

Anaplastic lymphoma kinase inhibitor related pneumonitis in patients with non-small cell lung cancer

Clinical and radiologic characteristics and risk factors

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Abstract

Anaplastic lymphoma kinase (ALK) inhibitor-related pneumonitis (ALK-IIP) is relatively rare but sometimes fatal, so the timely diagnosis of ALK-IIP is important for enabling prompt management. However, the detailed radiologic characteristics and clinical course of ALK-IIP are still unclear. This study was performed to investigate the clinical and radiologic characteristics and risk factors of ALK-IIP in patients with non-small cell lung cancer (NSCLC).

A total of 250 NSCLC patients who had been treated with ALK inhibitors were retrospectively enrolled. Chest computed tomography (CT) was classified into 4 CT patterns using the 2013 guideline for idiopathic interstitial pneumonia: cryptogenic organizing pneumonia (COP), hypersensitivity pneumonitis (HP), acute interstitial pneumonia (AIP), and nonspecific interstitial pneumonia. Clinical characteristics including toxicity grading and treatment course were analyzed in regarding to CT patterns. Clinical characteristics were compared between patients with ALK-IIP and without ALK-IIP.

ALK-IIP was identified in 11 patients (4.4%). The most common CT pattern was the COP pattern (n = 7, 63.6%) and followed by HP and AIP patterns (both, n = 2, 18.2%). ALK-IIP showed pneumonitis toxicity grade ranged from 1 to 4, and AIP pattern had the highest toxicity grade, followed by HP and COP patterns (median grade: 3.5, 2.5, 1). All of the patients with the COP pattern were successfully treated, while half of patients with the AIP pattern died during treatment. The smoking history and extrathoracic metastasis were more frequent in patients with ALK-IIP ($P < .005$). The smoking history was associated with a higher incidence of ALK-IIP (odds ratio: 3.586, 95% confidence interval: 1.058–13.432, $P = .049$).

ALK-IIP showed a spectrum of chest CT patterns, which reflected the toxicity grades. The COP pattern was the most common CT pattern of ALK-IIP, and patients with ALK-IIP of the COP pattern were successfully treated. ALK inhibitors should be used with caution in NSCLC patients with smoking history.

Abbreviations: AIP = acute interstitial pneumonia, ALK = anaplastic lymphoma kinase, ALK-IIP = anaplastic lymphoma kinase inhibitor-related pneumonitis, COP = cryptogenic organizing pneumonia, HP = hypersensitivity pneumonitis.

Keywords: acute interstitial pneumonia, anaplastic lymphoma kinase, anaplastic lymphoma kinase inhibitor-related pneumonitis, cryptogenic organizing pneumonia, hypersensitivity pneumonitis

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1. Introduction

The echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (ALK) fusion gene is one of the molecular alterations in a small subset of non-small cell lung cancer (NSCLC). This fusion gene is present in 3% to 7% of patients with NSCLC.^[1–4] Recently, the therapeutic strategy for advanced NSCLC with ALK rearrangement has been changed as a potent and selective ALK inhibitor has been developed. Crizotinib is the first-generation ALK inhibitor, and several clinical trials demonstrated the efficacy of crizotinib for the treatment of advanced ALK-rearranged NSCLC compared to cytotoxic chemotherapy, and thus establishing crizotinib as a standard treatment for advanced ALK-positive NSCLC.^[5,6] Most patients are highly sensitive to crizotinib; however, they ultimately develop acquired resistance during therapy. Recently, second-generation ALK inhibitors (e.g., ceritinib, alectinib, and brigatinib), have also been approved for treatment of patients upon disease progression.

Serious, adverse events, such as the occurrence of interstitial lung disease (ILD), have also been reported, although ALK

inhibitors showed tolerable safety profiles in several clinical trials.^[5–8] ALK inhibitor-related pneumonitis (ALK-IIP) is relatively rare and has been reported to occur in 1.2% to 8% of patients.^[7,9] However, as it is sometimes fatal, the monitoring of patients for respiratory symptoms indicative of drug-related pneumonitis is recommended during their treatment. The timely diagnosis of ALK-IIP is important for enabling prompt management such as withdrawal of the ALK inhibitor and/or steroid medication. However, only a small number of studies and case reports about ALK-IIP have been reported,^[9–12] and clinical course and characteristics including risk factors of ALK-IIP are still unclear. Moreover, there were only brief descriptions of the presence of ground-glass opacity (GGO) in the previous studies, and no detailed radiologic characterizations or classification of computed tomography (CT) patterns according to the American Thoracic Society (ATS)/European Respiratory Society (ERS) classifications of interstitial pneumonias.^[13]

Therefore, the purpose of this study is to investigate clinical characteristics, clinical course, detailed radiologic findings focusing on the high-resolution chest CT and risk factors of ALK-IIP in patients with NSCLC.

2. Materials and methods

2.1. Patients

This retrospective study was approved by the Institutional Review Board of our hospital and patient's informed consent was waived due to the retrospective manner of the study. We searched the electronic database of our hospital to identify the patients who received ALK inhibitor therapy for advanced NSCLC between January 2015 and January 2018. The histologic diagnoses were made through a percutaneous core needle and/or by bronchoscopic biopsy in all patients, and all patients were diagnosed as having NSCLC with ALK rearrangement on genetic analysis. The diagnosis of ALK-IIP was made based on the review of the serial chest CTs, clinical and laboratory findings. We diagnosed ALK-IIP according the inclusion criteria as follows:

- (1) development of new symptoms and radiologic abnormalities while the patient was being treated with the drug;
- (2) resolution of the pulmonary abnormalities after cessation of suspected drug or steroid therapy;
- (3) negative results in cultures of sputum, blood, urine and bronchoalveolar lavage fluid (BAL);
- (4) normal range of complete blood count if examinations of (3) were not evaluated; and
- (5) the absence of an alternative explanation of the abnormalities observed.

Patients with other causes for the pulmonary abnormality, such as pulmonary infection or edema, were excluded on the basis of bronchoscopy with BAL, echocardiography, and laboratory tests.^[14,15] The onset of ALK-IIP was defined as the interval between the starting date of initial ALK inhibitor therapy and the date of chest CT which showed new pulmonary abnormalities. The toxicity grades for ALK-IIP were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE). The treatment regimen and the clinical course of ALK-IIP were reviewed. The diagnosis of emphysema and ILD was based on the results of baseline chest CT. Extrathoracic metastasis, history of thoracic irradiation, lung cancer operation, and previous cytotoxic chemotherapy were assessed at the time of the initiation of ALK inhibitor therapy.

2.2. CT examination

Chest CT was performed using SOMATOM Definition flash, or SOMATOM Definition AS plus scanners (Siemens Medical Solutions, Erlangen, Germany), as well as LightSpeed VCT scanners (GE Healthcare, Milwaukee, WI). The scan parameters were 120kV and 100 to 400mA with dose modulation. Intravenous contrast medium (120–150mL of 300–370mgI/mL) was administered at a rate of 2 to 3 mL/seconds using an automatic power injector. A fixed delay of 50seconds after contrast administration was used. All of the images were obtained in a caudo-cranial direction from the lung base through the thoracic inlet level and with an inspiratory breath-hold. Reconstruction intervals were 3/5-mm thickness and 3/5-mm interval without a gap using the B50 or lung algorithm and 1-mm reconstruction with a 5-mm gap using the B60 or bone algorithm. All of the images were reviewed using our picture archiving and communication system.

2.3. CT analysis

Chest CTs for staging underlying disease, initial chest CTs of ALK-IIP (Time1CT), and subsequent chest CTs were reviewed in consensus by 2 thoracic radiologist (MYK and HJH with 20 and 9 years of experience of thoracic radiology, respectively). The pulmonary abnormalities suspicious for ALK-IIP on Time1CTs were classified as

- (1) nonspecific interstitial pneumonia (NSIP) pattern,
- (2) cryptogenic organizing pneumonia (COP) pattern,
- (3) hypersensitivity pneumonitis (HP) pattern
- (4) acute interstitial pneumonia (AIP) pattern, and
- (5) not applicable, referring to the ATS/ERS guidelines.^[13,16]

The pulmonary abnormalities suspicious for ALK-IIP were evaluated with regard to the distribution of parenchymal abnormalities as follows: 4 instances of craniocaudal dominance (upper, mid, lower, none; referent to the carina and right lower pulmonary vein, respectively); 3 instances of axial zonal dominance (central, peripheral, none; referent to an imaginary middle line); bilaterality and symmetry of pulmonary abnormalities seen on Time1CTs. The extent of pulmonary abnormalities including emphysema, reticulation, GGO, and consolidation were assessed and the extent of each pulmonary abnormalities were scored using a 5% volumetric scale for 6 lobes, that is, the right upper lobe, right middle lobe, right lower lobe, left upper lobe, lingular segment, and left lower lobe.^[16]

2.4. Statistical analysis

The Student's *t*-test was used for continuous variables. Pearson Chi-square test for categorical variables was used to evaluate differences in clinical characteristics between patients with ALK-IIP and without ALK-IIP. Multivariate logistic regression analysis was performed to determine potential influencing factors associated with patients with ALK-IIP. Statistical package SPSS version 18.0 (SPSS Inc, Chicago, IL) was used. A *P*-value <.05 was considered to be statistically significant.

3. Results

3.1. Clinical characteristics

We included 250 NSCLC patients treated with ALK inhibitor, of which 11 patients were diagnosed as having ALK-IIP (4.4%) (6 males, 5 females; median age 57.0 years, range 36–79) (Fig. 1).

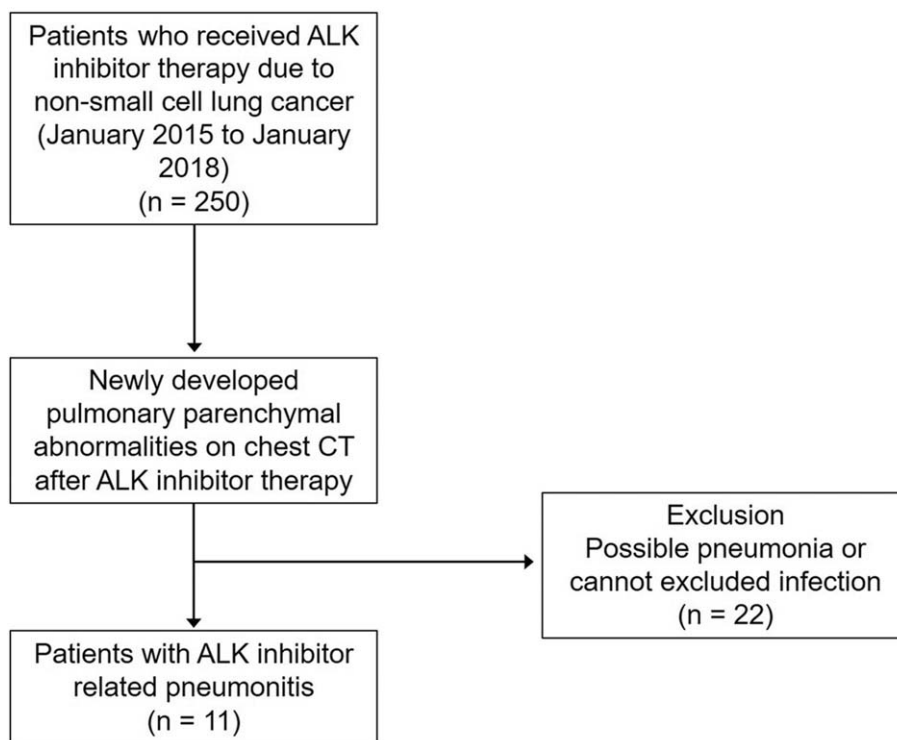


Figure 1. Flowchart of the patient selection process.

The percutaneous lung biopsy was also performed in 2 patients with ALK-IIP to exclude metastasis or disease progression, and the pathologic findings revealed organizing pneumonia (Patients #1 and 2). Bronchoscopy and BAL were performed in 6 patients with ALK-IIP. The clinical and baseline disease characteristics of the 11 patients are summarized in Table 1. All patients were NSCLC cancer patients with adenocarcinoma. The most commonly used ALK inhibitors were Crizotinib and Ceritinib (both n=5, 45.5%) and followed by Alectinib (n=1, 9.1%). The median time from initiation of the ALK inhibitor to the development of pneumonitis was 5.0 months (range, 0.5–11.0

months), and it did not differ significantly in the patients with Crizotinib and Ceritinib treatment ($P = .222$).

3.2. CT patterns and clinical features according to CT patterns

The most common chest CT pattern of ALK-IIP was the COP pattern (n=7, 63.6%) (Fig. 2A and B), followed by the HP pattern (Fig. 2C and D) and the AIP pattern (Fig. 2E and F) (both n=2, 18.2%) (Table 1). The NSIP pattern was not observed in our patients. Time to onset of ALK-IIP was shortest in patients

Table 1

Clinical characteristics of 11 patients with ALK inhibitor-related pneumonitis.

Pt	Sex/age	Smoker Stage (PY)	Pulmonary comorbidities	ALK inhibitor	Prior CTx	Onset, mo	Toxicity grade	Symptoms	Stopping ALK inhibitor/steroid Tx	CT pattern	CT Outcome	Re-challenge/recurrent pneumonitis
1	F/43	Iva Ex (0.3)	None	Ceritinib	Crizotinib	3	1	None	No/Yes	COP	Recovery	Yes/No
2	M/56	Iva Ex (20)	Emphysema	Ceritinib	Crizotinib	6	1	None	No/Yes	COP	Recovery	Yes/Yes
3	M/74	Iib Never	Post-op	Crizotinib	None	5	3	Dyspnea	Yes/Yes	AIP	Recovery	Yes*/No
4	M/56	Ib Ex (9.1)	Post-op	Crizotinib	Alimta	1	1	Mild dyspnea	Yes/Yes	COP	Recovery	Yes*/No
5	F/36	Iva Never	None	Crizotinib	Alimta	11	1	None	Yes/Yes	COP	Recovery	Yes*/No
6	F/58	Ivb Ex (0.2)	Post-op	Ceritinib	Crizotinib	7	1	None	Yes/No	COP	Recovery	Yes*/No
7	F/79	Iva Never	None	Crizotinib	None	0.5	2	Dyspnea, fever	Yes/No	HP	Recovery	No/NA
8	M/77	Iva Ex (80)	Emphysema	Alectinib	None	5	1	None	Yes/No	COP	Recovery	Yes*/No
9	M/57	Iva Ex (10)	Post-op	Ceritinib	Alimta	9	2	Dyspnea, fever	Yes/Yes	COP	Recovery	Yes*/No
10	F/69	Iva Never	Post-op	Ceritinib	Crizotinib	2	4	Dyspnea	Yes/No	AIP	Expired	
11	M/55	Iva Ex (30)	None	Crizotinib	None	0.5	3	Dyspnea, fever	Yes/Yes	HP	N/A [†]	

Patients 1 and 2 underwent percutaneous lung biopsy to exclude lung metastasis, and the pathologic findings revealed organizing pneumonia.

AIP = acute interstitial pneumonia, COP = cryptogenic organizing pneumonia, CTx = chemotherapy, Ex = ex-smoker, F = female, HP = hypersensitivity pneumonitis, M = male, mo = months, N/A = not available, Post-op = post-operation, Pt = patient, PY = pack-year.

* ALK inhibitor therapy was re-initiated; however, second- or third-generation ALK inhibitor was used in place of the ALK inhibitor used previously.

[†] Patient 11 were transferred to other hospitals.

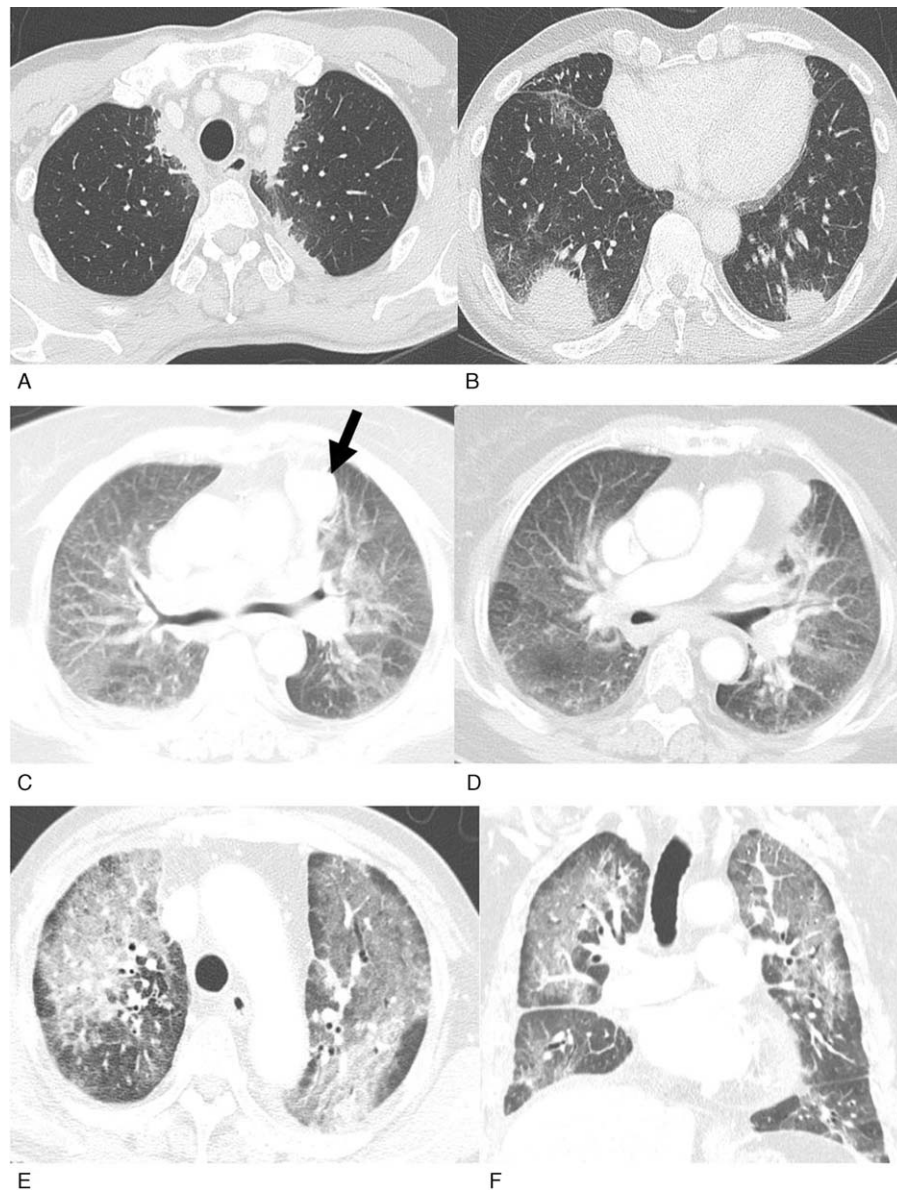


Figure 2. Spectrum of the CT patterns of ALK-IIP. (A and B) ALK-IIP with a COP pattern in a 56-yr-old male patient. Chest CT demonstrated the development of multifocal mass-like consolidations with ill-defined GGO and mild interstitial thickening involving the subpleural areas of both upper lobes and both lower lobes representing the COP pattern. (C and D) ALK-IIP with a HP pattern in a 79-yr-old female patient. Chest CT demonstrated diffuse GGO with focal areas of air trapping in both lungs and thus indicative of HP pattern. Lung cancer was noted in the left upper lobe (arrow). (E and F) ALK-IIP with AIP pattern in a 74-yr-old male patient. Chest CT axial and coronal images demonstrated diffuse and patchy consolidation and ground glass opacity with mild thickening of the interlobular septa in both lungs. AIP = acute interstitial pneumonia, ALK-IIP = anaplastic lymphoma kinase inhibitor-related pneumonitis, COP = cryptogenic organizing pneumonia, CT = computed tomography, GGO = ground-glass opacity, HP = hypersensitivity pneumonitis.

with HP pattern (mean=0.5 months), followed by AIP pattern (3.5 months) and COP pattern (6.0 months). Six patients (54.4%) initially presented with dyspnea and/or fever, and 5 patients (45.5%) were asymptomatic. All patients without symptoms showed COP pattern on CT. Pneumonitis toxicity grades ranging from 1 to 4 were observed, and AIP pattern had the highest grade of pulmonary toxicity (median grade, 3.5), followed by HP pattern (median grade, 2.5), and COP pattern had the lowest grade (median grade 1). Administration of ALK inhibitor was discontinued in 9 patients (81.8%). The remaining 2 patients maintained ALK inhibitor therapy, and all of these patients have no symptoms and showed COP pattern of ALK-IIP.

Seven patients were treated with oral or intravenous steroid therapy. All of the patients with the COP pattern and 1 patient with HP pattern showed clinical and radiologic improvement after treatment (Fig. 3). Half of the patients with the AIP pattern died of respiratory failure within 10 days of their symptom onset despite discontinuation of the ALK inhibitor.

ALK inhibitor therapy was reinitiated in 8 patients (Table 1). Two of these patients (25%) with COP pattern received the same ALK inhibitor as previously used, and 6 of them (75%) received second- or third-generation ALK inhibitor in place of the ALK inhibitor previously used. Among the 8 patients with retreatment, the recurrent pneumonitis with the COP pattern was noted in 1

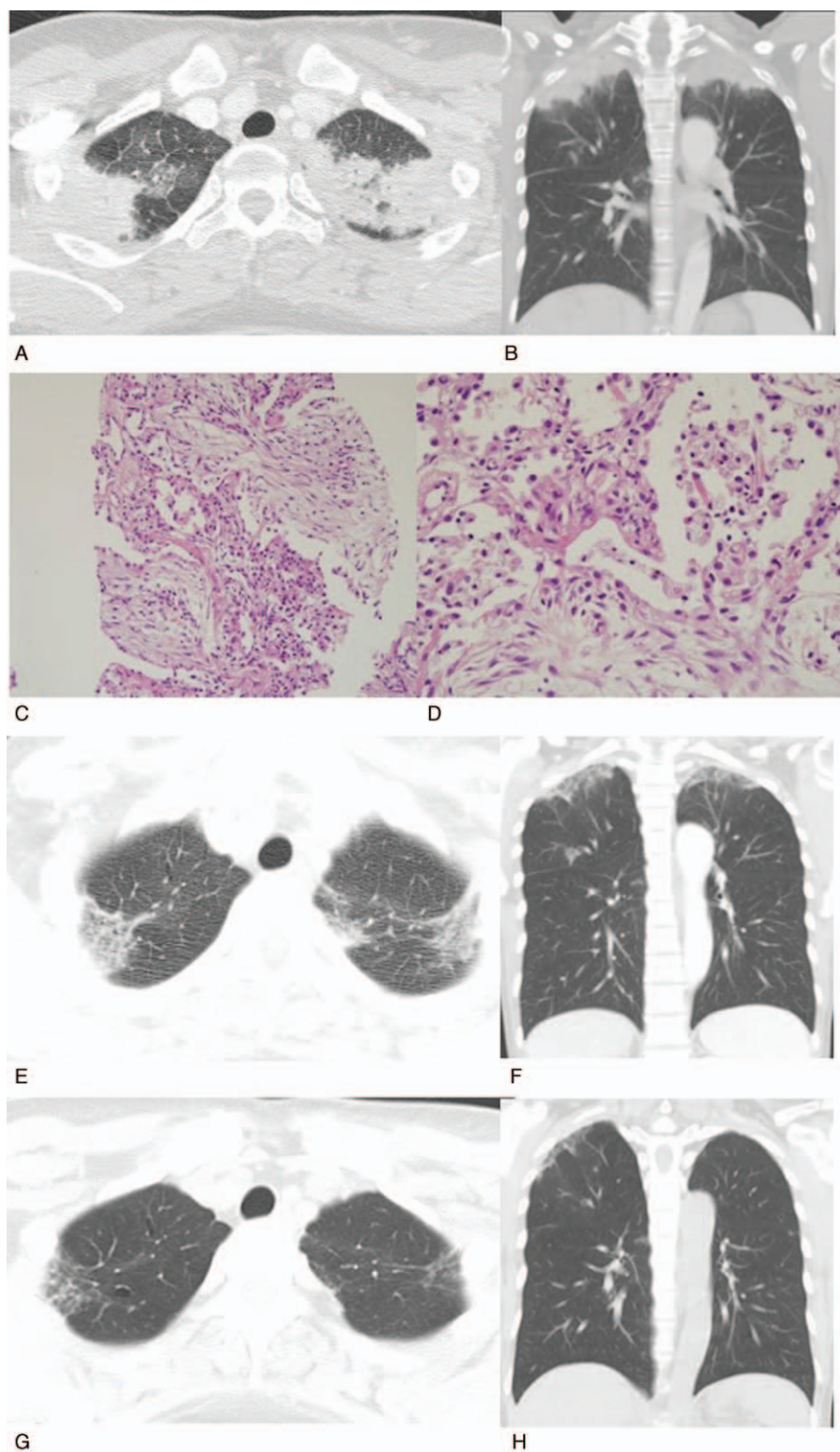


Figure 3. ALK-IIP with the COP pattern in a 43-yr-old female patient with NSCLC treated with Ceritinib. (A and B) Chest CT with axial and coronal images after 3 mo of Ceritinib therapy demonstrated the development of multifocal patchy consolidation with peripheral GGO and mild interstitial thickening involving the subpleural areas of both upper lobes. (C and D) Hematoxylin-eosin staining of a percutaneous lung biopsy specimen from the left apex mass-like consolidation showed filling of airspace with plugs and lymphocyte-predominant interstitial pneumonitis with histiocytes. The plugs comprise of loose fibroblasts (hematoxylin-eosin stain, $\times 10$ and 40 objective lens). Ceritinib was withheld, and the patient was treated with corticosteroid for 2 wk and with a 2-mo course of corticosteroid taper. (E and F) Follow-up chest CT images at 1 mo after completing corticosteroid showed a decrease in the extent and density of the patchy consolidations in both upper lobes. (G and H) Follow-up chest CT images at 6 mo later showed residual reticular opacity and GGO in the subpleural areas of both upper lobes, but which had decreased in extent. ALK-IIP = anaplastic lymphoma kinase inhibitor-related pneumonitis, COP = cryptogenic organizing pneumonia, CT = computed tomography, GGO = ground-glass opacity, NSCLC = non-small cell lung cancer.

Table 2
Comparison of baseline characteristics of patients with ALK inhibitor-related pneumonitis and patients without ALK inhibitor-related pneumonitis.

Variable	Patients with ALK-IIP (n=11)	Patients without ALK-IIP (n=239)	P
Age ≥60	4 (36.4)	81 (33.9)	.866
Male sex	6 (54.5)	113 (47.3)	.637
ECOG ≥2	0 (0)	12 (5.0)	.446
Smoking history	7 (63.6)	78 (32.6)	.034
Emphysema	2 (18.2)	17 (7.1)	.176
Interstitial lung disease	0 (0)	3 (1.3)	.709
Extrathoracic metastasis	10 (90.9)	142 (59.4)	.036
Thoracic irradiation	0 (0)	34 (14.2)	.178
Postoperative state for lung cancer	5 (45.5)	56 (23.4)	.096
Previous cytotoxic chemotherapy	3 (27.3)	112 (46.9)	.202
ALK inhibitor line			.069
1st generation	5 (45.5)	170 (91.6)	
≥2nd generation	6 (54.5)	69 (9.1)	

Numbers of the data are the number of patients, and numbers in parentheses are percentages.
 ALK-IIP=ALK inhibitor-related pneumonitis, ECOG=Eastern Cooperative Oncology Group.

patient (12.5%) who was restarted on maintenance of the same ALK inhibitor as previously used (Patient #2). The ALK inhibitor was again withheld, and recurrent ALK-IIP with COP pattern was successfully treated with corticosteroid. In this patient, ALK inhibitor therapy was reinitiated with second-generation ALK inhibitor, and showed no recurrent pneumonitis.

3.3. Comparison between patients with ALK-IIP and patients without ALK-IIP

Patients with smoking history and extrathoracic metastasis were significantly more frequent in the patients with ALK-IIP as compared with patients without ALK-IIP (63.6% vs 32.6%; $P=.034$ and 90.9% vs 59.4%; $P=.036$). Patients older than 60 years of age, the pre-existing ILD, and history of previous cytotoxic chemotherapy were not significantly different between the 2 groups (Table 2). In multivariate analysis with 2 candidate factors (smoking history and extrathoracic metastasis), the smoking history was associated with a significantly higher incidence of ALK-IIP (odds ratio: 3.769, 95% confidence interval: 1.058–13.432, $P=.041$) (Table 3).

3.4. CT characteristics of ALK-IIP

The AIP pattern showed the greatest extent of pulmonary abnormalities showing as diffuse consolidation and GGO on chest CT. Craniocaudal dominance was generally absent ($n=6$, 54.5%), and among 7 patients with the COP pattern, 3 patients showed the upper lung zone predominance and 2 patients showed no zonal predominance on chest CT (Fig. 2A and B).

With regard to the axial distribution, all of the patients with the COP pattern showed peripheral predominance of pulmonary abnormalities and those with the AIP pattern showed central predominance. The ALK-IIP often showed bilateral (72.7%) and symmetric distribution (54.5%) (Tables 4 and 5).

4. Discussion

Clinicians and radiologists encounter not infrequently drug-induced pneumonitis as the number of new drugs for lung cancer treatment are increasing. Despite the wide spectrum of chest CT images of drug-induced pneumonitis, the radiologists and clinicians make a differential diagnosis of drug toxicity. Thus, it is important to know the diverse chest CT patterns of drug-related pneumonitis and what CT patterns are common in drug-related pneumonitis when using certain drugs. This is a small cohort descriptive study to evaluate the systematic characterization of a spectrum of CT patterns of ALK-IIP according to the ATS/ERS classification. We also analyzed the clinical features and clinical course of ALK-IIP according to the CT patterns.

We reported 11 cases (4.4%) of ALK-IIP among the 250 patients with NSCLC treated by ALK inhibitor in our study. This incidence was higher than the previous studies (1.3%).¹⁹ There are several possible explanations for this difference. First, asymptomatic patients who may have with ALK-IIP with the COP pattern on chest CT may not have been reported as Crizotinib-associated ILD in previous studies. The retrospective review of 4 PROFILE trials have reported more severe symptoms and reported that all patients required hospitalization. However, patients with ALK-IIP in our study showed various grade of pneumonitis toxicity, and 45.5% of patients showed no

Table 3
Risk factors of ALK inhibitor-related pneumonitis.

Variable	Univariate		P	Multivariate		P
	OR	95% CI		OR	95% CI	
Ex/current smoker	3.612	1.027–12.707	.045	3.769	1.058–13.432	.041
Extrathoracic metastasis	6.831	0.860–54.231	.069	7.126	0.890–57.029	.064

CI=confidence interval, OR=odds ratio.

Table 4
CT characteristics of ALK inhibitor-related interstitial pneumonitis.

Thin-section CT findings	Total	COP pattern	HP pattern	AIP pattern
Patients number	11 (100)	7 (63.6)	2 (18.2)	2 (18.2)
Extent (%)*				
Emphysema	0	0	0	0
Reticulation	0.5	0.7	0	0
GGO	24.9	9.1	55.0	50.0
Consolidation	12.7	11.3	0	30.0
Total	38.0	21.1	55.0	80.0
Distribution				
Craniocaudal				
Upper	3 (27.3)	3 (42.9)	0 (0)	0 (0)
Middle	0 (0)	0 (0)	0 (0)	0 (0)
Lower	2 (18.2)	2 (28.6)	0 (0)	0 (0)
None	6 (54.5)	2 (28.6)	2 (100)	2 (100)
Axial				
Central	2 (18.2)	0 (0)	0 (0)	2 (100)
Peripheral	7 (63.6)	7 (100)	0 (0)	0 (0)
None	2 (18.2)	0 (0)	2 (100)	0 (0)
Bilateral	8 (72.7)	4 (57.1)	2 (100)	2 (100)
Symmetric	6 (54.5)	3 (42.9)	1 (50)	2 (100)

Numbers of the data are numbers of patients, with percentages in parentheses except the extent (%) of pulmonary abnormalities. Extent (%) is expressed as a percentage of the mean value. AIP = acute interstitial pneumonia, COP = cryptogenic organizing pneumonia, HP = hypersensitivity pneumonitis.

symptoms. There have been some recent case reports regarding patients with no symptom or very few symptoms in ALK-IIP.^[17,18] Second, this study only included Asian populations, who may be more prone to develop drug-related pneumonitis. The incidence of Crizotinib-related pneumonitis in the Japanese population in these trials was up to 3.7%.^[9] Gemma et al also reported the higher incidence of ILD in Japanese patients with NSCLC treated with Crizotinib.^[19] Thus, future studies should evaluate the relationship between genetic factors and susceptibility to ALK-IIP.

Among the CT patterns, ALK-IIP with the COP pattern was most commonly observed in our study. However, ALK-IIP with the COP pattern has been rarely reported until now.^[17,18] In previous studies, the CT findings of ALK-IIP were usually described as bilateral diffuse GGO^[9,11,20] and were not assessed in detail and categorized according to ATS/ERS classifications of

idiopathic interstitial pneumonias.^[13] Although drug-related pneumonitis can manifest with diverse CT findings, a specific agent may be associated with the predominant CT pattern. The AIP pattern is commonly observed in the epidermal growth factor receptor tyrosine kinase inhibitor-related pneumonitis and the COP pattern was common in the programmed cell death-1/programmed death ligand 1 inhibitors-related pneumonitis.^[21,22] Knowledge regarding the predominant CT pattern of drug-related pneumonitis in a specific drug may contribute to improving the diagnostic accuracy of drug-related pneumonitis, and the pattern approach in the diagnosis of drug-related pneumonitis may be more effective in clinical practice.

The chest CT patterns of ALK-IIP appear to be associated with the toxicity grade of drug-related pneumonitis and the clinical course in our study. The NCI CTCAE toxicity grades were highest in the AIP pattern, followed by the HP, and lowest in the

Table 5
CT characteristics of 11 patients with ALK inhibitor-related interstitial pneumonitis.

Pt	CT pattern	Extent (%)					Distribution				
		GGO	Consolidation	Reticulation	Emphysema	Total	Craniocaudal (upper/middle/lower/none)	Axial (central/peripheral/none)	Bilateral/unilateral	Symmetric/asymmetric	
1	COP	3.3	14.2	0	0	17.5	Upper	Peripheral	Bilateral	Symmetric	
2	COP	10	16.7	0	0	26.7	None	Peripheral	Bilateral	Symmetric	
3	AIP	50	30	0	0	80	None	Central	Bilateral	Symmetric	
4	COP	12.5	10	0	0	22.5	Upper	Peripheral	Bilateral	Asymmetric	
5	COP	6.7	10	0	0	16.7	None	Peripheral	Unilateral	Asymmetric	
6	COP	3.3	8.5	5	0	11.8	Upper	Peripheral	Bilateral	Symmetric	
7	HP	80	0	0	0	80	None	None	Bilateral	Asymmetric	
8	COP	6.0	9.9	0	0	15.9	Lower	Peripheral	Unilateral	Asymmetric	
9	COP	21.7	10	0	0	31.7	Lower	Peripheral	Unilateral	Asymmetric	
10	AIP	50	30	0	0	80	None	None	Bilateral	Symmetric	
11	HP	30	0	0	0	30	None	None	Bilateral	Symmetric	

Extent (%) is expressed as a percentage of the mean value. The extent of pulmonary abnormalities was assessed and the extent of each pulmonary abnormalities was scored using a 5% volumetric scale for 6 lobes, that is, the right upper lobe, right middle lobe, right lower lobe, left upper lobe, lingular segment, and left lower lobe. AIP = acute interstitial pneumonia, COP = cryptogenic organizing pneumonia, HP = hypersensitivity pneumonitis.

COP patterns. Moreover, all of the patients with the COP pattern of ALK-IIP were successfully treated with steroid treatment with/without discontinuation of the ALK inhibitor, while half of the patients with the AIP died. In the previously published study by Lee et al, the patients with chemotherapy-related pneumonitis with the AIP or HP patterns also showed more active and acute clinical manifestations than the patients with drug-related pneumonitis with the NSIP or COP pattern. The patients with ALK-IIP with COP pattern in the previously published case reports were also successfully treated with corticosteroid treatment.^[17,18] In the retrospective review of 4 PROFILE trials, 10 of 20 patients with Crizotinib-related pneumonitis died from the drug-related pneumonitis, and in most of these patients the CT findings were described as bilateral and diffuse GGO suspected to be the AIP or HP pattern.^[9] The pattern-based approach of chest CT analysis may be also helpful in predicting the patient response to the treatment of ALK-IIP.

The risk factors for the increase in the incidence of drug-related pneumonitis vary according to the disease, drug, and population being treated.^[23] Among the various risk factors, increased age, pre-existing lung disease, for example, ILD and chronic obstructive lung disease, and smoking history, are frequently reported as risk factors for various drug-related pneumonitis. ALK fusion oncogene in patients with NSCLC is reported to be associated with a history of never or light smoking, and the percentage of patients with smoking history in a total of 250 patients in our study was 34.0% similar to previous studies.^[9,24,25] In our study, smoking history was associated with an increase in the risk of ALK-IIP. Gemma et al also reported the smoking history was one of the risk factors of Crizotinib-related pneumonitis.^[19] ALK inhibitors, including Crizotinib, should be used with caution in NSCLC patients with smoking history.

The characteristic CT features of COP are multifocal and bilateral consolidations with peripheral and lower lung distribution. However, ALK-IIP with the COP pattern may manifest as a nontypical form of COP. In our study, some cases of ALK-IIP with the COP pattern had chest CTs which showed multiple, mass-like consolidation with upper lung zone predominance or no zonal predominance as well as unilateral or asymmetric lung involvement. These CT findings initially assumed the disease progression or pleural metastasis, and CT-guided percutaneous lung biopsies were performed in 2 of our study patients. Lim et al also reported Ceritinib-related pneumonitis with the COP pattern which was seen multifocal, mass-like consolidation in both upper lobes.^[18] Therefore, if pulmonary abnormalities, such as mass-like consolidation, newly developed on chest CT in patients using an ALK inhibitor, the radiologist should consider drug-induced pneumonitis with the COP pattern in the differential diagnoses, although it is not easy to distinguish from pneumonia with the pathogen or tumor progression.

Our study has several limitations. First, it was retrospective in nature and performed with a relatively small number of patients in a single tertiary center. However, considering the low incidence of ALK-IIP, it is inevitable that the number of patients is small in the single cohort study. Second, we did not have pathologic confirmation of ALK-IIP in most cases. Although the pathologic examination may help to determine the morphologic pattern of pulmonary abnormalities, identifying the etiologies, such as drug-related pneumonitis, usually requires a multidisciplinary approach in clinical practice. Third, the analysis of the CT pattern and radiologic characteristics could be subjective. However, in our study CT image analysis was performed by 2 chest

radiologists who were clinically experienced in the CT pattern analysis of ILD.

In conclusion, ALK-IIP showed a spectrum of chest CT patterns and various toxicity grades, and CT patterns reflected the toxicity grades of ALK-IIP. The COP pattern was the most common CT pattern of ALK-IIP followed by the AIP and HP patterns, and patients with ALK-IIP of the COP pattern were successfully treated. A pattern approach in diagnosing ALK-IIP on chest CT is more appropriate and effective in routine practice. ALK inhibitors should be used with careful monitoring in NSCLC patients with smoking history.

Author contributions

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