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A Case of a Patient with Idiopathic Pulmonary Fibrosis with Lung Squamous Cell Carcinoma Treated with Nivolumab

To the Editor:

Immunotherapies harnessing preexisting anticancer immune responses by targeting the immune checkpoint pathways, particularly the programmed death 1 (PD-1) pathway, have shown remarkable clinical activity across several tumor types, including NSCLC. Several drugs targeting the PD-1 pathway are currently in clinical development, and two of these agents (nivolumab and pembrolizumab) are U.S. Food and Drug Agency–approved for use in advanced-stage NSCLC. In clinical trials with the anti–PD-1 agents, immune-mediated pneumonitis was seen in nearly 10% of patients.[1] Patients with interstitial lung disease (ILD) were not eligible to participate in trials with these agents out of concern for adverse outcomes. There are no reports in the literature on the safety of anti–PD-1 immunotherapy in patients with preexisting ILD.

We report the case of a patient with NSCLC with concomitant idiopathic pulmonary fibrosis (IPF) treated with nivolumab. A 67-year-old man with a diagnosis of IPF for nearly a decade was first found to have a left lower lobe nodule in 2012; it was followed up with serial imaging with computed tomography and found to be progressively increasing in size ($22 \times 18 \times 22$ mm) and fludeoxyglucose F 18–avid (maximum standardized uptake value 13.7). Some fludeoxyglucose F 18–avid hilar and mediastinal lymphadenopathy was found on a positron emission tomography/computed tomography in 2014. Bronchoscopy with endobronchial ultrasonography revealed no hilar or mediastinal lymph node involvement. Transbronchial biopsy confirmed a moderately differentiated squamous cell carcinoma of the left lower lobe (T1aN0M0, stage 1A). In consideration of the patient's poor pulmonary functional status, he underwent a video-assisted nodulectomy in early 2015, with negative margins and an uneventful postoperative course. Pathologic examination revealed a 1.5-cm moderately differentiated squamous cell carcinoma with clear margins. The background lung showed emphysema and severe pulmonary fibrosis with a patchwork pattern and fibroblast foci, as well as foci of parenchymal scarring and microscopic honeycomb change consistent with a diagnosis of combined IPF and emphysema. No adjuvant chemotherapy was recommended, and surveillance was conducted with imaging. Follow-up scans at 4 months showed development of a new peripheral nodule measuring 1.3 cm in the lingula, additional peribronchial nodular opacities measuring up to 5 mm in the left upper lobe, and left hilar lymphadenopathy. Bronchoscopy with a transbronchial biopsy confirmed squamous cell carcinoma with necrosis in the left hilar lymph node. Because of the patient's underlying severe ILD, concurrent chemoradiation was not considered safe and systemic therapy with carboplatin and docetaxel was initiated. He had poor tolerance of chemotherapy, with severe fatigue and skin reactions to docetaxel, and after two cycles of chemotherapy he had mild progression of disease. The left lower lobe tumor was tested for programmed death ligand 1 (PD-L1) (E1L3N). The patient had 1% tumor PD-L1 positivity; in addition, he had PD-L1 positivity in the tumor-associated macrophages.

He began receiving nivolumab in September 2015. Before initiation of nivolumab, he had pulmonary function tests that showed a diffusion capacity of lung for carbon monoxide of 27% and he was given 2 to 3 liters oxygen by nasal cannula. He tolerated nivolumab without any significant toxicities or significant adverse events. He had mild shrinkage of his tumor, stable response in his tumor per the Response Evaluations Criteria in Solid Tumors (Fig. 1*A*), improved exercise tolerance, and stable to slightly improved oxygen requirements. Interestingly, his positron emission tomography scan after 5 months of treatment with nivolumab showed a modest improvement compared with his pretreatment baseline scan (Fig. 1*B*). He had tolerated nivolumab well with good disease control for 8 months, at which time he presented to the hospital with progressive shortness of breath, cough, and fever. He was found to have new bilateral infiltrates. He had a bronchoscopy for further evaluation and work-up revealed infection with coronavirus infection. His oxygen requirements had increased to 6 liters of oxygen by nasal cannula. He had prolonged hospitalization for 2 weeks, with respiratory and supportive care with improvement of symptoms. However, in consideration of his severe deconditioning and decline in performance status, nivolumab was discontinued; he was transitioned to hospice and died 4 months later.

IPF is a progressive and excessive remodeling of the pulmonary alveolar hyperplasia associated with deposition of extracellular matrix. IPF results from an inflammatory process characterized by chronic inflammation and

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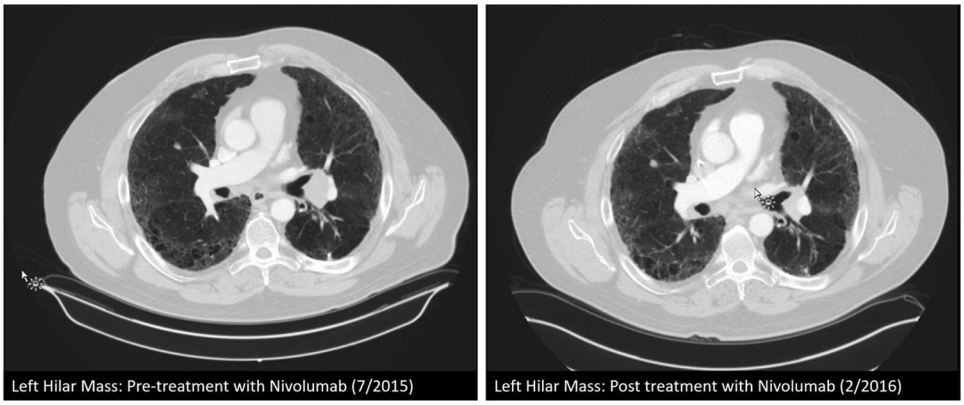

B

Pulmonary Function Tests	FEV1	FVC	DLCO
Pre-treatment with Nivolumab (8/2015)	2.65	3.44	27
Post treatment with Nivolumab (3/2016)	2.93	3.72	35

Figure 1. (*A*) Chest computed tomography images at baseline before nivolumab treatment (*left*) and after 5 months of nivolumab therapy (*right*) in a patient with NSCLC with underlying pulmonary fibrosis that reveal a decrease in size of the dominant left hilar mass. (*B*) Pulmonary function tests before and after treatment with nivolumab. FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; DLCO, diffusion capacity of lung for carbon monoxide.

alveolar epithelial hyperplasia, resulting in the clinical and physiologic derangements characteristic of IPF.[2] There are striking similarities in the pathobiology and dire clinical outcomes of both IPF and lung cancer. PD-1 plays a role in controlling inflammatory response to injury in the normal lung tissues and could be critical in the pathogenesis of both IPF and lung cancer.[3] Risk factors such as smoking and occupational and environmental exposures result in stimulus producing episodes of acute lung injury followed by pathological wound healing predisposing to genetic mutations, including atypia, dysplasia, and ultimately development of IPF and lung cancer.[2] Anti–PD-1 agents are an important class of agents for treating patients with NSCLC. These drugs are well tolerated, with fewer adverse events compared with cytotoxic chemotherapy; however, they can cause a unique class of side effects called immune-related toxicities.[4] Pulmonary toxicity with anti–PD-1 agents is more common in patients with NSCLC that in patients with other tumor types, which is possibly due to impaired immune tolerance resulting from smoking-induced changes in the normal lungs. Clinical trials with anti–PD-1 and anti–PD-L1 agents excluded patients with underlying ILD. Patients with IPF have an increased risk for lung cancer.[2,5] Patients with advanced-stage NSCLC have limited treatment options, and it is important to consider treatment anti–PD-1 agents when appropriate.

To our knowledge this is the first case of NSCLC with concomitant diagnosis of ILD treated with nivolumab with good disease control and a safe outcome without exacerbation of the ILD. However, more studies are needed to establish the safety of agents targeting the PD-1/PD-L1 pathway in patients with interstitial lung disease.

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