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FULL PAPER

Clinical and radiological features of immune checkpoint inhibitor-related pneumonitis in lung cancer and non-lung cancers

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Objective: To investigate the clinical and radiological features of immune checkpoint inhibitor-related pneumonitis (ICI-P), a rare but serious pulmonary complication of cancer immunotherapy and to evaluate key differences between lung cancer (LC) and non-LC patients.

Methods: 247 patients (LC, $n = 151$) treated with ICI for malignancies were retrospectively screened in a single institute. The number of patients, history of other immune-related adverse events (irAE), the onset, serum KL-6 levels, and chest CT features (types of pneumonitis, symmetry, laterality, location) were recorded for the ICI-P population and compared for LC and non-LC groups.

Results: ICI-P was identified in 26 patients in total (LC, $n = 19$; non-LC, $n = 7$). The incidence of other irAE was significantly higher in ICI-P group (63%) compared with patients without ICI-P (34%) ($p = 0.0056$). An earlier onset of ICI-P was recorded in LC (78 days) compared to non-LC patients (186 days) ($p = 0.0034$). Serum KL-6 was significantly elevated only in the non-LC group

when ICI-P was noticed ($p = 0.029$). Major CT findings of ICI-P, irrespective of primary disease, were organizing pneumonia pattern and ground glass opacities. LC patients commonly exhibited consolidation and traction bronchiectasis and were prone to asymmetrical shadows ($p < 0.001$). Non-LC patients were more likely to exhibit symmetrical infiltrations. A small fraction of both groups experienced relapse or moving patterns of ICI-P.

Conclusion: ICI-P patients more often experienced other irAE prior to the development of ICI-P. The characteristics of ICI-P can differ in terms of the onset, KL-6 reliability, and chest CT findings between LC and non-LC patients.

Advances in knowledge: In ICI-P patients, a history of other irAE can be more frequently observed. Differences in disease onset and radiological patterns between LC and non-LC patients might be helpful to make a diagnosis of ICI-P; however, longitudinal observation of chest CT scans is advised to observe the pneumonitis activity irrespective of cancer types.

INTRODUCTION

Immune checkpoint inhibitors (ICI) have revolutionized the therapeutic management of a number of malignancies, in particular lung cancer (LC) and melanoma, where they are now approved for use as first- and second-line treatments. A growing number of ICI drugs are approved for clinical use including the Programmed cell death1 (PD-1) inhibitors (e.g. nivolumab and pembrolizumab),^{1–4} programmed cell death ligand 1 (PD-L1) inhibitors (e.g. atezolizumab and durvalumab),^{5,6} and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitors (e.g. ipilimumab).⁷ ICIs have a unique mechanism of action that drives the antitumor response, completely distinct from conventional cancer therapies. ICIs have achieved remarkable successes in the

clinical setting and has pushed immunotherapy at the forefront of cancer treatment.

However, local or systemic adverse events, so-called immune-related adverse events (irAEs) are a major complication of ICI and includes skin rash, enterocolitis, myocarditis, hepatitis, and inflammation of endocrine organs.^{8–11} Depending on the severity of the adverse events that manifest, clinicians need to decide if they should cease the use of ICI or potentially continue its use in conjunction with steroid therapy. Among the irAEs, immune checkpoint inhibitor-related pneumonitis (ICI-P) is defined as the development of dyspnea and/or other respiratory symptoms in the presence of new infiltrates on chest imaging

without presence of new infections. ICI-P is known as a potentially fatal disease and warrants early detection. Indeed, once pneumonitis is suspected, usually through the observation of radiological abnormalities (Common Terminology Criteria for Adverse Events (CTCAE) v. 5.0, Grade 1), it is recommended that the ICI be withheld,^{12,13} while other irAEs at the same grade often allow for continuation of ICI under careful observations. Despite the pressing feature of the disease, the symptoms of ICI-P can be varied making it challenging to reach an accurate and prompt diagnosis. Since it is currently not possible to predict the development of irAEs prior to starting therapy,¹⁴ chest CT scans play a major role in the diagnosis of ICI-P. It is therefore pertinent for radiologists to understand the CT characteristics and variations of ICI-P in the management of malignancies.

Notably, primary LC patients potentially have damaged lungs influenced not only by habitual/environmental causes (e.g. smoking) and benign diseases which could cause neoplasms,¹⁵⁻¹⁷ but also as a result of radiation treatment and chemotherapy.^{18,19} This raises a possible hypothesis that the characteristics of ICI-P in LC patients may well be different from that of non-LC patients. Although several lines of evidence have shown the chest CT findings of ICI-P in non-small cell lung cancer (NSCLC),^{20,21} differences in ICI-P characteristics between LC and primary cancers of other organs, have not been fully researched yet. We were therefore motivated to investigate the radiological features of ICI-P, taking into consideration the clinical findings.

Our study aimed to parse the clinical and radiologic features of ICI-P according to the disease type, especially comparing LC and non-LC patients.

METHODS

Patients

This retrospective study was approved by the institutional review board. Adult patients (age >20) who were treated with immune checkpoint inhibitors for various malignancies were screened from April 2015 to July 2019. Patients were excluded if they died or censored within 14 days without signs of new lung diseases. December 31, 2019 was set as the end of the follow-up period. ICI-P was defined as non-infectious pneumonitis that developed post-ICI and was clinically diagnosed by attending physicians. Possible cases were excluded if the patient developed pneumonitis after switching to other chemotherapies because of the challenge in attributing the disease to the ICI. The patient age, sex, ICI drug, malignant disease, smoking history, overall survival days, and history of ICI-P were collected or calculated from the medical record, and compared between the LC and non-LC patient groups. The existence of emphysema or interstitial pneumonia at the baseline CT prior to the start of ICI were also checked by board-certified radiologists, to correlate any potential relationship with ICI-P. Other irAEs development frequency was also checked for with and without (w/o) ICI-P groups to explore any relevance to ICI-P.

Any history of radiation therapy in the lung field was also considered in LC patients, since radiation recall pneumonitis in the former radiation field is a well-documented common adverse

event in ICI users. Therefore, the patients who developed ICI-P were grouped into three; LC(RT-), LC(RT+), and non-LC. The ICI-P onset, CTCAE grade,²² duration, treatments, and Krebs von den Lungen-6 (KL-6) at pre- and at onset of ICI-P were recorded where available. KL-6 is secreted by Type 2 alveolar pneumocytes and bronchial epithelial cells in response to damage and degeneration of interstitial lung disease, both drug-induced and idiopathic. In previous studies, changes of KL-6 in drug-induced lung diseases corresponded with the clinical course and was suggested as an important marker of disease activity.^{23,24} As such, KL-6 is considered as a potential circulating biomarker to monitor drug-induced lung disease,^{25,26} and recommended to check periodically²⁷ although the specificity of KL-6 in drug induced lung disease has yet not clarified. We therefore evaluated the duration between the initiation of ICI and ICI-P onset, comparing in LC(RT-), LC(RT+), and non-LC groups as well as serum KL-6 elevation due to ICI-P.

Radiological evaluation

Chest CT scans to first indicate ICI-P onset were carefully read and categorized into patterns (organizing pneumonia, OP; non-specific interstitial pneumonia, NSIP; diffuse alveolar damage, DAD; hypersensitivity pneumonitis, HP), referring to a guideline advocated by the American Thoracic Society, the European Respiratory Society, the Japanese respiratory Society, and the Latin American Thoracic Association²⁸ and previous publications.^{20,21} NSIP in this study was described as cellular NSIP pattern which represent ground glass opacities (GGOs) which may accompany septal lines but does not represent fibrosis or honeycombing.^{29,30} Plus, five findings relevant to pneumonitis were checked such as GGO, consolidation, traction bronchiectasis, nodular lesions, and reversed halo sign. Nodular lesions were defined as small patchy parenchymal opacities randomly distributed in both lungs, and centrilobular nodules were excluded that suggests inflammatory lesions. As for the definition of GGO, consolidation, traction bronchiectasis, and reversed halo sign, we followed a previously published glossary of terms for thoracic imaging.³¹ Location information such as the predominant lobe (upper/middle lobe or lower lobe), symmetry (if ICI-P distributes symmetrical or asymmetrical) and laterality were also evaluated. The ICI-P shadows were followed up and divided into six outcome categories (improved, persisting, moved, relapse, fibrosis, and no follow-up.)

All the findings of ICI-P were confirmed with a reach of consensus of three board-certified experts in chest radiology (TN, 13 years, YN, 25 years, and SN, 40 years of experience).

Statistics

Non-parametric statistical analyses were performed in this study considering the small number of patients. ICI-P frequency with regard to smoking history and emphysema was compared between LC and non-LC groups using Fisher's exact test. Other irAEs frequency in with or w/o ICI-P was also compared with Fisher's exact test. Survival analysis was calculated by Kaplan-Meier method. Time to onset of ICI-P was compared among LC(RT-), LC(RT+), and non-LC groups using Kruskal-Wallis test. Serum KL-6 values were compared between baseline and

Table 1. Cancer types

Cancer type	n
Lung cancer	151
Non-lung cancer	96
Gastrointestinal cancer	29
Urinary tract cancer	27
Head and neck cancer	22
Malignant melanoma	11
Malignant pleural mesothelioma	2
Hodgkin's lymphoma	2
Others	3

ICI-P onset in each LC(RT-), LC(RT+), and non-LC group, using Mann-Whitney *U* test, followed by Bonferroni correction. The lobe predominance, symmetry, and laterality of ICI-P findings on chest CT scans were again analyzed with Fisher's exact test and Bonferroni correction. All statistics were performed with Prism v. 8.3.0 or R v. 3.6.1. Two-tailed *p* values under 0.05 was considered as significant.

RESULTS

Patients

256 patients were detected with an episode of ICI for malignancies. Nine patients were excluded either due to death from disease progression (*n* = 6) or transfers to other hospitals (*n* = 3) within 14 days after starting ICI. Overall, 247 patients (median age, range; 68, 45–88) were included in this study. The patient characteristics are summarized in Tables 1 and 2. LC and non-LC patients consisted of 61% (*n* = 151) and 39% (*n* = 96) of the entire population. All LC patients were confirmed as NSCLC. The primary locations of the non-LC group included gastrointestinal organs, urinary tract, head and neck, skin (melanoma), mesothelioma, Hodgkin's diseases, unknown primary, and pelvis. There was no significant difference in age and sex between LC and non-LC patients. In both groups, the majority of patients were treated with nivolumab followed by pembrolizumab. Only one melanoma patient received ipilimumab. Smoking history was detected in 79% of LC and 52% of non-LC patients. In baseline

Table 3. Characteristics of ICI-P patients

	LC (<i>n</i> = 19)	Non-LC (<i>n</i> = 7)
Age	70, 54–82	68, 63–79
Male : Female	16 : 3	7 : 0
Steroid treatment	13 (68%)	3 (43%)
ICI drug		
Nivolumab	7 (37%)	7 (100%)
Pembrolizumab	10 (53%)	0
Durvalumab	2 (11%)	0
ICI as a first line	4 (21%)	1 (14%)
Chemo combo	2 (11%)	0
OS (d, mean ± SD)	406 ± 379	353 ± 190

ICI-P, immune checkpoint inhibitor-related pneumonitis; LC, lung cancer; OS, overall survival; SD, standard deviation.

CT scans acquired prior to starting ICI, emphysema was found in 36% of LC and 17% of non-LC patients. Minimum to mild interstitial changes were observed in two and four patients in the LC and non-LC group respectively. Coexisting emphysema and mild interstitial changes were observed in five and three patients from the LC and non-LC group respectively.

Clinical characteristics of immune checkpoint inhibitor-related pneumonitis (ICI-P)

ICI-P was identified in 12.6% of LC patients (*n* = 19) and in 7.3% of non-LC patients (*n* = 7). LC subtypes consisted of squamous cell carcinoma (*n* = 8), adenocarcinoma (*n* = 6), and indeterminate NSCLC (*n* = 5). Non-LC patients consisted of head and neck (*n* = 4), Hodgkin's disease, gastric cancer and renal cell carcinoma. The characteristics of ICI-P patients were described in Table 3. ICI-P was diagnosed with combination of clinical findings (symptoms, auscultation, and blood tests) in 25 patients. Symptoms and CTCAE pneumonitis grade was detailed in Tables 4 and 5. Major symptoms were fever lasting for a few days or more, which led clinicians to proceed further examinations. Grade 3 or more ICI-P was found in 8 (42.1%) LC and two non-LC patients (28.6%). Differential diagnosis of ICI-P such as infection, pulmonary embolism, congestive heart failure

Table 2. Characteristics of all patients

	LC (<i>n</i> = 151)	Non-LC (<i>n</i> = 96)
Age (median, range)	68, 45–85	68, 45–88
Male : Female (female %)	117:34 (23%)	70:26 (27%)
ICI drugs		
Nivolumab (PD-1 blockade)	87 (58%)	77 (80%)
Pembrolizumab (PD-1 blockade)	52 (34%)	18 (19%)
Atezolizumab (PD-L1 blockade)	8 (5%)	0
Durvalumab (PD-L1 blockade)	4 (3%)	0
Ipilimumab (CTLA-4 blockade)	0	1 (1%)

CTLA-4, cytotoxic T-lymphocyte-associated protein 4; ICI, immune checkpoint inhibitor; LC, lung cancer; PD-L1, programmed cell death ligand 1.

Table 4. Symptoms at diagnosis of ICI-P

Symptoms	LC (n = 19)	Non-LC (n = 7)	Total (n = 26)
Fever	5	3	8 (30%)
Dyspnea	6	1	7 (26%)
Low oxygen saturation	3	1	4 (15%)
Cough	4	0	4 (15%)
Malaise	1	1	2 (7%)
Rash	1	0	1 (4%)
Anorexia	1	0	1 (4%)
None	4	3	10 (37%)

ICI-P, immune checkpoint inhibitor-related pneumonitis; LC, lung cancer.

was clinically denied in all patients. Bronchoalveolar lavage under bronchoscopy was collected in six patients among them. Elevated lymphocytes (mean, 69.2% v.s. normal, 10–15%) and eosinophils (mean, 5.3% v.s. normal, <1%) ratio was confirmed in all cases, supporting the diagnosis of ICI-P. Pulmonary function tests of pre- and onset of ICI-P were referred in four patients. %Vital capacity (%VC) decreased in all cases (range, –8.1 to –38.5%). Either (or both) elevation of total white blood cell (WBC) count or serum CRP elevation was observed in 25 patients in total (mean $\pm$ SD: WBC, $8.2 \pm 3.7 \times 10^3/\mu\text{l}$; CRP, $7.0 \pm 6.1 \text{ mg dl}^{-1}$). Remaining two patients did not show any clinical findings but incidentally exhibited radiological findings of ICI-P such as bilateral organizing pneumonia otherwise not explained. Of these, one patient experienced ICI-related rash 2 months before ICI-P onset. The other patient manifested ICI-P-related thyroid dysfunction 11 months prior to ICI-P. Indeed, of these 27 ICI-P patients, 17 (63%) had a history of irAE in one or multiple organs at the diagnosis of ICI-P. On the other hand, in w/o ICI-P group, 76 patients (34%) manifested at least one irAE during clinical time course. This incidence was significantly lower than ICI-P group ($p = 0.0056$). Each irAE incidence was compared according to the development of ICI-P (Table 6). Thyroid dysfunction and rash were common in both ICI-P and w/o ICI-P groups; however, the frequency was significantly higher in ICI-P. Other organ dysfunctions or symptoms were variously observed irrespective of existence of ICI-P. No statistical differences were observed in ICI-P incidence based on smoking history (Figure 1a); however, more patients in the

Table 5. CTCAE grade of ICI-P

Grade	LC (n = 19)	Non-LC (n = 7)
1	8	3
2	5	2
3	5	2
4	1	0
5	0	0

CTCAE, Common Terminology Criteria for Adverse Events; ICI-P, immune checkpoint inhibitor-related pneumonitis; LC, lung cancer.

LC group who presented with emphysema at baseline CT scans developed ICI-P (Figure 1b). The majority of ICI-P population were male (88.5%) and had history of smoking (88.5%). 53% of LC patients used pembrolizumab while all non-LC patients were treated with nivolumab. With the exception of two patients in the LC group who received combination therapy, all others received monotherapy. ICI was introduced as the first-line therapy for four patients in the LC group and for one in the non-LC group. The mean overall survival was 406 days in LC and 353 days in non-LC patients. No significant differences in survival was observed in terms of development of ICI-P in both population (Figure 1c).

ICI-P onset and its relationship with KL-6

The mean time to ICI-P onset was 108 days overall. ICI-P development occurred earlier in LC (78 days) than in non-LC patients (186 days) ($p = 0.0034$). To evaluate the influence of prior radiation therapy in the lung field in LC patients, we conducted the same analysis with three different groups (LC(RT-) ($n = 9$), LC(RT+) ($n = 10$), and non-LC ($n = 7$)). LC(RT-) showed significantly earlier onset of ICI-P than non-LC ($p = 0.0019$). LC(RT-) also showed earlier onset compared to LC(RT+) ($p = 0.041$), and so did LC(RT+) compared to non-LC ($p = 0.040$); however, they were not significant after Bonferroni's correction (Figure 2a). The peak onset was seen after 1–2 cycles of ICI in LC(RT-), 3–5 cycles in LC(RT+), and 6–10 cycles in non-LC (Figure 2b). Radiation recall pneumonitis (RRP) was seen in six patients in LC(RT+), and the average onset was 79 days. KL-6 became significantly elevated after ICI-P development in non-LC group ($p = 0.029$) but not in the LC population (Figure 2c).

Radiologic features of ICI-P

All ICI-P patients had chest CT evaluations prior to the start of ICI (baseline) and at the onset of ICI-P. Baseline CT scans indicated emphysema in three patients and comorbid NSIP with emphysema in one patient in LC(RT-) group. CT scans at the diagnosis of ICI-P were analyzed according to the pneumonitis patterns, types of findings, location, symmetry, and laterality. Representative CT images of ICI-P are shown in Figure 3a and b. One patient in LC(RT-) and two in non-LC showed NISP pattern while the rest showed OP pattern. No patient presented pure DAD or HP pattern; however, one patient with Grade 4 pneumonitis presented with DAD/OP pattern afterwards. Among five major types of findings, GGO was seen in the majority of ICI-P patients in all groups (LC(RT-); 89%, LC(RT+); 90%, non-LC; 100%) (Figure 3c). Consolidation was also common in LC patients irrespective of radiation history (~80%), whereas non-LC group had lower frequency (29%). Bronchiectasis was also frequently observed in LC groups (50–78%). Nodular lesion was found only in a few non-LC patients (29%). Reversed halo sign, as a typical finding of organizing pneumonia, was only observed in one LC(RT-) patient.

ICI-P findings were more likely to be observed in the lower lobes except for several cases in LC(RT+), presumably due to RRP at the upper lobe LCs (Figure 3d). ICI-P was seen almost symmetrically in non-LC group, whereas LC patients tended to present asymmetrical laterality to either side of the lungs ($p < 0.001$).

Table 6. Incidence of other irAEs

irAE	ICI-P			w/o ICI-P			<i>p</i> -value
	LC (<i>n</i> = 19)	Non-LC (<i>n</i> = 7)	Total (<i>n</i> = 26)	LC (<i>n</i> = 132)	Non-LC (<i>n</i> = 89)	Total (<i>n</i> = 221)	
Thyroid dysfunction	7	1	8	18	10	28	0.034
Rash	4	2	6	6	8	14	0.011
Colitis	2	0	2	7	5	12	n.s.
Liver dysfunction	1	0	1	7	3	10	n.s.
Adrenal dysfunction	2	0	2	2	6	8	n.s.
Mucosal disorder	0	0	0	3	0	3	n.s.
Renal injury	0	0	0	1	1	2	n.s.
Neuropathy	0	0	0	1	1	2	n.s.
Arthritis	1	0	1	2	0	2	n.s.
Pituitary dysfunction	0	0	0	2	0	2	n.s.
Collagen disease	0	1	1	2	0	2	n.s.
Type 1 diabetes	0	0	0	1	0	0	n.s.
Esophagitis	0	0	0	1	0	1	n.s.
Anorexia	1	0	1	0	1	1	n.s.
Thrombosis	0	0	0	0	1	1	n.s.
Purpura	0	0	0	1	0	1	n.s.
Cold agglutinin disease	0	0	0	0	1	1	n.s.

ICI-P, immune checkpoint inhibitor-related pneumonitis; LC, lung cancer; irAE, immune-related adverse events.

Fisher's exact test was performed for total ICI-P and w/o ICI-P patients to compare the irAE frequency. *p* values < 0.05 indicate that the corresponding irAE was significantly more frequently observed in ICI-P group.

(Figure 3e); however, the laterality could be seen in either ipsilateral or contralateral side of the primary cancer site, except for in RRP (Figure 3f).

Time course of ICI-P

Follow-up chest CT scans revealed a few cases which demonstrated moving shadows or a relapse of ICI-P (the representative cases are shown in Figure 4a and b. Two patients from each group, the LC(RT-) and non-LC, experienced ICI-P relapse after initially recovering from the first onset. The two LC(RT-) patients showed relapsing shadows in a different area of the primary ICI-P, while the two non-LC patients showed relapse close to the same-site. One patient in LC(RT-) and two in LC(RT+) who all showed an OP pattern had moving shadows during follow-up. LC(RT+) patients had a higher incidence of fibrosis. Radar charts of outcome are shown in Figure 4c.

DISCUSSION

Immune checkpoint blockade has emerged as a promising treatment option for several malignancies. At the same time, patients need to be followed closely considering the relatively high incidence of adverse events, so-called irAE. ICI-P is a serious irAE with potential for significant morbidity and mortality, requiring each patient to be carefully monitored since its development is challenging to predict.¹⁴ As radiologists are key players in ICI-P diagnosis, it is important to characterize radiological features of ICI-P in conjunction with clinical information. In this study,

we investigated the onset, association with KL-6, radiological patterns and time course of ICI-P, focusing on whether the primary cancer location was in the lungs or not. LC patients tended to develop ICI-P more frequently and earlier than non-LC patients. Emphysema was likely to be associated with ICI-P development in LC patients. Other irAE development rate was significantly higher in ICI-P patients. Especially, thyroid dysfunction and rash as irAE were more often observed in ICI-P patients. A novel serum marker KL-6 correlated with the onset of ICI-P in non-LC patients. Chest CT observation revealed that GGOs is a common feature irrespective of the type of cancer. On the other hand, consolidation formation was more frequent in LC. Some LC patients with a radiation history in the lungs showed radiation recall pneumonitis, however, the LC patients otherwise tended to show ICI-P in the contralateral side of the primary cancer. The relapse of ICI-P was observed in a small fraction of all patients.

ICI-P was found in 10% of entire population. This incidence was higher than that reported by previous studies (1 to 5% of all malignancies).^{8,32,33} This discrepancy could arise from the dominance of male LC patients, and a larger number of smokers in our analysis. Smoking is regarded as one of risk factors in ICI-P.³³ Moreover, a recent meta-analysis reported that NSCLC patients develop ICI-P more frequently compared with melanoma.³² Another reason for the discrepancy compared with previous reports could be attributed to the fact that fewer melanoma

Figure 1. Incidence of ICI-P in the LC and non-LC patient groups, according to: (a) smoking history and (b) existing of emphysema at the baseline CT scans. No significant difference was seen between past/current smokers and non-smokers in either of groups, although smokers more frequently occurred ICI-P in both LC and non-LC groups. On the other hand, a significantly larger percentage of patients with findings of emphysema occurred ICI-P in LC group ($p = 0.019$). (c) Kaplan-Meier survival curves of depending on ICI-P occurrence in LC and non-LC groups. No significant difference in survival was observed between the groups. ICI-P, immune checkpointinhibitor-related pneumonitis; LC, lung cancer.

patients were included in this study. In this study, ICI-P in non-LC group primarily had head and neck cancers, in which male gender and smoking history are also known as risk factors. Additionally, combination immunotherapy (vs monotherapy),³² and in NSCLC, the use of PD-1 inhibitors (vs PD-L1 inhibitors) and use of ICI as a first-line therapy (vs second-line or further)³⁴ are also associated with a higher risk of ICI-P.

The incidence of other irAEs were significantly higher in ICI-P patients compared with patients who did not develop ICI-P. This may conversely indicate that the patient should be more carefully

managed, once irAE was detected, to alert potential risk of ICI-P development.

ICI-P occurred around 3 months after starting ICI, and the onset was earlier in LC group than non-LC. These results were concordant with previous studies; the average interval was reported as 2–3 months overall,^{33,35,36} and it is shorter in LC than the other cancers (1–2 months vs 3–5 months respectively).^{33,36} Interestingly, our results indicated that radiation history does not accelerate onset of ICI-P. In contrast, radiation naïve LC patients tended to develop ICI-P earlier. As the majority of LC patients

Figure 2. (a) Time to the onset and (b) cycles to ICI-P development. Radiation naïve lung cancer patients (LC(RT-)) developed ICI-P significantly earlier than non-LC patients, with an average of 49 ± 38 days and peaked after 1 or 2 cycles of ICI. LC patients with radiation history (LC(RT+)) showed slower onset with greater variability within the group (average, 105 ± 95 days), which peaked at 3 to 5 cycles. (c) KL-6 was significantly elevated in the non-LC group ($p = 0.029$) while LC patients showed no significant change in KL-6 levels between baseline and onset of ICI-P. ICI-P, immune checkpointinhibitor-related pneumonitis; LC, lung cancer.

Figure 3. (a) 66-year-old male with renal cell carcinoma. Bilateral and symmetrical OP-EP pattern in the upper lungs was detected at 161 days, 11 cycles after initiating nivolumab, diagnosed as Grade 2 ICI-P. KL-6 became elevated from 266 (baseline) to 610 U ml⁻¹ (ICI-P onset). Oral prednisolone treatment was initiated and tapered as the pulmonary opacity disappeared. (b) 72-year-old male with squamous cell lung carcinoma who presented dyspnea at 35 days, after 2 cycles of nivolumab, was diagnosed as Grade 3 ICI-P and treated with steroid pulse. Consolidation in right lower lobe showing OP pattern disappeared and new opacities emerged in right middle, left lingual and lower lobes in 2 months. All these shadows resolved in the following 2 months. (c) Radar chart of CT findings at the diagnosis of ICI-P in LC(RT-), LC(RT+), and non-LC groups. GGO was frequently observed across all groups. In LC groups, consolidation and traction bronchiectasis were also common findings, irrespective of radiation therapy history. Nodular lesions and reversed halo like appearance were occasionally observed. (d) Lobe predominance of ICI-P. Lower lobes were mainly affected across all groups except for a few cases. The larger number of upper lobes-dominant ICI-P in LC(RT+) is attributed to radiation recall pneumonitis for the primary upper lobe cancer. (e) Symmetry of ICI-P. In LC groups, either side lung inclined to show more extensive ICI-P findings to the other, while a majority of non-LC group demonstrated bilateral symmetrical shadows of ICI-P. (f) Laterality of ICI-P to primary cancer location in LC groups. In LC(RT+), radiation recall pneumonitis was seen in six patients, which pushed up the ipsilateral ICI-P population; however, ICI-P was seen in both ipsilateral and contralateral sides to the primary cancers. Two patients in LC(RT-) were excluded from the analysis of laterality due to bilateral primary LCs. GGO, ground glass opacity; ICI-P, immune checkpointinhibitor-related pneumonitis; LC, lung cancer; OP, organizing pneumonia.

Figure 4. (a, b) Two cases of relapsing ICI-P. (a) 62-year-old male squamous cell lung carcinoma patient presenting emphysema at baseline CT. He developed ICI-P at 42 days, after 2 cycles of pembrolizumab monotherapy as the first-line after resection of right lower lobe cancer. Consolidation in the right lower lobe representing OP pattern alleviated with steroid pulse treatment in 1 month, but new GGO emerged in the left lung as a relapse of ICI-P in the following month. (b) 63-year-old male patient with hypopharyngeal cancer developed ICI-P after 186 days, after 9 cycles of nivolumab treatment. Symmetrical GGOs were observed in bilateral lower lobes, disappearing 1 month after nivolumab was withheld. In the next month, GGOs were detected once again at the similar sites of prior pneumonitis. (c) Radar charts of ICI-P findings outcome. Improvement was seen mostly in LC(RT-) patients while persisting shadows remained in a few patients in non-LC, probably due to higher frequency of active treatment with steroids in LC(RT-) (7 patients out of 9) rather than just from withholding ICI. Fibrosis was mainly seen in LC(RT+). Moving shadows were seen in a few patients in LC groups. Relapse of ICI-P was detected in a small number of patients in LC(RT-) and non-LC groups. GGO, ground glass opacity; ICI-P, immune checkpoint inhibitor-related pneumonitis; LC, lung cancer; OP, organizing pneumonia.

developed ICI-P after 1 or 2 cycles of ICI, closer follow-up will be required especially for the first month, irrespective of radiation history. Meanwhile, it should be noted that longitudinal observation is needed as the temporal window of onset was observed to be wide.

Radiological features of ICI-P are diverse³⁵; however, OP pattern is most commonly seen,^{33,35,37,38} likewise other entities of drug-induced pneumonitis,³⁹ followed by NSIP pattern³⁶ and HP pattern.³³ Patients in this study also predominantly showed OP pattern in both LC and non-LC groups. All patients with Grade 3 or more severe ICI-P showed OP pattern, consistent with the report that shows OP pattern most likely requires treatment of pneumonitis beyond drug hold.³⁵ Of note, one patient with Grade 4 pneumonitis developed comorbid DAD pattern at a follow-up

CT, as similar to the previous article that shows DAD pattern is strongly correlated with a high mortality.²⁰

GGO was a common radiological finding across all groups. Previous studies have also indicated that GGO was the major pulmonary finding followed by consolidation.^{33,36} In our study, consolidation and traction bronchiectasis were more frequently seen in LC group. Taken together with the earlier onset in LC, ICI-P might develop so rapidly that lung infiltration has already progressed when ICI-P is identified. Indeed, Nishino et al suggested that ICI-P in LC patients had more extensive involvement on CT than others. Reversed halo sign is a well-known finding in COP; however, it can lack specificity and is seen in a wide spectrum of lung diseases including metastatic diseases and infections as a result of immunosuppression.⁴⁰

Taken together that the finding was only encountered in one patient in each group, LC and non-LC, reversed halo sign might not be a key finding for ICI-P diagnosis, nevertheless it majorly shows OP pattern. Nodular lesions were also occasional, consistent with a previous report.³⁶ The dominant pneumonitis opacity was seen at the highest levels in the lower lobes as has been previously reported,³⁶ except for LC group with radiation history, probably due to the high incidence of radiation therapy to upper lobes.

RRP is defined as an inflammatory reaction within previously irradiated fields after introducing pharmacological agents including anticancer drugs.⁴¹ A study shows late onset RRP which occurred 22 months after starting nivolumab,⁴² compared to previous reports by cytotoxic drugs (3 months).⁴³ In this study, RRP onset was seen earlier (average, 3 months) similar to non-RRP population in LC, suggesting that RRP can occur at anytime with a broad timeframe.

The distribution of ICI-P infiltration was different between LC and non-LC groups. LC patients showed asymmetrical shadows in CT scans while most of the non-LC patients demonstrated symmetrical opacities. This finding might be explained by an assumption that the lungs in LC patients are heterogeneously damaged enough to generate cancers, consequently leading to diverse reaction to immunotherapy, contrary to the uniform response of unaffected lungs in non-LC patients. Predominant ICI-P findings in the radiation naïve LC group was seen mostly evenly at either ipsilateral or contralateral side of the primary tumor, indicating random immune reaction to ICI possibly depending on, e.g. blood supply.

A few patients demonstrated recurrence of ICI-P in this study. Recurrent ICI-P was reported in approximately 30% of patients.^{33,36} There is no recommendation for rechallenging of ICIs, therefore, the decision should be discussed, weighing the expected risks and benefits for each case.⁴⁴

KL-6 is a novel serum marker for evaluation of interstitial pneumonia; however, this was significantly elevated only in non-LC patients at ICI-P onset but not in LC. This is well-understood based on previous reports that shows KL-6 is also frequently expressed in LC and other types of cancers, especially adenocarcinoma.^{45,46} This is an important caveat for radiologists when using blood data to support ICI-P diagnosis. Meanwhile, KL-6 is presumed to be an accurate and reliable marker for ICI-P in non-LC patients unless the primary cancer is of the pancreas, breast, or other adenocarcinomas.

This study was conducted retrospectively in a single institute with a small number of patients, leading to several limitations. Namely, heterogeneous non-LC patients were pooled into the same group and further differences between the cancer types were unable to be parsed, nor the effect of the different ICI drugs. Investigations with larger cohorts are needed to establish more conclusive observations.

As immunotherapy is widely approved for a growing number of malignancies, clinicians and radiologists are more likely to encounter the need to diagnose irAEs. Considering the higher possibility of diagnosing pneumonitis through chest CT scans, it is crucial to understand the characteristic presentations of pneumonitis, at early stages according to cancer type. Further investigation is warranted to accumulate the evidence of pneumonitis induced by immunotherapy for various cancer entities.

CONCLUSIONS

ICI-P patients demonstrated higher frequency of history of other irAE prior to development of ICI-P. In LC patients, ICI-P occurred earlier than in other cancers and its onset was not influenced by the radiation history. Organizing pneumonia pattern and GGO were predominant findings irrespective of cancer type, while consolidation and asymmetrical shadows are more likely to be observed in LC. Elevated KL-6 was helpful for pneumonitis diagnosis in non-LC patients. These findings may assist diagnosis of irAE for patients receiving ICIs.

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