# Late-onset pulmonary and cardiac toxicities in a patient treated with immune checkpoint inhibitor monotherapy

## Pozdní nástup plicní a srdeční toxicity u pacienta léčeného checkpoint inhibitorem v monoterapii

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### Summary

***Background:*** Immune checkpoint inhibitors (ICPIs) can cause immune-related adverse events (irAEs) in organs throughout the body. Of the irAEs, ICPI-induced interstitial lung disease (ILD) is the most notable one that can be life-threatening. No less than that, ICPI-induced cardiac irAEs are serious ones and are recently attracting attention. IrAEs usually develop within a few months after the initiation of ICPI treatment, but some of them occur after a long period of time from the start of treatment. ***Case:*** A 60-year-old male patient with squamous cell carcinoma developed ICPI-induced ILD more than 2 years after the initiation of ICPI therapy. A few months after the ICPI-induced ILD improved, he developed heart failure, which was presumed to be caused by impaired cardiac ejection. Both irAEs improved without administration of corticosteroids. ***Conclusion:*** Although rare, these irAEs may appear even after a long period of time from the start of administration, and chest physicians should be careful of late-onset irAEs.

### Key words

late-onset – pulmonary toxicity – cardiac toxicity – immune-related adverse event – immune checkpoint inhibitor monotherapy – lung cancer

### Souhrn

***Východiska:*** Checkpoint inhibitory (immune checkpoint inhibitors – IPI) mohou vyvolat nežádoucí účinky (immune-related adverse events – irAE) v orgánech celého těla. Z irAE je nejvýznamnější intersticiální plicní nemoc (interstitial lung disease – ILD) vyvolaná IPI, která může ohrožovat život. Neméně závažné jsou srdeční irAE vyvolané IPI, které v poslední době vzbuzují pozornost. IrAE obyvkle vznikají během několika měsíců po zahájení léčby IPI, ale některé z nich se vyskytují po delší době. ***Případ:*** U 60letého muže s dlaždicobuněčným karcinomem se vyskytla ILD vyvolaná IPI za déle než 2 roky od zahájení terapie. Několik měsíců po zlepšení ILD vyvolané IPI se u tohoto pacienta projevilo srdeční selhání, o kterém se předpokládalo, že je důsledkem narušení ejekce. Ke zlepšení obou typů irAE došlo bez podání kortikosteroidů. ***Závěr:*** I když jsou tyto irAE vzácné, mohou se projevit i po dlouhé dobe od zahájení léčby. Pneumologové by si tudíž na irAE s pozdním nástupem měli dát pozor.

### Klíčová slova

pozdní nástup – plicní toxicita – srdeční toxicita – nežádoucí účinek na imunitní systém – monoterapie checkpoint inhibitory – karcinom plic

The authors declare they have no potential conflicts of interest concerning drugs, products, or services used in the study.

Autoři deklarují, že v souvislosti s předmětem studie nemají žádné komerční zájmy.

The Editorial Board declares that the manuscript met the ICMJE recommendation for biomedical papers.

Redakční rada potvrzuje, že rukopis práce splnil ICMJE kritéria pro publikace zasílané do biomedicínských časopisů.

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Submitted/Obdrženo: 5. 9. 2021
Accepted/Přijato: 11. 2. 2022

doi: 10.48095/ccko2022150

## Introduction

Immune checkpoint inhibitors (ICPIs) have revolutionized the treatment of patients with advanced non-small cell lung cancer (NSCLC) [1,2]. In particular, it is an epoch-making that the "ratio of patients leading to cure", which could not be expected with cytotoxic antitumor agents, has increased significantly [1,2]. While the long-term prognosis has become promising, new issues have arisen regarding how long ICPI should be continuously administered and how long attention should be paid to the onset of immune-related adverse events (irAEs) associated with treatment [3,4]. Among irAEs, ICPI-induced interstitial lung disease (ILD) is recognized as a serious life-threatening irAE [5]. Therefore, most of chest physicians evaluate that ICPI administration should not be continued and resumed in the event of ICPI-induced ILD. Many researchers reported that corticosteroid preparations should be administered without hesitation for the treatment of ICPI-induced ILD [3–5]. In a clinical trial of nivolumab, the first clinically available ICPI, the onset of ICPI-induced ILD was 18–596 (median 201) days [6]. The longest was 16 months and 71 weeks [7,8], but the median onset of the irAE was reported to be < 10 weeks [7–10]. In addition to ICPI-induced ILD, ICPI-induced cardiac irAEs are serious ones and have recently been attracted attention [11]. Herein we report a case with ICPI-induced ILD that developed 2.5 years after the initiation of ICPI monotherapy after long-term good disease control. A few months after the ICPI-induced ILD improved, the patient developed heart failure, which was presumed to be caused by impaired cardiac ejection. Our clinical experience might provide some suggestions for the management of patients who have a similar course.

## Case

A 60-year-old man who had a 60 pack-year smoking history presented with cough and dyspnea on exertion for several months. He had no history of cardiac diseases and risk factor for these diseases. Physical examination was unremarkable, but a large mass in the right upper lobe of the lung with ipsilateral lymph node swelling were revealed in a chest CT (Fig. 1A). The patient also had low attenuation areas in both upper lobe of the lung (Fig. 1B). On the basis of the histopathological examination of transbrochial biopsy specimens, the patient was diagnosed with squamous cell carcinoma. No driver gene was found, but 90% of the cancer cells were positively stained on immunohistochemical staining for programmed death-ligand 1 (PD-L1) using the PD-L1 IHC 22C3 (PharmDX Dako, Merck & Co, NJ, USA). On the pulmonary function test, he had a forced expiratory volume in 1 second (FEV1.0) of 1.26 L and forced vital capacity of 3.08 L; therefore, he was diagnosed with chronic obstructive pulmonary disease (COPD). Due to his impaired respiratory function, the patient received irradiation (2 Gy/day, total 60 Gy). As the general and respiratory condition of the patient were improved, he received pembrolizumab as second-line therapy, considering high PD-L1 results. The therapeutic effect was evaluated to be partial response (PR), and pembrolizumab treatment at 3-week intervals was performed for 41courses in total. Despite the treatment, regrowth in the right mediastinal lymph nodes was detected on CT taken 124 weeks after the start of the treatment. He received irradiation (2 Gy/day, total 45 Gy) and then pembrolizumab again. Six weeks after the re-administration of pembrolizumab (130 weeks from the initiation of the first pembrolizumab treatment), ground glass opacities (GGOs) appeared in both lungs, including those outside the irradiation field (Fig. 2). Since it was determined to be ICPI-induced ILD, pembrolizumab was discontinued, and the patient was closely followed for 12 weeks and dyspnea of the patient gradually improved. On CT at that time, GGOs disappeared; on the other hand, recurrence of lung cancer was not found. During

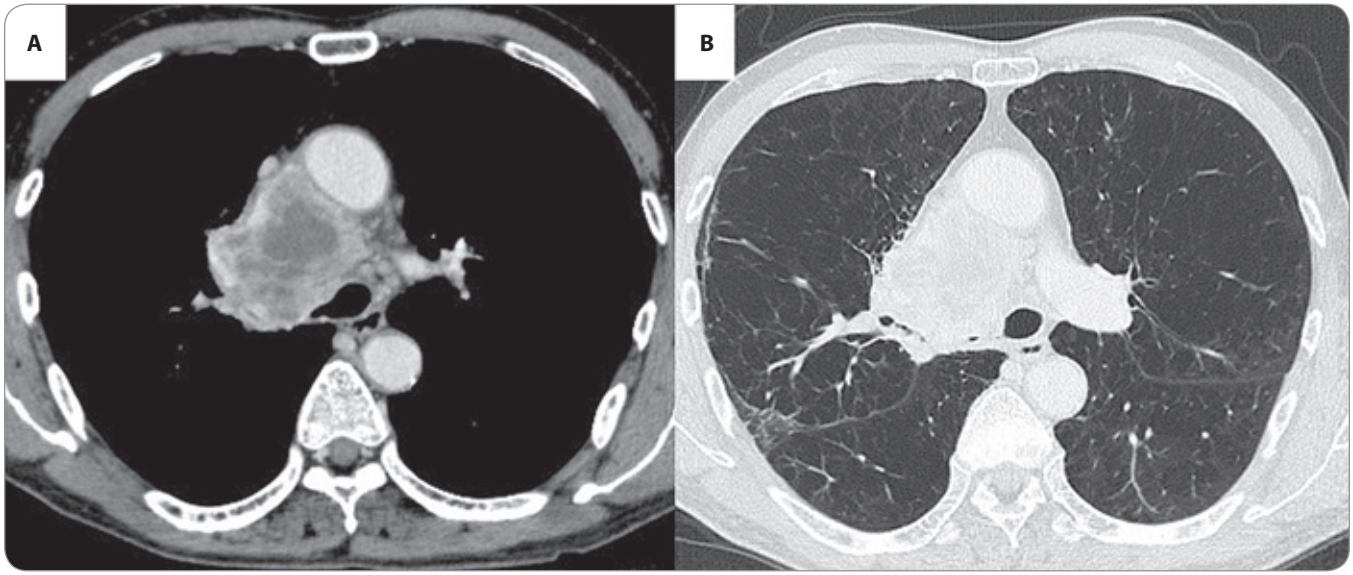


**Fig. 1. Chest CT scan taken at admission. A) Large mass in the right upper lobe of the lung with ipsilateral lymph node swelling. B) Low attenuation areas in both upper lobes of the lung.**

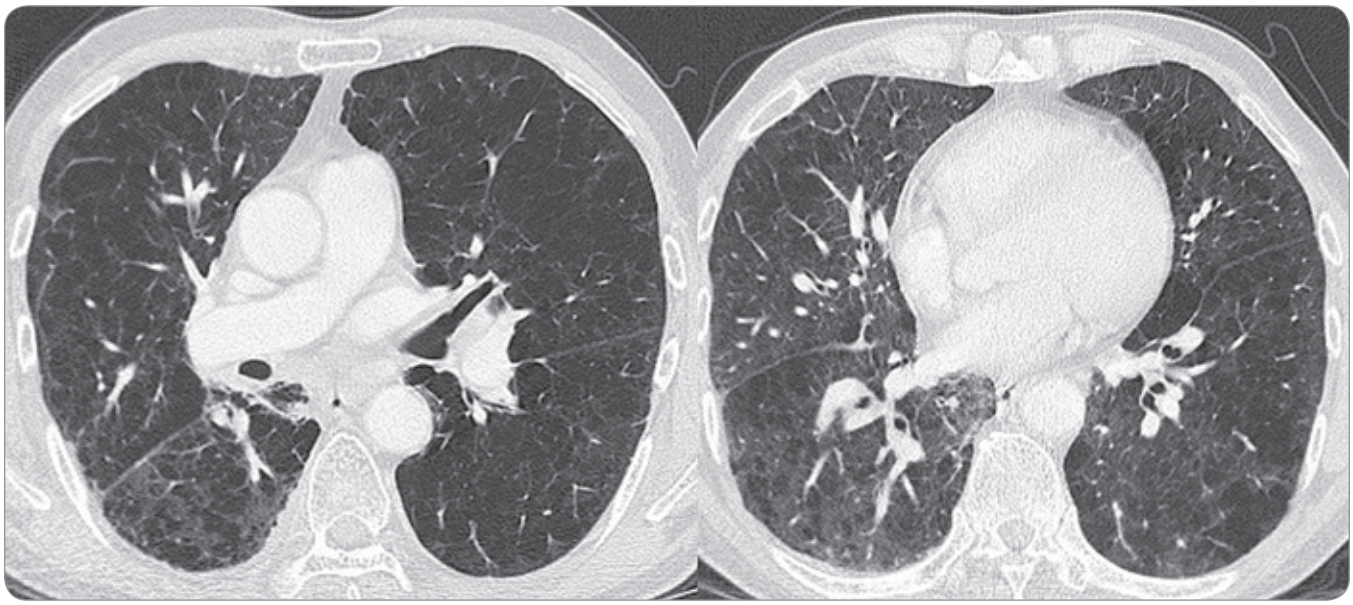

**Fig. 2. Chest CT scan taken at 6 weeks after the re-administration of pembrolizumab (130 weeks from the initiation of the first pembrolizumab treatment) showed ground glass opacities in both lungs, including those outside the irradiation field.**

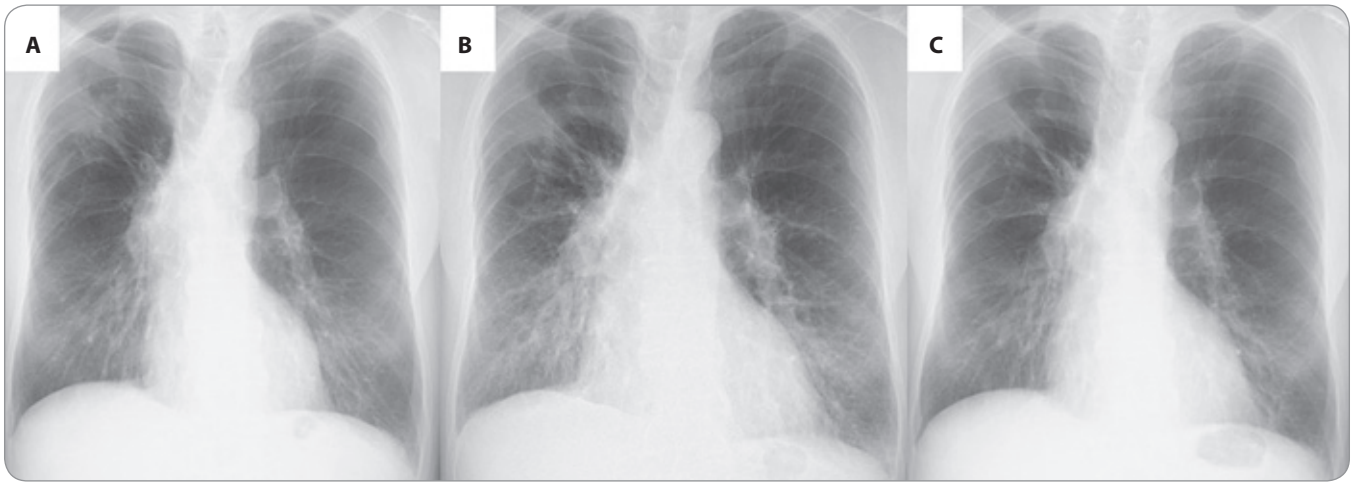


**Fig. 3. Plain X-ray film taken A) at re-administration of pembrolizumab; B) at one month later; C) after the treatment diuretics and beta-blocker. There was observed an increase in cardiac size and congestion, with later improvement of these findings.**

diagnostic workup of cardiac irAE, there were any changes in ECG or troponin level. However, one month later, the patient again complained of dyspnea and malaise. A plain X-ray film showed enlargement of the cardiac shadow (Fig. 3). Plasma brain natriuretic peptide (BNP) increased to 683.7 pg/mL, and cardiac echo showed a left ventricular ejection fraction of 17%. Administration of diuretics and beta blocker confirmed relief of symptoms, improvement of cardiomegaly. Three months later, BNP and echocardiographic ejection fraction (EF) improved to 369.9 ng/mL and BNP to 24% respectively. Corticosteroids were not given because the patient did not wish. On CT taken 20 weeks after the discontinuation of ICPI, improvement of cardiac size and congestion were observed. Twenty-eight weeks have passed since the occurrence of pulmonary irAE (164 weeks have passed since the start of lung cancer treatment), no recurrence has been observed, and the patient is fine.

## Discussion

IrAE usually develops within a few months after the initiation of ICPI treatment [7,12–15]. As with irAE in other organs, there are many reports that the onset time of ICPI-induced ILD is within 10 weeks from the start of ICPI treatment [7–9]. At present, there is no clear definition for late onset irAE. It is not clear when the onset irAE should be late onset irAE. Therefore, there is a report that early onset and late onset were evaluated separately at 6 weeks after the start of ICPI treatment [8]. The "latest" onset of ICPI-induced ILD had been reported to be 70 weeks after the initiation of ICPI treatment, as far as we could research [8]. The ICPI-induced ILD in our patient, therefore, was the latest one. Regarding pulmonary irAE, in addition, ICPI-induced ILD after completing ICPI

treatment have also been reported [16–18]. One case report showed the latest onset of this pulmonary irAE developed 10 months after the end of ICPI administration [17], but many previous studies indicated that the period from the end of ICPI administration to the onset of the irAE was within 10 weeks [16,18]. In our patient, irradiation for mediastinal lymph node recurrence and then ICPI was resumed. ICPI-induced ILD developed 1 week after the resumption of ICPI. Considering this background, it was speculated that chest re-irradiation also contributed to the onset of irAE. In other words, ICPI-induced ILD might be triggered by the effect of chest irradiation on the recurrence site. Regarding the differentiation of radiation pneumonia, we evaluated it as ICPI-Induced ILD because GGO spread widely outside the irradiation field. Post-irradiation ICPI-Induced ILD has been often a problem in locally advanced NSCLC patients treated with chemoradiotherapy and concomitant ICPI [10,19]. The onset of pulmonary irAE with this treatment was reported to be within 8 weeks after ICPI administration [10,19]. Regarding the time of onset, it coincided with the time of onset of irAE with this treatment. Bronchoalveolar lavage fluid (BALF) is a useful tool for differentiating diffuse pulmonary diseases. However, whether it was radiation pneumonia or ICPI-induced ILD, BALF was lymphocyte-dominant and might not be useful in differentiating these pathologies. Considering the risk of exacerbation of interstitial pneumonia triggered by the implementation of bronchoscopy [20], and patient's refusal of performing bronchoscopy, our patient was followed-up with examination of physical condition and imaging.

The most typical cardiac irAE is myocarditis, which is histopathologically characterized by infiltration of CD8-positive T cells and macrophages into the myocardial tissue. Inflammation often spreads to the cardiac conduction system and is complicated by conduction disorders and lethal arrhythmias. Other cardiac irAEs have been reported as congestive heart failure, asymptomatic heart dysfunction, cardiomyopathy, pericardial disease, arrhythmia, and angina [21]. The incidence of cardiac irAE was reported to be 0.27–1.14%, which was considered to be a relatively rare irAE [21]. However, the fatality rate of cardiac irAE is reported to be extremely high at 50% [22]. The period from the administration of ICPIs to the onset of myocarditis has been generally within 3 months, but there were reports that the onset occurred more than 1 year after the initial administration of ICPIs [23,24]. In our patient, congestive heart failure was diagnosed by elevated BNP, cardiac enlargement with bilateral pleural effusion, and decreased EF. This congestive heart failure occurred 3 months after the improvement of ICPC-induced ILD. During this period, there were no other newly occurred comorbidity or initiated drugs. There were no findings suggestive of myocardial infarction or angina on electrocardiogram or echocardiography. In past history and during the clinical course of lung cancer treatment, the patient had no infection that caused myocardial damage. Irradiation was applied to the primary lesion in the upper right lobe and the right mediastinum, but the heart was not included in the irradiation field. From the above, it was evaluated that ischemic heart disease, infectious myocarditis, and radiation-induced myocardial damage can be excluded from the differentiation. Therefore, the cause of heart failure was determined to be ICPI-induced myocardial contraction dysfunction. It was quite possible that ICPI-induced ILD affected this cardiac irAE. However, given the timing of onset and improvement of these two conditions, we speculated that it was unlikely that this cardiac irAE was caused by ICPI-induced ILD. Diuretics and beta-blockers were given because the symptoms of cardiac irAE were relatively mild and the patient refused myocardial biopsy or corticosteroid therapy. As a result, treatment with these drugs improved symptoms and laboratory data, so administration of corticosteroids was not performed. As observed in our patient, some patients might not need to receive corticosteroids for the treatment of pulmonary and cardiac irAEs [25,26]. The indications for corticosteroids for irAE and their doses may be controversial. It goes without saying that corticosteroid administration should not be hesitated in cases of serious condition or rapid progression.

## Conclusion

Even during the course of long-term administration of ICPI, ICPI-induced ILD and cardiac irAEs can occur. Although it is considered that administration of corticosteroid should not be hesitated if pulmonary and cardiac irAE are diagnosed, there might be pulmonary and cardiac irAEs that do not necessarily require administration of corticosteroids. Although clinical trials are very important, it is necessary to accumulate clinical knowledge that cannot be obtained in clinical trials.

### Author contributions

SO, YS, and HS collected the data. SO, YS, HY and HS analyzed the data and prepared the manuscript. All authors approved the final version of the article.

### Ethics

This study conformed to the Ethical Guidelines for Clinical Studies issued by the Ministry of Health, Labor, and Welfare of Japan. Written informed consent for a non-interventional retrospective study was obtained from each patient. The analysis of the medical records of patients with lung cancer was approved by the ethics committee of Mito Medical Center–University of Tsukuba Hospital.

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