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ORIGINAL REPORT

Pneumonitis in Patients Treated With Anti–Programmed Death-1/Programmed Death Ligand 1 Therapy

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ABSTRACT

Purpose

Pneumonitis is an uncommon but potentially fatal toxicity of anti–programmed death-1 (PD-1)/programmed death ligand 1 (PD-L1) monoclonal antibodies (mAbs). Clinical, radiologic, and pathologic features are poorly described.

Methods

Patients who received anti–PD-1/PD-L1 monotherapy or in combination with anti–cytotoxic T-cell lymphocyte-4 mAb were identified at two institutions (Memorial Sloan Kettering Cancer Center: advanced solid cancers, 2009 to 2014, and Melanoma Institute of Australia: melanomas only, 2013 to 2015). Pneumonitis was diagnosed by the treating investigator; cases with confirmed malignant lung infiltration or infection were excluded. Clinical, radiologic, and pathologic features of pneumonitis were collected. Associations among pneumonitis incidence, therapy received, and underlying malignancy were examined with Fisher's exact test as were associations between pneumonitis features and outcomes.

Results

Of 915 patients who received anti–PD-1/PD-L1 mAbs, pneumonitis developed in 43 (5%; 95% CI, 3% to 6%; Memorial Sloan Kettering Cancer Center, 27 of 578 [5%]; Melanoma Institute of Australia, 16 of 337 [5%]). Time to onset of pneumonitis ranged from 9 days to 19.2 months. The incidence of pneumonitis was higher with combination immunotherapy versus monotherapy (19 of 199 [10%] *v* 24 of 716 [3%]; $P < .01$). Incidence was similar in patients with melanoma and non–small-cell lung cancer (overall, 26 of 532 [5%] *v* nine of 209 [4%]; monotherapy, 15 of 417 *v* five of 152 [$P = 1.0$]; combination, 11 of 115 *v* four of 57 [$P = .78$]). Seventy-two percent (31 of 43) of cases were grade 1 to 2, and 86% (37 of 43) improved/resolved with drug holding/immunosuppression. Five patients worsened clinically and died during the course of pneumonitis treatment; proximal cause of death was pneumonitis (n = 1), infection related to immunosuppression (n = 3), or progressive cancer (n = 1). Radiologic and pathologic features of pneumonitis were diverse.

Conclusion

Pneumonitis associated with anti–PD-1/PD-L1 mAbs is a toxicity of variable onset and clinical, radiologic, and pathologic appearances. It is more common when anti–PD-1/PD-L1 mAbs are combined with anti–cytotoxic T-cell lymphocyte-4 mAb. Most events are low grade and improve/resolve with drug holding/immunosuppression. Rarely, pneumonitis worsens despite immunosuppression, and may result in infection and/or death.

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INTRODUCTION

Anti–programmed death-1 (anti–PD-1) and anti–programmed death ligand 1 (anti–PD-L1) monoclonal antibodies (mAbs) for patients with multiple malignancies are now Food and Drug Administration–approved therapies, which include nivolumab and pembrolizumab for melanoma[1,2] and non–small-cell lung cancer (NSCLC),[3-6] nivolumab for renal cell carcinoma[7] and Hodgkin lymphoma,[8] atezolizumab for bladder cancer,[9] and nivolumab plus ipilimumab for melanoma.[10] These agents also have been studied in other diseases[11-13] along with durvalumab (PD-L1 mAb) and tremelimumab (cytotoxic T-cell lymphocyte-4 [CTLA-4] mAb).[14,15] One of the remarkable characteristics of anti–PD-1/PD-L1 mAbs is their relatively mild

ASSOCIATED CONTENT

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toxicity profile. However, immune-related adverse events can occur and may be severe.[16,17] Pneumonitis is an immune-related adverse event that accounted for three deaths in an early-phase study with an anti–PD-1 mAb.[18]

Pneumonitis is defined as a focal or diffuse inflammation of the lung parenchyma,[19] and its incidence in studies with anti–PD-1/PD-L1 mAbs has ranged from 0% to 10%.[20] Drug-related pneumonitis can also occur with chemotherapy (docetaxel,[21] gemcitabine,[22] bleomycin[23]), targeted therapy (epidermal growth factor receptor inhibitors,[24,25] mammalian target of rapamycin inhibitors[26]), and radiation therapy.[27,28] Previous experience with these pneumonitides highlighted that clinical, radiologic, and pathologic characterization may facilitate early recognition, treatment optimization, and improved outcomes. The underlying etiology and mechanisms of pneumonitis associated with anti–PD-1/PD-L1 mAbs are unknown.

With the recent approval of anti–PD-1/PD-L1 mAbs, and several other anticipated indications, use is expected to expand rapidly. A critical need exists to gain familiarity with the clinical features of pneumonitis and to optimize management. The clinical experience of patients with anti–PD-1/PD-L1–associated pneumonitis has not been comprehensively described, and data are sparse with regard to management and outcomes. We describe the clinical, radiologic, and pathologic features and management of 43 cases of pneumonitis as a result of anti–PD-1/PD-L1 mAbs from two separate institutions.

METHODS

Patients

After institutional review board approval, patients treated with anti–PD-1/PD-L1 mAbs either as monotherapy or in combination with anti–CTLA-4 mAb were identified from Memorial Sloan Kettering Cancer Center (MSKCC; January 2009 to September 2014; all advanced cancers) and the Melanoma Institute of Australia (MIA) and affiliated hospitals (January 2013 to August 2015; melanomas only). Anti–PD-1/PD-L1 mAbs were delivered either as part of an institutional review board–approved therapeutic study or as an expanded access program. Patients treated concurrently with chemotherapy, targeted therapy, and immunotherapy other than anti–CTLA-4 mAb, and in whom the treatment received was still blinded, were excluded. Cases were identified and reviewed retrospectively (MSKCC, J.N., H.R., X.H., M.D.H.; MIA, X.W., A.M.M., A.D.G., M.S.C., B.Y.K., G.V.L.). Those with a clear alternative etiology, such as proven malignant lung infiltration or active lung infection, were excluded. Grading was performed by the treating investigator in real time by using Common Toxicity Criteria for Adverse Events (version 4.0); the reported grade refers to the highest grade of pneumonitis experienced.

Methods

For all patients, the treatment regimen received (anti–PD-1/PD-L1 monotherapy or combination with anti–CTLA-4 mAb) and primary tumor site were recorded. In patients with pneumonitis, the following data were collected retrospectively: demographics, prior oncologic therapy, clinical features of pneumonitis, and pneumonitis treatment. Clinical and radiologic outcomes were classified as completely resolved, improved, or worsened. Patients in whom recurrent pneumonitis developed, either with or without drug rechallenge, were noted. Assessment of final clinical outcomes as well as highest grade of pneumonitis included periods of recurrent pneumonitis, if applicable.

Retrospective radiology review of the serial chest computed tomography (CT) scans of patients with pneumonitis was performed in the MSKCC cohort by two independent radiologists (T.I., J.C.) blinded to patient clinical data followed by a consensus read if there was disagreement. Each radiologist described the phenotypic appearance and severity of pneumonitis by using criteria for interstitial lung diseases.[29-31] When available, chest x-rays at the time of pneumonitis were also reviewed. Lung biopsy specimens obtained at the time of pneumonitis at MSKCC were reviewed by thoracic pathologists (C.L., N.R.) and phenotypically described.

Outcomes Analysis

For all patients treated with anti–PD-1/PD-L1 mAbs, associations between development of pneumonitis and treatment received (anti–PD-1 versus anti–PD-L1 mAb; monotherapy versus combination) and disease type (melanoma versus NSCLC stratified by monotherapy versus combination) were assessed by Fisher's exact test. In patients with pneumonitis, best objective response rates to anti–PD-1/PD-L1 mAbs were calculated with exact 95% CIs. Associations among clinical or radiologic features of pneumonitis, treatment course, and outcomes from pneumonitis treatment were examined. In the radiologic assessment, agreement between individual radiologists was evaluated by Cohen κ-coefficient such that a score of 1 indicated complete agreement and 0 indicated no agreement other than what would be expected by chance. All statistical tests were two sided, and 5% was set as the level of significance. Statistical analyses were performed with R version 3.1.1 software (R Development Core Team), including the irr and Hmisc packages.

RESULTS

Incidence of Pneumonitis

Nine hundred fifteen patients received anti–PD-1/PD-L1 mAbs as monotherapy or in combination with anti–CTLA-4 mAb (Table 1). The overall incidence of pneumonitis was 5% (43 of 915; 95% CI, 3% to 6%) and was similar within institutional cohorts (MSKCC, 27 of 578 [5%]; 95% CI, 3% to 7%; MIA, 16 of 337 [5%]; 95% CI, 3% to 8%). The incidence of pneumonitis was greater in patients who received combination therapy than in those who received monotherapy (19 of 199 [10%] *v* 24 of 716 [3%], $P < .001$) and was not statistically different in those treated with anti–PD-1 compared with anti–PD-L1 mAb (monotherapy, 22 of 564 [4%] *v* two of 152 [1%], $P = .13$; combination, 18 of 178 [10%] *v* one of 21 [5%], $P = .70$).

Patients With Pneumonitis

Pneumonitis occurred in patients with metastatic melanoma (26 of 532 [5%]) and NSCLC (nine of 209 [4%]), hematologic malignancies (four of 35 [11%]), bladder carcinoma (one of 30 [3%]), breast carcinoma (one of 14 [7%]), pancreatic carcinoma (one of 18 [6%]), and head and neck squamous carcinoma (one of 10 [10%]; Table 2). Incidence was similar among patients with melanoma and NSCLC for monotherapy (15 of 417 [3.6%] *v* five of 152 [3.3%], $P = 1.0$) and combination therapy (11 of 115 [9.6%] *v* four of 57 [7.0%], $P = .78$). Pneumonitis developed in both former/current smokers (24 of 43 [56%]) and never smokers (19 of 43 [44%]); the majority had not received prior chest radiation therapy (27 of 43 [63%]). Pneumonitis occurred irrespective of line of therapy in which immunotherapy was received (first line, 32%; second line, 40%; third line or more, 28%). Across all evaluable patients (n = 41), the best objective response to therapy was 61% (25 of 41; 95% CI, 45% to 76%; Table 2). Among patients with melanoma, the response rate to monotherapy was 73% (11 of 15; 95% CI, 45% to 91%) and to combination therapy, 73% (eight of 11; 95% CI, 39% to 94%).

Clinical Features

Median time to onset of pneumonitis was 2.8 months, with a wide range (9 days to 19.2 months; Fig 1). Onset tended to be

Table 1. Patients Who Received Anti–PD-1/PD-L1 Therapy in Two Institutions: Complete Patient Database

	MSKCC, No. (%)	MIA, No. (%)
No. of patients	578	337
Single agent *v* combination		
Monotherapy	441 (76)	275 (82)
Combination	137 (24)	62 (18)
PD-1 *v* PD-L1		
PD-1	405 (70)	337 (100)
PD-L1	173 (30)	0
Primary cancer type		
Non–small-cell lung carcinoma	209	0
Metastatic melanoma	195	337
Renal cell carcinoma	24	0
Hematologic malignancy	35	0
Bladder carcinoma	30	0
Pancreatic carcinoma	18	0
Breast carcinoma	14	0
Head and neck squamous carcinoma	10	0
Sarcoma	7	0
Colorectal carcinoma	6	0
Gastroesophageal carcinoma	12	0
Ovarian carcinoma	7	0
Hepatocellular carcinoma	4	0
Prostate carcinoma	3	0
Anal carcinoma	2	0
Small-cell lung carcinoma	2	0
Pneumonitis		
No	551 (95)	321 (95)
Yes	27 (5)	16 (5)

NOTE. Patients who received either an anti–PD-1 or an anti–PD-L1 monoclonal antibody either as monotherapy or in combination with anti–CTLA-4 monoclonal antibody.

Abbreviations: CTLA-4, cytotoxic T-cell lymphocyte-4; MIA, Melanoma Institute of Australia; MSKCC, Memorial Sloan Kettering Cancer Center; PD-1, programmed death-1; PD-L1, programmed death ligand 1.

earlier in patients who received combination therapy than in those who received monotherapy (median, 2.7 months [range, 9 days to 6.9 months] *v* 4.6 months [range, 21 days to 19.2 months]; $P = 0.02$). Seventeen (40%) patients experienced grade 1 pneumonitis, 14 (33%) experienced grade 2, 10 (23%) experienced grade 3, one (2%) experienced grade 4, and one (2%) experienced grade 5; no difference in distribution of severity between monotherapy and combination therapy was found (Fig 2).

The most common presenting symptoms of pneumonitis were dyspnea (23 of 43 [53%]) and cough (15 of 43 [35%]). Fever (five of 43 [12%]) and chest pain (three or 43 [7%]) were less common. One third of patients were asymptomatic at the onset of pneumonitis (14 of 43 [33%]). Three patients recorded as having grade 1 pneumonitis had symptoms on retrospective chart review, but grading was not changed retrospectively.

More than one half of patients with pneumonitis experienced additional immune-related toxicity (25 of 43 [58%]), which included skin rash (n = 8); colitis (n = 6); hypophysitis, arthritis, and thyroiditis (n = 3 each); and hepatitis, esophagitis, duodenitis, hyperthyroidism, nephritis, myositis, vitiligo, pernicious anemia, and hemolytic anemia (n = 1 each).

Pneumonitis Management

Most patients with grade 1 to 2 pneumonitis were managed as outpatients (25 of 31 [81%]), whereas 19% (six of 31, all grade 2) were hospitalized. All grade 3 and higher cases (n = 12) required hospitalization. In patients with grade 1 pneumonitis, maximum treatment received was drug holding (15 of 17 [88%]) or oral corticosteroids (two of 17 [12%]; Table 3). All patients with grade 2 pneumonitis were treated initially with oral/intravenous corticosteroids (n = 14). All patients with grade 3 or higher pneumonitis received oral/intravenous corticosteroids initially (n = 12), five (42%) of whom required additional immunosuppression (three with infliximab and two with both infliximab plus cyclophosphamide).

Among all patients who received corticosteroids (28 of 43 [65%]), 61% (17 of 28) began with oral treatment, and 39% (11 of 28) began with intravenous treatment. For most patients who began oral corticosteroids, this was the maximum immunosuppression used (14 of 17 [82%]), with a median starting dose of prednisone of 50 mg (range, 20 to 80 mg) and median duration of corticosteroid treatment of 68 days (range, 20 to 154 days).

Clinical Outcomes and Mortality Associated With Pneumonitis

Pneumonitis improved/resolved in 88% (37 of 43) of cases (Table 3), which included all grade 1 (17 of 17), 93% (13 of 14; one patient lost to follow-up and outcome unknown) of grade 2, and 64% (seven of 12) of grade 3 and higher events.

Five (12%) patients clinically worsened during treatment of pneumonitis. All had grade 3 and higher pneumonitis, were treated with additional immunosuppression beyond corticosteroids, and ultimately died. Although one patient's death was solely attributable to pneumonitis, the cause of clinical worsening and death was multifactorial in most cases. Three patients had infections associated with immunosuppression, and one patient had progressive cancer, which seemed to be the most proximal contributors to death.

The patient with grade 5 pneumonitis had initially presented with grade 2 pneumonitis after six doses of anti–PD-1 monotherapy for the treatment of metastatic NSCLC. Oral corticosteroids were initiated, with initial clinical and radiologic improvement. However, pneumonitis recurred during corticosteroid taper and did not improve with high-dose intravenous corticosteroids, infliximab, and cyclophosphamide, and the patient died.

Three patients died as a result of infection in the context of immunosuppression for pneumonitis. One patient received one dose of the anti–PD-1 plus anti–CTLA-4 mAb for melanoma and then was treated for grade 3 pneumonitis with a prolonged course of oral/intravenous corticosteroids over 2 months as well as infliximab. Although the pneumonitis initially seemed to improve, the patient developed pseudomonas pneumonia during corticosteroid treatment and subsequently died. A second patient received two doses of anti–PD-1 mAb for NSCLC and grade 3 pneumonitis developed, which was treated with methylprednisone and infliximab. The patient's condition was complicated by herpes simplex virus 1 sepsis, which resulted in death. A third patient with NSCLC received 38 doses of anti–PD-1 mAb before grade 3 pneumonitis developed that required long-term corticosteroids, infliximab, and cyclophosphamide treatment. The patient died, and on autopsy, fulminant necrotizing fungal pneumonia (mucormycosis) was identified and attributed as the cause of death; no residual cancer was identified.

Table 2. Demographic Characteristics and Treatment and Response Data for Patients With Pneumonitis

Clinical Feature	No. (%)
Patient feature	
Median age, years (range)	67 (36-89)
Smoking status	
Current/former	24 (56)
Never*	19 (44)
Single agent *v* combination therapy	
Monotherapy	24 (56)
Combination	19 (44)
Underlying lung condition	
None	27 (63)
Asthma	4 (9)
Bronchiectasis	1 (2)
COPD	1 (2)
Interstitial lung disease	1 (2)
Pleural effusion	2 (5)
Pulmonary embolus	4 (9)
Pleural effusion and pulmonary embolus	1 (2)
Sleep apnea	2 (5)
Primary disease type	
NSCLC	9 (20)
Malignant melanoma	26 (60)
Hematologic malignancy	4 (9)
Bladder carcinoma	1 (2)
Breast carcinoma	1 (2)
Head and neck squamous cell carcinoma	1 (2)
Pancreatic carcinoma	1 (2)
Line of therapy	
1	14 (33)
2	17 (40)
≥ 3	12 (27)
Prior chest radiation therapy	
No	27 (63)
Yes	16 (37)
Prior immune checkpoint blockade	
No	32 (74)
Yes	11 (26)
Anti–PD-1/PD-L1 treatment data	
Single agent *v* combination therapy	
Combination	19 (44)
Monotherapy	24 (56)
PD-1 *v* PD-L1	
PD-1	40 (93)
PD-L1	3 (7)
Median No. of doses (range)	4 (1-38)
Best objective response†	
CR/PR	25
PD	2
SD	14

Abbreviations: COPD, chronic obstructive pulmonary disease; CR, complete response; NSCLC, non–small-cell lung carcinoma; PD, progressive disease; PD-1, programmed death-1; PD-L1, programmed death ligand 1; PR, partial response; SD, stable disease.

*Never smokers smoked < 100 cigarettes in lifetime.

†Assessed with Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 (n = 27), Immune-Related Response Criteria (n = 10), Cheson criteria (n = 2), International Myeloma Working Group Criteria (n = 1), and modified Severity Weighted Assessment Tool (n = 1); two patients not assessed.

Recurrent Pneumonitis: With or Without T-Cell Checkpoint Rechallenge

Eleven patients experienced recurrent pneumonitis during drug holding/corticosteroid therapy after initial clinical improvement (Appendix Table A1, online only). Of these patients in whom recurrence occurred without drug rechallenge, eight experienced resolution/improvement with further management and three worsened and died despite immunosuppression.

Twelve patients underwent rechallenge with immunotherapy after an initial pneumonitis event (nine grade 1 and three grade 2; nine treated with drug holding only and three treated with corticosteroids for initial event; Appendix Table A2, online only). All rechallenged cases occurred after complete clinical resolution of pneumonitis. Nine patients did not experience a second pneumonitis event on rechallenge (eight grade 1 and one grade 2), whereas three experienced recurrent pneumonitis after rechallenge of whom one patient initially had grade 1 pneumonitis treated with drug hold only, and had recurrent pneumonitis that was again grade 1 and resolved with drug holding. The other two patients had grade 2 pneumonitis initially, were treated with corticosteroids, and had recurrent grade 2 pneumonitis that again resolved with oral corticosteroids.

Radiologic Features

Radiologic and clinical outcomes of pneumonitis were aligned in all patients who experienced clinical improvement/resolution (37 of 37), and four of five patients who experienced clinical worsening of their pneumonitis. Serial chest CT scans were available for all MSKCC patients. Radiologic features of pneumonitis were classified into five subtypes (Fig 3): cryptogenic organizing pneumonia (COP) like (five of 27 [19%]), ground glass opacities (GGO; 10 of 27 [37%]), interstitial (two of 27 [7%]), hypersensitivity (six of 27 [22%]), and pneumonitis not otherwise specified (four of 27 [15%]). Radiologic severity at the time of pneumonitis was classified as mild (15 of 27 [56%]), moderate (six of 27 [22%]), or severe (six of 27 [22%]; Appendix Fig A1, online only). Cohen κ-coefficients were 0.66 for radiologic subtype and 0.88 for radiologic severity grading, respectively. Radiologic subtypes were consistent throughout a patient's clinical course, except in two cases where COP-like pneumonitis evolved into a severe GGO type, and where GGO type developed additional interstitial appearances. COP-like appearance was more common among patients with NSCLC than among patients with other cancers (four of nine *v* one of 18, $P = .03$). In addition, patients with the COP-like subtype were more likely to require treatment of pneumonitis (beyond drug hold) than those with other radiologic subtypes (five of five *v* 11 of 22, $P = .06$). Chest x-rays obtained at the time of pneumonitis (n = 9) demonstrated possible pneumonitis in 67% of cases (six of nine), possible progressive cancer in 11% (one of nine), and no new radiographic abnormality in 22% (two of nine).

Pathologic Features

Eleven of 27 (41%) patients at MSKCC underwent lung biopsy at the time of pneumonitis (eight bronchoscopic, two core biopsies, one wedge resection; Appendix Table A3, online only). Histopathologic findings were cellular interstitial pneumonitis (four of 11; Appendix Fig A2A, online only), organizing pneumonia (three of 11; Appendix Fig A2B), diffuse alveolar damage (one of 11; Appendix Fig A2C), and no abnormalities identified (three of 11). The interstitial inflammatory infiltrate included poorly formed granulomas in

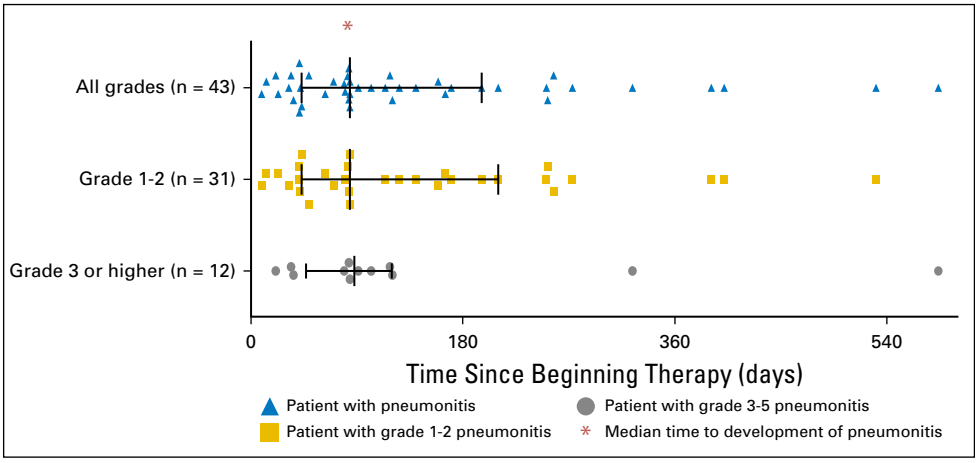


Fig 1. Time from first dose of anti–programmed death-1/programmed death ligand 1 therapy to date of pneumonitis event stratified by grade, with interquartile range and median values shown.

three cases (Appendix Fig A2D) and eosinophils in two cases (Appendix Fig A2E).

Associations Between Clinical Features and Pneumonitis Outcomes

Worsening clinical outcomes with pneumonitis were more frequent in current versus former smokers (five of 23 *v* zero of 19, $P = .053$) and those with underlying lung conditions versus no lung conditions (four of 15 *v* one of 27, $P = .047$; Appendix Table A4, online only). Forced expiratory volume in 1 second and diffusing capacity of lung for carbon monoxide adjusted for hemoglobin were completed in a subset of patients at the time of pneumonitis (16 of 43 and 12 of 43, respectively); no associations between these parameters and clinical outcomes were seen.

DISCUSSION

We describe the first large series of pneumonitis to our knowledge associated with anti–PD-1/PD-L1 mAbs in patients with advanced cancers and comprehensively characterize the clinical, radiologic, and pathologic features, and management of this toxicity. Any-grade pneumonitis developed in approximately 5% of patients treated with anti–PD-1/PD-L1 mAbs, and grade 3 and higher pneumonitis developed in 1%. Pneumonitis was more common in

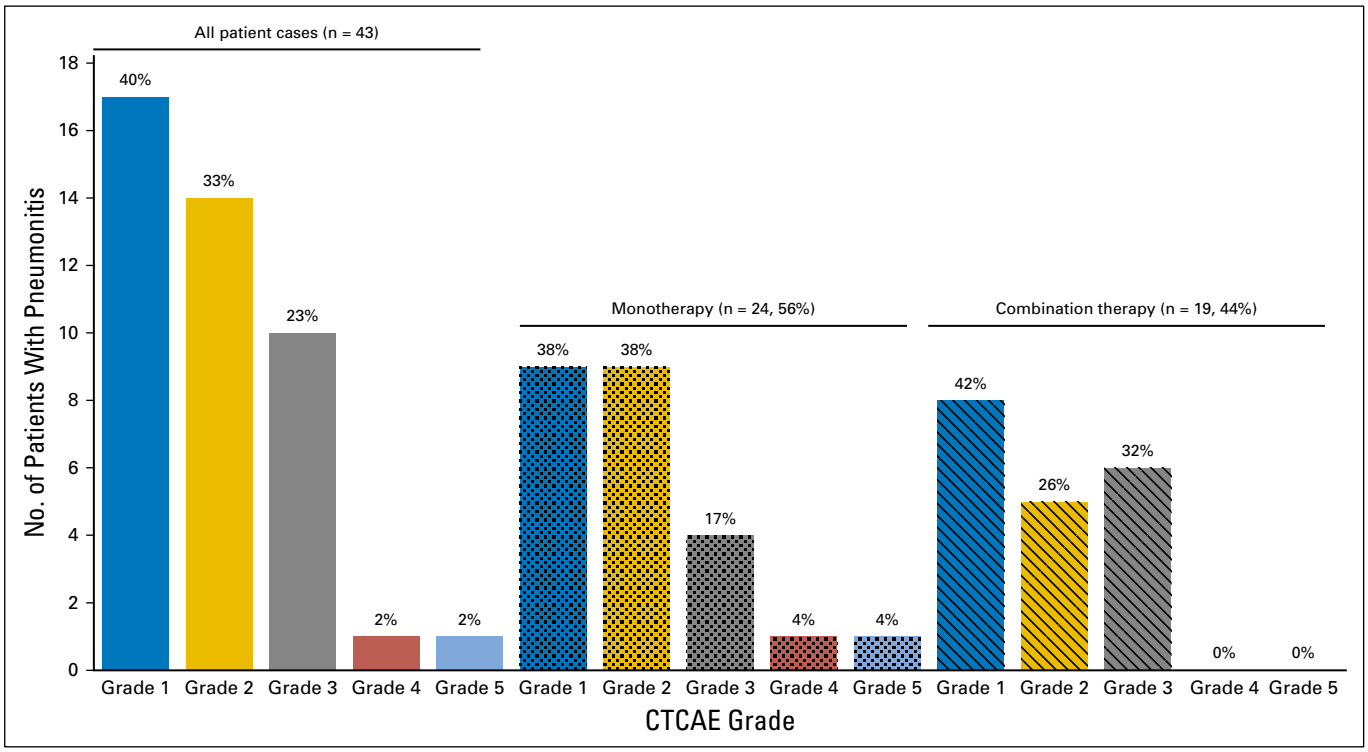


Fig 2. Patients in whom pneumonitis developed stratified by highest Common Terminology Criteria for Adverse Events (version 4.0; CTCAE) grade, including whether patients received anti–programmed death-1/programmed death ligand 1 monotherapy versus in combination with anti–cytotoxic T-cell lymphocyte-4 monoclonal antibody.

Table 3. Pneumonitis Management and Outcomes

Highest CTCAE Grade	Highest Treatment Required for Pneumonitis Management, No. (%)				
	Treatment Hold	Oral Corticosteroids	Intravenous Corticosteroids	Additional Immunosuppression*	Total
1	15 (83)	2 (12)	0 (0)	0 (0)	17
2	0 (0)	10 (71)	4 (29)	0 (0)	14
3	0 (0)	2 (20)	4 (40)	4 (40)	10
4	0 (0)	0 (0)	1 (100)	0 (0)	1
5	0 (0)	0 (0)	0 (0)	1 (100)	1
Total	15	14	9	5	43
	Clinical Outcomes of Pneumonitis Management, No. (%)				
	Completely Resolved	Improved	Worsened	Unknown	Total
1	17 (100)	0 (0)	0 (0)	0 (0)	17
2	10 (71)	3 (21)	0 (0)	1 (8)	14
3	4 (40)	2 (20)	4 (40)	0 (0)	10
4	1 (100)	0 (0)	0 (0)	0 (0)	1
5	0 (0)	0 (0)	1 (100)	0 (0)	1
Total	32	5	5	1	43

Abbreviation: CTCAE, Common Terminology Criteria for Adverse Events (version 4).
*Additional immunosuppression: Three patients received infliximab alone (all grade 3), and two patients received both infliximab and cyclophosphamide (one grade 3 and one grade 5).

patients treated with anti–PD-1/PD-L1 mAbs plus anti–CTLA-4 mAb compared with anti–PD-1/PD-L1 monotherapy. Rates of pneumonitis with anti–PD-1 versus anti–PD-L1 mAb in this series were not statistically different; however, larger data sets that include meta-analyses across tumor types are needed to determine conclusively whether a difference exists. Most cases of pneumonitis were mild, which is reassuring, but with the increasing use of anti–PD-1/PD-L1 mAbs in many disease settings, the absolute burden of pneumonitis undoubtedly will rise.

Most patients with pneumonitis were symptomatic at presentation, with one third of cases identified incidentally by imaging. Because timing of pneumonitis onset varied widely, constant vigilance for the signs and symptoms of this toxicity is required.

The majority of patients with pneumonitis in this study were also responders to immunotherapy, although they also had a variety of diseases, treatments, and systems of assessment. Additionally, there may be confounding between increased time on therapy and the association between both risk of pneumonitis and likelihood of benefit from immunotherapy. Nevertheless, it is intriguing to consider a possible mechanistic association between benefit and toxicity with anti–PD-1/PD-L1 agents.

We also describe the varied clinical, radiologic, and pathologic features of anti–PD-1/PD-L1 pneumonitis. Unlike bleomycin-induced pneumonitis, which is characterized by specific radiologic appearances[23] and changes in diffusing capacity of lung for carbon monoxide,[32] we did not identify any pathognomonic radiographic or pathologic features of anti–PD-1/PD-L1 pneumonitis. To provide a common language for this toxicity, we describe distinct radiologic phenotypes by CT[26,33] and found acceptable concordance between independent radiologic reviewers. Because radiology review was only performed in clinically determined pneumonitis cases, the real-world interobserver concordance of radiologic assessments may be lower. Of note, chest x-ray did not detect a new radiographic abnormality in nearly one quarter of pneumonitis cases, which suggests that it may be an inadequate tool for evaluating suspected pneumonitis.

Clinically, nearly all cases of pneumonitis improved/resolved with drug holding and/or immunosuppression. However, some cases worsened and were fatal. In this series, worsening cases were restricted to current and former smokers and were more common in patients with underlying lung conditions; such patients may require particularly careful management. Among patients in whom pneumonitis improved/resolved, 12 (all with grade 1 to 2) underwent rechallenge with anti–PD-1/PD-L1 mAbs, and recurrent pneumonitis occurred in three (25%). This suggests that in mild cases, one may cautiously resume therapy after pneumonitis has improved/resolved and after careful discussion with the patient.

Although most instances of pneumonitis were not severe, five deaths occurred, and in three cases, infection from prolonged immunosuppression contributed to death. No patient who received immunosuppression beyond corticosteroids (infliximab with or without cyclophosphamide) recovered from pneumonitis. Improvement is needed in the choice, dose, and duration of therapies for pneumonitis with consideration of the role of antimicrobial prophylaxis in the context of prolonged immunosuppression.

Drug-induced pneumonitis remains a diagnosis of exclusion and requires consideration of competing diagnoses, including infection and malignant lung infiltration. Diagnostic bronchoscopy with lung biopsy may play an important role in excluding competing diagnoses. We attempted to exclude cases with alternative etiologies and evidence of pulmonary infection or infiltrative cancer. However, the excluded cases may have represented true pneumonitis or mixed presentation. In addition some cases of pneumonitis may not have been detected radiologically, so the true incidence of pneumonitis may be higher than that described here. This series largely comprised patients with melanoma and NSCLC; a larger series that investigates pneumonitis as a result of anti–PD-1/PD-L1 mAbs in other malignancies are needed. Finally, this series describes the features of pneumonitis, but did not seek to identify risk factors for its development, which remains an open question for future investigation.

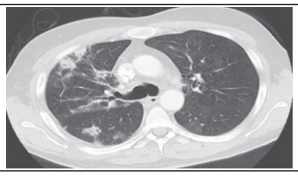
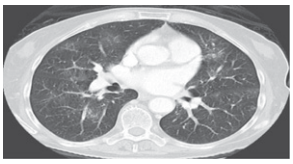
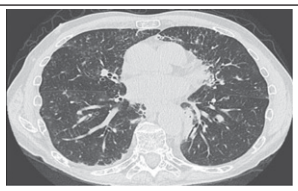
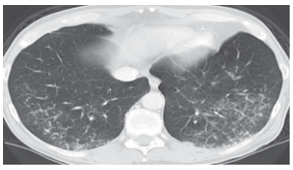
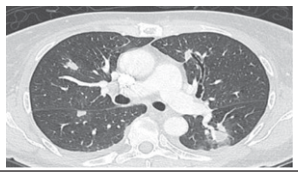
Radiologic Subtypes	Representative Image	Description
Cryptogenic organizing pneumonia-like (n = 5, 19%)		Discrete patchy or confluent consolidation with or without air bronchograms Predominantly peripheral or subpleural distribution
Ground glass opacities (n = 10, 37%)		Discrete focal areas of increased attenuation Preserved bronchovascular markings
Interstitial (n = 6, 22%)		Increased interstitial markings, interlobular septal thickening Peribronchovascular infiltration, subpleural reticulation Honeycomb pattern in severe patient cases
Hypersensitivity (n = 2, 7%)		Centrilobular nodules Bronchiolitis-like appearance Tree-in-bud micronodularity
Pneumonitis not otherwise specified (n = 4, 15%)		Mixture of nodular and other subtypes Not clearly fitting into other subtype classifications

Fig 3. Radiologic features of pneumonitis associated with anti–programmed death-1/programmed death ligand 1 therapy stratified into five distinct phenotypes.

This study fills an important gap in the literature because the only published data on anti–PD-1/PD-L1 pneumonitis are from two small case reports[34,35] and two larger case series reported at ASCO 2016.[36,37] Collectively, these reports affirm the variable timing of onset and potential for recurrent pneumonitis during pneumonitis management. Although these studies cannot make firm recommendations about optimal pneumonitis management, grade 1 pneumonitis seems reasonable to treat with drug holding alone, with close clinical and radiologic follow-up (2 to 4 weeks) for resolution/improvement. If symptoms arise or no radiologic improvement is seen, corticosteroids are appropriate. Grade 2 and higher pneumonitis should be treated with corticosteroids in addition to drug holding, with continued close clinical and radiologic follow-up. Patients in whom worsening pneumonitis develops can be resistant to traditional immunosuppression and may benefit from studies of early additional or new/alternative immunosuppression.

In summary, pneumonitis is an uncommon but potentially serious toxicity that occurs in 5% of patients who receive anti–PD-1/PD-L1 mAbs. Treating physicians should be aware of its diverse clinical, radiologic, and pathologic features and that it may develop at any time during a patient's treatment course. Most cases are mild and managed successfully with favorable outcomes. However, worsening pneumonitis may develop in a subset of patients despite additional immunosuppression, and they may suffer from the immunosuppressive consequences of pneumonitis treatment. Improvements in the treatment and understanding of the biology of pneumonitis are needed to optimize management.

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Appendix

Table A1. Recurrent Pneumonitis Without Rechallenge

Highest CTCAE Grade	No. of Patients With Recurrent Pneumonitis Without Rechallenge (n = 11)
1	0
2	4
3	6
4	0
5	1

	Highest Treatment Required for Re-Emergence of Pneumonitis Without Rechallenge				
	Treatment Hold	Oral Corticosteroids	Intravenous Corticosteroids	Additional Immunosuppression*	Total
1	0	0	0	0	0
2	0	1	3	0	4
3	0	1	3	2	6
4	0	0	0	0	0
5	0	0	0	1	1
Total	0	2	6	3	11

	Clinical Outcomes of Re-Emergence of Pneumonitis Without Rechallenge				
	Completely Resolved	Improved	Worsened	Unknown	Total
1	0	0	0	0	0
2	1	3	0	0	4
3	2	2	2	0	6
4	0	0	0	0	0
5	0	0	1	0	1
Total	3	5	3	0	11

NOTE. Patients in whom recurrent pneumonitis developed without rechallenge with anti–PD-1/PD-L1 therapy.
Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events (version 4.0); PD-1, programmed death-1; PD-L1, programmed death ligand 1.
*Additional immunosuppression: Recurrent pneumonitis developed without rechallenge in three patients who received immunosuppression beyond corticosteroids (one with infliximab alone [highest grade 3] and two with both infliximab and cyclophosphamide [one each highest grade 3 and 5]).

Table A2. Recurrent Pneumonitis With Rechallenge: Treatment and Outcomes

Highest CTCAE Grade	No. of Patients With Recurrent Pneumonitis With Anti–PD-1/PD-L1 Therapy Rechallenge (n = 12)
1	9
2	3
3-5	0

	Highest Treatment Required for Recurrent Pneumonitis With Rechallenge (n = 3)				
	Treatment Hold	Oral Corticosteroids	Intravenous Corticosteroids	Additional Immunosuppression	Total
1	1	0	0	0	1
2	0	2	0	0	2
3-5	0	0	0	0	0
Total	1	2	0	0	3

	Clinical Outcomes of Recurrent Pneumonitis With Rechallenge (n = 3)				
	Completely Resolved	Improved	Worsened	Unknown	Total
1	0	1	0	0	1
2	1	1	0	0	2
3-5	0	0	0	0	0
Total	1	2	0	0	3

NOTE. Patients in whom recurrent pneumonitis developed after being rechallenged with anti–PD-1/PD-L1 therapy after improvement/resolution of the initial pneumonitis event.
Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events (version 4.0); PD-1, programmed death-1; PD-L1, programmed death ligand 1.

Table A3. Pathologic Features of Pneumonitis

Specimen Type	Procedure Type	Timing of Sample	Main Pathologic Finding	Radiologic Subtype	Other Sample
Transbronchial biopsy	Bronchoscopy	Before corticosteroids	Nondiagnostic (mild chronic inflammation)	COP-like	NA
Transbronchial and endobronchial biopsies	Bronchoscopy	After corticosteroids	Organizing pneumonia, CIP	COP-like	Wedge resection: organizing pneumonia and fibrosis
Transbronchial and endobronchial biopsies	Bronchoscopy	Before corticosteroids	CIP, granulomas	NOS	NA
Bronchoscopic biopsy	Bronchoscopy	Before corticosteroids	CIP with focal fibrin (focal acute lung injury)	GGO	NA
Transthoracic core biopsy	CT-guided core biopsy	After corticosteroids	CIP, granulomas	Hypersensitivity	NA
Transbronchial biopsy	Bronchoscopy	After corticosteroids	Nondiagnostic (benign bronchial mucosa)	COP-like	NA
Transbronchial biopsy	Bronchoscopy	Before corticosteroids	Nondiagnostic (benign bronchial mucosa)	COP-like	NA
Transbronchial biopsy	Bronchoscopy	After corticosteroids	Diffuse alveolar damage	GGO	NA
Transthoracic core biopsy and transthoracic fine-needle aspiration	CT-guided core biopsy	Before corticosteroids	Organizing pneumonia, CIP, eosinophils, vessels with recanalized thrombi	NOS	NA
Transbronchial biopsy	Bronchoscopy	Before corticosteroids	CIP, eosinophils	GGO	NA
Wedge resection	Thoracoscopic surgery	Before corticosteroids	Granulomatous inflammation, organizing pneumonia	Interstitial	NA

NOTE. Pathologic features of patients who underwent histopathologic assessment with lung biopsy for anti–PD-1/PD-L1 pneumonitis. Before corticosteroids indicates lung biopsy performed before administration of corticosteroid medications, and After corticosteroids indicates lung biopsy performed after a minimum of 1 day of corticosteroid therapy.

Abbreviations: CIP, cellular interstitial pneumonitis; COP, cryptogenic organizing pneumonia; CT, computed tomography; GGO, ground glass opacity; NA, not applicable; NOS, not otherwise specified; PD-1, programmed death-1; PD-L1, programmed death ligand 1.

Table A4. Association Between Clinicopathologic Features and Treatment Data With Clinical Outcomes of Pneumonitis

Clincopathologic Feature and Treatment Data	Clinical Outcome*		*P*
	Resolved/ Improved, No. (%)	Worsened, No. (%)	
No. of patients	37	5	
No. of doses received			.99
≤ 4	20 (54)	3 (60)	
> 4	17 (46)	2 (40)	
Smoking status			.053
Current/former	18 (49)	5 (100)	
Never	19 (51)	0	
Underlying lung condition			.047
No	26 (70)	1 (20)	
Yes	11 (30)	4 (80)	
Primary disease type			.18
Non–small-cell lung carcinoma	5 (14)	3 (60)	
Melanoma	24 (65)	2 (40)	
Hematologic malignancy	4 (11)	0	
Other	4 (11)	0	
Line of therapy			.99
1	11 (30)	2 (40)	
2	15 (41)	2 (40)	
≥ 3	11 (30)	1 (20)	
Prior chest radiation therapy			.99
No	24 (65)	3 (60)	
Yes	13 (35)	2 (40)	
Low DLCO at pneumonitis diagnosis (n = 12)			.99
No	3 (30)	0	
Yes	7 (70)	2 (100)	
Low FEV_1 at pneumonitis diagnosis (n = 16)			.99
No	7 (54)	1 (33)	
Yes	6 (46)	2 (67)	
Radiologic outcome			< .001
Resolved/improved	37 (100)	1 (20)	
Worsened	0 (0)	4 (80)	
Main pathologic pattern (n = 8)			.68
Cellular interstitial pneumonitis	3 (60)	1 (33)	
Diffuse alveolar damage	0	1 (33)	
Organizing pneumonia	2 (40)	1 (33)	
Starting corticosteroid dose (n = 26, prednisone equivalents)†, mg			.32
< 60	8	0	
60-100	6	2	
> 100	7	3	
Time to commencement of corticosteroids (n = 27), days			.30
0-4	18	3	
≥ 5	4	2	
Length of corticosteroid taper (n = 26)†, days			.19
< 28	2	2	
28-56	8	2	
> 56	11	1	
Use of additional immunosuppression beyond corticosteroids			< .001
Yes	0	5	
No	37	0	

NOTE. Associations between the clinicopathologic features of pneumonitis associated with anti–PD-1/PD-L1 monoclonal antibodies and the clinical outcomes of pneumonitis management by Fisher's exact test.

Abbreviations: DLCO, diffusing capacity of lung for carbon monoxide; FEV_1, forced expiratory volume in 1 second; PD-1, programmed death-1; PD-L1, programmed death ligand 1.

*One patient was lost to follow-up and had an unknown clinical outcome of pneumonitis.

†Fifteen patients were not treated with corticosteroids; in one patient, the starting corticosteroid dose was not known.

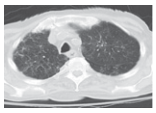
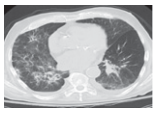
Severity	Mild	Moderate	Severe
CT Image			
Description	Confined to one lobe of the lung or Confined to < 25% of lung parenchyma	Involves more than one lobe of the lung or Involves 25%-50% of lung parenchyma	Involves all lobes of the lung or Involves > 50% of lung parenchyma

Fig A1. Radiologic severity of pneumonitis associated with anti–programmed death-1/programmed death ligand 1 therapy stratified into mild, moderate, and severe. CT, computed tomography.

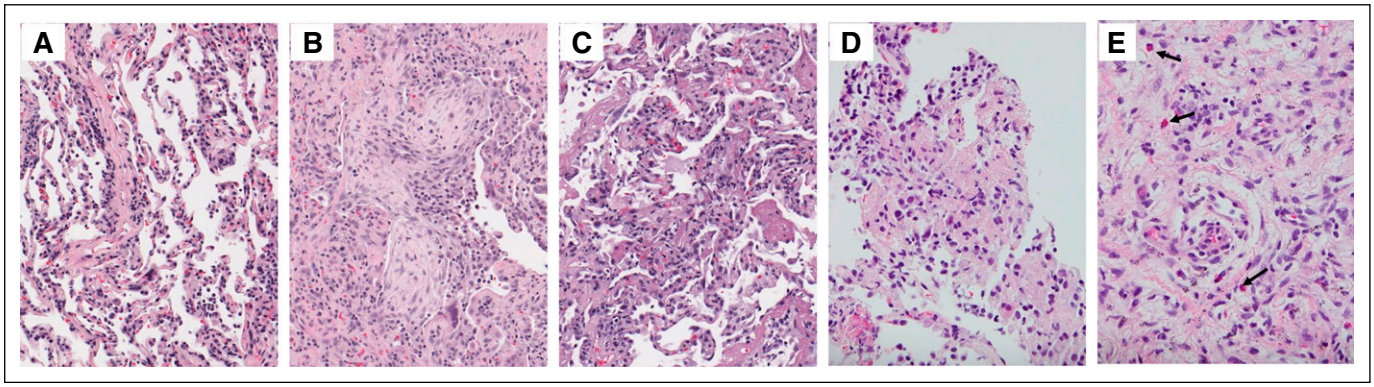


Fig A2. Histologic patterns of pneumonitis associated with anti–programmed death-1/programmed death ligand 1 therapy on lung biopsy (hematoxylin and eosin [HE] stain magnification, ×200) included (A) cellular interstitial pneumonitis (mild case shown), (B) organizing pneumonia, and (C) diffuse alveolar damage. Additional findings (HE stain magnification, ×400) include (D) poorly formed granulomas, and (E) eosinophils (arrows).