Focal lung infiltrate complicating PD-1 inhibitor use: A new pattern of drug-associated lung toxicity?

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ABSTRACT

A 58-year-old woman with stage 4 adenocarcinoma of the lung being treated with pembrolizumab developed dyspnea, non-productive cough, and a right middle lobe infiltrate. Complete resolution of the infiltrate with cessation of pembrolizumab, initiation of prednisone and no antibiotic therapy suggested drug-associated lung toxicity as the cause. While the programmed death-1 (PD-1) inhibitors pembrolizumab and nivolumab have been implicated as a cause of diffuse or multifocal pulmonary infiltrates, the current case represents, to our knowledge, the first instance of a unilobar, focal infiltrate associated with their use. We speculate that the blockade of immune tolerance that is the hallmark of PD-1 inhibitors might cause atypical inflammatory reactions such as the focal lobar infiltrate seen in the current patient. Awareness of this novel radiographic pattern of drug-associated lung toxicity may enhance clinicians’ management of patients receiving.

1. Introduction

The programmed death-1 (PD-1) pathway is a critical mechanism of immune evasion used by lung tumors to co-opt the host immune response. PD-1 is a co-inhibitory receptor expressed mainly on T-cells and, to a lesser extent, on other immune cells. The degree of PD-1 expression and engagement with its ligands determines the fate of T-cells. Complex orchestration of co-activation signals and co-inhibitory signals is critical to prevent autoimmunity. PD-1 has two known ligands, PD-L1 and PD-L2. PD-1 interactions with PD-L1/PD-L2 in the normal lung are tightly regulated to prevent inadequate or excessive inflammation [1–3].

Two new drugs that target the PD-1 pathway - nivolumab and pembrolizumab, also called checkpoint inhibitors - have shown promising clinical activity in lung cancer, melanoma, and renal cell cancer [4]. Several reports have described pulmonary toxicity with these drugs [5,6,11,12]. The reported radiographic patterns in these cases have been either multifocal or diffuse. To our knowledge, radiologically focal lung toxicity attributable to checkpoint inhibitors has not been reported. Based on our recent experience with a patient who developed a right middle lobe infiltrate ascribed to pembrolizumab, we suggest that focal lung toxicity may be a pattern of checkpoint inhibitor-associated lung injury. We also summarize our experience with 4 additional patients who developed pulmonary infiltrates while being treated with PD-1 inhibitors.

2. Case report

A 58-year-old woman diagnosed with stage IV lung adenocarcinoma 8 months earlier presented with a 2-week history of progressive exertional dyspnea and non-productive cough. She had been treated initially with first-line systemic chemotherapy using carboplatin, pemetrexed, and pembrolizumab (2 mg/kg). Four cycles of induction chemotherapy resulted in an excellent partial response (Response Evaluation Criteria in Solid Tumors [RECIST] v 1.1[9]). As part of a clinical trial, maintenance pembrolizumab (2 mg/kg) every 3 weeks was then started, 5 months prior to her current presentation. Currently, she denied fever, chills, chest pain, hemoptysis, palpitations, pedal edema, orthopnea, or pleuritic chest pain. She was a 60-pack-year smoker.

On examination, she was afebrile and in mild respiratory
distress. Oxygen saturation at rest was 94%, decreasing to 88% with ambulation. Her chest examination showed a focal wheeze over the right middle lobe. There was no cyanosis, clubbing, or edema. Laboratory assessment included a normal total leukocyte count and hemoglobin. A complete metabolic panel was normal. Two blood cultures were negative.

Compared with images from 5 weeks earlier, a contrast-enhanced chest CT showed new focal airspace opacities in the right middle lobe (Fig. 1A). There was no evidence of pulmonary embolism. In addition, there was evidence of persistent/residual tumor in the form of a spiculated right upper lobe density. Bronchoscopy showed no endobronchial lesions or airway secretions. Bronchoalveolar lavage (BAL) fluid was predominantly neutrophilic (N 39, L5, M48, E3). Cultures of the BAL fluid were negative, as were special stains for microorganisms. A transbronchial biopsy of the right middle lobe was performed. It included mainly bronchial wall fragments with minute portions of attached alveolated lung. A moderate to severe inflammatory infiltrate was seen in the bronchial mucosa, with pathologic evidence of damage to the bronchial epithelium. The inflammatory infiltrate in the bronchial mucosa was composed mainly of lymphocytes and eosinophils (Fig. 2A). Only a few of these inflammatory cells extended into adjacent alveolar septa. As expected in a reactive inflammatory infiltrate, the lymphocytes were mainly CD3-positive T cells (CD4+CD8−) (Fig. 2B−E).

No antibiotics were prescribed. Based on clinical suspicion for drug-associated lung toxicity and compatible pathologic findings, pembrolizumab was stopped and she was treated with prednisone (1 mg/kg/day) with a taper to discontinuation over 8 weeks. Over the first 3 days on prednisone, her symptoms improved markedly. At her 1-month outpatient follow-up visit, her symptoms had resolved completely. A follow-up chest CT showed complete resolution of the right middle lobe infiltrate (Fig. 1B).

The main role of lung biopsy in the diagnosis of drug-associated lung toxicity is the exclusion of alternative diagnoses such as infection or tumor. In addition, although histologic findings are never pathognomonic of drug toxicity, the identification of an inflammatory infiltrate in the lung in the absence of an obvious etiology can be helpful in supporting the clinical impression of drug toxicity. In the current case, there was no evidence of a specific alternative pathologic diagnosis, and the composition of the inflammatory infiltrate (lymphocytes and eosinophils) was compatible with drug-associated toxicity. This impression was supported by the lack of objective evidence of infection and prompt resolution of clinical and radiographic findings with corticosteroid therapy. Based on these findings, we suspected pembrolizumab-induced focal lung toxicity and pembrolizumab was discontinued. The patient is currently being monitored off cancer-directed therapy without evidence of disease progression at the time of this writing.

To extend available reports in the literature on PD-1 inhibitor-associated pneumonitis, we also reviewed clinical records in 4 additional patients seen at Cleveland Clinic in the 7 months between September 2015 and March 2016 (Table 1), of whom one showed a predominantly unilobar infiltrate (Case 1).

3. Discussion

Our patient’s presentation and clinical course suggested pembrolizumab as the cause of a right middle lobe infiltrate. Although checkpoint inhibitors have been implicated as a cause of diffuse and/or multifocal pulmonary infiltrates, focal disease has not been reported, making the current case novel. It is possible that the blockade of immune tolerance that is the hallmark of PD-1 inhibitors might cause atypical inflammatory reactions such as focal lobar infiltrates.

This report extends the available experience of adverse pulmonary reactions with PD-1 inhibitors, which have been reported in 1−11% of phase 2 and 3 trial participants [6]. In a meta-analysis of PD-1 inhibitor-related pulmonary reactions, Abdel-Rahman et al. reported severe (National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] [8] grade 3/4) toxicity in 0.3−2% of patients treated with these drugs and “low grade” (NCI CTCAE grade 1/2) toxicity in 1−9% [6]. Respiratory failure and death from pneumonitis have also been anecdotally described [5,7,10].

To our knowledge, the current report is the first to describe possible PD-1 inhibitor-associated focal pulmonary toxicity, and is also the first to report details of the pathologic findings associated with this novel manifestation of checkpoint inhibitor-associated pulmonary toxicity. The possibility of drug-associated toxicity
should be considered when focal pneumonia-like lung infiltrates are encountered in individuals being treated with PD-1 inhibitors.

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