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【 CASE REPORT 】

Successful Radiotherapy of Primary Malignant Peripheral Nerve Sheath Tumor of the Lung

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Abstract:

A 71-year-old man presented with cough and bloody sputum. Computed tomography showed a mass in the lower lobe of the left lung. Histological findings in biopsy tissue revealed a malignant peripheral nerve sheath tumor (MPNST). The patient was diagnosed with primary lung MPNST based on a systemic examination. Although initial chemotherapy treatment with doxorubicin failed to control the disease, radiotherapy considerably shrank the tumor. Primary lung MPNSTs are rare, and there is no established treatment for inoperable cases. This case suggests that radiotherapy is a treatment option for primary lung MPNST.

Key words: radiotherapy, malignant peripheral nerve sheath tumor, sarcoma

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Introduction

Malignant peripheral nerve sheath tumors (MPNSTs) are rare, accounting for approximately 5-10% of all sarcomas (1). Fifty percent of MPNST cases are associated with neurofibromatosis type 1. MPNSTs commonly occur in the extremities, head, and neck, but MPNSTs arising in the lung parenchyma are extremely rare (2), with an estimated rate of 0.013-0.2% among all pulmonary malignancies (1). Surgical resection is the standard choice of treatment. Previously reported cases of primary lung MPNST were all resectable (3). However, treatment for inoperable MPNSTs has not yet been established, and MPNSTs are considered to be poorly responsive to chemotherapy and radiotherapy (2).

We herein report a patient with an inoperable primary lung MPNST who successfully responded to radiotherapy but not chemotherapy.

Case Report

A 71-year-old man presented at a hospital with complaints of cough and bloody sputum. Computed tomography (CT) showed a mass in the lower lobe of the left lung, and bronchoscopy suggested sarcoma. Positron emission tomography (PET) also showed a mass in only the lower lobe of the left lung. Unfortunately, the patient stopped visiting the hospital, and serial follow-up and treatment could not be continued. One year later, his symptoms worsened, and he presented to our hospital.

He was 168 cm tall and weighed 66 kg. His vital signs were as follows: body temperature, 35.9 °C; pulse, 105 beats per minute; blood pressure, 122/71 mmHg; oxygen saturation 95%; and performance status (PS), 1. The patient was a current smoker (1 pack/day). He had no medical or family history of neurofibromatosis type 1 (NF-1). He had not previously undergone radiotherapy or received a report of a chest X-ray abnormality, as he had never had an annual medical checkup. Physical examination results were normal, and there were no skin abnormalities.

Laboratory tests showed elevated tumor markers as follows: sialyl Lewis X-1, 43.1 U/mL (reference range, 0-38 U/mL); neuron-specific enolase, 17.9 mg/mL (reference range, 0-5.4 mg/mL); and pyridinoline cross-linked car-

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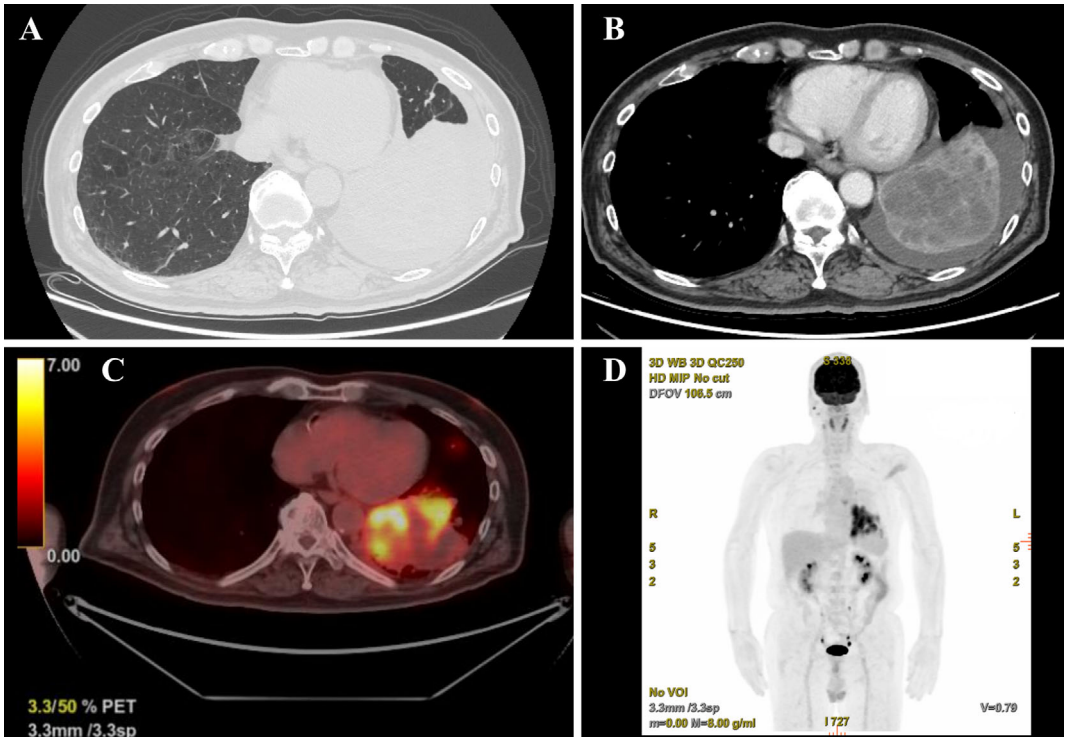

Figure 1. **(A, B) Areas S8–S10 of the left lower lobe of the lung were occupied by tumor. The left main bronchial lymph nodes were mildly enlarged. (C, D) The FDG accumulation showed an SUV_{max} of 9.0 in the mass in the left lower lobe of the lung and 3.4 in the left main bronchial lymph node. FDG: fluorodeoxyglucose ^{18}F, SUV_{max}: maximum standardized uptake value**

boxyterminal telopeptide of type I collagen, 7.6 ng/mL (reference range, 0-5.4 ng/mL). Chest CT showed a 102×82-mm mass in the lower lobe of the left lung (Fig. 1A, B). Bronchoscopy showed a necrotic white lesion obstructing the left lower lobe branch. PET showed the accumulation of fluorodeoxyglucose ^{18}F (FDG) with a maximum standardized uptake value (SUV_{max}) of 9.0 in the left lower lobe mass (Fig. 1C, D).

A histological examination of the biopsy tissue with hematoxylin and eosin staining showed a sarcoma in which necrotic tissue was conspicuous while cells with round to short spindle-shaped atypical nuclei were infiltrating and proliferating in a disorderly fashion (Fig. 2A, B). Immunohistochemical examinations were negative for epithelial stains (cytokeratin AE1/AE3, cytokeratin 7, cytokeratin 20, p 40, and 34βE12), neuroendocrine stains (thyroid transcription factor-1 and chromogranin A), hematologic stains (CD 3, CD8, CD20, and leukocyte common antigen), and mesenchymal stain (monoclonal muscle-specific anti-actin, desmin, and S100). Examinations were partially positive for α-smooth muscle actin, anti-Ki67, and p53. The biopsy tissue was negative for the tri-methylation of lysine 27 on histone H3 (H3K27me3) protein (Fig. 2C). The patient was diagnosed with MPNST of the lung (cT4N1M0, stage IIIB) based on systemic and immunohistochemical examinations.

The patient did not agree to the risks of left pneumonectomy due to concerns about the possibility of not being cured and of the potential decrease in his quality of life. In addition, the patient failed to quit smoking in order to undergo surgery. For these reasons, we were unable to perform surgery. Despite two courses of doxorubicin chemotherapy, the tumor increased in size, and chest CT showed atelectasis of the left lung (Fig. 3A, B). However, the disease stage progressed to PS 4, which we presumed to be due to respiratory failure caused by atelectasis in the left lung. We concluded that doxorubicin was ineffective and initiated radiotherapy (30 Gy in 10 fractions) for left thoracic lesions to improve atelectasis (Fig. 3B, E).

Six days later, his respiratory failure had improved, and the tumor had shrunk remarkably to 71×67 mm (Fig. 3C, F). As radiotherapy was more effective than expected, additional irradiation (15 Gy in 5 fractions) was administered. As the tumor had shrunk in size, surgical resection was recommended for a cure, but the patient refused due to concerns regarding surgical risks. The tumor stabilized in size after three months.

Discussion

The present case provides an important clinical perspective for the treatment of primary lung MPNST. This is the first case report of tumor shrinkage after radiotherapy in unresectable primary lung MPNST.

There are several diagnostic options for MPNSTs: bronchoscopy, thoracoscopy, and percutaneous and open chest biopsies. Currently, bronchoscopy is the most common ap-

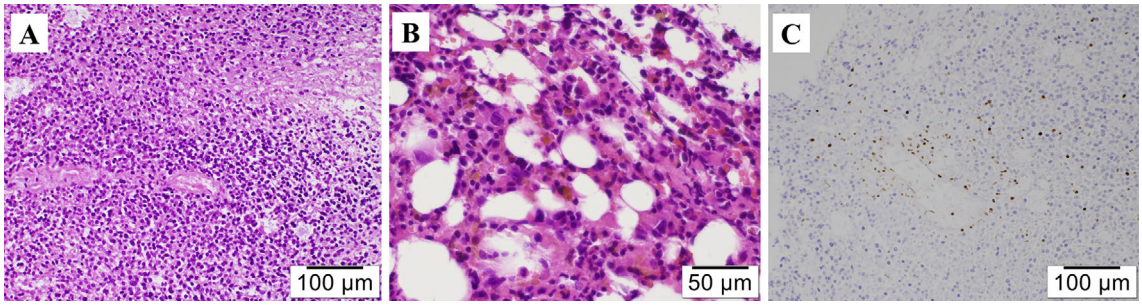

Figure 2. **(A, B) Hematoxylin and Eosin staining: necrotic tissue is conspicuous, and cells with round to short spindle-shaped atypical nuclei are infiltrating and proliferating in a disorderly fashion. (C) Immunohistochemistry was negative for the tri-methylation of lysine 27 on histone H3 protein.**

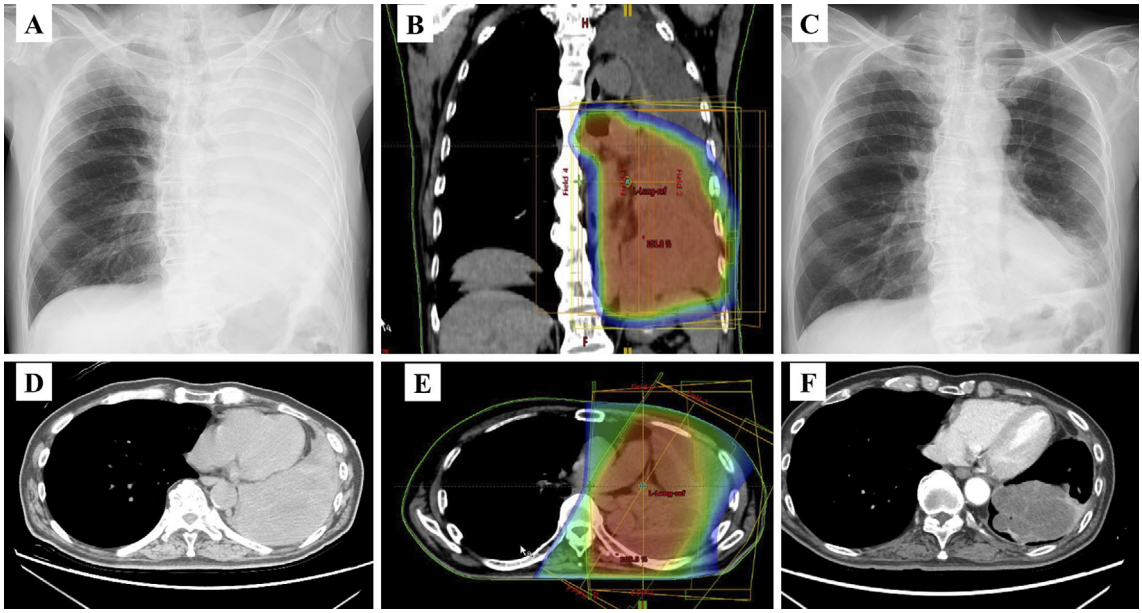

Figure 3. **The tumor shrank considerably with radiotherapy. Before (A, D) and after (C, F) radiotherapy. B and E show the field of radiotherapy.**

proach, but the quality and quantity of specimens is insufficient for a positive diagnosis, and the rarity and variety of morphological features can make diagnosis very difficult. In many cases, sarcoma is diagnosed after primary lung cancer has been diagnosed using postoperative specimens (3). Leiomyosarcoma is the most frequent sarcoma, but fibrosarcoma and angiosarcoma are also reported to be common. However, because of the low incidence of each, the exact frequency is unknown; there is wide variation in the literature (4). MPNST is reported to be difficult to diagnose, due its low incidence. A genomic analysis of MPNST identified loss-of-function genomic alterations of *SUZ12* and *EED* in approximately 70-90% of MPNSTs (5, 6). Recent studies have shown that recurrent mutations in polycomb repressive complex 2 core components, *SUZ12* and *EED*, induce global loss of the H3K27me3 epigenetic mark, with subsequent gain in acetylation. This altered chromatin state has been shown to promote MPNST (7). Schaefer et al. reported that 45-51% of all MPNSTs were negative for H3K27me3, with 83% of the cases being negative in a particularly aggressive group and 90% of sporadic MPNSTs being negative (5). In the present case, an immunohistochemical analysis revealed that the biopsy specimen was negative for H3K27me3, which strongly suggested the diagnosis of MPNST (5, 6).

The first choice of treatment for MPNST is surgical resection with margins (8-11). Several studies reported surgical resection of primary MPNSTs in the lung (11-14), and an improved disease-free survival was reported in cases where complete resection was achieved. The 5-year survival rate is between 15% and 40%. Adverse prognostic factors for MPNSTs are tumor size >5 cm, mitotic rate >20×10 per high-power field, central location, and incomplete resection (15). However, MPNST is often diagnosed at an advanced stage because of its high malignancy, invasiveness, and lack of symptoms in early stages (9-11). Mediastinal MPNST that successfully responded to ifosfamide plus doxorubicin chemotherapy was reported by Seno et al. (9). Although we administered doxorubicin for lung sarcoma, it

failed to achieve an effect. Although not part of the initial treatment plan, the present patient was treated with radiotherapy after chemotherapy. The previous doxorubicin administration may have enhanced the effect of radiotherapy. In addition, there is no established treatment for unresectable MPNSTs. Radiotherapy for MPNST in other organs has already been reported to be effective in some cases (8, 14). However, successful radiotherapy for lung MPNSTs has not been previously reported, and to our knowledge, this is the first report of lung MPNST successfully treated with radiotherapy. Our results indicate that this approach should be considered as a treatment option for lung MPNST.

Conclusion

Since the number of cases of lung MPNST is very small, it is difficult to prove the efficacy of radiotherapy. However, we believe that radiotherapy can be recommended for patients with unresectable, chemoresistant lung MPNST.

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

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