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ORIGINAL ARTICLE

Clinical and computed tomography characteristics of non-small cell lung cancer with ALK gene rearrangement: Comparison with EGFR mutation and ALK/EGFR-negative lung cancer

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Keywords
Anaplastic lymphoma kinase; computed tomography; epidermal growth factor receptor; histological subtype; non-small cell lung cancer.

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Abstract

Background: The study was conducted to evaluate the clinical and computed tomography (CT) findings of non-small cell lung cancer (NSCLC) patients to distinguish between *ALK* gene rearrangement, *EGFR* mutation, and non-*ALK*/*EGFR* (no genetic abnormalities).

Methods: We enrolled 201 patients with primary NSCLC who had undergone molecular testing for both *ALK* gene rearrangement and *EGFR* mutation. The clinical features and CT findings of the main lesion and associated pulmonary abnormalities were investigated.

Results: Female gender ($P = 0.0043$ vs. non-*ALK*/*EGFR*), young age ($P = 0.0156$ vs. *EGFR*), and a light or never smoking history ($P = 0.0039$ vs. non-*ALK*/*EGFR*) were significant clinical characteristics of NSCLC with *ALK* gene rearrangement. The significant CT characteristics compared to NSCLC with *EGFR* mutation were a large mass ($P = 0.0155$), solid mass ($P = 0.0048$), and no air bronchogram ($P = 0.0148$). A central location ($P = 0.0322$) and lymphadenopathy ($P = 0.0353$) were also more frequently observed. Coexisting emphysema was significantly less frequent in NSCLC patients with *ALK* gene rearrangement ($P = 0.0135$) than non-*ALK*/*EGFR*.

Conclusions: NSCLC with *ALK* gene rearrangement was more likely to develop in younger women with a light or never smoking history. The characteristic CT findings of NSCLC with *ALK* gene rearrangement were a large solid mass, less air bronchogram, a central location, and lymphadenopathy.

Introduction

Lung cancer is the leading cause of cancer-related death worldwide. Recently, lung cancer treatment has undergone remarkable changes. Some genetic abnormalities of non-small cell lung cancer (NSCLC) can be diagnosed from tissue samples,[1–3] and effective small-molecule tyrosine kinase inhibitors (TKIs) have enabled individualized treatment for subgroups that are sensitive to ALK and EGFR

inhibitors.[4–6] These genetic abnormalities can be determined by specific analyses of histological samples obtained by invasive procedures, including biopsy or surgical resection. In general, *ALK* gene rearrangement and *EGFR* mutation are mutually exclusive: they are not present at the same time.[7–9] Therefore, it would be beneficial to clarify the radiological features of each molecular subtype to determine when such invasive diagnostic procedures are warranted.

ALK rearrangements occur in 5% of NSCLC cases in East Asian countries.[6] They typically occur in younger patients with a history of light or never smoking.[6] *ALK*-positive NSCLC is common among adenocarcinomas, and is associated with the solid histological subtypes. Therefore, these tumors tend to present on thin-section computed tomography (CT) as a solid mass with little or no ground-glass opacity (GGO) components.[8,10] In addition, according to previous studies, tumors with *ALK* gene rearrangement tend to be centrally located, relatively large masses without a cavity or pleural indentation.[11–13] They may have a high incidence of associated pleural effusion, carcinomatous lymphangiosis, and lymphadenopathy.[12,14–16] However, there has been no consensus on imaging findings for *ALK*-positive NSCLC.

The aim of this study was to evaluate the clinical and CT findings of NSCLC with *ALK* gene rearrangement that may enable distinction from NSCLC with *EGFR* mutation or with neither genetic abnormality.

Methods

Study population

We retrospectively searched our cancer database for patients who were diagnosed with primary NSCLC and had undergone molecular testing for both *ALK* gene rearrangement and *EGFR* mutation from June 2012 to December 2014 in our two institutions. The institutional review board approved this retrospective study and waived the need for written informed consent. The review committee of our two institutions approved the study in accordance with the declaration of Helsinki.

In total, 267 cases were identified from our database. Sixty-six cases were excluded: re-biopsy taken for recurrence (n = 28); extremely advanced cases in which the main tumor could not be evaluated (n = 14); multifocal primary tumors (n = 10); CT images taken before medication or surgery were not available (n = 7); tumors were located mainly in the mediastinum (n = 4); and complicated by severe infection (n = 2) and severe organizing pneumonia (n = 1). Finally, a total of 201 patients were included (Fig. 1). Of these cases, 91 underwent surgical resection and the remaining 110 underwent a biopsy of the primary tumor or metastatic lesions.

Data on age, gender, and smoking status were extracted from each patient's medical record. All patients were ethnically Asian, and the mean age was 67.5 (range: 30–90) years. Almost half of the patients were female (102/201, 50.7%) and non-smokers (95/183, 51.9%); smoking history was not available for 18 cases.

Molecular testing and histological examination

Molecular analysis was performed for all tumor samples to determine the mutation status of *EGFR* exons 18, 19, 20, and 21 via real-time PCR or PCR-invader method, and *ALK* gene rearrangement via fluorescence in situ hybridization (FISH).[1,2] The 201 patients were divided into three subgroups: ALK (21 patients), EGFR (124 patients), and non-ALK/EGFR (56 patients).

The histological predominant subtypes of the 91 surgically resected patients (ALK group, 8 patients; EGFR group, 66 patients; and non-ALK/EGFR group, 17 patients) were evaluated according to the 2015 World Health Organization (WHO) classification.[17]

Computed tomography (CT) analysis

CT examinations were performed using one of four CT systems (Aquilion ONE and Aquilion 64, Toshiba, Nasu, Japan; Somatom Definition Flash and Definition, Siemens, Erlangen, Germany). The CT parameters were as follows: detector collimation, 0.5–0.6 mm; beam pitch, 0.6–1.2;

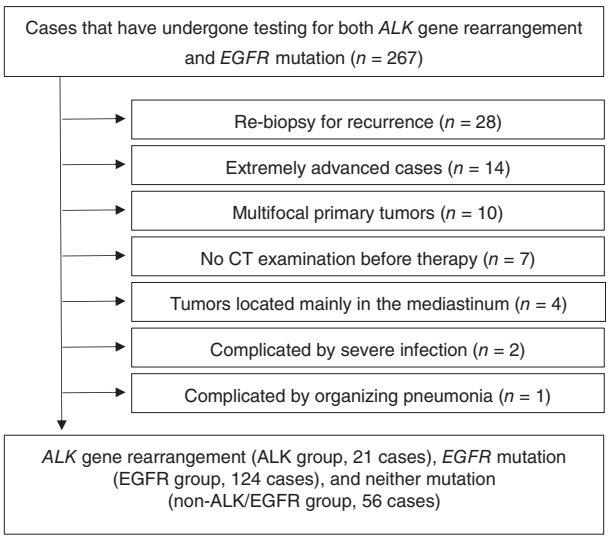

Figure 1 The selection process for the study cohort. CT, computed tomography.

rotation time, 0.5 seconds; tube voltage, 120 kVp; tube current adjusted automatically with CT-automatic exposure control; and a reconstruction kernel with a high-frequency algorithm. The reconstruction thicknesses and intervals were 1.0–2.0 mm and 1.0–2.0 mm on the pulmonary window setting (WS) (width, 1500 HU; level, −600 Hounsfield units [HU]), and 3.0–4.0 mm and 2.4–4.0 mm on the mediastinal WS (width, 300 HU; level, 25 HU), respectively. Nonionic contrast medium (100 mL of Omnipaque 240, Daiichi-Sankyo, Tokyo, Japan; 100 mL of Oypalomin 300 and 65 mL of Oypalomin 370, Konica Minolta, Tokyo, Japan) at a dose of 520–600 mgI/kg was used for CT examination in 137 patients (68.2%).

Two of three experienced radiologists independently evaluated the main tumor in terms of its size (the maximum axial diameter on pulmonary WS), type (solid, part-solid GGN, or pure GGN based on the presence of GGO), air bronchogram, cavity, pleural indentation, margin (smooth/irregular, lobulated, or spiculated), site of the lesion (right upper lobe, middle lobe, right lower lobe, left upper lobe, or left lower lobe), location of the lesion (central [involving segmental or more proximal bronchi] or peripheral), and contrast-enhanced characteristics (homogeneous, heterogeneous, or ring-enhancement pattern, and presence or absence of inner vessels on CT). In addition, coexisting pulmonary emphysema (low attenuation areas compared to normal lung parenchyma), fibrosis (reticular opacities and honeycombing), pleural effusion, pulmonary metastasis (lung nodules < 5 mm [military] and ≥ 5 mm [scattered]) or lymphangitic metastasis, and lymphadenopathy (lymph nodes with a short axis ≥ 10 mm on the mediastinal WS) were also evaluated. When there was interobserver disagreement, a conclusion was reached by consensus.

Statistical analysis

All statistical analyses in this study were performed using the SAS version 9.2. Comparisons between *ALK*-positive and *EGFR*-positive cases, *ALK*-positive and non-*ALK*/*EGFR* cases, and *ALK*-positive and non-*ALK* cases (including both *EGFR*-positive and non-*ALK*/*EGFR* cases) were performed using Fisher's exact test for categorical variables and the Student's *t*-test for continuous variables. A multivariate logistic regression model was applied with factors that showed a significant difference in univariate analysis. Variables that showed a significant difference in multivariate analysis were selected using a backward elimination method. The dependent variable was mutation status, and the independent variables were clinical and CT characteristics. The Akaike information criterion was used to select the most informative variables for a single parsimonious model.

Interobserver agreement was assessed by computing the κ coefficient and its 95% confidence interval (CI): κ 0.21–0.40 indicated fair agreement, κ 0.41–0.60 indicated moderate agreement, κ 0.61–0.80 indicated substantial agreement, and κ 0.81–1.00 indicated almost perfect agreement.[18]

Results

Clinical and histological characteristics

The clinical characteristics of the patients are shown in Table 1. Results of the *t*-test indicated that *ALK*-positive patients were younger than *EGFR*-positive patients (mean age 63 ± 13 vs. 68 ± 9 years, respectively; $P = 0.0156$) and non-*ALK* cases ($P = 0.0187$). There was a significantly higher proportion of women in the ALK group than in the non-ALK/EGFR group (13/21, 62%, and 15/56, 27%, respectively; $P = 0.0043$), and the proportion of patients who had a history of light or never smoking was lower in the ALK group than in the non-ALK/EGFR group ($P = 0.0039$).

The histological predominant subtypes of the surgically resected cases are shown in Table 2. The most common was invasive adenocarcinoma with a predominantly papillary subtype (28/91, 30.8%). *EGFR*-positive cases were associated with a high frequency of papillary, lepidic, and

Table 1 Clinical patient characteristics

Characteristic	*ALK* (*n* = 21)	*EGFR* (*n* = 124)	Non-*ALK*/*EGFR* (*n* = 56)	*P* *ALK* versus *EGFR*	*P* ALK versus non-*ALK*/*EGFR*	*P* *ALK* versus non-*ALK*
Age†	30–80 (63 ± 13)	46–88 (68 ± 9)	45–90 (67 ± 10)	**0.0156**	0.0979	**0.0187**
Gender, N (%)	—	—	—	0.8472	**0.0043**	0.2798
Male	8 (38)	50 (40)	41 (73)	—	—	—
Female	13 (62)	74 (60)	15 (27)	—	—	—
Smoking history‡	0 (0, 23)	0 (0, 21)	38 (7, 56)	0.6736	**0.0039**	0.4729

†Age (years), range (mean ± SD). ‡Smoking history (pack-year), median (the first quartile, the third quartile). Values in bold indicate a statistically significant result.

Table 2 Histological predominant subtypes among surgically resected cases

Predominant subtype	*ALK* (*n* = 8)	*EGFR* (*n* = 66)	Non-*ALK*/*EGFR* (*n* = 17)
Solid, N (%)	2 (25)	5 (8)	5 (29)
Papillary, N (%)	1 (13)	23 (35)	4 (24)
Micropapillary, N (%)	1 (13)	3 (5)	1 (6)
Acinar, N (%)	3 (38)	6 (9)	1 (6)
Lepidic, N (%)	0 (0)	15 (23)	1 (6)
Minimally invasive adenocarcinoma, N (%)	0 (0)	14 (21)	1 (6)
Other, N (%)	1 (13)	0 (0)	4 (24)

minimally invasive adenocarcinoma as the predominant subtypes (23, 15, and 14 of 66; 35%, 23%, and 21%, respectively). In contrast, these subtypes were less frequent in the *ALK*-positive cases, where the most predominant subtype was acinar (3/8, 38%). The non-ALK/EGFR group showed various predominant patterns, with the solid pattern being the most frequent (5/17, 29%).

CT characteristics

The interobserver agreement was fair to almost perfect (κ coefficient range: 0.379–0.910). The CT characteristics of

Table 3 Computed tomography characteristics of the main mass and coexisting lung abnormalities

Characteristic	*ALK* (*n* = 21)	*EGFR* (*n* = 124)	Non-*ALK*/*EGFR* (*n* = 56)	*ALK* versus *EGFR*	*P* *ALK* versus non-*ALK*/*EGFR*	*ALK* versus non-*ALK*
Size†	14–78 (39 ± 19)	9–68 (31 ± 13)	9–115 (44 ± 23)	**0.0155**	0.3548	0.3423
Type, N (%)	—	—	—	**0.0048**	0.1183	**0.0206**
Solid	21 (100)	80 (65)	59 (89)	—	—	—
Part-solid GGN	0 (0)	40 (32)	6 (11)	—	—	—
Pure GGN	0 (0)	4 (3)	0 (0)	—	—	—
Margin, N (%)	—	—	—	0.1783	0.3698	0.5930
Irregular	14 (67)	99 (80)	31 (55)	—	—	—
Smooth	7 (33)	25 (20)	25 (45)	—	—	—
Spiculation, N (%)	6 (29)	57 (46)	15 (27)	0.1369	0.8755	0.3091
Lobulation, N (%)	8 (38)	30 (24)	19 (34)	0.1804	0.7329	0.2955
Air bronchogram, N (%)	6 (29)	71 (57)	16 (29)	**0.0148**	1.0000	0.0857
Cavity, N (%)	2 (10)	10 (8)	7 (13)	0.8224	0.7173	0.9906
Pleural indentation, N (%)	8 (38)	64 (52)	19 (34)	0.2519	0.7329	0.4850
Site of the lesion, N (%)	—	—	—	0.7055	0.9730	0.8230
RUL	5 (24)	40 (32)	16 (29)	—	—	—
ML	1 (5)	13 (10)	3 (5)	—	—	—
RLL	6 (29)	22 (18)	13 (23)	—	—	—
LUL	6 (29)	33 (27)	14 (25)	—	—	—
LLL	3 (14)	16 (13)	10 (18)	—	—	—
Location, N (%)	—	—	—	**0.0332**	0.1916	**0.0486**
Central	8 (38)	22 (18)	13 (23)	—	—	—
Peripheral	13 (62)	102 (82)	43 (77)	—	—	—
Contrast enhancement pattern, N (%)	—	—	—	0.7631	0.8535	0.8866
Homogeneous	3 (21)	25 (29)	6 (16)	—	—	—
Heterogeneous	10 (71)	52 (61)	28 (74)	—	—	—
Ringed	1 (7)	8 (9)	4 (11)	—	—	—
Inner vessel, N (%)	4 (27)	9 (10)	7 (18)	0.0800	0.5049	0.1470
Lung metastasis pattern, N (%)	—	—	—	—	—	—
Miliary	3 (14)	17 (14)	2 (4)	0.9436	0.0893	0.6044
Scattered	3 (14)	15 (12)	5 (9)	0.7785	0.4926	0.6654
Lymphangitic	4 (19)	9 (7)	10 (18)	0.0803	0.9040	0.2473
Lymphadenopathy, N (%)	14 (67)	52 (42)	32 (57)	**0.0353**	0.4479	0.0827
Emphysema, N (%)	5 (24)	13 (10)	31 (55)	0.0868	**0.0135**	0.9489
Fibrosis, N (%)	2 (10)	7 (6)	9 (16)	0.4957	0.4646	0.9232
Pleural effusion, N (%)	3 (14)	18 (15)	12 (21)	0.9779	0.4809	0.7805

†Size (mm), range (mean ± standard deviation). Values in bold indicate a statistically significant result. GGO, ground glass opacity; LLL, left lower lobe; LUL, left upper lobe; ML, middle lobe; RLL, right lower lobe; RUL, right upper lobe.

the ALK group that significantly differed from the EGFR group were: a large mass ($P = 0.0155$), a solid mass ($P = 0.0048$), no air bronchogram ($P = 0.0148$), central location ($P = 0.0322$), and lymphadenopathy ($P = 0.0353$). Coexisting emphysema was significantly less frequent in the ALK group than in the non-ALK/EGFR group (24% vs. 55%; $P = 0.0135$) (Table 3, Figs 2, 3).

Multivariate analysis using the Akaike information criterion was performed including all clinical and CT variables; the results are summarized in Table 4. Among the variables analyzed, air bronchogram, emphysema, and a central location were independent predictive factors of *ALK* gene rearrangement status.

Discussion

In this study, we investigated the characteristics of clinical and CT findings of NSCLC with *ALK* gene rearrangement. We found that a relatively large solid mass without air bronchogram was a significant characteristic CT finding for NSCLC with *ALK* gene rearrangement. NSCLC with *ALK* gene rearrangement was also more often associated with a central location and lymphadenopathy when compared to NSCLC with *EGFR* mutation; it was also more often associated with pulmonary emphysema when compared to non-ALK/EGFR NSCLC patients. Patients who were younger, female, or had a light or no smoking history were more likely to have NSCLC with *ALK* gene rearrangement. These results are consistent with those of a previous clinical study.[6] None of the *ALK*-positive NSCLC cases in this study showed a lepidic growth pattern as the predominant histologic subtype.

The genetic abnormalities involved in NSCLC can be determined by specific analyses of histological samples obtained by invasive procedures. However, Isaka *et al.* reported that only approximately 50% of transbronchial biopsy specimens contain sufficient amounts of DNA for amplicon-based massively parallel sequencing.[19] Therefore, it would be beneficial to understand the clinical and radiological features that might help distinguish the different molecular subtypes in advance before invasive diagnostic procedures are performed. Moreover, *ALK* gene rearrangement and *EGFR* mutation are generally mutually exclusive,[7–9] and *ALK* gene rearrangement is less common.[6] It is important to distinguish the clinical and radiological findings of NSCLC with *ALK* gene rearrangement from other types of NSCLC, because it may enable medical oncologists to evaluate the consistency between these findings and molecular testing results, and patients could then receive potentially beneficial TKI therapy.

In the current study, pulmonary emphysema was less commonly observed in patients with *ALK* gene rearrangement than in those with non-*ALK*/*EGFR* NSCLC. This result seems to reflect the fact that most of these patients had a history of light or never smoking. However, coexisting emphysema was an independent predictive factor of *ALK* gene rearrangement status when compared to *EGFR* mutation. A plausible reason for this is that *EGFR* mutation status has a stronger association with non-emphysema status.

There has been no consensus on the imaging findings of *ALK*-positive NSCLC. Wang *et al.* reported that a relatively large solid mass without "bubble-like lucency" was more likely to be *ALK*-positive than *EGFR*-positive NSCLC.[16] Ko *et al.* reported that *ALK*-positive tumors were larger and had a solid proportion when compared to non-*ALK* tumors.[11] Consistent with these findings, our results indicate that a relatively large solid mass was a CT

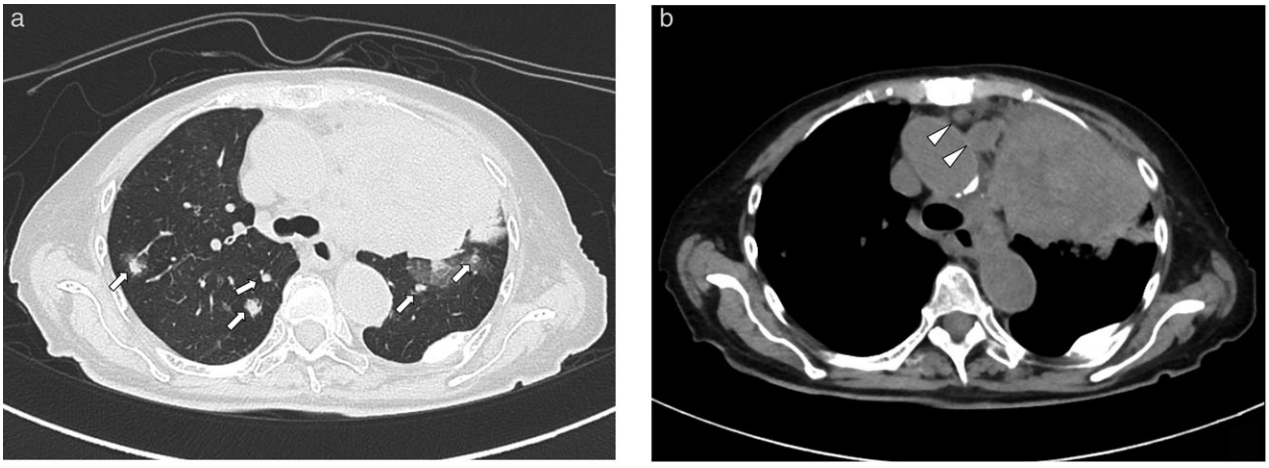

Figure 2 Computed tomography images of an 80-year-old woman with adenocarcinoma with *ALK* gene rearrangement. (**a**) Lung window image showing a large solid mass in the central area of the left upper lobe. Multiple scattered nodules suggest lung metastasis (arrows). (**b**) Mediastinal window image showing lymphadenopathy (arrowheads).

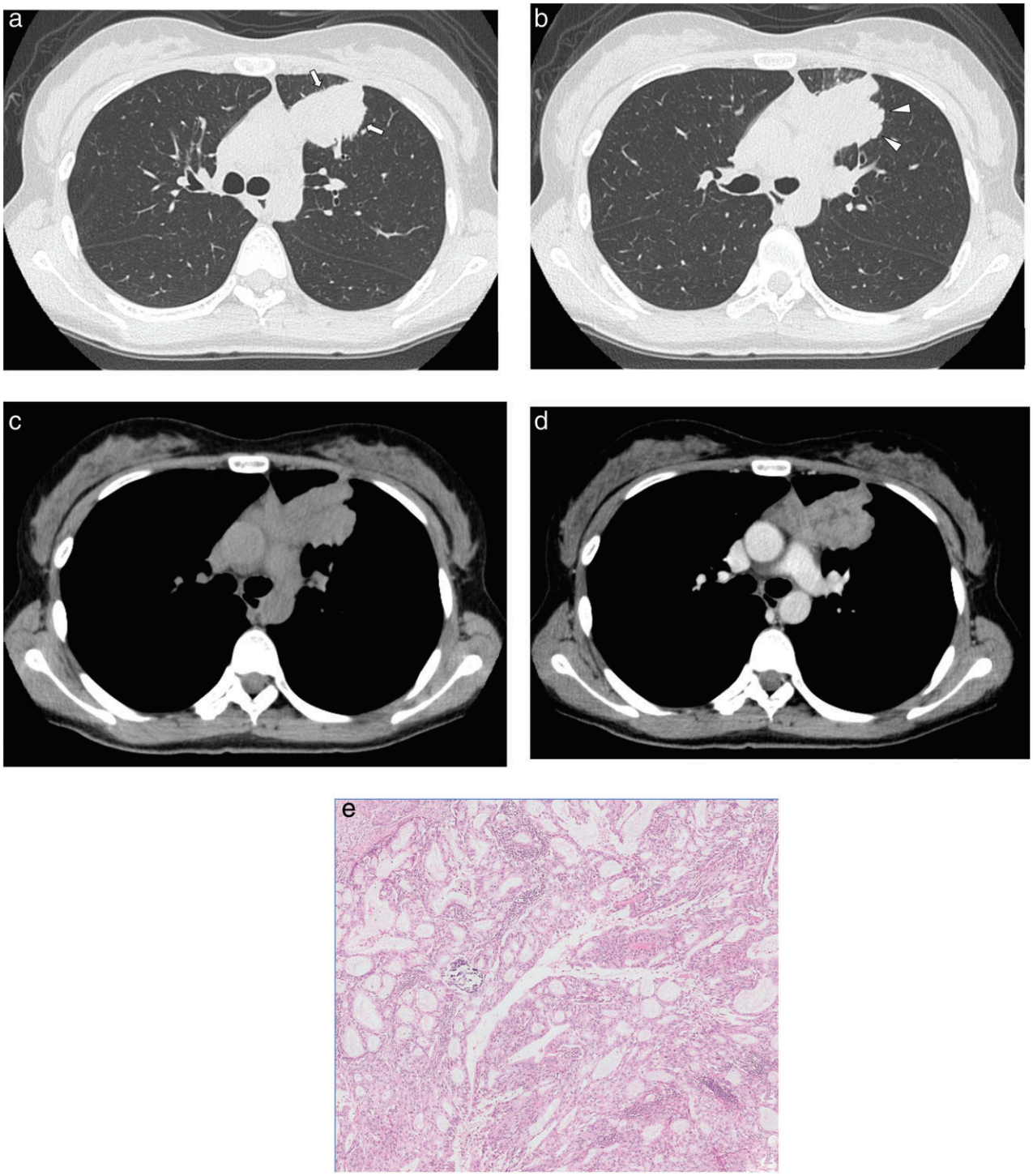

Figure 3 Computed tomography images of a 30-year-old woman with adenocarcinoma with *ALK* gene rearrangement. (**a,b**) Lung window images show a solid mass with a spiculated (arrow) and lobulated (arrowhead) margin in the periphery of the left upper lobe. (**c,d**) Mediastinal window images show the heterogeneous enhancement pattern of the mass. (**e**) High-power photomicrograph of the tumor show the acinar predominant subtype (original magnification ×50; hematoxylin and eosin staining).

Table 4 Multivariable logistic regression analyses

Characteristic	Multivariate odds ratio (95% CI)	*P*
ALK vs. *EGFR*		
Air bronchogram (–)	3.508 (1.256–9.800)	0.0166
Emphysema (+)	2.933 (0.880–9.780)	0.0799
ALK vs. non-*ALK*/*EGFR*		
Emphysema (–)	3.968 (1.277–12.332)	0.0172
ALK vs. non-*ALK*		
Air bronchogram (–)	2.339 (0.868–6.299)	0.0929
Central location	2.550 (0.981–6.625)	0.0547

CI, confidence interval.

characteristic of NSCLC with *ALK* gene rearrangement. We found that air bronchogram occurred significantly less frequently in NSCLC with *ALK* gene rearrangement. According to previous studies, a more lobulated margin,[14,20] a less spiculated margin,[13,14] or less pleural indentation[12,13] are characteristics of the main lesion. However, few articles have reported the significant inner or margin characteristics of the main mass; thus, no consensus on the significance of these observations has been reached.

In this study, the main lesions of *ALK*-positive NSCLC were more commonly located in the central region compared to *EGFR*-positive or non-*ALK* NSCLC. Yamamoto *et al.* similarly reported that *ALK*-positive tumors were more commonly located in the central region, and that there were fewer operable cases in *ALK*-positive than in non-*ALK* NSCLC (8/47 and 44/123 cases, respectively).[12] In our study, only 8 of the 21 cases underwent surgery. Similar to our results, several articles have reported that coexisting lymphadenopathy, which suggests lymph node metastasis, is more often observed in patients with *ALK*-positive NSCLC.[14,16,21] This finding seems to reflect the fact that patients with *ALK*-positive NSCLC have a poor prognosis.

Histological examination is important for analyzing the main tumor. Previous studies have shown that *ALK*-positive NSCLC is associated with the solid predominant subtype.[10,16,22] Inamura *et al.* reported a relationship between *ALK*-positive NSCLC and the papillary or acinar subtypes.[8] No consensus on the significance of these histological characteristics has been reached; however, it seems that lepidic predominant adenocarcinomas (adenocarcinoma in situ, minimally invasive adenocarcinoma, and lepidic predominant invasive adenocarcinoma) are less likely to develop *ALK* gene rearrangement. None of the *ALK*-positive NSCLC cases in this study showed a lepidic growth pattern as the predominant histological subtype.

This study has several limitations. First, this was a retrospective study. Second, there were fewer NSCLC patients in our sample with *ALK* gene rearrangement than with *EGFR*-positive tumors; however, the prevalence of *ALK* gene rearrangement in NSCLC patients is approximately 5%,[6] while that of *EGFR* mutation is 40–80%.[1] The results of multivariate regression analysis in our study require further verification because of the small number of *ALK*-positive NSCLC patients in our sample. Selection bias may be an issue, as we did not perform molecular testing in all NSCLC patients. Our sample may also have included more advanced cases that were considered for chemotherapy than would be found in the general NSCLC population. However, we believe that these limitations did not affect the main results of this study.

NSCLC with *ALK* gene rearrangement is more likely to develop in younger women with a history of light or never smoking. The characteristic CT findings of NSCLC with *ALK* gene rearrangement in comparison to *EGFR* mutation were a large solid mass, less air bronchogram, a central location, and lymphadenopathy. Combining these results may assist clinicians to assess the likelihood of NSCLC with *ALK* gene rearrangement.

Disclosure

No authors report any conflict of interest.

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