

[ CASE REPORT ]

## Pazopanib Confers a Progression-free Survival in a Patient with Ewing's Sarcoma/Primitive Neuroectodermal Tumor of the Lung

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### Abstract:

Ewing's sarcoma (ES)/primitive neuroectodermal tumors (PNETs) are highly malignant neoplasms that usually affect the bones and soft tissues in children and young adults. ES/PNET of the lung is very rare and is associated with a poor prognosis. We herein report a case of ES/PNET of the left lung in a 45-year-old man. He was treated with neoadjuvant chemotherapy and pneumonectomy, but unfortunately his disease recurred 1.5 months after surgery. He was started on pazopanib, which resulted in a five-month progression-free survival. To our knowledge, this is the first demonstration of pazopanib efficacy in ES/PNET of the lung.

**Key words:** Ewing's sarcoma, primitive neuroectodermal tumors, pazopanib

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### Introduction

Ewing's sarcoma (ES)/primitive neuroectodermal tumor (PNET) is a relatively rare malignant bone neoplasm that usually occurs in children and young adults. ES/PNET of the lung is extremely rare and is associated with a poor prognosis.

The standard first-line treatment for patients with these tumors includes chemotherapy with the five-drug regimen of vincristine, doxorubicin, cyclophosphamide, ifosfamide and etoposide (VDC/IE). However, despite the number of salvage regimens available, a second-line standard therapy has not been established.

We herein report a rare case of refractory ES/PNET of the lung responding to pazopanib, an oral multi-target tyrosine kinase inhibitor.

### Case Report

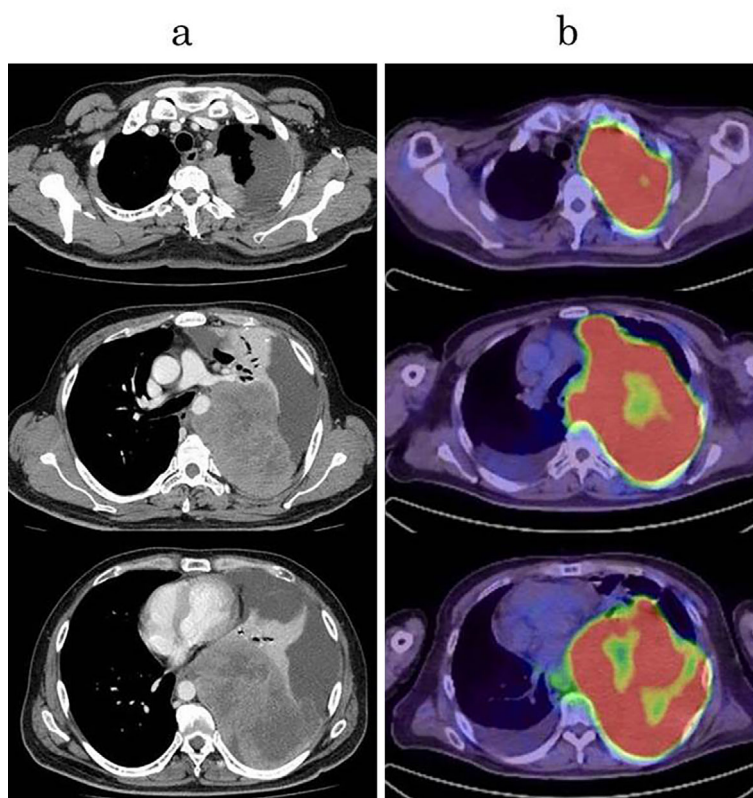
A previously healthy 45-year-old man was admitted to a regional hospital because of a low-grade fever, coughing and shortness of breath. He was initially diagnosed with a cold, but his symptoms worsened daily. A postanterior chest radiograph view suggested left-sided massive pleural effusion. He was referred to our hospital and admitted 10 days later.

The findings of a laboratory examination were as follows: white blood cell count 8,100/ $\mu$ L, hemoglobin 12.6 g/dL, platelet count 458,000/ $\mu$ L, C-reactive protein 5.11 mg/dL, lactate dehydrogenase (LDH) 775 U/L. Renal function test findings were normal. The neuron-specific enolase (NSE) level was 250.8 ng/mL (upper limit 12.0 ng/mL), and the pro-gastrin-releasing peptide (ProGRP) level was 742 pg/mL (upper limit 81 pg/mL). Computed tomography (CT) of an axial section of the chest revealed a large, well-defined, heterogeneously enhanced soft tissue mass lesion in the left

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**Figure 1.** Computed tomography (axial section) of the thorax showing a large heterogeneously enhanced soft tissue mass lesion involving the left hemithorax and gross left pleural effusion (a).  $^{18}\text{F}$ FDG-PET/CT imaging showed an increased FDG uptake in the mass lesion of the left lung (b).

lung, and gross left pleural effusion (Fig. 1a). Positron emission tomography (PET) using  $^{18}\text{F}$ -fluorodeoxyglucose (FDG) showed an increased FDG uptake (maximal standard uptake value 14.59) in the left lung lesion but no evidence of distant metastasis (Fig. 1b).

Since the NSE and ProGRP levels were very high, we suspected small cell lung cancer at first. We performed thoracoscopy under local anesthesia and found small and large elevated lesions on the visceral pleura surface. No evidence of malignancy was found in the chest wall and parietal pleura. The patient then underwent a thoracoscopy biopsy under general anesthesia, which revealed small round cells with scant cytoplasm, round to oval nuclei, and fine granular to vesicular chromatin; these characteristics were suggestive of a malignant small round cell tumor. Immunohistochemistry revealed that the tumor cells were strongly positive for CD99/MIC2 and NSE. The tumor cells also demonstrated focal reactivity for AE1/AE3 and were desmin-negative (Fig. 2). These histological and immunohistochemical findings were compatible with ES/PNET. A fluorescent *in situ* hybridization (FISH) assay demonstrated positive rearrangement of the ESWR1 gene at the 22q12 locus (Fig. 3). Thus, a definitive diagnosis of primary ES/PNET of the lung was made.

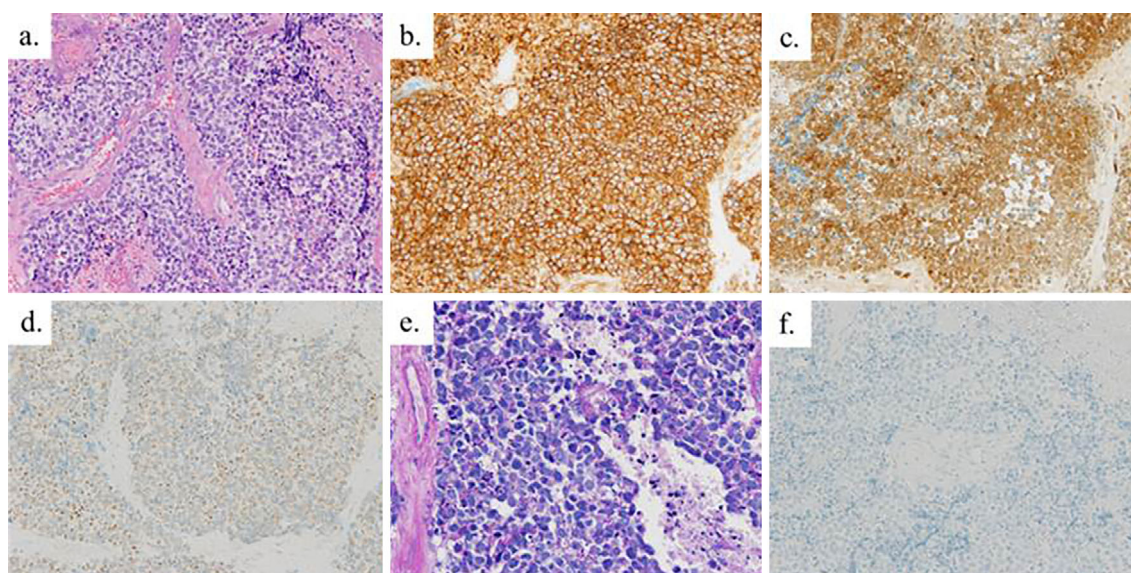
The tumor was massive and close to the descending aorta, necessitating tumor volume reduction by neoadjuvant chemotherapy. He therefore received vincristine, doxorubicin, cyclophosphamide, ifosfamide and etoposide (VDC/IE).

During each cycle of chemotherapy, the patient required frequent blood transfusions and continuous use of granulocyte colony-stimulating factor due to severe bone marrow suppression.

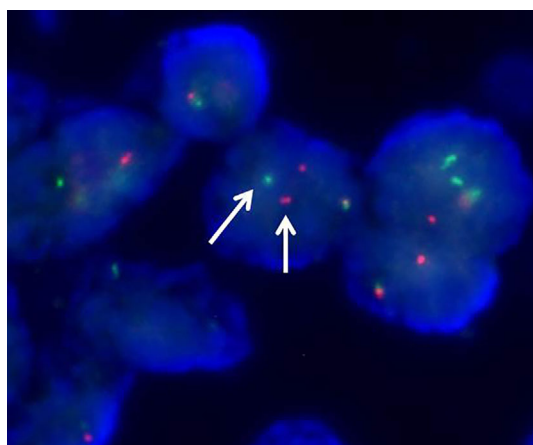
After five cycles of neoadjuvant chemotherapy, the tumor size was remarkably reduced (Fig. 4). The patient underwent left pneumonectomy and aortic stent placement five months after diagnosis. The tumor strongly adhered to the chest wall and the aorta. It was difficult to remove the tumor from the visceral pleura. Histologically, the tumor cells showed almost the same findings as the thoracoscopy biopsy. The pleural surgical margin was positive.

About 1.5 months after surgery, a soft tissue mass lesion was found in the left hemithorax, which was confirmed to be a postoperative recurrence (Fig. 5a). Because the cumulative dose of doxorubicin was close to  $500\text{ mg/m}^2$ , the patient received 1 course of VAC/IE, in which doxorubicin was replaced with actinomycin D. However, the tumor grew rapidly.

Pazopanib was started 9 months after the diagnosis at  $800\text{ mg}$  a day. Four weeks later, chest CT showed a reduction in tumor size that qualified as stable disease according to the RECIST criteria (Fig. 5b); the serum LDH level and CRP were also decreased. Neutropenia and thrombocytopenia were observed as pazopanib-related adverse events. We decided that interruption and dose reduction of pazopanib was appropriate. Following this, treatment was continued. After five months of pazopanib treatment, the patient complained



**Figure 2.** A biopsy of the lung lesion showing small round cells with condensed chromatin on Hematoxylin and Eosin staining (a). Immunohistochemistry shows strong positivity for CD99 (b) and NSE (c). Focal reactivity for AE1/AE3 (d) and PAS (e). Negativity for desmin (f).



**Figure 3.** A fluorescence *in situ* hybridization analysis showing EWSR1 22q12 rearrangement (arrows).

of fatigue and dyspnea. Chest CT at that point showed disease progression (Fig. 5c) and increased serum levels of LDH, CRP, and NSE; ProGRP was also increased.

Trabectedin (1.5 mg/m<sup>2</sup> as a 24-h continuous infusion every 3 weeks) was initiated as the next-line therapy. However, the patient's condition rapidly worsened, and he died 15 months after the diagnosis.

## Discussion

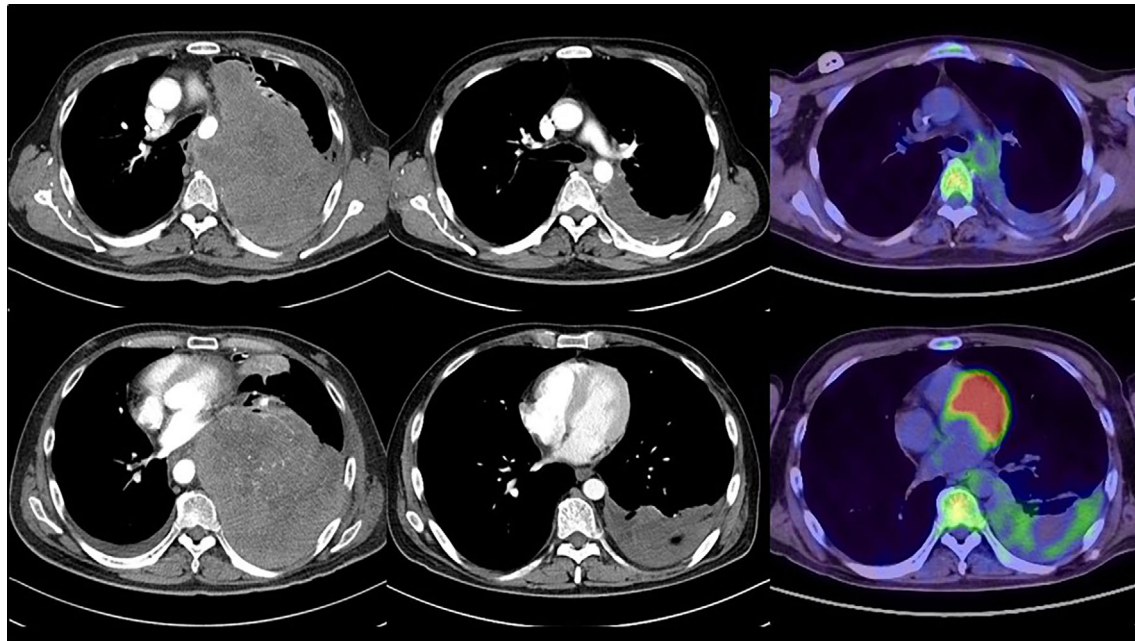
PNET was first reported as an undifferentiated small round cell tumor of the ulnar nerve development by Stout et al. in 1918 (1). ES was first described in 1921 by James Ewing, who reported a case of a highly malignant tumor in the diaphysis of the long bones in a 14-year-old girl (2). In 1979, Askin et al. described a similar rare malignant small-cell tumor of the thoracopulmonary region in 20 children

and adolescents with a mean age of 14 years; this became known as an 'Askin's tumor' (3). The initiating lesions that give rise to these tumors were unknown for many years. However, a common characteristic gene translocation that results in the expression of a fusion gene product has been identified, and the above tumors are now all considered subtypes of the same disease.

ES/PNET is a highly malignant neoplasm that usually affects the bones and soft tissues in children and young adults. ES/PNET of the lung is rare: only 18 cases have been described in adults in the English literature since 2010 (4-14). The tumor tends to occur at a relatively young age and has no gender preference. Prior to the use of multi-agent chemotherapy, the long-term survival of ES/PNET was less than 10%. At present, most clinical centers performing intensive chemotherapy report long-term survival rates of 60-70%, suggesting that ES/PNET is sensitive to anti-cancer drugs. The current chemotherapy protocols used to treat ES/PNET include various combinations of the following six drugs: doxorubicin, cyclophosphamide, vincristine, actinomycin-D, ifosfamide and etoposide. Chemotherapy is the first-choice treatment for ES/PNET, and the subsequent combination of surgery and radiation constitutes the standard therapy.

Several trials have attempted to determine an appropriate second-line therapy, including studies on the ICE regimen (ifosfamide, carboplatin, and etoposide), topotecan plus cyclophosphamide, and the irinotecan (CPT-11) plus temozolomide regimen, as well as new drugs, such as pazopanib, eribulin and trabectedin. Despite the number of salvage regimens available, refractory recurrent or metastatic ES/PNET is usually fatal, and a second-line standard therapy has yet to be established.

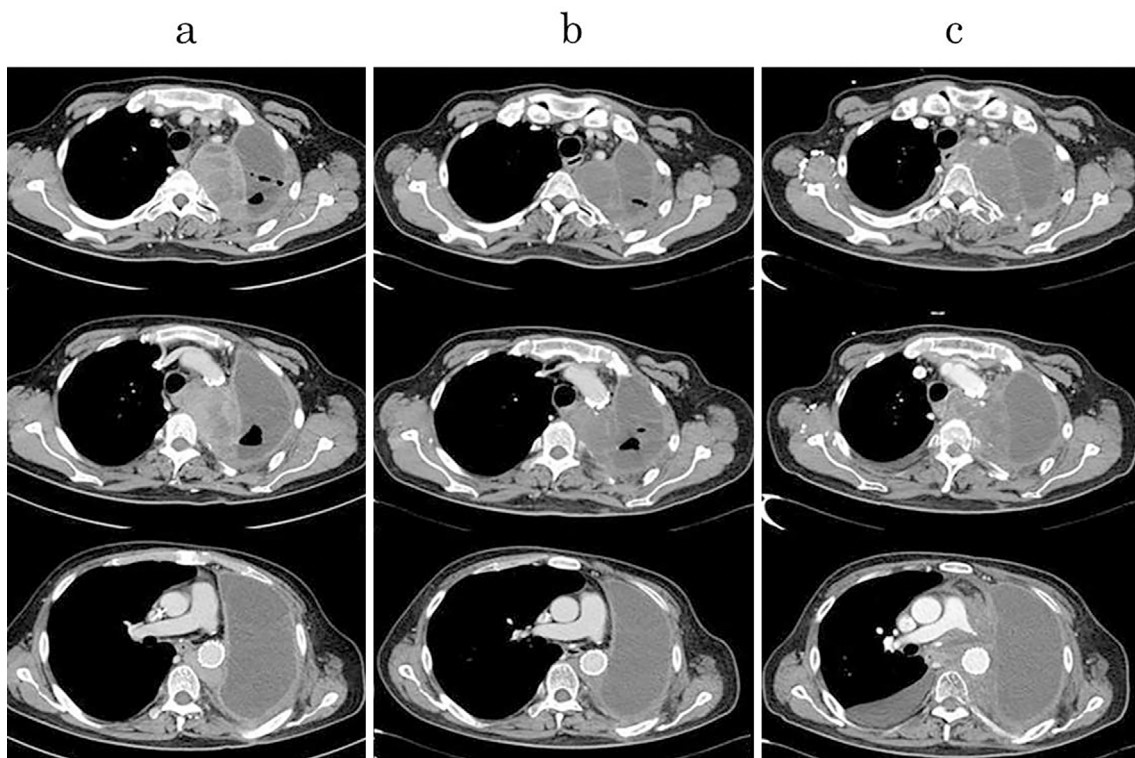
Pazopanib is an orally available, multi-target tyrosine



Before treatment

After 5 cycles of VDC/IE

**Figure 4.** Computed tomography (axial section) of the thorax and <sup>18</sup>F-FDG-PET/CT during VDC/IE. After five cycles of VDC/IE, the tumor size was remarkably reduced.



**Figure 5.** Computed tomography (axial section) of the thorax (a: postoperative recurrence, b: pazopanib day 28, c: pazopanib day 163).

kinase inhibitor with activity against vascular endothelial growth factor receptor 1 (VEGFR-1), VEGFR-2 and VEGFR-3 and against platelet-derived growth factor receptor a (PDGFR-a), PDGFR-b and c-Kit. The European Organiza-

tion for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group (STBSG) carried out a Phase 3 study [pazopanib for metastatic soft-tissue sarcoma (PALETTE)] to evaluate the efficacy of pazopanib in patients with soft

tissue sarcoma who relapse after previous chemotherapy (15). The median progression-free survival (PFS) was 4.6 months [95% confidence interval (CI) 3.7-4.8] for pazopanib compared with 1.6 months (0.9-1.8) for placebo [hazard ratio (HR) 0.31, 95% CI 0.24-0.40;  $p < 0.0001$ ]. Thus, a significant 3-month advantage with regard to the PFS was observed in the pazopanib arm. Two cases of ES/PNET were included in this study, but both were assigned to the placebo group, so the effect of pazopanib could not be determined. Pazopanib is not considered a standard therapy for ES/PNET of the lung. The present patient required frequent blood transfusions and the continuous use of granulocyte colony-stimulating factor due to severe bone marrow suppression during each cycle of VDC/IE. We therefore considered pazopanib as a treatment option for our patient. In our case, the patient responded to pazopanib with carefully planned withdrawal and dose reduction. The patient was able to continue the treatment for about five months.

Interestingly, there have been two previous reports of ES/PNET patients responding to pazopanib (16, 17). However, the sites of the primary tumors in these cases were the pelvis and vertebral body, not the lung. To our knowledge, this is the first report of a case of refractory ES of the lung responding to pazopanib.

In summary, we encountered a case of pulmonary primary ES that responded to pazopanib treatment for about five months. When standard treatment is ineffective, pazopanib may be a useful treatment option for this disease.

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

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