PD-1 Inhibitor–Related Pneumonitis in Advanced Cancer Patients: Radiographic Patterns and Clinical Course

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Abstract

Purpose: Investigate the clinical characteristics, radiographic patterns, and treatment course of PD-1 inhibitor–related pneumonitis in advanced cancer patients.

Experimental Design: Among patients with advanced melanoma, lung cancer, or lymphoma treated in trials of nivolumab, we identified those who developed pneumonitis. Chest CT scans were reviewed to assess extent, distribution, and radiographic patterns of pneumonitis.

Results: Among 170 patients treated in 10 different trials of nivolumab, 20 patients (10 melanoma, 6 lymphoma, and 4 lung cancer) developed pneumonitis. Five patients received nivolumab monotherapy, and 15 received combination therapy. The median time from therapy initiation to pneumonitis was 2.6 months. Radiographic pattern was cryptogenic organizing pneumonia (COP) in 13, nonspecific interstitial pneumonia (NSIP) in 3, hypersensitivity pneumonitis (HP) in 2, and acute interstitial pneumonia (AIP)/acute respiratory distress syndrome (ARDS) in 2 patients. The AIP/ARDS pattern had the highest grade, followed by COP, whereas NSIP and HP had lower grade (median grade: 3, 2, 1, 1, respectively; $P = 0.006$). The COP pattern was most common in all tumors and treatment regimens. Most patients (17/20; 85%) received corticosteroids, and 3 (15%) also required infliximab. Seven patients restarted nivolumab therapy; 2 of them developed recurrent pneumonitis and were successfully retreated with corticosteroids. One of the patients experienced a pneumonitis flare after completion of corticosteroid taper without nivolumab retreatment.

Conclusions: PD-1 inhibitor–related pneumonitis showed a spectrum of radiographic patterns, reflecting pneumonitis grades. COP was the most common pattern across tumor types and therapeutic regimens. Most patients were successfully treated with corticosteroids. Recurrent pneumonitis and pneumonitis flare were noted in a few patients. *Clin Cancer Res; 22(24); 6051–60. ©2016 AACR.*

See related commentary by Castanon, p. 5956

Introduction

Immune checkpoint inhibitor therapy has emerged as a promising treatment option for advanced cancers (1–3). Programmed cell death (PD)-1 inhibitors are the most actively studied group of agents and have shown marked efficacy in trials for advanced melanoma (4–9), non–small-cell lung cancer (NSCLC; refs. 10–14), renal cell carcinoma (RCC; refs. 15–17), and Hodgkin lymphoma (18). Two PD-1 inhibitors have been approved by the FDA for clinical cancer treatment, including nivolumab for advanced melanoma, NSCLC, and RCC, and pembrolizumab for melanoma and NSCLC. A combination therapy using nivolumab and ipilimumab, a CTLA-4 inhibitor, has also been approved as a treatment for advanced melanoma (19, 20). Given the evidence for clinical efficacy in a wide spectrum of tumor types, PD-1 immune checkpoint inhibitor therapy as monotherapy or in combination is projected to be increasingly used by oncologists.

Immune checkpoint blockade by PD-1 inhibitors is associated with unique toxicities, termed "immune-related adverse events" (irAE), which can involve different organs throughout the body (21–23). Among the irAEs, pneumonitis is a relatively rare but clinically serious and potentially life-threatening toxicity, and is recognized as an "event of special interest" (2, 6). In a phase I trial of nivolumab in advanced solid tumors (2), three pneumonitis-related deaths were reported. Subsequently, a phase I trial of nivolumab for advanced NSCLC reported three pneumonitis-related deaths (13), and a phase I trial of pembrolizumab for advanced NSCLC reported one pneumonitis-related death (12). In spite of the potentially serious outcome of PD-1 inhibitor–related pneumonitis, there have been no systematic investigations of this entity focusing on its radiographic manifestations, treatment, and follow-up. Although the incidence of PD-1 inhibitor–related pneumonitis in these trials was reported as part of the safety assessments, the description of the clinical and radiographic details has been limited, and comparisons across different cohorts have not been performed because of the relatively low incidence of pneumonitis.

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Translational Relevance

PD-1 inhibitor–related pneumonitis is a clinically serious and potentially life-threatening toxicity, resulting in pneumonitis-related deaths in phase I trials, and is recognized as an "event of special interest"; however, little is known about the clinical and radiographic details of the entity. The present study systematically investigated the clinical characteristics, radiographic patterns, treatment, and outcome of pneumonitis in patients treated in trials of PD-1 inhibitors and characterized a spectrum of radiographic patterns of pneumonitis that were associated with toxicity grades. Most cases were responsive to corticosteroids, and one third of the patients were able to restart PD-1 inhibitor therapy, though a few patients experienced recurrent pneumonitis during retreatment. The results of the study are directly relevant to the current practice of oncology with increasing use of immune checkpoint inhibitors, meet the urgent needs of the community to advance knowledge of this serious toxicity, and provide a basis for further studies.

Several cases of PD-1 inhibitor–related pneumonitis were reported recently, describing the radiographic and clinical details of pneumonitis in the initial experiences with PD-1 inhibitors in melanoma (24) and NSCLC (25). These cases indicated that PD-1 inhibitor–related pneumonitis may have a spectrum of radiologic manifestations that includes different radiographic patterns described in the American Thoracic Society (ATS)/European Respiratory Society (ERS) classifications of interstitial pneumonias (24, 25). Clinical courses of pneumonitis were also variable among patients; some patients required admission to the intensive care unit (ICU) and intubation, whereas others were treated successfully with oral corticosteroids on an outpatient basis and were able to restart their anti–PD-1 therapy without experiencing recurrent pneumonitis (24, 25). The variability of clinical presentation and outcome of PD-1 inhibitor–related pneumonitis reported in these initial cases indicated a need for the systematic study of a larger number of cases.

The purpose of the present study is to investigate the clinical characteristics, radiographic patterns, treatment, and outcome of PD-1 inhibitor–related pneumonitis in patients treated on clinical trials of PD-1 inhibitor therapy and to compare these characteristics among patients with different tumor types and different treatment regimens.

Materials and Methods

Patients

Patients with advanced melanoma, lung cancer, or lymphoma who developed pneumonitis while enrolled on clinical trials using nivolumab at Dana-Farber Cancer Institute were identified based on review of the clinical trial records (ClinicalTrials.gov Identifiers: NCT00730639, NCT01721746, NCT01714739, NCT01783938, NCT01928394, NCT02186249, NCT01592370, NCT02038933, NCT02038946, and NCT02181738). The medical records and the imaging studies of these patients were retrospectively reviewed with approval from the institutional review board.

Evaluation of chest CT findings of pneumonitis

Chest CT scans obtained at the time of the diagnosis of pneumonitis were reviewed by a consensus of three radiologists with expertise in thoracic and oncologic imaging (M. Nishino, N.H. Ramaiya, and H. Hatabu), as described previously (24–27). CT findings of pneumonitis were evaluated for (i) extent in upper, middle, and lower lungs (none, <5%, 5%–25%, 25%–50%, >50%); (ii) distributions in terms of (a) peripheral, diffuse, central, or mixed and (b) upper, lower, diffuse, multifocal, or focal; (iii) lobar involvement; and (iv) specific CT findings including traction bronchiectasis, consolidation, reticular opacities, ground-glass opacities (GGO), centrilobular nodularity, and honeycombing (24–27). In each case, radiographic patterns of pneumonitis were classified according to the ATS/ERS international multidisciplinary classification of interstitial pneumonias as (i) usual interstitial pneumonia (UIP) pattern, (ii) nonspecific interstitial pneumonia (NSIP) pattern, (iii) cryptogenic organizing pneumonia (COP) pattern, (iv) acute interstitial pneumonia (AIP)/acute respiratory distress syndrome (ARDS) pattern, (v) hypersensitivity pneumonitis (HP) pattern, and (vi) not applicable, as described previously (24–28). Follow-up chest imaging studies after the onset of pneumonitis were also reviewed to assess the resolution of the findings.

Medical record review

The toxicity grades for pneumonitis assigned during the trials, according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), were obtained from the records. Clinical presentations, the treatment regimen for pneumonitis, and the clinical course were obtained from the medical records.

Statistical analysis

Comparison between the groups divided according to tumor types, therapeutic regimen, and radiographic patterns of pneumonitis was performed using the Fisher exact test for categorical data and the Wilcoxon test for continuous data. All P values were based on a two-sided hypothesis. A P value of less than 0.05 was considered to be statistically significant.

Results

Clinical characteristics of patients with pneumonitis

Among 170 patients treated on 10 different trials of nivolumab, either alone ($n = 74$) or in combination with other immune checkpoint inhibitors ($n = 96$), 20 patients (11.8%) developed pneumonitis. Thirteen of these 20 patients (65%) were female, and their median age was 52 (range, 28–71); 5 patients received nivolumab monotherapy, and 15 patients received combination therapy [with ipilimumab in 12 patients and with the anti-KIR (killer IgG-like receptor) antibody lirilumab in 3 patients]. Ten patients had melanoma, 6 had lymphoma, and 4 had lung cancer, including 3 with NSCLC and 1 with small–cell lung cancer (SCLC). Three patients (2 lymphoma and 1 SCLC) had received chest radiotherapy prior to PD-1 inhibitor therapy. The cases of 3 of the melanoma patients were reported previously in the initial experience of PD-1 pneumonitis at our institution (24). Severity of pneumonitis was grade 1 in 5 patients (25%), grade 2 in 10 patients (50%), and grade 3 in 5 patients (25%). The most common symptoms were cough in 12 patients (60%) and dyspnea in 11

Table 1. Clinical characteristics of 20 patients with PD-1 pneumonitis

Pt	Tumor	Sex	Age, y	Agents	Treatment regimen and drug dosage	Time to the onset of pneumonitis, mo	Grade	Symptoms
1	Melanoma	M	58	Nivolumab	Nivolumab (1 mg/kg q2w)	1.7	2	Cough
2	Melanoma	F	38	Nivolumab	Nivolumab (3 mg/kg q2w)	3.6	3	Dyspnea, hypoxia
3	Melanoma	M	70	Nivolumab and ipilimumab	Nivolumab (3 mg/kg q2w) × 6, then ipilimumab (3 mg/kg q3w) × 4	5.6	3	Cough, dyspnea, hypoxia, subacute fever
4	Melanoma	F	66	Nivolumab and ipilimumab	Nivolumab (3 mg/kg q2w) × 6, then ipilimumab (3 mg/kg q3w) × 4	5.4	1	None
5	Melanoma	F	40	Nivolumab and ipilimumab	Nivolumab (3 mg/kg q2w) × 6, then ipilimumab (3 mg/kg q3w) × 4	7.3	2	Cough, dyspnea
6	Melanoma	M	64	Nivolumab and ipilimumab	Nivolumab (3 mg/kg q2w) × 6, then ipilimumab (3 mg/kg q3w) × 4	3.7	2	Cough, dyspnea
7	Melanoma	M	57	Nivolumab and ipilimumab	Nivolumab (1 mg/kg) and ipilimumab (3 mg/kg) q3w × 4, then nivolumab alone (3 mg/kg q2w)	2.7	2	Cough, dyspnea
8	Melanoma	F	47	Nivolumab and ipilimumab	Nivolumab (1 mg/kg) and ipilimumab (3 mg/kg) q3w × 4, then nivolumab alone (3 mg/kg q2w)	2.4	1	None
9	Melanoma	F	35	Nivolumab and ipilimumab	Nivolumab (1 mg/kg) and ipilimumab (3 mg/kg) q3w × 4, then nivolumab alone (3 mg/kg q2w)	1.6	3	Cough, dyspnea, fever
10	Melanoma	F	52	Nivolumab and ipilimumab	Nivolumab (1 mg/kg) and ipilimumab (3 mg/kg) q3w × 4, then nivolumab alone (3 mg/kg q2w)	2.7	1	None
11	Lung (adenoca)	F	56	Nivolumab	Nivolumab (10 mg/kg q2w)	1.4	3	Cough, dyspnea, fever
12	Lung (adenoca)	F	40	Nivolumab	Nivolumab (1 mg/kg q2w)	1.2	1	None
13	Lung (adenoca)	F	52	Nivolumab and lirilumab	Nivolumab (3 mg/kg q2w) and lirilumab (3 mg/kg q4w)	1.1	2	Dyspnea, hypoxia
14	Lung (SCLC)	M	59	Nivolumab	Nivolumab 3 mg/kg q2w	0.5	3	Dyspnea, hypoxia
15	Lymphoma (Hodgkin)	F	30	Nivolumab and ipilimumab	Nivolumab (3 mg/kg) and ipilimumab (1 mg/kg) q3w × 4, then nivolumab (3 mg/kg q2w)	11.5	2	Cough
16	Lymphoma (Hodgkin)	F	33	Nivolumab and ipilimumab	Nivolumab (3 mg/kg) and ipilimumab (1 mg/kg) q3w × 4, then nivolumab (3 mg/kg q2w)	1.4	2	Cough, dyspnea
17	Lymphoma (Hodgkin)	F	71	Nivolumab and ipilimumab	Nivolumab (3 mg/kg) and ipilimumab (1 mg/kg) q3w × 4, then nivolumab (3 mg/kg q2w)	1.4	2	Cough, dyspnea
18	Lymphoma (T cell)	F	62	Nivolumab and ipilimumab	Nivolumab (3 mg/kg) and ipilimumab (1 mg/kg) q3w × 4, then nivolumab (3 mg/kg q2w)	4.6	2	Cough
19	Lymphoma (Hodgkin)	M	30	Nivolumab and lirilumab	Nivolumab (3 mg/kg q2w) and lirilumab (3 mg/kg q4w)	4.1	1	None
20	Lymphoma (Hodgkin)	M	28	Nivolumab and lirilumab	Nivolumab (3 mg/kg q2w) and lirilumab (3 mg/kg q4w)	0.8	2	Cough, fever

Abbreviations: adenoca, adenocarcinoma; F, female; M, male; mo, months; Pt, patient; q, every; w, weeks; y, years.

patients (55%). Further clinical details of each patient are summarized in Table 1.

The median time from treatment initiation to the development of pneumonitis was 2.6 months (range, 0.5–11.5) in the whole cohort of 20 patients; of note, it was shorter in the 4 lung cancer patients compared with the 16 patients with melanoma and lymphoma (median time to pneumonitis, 1.1 vs. 3.1 months, respectively; $P = 0.008$).

CT findings and radiographic patterns of pneumonitis

Table 2 summarizes the CT characteristics of pneumonitis during nivolumab therapy in all 20 patients. The extent of lung involvement by pneumonitis was highest in the lower lungs, followed by the middle lungs, and was lowest in the upper lungs, with a median extent score of 3 (25%–50%) for the lower, 2.5 for the middle, and 2 (5%–25%) for the upper lungs. The most common distribution of CT findings of pneumonitis was mixed and multifocal ($n = 8$), followed by peripheral and lower ($n = 4$), and diffuse ($n = 4$). In 15 patients (75%), all lobes of the lung, including the lingula, were involved. Among the specific CT findings, GGOs were present in all 20 patients, with reticular opacities in 19 and consolidations in 12 patients. Centrilobular nodularity was present in 3 patients. Traction bronchiectasis was noted in 2 patients. Pneumonitis in lung cancer patients had more extensive involvement on CT than others ($P = 0.007$).

The overall radiographic pattern of pneumonitis on chest CT was the most common COP pattern noted in 13

Table 2. CT findings and radiographic patterns of PD-1 pneumonitis

Pt	Extent			Distribution	Lobar involvement	Specific CT findings	Radiographic pattern
	Upper	Middle	Lower				
1	5%–25%	5%–25%	25%–50%	Peripheral and lower	All lobes	GGOs, reticular opacities, consolidations	NSIP
2	>50%	>50%	>50%	Diffuse	All lobes	GGOs, reticular opacities, consolidations, traction BE, centrilobular nodularity	AIP/ARDS
3	25%–50%	>50%	>50%	Diffuse	All lobes	GGOs, reticular opacities, consolidations, traction BE	AIP/ARDS
4	None	<5%	5–25%	Mixed and lower	RLL	GGOs, reticular opacities	NSIP
5	5%–25%	25%–50%	>50%	Peripheral and lower	All lobes	GGOs, reticular opacities, consolidations	COP
6	5–25%	5%–25%	5%–25%	Mixed and multifocal	LUL, lingula, LLL	GGOs, reticular opacities, consolidations	COP
7	5–25%	5%–25%	<5%	Mixed and multifocal	All lobes	GGOs, reticular opacities	COP
8	>50%	25%–50%	25%–50%	Diffuse	All lobes	GGOs, reticular opacities	HP
9	5%–25%	5%–25%	25%–50%	Peripheral and lower	All lobes	GGOs, reticular opacities, consolidations	COP
10	<5%	5%–25%	25%–50%	Peripheral and lower	All lobes	GGOs, reticular opacities, consolidations	NSIP
11	25%–50%	25%–50%	>50%	Mixed and multifocal	All lobes	GGOs, reticular opacities	COP
12	>50%	>50%	>50%	Diffuse	All lobes	GGOs, centrilobular nodularity	HP
13	>50%	>50%	25%–50%	Mixed and upper	All lobes	GGOs, reticular opacities	COP
14	25%–50%	25%–50%	>50%	Mixed and multifocal	All lobes	GGOs, reticular opacities	COP
15	25%–50%	25%–50%	25%–50%	Peripheral and multifocal	All lobes	GGOs, reticular opacities, consolidations	COP
16	5%–25%	5%–25%	25%–50%	Mixed and multifocal	All lobes	GGOs, reticular opacities, consolidations	COP
17	<5%	<5%	5%–25%	Mixed and lower	RLL, LLL	GGOs, reticular opacities, consolidations	COP
18	5%–25%	5%–25%	>50%	Mixed and multifocal	All lobes	GGOs, reticular opacities, consolidations	COP
19	None	5%–25%	5–25%	Mixed and multifocal	LLL	GGOs, reticular opacities, consolidations	COP
20	5%–25%	25%–50%	25%–50%	Mixed and multifocal	RUL, RML, LLL	GGOs, reticular opacities, centrilobular nodularity	COP

Abbreviations: BE, bronchiectasis; LLL, left lower lobe; LUL; left upper lobe; Pt, patient; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe.

patients (65%; Fig. 1A and B), followed by the NSIP pattern in 3 (15%; Fig. 1C and D), the HP pattern in 2 (10%; Fig. 1E and F), and the AIP/ARDS pattern in 2 patients (10%; Fig. 1G and H). The radiographic patterns were associated with the toxicity grades of pneumonitis; the AIP/ARDS pattern had the highest grade (median grade, 3), followed by the COP pattern (median grade, 2), and the NSIP and HP patterns had lower grade (median 1 for both; $P = 0.006$).

The COP pattern was the most common pattern in all tumor types (3/4 in lung, 6/6 in lymphoma, 4/9 in melanoma) and in both monotherapy (2/5) and combination therapy (11/15). No significant differences were observed in the radiographic patterns between monotherapy and combination therapy ($P = 0.30$) or among different tumor types ($P = 0.19$).

Treatment for pneumonitis and follow-up

The details of the treatment regimen for pneumonitis and the clinical course are shown in Table 3. Nivolumab therapy was held at the time of pneumonitis in all patients. The majority (17/20; 85%) of the patients received corticosteroids as a treatment for pneumonitis. Three patients (15%) also received infliximab in addition to corticosteroids. Three patients received no corticosteroids for pneumonitis; of these, one patient was on hydrocortisone 15 mg daily for adrenal insufficiency that had been previously diagnosed. Seven patients

were admitted to the hospital for treatment of pneumonitis, including 3 patients with melanoma and all 4 patients with lung cancer. Two of the melanoma patients were admitted to the ICU, and 1 patient required intubation during ICU admission.

During the treatment and follow-up course, 14 patients with grade 2 or above had clinical and radiographic improvement, and 4 patients with grade 1 pneumonitis without symptoms had radiographic improvement. One patient with grade 1 pneumonitis started the next systemic therapy without further follow-up CT. One patient was referred to hospice care without follow-up CT and passed away.

Nivolumab therapy was restarted in 7 patients (35%), including 3 patients with melanoma and 4 patients with lymphoma; of these patients, 5 had a COP pattern and 2 had an NSIP pattern. One patient received nivolumab monotherapy and 6 had received combination therapy at the time of pneumonitis. During retreatment, 4 patients received nivolumab monotherapy (including 3 patients who restarted on maintenance monotherapy after the initial doses of the combination regimen), and 3 patients restarted combination therapy (nivolumab and ipilimumab in 1, nivolumab and lirilumab in 2; Table 3).

Among the 7 patients with retreatment, recurrent pneumonitis was noted in 2 patients. One of them was a patient with melanoma who was restarted on maintenance nivolumab

Figure 1.
Spectrum of radiographic manifestations of PD-1 inhibitor–related pneumonitis. **A** and **B,** Pneumonitis with a COP pattern in a 30-year-old female with Hodgkin lymphoma treated with nivolumab and ipilimumab combination therapy (patient 15). CT scan of the chest at 11.5 months of therapy demonstrated a development of ground-glass and reticular opacities and consolidations involving both lungs with a multifocal distribution (arrowheads, **A**), representing a COP pattern. One of the involved areas in the left lower lobe demonstrated a "reversed halo" sign (arrow, **B**) with central GGO surrounded by dense air-space consolidation of crescentic shape, which has been reported as a radiographic manifestation of COP. **C** and **D,** Pneumonitis with an NSIP pattern in a 58-year-old male with melanoma treated with nivolumab monotherapy (patient 1). Chest CT scan at 1.7 months of therapy demonstrated new ground glass and reticular opacities and consolidations (arrowheads, **C** and **D**) indicative of an NSIP pattern. **E** and **F,** Pneumonitis with an HP pattern in a 40-year-old female with lung adenocarcinoma treated with nivolumab monotherapy (patient 12). Chest CT scan at 1.2 months of therapy demonstrated new diffuse GGOs and centrilobular nodularity in both lungs, indicative of an HP pattern of pneumonitis. Note that the consolidations and interlobular septal thickening in the right lung demonstrate tumor involvement by lung cancer, which were present since the baseline scan. **G** and **H,** Pneumonitis with an AIP/ARDS pattern in a 70-year-old man with melanoma treated with sequentially administered nivolumab and ipilimumab combination therapy (patient 3). Chest CT scan at 5.6 months of therapy demonstrated ground-glass and reticular opacities, consolidations, and traction bronchiectasis as well as pleural effusions (asterisks) involving both lungs.
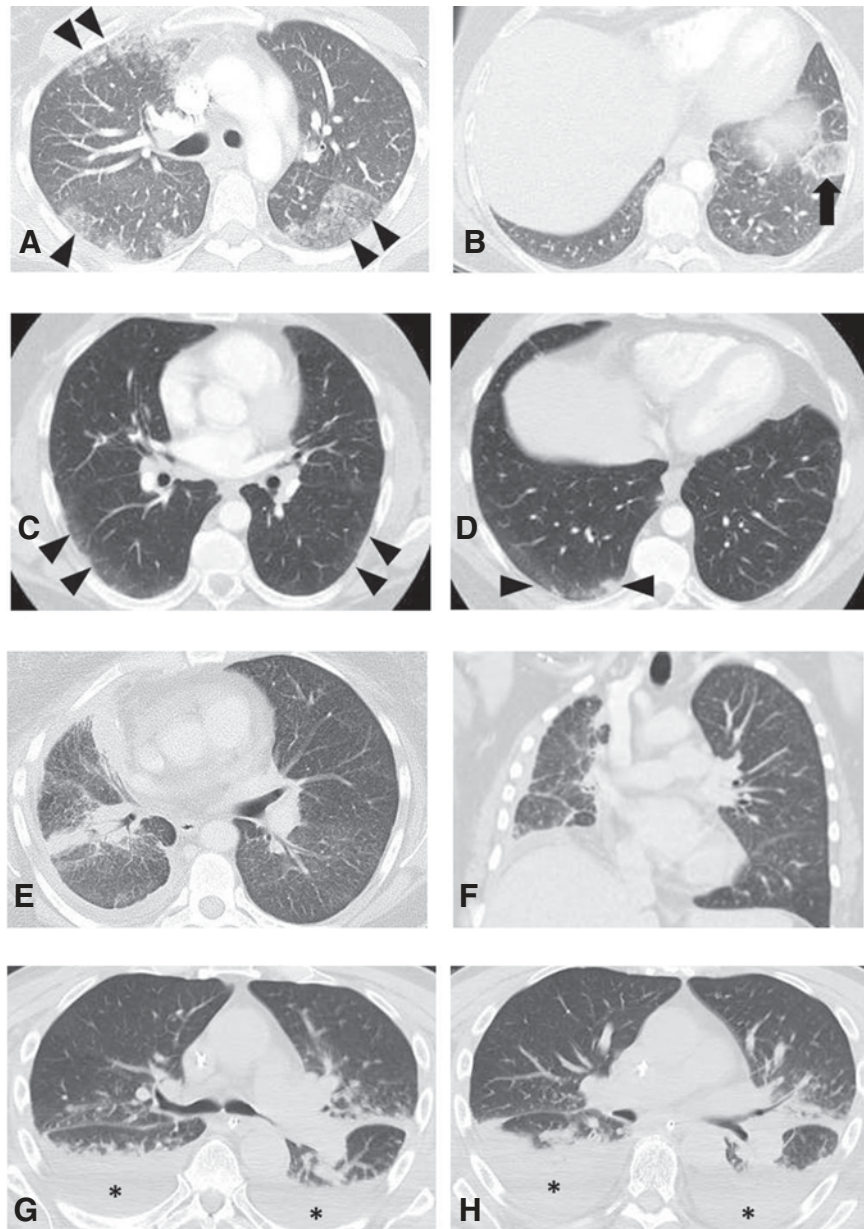
monotherapy, and developed recurrent pneumonitis after 4 doses of nivolumab, which was successfully treated with corticosteroid taper without further nivolumab retreatment or recurrence for 4 months after the second episode. The other was a lymphoma patient who restarted on nivolumab and ipilimumab therapy and developed recurrent pneumonitis after receiving 2 doses of nivolumab and ipilimumab and 2 doses of nivolumab (Fig. 2). Nivolumab was again held, and the patient was again treated with prednisone taper with subsequent improvement; 1 month after the completion of the 2-month course of the prednisone taper, the patient again developed pneumonitis without nivolumab retreatment or any other systemic therapy, indicating a "pneumonitis flare" phenomenon. Another course of prednisone taper was given for

2.7 months. After 2 weeks from the completion of the prednisone taper, the patient again experienced a pneumonitis flare, which was histologically confirmed (Fig. 3). Prednisone taper at 60 mg daily was again initiated, with subsequent clinical improvement.

Discussion

Among the patients who developed PD-1 inhibitor–related pneumonitis during nivolumab therapy for advanced cancers, including melanoma, lung cancer, and lymphoma, a COP pattern was the most common radiographic pattern of pneumonitis in all tumor types and therapeutic regimens. The radiographic patterns were associated with the toxicity grades of pneumonitis. Most

Table 3. Treatment for pneumonitis and follow-up course

Pt	Treatment for pneumonitis[a]	Admission for pneumonitis	Outcome of pneumonitis treatment	Reinitiation of nivolumab therapy	Recurrent pneumonitis	Details of follow-up and retreatment
1	Oral prednisone taper starting with 120 mg daily	No	Clinical and radiographic improvement	Yes	No	Restarted nivolumab; no recurrent pneumonitis for 46 months
2	i.v. methylprednisolone taper 240 mg daily, i.v. infliximab (5 mg/kg), ICU admission	Yes	Referred for hospice care and died	No	No	Referred for hospice care and died
3	i.v. methylprednisolone taper 150 mg daily, i.v. infliximab (5 mg/kg), ICU admission, intubation	Yes	Clinical and radiographic improvement	No	No	Follow-up without therapy; no recurrent pneumonitis for 26 months
4	None[b]	No	Radiographic improvement	Yes	No	Restarted maintenance nivolumab monotherapy (3 mg/kg q2w); no recurrent pneumonitis for 22 months
5	None	No	Clinical and radiographic improvement	No	No	Started on next systemic therapy
6	Oral prednisone 120 mg daily	No	Clinical and radiographic improvement	No	No	Started on next systemic therapy
7	Oral prednisone taper starting at 80 mg	No	Clinical and radiographic improvement	Yes	Yes	Restarted nivolumab (3 mg/kg q2w) and developed recurrent pneumonitis after receiving 4 doses of nivolumab[c]
8	Oral prednisone taper starting at 100 mg	No	Radiographic improvement	No	No	Follow-up without therapy; no recurrent pneumonitis for 3 months
9	Oral steroid taper at outside institution[d]	Yes	Clinical and radiographic improvement	No	No	Follow-up without therapy; no recurrent pneumonitis for 7 months
10	None	No	Radiographic improvement	No	No	Started on next systemic therapy
11	i.v. methylprednisolone 120 mg, then oral prednisone taper starting at 60 mg, and i.v. infliximab (5 mg/kg)	Yes	Clinical and radiographic improvement	No	No	Referred for palliative care
12	Oral prednisone taper starting at 60 mg daily	Yes	No imaging before next therapy	No	No	Started on next systemic therapy
13	i.v. methylprednisolone 250 mg, then oral dexamethasone 12 mg daily and prednisone taper starting at 60 mg daily	Yes	Clinical and radiographic improvement	No	No	Referred for palliative care
14	i.v. methylprednisolone 140 mg daily, then oral prednisone taper starting at 140 mg daily	Yes	Clinical and radiographic improvement	No	No	Started on next systemic therapy
15	Oral prednisone taper starting at 60 mg daily	No	Clinical and radiographic improvement	Yes	No	Restarted nivolumab monotherapy; no recurrent pneumonitis for 5 months
16	Oral prednisone taper starting at 100 mg daily	No	Clinical and radiographic improvement	Yes	Yes	Restarted nivolumab and ipilimumab and received 2 doses of nivolumab and ipilimumab, and 2 doses of nivolmab; developed recurrent pneumonitis[e]
17	Oral prednisone taper starting at 70 mg daily	No	Clinical and radiographic improvement	No	No	Follow-up without therapy without recurrent pneumonitis for 8 months
18	Oral prednisone taper starting at 40 mg daily	No	Clinical and radiographic improvement	No	No	Started on next systemic therapy
19	Oral prednisone taper starting at 60 mg daily	No	Radiographic improvement	Yes	No	Restarted nivolumab and lirilumab; no recurrent pneumonitis for 2 months
20	Oral prednisone taper starting at 80 mg daily	No	Clinical and radiographic improvement	Yes	No	Restarted nivolumab and lirilumab; no recurrent pneumonitis for 3 months

[a]Nivolumab therapy was held at the time of pneumonitis in all patients.

[b]The patient has been on hydrocortisone 15 mg/day for adrenal insufficiency.

[c]Nivolumab was held, and the patient was treated again with prednisone taper and improved; followed without rechallenge or therapy for 4 months.

[d]No further treatment details are available for this patient treated at the outside institution.

[e]Nivolumab was held, and the patient was again treated with prednisone taper starting at 100 mg, with subsequent improvement; however, the patient experienced two episodes of pneumonitis flare, where a similar pattern of pneumonitis recurred after the completion of corticosteroid taper without retreatment of nivolumab or other systemic therapy (see Fig. 3).

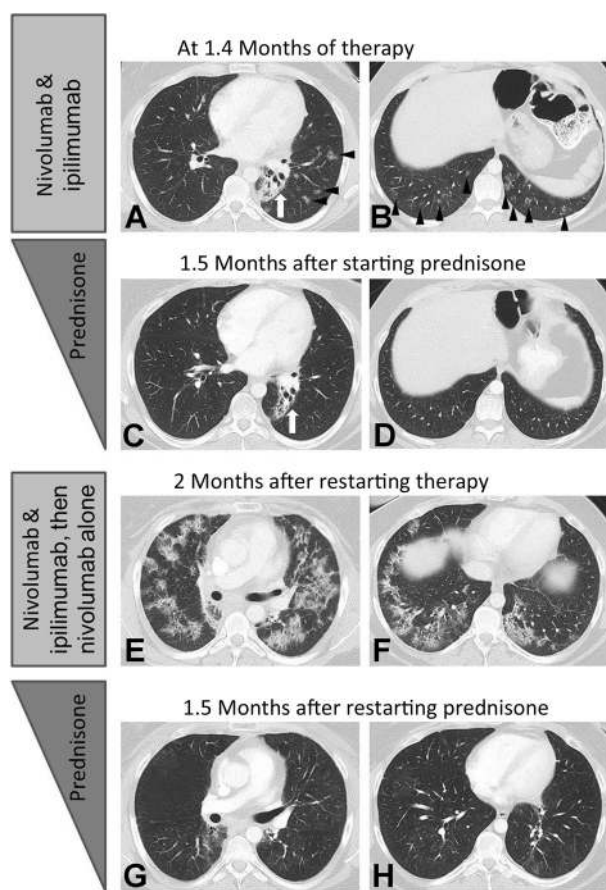Abbreviations: Pt, patient; q, every; w, weeks.

Figure 2.
Pneumonitis with a COP pattern in a 33-year-old female with Hodgkin lymphoma treated with nivolumab and ipilimumab combination therapy (patient 16), with a recurrence during retreatment and two episodes of pneumonitis flare after completion of corticosteroid taper. **A** and **B,** CT scan of the chest at 1.4 months of therapy demonstrated ground-glass and reticular opacities and consolidations with multifocal distribution, indicative of a COP pattern of pneumonitis (arrowheads). Left perihilar opacity and traction bronchiectasis are due to prior radiotherapy (arrows). **C** and **D,** The patient was treated with oral prednisone taper, and the findings have resolved on the follow-up scan performed 1.5 month later. **E** and **F,** The patient restarted therapy and received 2 doses of nivolumab and ipilimumab and 2 doses of nivolmab monotherapy, and then developed recurrent pneumonitis after 2 months since restarting therapy. The scan at the time of recurrent pneumonitis demonstrated similar findings with multifocal ground-glass and reticular opacities and consolidations, again representing a COP pattern. The findings were more extensive than the first episode. **G** and **H,** Nivolumab was held, and the patient was treated again with prednisone taper for pneumonitis, with subsequent improvement.

patients were successfully treated with corticosteroids. Seven patients (35%) restarted nivolumab therapy, with recurrent pneumonitis noted in 2 patients during retreatment. To our knowledge, this is the first study that systematically characterized a spectrum of the radiographic patterns of PD-1 inhibitor–related pneumonitis according to the ATS/ERS classification, and provided treatment and follow-up details in advanced cancer patients treated with nivolumab.

The distribution of the toxicity grades in our cohort is similar to the published trial reports in that more patients had grade ≤ 2

than grade ≥ 3 (2, 5, 7, 19, 20, 29). Distributions between grade 1 and grade 2 are not described in most trial reports, because toxicities are categorized as "all grades" and "grade 3 or above" in trial reports. Most patients (75%) were symptomatic with cough and dyspnea, which is similar to the prior clinical reports of the entity (24, 25).

Time from initiation of therapy to the development of pneumonitis had a wide range (0.5–11.5 months), indicating an importance of careful observation and follow-up for signs
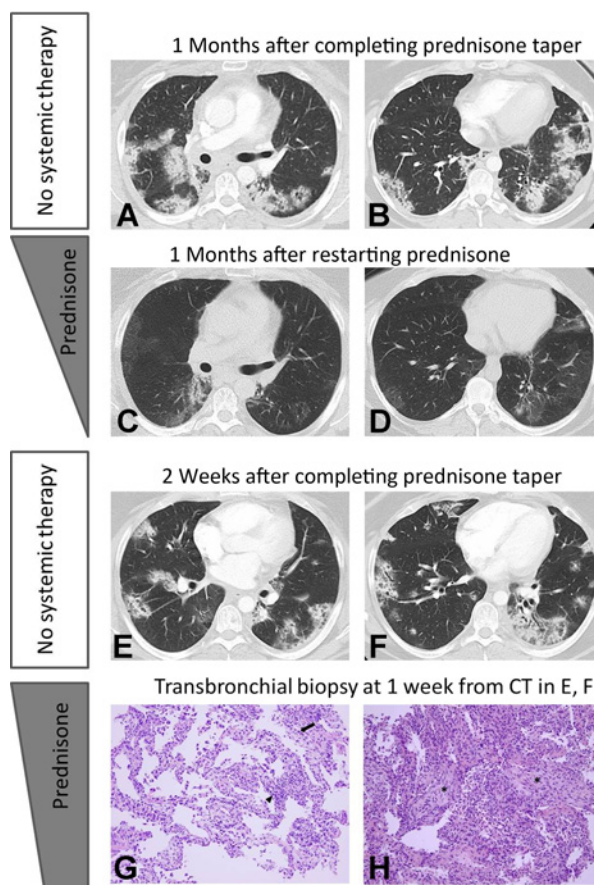

Figure 3.
Pneumonitis with a COP pattern in a 33-year-old female with Hodgkin lymphoma treated with nivolumab and ipilimumab combination therapy (patient 16), with a recurrence during retreatment and two episodes of pneumonitis flare after completion of corticosteroid taper. **A** and **B,** The patient completed 2 months of corticosteroid taper, and after 1 month, she experienced another episode of pneumonitis with a very similar radiographic pattern, without nivolumab retreatment or other systemic therapy, indicating a pneumonitis flare. **C** and **D,** Another course of corticosteroid taper was given and with subsequent improvement. **E** and **F,** The 2.7-month course of corticosteroid taper was completed, and after 2 weeks, the patient again developed a pneumonitis flare with a similar radiographic pattern as the prior episodes. **G** and **H,** The sampled fragments of lung obtained by transbronchial biopsies showed interstitial pneumonitis evolving to organizing pneumonia. Findings included lymphocyte-predominant interstitial pneumonitis (arrowhead, **G**; H&E stain, 200×) with rare eosinophils (arrow, **O**), and areas of organizing pneumonia with fibroblast plugs and foamy macrophages filling the airspaces (asterisks, **H**; H&E stain, 200×). No tumor cells, microorganisms, or viral cytopathic changes were identified. The patient started another course of prednisone taper with subsequent clinical improvement and is scheduled for a follow-up CT scan.

and symptoms of pneumonitis throughout treatment. Shorter time to onset of pneumonitis in lung cancer compared with melanoma and lymphoma may be due to a higher pulmonary tumor burden among lung cancer patients, which can result in an earlier onset of respiratory symptoms. In addition, clinicians may have a lower threshold for performing additional chest CT scans in lung cancer patients. In a prior report of two cases of PD-1 pneumonitis in advanced NSCLC, pneumonitis was also noted during early course of nivolumab therapy (at 1 month of therapy in 1 patient and at 2 months in the other patient; ref. 25). These observations indicate a trend of early onset of PD-1 pneumonitis among patients with lung cancer, which can be further studied in a larger cohort.

The CT characteristics of pneumonitis showed a higher extent of involvement in lower lobes, which is often seen in pneumonitis related to other molecular targeting agents, including mTOR inhibitors (26, 27). Mixed and multifocal distribution was most common, and all lung lobes plus the lingula were involved in 75% of the patients, reflecting a relatively extensive lung involvement by PD-1 inhibitor–related pneumonitis, as noted in prior reports (24, 25). Among the specific CT findings, GGOs ($n = 20$), reticular opacities ($n = 18$), and consolidation ($n = 12$) were most commonly noted, as in most of the cases with drug-related pneumonitis during immune checkpoint inhibitor therapies and molecular targeting therapies (22, 24–27, 30). The extent of involvement was higher in patients with lung cancer, which goes along with the trial reports of PD-1 inhibitors in NSCLC describing high-grade pneumonitis with serious consequence, including pneumonitis-related deaths in phase I trials (12, 13).

A radiographic pattern of pneumonitis according to ATS/ERS classification was most frequently a COP pattern, noted in 65% of the patients, without significant differences among different tumor types or therapeutic regimen. The COP pattern was seen in the previous report of commercially treated NSCLC patients with nivolumab-related pneumonitis (25) and was also the most common pattern for mTOR inhibitor–related pneumonitis in advanced neuroendocrine tumors and Waldenstrom macroglobulinemia (26, 27). However, other patterns were noted in the remaining patients in the present study, including NSIP, HP, and AIP/ARDS patterns, demonstrating a wide spectrum of radiographic presentation of PD-1 pneumonitis. Notably, these radiographic patterns were associated with the NCI CTCAE grade of pneumonitis, where the grades were highest in the AIP/ARDS pattern, followed by the COP, and lowest in the NSIP and HP patterns. The results indicate the value of the radiographic pattern-based approach in categorizing and prognosticating PD-1 inhibitor–related pneumonitis.

Treatment and follow-up course of PD-1 inhibitor–related pneumonitis are an important and challenging issue in current immuno-oncology practice. Nivolumab therapy was held at the diagnosis of pneumonitis in all patients; most patients were treated with corticosteroids, with a median time of corticosteroid therapy of 6.1 weeks. Varying doses of oral and intravenous corticosteroids were used, which reflects a spectrum of clinical severity of PD-1 pneumonitis, and a need for consensus as to the optimal treatment algorithm. All 4 patients with lung cancer were admitted at the time of pneumonitis treatment, indicating higher clinical severity and concerns in this subgroup of patients. All lung cancer patients had been heavily treated prior to PD-1 inhibitor therapy, with 3 to 5 lines of systemic therapy, including platinum-based chemotherapy and tyrosine kinase inhibitors in 3 patients

with NSCLC, and with platinum-based chemotherapy plus concurrent chest radiotherapy in a patient with SCLC, which may have also contributed to the clinical severity of pneumonitis.

In most patients, clinical and radiographic improvements were noted after treatment, indicating that this entity, although potentially serious, is treatable if diagnosed and managed appropriately. The observation emphasizes the importance of timely recognition, accurate diagnosis, and early intervention in the setting of PD-1 inhibitor–related pneumonitis. Bronchoscopy and bronchoalveolar lavage (BAL) were performed at the time of pneumonitis in 4 patients (1 patient with melanoma, 2 with NSCLC, and 1 with lymphoma) and demonstrated acute inflammation in 2 patients, reactive pneumocytes in 1 patient, and malignant cells due to underlying lung metastasis that has been present before starting PD-1 inhibitor therapy in 1 patient with NSCLC; this patient's pneumonitis was radiographically distinct from underlying lung metastasis and improved after corticosteroid treatment. Given the limited available data of BAL in PD-1 inhibitor–related pneumonitis, as well as its sensitivity and specificity in diagnosing this entity, its exact role in this context remains to be established.

Retreatment with anti–PD-1 therapy in patients with pneumonitis after nivolumab is another challenging issue with very limited data. Of the 7 patients who restarted nivolumab therapy, 2 patients developed recurrent pneumonitis, whereas pneumonitis did not reoccur in the remaining 5 patients at the time of analysis, with a follow-up time ranging from 2 to 46 months. Further studies are needed to effectively identify patients who can safely restart PD-1 therapy after experiencing pneumonitis. Both patients with recurrent pneumonitis were successfully treated with corticosteroids, again demonstrating the steroid responsive nature of the entity in the setting of increased awareness and early recognition. However, 1 of the 2 patients subsequently developed "pneumonitis flare," where pneumonitis recurred after completing corticosteroid taper in the absence of nivolumab retreatment, as seen in a case described in the prior report among patients with NSCLC (25). Notably, the patient in the present study experienced two episodes of pneumonitis flare, which may suggest a recurrent nature of the phenomenon and, thus, indicate another clinical challenge as to when to complete corticosteroid therapy for pneumonitis. Although the exact incidence and further characteristics of a pneumonitis flare remain to be systematically investigated, the histologic findings consistent with pneumonitis obtained during the flare episode in this patient provide further support of this unique phenomenon among patients treated with PD-1 inhibitors.

The limitations of the present study include a relatively small number of patients with PD-1 inhibitor–related pneumonitis treated in a single institution. However, to our knowledge, this is the first report of systematic investigation focusing on clinical and radiographic details of this entity. Retrospective design for the imaging review is a limitation; however, patients were treated in clinical trials and, thus, prospectively assessed and diagnosed for PD-1 inhibitor–related pneumonitis. The treatment regimen included nivolumab monotherapy and combination therapy, which is a reflection of the heterogeneous nature of the trial designs. To allow the study to focus on pneumonitis noted as an irAE, the combination regimen only included those with other immune checkpoint inhibitors (anti–CTLA-4 and anti-KIR) and did not include cytotoxic chemotherapy or targeted agents. The study focused on the clinical and radiographic description of pneumonitis, and the assessment of risk factors and predictors of

pneumonitis was not performed. Of note, 3 of the 20 patients had prior chest radiotherapy, including a lymphoma patient who developed recurrent pneumonitis and two episodes of pneumonitis flare. Further studies are needed to determine the impact of prior chest radiotherapy on the development, severity, and treatment outcome of PD-1 inhibitor–related pneumonitis.

In conclusion, PD-1 inhibitor–related pneumonitis showed a spectrum of radiographic patterns, which were associated with toxicity grades. Most cases were responsive to corticosteroids and one third of the patients were able to restart nivolumab therapy, though a few patients experienced recurrent pneumonitis during retreatment. These observations emphasize the importance of increased awareness of the entity for the early diagnosis and treatment. The wide spectrum of radiographic manifestations and complex clinical courses noted in some of the cases provide additional diagnostic and management challenges in the clinical setting, which calls for a multidisciplinary approach using expertise from oncology, radiology, pulmonology, and pathology to optimize patient care. Future studies in larger cohorts are needed to identify risk factors and early markers for pneumonitis development and recurrence, and to establish optimal management guidelines for this entity.

Disclosure of Potential Conflicts of Interest

Authors' Contributions

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