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Case Report

Pulmonary Spindle Cell Carcinoma Presenting Anaplastic Lymphoma Kinase Rearrangement

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Keywords
Anaplastic lymphoma kinase rearrangement · Pulmonary sarcomatoid carcinoma · Pulmonary spindle cell carcinoma · Alectinib · Case report

Abstract
Pulmonary spindle cell carcinoma is a subtype of pulmonary sarcomatoid carcinoma and a very rare tumor type with a poor prognosis. A few case reports have documented patients with pulmonary sarcomatoid carcinoma with anaplastic lymphoma kinase rearrangement, and the efficacy and outcomes of anaplastic lymphoma kinase inhibitors remain unclear. Herein, we present the case of a 60-year-old woman with stage IVB disease who was diagnosed with a metastatic brain tumor. This patient showed high levels of programmed cell death ligand 1 expression and anaplastic lymphoma kinase rearrangement and received pembrolizumab as the first-line treatment. Three weeks later, pembrolizumab failed to reduce the size of the primary pulmonary tumor, and the patient's general condition did not improve. The patient received alectinib as the second-line treatment. Two months later, multiple brain metastases were observed. Hence, whole-brain irradiation was performed as treatment for multiple brain metastases, while another anaplastic lymphoma kinase inhibitor was administered; however, both treatments remained ineffective. The patient eventually died 9 months after the initiation of first-line treatment. The present case report describes the therapeutic course of a patient with pulmonary spindle cell carcinoma with an anaplastic lymphoma kinase rearrangement.

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Introduction

Pulmonary sarcomatoid carcinoma (PSC) is a rare type of non-small cell lung cancer (NSCLC) that accounts for 0.1–0.4% of lung cancer cases [1]. Pulmonary spindle cell carcinoma (PSCC) accounts for 28.7% of all PSC cases [2]. PSC progresses rapidly and is resistant to chemotherapy and conventional radiotherapy [3]. The prognosis of NSCLC dramatically improves with targeted tyrosine kinase inhibitors, such as epidermal growth factor receptor and anaplastic lymphoma kinase (ALK) inhibitors. However, the efficacy of targeted therapy for advanced PSC was only confirmed based on the results of case reports. In particular, the efficacy of ALK inhibitors in patients with PSC with ALK rearrangements remains unclear, as only a few cases have been reported [4]. Herein, we present a rare case of PSCC with ALK rearrangements treated with ALK inhibitors.

Case Presentation

A 60-year-old woman with no history of smoking or comorbidities visited a hospital due to complaints of headache and nausea in December 2021. Brain magnetic resonance imaging (MRI) revealed a solitary cerebellar tumor, which prompted the patient's hospital admission (Fig. 1a). Brain tumorectomy was performed to alleviate the patient's symptoms. Histological examination of the brain tumor showed malignant spindle cells and absence of carcinomatous components (Fig. 2a). Histopathological staining of malignant spindle cells showed the presence of cytokeratin (AE1/AE3) and absence of thyroid transcription factor 1, Napsin A p40. Chest computed tomography (CT) showed a mass shadow in the right lower lobe and mediastinal lymph nodes, which suggests that the patient had a lung cancer lesion that metastasized to the brain, which prompted her admission in our hospital (Fig. 1b, c).

The metastatic brain tumor continued to enlarge 1 month after tumorectomy (Fig. 1d). The patient experienced headache and nausea and had an Eastern Cooperative Oncology Group performance status (PS) score of 3. Genetic testing results were unavailable, and the programmed cell death protein ligand 1 (PD-L1) tumor proportion score was 85% (Dako 22C-3 antibody). Tissue biopsy of the lung was impossible due to the poor PS score. Chest and abdominal CT showed cancer metastases to the heart, bilateral adrenal glands, and left ilium. The patient was diagnosed with PSSC clinical T3N2M1c stage IVB ADR BRA OSS OTH (according to the eighth edition of the TNM Classification of Malignant Tumors) (Fig. 1e, f). Thus, pembrolizumab monotherapy (200 mg intravenously every 3 weeks) was initiated as first-line treatment in January 2022. In addition, stereotactic radiotherapy (35 Gy delivered in five fractions) was performed as treatment for metastatic brain tumors.

Three weeks later, the PS did not improve, and chest CT showed no reduction in the mass shadow in the right lower lobe. Echinoderm microtubule-associated protein-like 4 ALK fusion in the brain tumor tissue was identified using the Oncomine Dx Target Test Multi-CDx System, and ALK was detected through immunohistochemistry of the brain tumor tissue (Fig. 2b). Therefore, alectinib (300 mg twice daily) was initiated as second-line treatment in February 2022. After the initiation of alectinib therapy, the patient's headache and nausea disappeared, and the PS score improved to 2. In April 2022 (2 months after the initiation of alectinib therapy), chest CT showed a reduction in the mass shadow in the right lower lobe; however, a new nodule shadow was noted in the right lower lobe (Fig. 3a, b). The brain MRI revealed multiple brain metastases (Fig. 3c, d).

After whole-brain radiotherapy (30 Gy delivered in 10 fractions), lorlatinib (100 mg once daily) was initiated as third-line treatment. In June 2022 (2 months after the initiation of lorlatinib therapy), brain MRI showed brain tumor growth in the cerebellum; hence, gamma

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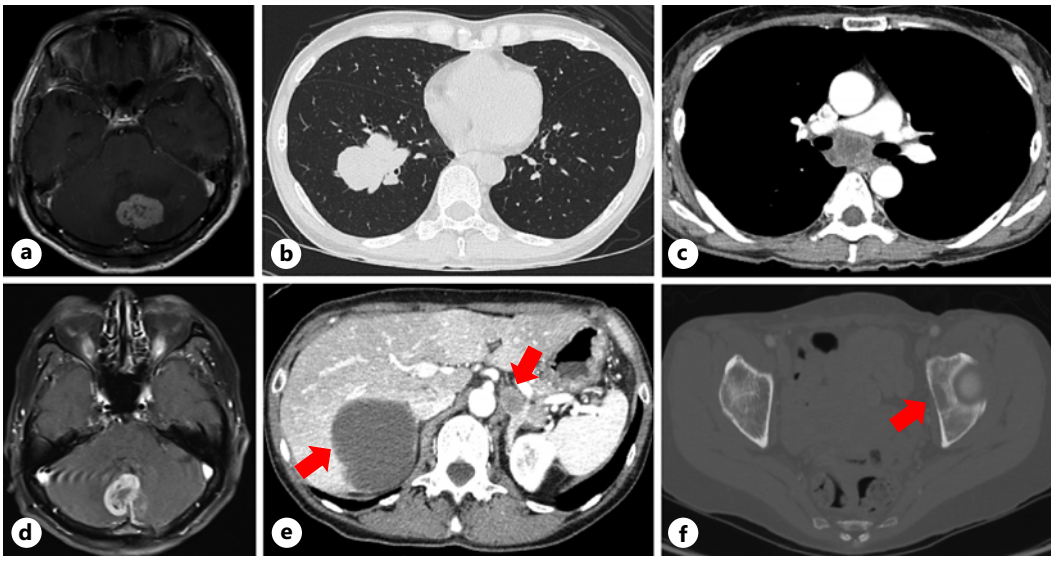

Fig. 1. a Brain magnetic resonance imaging (MRI) before brain tumorectomy shows solitary tumor in the cerebellum. **b**, **c** Chest computed tomography (CT) before first-line treatment shows a mass shadow in the right lower lobe and mediastinal lymph nodes. **d** Brain MRI 1 month after brain tumorectomy shows metastatic brain tumor re-enlargement. **e**, **f** Abdominal CT before first-line treatment shows metastases to the bilateral adrenal glands and left ilium.

knife radiosurgery was performed while continuing lorlatinib treatment. In August 2022 (4 months after the initiation of lorlatinib), brain MRI showed tumor growth in the right frontal and left occipital lobes (Fig. 3e, f). Brigatinib (90 mg once daily) was administered as fourth-line treatment; however, 1 week later, she developed right lower extremity paralysis and experienced worsening of her general condition. The patient received the best supportive care and subsequently died on October 10, 2022 (9 months after the initiation of first-line treatment).

Discussion

Herein, we describe a rare case of PSCC with an ALK rearrangement that did not respond to ALK inhibitors. PSC is generally resistant to chemotherapy compared to NSCLC. Previous studies have reported an overall response rate of 8.0–16.5% for first-line chemotherapy in patients with PSC [5, 6]. The efficacy of chemotherapy for PSC remains controversial. Recently, immunotherapy and targeted therapy for PSC have been performed, but the therapeutic efficacy is unclear. Regarding targeted therapy, the frequent genomic alterations in PSC include tumor protein p53, mesenchymal-epithelial transition, epidermal growth factor receptor, and Kirsten rat sarcoma viral oncogene [7]. A few case reports have compared the frequency and clinical profile of PSC with ALK rearrangement with those of NSCLC; however, the results remain controversial. Although in a retrospective study with a small sample size, Chen et al. [8] reported that five (3.5%) of 141 patients with PSC had ALK rearrangements. Alectinib, a second-generation ALK inhibitor, is highly effective in patients with advanced NSCLC with ALK rearrangement, with a median progression-free survival (PFS) of 34.8 months, as reported in the ALEX trial [9].

A summary of case reports in which ALK inhibitors were used to treat PSC with ALK rearrangements is shown in Table 1 [4, 10–12]. The 5 patients with PSC with ALK rearrangement were younger and non-smokers, which was consistent with the characteristics

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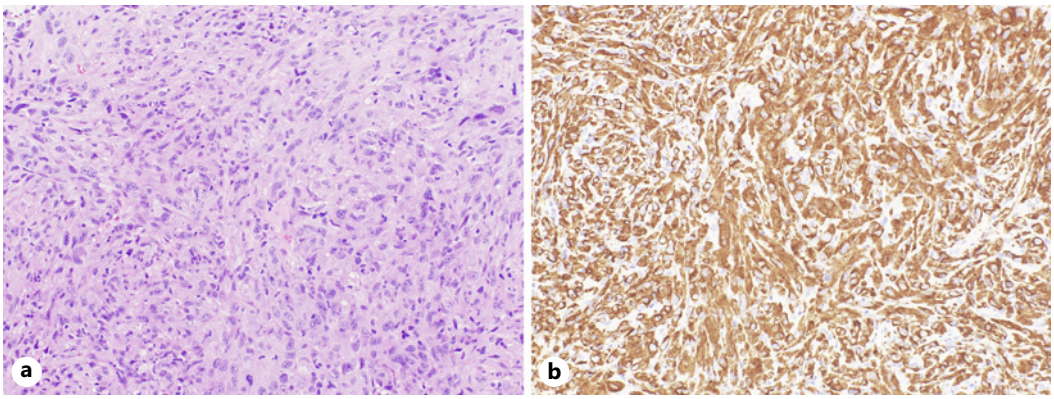

Fig. 2. a Histological staining of the brain tumor tissue shows malignant spindle cells (hematoxylin-eosin staining, magnification ×20). **b** Immunohistochemistry analysis of the brain tumor detected the high expression of echinoderm microtubule-associated protein-like 4 anaplastic lymphoma kinase.

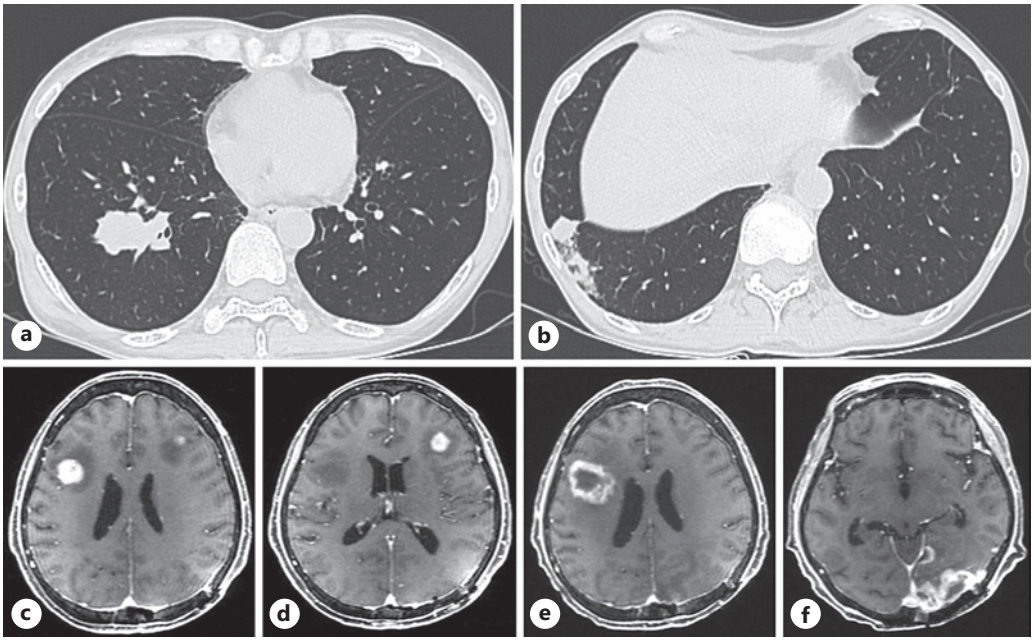

Fig. 3. Chest CT 2 months after second-line alectinib treatment (3 months after initiation of first-line treatment). **a** The mass shadow in the right lower lobe had been reduced. **b** A new nodule shadow was observed in the right lower lobe. **c**, **d** Brain magnetic resonance imaging (MRI) 2 months after initiating second-line alectinib treatment (3 months after initiation of first-line treatment) shows multiple brain metastases. **e**, **f** Brain MRI 4 months after initiating third-line lorlatinib treatment (7 months after initiation of first-line treatment) shows growth of tumors in the right frontal and left occipital lobes.

of patients with NSCLC with ALK rearrangement. Crizotinib, a first-generation ALK inhibitor, was used in 3 patients; 1 patient achieved a PFS of ≥11 months, whereas two showed relatively early progression with PFS of 3 and 7 months, respectively. The PFS with alectinib in the present case was 2 months, which was shorter than that reported in a previous study, and the overall survival was approximately 9 months. The poor prognosis of the present case might be attributed to the fact that the tumor tissue did not contain adenocarcinoma components that responded to ALK inhibitors.

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Table 1. List of pulmonary sarcomatoid carcinoma patients with ALK rearrangement treated with ALK inhibitor

Author	Age, years	Sex	Smoking	Staging	Pathology	Epithelial component type	Sarcomatous component type	Type of ALK inhibitors	Lines of ALK inhibitors	PFS
Murakami et al. [7]	50	Male	No	IV	PPC	Not listed	Spindle cells	Crizotinib	Second	3 months
Lin et al. [8]	60	Female	No	IA	PPC	Adenocarcinoma (70%)	Spindle cells (30%)	Crizotinib	First	7 months
Antonio et al. [9]	46	Female	No	IV	PSC	Not listed	Not listed	Ceritinib	Third	5 months
Chen et al. [4]	40	Female	No	IV	PPC	Adenocarcinoma (20%)	Spindle cells (80%)	Crizotinib	First	>11 months
Present case	60	Female	No	IV	PSCC	None	Spindle cells (100%)	Alectinib	First	2 months

ALK, anaplastic lymphoma kinase; PFS, progression-free survival; PPC, pulmonary pleomorphic carcinoma; PSC, pulmonary sarcomatoid carcinoma; PSSC, pulmonary spindle cell carcinoma.

Domblides et al. [13] have reported the efficacy of nivolumab in patients with previously treated PSC. The overall response and disease control rates were 40.5% and 64.8%, respectively. The efficacy of immune checkpoint inhibitor (ICI) monotherapy in patients with PSC with ALK rearrangement is unknown, as only a few reports have investigated this condition. The immunotarget registry reported a 0% overall response rate and 2.5-month median PFS in NSCLC patients with ALK rearrangement. Considering that the immunotarget registry included a relatively small number of ALK-positive NSCLC patients with high PD-L1 expression in tumor cells, it was suggested that NSCLC patients with ALK rearrangement are resistant to ICI monotherapy [14]. In the present case, only one cycle of pembrolizumab treatment was administered; therefore, the therapeutic efficacy could not be accurately evaluated. However, since the primary lesion in the lung did not shrink and PS did not improve, the therapeutic effect of ICI could not be expected.

In conclusion, PSC with ALK rearrangement is a rare type of tumor; the clinical characteristics and efficacy of ALK inhibitors and ICIs have not yet been fully investigated. Therefore, it is necessary to collect more cases from multiple institutions and conduct further investigations. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000532101).

Statement of Ethics

This study protocol and consent procedure were reviewed and approved by the Research Ethics Board of Shinshu University School of Medicine, Approval No. 4772. Written informed consent was obtained from the patient's next of kin for publication of the details of their medical case and any accompanying images. All data were conducted in accordance with the principles of the Declaration of Helsinki.

Conflict of Interest Statement

The authors declare that they have no conflict of interest.

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Author Contributions

K.S. wrote and reviewed the manuscript. K.S., S.N., Y.S., T.A., M.K., K.T., and M.H. collected patients' data.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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