A case report of advanced thymoma re-treated with PD-1 inhibitor after initial immune-related pneumonitis

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Abstract: With the growing use of immune checkpoint inhibitors (ICIs), recurrent immune-related adverse events (irAEs) have become more common after recovery from initial immune toxicity. Here we report one case of anti-PD-1-related pneumonitis in a patient with advanced thymoma, who experienced two episodes of pneumonitis during 10 months of treatment with a PD-1 inhibitor. By reviewing recent advances in ICI-related adverse events, we summarize the clinical characteristics of recurrent immune-related pneumonitis, illustrate potential predictive biomarkers for irAEs, and evaluate the value of resuming anti-PD-1 treatment in this patient. To date, evidence regarding retreatment following improvement from an irAE is scarce, and further clinical trials are needed to address this scenario.

Keywords: Immune-related adverse event (irAE); recurrent pneumonitis; anti-PD-1; case report

Introduction

To date, the FDA has approved six immune checkpoint inhibitors (ICIs) targeting the PD-1/PD-L1 pathway for treating advanced tumors. Compared with chemotherapy, PD(L)-1 inhibitors have a relatively modest toxicity profile. However, the toxic effects of monoclonal antibodies against immune checkpoint receptors may affect any organ, including the lungs, colon, thyroid, skin, pituitary, heart, and nervous system (1,2). Pneumonitis is the leading cause of anti-PD(L)1-related death and discontinuation of ICIs (3,4). Most immune-related adverse events (irAEs) are manageable with corticosteroids or other immune modulators. According to the ESMO guideline, a checkpoint inhibitor can be reintroduced after the daily dose of steroids is less than or equal to 10 mg of oral prednisone per day for grades 1–2 (5). Recurrent or new immune-related irAEs have been documented in several studies (4,6-9). Naidoo *et al.* reported that the incidence of recurrent pneumonitis was up to 25% among patients who were rechallenged with ICIs (10). Herein, we present one case of recurrent immune-related pneumonitis to highlight the clinical characteristics of recurrent irAEs and answer several frequently asked questions about recognizing and managing this condition.

We present the following article following the CARE reporting checklist (available at https://dx.doi.org/10.21037/apm-21-943).

All procedures performed in studies involving human participants were in accord with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for

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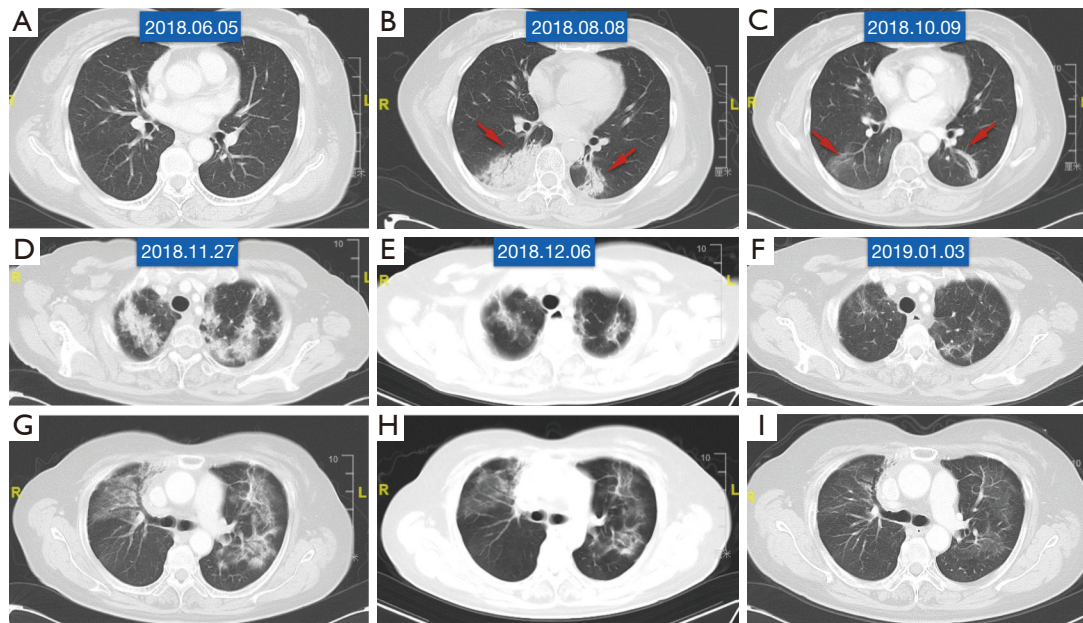
Figure 1 Chest CT scans demonstrate the clinical course of the two episodes of immune-related pneumonitis in this case example. (A) Chest CT before initiation of PD-1 inhibitor treatment. (B) Image of pneumonitis before prednisone treatment shows consolidation lesions involving the bilateral lower lobes with air bronchograms (red arrow). (C) Image captured after 6 weeks of prednisone treatment reveals resolution of opacities. (D,G) Chest CT following onset of the second pneumonitis shows GGO-like lesions involving multiple bilateral lobes with air bronchograms. (E,H) Images after 1 week of prednisone resumption demonstrate improvements in the second pneumonitis. (F,I) CT scans show the second pneumonitis has resolved with prednisone. CT, computed tomography; GGO, ground-glass opacity.

publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Case vignette

This case was a 62-year-old woman diagnosed with resected thymoma, metastatic to the lungs, subpleural, and mediastinum. She did not smoke or drink alcohol. There was no surgical history, no other prior diseases, and no family history of malignant diseases. She underwent adjuvant concomitant radiochemotherapy-60GY/30FX combined with four cycles of cisplatin and etoposide. The PE regimen was ceased for 5 months due to severe leukocytopenia (grade 3). She was then treated with two cycles of a TC regimen (paclitaxel + carboplatin). However, the patient's disease progressed despite these therapies. Treatment was initiated with a PD-1 inhibitor 200 mg every 3 weeks. After five administrations, the patient reported malaise, cough, and dyspnea. Upon physical examination, she had an oxygen saturation of 98% in an open environment; the

remainder of the physical examination was normal. Her serum C-reactive protein (CRP) level was 6.6 mg/L (normal range, 0–5 mg/L). The blood count showed a normal white blood cell (WBC) count. The serum procalcitonin (PCT) level was normal. A chest computed tomography (CT) evidenced patchy bilateral consolidation involving the lower lobes without signs of pulmonary thromboembolism (*Figure 1A,1B*). next-generation sequencing (NGS)-based detection (11) ruled out causative pathogens. She was diagnosed with grade 2 ICI-related pneumonitis. Corticosteroid therapy was introduced with prednisone 1 mg/kg per day, tapering to 5–10 mg/week for 5 weeks. The controlled CT scan after corticosteroid therapy showed almost full resolution of pulmonary opacities (*Figure 1C*). The anti-PD-1 inhibitor was then resumed in this patient. After three doses of PD-1 inhibitor retreatment, the patient reported a nonproductive cough and shortness of breath. On physical examination, her blood pressure was 123/81 mmHg, her pulse was 117 beats per minute, her temperature was 37.3 ℃, and her pulse oximetry was 94%. The blood count result was normal. The serum CRP

Table 1 Clinical tests were performed to rule out etiologies other than immune-related pneumonitis

Test	Results-1st episode	Results-2nd episode
NGS-based pathogen detection	No causative organism detected	N/A
WBC counts	Normal	Normal
CRP	6.6 mg/L (0–5 mg/L)	34.8 mg/L (0–5 mg/L)
PCT	Normal	Normal
Chest CT	Bilateral patchy consolidation involving lower lobes without signs of pulmonary thromboembolism	Bilateral GGO with air bronchograms involving multiple lobes

NGS, next-generation sequencing; N/A, not available; WBC, white blood cell; CRP, C-reactive protein; PCT, procalcitonin; CT, computed tomography; GGO, ground-glass opacities.

level was 34.8 mg/L (*Table 1*). A CT scan showed bilateral ground-glass opacities with air bronchograms involving multiple lobes (*Figure 1D,1G*). She was re-treated with prednisone at a dose of 1 mg/kg per day. The controlled CT performed 5 weeks after prednisone treatment showed significant improvement (Figure *1F,1I*). However, according to the latest response evaluation, her thymoma continued to progress.

Discussion

The incidence of recurrent irAEs is rare. In a recent retrospective analysis conducted by Simonaggio *et al.* (4), 13 patients experienced initial immune-related pneumonitis, and five patients were rechallenged with the same PD(L)-1 inhibitors. Of the rechallenged group, one patient (20%) experienced a second pneumonitis. Pollack *et al.* (8) reported that 33% of patients (1 in 3) with pneumonitis experienced recurrence. Naidoo *et al.* (10) identified 12 patients rechallenged with immunotherapy after complete clinical resolution of initial pneumonitis, three (25%) of whom experienced recurrent pneumonitis. In another retrospective study (7), 482 patients with lung cancer were treated with anti-PD(L)-1 (± CTLA-4). Of the patients who developed irAEs, 26% (10/39) experienced recurrent irAEs but improved after retreatment with anti-PD(L)1. Two out of six patients (33%) with pneumonitis had recurrent or new irAEs.

In our patient, we wondered if any predisposing factors caused the recurrence of the immune-related pneumonitis. Pollack *et al.* (8) assessed whether the length and type of immunosuppressive treatment, the severity of initial toxicity, presence of ongoing steroids, symptoms at the anti-PD-1 resumption, or delay in resuming anti-PD-1 influenced the recurrence rate of irAEs in patients with

advanced melanoma treated with anti-PD-1. They found that the duration between the final dose of CTLA-4 and PD-1 blockade to the resumption of anti-PD-1 was a little longer in patients without toxicities than those who experienced toxicities (median 62 days versus 56 days, P=0.03). In our patient, the gap between the final dose of anti-PD-1 and the resumption of anti-PD-1 was 61 days. Delaying the PD-1 inhibitor retreatment after recovery from the first episode of pneumonitis may have reduced her risk of pneumonitis-flare. Nevertheless, the optimal time frame for the resumption of treatment should be confirmed by further studies. Other evidence revealed that anti-PD-1-related pneumonitis occurred more frequently in patients with a history of thoracic radiation than those without (6.0% versus 2.6%), consistent with our case.

In Pollack's study (8), the same irAE that caused the initial ICI treatment discontinuation reoccurred in 14 (18%) patients at a median of 14 days following ICI resumption (range, 7–167 days). The second episode of pneumonitis in our case occurred 49 days after ICI resumption. Symptoms of pneumonitis include nonproductive cough and dyspnea (10). Fever, chest pain, and hypoxia are less common, while one-third of patients are reportedly asymptomatic (12).

Although cases with recurrent irAEs are uncommon, the absolute number of patients experiencing irAEs is likely to increase as the use of anti-PD(L)-1 becomes more widespread. Therefore, biomarkers to predict which patients will experience immune-related toxicities are needed. Here we summarize some of the candidate markers from current evidence (*Table 2*).

Radiomics

Radiomics is a new field that provides comprehensive visualization and characterization of the tissue of interest

Table 2 Potential biomarkers predicting anti-PD-1 toxicity

Type	Biomarkers	Association
Radiomics	Radiomic signature	Radiomic features can help classify and predict patients at baseline who will subsequently develop immune-related pneumonitis
Blood	Serum antibody profiles	A subset of toxicity-associated antibodies could identify patients at risk of irAEs from immunotherapy
	Circulating B cells	Early changes in the frequency of circulating B cells in patients treated with anti-CTLA-4 and anti-PD-1 could be associated with an increased risk of irAEs
	WBC and RLC	An increased WBC count and a decreased RLC count have been associated with nivolumab-related G3/4 and lung/GI irAEs
	CXCL2	Changes in the plasma CXCL2 level have been significantly associated with nivolumab-related irAEs in NSCLC patients
Tissue	T cell repertoire	A significant overlay of T cell clones infiltrating pneumonitis lesions and tumors has been identified
	MicroRNA-146a	MIR146A SNP rs2910164 has been identified as a biomarker to predict severe irAE development in ICI-treated patients

irAEs, immune-related adverse events; WBC, white blood cell; RLC, relative lymphocyte cell; CXCL2, chemokine ligand 2; NSCLC, non-small cell lung cancer; ICI, immune checkpoint inhibitor.

and the related microenvironment by automated extraction of high fidelity, high-dimensional medical imaging features from standard images. According to Sun *et al.* (13), radiomics could be useful in predicting clinical outcomes of patients treated with immunotherapy. Furthermore, Colen *et al.* (14) performed a radiomic analysis of baseline chest computed tomography (CT) images of patients who did. It did not develop ICI-induced pneumonitis and constructed a one-way algorithm to predict which patients were likely to experience ICI-induced pneumonitis successfully. Although the study was retrospective, included only two cases and 30 controls, and lacked external validation, it demonstrated a possible, non-invasive way to predict irAEs, especially pneumonitis. The results of their prospective studies are expected.

Baseline serum antibody profile

Gowen *et al.* (15) identified a panel of specific antibodies differentially expressed in patients with severe anti-PD-1-related toxicity. *Table 3* summarizes the top 10 differentially expressed antibodies, four of which are highly expressed in brain tissues and two of which are generally expressed in most tissues. However, this study did not specifically address pneumonitis-related antibodies or other specific irAE-related antibodies. A more detailed analysis of pneumonitis and further independent validation are needed in a clinical trial setting.

Circulating B cells

Liudahl *et al.* (16) found that patients with a 30% or more decrease in baseline levels of total circulating B cells and a twofold or greater elevation in $CD21^{lo}$ B cells or plasmablasts were more susceptible to high-grade irAEs than patients without B cell alterations.
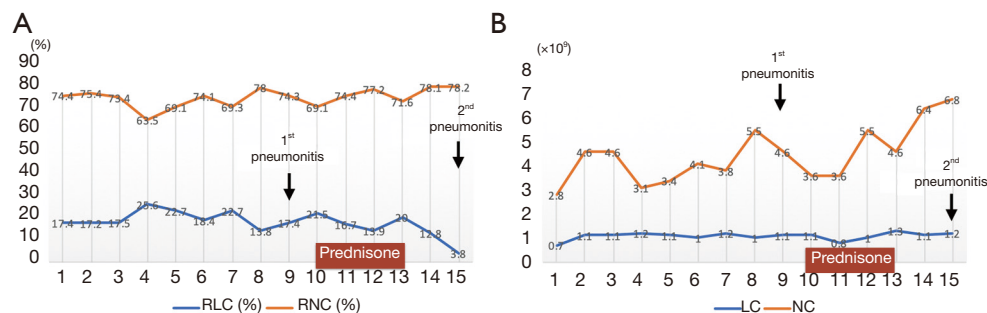
Routine blood counts

A retrospective study showed that an increased WBC count and a decreased relative lymphocyte cell (RLC) count were associated with nivolumab-related G3/4 and lung/GI irAEs (17). In our patient, a decrease in the RLC count was noticed at the time of the second episode of pneumonitis, without an abnormal WBC count (*Figure 2A,2B*). In our view, the routine peripheral blood count is affected by many factors, such as the use of glucocorticoids, which lowers its reliability as a potential marker.

Chemokine ligand 2 (CXCL2)

The plasma level of CXCL2 was found to be related to nivolumab-associated irAEs in non-small cell lung cancer (NSCLC) patients (18). In a cohort study, Matsuo *et al.* found that an elevation of CXCL2 above the baseline was significantly correlated with disease progression.

Table 3 Top 10 differentially expressed antibodies associated with anti-PD-1-related toxicity

Name	Protein expression
NECAP1	Highly expressed in the brain
NRCAM	Highly expressed in cerebrospinal fluid and the brain
PEX19	Highly expressed in the pancreas and bones
PSMD4	Expressed in most tissues
C6orf106	General cytoplasmic and membranous expression
SLC2A11	Highly expressed in the retina
ZBTB21	Highly expressed in the brain and adrenal
RCAN3	Highly expressed in CD4 T cells, lymph nodes, peripheral blood mononuclear cells, and CD8 T cells
AP2M1	Highly expressed in the brain
ING3	Highly expressed in CD8 T cells and peripheral blood mononuclear cells

Figure 2 Routine blood tests in this case example. (A) Relative lymphocyte count (blue line) and relative neutrophil count (yellow line) of this patient: a slight decrease of RLC was noticed at the time of the second pneumonitis. (B) Absolute lymphocyte counts (blue line) and absolute neutrophil counts (yellow line) of this patient. RLC, relative lymphocyte cell.

T cell repertoire

By sequencing the T cell receptor, Läubli *et al.* (19) found that irAEs lesions in patients under PD-1 blockade were infiltrated by T cells with a similar specificity as tumor-infiltrating T cells.

MicroRNA-146a

Reduced microRNA-146a was found to be associated with an increased risk of developing irAEs (20).

Since no prospective trials have defined the best treatment approaches for ICI-related pneumonitis recurrence, patients are generally treated as per the initial pneumonitis following the guidelines published by American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO), or Society for Immunotherapy of

Cancer (SITC). This case report presents the clinical course, diagnostic evaluation, management, and outcome of anti-PD-1-related recurrent pneumonitis. This patient was diagnosed with thymoma and was enrolled in a clinical trial of a PD-1 inhibitor. Though no PD(L)-1 inhibitors have been recommended by National Comprehensive Cancer Network (NCCN) for thymoma (21), evidence showed that positive PD-L1 expressions were detected in thymomas (22), which implied that anti-PD-1/PD-L1 drugs could be of potential use in unresectable or relapsed thymomas. Indeed, a partial response was observed in this patient after four doses of PD-1 inhibitor (*Figure 3A,3B*), although followed by pneumonitis. She was sensitive to prednisone treatment. However, retreatment with the PD-1 inhibitor led to recurrent pneumonitis, even more severe on the CT scan than the initial pneumonitis.

Although some experts do not recommend retreatment

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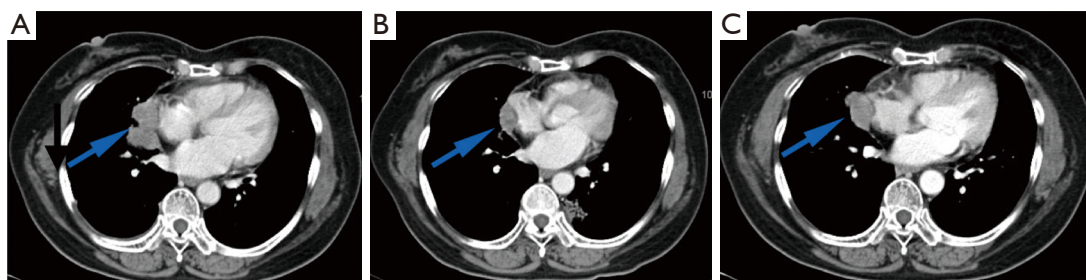
Figure 3 Contrast-enhanced CT scans demonstrate a partial response in this case example. (A) Chest CT prior to the treatment with the PD-1 inhibitor shows a right upper lobe mass (blue arrow). (B) Chest CT after four doses of the PD-1 inhibitor shows a 30% decrease in the diameter of the target lesion. (C) After discontinuing the PD-1 inhibitor for 2 months, chest CT shows the size of the target lesion has increased by at least 20%. CT, computed tomography.

with ICIs, no current evidence supports this opinion. Several studies have found that most recurrent toxicities due to immunosuppressant drugs are remediable. We believe that retreatment with PD-1 inhibitors can be carefully considered in some patients with irAEs.

Santini *et al.* (7) found that the efficacy analysis of patients who had an objective response before the onset of an irAE was similar in the retreatment and discontinuation cohorts. Our patient had a PR before the first episode of pneumonitis and resumed the PD-1 inhibitor for three doses after recovering from the irAE. Her disease progressed following the second pneumonitis, with the size of the target lesion increasing over 20% (*Figure 3C*). The patient would not have benefited from further anti-PD-1 inhibitor retreatment based on recent evidence and expert consensus. Thus, anti-PD-1 treatment was permanently discontinued in this patient.

Several studies have reported a positive association between the development of irAEs and clinical outcomes in patients treated with PD-1 inhibitors or CTLA-4 inhibitors (23,24). Das *et al.* (25) summarized several clinical studies showing the outcomes of patients with and without irAEs in each study. Interestingly, most of the studies reported a better objective response rate (ORR) in patients with irAEs. However, the underlying molecular mechanisms between irAEs, or some specific irAEs, and clinical efficacy have not been fully uncovered.

Conclusions

This case report provides a detailed clinical course of recurrent ICI-related pneumonitis. By reviewing the "state of the art" literature, we summarize the clinical characteristics of this rare but fatal irAE, list the potential biomarkers and management guidelines for ICI-related pneumonitis, and discuss the value of ICI resumption for patients with irAEs. The biomarkers above may predict anti-PD-1-related toxicity in patients. However, there is a long way to go before the routine application of ICI retreatment in clinical practice. First, the efficacy of retreatment should be verified in larger, prospective studies. Since the mechanisms of irAEs are poorly understood, further studies will help us find more biomarkers to define patients who will benefit most from these effective but potentially toxic drugs. Furthermore, more clinical data will enable treating clinicians to select appropriate patients who would benefit from ICI resumption after initial toxicities.

Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://dx.doi.org/10.21037/apm-21-943

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/apm-21-943). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are

appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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