Review Article

OPEN

Immune Checkpoint Inhibitor-Related Pulmonary Toxicity: Focus on Nivolumab

Hazim Bukamur, MD, Heather Katz, DO, Mohamed Alsharedi, MD, Akram Alkrekshi, MD, PgDip, MRCP(UK), Yousef R. Shweihat, MD, and Nancy J. Munn, MD

Abstract: The development of checkpoint inhibitors has changed the treatment paradigm for cancer. Checkpoint inhibitors nivolumab, pembrolizumab, and cemiplimab target programmed death-1 (PD-1), whereas durvalumab, avelumab, and atezolizumab target PD-ligand 1. Ipilimumab targets cytotoxic T lymphocyte–associated antigen 4. Used as monotherapy or in combination, these inhibitors have shown remarkable efficacy in melanoma, lung cancer, urothelial cancer, and many other solid tumors, and indications are continuing to evolve. Checkpoint inhibitors are well tolerated when compared with traditional chemotherapy. The major adverse effect profiles are idiosyncratic immune-mediated toxicities resulting from the abnormal activation of autoreactive T cells, which can lead to inflammation in any organ system. The most commonly affected organs are bowel, lung, skin, and endocrine. Pulmonary toxicity is important to recognize, and it can be more challenging to diagnose in lung cancer patients, given the nature of the disease course and treatment. This review article focuses on all of the pulmonary adverse effects of a single PD-1 inhibitor (nivolumab) that have been described in the literature. These complications include dyspnea, pneumonitis, pleural effusion, pulmonary sarcoidosis, pulmonary tuberculosis, acute fibrinous organizing pneumonia, organizing pneumonia, eosinophilic pneumonia, adult respiratory distress syndrome, and lung cavitation. Clinicians must be aware of these toxicities and mindful when prescribing these medications in patients with known lung dysfunction due to chronic lung diseases or lung cancer.

Key Words: checkpoint inhibitors, immunotherapy, nivolumab, PD-1 inhibitors, pembrolizumab

Immune checkpoint inhibitors have become prevalent as first- and second-line treatments for many advanced and metastatic solid tumors (Table).[1] The principal mechanism for an immune checkpoint inhibitor is the removal of tumor-suppressing factor on the tumor cell rendering it exposed to the host immune system. This results in the enhancement of T cell activity, and destruction of the tumor cell follows. It starts with T cell receptors recognizing an antigen on the cell surface of tumor cells or host cells. What follows depends on the balance between co-stimulatory and co-inhibitory signals (immune checkpoints) on the interacting cells. When co-stimulatory signals overwhelm co-inhibitory signals, T cell activation occurs and vice versa. In the programmed death ligand-1(PD-L1)/PD-1 pathway, when PD-1 engages PD-L1, it attenuates T cell receptor and CD28 signaling through the recruitment of tyrosine phosphatases, resulting in T cell exhaustion.[2]

Nivolumab-Related Interstitial Lung Disease

Nivolumab-related interstitial lung disease (ILD) was described in Japanese patients with recurrent or advanced non-small-cell lung cancer (NSCLC) by Kato et al[3] in two phase II studies (ONO-4538-05 and ONO-4538-06). Eight of 111 patients included in these two studies developed ILD, with a median number of 3 nivolumab doses administered before the onset of ILD. Four of these 8 patients had grade 3 or higher toxicity and were considered to have a serious treatment-related adverse event. All of the patients who had ILD were male and had a history of smoking. The median age was 65 years. ILD was rapidly resolving or resolved with steroids in 7 of the 8 patients, and their computed tomography (CT) scan showed organizing pneumonia (OP) or nonspecific interstitial pneumonia (NSIP) without traction bronchiectasis. One patient who was started on docetaxel after severe ILD toxicity due to nivolumab died of respiratory failure, with the CT scan showing traction bronchiectasis.[3]

Nakahama et al[4] reported 119 stage IV NSCLC patients treated with nivolumab between December 2015 and July 2016. Seven

Key Points

- Recognition and management of pulmonary toxicity caused by immunotherapy are critical.
- Continued reports of pulmonary toxicity due to immunotherapy are essential.
- Identifying toxicity quickly and treating patients appropriately are important.

From the Department of Pulmonary and Critical Care Medicine, Texas Tech University Health Sciences Center, Lubbock, the Departments of Pulmonary and Critical Care Medicine, Hematology, and Oncology Medicine, Joan C. Edwards School of Medicine, Marshall University, Huntington, West Virginia, the Huntington Veterans Administration Medical Center, Huntington, West Virginia, and the MetroHealth System Campus, Case Western Reserve University, Cleveland, Ohio.

Correspondence to Dr Hazim Bukamur, Department of Pulmonary and Critical Care Medicine, Texas Tech University Health Sciences Center, Lubbock, 110 Ranee Lane Unit D2, Pikeville, 41501 TX. E-mail: hazimbukamur@yahoo.com.

The authors did not report any financial relationships or conflicts of interest.

Accepted July 15, 2020.

0038-4348/0–2000/113-600

DOI: 10.14423/SMJ.0000000000001166

Table. Current indications of check point inhibitors.

Drug	Target	Indications
Atezolizumab	PD-L1	Urothelial carcinoma; locally advanced or metastatic NSCLC; metastatic Small-cell lung cancer; extensive stage Breast cancer; triple negative locally advanced or metastatic
Avelumab	PD-L1	Merkel cell carcinoma; metastatic Urothelial carcinoma; locally advanced or metastatic
Cemiplimab	PD-1	Cutaneous squamous cell carcinoma; locally advanced or metastatic
Durvalumab	PD-L1	Urothelial carcinoma; locally advanced or metastatic NSCLC; unresectable stage III or metastatic
Ipilimumab	CTLA-4	Melanoma; adjuvant, unresectable, or metastatic Renal cell carcinoma; advanced Colon cancer, metastatic (MSI-H or dMMR) Mesothelioma
Nivolumab	PD-1	Melanoma; adjuvant, unresectable, or metastatic NSCLC; metastatic Small cell lung cancer; metastatic Renal cell carcinoma; advanced, or metastatic Hodgkin lymphoma Head and neck squamous cell carcinoma; recurrent or metastatic Urothelial carcinoma; locally advanced or metastatic Colon cancer, metastatic (MSI-H or dMMR) Hepatocellular carcinoma Glioblastoma Gastric cancer; recurrent locally advanced or metastatic Anal cancer; metastatic Mesothelioma
Pembrolizumab	PD-1	Melanoma; adjuvant, unresectable, or metastatic NSCLC; unresectable stage III or metastatic Hodgkin lymphoma Head and neck squamous cell carcinoma; recurrent or metastatic Urothelial carcinoma; locally advanced or metastatic Colon cancer, metastatic (MSI-H or dMMR) Gastric cancer; recurrent locally advanced or metastatic Cervical cancer recurrent or metastatic Primary mediastinal large B cell lymphoma Hepatocellular carcinoma Renal cell carcinoma; advanced or metastatic Merkel cell carcinoma

CTLA, cytotoxic T lymphocyte–associated protein 4; dMMR, deficient mismatch repair; MSI-H, high levels of microsatellite instability; NSCLC, non–small-cell lung cancer; PD-1, programmed death-1; PD-L1, programmed death-ligand 1.

patients had signs of lung obstruction caused by tumor-mediated compression, which was demonstrated on imaging performed at the initiation of nivolumab treatment. These patients developed ILD, which progressed rapidly in 3 of 7 patients (43%). ILD occurred in only 12 patients (11%) among 112 who did not show signs of lung obstruction. In this study, the authors suggested that obstructive findings are more likely to be important risk factors for ILD than previous radiation therapy.[4] Two phase III trials, CheckMate 017[5] and CheckMate 057,[6] also described nivolumab-related pneumonitis or ILD in 6 of 131 (4.6%)[5] and in 10 of 287 (3.5%) patients, respectively.[6]

Nivolumab-Related Pneumonitis

Pneumonitis is a relatively uncommon but potentially life-threatening adverse event.[7–9] Patients present with a wide range of symptoms, including dyspnea, nonproductive cough, tachypnea, fever, and fatigue. In more severe cases they may present with progressive dyspnea with severe hypoxemia and respiratory failure.[10,11]

Pneumonitis is graded based on the severity of its associated clinical symptoms and radiographic alterations. Grade 1 pneumonitis presents without respiratory symptoms and has radiographic alterations. Grade 2 pneumonitis has both low-intensity clinical symptoms and radiographic alterations, and grades 3 to 4 pneumonitis cause severe clinical symptoms, such as shortness of breath, hypoxia, and cough.[12]

Other conditions that may resemble the presentation of nivolumab-related pneumonitis include but are not restricted to pulmonary edema, alveolar hemorrhage, immune-related tumor inflammation and tumor progression.[10,11] If pneumonitis is suspected, then workup should include at least a chest x-ray (CXR), chest CT, and bronchoscopy with bronchoalveolar lavage (BAL) and fluid should be sent for culture.[11] Radiographic

findings of nivolumab-related pneumonitis range from isolated radiographic abnormalities to progressive, diffuse infiltrates on CXR and/or chest CT. CXR may show nonspecific lung infiltrate or blunting of the costophrenic angle, indicating a pleural effusion. CT imaging is the imaging modality of choice for diagnosing pneumonitis,[13] which can show a spectrum of findings that can include but are not limited to an isolated lung consolidation with air bronchograms, diffuse consolidation, ground-glass opacities (GGOs), pleural effusions, patchy shadows, reticular opacities, traction bronchiectasis, centrilobular nodularity, interlobular septal thickening and intralobular lines, honeycombing, and nonspecific interstitial pneumonia pattern. In severe cases CT imaging may show a pattern suggestive of diffuse alveolar damage.[4,10,11,14,15]

The precise role of bronchoscopy and BAL in the management of PD-1 pneumonitis is unclear, but BAL may help identify an underlying pulmonary infection.[13,16] It is important to exclude infectious causes before committing patients to high dose or a long course of steroids.[11] The identification of an inflammatory infiltrate (lymphocytes and eosinophils) in the lung in the absence of an obvious etiology can be helpful in supporting the suspicion of drug-related pneumonitis.[17] There should be a high suspicion for nivolumab-related pneumonitis, especially if there is a lack of improvement with antibiotics and all of the cultures are negative, including sputum, BAL, and pleural fluid cultures.

The exact mechanism of pneumonitis related by PD-1 blockade is unclear.[7] It has been suggested that the T lymphocytes could regulate dendritic cell and macrophage function during acute infection.[4,7,10] Furthermore, PD-1 could induce negative feedback to attenuate innate immunoinflammatory responses and tissue damage elicited by Toll-like receptors and cytokine signaling.[7] As such, nivolumab may cause excessive activation of immune cells by blocking the PD-1–PD-L1 pathway, which negatively regulates the immune response during infections. In lung infections a plethora of lung tissue–derived antigens may be recognized by activated immune cells.[4,7]

The incidence of all grades of immune-related pneumonitis induced by nivolumab was 4.6 (6.2%) in NSCLC patients.[4] Death related to nivolumab toxicity was more prevalent among those with NSCLC than among those with other cancer types.[4,9,15,18] It is hypothesized that NSCLC patients are more susceptible to developing pulmonary adverse effects from nivolumab because of their exposure to smoking and underlying lung conditions, including chronic obstructive pulmonary disease and pulmonary fibrosis.[9] Nivolumab-related pneumonitis commonly occurs several months after nivolumab therapy[3,4,8,14,19]; however, in some cases the onset of nivolumab-related pneumonitis can be immediate.[4]

A previous meta-analysis revealed that the incidence of pneumonitis associated with the monotherapy of PD-1 inhibitors, nivolumab, or pembrolizumab, was 2.7% for all-grade and 0.8% for grades ≥3.[20] Furthermore, this report showed that pneumonitis related to nivolumab monotherapy occurred in 4.1% (1.4%–8.5%) of patients with NSCLC with all grades and 1.7% (0%–3.4%) with grades ≥3 toxicity, whereas pneumonitis occurred in 1.5% (0%–1.9%) of patients with malignant melanoma (MM) at all grades and 0.1% (0%–0.3%) with grades ≥3 toxicity.[9] Another study reported that the incidence of pneumonitis associated with nivolumab monotherapy was 2.9% and 11.8% for combination therapy with nivolumab and other immune checkpoint inhibitors.[14]

Rizvi et al[21] described a phase II single-arm trial that involved patients who had received ≥2 previous treatments for squamous NSCLC and were subsequently started on intravenous nivolumab (3 mg/kg) every 2 weeks until progression or unacceptable toxic effects. They enrolled and treated 117 patients. Six patients had treatment-related pneumonitis (none grade 4 or 5); 1 additional grade 3 pneumonitis was reported between 30 and 100 days after the last dose of nivolumab. All of the patients with pneumonitis were treated with corticosteroids, with a median time to resolution of 3.4 weeks (range 1.6–13.4). Two deaths were attributed to nivolumab by the investigator. One patient died of hypoxic pneumonia 28 days after the last dose of nivolumab. That patient had rapid tumor progression and bronchial obstruction with possible associated opportunistic infection. Although this condition was distinct from pneumonitis, the investigator reported the adverse event as possibly related to nivolumab because an inflammatory component could not be ruled out and no bronchoscopy or autopsy was performed.[20]

Gettinger et al reported results from 129 patients with heavily pretreated NSCLC who received nivolumab 1, 3, or 10 mg/kg intravenously once every 2 weeks in 8-week cycles for up to 96 weeks. Although nivolumab therapy was generally well tolerated, 14% of patients experienced grade 3 to 4 treatment-related adverse events. Four patients (3%) had treatment-related grade 3 pneumonitis, and 1 had grade 5 pneumonitis. In this study, there were 3 treatment-related deaths associated with pneumonitis (2 with unresolved grade 4 pneumonitis, and 1 with grade 5 pneumonitis). Two of the deaths occurred early in the trial, and the third occurred after the date of the last safety analysis. The authors found no clear relations between the occurrence of pneumonitis and dose level or treatment duration.[20] Toxicities did not seem to be cumulative. The importance of early identification and management of pneumonitis is elucidated in this study as two of the fatal cases occurred early in the trial, before pneumonitis was recognized as a toxicity of treatment. Although identifying drug-induced pneumonitis can be challenging and difficult, a delay in diagnosis may lead to prolonged clinical course and worse prognosis.[20]

Topalian et al[22] enrolled a total of 296 patients in a phase I study to assess the safety, antitumor activity, and pharmacokinetics of nivolumab. In this study, drug-related pneumonitis occurred in 9 of the 296 patients (3%), with grade 3 or 4 pneumonitis developing in only 3 patients (1%). There were 3 drug-related deaths (1%) from pneumonitis (2 in patients with NSCLC and 1 in a patient with colorectal cancer). The authors found no clear relation between the occurrence of pneumonitis and tumor type, dose level, or the number of doses received. Six patients with

early-grade pneumonitis were treated by the discontinuation of nivolumab, glucocorticoid administration, or both. In other patients with grade 3 or 4 pneumonitis, infliximab, mycophenolate, or both were used for additional immunosuppression.[22] Further studies regarding the prevalence, risk factors, clinical features, chest CT findings, the utility and yield of BAL,[13] and treatment outcomes for nivolumab-induced pneumonitis are warranted.[10]

Nivolumab-Related OP

OP is characterized by radiological features of bilateral alveolar consolidations, GGOs, and patchy infiltrates with air bronchograms. The lack of any infectious pathogens in BAL samples and a $CD8^+$ lymphocytic alveolitis is suggestive of a lung immunoreactive process. There is rapid resolution with corticosteroids, but relapse after treatment interruption. Such recurrence could be the consequence of the long mean elimination half-life of Nivolumab, approximately 27 days, and thus needing >4 months for complete tissue clearance.[23] All of these findings are well-known characteristics of bronchiolitis with OP and generally considered as a good surrogate marker supporting the immune origin, avoiding open-lung biopsy.[23] Three cases of OP related to nivolumab[23–25] have been described in the literature.

Sano et al[24] described a case of a 70-year-old woman with vaginal melanoma with multiple metastases in her brain, lung, liver, pancreas, pelvis, and bone. She was treated with nivolumab 2 mg/kg every 3 weeks. Although she was asymptomatic, crackles were auscultated on physical examination and CT scan findings of GGOs and consolidation with air bronchograms were noted.[24] The patient had a bronchoscopy with BAL and lung biopsy. She was started on steroids, with a prolonged taper after stopping nivolumab.[24]

Nakashima et al[25] reported a 70-year-old woman never smoker who had MM with pulmonary metastasis. She was taking nivolumab 2 mg/kg every 3 weeks and presented with fever, anorexia, exertional dyspnea and productive cough. Negative BAL and lung biopsy studies were obtained. She was started on steroids, with relief of her symptoms.

A 70-year-old man with sarcomatoid carcinoma and metastasis to the small intestine and spleen was noted by Gounant et al.[23] He was treated with nivolumab 3 mg/kg every 2 weeks. He presented with fever, exertional dyspnea, and productive cough. The physical examination revealed crackles. He was started on steroids, with improvement of his symptoms.

Nivolumab-Related Fibrinous OP (FOP)

Acute FOP (AFOP) is an extremely rare occurrence with nivolumab treatment and has only been discussed once in the literature by Ishiwata et al.[26] Although chest CT scan findings of GGOs with interlobular thickening can be seen in nivolumab-related pneumonitis, pulmonary edema, lymphangitic carcinomatosis, and pulmonary lymphoma, bronchoscopy with BAL and transbronchial biopsy can help to differentiate among these causes. BAL may show the presence of lymphocytosis, neutrophilia, and eosinophilia, suggesting either AFOP or acute respiratory distress syndrome. Lung biopsy, either transbronchial or open, can demonstrate the absence of marked neutrophilia in lung tissue which rules out a diagnosis of acute respiratory distress syndrome.[26]

Ishiwata et al[26] reported a 68-year-old man treated with nivolumab because of unresectable sinonasal melanoma. He achieved a complete response soon after the initiation of the therapy and was maintained for 30 weeks until he experienced dyspnea of subacute onset. CT images revealed patchy infiltrates and GGOs with interlobular septal thickening. The BAL fluid contained elevated percentages of lymphocytes (53%) and neutrophils (30%); BAL culture was negative. A transbronchial lung biopsy revealed intraalveolar fibrin balls without hyaline membranes, which was considered to be consistent with the pattern of AFOP.[26] The patient had negative serological findings, including autoantibodies, cytomegalovirus antibody, and β-glucan. The patient was started on high-dose corticosteroid administration (intravenous methylprednisolone at a dose of 1000 mg for 3 days, followed by oral prednisolone at a dose of 1 mg/kg). The treatment was effective for ameliorating dyspnea and for improving the findings on imaging.[26]

Nivolumab-Related Pulmonary Sarcoidosis

Sarcoidosis is a systemic inflammatory disease marked by noncaseating sterile granulomatous inflammation developing in multiple organ systems.[27,28] The cause remains uncertain, but it presumably results from aberrant immune responses to unknown antigens.[27,28] Thoracic disease, when it includes lymphadenopathy, is the most common site, but sarcoidosis can involve other organs. The diagnosis of sarcoidosis is established by a combination of clinical and histological findings.[27,28] Pulmonary sarcoidosis and sarcoid-like reaction have been observed in 5% to 7% of nivolumab-treated patients.[29] Concomitant diffuse lymphadenopathy and other extrathoracic manifestations of sarcoidosis, including cutaneous noncaseating granulomas, also have been described.[29]

Montaudié et al[27] reported a case of pulmonary sarcoid-like granulomatosis in a 56-year-old man with stage IIIC melanoma treated with nivolumab in combination with stereotactic radiotherapy after disease progression on a previous regimen. He presented with dry cough and progressive shortness of breath after the second cycle of nivolumab. He also had facial edema and bilateral swelling of the parotid glands. CT scan showed bilateral widespread GGOs, micronodules concentrated around major fissures, bronchovascular sheaths and lower interlobular septae, and thickened tracheobronchial mucosa. A positron emission tomography CT scan showed heterogenous uptake in the parotid glands and bilateral cervical lymph nodes. A bronchoscopy was performed, showing diffuse nodular mucosa bilaterally. The BAL differential cell count revealed 32% lymphocytes, with an increased CD4 to CD8 ratio of 4.2. Malignancy and cancer were excluded. Bronchial biopsies showed noncaseating epithelioid granulomas. The other workup was negative (electrocardiogram, angiotensin-converting enzyme, calcemia, and calciuria).

The diagnosis of sarcoid-like reaction induced by nivolumab was established, and the patient was treated with oral prednisone, which resulted in progressive symptom resolution. Repeat CT scan after 4 weeks of prednisone showed the disappearance of lung nodules and infiltrate.[27]

Nivolumab-Related Recurrent Pleural Effusion

Pleural effusions are a rare adverse event with immune checkpoint inhibitors, especially nivolumab. In the CheckMate 057 trial, a phase III trial comparing nivolumab versus docetaxel in advanced squamous NSCLC, 6% of the patients in the nivolumab arm and 3% in the docetaxel arm had a pleural effusion. No pleural effusions were reported as treatment-related serious adverse events.[6]

Nivolumab-Related Pulmonary Infection Reactivation (Tuberculosis/Aspergillosis)

Case reports have described the reactivation of latent infection after starting immune checkpoint inhibitors which may indicate an immunomodulatory effect that enhances the immune reaction to infectious disease, simulating the immune reconstitution inflammatory syndrome.[30,31] In addition, immunosuppressive therapy for immune-related adverse events can be a risk factor for infectious disease.[30]

Two cases of pulmonary infection reactivation after starting nivolumab have been reported thus far. One case was an acute exacerbation of progressive pulmonary aspergillosis in a patient with stage IIB adenocarcinoma treated by nivolumab as a third-line therapy. A CT scan of this patient revealed a remarkable remission of the tumor but acute progression of a fungus ball in the cavity with infiltration, suggesting the exacerbation of progressive pulmonary aspergillosis. He was treated with voriconazole with stabilization of the cavitary lesion, and the patient became asymptomatic and was able to continue receiving nivolumab afterward.[30]

The other case was a reactivation of pulmonary tuberculosis in a patient with stage IV lung cancer started on nivolumab as a third-line therapy after documented disease progression on CT scan despite first- and second-line therapies. After eight cycles, CT scan showed a reduction in tumor size; however, new centrilobular nodules with a tree-in-bud appearance were detected in the bilateral upper to lower lobes. Repeat interferon gamma release assay showed positive conversion. Bronchoscopy with BAL and transbronchial biopsy was performed. The BAL fluid culture was positive for acid-fast bacilli confirmed as *Mycobacterium tuberculosis* by polymerase chain reaction. A transbronchial lung biopsy showed no caseous necrosis, but it did show diffuse lymphocytic infiltration. Nivolumab was withheld and antituberculosis treatment was started.[30]

In both cases infection reactivation happened during nivolumab treatment and not during the chemotherapy period, which may indicate not an immunosuppression mechanism, but rather a hyperreaction to microorganisms, through the activation of T cell immunity.[30]

Nivolumab-Related Lung Cavitation

There have been two case reports of lung cavitation after the institution of nivolumab treatment in squamous cell carcinoma (SCC) as a second-line therapy[32] and in a patient with SCC as a fourth-line therapy.[33] The first patient was a 72-year-old former smoker with metastatic SCC treated with carboplatin and gemcitabine and subsequently started on nivolumab after disease progression. After 12 cycles of nivolumab, his CT scan showed radiological evidence of multiple lung metastases, with permanent damage of the lung parenchyma, loss of tissue, and development of bulla-like lesions.[32] The second case was a 62-year-old man, current smoker, with stage IV SCC who was started on fourth-line therapy with nivolumab after a CT scan showed progression of the disease. The scan showed that the patient developed GGOs after the second dose of nivolumab. Nivolumab was stopped with initiation of prednisolone, and the pneumonitis resolved after 2 weeks. On follow-up CT scan, a cavitary lesion appeared in the mass. Subsequently, the mass shadow gradually reduced in size, despite not receiving other additional treatments for his lung cancer.[33]

Nivolumab-Related Respiratory Discomfort Secondary to Myositis

Yoshioka et al[34] reported a case of MM of the left heel treated with nivolumab after failing chemotherapy. The patient was admitted 7 weeks after initiation of nivolumab for shortness of breath. The workup revealed myositis, a chest x-ray showed an elevated diaphragm with clear lung fields, and the vital capacity percentage was decreased compared with a previous one. Nivolumab was stopped, as was atorvastatin. The patient's symptoms resolved, with improvement in laboratory values within 7 weeks. The authors entertained the possibility that myositis could have been caused by atorvastatin, but they did not believe that the myositis was caused by atorvastatin alone because the patient had been taking that medication for 10 years without problems. In patients with respiratory symptoms on nivolumab, physicians should consider not only interstitial pneumonitis but also other causes such as myopathies with workup including serum creatine kinase level to rule out myositis.

Nivolumab-Induced Asthma

Maeno et al[35] reported a case of a 50-year-old man with stage IV adenocarcinoma. He was started on nivolumab (3 mg/kg every 2 weeks) as a third-line treatment. Nine months later, he presented with cough and wheezing, which worsened at night and in the early morning. The patient had no personal or family history of asthma or atopy. A CT scan of the chest showed no new changes. On laboratory testing, there was peripheral blood eosinophilia (11%) and elevation of serum levels of total immunoglobulin E (863 IU/mL) relative to values obtained 9 months earlier (238 IU/mL). Spirometry showed reversible airflow obstruction. The fraction of exhaled nitric oxide was markedly elevated at 113.0 ppb, indicative of eosinophilic airway inflammation. A clinical diagnosis of asthma was established,

and the patient was started on oral prednisolone and daily inhalation of fluticasone propionate/formoterol fumarate dehydrate, with rapid improvement in his symptoms the next day. The authors advise physicians not to misconceive symptoms of asthma as those related to lung cancer because it can also be an adverse effect of the treatment.

Conclusions

The recognition and management of pulmonary toxicity caused by immunotherapy is critical because cancer treatment paradigms have shifted and immunotherapy is more frequently used. Continued reports of pulmonary toxicity due to immunotherapy is essential to provide a comprehensive understanding of possible complications that providers need to be able to recognize and treat. Identifying toxicity quickly and treating patients appropriately will prevent morbidity and mortality in cancer patients treated with checkpoint inhibitors.

Acknowledgment

The authors acknowledge and thank the Department of Pulmonary Medicine at Marshall University for their help.

References

1. Rotte A, Jin JY, Lemaire V. Mechanistic overview of immune checkpoints to support the rational design of their combinations in cancer immunotherapy. *Ann Oncol* 2017;29:71–83.
2. Wei SC, Levine JH, Cogdill AP, et al. Distinct cellular mechanisms underlie anti-CTLA-4 and anti-PD-1 checkpoint blockade. *Cell* 2017;170:1120–1133.
3. Kato T, Masuda N, Nakanishi Y, et al. Nivolumab-induced interstitial lung disease analysis of two phase II studies patients with recurrent or advanced non-small-cell lung cancer. *Lung Cancer* 2017;104:111–118.
4. Nakahama K, Tamiya A, Taniguchi Y, et al. Severe acute interstitial lung disease after nivolumab in three non-small cell lung cancer patients with imaging findings of airway obstruction adjacent to lung tumors. *J Infect Chemother* 2017;23:826–829.
5. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non–small-cell lung cancer. *N Engl J Med* 2015;373:123–135.
6. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non–small-cell lung cancer. *N Engl J Med* 2015;373:1627–1639.
7. Kyi C, Postow MA. Checkpoint blocking antibodies in cancer immunotherapy. *FEBS Lett* 2014;588:368–376.
8. Koyama N, Iwase O, Nakashima E, et al. High incidence and early onset of nivolumab-induced pneumonitis: four case reports and literature review. *BMC Pulm Med* 2018;18:23.
9. Nishino M, Giobbie-Hurder A, Hatabu H, et al. Incidence of programmed cell death 1 inhibitor–related pneumonitis in patients with advanced cancer: a systematic review and meta-analysis. *JAMA Oncol* 2016;2:1607–1616.
10. Watanabe S, Kimura H, Takato H, et al. Severe pneumonitis after nivolumab treatment in a patient with melanoma. *Allergol Int* 2016;65:487–489.
11. Chow LQ. Exploring novel immune-related toxicities and endpoints with immune-checkpoint inhibitors in non-small cell lung cancer. *Am Soc Clin Oncol Educ Book* 2013; doi: 10.1200/EdBook_AM.2013.33.e280.
12. Cui P-F, Ma J-X, Wang F-X, et al. Pneumonitis and pneumonitis-related death in cancer patients treated with programmed cell death-1 inhibitors: a systematic review and meta-analysis. *Ther Clin Risk Manag* 2017;13:1259.
13. Suresh K, Naidoo J, Lin CT, et al. Immune checkpoint immunotherapy for non-small cell lung cancer: benefits and pulmonary toxicities. *Chest* 2018;154:1416–1423.
14. Nishino M, Ramaiya NH, Awad MM, et al. PD-1 inhibitor-related pneumonitis in advanced cancer patients: radiographic patterns and clinical course. *Clin Cancer Res* 2016;22:6051–6060.
15. Delaunay M, Cadranel J, Lusque A, et al. Immune-checkpoint inhibitors associated with interstitial lung disease in cancer patients. *Eur Respir J* 2017;50:1700050.
16. Nishino M, Chambers ES, Chong CR, et al. Anti–PD-1 inhibitor–related pneumonitis in non–small cell lung cancer. *Cancer Immunol Res* 2016;4:289–293.
17. Sehgal S, Velcheti V, Mukhopadhyay S, et al. Focal lung infiltrate complicating PD-1 inhibitor use: A new pattern of drug-associated lung toxicity? *Respir Med Case Rep* 2016;19:118–120.
18. Wu J, Hong D, Zhang X, et al. PD-1 inhibitors increase the incidence and risk of pneumonitis in cancer patients in a dose-independent manner: a meta-analysis. *Sci Rep* 2017;7:44173.
19. Freeman-Keller M, Kim Y, Cronin H, et al. Nivolumab in resected and unresectable metastatic melanoma: characteristics of immune-related adverse events and association with outcomes. *Clin Cancer Res* 2016;22:886–894.
20. Gettinger SN, Horn L, Gandhi L, et al. Overall survival and long-term safety of nivolumab (anti–programmed death 1 antibody, BMS-936558, ONO-4538) in patients with previously treated advanced non–small-cell lung cancer. *J Clin Oncol* 2015;33:2004.
21. Rizvi NA, Mazières J, Planchard D, et al. Activity and safety of nivolumab, an anti-PD-1 immune checkpoint inhibitor, for patients with advanced, refractory squamous non-small-cell lung cancer (CheckMate 063): a phase 2, single-arm trial. *Lancet Oncol* 2015;16:257–265.
22. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti–PD-1 antibody in cancer. *N Engl J Med* 2012;366:2443–2454.
23. Gounant V, Brosseau S, Naltet C, et al. Nivolumab-induced organizing pneumonitis in a patient with lung sarcomatoid carcinoma. *Lung Cancer* 2016;99:162–165.
24. Sano T, Uhara H, Mikoshiba Y, et al. Nivolumab-induced organizing pneumonia in a melanoma patient. *Jpn J Clin Oncol* 2016;46:270–272.
25. Nakashima K, Naito T, Omori S, et al. Organizing pneumonia induced by nivolumab in a patient with metastatic melanoma. *J Thorac Oncol* 2016;11:432–433.
26. Ishiwata T, Ebata T, Iwasawa S, et al. Nivolumab-induced acute fibrinous and organizing pneumonia (AFOP). *Intern Med* 2017;56:2311–2315.
27. Montaudié H, Pradelli J, Passeron T, et al. Pulmonary sarcoid-like granulomatosis induced by nivolumab. *Br J Dermatol* 2017;176:1060–1063.
28. Patterson KC, Chen ES. The pathogenesis of pulmonary sarcoidosis and implications for treatment. *Chest* 2018;153:1432–1442.
29. Shannon VR. Pneumotoxicity associated with immune checkpoint inhibitor therapies. *Curr Opin Pulm Med* 2017;23:305–316.
30. Uchida N, Fujita K, Nakatani K, et al. Acute progression of aspergillosis in a patient with lung cancer receiving nivolumab. *Respirol Case Rep* 2018;6: e00289.
31. Fujita K, Terashima T, Mio T. Anti-PD1 antibody treatment and the development of acute pulmonary tuberculosis. *J Thorac Oncol* 2016;11:2238–2240.
32. Rampinelli C, Spitaleri G, Passaro A, et al. Lung tissue injury as an atypical response to nivolumab in non–small cell lung cancer. *Am J Respir Crit Care Med* 2017;196:1349–1350.
33. Kimura H, Sone T, Murata A, et al. Long-lasting shrinkage in tumor mass after discontinuation of nivolumab treatment. *Lung Cancer* 2017;108:7–8.
34. Yoshioka M, Kambe N, Yamamoto Y, et al. Case of respiratory discomfort due to myositis after administration of nivolumab. *J Dermatol* 2015;42:1008–1009.
35. Maeno K, Fukuda S, Oguri T, et al. Nivolumab-induced asthma in a patient with non-small-cell lung cancer. *Ann Oncol* 2017;28:2891.