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Case Study

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A CASE OF POSTOPERATIVE RECURRENCE OF JUVENILE LUNG CANCER SUCCESSFULLY TREATED WITH ANAPLASTIC LYMPHOMA KINASE-TYROSINE KINASE INHIBITOR SEQUENTIAL THERAPY

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ABSTRACT

Anaplastic lymphoma kinase (ALK)-tyrosine kinase inhibitors (TKIs) have been approved for the treatment of postoperative recurrence of non-small cell lung cancer (NSCLC) caused by ALK rearrangement. A 38-year-old man underwent left upper lobectomy with mediastinal lymph node dissection for lung cancer (pT2aN2M0, stage IIIA). A gene mutation analysis showed negative epidermal growth factor receptor mutations and an ALK-positive translocation (fluorescence in situ hybridization-positive, ALK iScore 3 by iAEP immunohistochemistry). Crizotinib was administered postoperatively. Seventeen months later, computed tomography and positron emission tomography revealed paratracheal lymph node metastases. Crizotinib was discontinued, and treatment with a second-generation ALK-TKI, alectinib, was begun. Two months later, a partial response was achieved. No severe adverse events were observed. We continued the treatment with alectinib for more than 48 months, and a near-complete response was achieved. This patient's management suggests that ALK-TKI sequential therapy (crizotinib to alectinib) may be safe and effective in ALK-positive NSCLC.

KEYWORDS: Anaplastic lymphoma kinase (ALK), tyrosine kinase inhibitor (TKI), lung cancer, crizotinib, alectinib.

BACKGROUND

Alectinib is a second-generation anaplastic lymphoma kinase (ALK) inhibitor with a favorable clinical activity in crizotinib-resistant ALK-positive non-small cell lung cancer. A previous phase II study reported its effectiveness in patients pretreated with other ALK inhibitors, including crizotinib.[1][2] Moreover, the phase III ALEX and J-ALEX studies showed that alectinib significantly reduced the risk of disease progression than crizotinib, when used as an initial treatment for ALK positive non-small cell lung cancer (NSCLC).[3][4] Therefore, alectinib is one of the first-line ALK inhibitors. The use of alectinib as a first-line or second-line treatment for patients with ALK-positive NSCLC after crizotinib failure is still controversial. Therefore, we report the case of a 38-year-old with ALK-rearranged NSCLC, treated with alectinib after crizotinib failure.

CASE PRESENTATION

A 38-year-old man with no smoking history presented to our hospital with an incidentally found mass in the left lung, which was detected on a chest radiograph during a medical checkup (Fig. 1). Computed tomography (CT) and positron emission tomography (PET) findings were suggestive of lung cancer with left hilar lymph node metastasis (Fig. 2). The patient underwent left upper lobectomy with mediastinal lymph node dissection. The pathological diagnosis was invasive adenocarcinoma with subaortic lymph node and subcarinal lymph node metastasis (pT2aN2M0, stage IIIA). A gene mutation analysis showed negative epidermal growth factor receptor mutations. Tumor cells were positive for the ALK antibody, as seen during the immunohistochemical analysis (ALK iScore 3 by iAEP immunohistochemistry) (Fig. 3). ALK breakapart fluorescence in situ hybridization confirmed the presence of an ALK gene rearrangement with rearrangement-positive cell rates of 76.0%. Because of the multiple-station N2 disease, we selected crizotinib, an ALK tyrosine kinase inhibitor (TKI), for postoperative therapy. Seventeen months after crizotinib therapy initiation, CT and PET revealed paratracheal lymph node metastases, although there were no severe adverse events (Fig. 4). Crizotinib was discontinued, and we initiated a second-line therapy with another ALK-TKI, alectinib. After two months of treatment with alectinib, a remarkable radiological response was achieved (Fig. 5). We continued the

treatment with alectinib for more than 48 months without any adverse events, and a near-complete response was achieved (Fig. 6).

DISCUSSION

ALK gene rearrangement is detected in 2% to 5% of NSCLCs.[5][6][7] Crizotinib, a first-line ALK inhibitor, has shown a clinical efficacy in the treatment of NSCLC with ALK rearrangement.[8] However, most patients develop resistance to crizotinib within 1 year of therapy.[8][9][10] New ALK inhibitors such as ceritinib and alectinib have been developed to overcome resistance to crizotinib. Treatment with these second-generation ALK inhibitors have been well-tolerated and have shown an efficacy in crizotinib-resistant ALK-rearranged lung cancers, as shown by improved overall response rates (ORRs) and progression-free survivals (PFSs).[1][2][11]

As shown in a North American Study (NCT01871805), the ORR of alectinib after crizotinib failure was 48%.[2] Moreover, some Japanese retrospective studies of crizotinib followed by alectinib reported favorable median PFSs in patients treated with alectinib after crizotinib failure.[12][13]

Recently, two randomized, open-label, phase 3 trials of alectinib verus crizotinib in patients with ALK-positive NSCLC were conducted. One is the ALEX Study, and the other is the J-ALEX Study.[3][4] In these two clinical trials, alectinib was more effective than crizotinib. The median PFS was not yet attained with alectinib (95% confidence interval 20.3-not estimated) and was 10.2 months (8.2-12.0) with crizotinib in the J-ALEX Study.[4] The most important clinical question is whether the use of alectinib as a first-line therapy or second-line therapy after crizotinib failure is better for patients with ALK-positive NSCLC. To address this question, we compared the OS of patients treated with alectinib alone with those receiving sequential therapy with alectinib after crizotinib failure. The final PFS results from the J-ALEX Study were reported in 2020.[14] The median follow-up was 42.4 months for alectinib and 42.2 months for crizotinib. The median PFS with alectinib was 34.1 months versus 10.2 months with crizotinib. However, in the second interim overall survival (OS) analysis, no conclusion on the superiority of alectinib to crizotinib could be made (median OS not reached with alectinib versus 43.7 months for crizotinib).

Our patient was first treated with crizotinib for 17 months and was sequentially treated with alectinib for 48 months after crizotinib failure. The total therapeutic duration was 65 months and is still ongoing without any observed adverse events or lung cancer progression. Our case suggests that sequential therapy with crizotinib followed by alectinib after crizotinib failure provides a better clinical benefit than alectinib alone for the treatment of patients with ALK-positive NSCLC. However, to confirm these observations, well-controlled prospective studies of patients treated with alectinib alone and those receiving sequential therapy with crizotinib and alectinib after crizotinib failure are needed.

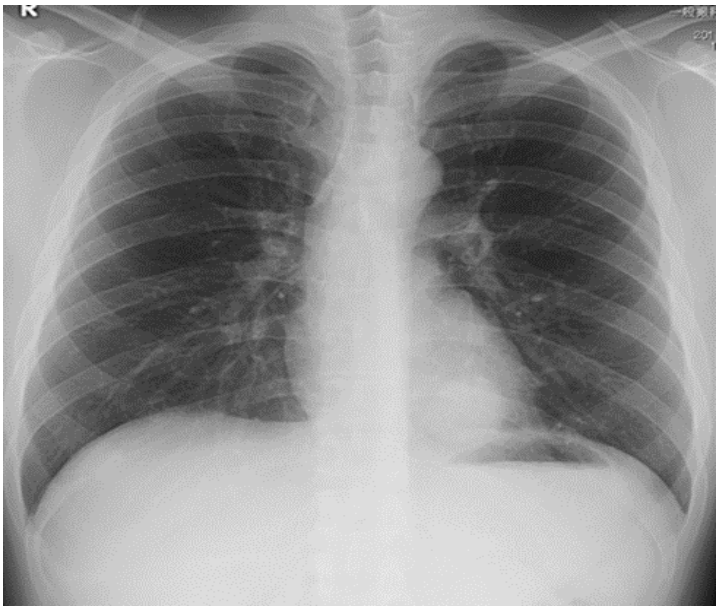

Fig. 1: Chest roentogenogram showed a mass lesion in the left lower lung field.

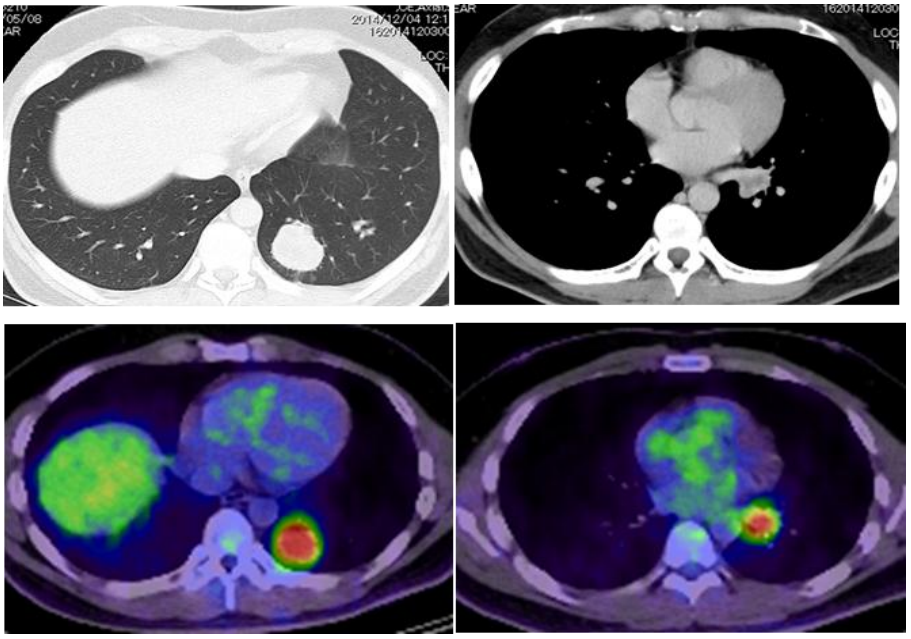

Fig. 2: Chest computed tomography (CT) and positron emission tomography (PET) suggested a primary lung tumor in the left lower lobe and left hilar lymph node metastasis.

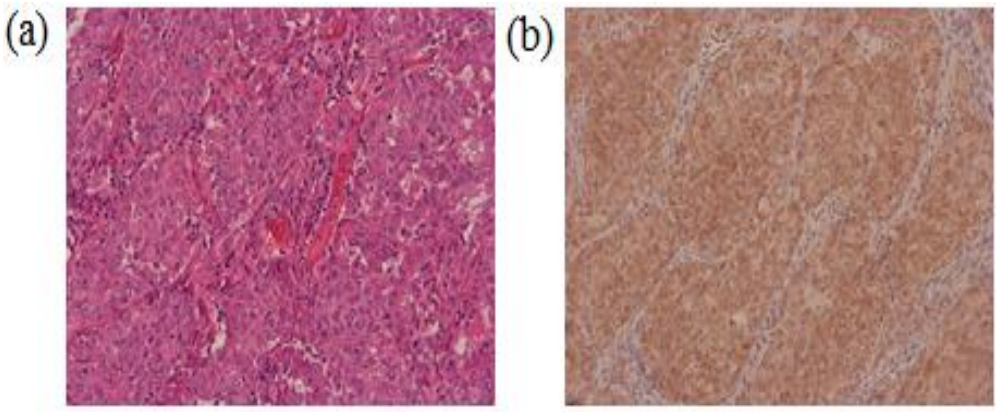

Fig. 3: Microscopic findings and anaplastic lymphoma kinase (ALK)-immunohisto-chemical findings of the tumor.

(a) Solid adenocarcinoma was suggested (Hamatoxylin-eosin ×200).

(b) Immunohistochemical analysis indicated that the tumor cells were positive for the ALK antibody. (ALK iScore 3 by iAEP immunohistochemistry ×200).

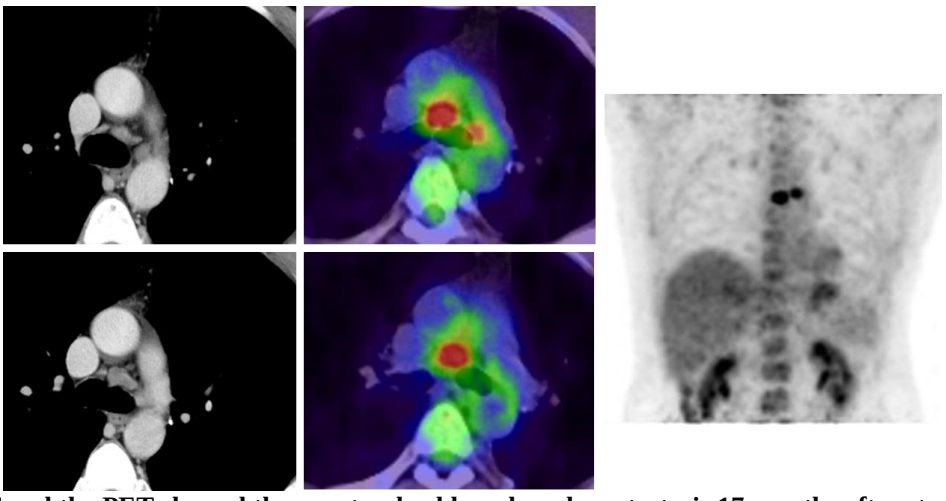

Fig. 4: The CT and the PET showed the paratracheal lymph node metastasis 17 months after starting crizotinib therapy.

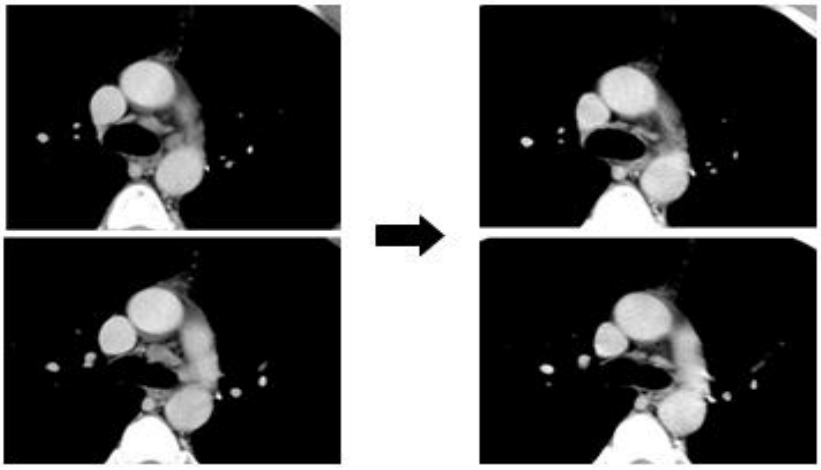

Fig. 5: The CT findings of pre- (left) and post- (right) alectinib treatment.
Two months after starting alectinib treatment, a remarkable radiological response was achieved.

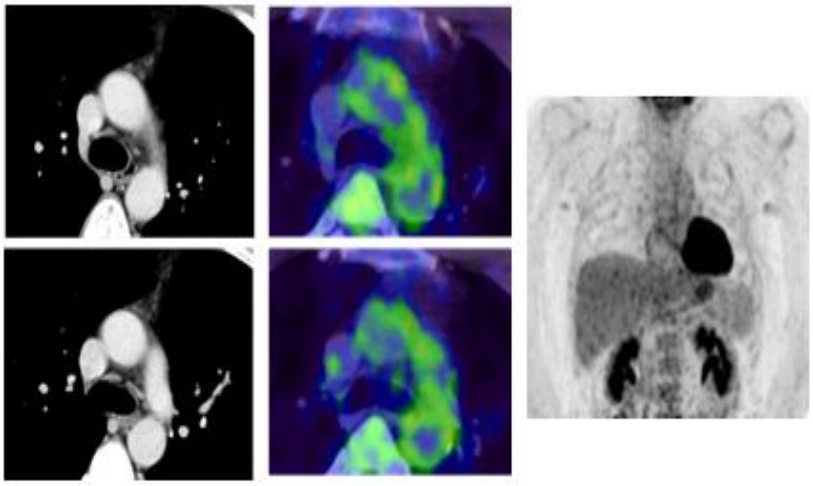

Fig. 6: The CT and the PET 24 months after starting alectinib treatment.
The therapeutic effect reached complete response (CR).

CONCLUSIONS

The management of this patient suggests that ALK-TKI sequential therapy (crizotinib to alectinib) may be safe and effective for ALK-positive NSCLC. The sequential use of multiple ALK-TKIs might prolong the survival of patients with ALK-rearranged NCSLC.

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