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Octogenarians With Anaplastic Lymphoma Kinase-rearranged Non-small-cell Lung Cancer: A Case Series

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Abstract. *Background/Aim: Anaplastic lymphoma kinase (ALK) rearrangements define a distinct group of patients with non-small-cell lung cancer (NSCLC), mainly represented by never-smoking young individuals. However, we also encounter elderly patients with ALK-rearranged NSCLC over the age of 80 years. We report herein three cases of these patients that we have experienced. Case Report: Three patients with ALK-rearranged NSCLC aged 80 years or older received therapy with the ALK-tyrosine kinase, alectinib. Of them, one was male and two had a history of smoking. Comorbidities, especially heart diseases, were prominent. Long-term survival was achieved with alectinib treatment in two patients. Conclusion: ALK-rearranged mutations should be evaluated even in octogenarians with NSCLC, regardless of sex and smoking history. Even if they have comorbid diseases, long-term control might be achieved with alectinib therapy in cooperation with physicians other than chest physicians and medical oncologists.*

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Key Words: Anaplastic lymphoma kinase, lung adenocarcinoma, long-term survivor, elderly, octogenarian.

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In general, it is estimated that the proportion of patients with comorbidities increases with age. This may be true for patients with non-small cell lung cancer (NSCLC) (1, 2). Chemotherapy is a burdensome treatment for patients. Therefore, the proportion of patients receiving it appears to decrease with increasing age (1, 2).

In some previous studies, patients with NSCLC aged ≥80 years were shown to be less likely to receive chemotherapy as initial treatment than those aged 70-79 years (1-3). In these studies, comorbidity, cigarette smoking, age ≥80 years, and Eastern Cooperative Oncology Group performance status ≥2 were considered to be poor prognostic factors in multivariate analysis (1-3). In our previous study of patients with NSCLC over the age of 80 years, 49.3% of patients had two or more comorbid diseases, and 27.8% of them had a Charlson Comorbidity Index of 2 or more (2). With regard to comorbid diseases in elderly patients with lung cancer, cardiovascular diseases (CVDs) were one of the most common (4-6). Although there are few reports on the frequency of CVD in patients over the age of 80 years with lung cancer, 41% of lung cancer patients 80 years old or over had CVDs in our previous study (3).

Anaplastic lymphoma kinase (*ALK*)-rearranged gene mutation is an oncogenic driver of NSCLC and commonly associated with younger age (7, 8). Studies over a decade after the discovery of *ALK* rearrangements have reported that the median or average age of patients with such rearrangements was 50 years (7, 8). However, some recent studies reported that the median age of patients with *ALK*-rearranged NSCLC was in the mid 60s (9, 10).

ALK-tyrosine kinase inhibitors (TKIs) are the standard treatment for *ALK*-rearranged NSCLC, and alectinib is currently the first-line drug (11). None of the guidelines provide specific treatment for very elderly ALK receptor tyrosine kinase (*ALK*) rearrangement-positive patients. Therefore, it seems that alectinib treatment is being performed in the same way as for younger patients but, as far as we are

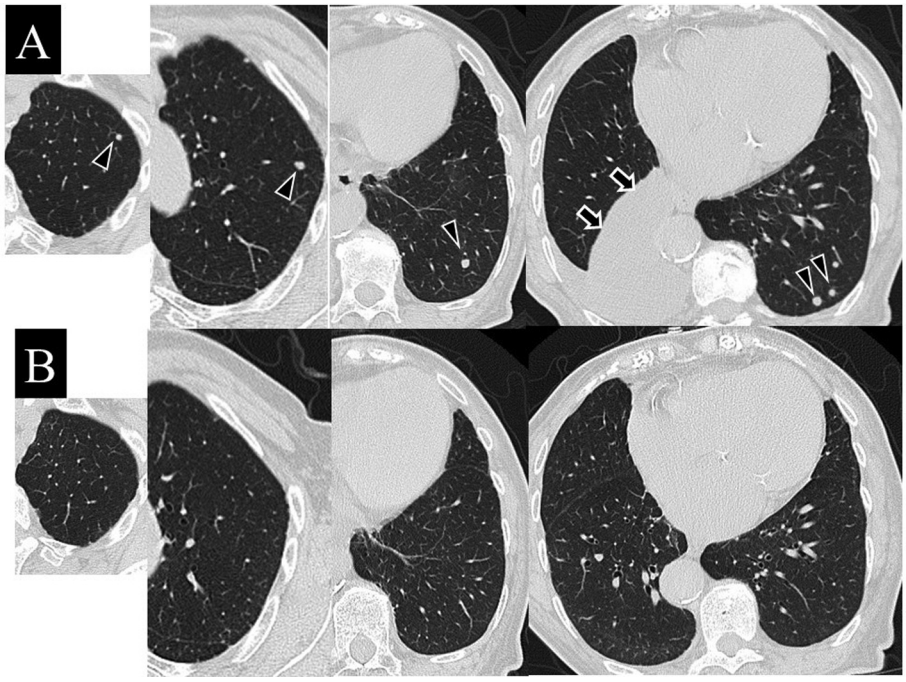

Figure 1. *Chest computed tomography of patient 1 taken at the time of the first visit showed a primary lesion in the right lower lobe (arrows) and metastatic lesions in both lungs (arrowheads) (A). Chest computed tomography taken 3 months after starting alectinib showed disappearance of bilateral lung lesions (B).*

aware, there has been no report on actual treatment for elderly patients. To the best of our knowledge, nor has there been any report on the long-term treatment with alectinib of *ALK*-rearranged NSCLC in patients aged 80 years or older.

We show herein the clinical courses of three such patients as we believe that this provides valuable information for the treatment of patients who have a similar course.

Case Report

This study was approved by the institutional Ethics Committee of our Institute (NO16-66). Written comprehensive informed consent at the time of admission for obtaining pathological specimens was obtained from the patient.

Case 1. An 83-year-old woman with a history of chronic heart failure due to aortic valve stenosis was referred to our hospital due to an abnormal opacity in the right lower lobe of the lung, which was detected by chance on a chest radiograph taken during follow-up for heart disease. Chest computed tomography (CT) showed multiple nodules in both lungs in addition to this opacity (Figure 1A). The patient was diagnosed as having stage VIA *ALK*-rearranged adenocarcinoma, and she was treated with alectinib. Chest CT taken 3 months after starting alectinib showed the disappearance of bilateral lung lesions (Figure 1B). Several times during the patient's clinical course, heart failure and cerebral infarction were exacerbated and required hospital treatment. But administration of alectinib was able to be continued except during the acute phase of these comorbid diseases. In spite of disease control with alectinib, she died of cerebral infarction 32 months after the initiation of alectinib. No adverse event of alectinib therapy was found.

Case 2. An 82-year-old man with a history of mitral valve regurgitation and diabetes mellitus was referred to us. He had a history of heavy smoking. A nodule was detected in the upper lobe of the right lung during the course of treatment for these diseases. The nodule was resected and was diagnosed as stage IA *ALK*-rearranged adenocarcinoma. However, it recurred 35 months after surgery, and alectinib treatment was started. This treatment has continued for 36 months and there has been no recurrence of lung cancer. No adverse effects in physical examination nor laboratory test values have been found.

Case 3. An 80-year-old woman with a history of thyroid cancer, diabetes mellitus, hypertension and *angina pectoris* presented to us. She had a history of smoking for 15 pack-years. A nodule in the left lower lobe was detected by chance on a chest radiograph taken during follow-up for heart disease. Chest CT showed a primary lesion and atelectasis in the lower lobe of the left lung, multiple nodes in both lungs and liver

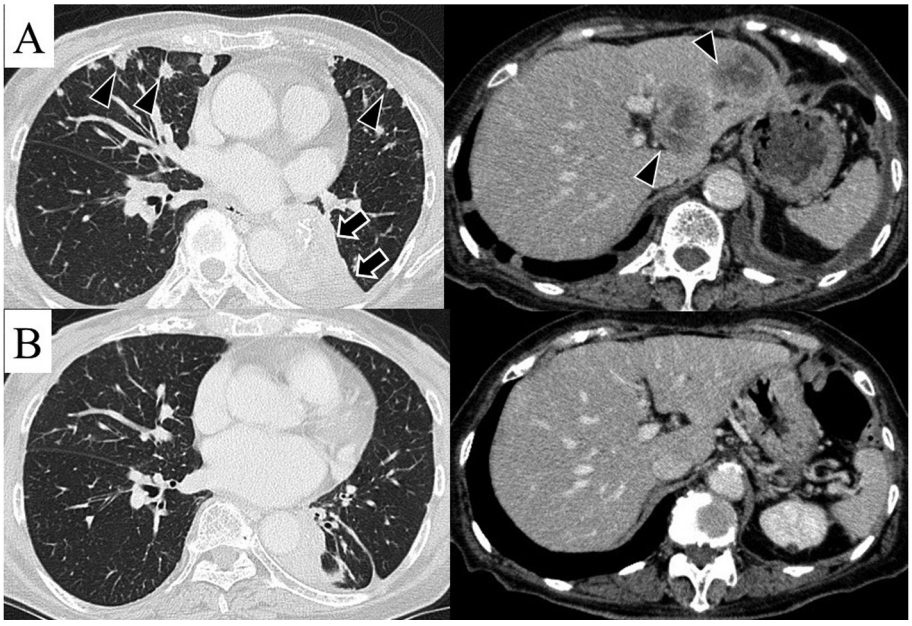

Figure 2. *Chest computed tomography of patient 3 showed the primary lesion and atelectasis in left lower lobe of the lung, multiple nodes in both lungs and liver metastases (A). Chest computed tomography scan taken 4 months after the initiation of alectinib showed shrinkage of the primary lesion and disappearance of lung and liver metastases (B).*

metastases (Figure 2A). The patient was diagnosed as having stage VIB *ALK*-rearranged adenocarcinoma, and she was treated with alectinib. Chest CT scan taken 4 months after the initiation of alectinib showed shrinkage of the primary lesion and disappearance of lung and liver metastases (Figure 2B). Thirteen months have passed since the start of alectinib therapy, and it is still ongoing. There has been no adverse effect on physical examination and laboratory test values.

Table I shows the background data and treatment of these octogenarians with *ALK*-rearranged NSCLC. All had adenocarcinoma, but not all were females. There was only one non-smoker; the other two patients were light and heavy smokers. All of them had comorbid diseases that could not be overlooked.

Discussion

In the study, we were unable to investigate the comorbid diseases in patients with *ALK*-rearranged NSCLC in detail. It would be meaningful to investigate their comorbidities from the viewpoint of understanding the patient's background and the influence on *ALK*-TKI treatment. In the present study, one of the three patients was male and two had a history of smoking. Of interest in the present study, two had valvular disease and one had angina. Patient 1 had had several episodes of congestive heart failure attributed to aortic valve stenosis.

There are few reports on the frequency of *ALK*-rearranged in patients aged 80 years or older with NSCLC. Tufman *et al*. reported that three (1.7%) out of 179 patients with NSCLC aged ≥80 years had *ALK*-rearranged NSCLC (12). In our previous population-based study of *ALK*-rearranged NSCLC, eight (6.2%) out of 129 patients were 80 years or older (13). In general, *ALK* rearrangement-positive patients are considered to be non-smokers or light smokers (14). As a case report, a few patients with *ALK*-rearranged NSCLC aged 80 years or older have been reported (15-18). At least one of them had a history of smoking (17). In our previous survey, three out of eight had a history of smoking, and their median pack-year smoking index was low, at 20 (13). With regard to comorbid diseases, no report has focused on this aspect, although there were reports of patients with poor performance status due to the progression of NSCLC (17, 18). As observed in the present study, very elderly patients with NSCLC have a higher prevalence of heart diseases (1, 2). Therefore, attention should be paid to this as a comorbidity and it would be desirable to select a treatment method that considers this complication.

Alectinib is now recommended as first-line therapy for patients with *ALK*-rearranged NSCLC (19). In a large-scale clinical trial in Japanese patients, median progression-free survival (PFS) was 34.1 months (20). Median PFS was also 31 months in our community-based retrospective survey (13). In that study, six patients 75 years or older received alectinib, and their PFS was 25 months, with 3-year survival of 50%.

Table I. *Characteristics of the three studies' patients.*

	Patient number		
	1	2	3
Age, sex	83 Years, female	82 Years, male	80 Years, female
ECOG PS at diagnosis	1	0	1
Smoking, pack-years	0	100	15
Comorbid disease	AS, chronic heart failure	DM, MR	Thyroid cancer, DM, angina, HT
Site of primary lesion, size	Right lower lobe, 20 mm	Right upper lobe, 18 mm	Left lower lobe, 53 mm
Pathology	Adenocarcinoma	Adenocarcinoma	Adenocarcinoma
TNM, stage	T2aN3M1a-IVA	pT1aN0M0 p-IA	T4N3M1c-IVB
Metastatic site at diagnosis	Lung (multiple)	None	Lung (multiple), liver (multiple)
ALK assessment method	FISH	Immunohistochemistry	FISH
PD-L1	0	Unknown	75%
CEA, ng/ml	123.0	3.8	210.6
CYFRA, ng/ml	3.2	1.0	7.6
Recurrence after surgery	-	Yes	-
First-line chemotherapy	Alectinib	Alectinib	Alectinib
Progression-free survival, months	32	>36	>13
Overall survival, months	32	>71	>13
Current status	Dead	Alive	Alive

ALK: ALK receptor tyrosine kinase; AS: aortic valve stenosis; CEA: carcinoembryonic antigen; CYFRA; cytokeratin 19 fragment; DM: diabetes mellitus; ECOG PS: Eastern Cooperative Oncology Group performance status; HT: hypertension; FISH: fluorescence *in situ* hybridization; MR: mitral regurgitation; PD-L1: programmed cell death 1 ligand 1.

All of them were still alive at the time of the study (13). To our best knowledge, there has been only one case report of a patient with *ALK*-rearranged NSCLC aged 80 years or more who was treated with alectinib (18). That was an 89-year-old female patient with postoperative recurrence and her Eastern Cooperative Oncology Group performance status was 4. Alectinib treatment resulted in a complete response and the patient survived 14 months with no side-effects (18).

Regarding the adverse effects of alectinib, unlike crizotinib, a first-generation *ALK*-TKI, alectinib is reported to have a lower frequency of cardiotoxicity (21, 22). Alectinib rarely causes electrocardiography abnormalities or changes in cardiac function (22). To our best knowledge, congestive heart failure with alectinib has not been reported. Our patient 1 had congestive heart failure due to valvular disease prior to administration of alectinib, and we determined that it was highly unlikely that alectinib caused congestive heart failure. In our three patients, including this patient, alectinib had no serious side-effects despite long-term administration. However, they had several comorbid diseases, and the cooperation of specialists in cardiology, metabolism, and neurology was necessary for their long-term management. As observed in our series, elderly patients with *ALK*-rearranged NSCLC might have several comorbid diseases. We do suppose that the cooperation of specialist of other than the Respiratory Department in the treatment of elderly patients with *ALK*-rearranged NSCLC with several comorbid diseases would be mandatory.

Conclusion

ALK-rearranged mutations should be evaluated even in octogenarians with NSCLC, regardless of their sex or smoking history. Even if they have comorbid diseases, long-term control might be achieved with alectinib therapy in cooperation with other physicians than chest physicians and medical oncologists.

Conflicts of Interest

None declared.

Authors' Contributions

SH, HS and NH designed the study. SH, EO, SO, YS, TS and HS collected the data. SH and HS analyzed the data and prepared the article. All Authors approved the final version of the article.

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