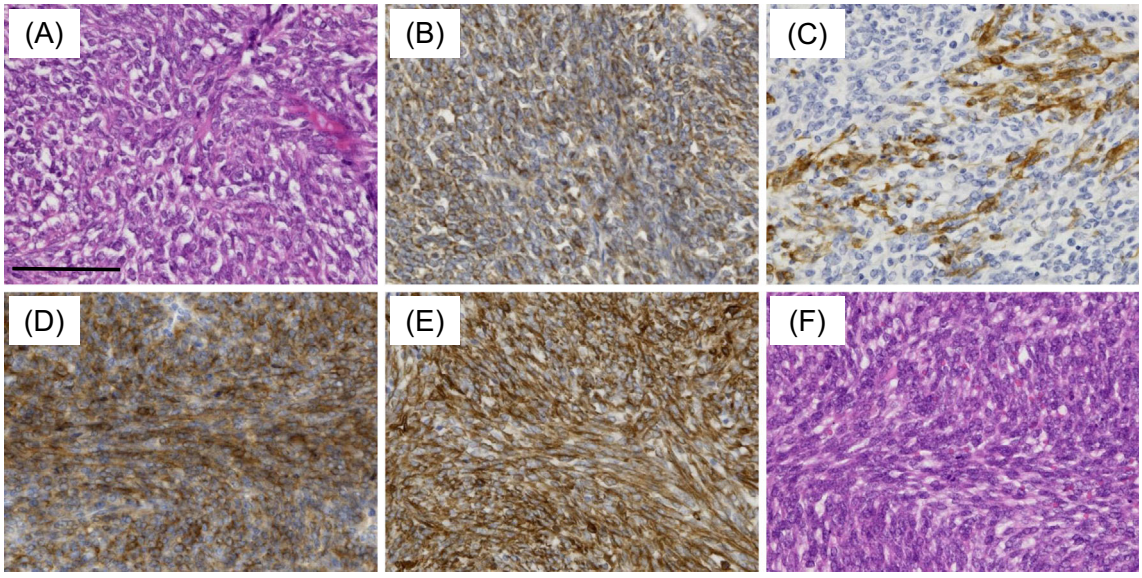

Figure 4. **Histopathology and immunohistochemistry of the tumors (×40). Bar indicates 100 μm. (A) Hematoxylin and Eosin (H&E) staining of the thoracic tumor showed the proliferation of malignant tumor cells with a high nuclear cytoplasmic ratio (N/C ratio), showing an oval or short spindle nucleus. Immunohistochemistry revealed positive reactivity for (B) Bcl-2, (C) AE1/3, (D) CD56, and (E) vimentin. (F) H&E staining of the brain tumor showed the proliferation of spindle-shaped malignant cells similar to those in the primary lung tumor.**

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

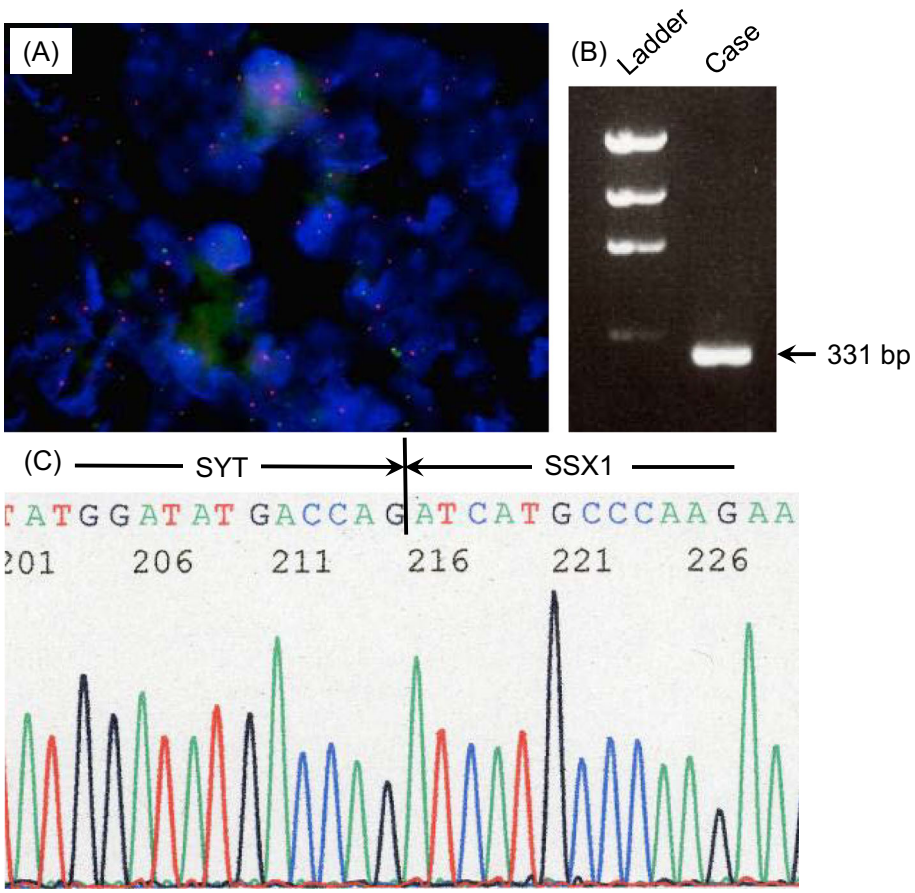

Figure 5. **A chromosome translocation of the *SYT* gene was detected in the thoracic tumor. (A) Fluorescence *in situ* hybridization (FISH) showed that the *SYT* split-signal was positive in 96% of tumor cells, which indicated that the tumor cells had the chromosome translocation of the *SYT* gene. (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'-CAACAGCAAGATGCATACCA-3' and R-primer: 5'-GGTGCAGTTGTTTCCCATCG-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.**

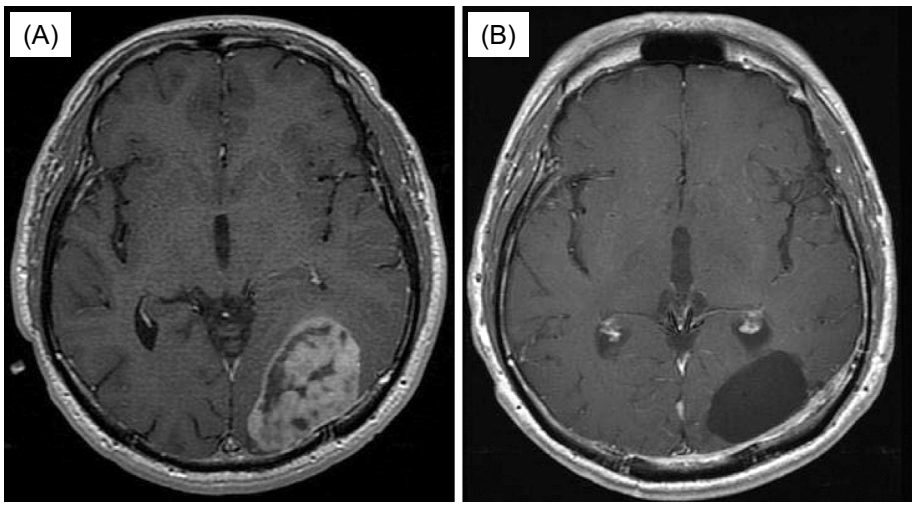

Figure 6. **Contrast-enhanced brain MRI findings. (A) A large ring-enhanced tumor with intratumoral hemorrhage and peripheral edema in the left occipital lobe was seen at the time of the development of visual field disturbance. (B) The brain tumor disappeared after brain tumor resection and radiotherapy.**

survival were 26%, 7.4 months and 14.3 months, respectively (17), indicating the limited efficacy of conventional chemotherapy for soft tissue sarcomas. Moreover, the development of novel systemic treatments has progressed little over the past few decades (18). Recently, several clinical studies of anti-angiogenic treatments were conducted because soft tissue sarcoma was reported to overexpress angiogenic 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 inhibitor with activity against VEGF receptor-1, -2, and -3 and platelet-derived growth factor receptor-α, β, significantly increased 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 pazopanib against primary pulmonary synovial sarcoma remains 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 spontaneous 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 systems and hormonal effects are thought to play important roles (25); however, the precise mechanisms are still unknown.

In summary, we encountered a rare case of primary pulmonary synovial sarcoma that developed a large brain metastatic focus with visual field disturbance. This case highlights the importance of an intensive diagnostic approach and an awareness of the aggressive metastatic potential of this rare tumor. The combined modality treatment successfully controlled the disease, indicating that a multidisciplinary 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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