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Clinical significance of interstitial lung abnormalities and immune checkpoint inhibitor-induced interstitial lung disease in patients with non-small cell lung cancer

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Abstract

Background: Interstitial lung abnormalities (ILAs) are known to be a risk of drug-induced pneumonitis. However, there are few reports on the relationship between ILAs and immune checkpoint inhibitor-related interstitial lung disease (ICI-ILD). We retrospectively investigated the clinical significance of ILAs in patients with non-small cell lung cancer (NSCLC) receiving ICIs.

Methods: We defined ILAs as nondependent abnormalities affecting more than 5% of any lung zone, including ground-glass or diffuse centrilobular nodularities, traction bronchiectasis, honeycombing, and nonemphysematous cysts. Early-onset ICI-ILD was defined as developing within 3 months after the initiation of ICI administration.

Results: Of 264 patients with advanced NSCLC, 57 patients (21.6%) had ILAs (43 fibrotic and 14 nonfibrotic ILAs). The difference between the incidence of ICI-ILD in patients with or without ILAs was not significant. Of 193 patients treated by ICI monotherapy, 18 (9.3%) developed early-onset ICI-ILD. Among patients receiving ICI monotherapy, the incidence of early-onset ICI-ILD was significantly higher in patients with than in patients without nonfibrotic ILAs.

Conclusion: The presence of nonfibrotic ILAs is a significant risk for early-onset ICI-ILD in patients with NSCLC undergoing ICI monotherapy. Clinicians should be aware of ILAs, especially nonfibrotic ILAs, before administering ICIs to lung cancer patients.

KEYWORDS
ICI-ILD, ILA, NSCLC, PD-1 inhibitor

INTRODUCTION

The immune-checkpoint inhibitor (ICI) is the latest therapeutic breakthrough in several types of advanced tumors such as lung cancer, melanoma, head and neck tumors, bladder cancer, and lymphoma.[1–5] Safety is a major concern as the number of patients receiving these new drugs increases. Although ICIs provide an overall favorable risk-to-benefit profile, they are known to cause unique toxicities named immune-related adverse events (irAEs), due to their mechanisms of action. Although irAEs are typically manageable, uncommon fatal irAEs have been reported, which tend to occur early in ICI treatment. Clinicians should recognize and manage these types of immune-mediated events early on, as they can be severe or fatal. Interstitial lung disease (ILD) induced by ICI treatment has been observed to be a clinically serious and fatal toxicity.[6,7] The majority of episodes of ILD occur within 3 months of the induction of immunotherapy, and the onset tends to be particularly early in patients with non-small cell lung cancer (NSCLC).[6–8] Some studies have found that the risk of ICI-related ILD (ICI-ILD) was associated with pre-existing ILD.[9] However, ICI-ILD is also frequently clinically developed in patients without pre-existing ILD.

Interstitial lung abnormalities (ILA) are specific findings on computed tomography (CT) that may be compatible with ILD in patients without clinical manifestations. ILAs that occur with normal aging are increasingly recognized to be common features on CT scans of the elderly. With the increasing use of CT for various purposes, ILAs will increasingly be observed on CT scans. These abnormalities are risk factors for increased mortality and complications from surgery and chemotherapy. Thus, these changes on chest CT scans have prognostic value and should be reported.[10–12]

ILAs seen in patients before they undergo treatment for cancer have been associated with cancer-related mortality.[11,13] The exact reason for increased mortality is unclear, but the risks of lung injury due to ILAs and cancer therapy have been speculated.[11] However, results of the studies on the association of ILAs and lung cancer treatments remain unclear. To our knowledge, only two reports have examined the relationship between pre-existing ILAs and ICI-ILDs.[14,15] Thus, we retrospectively investigated the clinical significance of ILAs on the incidence, subcategories, and onset of ICI-ILD in patients with NSCLC who received immunotherapy at our hospital.

METHODS

Study design

We retrospectively screened patients with pathologically confirmed advanced or recurrent NSCLC who had been treated with ICIs at our institution between February 2016 and March 2021. There were no pre-existing ILDs among patients who received ICI treatment. First-line treatment was defined as either primary chemotherapy or immunotherapy. Prior treatment with molecular targeted drugs were not counted in the treatment line. PD-L1 expression by tumor cells on preparations of the archived biopsy specimens was assessed by the PD-L1 IHC 22C3 pharmDx assay (Agilent). This study was performed in accordance with the provisions of the Declaration of Helsinki and was approved by the Institutional Review Board of the Kurume University Hospital (IRB No 20100).

Evaluation of high-resolution CT (HRCT) findings

We investigated the presence of abnormal findings, which included pre-existing ILAs, on the HRCT scans of the study patients. ILAs were defined based on the report of Hatabu et al,[11] as follows: nondependent abnormalities affecting more than 5% of any lung zone, including ground-glass or diffuse centrilobular nodularities, traction bronchiectasis, honeycombing, and nonemphysematous cysts. These types of ILAs were classified into two broad subcategories as fibrotic and nonfibrotic ILAs.

As previous reports and a position paper from the Fleischner Society,[11,16] fibrotic ILA was defined by the presence of pulmonary parenchymal architectural distortion (e.g., traction bronchiectasis, honeycombing) consistent with a fibrotic lung disease (definite fibrosis), which is not limited to those whose imaging pattern is consistent with a usual

TABLE 1 Patient characteristics

Variables	$N = 264$ (%)	
	No.	%
Age		
Median	70	
Range	63–75	
Gender		
Male	196	74.2
Female	68	25.8
Smoking status		
Past or current	202	76.5
Never	62	23.5
Histology		
Adenocarcinoma	164	62.1
Squamous	71	26.9
NSCLC	26	9.8
LCNEC	3	1.1
ILA	57	21.6
Fibrotic ILAs	43	16.3
Nonfibrotic ILAs	14	5.3
PD-L1 tumor proportion score (%)		
≥50	73	27.7
1–49	78	29.5
<1	59	22.3
Not tested	54	20.5
Driver mutation		
EGFR mutation	41	15.5
EML4-ALK fusion	4	1.5
RET fusion	1	0.4
Negative	218	82.6
Prior molecular targeted drugs		
EGFR-TKI	41	15.5
ALK-TKI	4	1.5
Others	0	0
Treatment		
ICI monotherapy	193	73.1
Combination therapy	71	26.9
Line of ICI therapy		
1	111	42
2,3	118	44.7
≥4	35	13.3

Abbreviations: ALK, anaplastic lymphoma kinase, EGFR, epidermal growth factor receptor, EML4-ALK, echinoderm microtubule-associated protein-like 4 - anaplastic lymphoma kinase, ICI, immune-checkpoint inhibitors, ILA, interstitial lung abnormalities, ILD, interstitial lung disease, LCNEC, large cell neuroendocrine carcinoma, NSCLC, non-small cell lung cancer, PD-L1, programmed death-ligand 1, RET, rearranged during transfection, TKI, tyrosine kinase inhibitor.

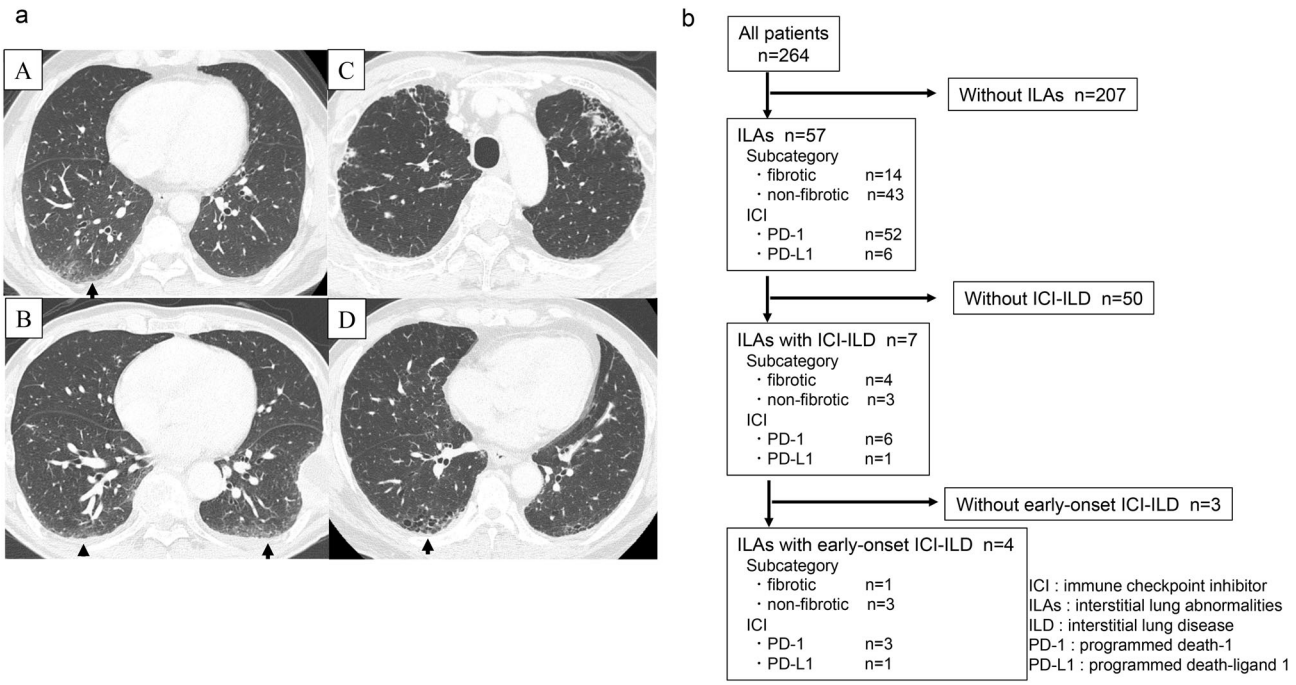

FIGURE 1 (a) Chest computed tomography images of interstitial lung abnormalities. (a, b) Patients with nonfibrotic interstitial lung abnormalities. (c, d) Patients with fibrotic interstitial lung abnormalities. (b) Flow diagram of the study population. In total, 264 patients were enrolled. Of the 264 patients, 57 had interstitial lung abnormalities (ILAs); 14 had fibrotic ILAs and 43 had nonfibrotic ILAs. There were 51 patients treated with a programmed death-1 (PD-1) inhibitor, five treated with a programmed death-ligand 1 (PD-L1) inhibitor, one patient was treated with both a PD-1 and PD-L1 inhibitor. Of the 57 ILA patients, seven developed immune checkpoint inhibitor-induced interstitial lung disease (ICI-ILD); four had fibrotic ILAs and three had nonfibrotic ILAs. There were six patients treated with a PD-1 inhibitor and one treated with a PD-L1 inhibitor. Of the seven ILA patients with ICI-ILD, 4 had early-onset disease; three cases had fibrotic and one had nonfibrotic ILAs. There were three patients treated with a PD-1 inhibitor and one treated with a PD-L1 inhibitor

interstitial pneumonia or probable usual interstitial pneumonia pattern. Nonfibrotic ILA was defined as ILA not included in fibrotic ILA.

A CT system was used to obtain HRCT data (1–10 mm slice thickness), which were obtained at the end of inspiration with the patient in the supine position. HRCT was used which was taken closest before ICI administration. The HRCT scans were reviewed by two independent pulmonologists. Final decisions were made by consent of two independent pulmonologists.

Diagnosis of ICI-induced ILD

ICI-ILD was diagnosed as follows: (1) occurring during treatment with an ICI, (2) new ground-glass attenuation (GGA) or consolidations in the bilateral lung fields of CT scan, (3) exclusion of pulmonary infection, and (4) exclusion of heart failure.[13,16–19] Pulmonary infections were ruled out by sputum culture and antibiotic efficacy, and heart failure was excluded by clinical examination and echocardiography. The radiographic patterns of the ILD were classified according to the American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association (ATS/ERS/JRS/ALAT) international multidisciplinary classification of interstitial pneumonias.[20] ILD was evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Early-onset ICI-ILD was defined as ILD developing within 3 months after the start of immunotherapy.

Statistical analysis

The Pearson $\chi 2$ test or Mann–Whitney U test was used for comparison of the two groups. Risk factors for ICI-ILD were examined using univariate and multivariate logistic regression models. Multivariate analysis was performed using fibrotic and nonfibrotic ILD as covariates to evaluate which ILD finding was an independent risk factor for ICI-ILD. A two-tailed p-value of <0.05 was considered statistically significant. Statistical analyses were conducted using JMP version 16.0 software (SAS Institute Inc.).

RESULTS

Patient characteristics

A total of 264 patients were enrolled in this study. Table 1 shows the clinical characteristics of the patients. The median age of patients was 70 years (63–75 years). Male patients (74.2%) were predominant. Many patients (76.5%) had a smoking history. Adenocarcinoma and squamous cell carcinoma

TABLE 2 Characteristics of patients with and without ICI-ILD

All patients	ICI-ILD + $n = 32$	ICI-ILD-$n = 232$	p-value
Gender			0.334
Male	26	170	
Female	6	62	
Smoking status			0.263
Past or current	27	175	
Never	5	57	
PD-L1 tumor proportion score (%)			0.377
≥50	13	60	
1–49	8	70	
<1	6	53	
Not tested	5	49	
Prior thoracic radiation therapy			0.786
+	7	46	
−	25	186	
Prior molecular targeted drugs			
EGFR-TKI	3	38	0.305
ALK-TKI	1	3	0.427
ILA	7	50	0.967
Fibrotic ILAs	4	39	0.536
Nonfibrotic ILAs	3	11	0.273
Treatment			0.495
ICI monotherapy	25	168	
Combination therapy	7	64	

accounted for 62.1 and 26.9%, of the cases, respectively. A driver mutation was harbored in 17.4% of patients, and an epidermal growth factor receptor (EGFR) mutation in 15.5%, anaplastic lymphoma kinase (ALK) fusion gene was 1.5%, and a rearrangement during transfection fusion was 0.4%. All patients with harbored *EGFR* and *ALK* mutations had been previously treated with tyrosine kinase inhibitors (TKIs), respectively. PD-L1 tumor proportion scores of ≥50%, 1%–49%, and <1% were seen in 27.7, 29.5, and 22.3% of patients, respectively. HRCT revealed ILAs in 57 (21.6%) patients, of whom 16.3 and 5.3% had fibrotic ILAs and nonfibrotic ILAs, respectively. Figure 1a shows examples of the CT scans of patients with ILAs. A total of 73.1% were treated by ICI monotherapy and 26.9% were treated by a combination of an ICI and chemotherapy. The median follow-up term was 8.8 months (0.2–61.3 months) for the ICI monotherapy group and 10.7 months (0.4–29.6 months) for the combined group, respectively.

Proportions and characteristics of patients with and without ICI-ILD

Table 2 shows the prevalence of ICI-ILD in the 264 study patients. Of the 264 patients, 25 (9.5%) who received ICI monotherapy and seven (2.7%) patients who received a combination of ICI therapy and chemotherapy developed ICI-ILD. The differences between the baseline characteristics of study patients with and without ICI-ILD were not significant.

Figure 1b shows a flow diagram of the various categories of patients with/without various iterations of ILA, ILD, ICI-ILD, and fibrotic and nonfibrotic disease, and numbers of patients in each category within the study population. Of the 264 patients, 32 (12.1%) developed ICI-ILD. Among the 32 patients with ICI-ILD, seven (21.9%) had ILAs, four (12.5%) had fibrotic ILAs, and three (9.3%) had nonfibrotic ILAs.

Figure 2a shows examples of HRCT scans of patents with ILAs who developed ILD after ICI monotherapy. Figure 2b shows the time to the onset of ICI-ILD after the start of immunotherapy. Seven (2.7%) of 264 patients underwent thoracic radiation therapy before the occurrence of ICI-ILD. The difference between the proportion of patients with and without ILA who developed ICI-ILD was not significant ($p = 0.967$).

Proportion and characteristics of patients with early-onset ICI-ILD

Table 3 shows that 21 (8.0%) of 264 patients developed early-onset ICI-ILD. Among the 21 patients with early-onset ICI-ILD, four (19.0%) had ILAs; one patient (4.8%) had fibrotic ILAs and three (14.3%) had nonfibrotic ILAs. Eighteen (9.3%) of 193 patients who received ICI monotherapy and three (4.2%) of 71 patients who received ICI and chemotherapy developed early-onset ICI-ILD. Seven patients (2.7%) underwent thoracic radiation therapy before the occurrence of early-onset ICI-ILD. Differences between the baseline characteristics of patients with and without early-onset ICI-ILD were not significant. The difference between the proportions of patients with and without ILA who developed early-onset ICI-ILD was not significant ($p = 0.765$).

Proportions and characteristics of patients with/without early-onset ICI-ILD who received ICI monotherapy

Table 4 shows the proportion of patients with early-onset ICI-ILD among the 193 patients who received ICI monotherapy. Of the 193 patients, 18 (9.3%) developed early-onset ICI-ILD. Among the patients with early-onset ICI-ILD, three (16.7%) had ILAs, one (5.6%) had fibrotic ILAs, and two patients (11.1%) had nonfibrotic ILAs. Seven (3.6%) patients underwent thoracic radiation therapy before the occurrence of ICI-ILD. ICI-ILD did not develop in patients who had previously received molecularly-targeted drugs. The differences between the baseline characteristics of patients with and without early-onset ICI-ILD were not significant. The difference between the proportions of

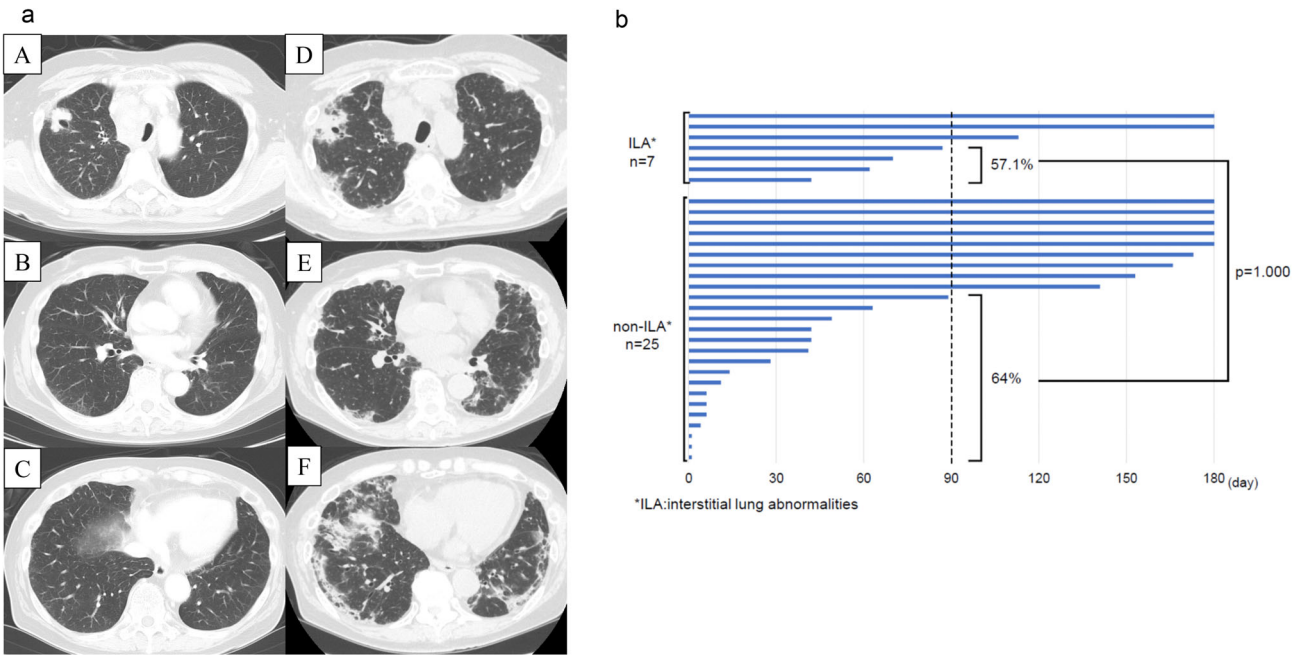

FIGURE 2 (a) A patient with nonfibrotic interstitial lung abnormalities leading to immune checkpoint inhibitor-related interstitial lung disease. The patient was a 67-year-old man with squamous cell carcinoma. (a)–(c) Chest computed tomography (CT) scans before the administration of immunotherapy. The scans show nonfibrotic subpleural interstitial lung abnormalities (ILAs). (d)–(f) Chest CT scans 2 months after the initiation of nivolumab monotherapy. CT showed consolidations in both peripheral lungs fields. The shadows are predominantly distributed in the right lower lobe. (b) Graph of the onset of immune checkpoint inhibitor-induced interstitial lung disease in study patients. There were 32 patients who developed immune checkpoint inhibitor-related interstitial lung disease; seven patients had ILAs and 25 did not have ILAs. Early onset cases accounted for 57.1% of the patients with ILAs and 64% of the patients without ILAs

patients with and without ILAs who developed early onset ICI-ILD was not significant ($p = 0.694$). In contrast, the incidence of early-onset ICI-ILD was significantly higher in patients with nonfibrotic ILAs than in patients with fibrotic ILAs ($p = 0.040$).

DISCUSSION

This study revealed that the presence of pre-existing nonfibrotic ILAs was an independent risk factor of early-onset ICI-ILD induced by ICI monotherapy. To the best of our knowledge, this is the first study to report on the relationship between a subcategory of ILAs and the onset time of ICI-ILD. In the present study, ILAs accounted for 21.6% (57/264) of study patients. Fibrotic ILAs accounted for 16.3% and nonfibrotic ILAs accounted for 5.3% of the study patients. Before administering ICIs to patients with ILAs, we should estimate their risk of developing ICI-ILD. Estimating the risk of ICI-ILD is especially important for patients with nonfibrotic ILAs.

Previous studies determined that the presence of GGAs, not including fibrotic area, was a risk for conventional chemotherapy and immunotherapy-related ILD.[13,14,21] We also found that the presence of nonfibrotic ILAs was an independent risk factor for early-onset ICI-ILD. GGA reflects inflammation by lymphocytes in the interstitium, and ICIs exert antitumor effects via activation of lymphocytes.[13,14,21] These results may explain why GGAs were involved with ICI-ILD.[13,14,21]

Nonfibrotic ILAs are known to have a better prognosis compared to fibrotic ILAs because fibrotic ILAs are associated with risk of progression on CT imaging and death.[16] For this reason, nonfibrotic ILAs are less emphasized than fibrotic ILAs in clinical practice. However, nonfibrotic ILAs were significantly associated with the risk of developing early onset ICI-ILD in this study, while fibrotic ILAs were not. Since ICI-ILDs are sometimes fatal, it is important to be careful about the presence of nonfibrotic ILAs in patients treated with cancer immunotherapy.

This study found that the combination of an ICI and chemotherapy did not lead to early-onset ICI-ILD, even in patients with nonfibrotic disease. This is the first report on the combination of ICI and chemotherapy, as previous reports have only focused on ICI monotherapy.[14,15] The combination of ICI and chemotherapy may be less likely to result in ICI-ILD, even in patients with pre-existing ILAs, compared to ICI monotherapy alone. We previously reported that the incidence of irAEs, especially pneumonitis, during the first 3 months after the start of treatment was significantly higher in patients receiving ICI monotherapy than in the patients receiving a combination of ICI and chemotherapy.[22]

The mechanism by which chemotherapy suppresses the development of ICI-ILD remains unclear. The reduced rate of ICI-ILD might be accounted for by the steroids

TABLE 3 Characteristics of patients with and without early-onset ICI-ILD

All patients	Early-onset ICI-ILD (+) $N = 21$	Early-onset ICI-ILD (−) $N = 243$	*p*-value
Gender			0.464
Male	17	179	
Female	4	64	
Smoking status			0.300
Past or current	18	184	
Never	3	59	
PD-L1 tumor proportion score (%)			0.201
≥50	10	63	
1–49	5	73	
<1	3	56	
Not tested	3	51	
Prior thoracic radiation therapy			0.114
+	7	46	
−	14	197	
Prior molecular targeted drugs			
EGFR-TKI	0	41	**0.041**
ALK-TKI	0	4	0.554
ILA	4	53	0.768
Fibrotic ILAs	1	42	0.136
Nonfibrotic ILAs	3	11	0.056
Treatment			0.174
ICI monotherapy	18	175	
Combination therapy	3	68	

Abbreviations: ALK, anaplastic lymphoma kinase, EGFR, epidermal growth factor receptor, ICI, immune-checkpoint inhibitors, ILAs, interstitial lung abnormalities, ILD, interstitial lung disease, PD-L1, programmed death-ligand 1, TKI, tyrosine kinase inhibitor.

TABLE 4 Characteristics of patients with and without early-onset ICI-ILD who received ICI monotherapy

ICI monotherapy	Early-onset ICI-ILD (+) $N = 18$	Early-onset ICI-ILD (−) $N = 175$	*p*-value
Gender			0.324
Male	15	127	
Female	3	48	
Smoking status			0.398
Past or current	15	130	
Never	3	45	
PD-L1 tumor proportion score (%)			0.341
≥50	9	52	
1–49	4	44	
<1	2	36	
Not tested	3	43	
Prior thoracic radiation therapy			0.101
+	7	38	
−	11	137	
Prior molecular targeted drugs			
EGFR-TKI	0	39	**0.025**
ALK-TKI	0	3	0.576
ILA	3	36	0.694
Fibrotic ILAs	1	32	0.172
Nonfibrotic ILAs	2	4	**0.040**

Abbreviations: ALK, anaplastic lymphoma kinase, EGFR, epidermal growth factor receptor, ICI, immune-checkpoint inhibitors, ILAs, interstitial lung abnormalities, ILD, interstitial lung disease, PD-L1, programmed death-ligand 1, TKI, tyrosine kinase inhibitor.

administered during chemotherapy. Steroids are the most common basic treatment for ICI-ILD. In addition, the myelosuppression induced by chemotherapy could suppress inflammation through the regulation of soluble immune mediators.

In older individuals (>60 years of age) the prevalence of ILAs has been reported to be 4%–9% of smokers and 2%–7% of nonsmokers.[10] However, in patients with lung cancer, the prevalence of ILAs has been reported to be 14%–22%.[13,23–26] In this study, 57 patients (21.6%) had ILAs, which is consistent with the prevalence reported in previous studies.[13,23–26] Based on the above, just as idiopathic pulmonary fibrosis and other ILDs,[26–28] patients with ILAs may be prone to complications from lung cancer. Additionally, the presence of nonfibrotic ILAs was seen in 5.3% of all of our study patients (264 patients). Nonfibrotic ILAs account for 24.6% of the total ILAs. Other studies have reported that the presence of nonfibrotic ILAs accounted for 53.8% to 67.6% of all the patients with ILAs,[13,14] results that are much higher than observed in our study. It should be noted that lung cancer tends to be a complication of ILAs, and it includes nonfibrotic ILA, which is a risk for ICI-ILD.

Male and smoking history have been reported as clinical risk factors for ILA.[11] In this study, being male was not associated with ILA, but smoking history was significantly associated with ILA (Table S2). Smoking history was also significantly associated with both fibrotic and nonfibrotic ILA. In addition, smoking history was not associated with ICI-ILD. Although smoking history is not directly related to ICI-ILD, it is involved in the development of ILA. Therefore, the presence of ILA should be confirmed at the start of immunotherapy in lung cancer patients with smoking history.

The present study had some limitations. First, ICI-ILD was not diagnosed by histopathological examinations. Second, this study was a retrospective single-center study.

Third, patients included in our study received heterogeneous regimens. Fourth, the number of ILA patient was small within the ICI-ILD group. A prospective multicenter study is warranted to validate the present findings. In conclusion, the presence of nonfibrotic ILAs was a significant risk factor for early-onset ICI-ILD in patients about to undergo ICI monotherapy. The presence of ILAs is more likely to be associated with lung cancer then the absence of ILAs, and early-onset ICI-ILD can interfere with the treatment of lung cancer and can be life-threatening. Clinicians should bear in mind the possible presence of ILAs, especially nonfibrotic ILAs, in patients with lung cancer, before they decide to administer ICIs.

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CONFLICT OF INTEREST

KA reports receiving personal fees from AstraZeneca, MSD, Bristol Myers Squibb, Ono Pharmaceutical, Takeda Pharmaceutical, Pfizer and Chugai Pharmaceutical. NM reports receiving personal fees from AstraZeneca, Bristol Myers Squibb, Ono Pharmaceutical and Chugai Pharmaceutical. TT reports receiving personal fees from AstraZeneca, Bristol Myers Squibb, MSD, Novartis and Chugai Pharmaceutical. The remaining authors have no conflicts of interest to disclose.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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