Introduction
Cancer immunotherapy has revolutionized the approach to treating high-risk cancers by harnessing the ability of the immune system to directly attack tumors. A rare side effect of checkpoint inhibitor therapy is pneumonitis, which typically presents as an interstitial lung disease. In this case report, we present a patient in whom combination therapy with the PD-1 inhibitor pembrolizumab and the CTLA-4 inhibitor ipilimumab induced severe airflow obstruction. This is the first report that shows that checkpoint inhibitors may induce airflow limitation.

Abstract
Checkpoint inhibitor therapies are members of a new, groundbreaking class of drugs that reinvigorate the immune system to directly attack tumors. A rare side effect of checkpoint inhibitor therapy is pneumonitis, which typically presents as an interstitial lung disease. In this case report, we present a patient in whom combination therapy with the PD-1 inhibitor pembrolizumab and the CTLA-4 inhibitor ipilimumab induced severe airflow obstruction. This is the first report that shows that checkpoint inhibitors may induce airflow limitation.

Keywords: Bronchiolitis, ipilimumab, pembrolizumab

Case Report
Our patient is a 44-year-old female who was a never smoker who was an avid athlete and in excellent physical condition. She was diagnosed with a left lung mass at the age of 42 and was found to have adenocarcinoma of the lung. Her tumor was negative for epidermal growth factor and activin receptor-like kinase 1 mutations. Testing for PD-L1 mutations was not performed. She underwent a left upper lobectomy with lymph node resection. Six out of 22 lymph nodes were positive, and she was staged as T2bN1.[13] She then underwent postoperative adjuvant chemotherapy with cisplatin and vinorelbine and was in remission for 6 months. Unfortunately, on routine imaging obtained 6 months after her chemotherapy, she

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was found to have disease recurrence in the mediastinum with brain metastases. She underwent a craniotomy to resect two of four brain lesions and underwent gamma knife therapy to treat the remaining two lesions. She then underwent chemotherapy with pemetrexed but 6 months later was found to have recurrent nodal metastasis in the aortopulmonary window.

She was then enrolled in a clinical trial of pembrolizumab and ipilimumab and received one dose of each agent. Two months later, she developed shortness of breath, cough, and acute thyroiditis. She was treated with dexamethasone, which resulted in improvement in her acute thyroiditis, but she eventually progressed to hypothyroidism and currently requires thyroid replacement therapy. Shortly thereafter, she developed diarrhea about 2 months after combination immunotherapy and was found to have colitis from Clostridium difficile infection. However, her diarrhea did not improve with treatment of C. difficile but eventually improved months later with corticosteroid therapy. She continued to have shortness of breath and cough, and underwent a computed tomography scan 6 months of age. The scan showed evidence of mucus plugging and airway wall thickening, concerning for bronchiolitis obliterans. She had developed moderately severe obstruction with air trapping, consistent with bronchiolitis. Pulmonary function testing was performed without testing for bronchodilator responsiveness, and the results are summarized in Table 1 (Visit 1). She had evidence of moderate airflow obstruction. A bronchoscopy was performed to evaluate for infection, but all microbiologic studies were negative. She was started on high-dose inhaled steroids, long-acting bronchodilators and anti-muscarinic agents, and a prednisone taper over 3 months starting at 60 mg/day. She was referred to our institution for further evaluation.

Her family history was negative for hereditary lung disease. Her maternal grandmother died of breast cancer and had smoking-related emphysema, her maternal grandfather died of colon cancer, and her paternal grandmother died of congestive heart failure. She was a never smoker and drank 1–2 drinks a week socially. She was an active athlete and routinely ran half marathons. No occupational exposures were identified.

When we evaluated the patient, she had completed her steroid taper and had some improvement in her shortness of breath. She had moderate shortness of breath associated with a persistent cough productive of scant and clear mucus. She had no fevers, chills, or night sweats to suggest infection. She has no skin findings or arthralgias to suggest the presence of autoimmune diseases such as rheumatoid arthritis. She was taking umeclidinium and vilanterol by inhaler and budesonide and as-needed albuterol by nebulizer. In addition, she was taking thyroid replacement therapy. On examination, her blood pressure was 105/83, oxygen saturation was 99% on room air, pulse was 114, temperature was 36.9, and respiration was 14. Her lung examination revealed diffuse inspiratory squeaks and a prolonged expiratory phase with audible expiratory wheezing. She had a regular tachycardia but no murmurs or gallops. The remainder of the examination was normal.

Pulmonary function testing from our institution is summarized in Table 1 (Visit 2). On a 6-minute walk test performed on room air, she walked 466 meters but desaturated from a resting SpO2 of 99% to a nadir of 85%. A complete blood count was within normal limits. An echocardiogram showed normal left and right ventricular function and no evidence of shunt. Computed tomography of the chest showed tree-in-bud opacities which were concerning for infection. Representative images are shown in Figure 1. We performed a bronchoscopy, and aerobic cultures of the bronchoalveolar lavage fluid revealed evidence of lower respiratory infection with Pseudomonas aeruginosa. All other microbiologic tests were negative. She underwent treatment with ciprofloxacin and had some improvement in her cough. We also started her on hypertonic saline therapy for sputum clearance, which resulted in minor symptomatic improvements. We also began thrice-weekly azithromycin at 250 mg/day.

She chose to continue her care closer to home, but her

| Table 1: Pulmonary function tests |
|----------------------------------|
| Pulmonary function test | Visit 1 pre‑BD values | Visit 2 pre‑BD values | Visit 2 post‑BD values |
| FEV1, L (%) | 1.76 (65) | 1.31 (52) | 1.45 (58) |
| FVC, L (%) | 2.79 (83) | 2.29 (77) | 2.52 (84) |
| FEV1/FVC, % | 63 | 57 | 58 |
| FEF 25%–75%, L/s (%) | 0.95 (33) | 0.51 (17) | 0.50 (17) |
| TLC, L (%) | 4.89 (109) | 2.24 (150) | 46 |
| DLCO, ml/min/mmHg | 18.6 (96) | 19.1 (100) |

FEV1: Forced expiratory volume in 1 s, FVC: Forced vital capacity, FEF: Forced expiratory flow, TLC: Total lung capacity, RV: Residual volume, DLCO: Diffusing lung capacity of carbon monoxide, BD: Bronchodilator

Figure 1: High-resolution computed tomography images of the chest. Panel A shows nonspecific bronchial wall thickening (white arrow), while panel B shows nonspecific tree-in-bud infiltrates suggestive of inflammation or infection (white arrow). No evidence of bronchiectasis or air trapping was seen.
dyspnea has been stable. At the time of this writing, she is well and has no recurrence of disease in her thorax. She has had three radiosurgical procedures to resect persistent intracranial tumors.

Discussion

We present a case of bronchiolitis after combination immunotherapy with pembrolizumab and ipilimumab. Pneumonitis after combination immune checkpoint inhibitor therapy typically presents as cryptogenic organizing pneumonia (COP) or nonspecific interstitial pneumonitis (NSIP).[14-16] COP is characterized by peripheral-based patchy alveolar infiltrates on imaging and granulation tissue occluding small bronchioles and alveoli on histopathology, while NSIP is characterized by more diffuse ground-glass infiltrates predominantly in the lower lung zones on imaging and diffuse inflammation and thickening of alveolar walls without loss of alveolar architecture on histopathology.[14,15] COP was formerly known as bronchiolitis obliterans organizing pneumonia, but this latter term has fallen out of favor due to confusion with bronchiolitis obliterans. Both NSIP and COP present typically as a restrictive lung disease. On the other hand, our patient presents with an obstructive lung disease and bronchiolitis obliterans, despite no history of asthma or chronic obstructive pulmonary disease.

Although myriad histologic presentations of bronchiolitis obliterans exist, generally bronchiolitis obliterans is characterized by submucosal and peribronchiolar fibrosis which results in narrowing and obliteration of bronchiolar lumens.[12] Bronchiolitis obliterans occurs as the result of a variety of exposures or infections. Common causes include viral infections such as adenovirus or respiratory syncytial virus, connective tissue diseases such as rheumatoid arthritis, inhalation of fumes of substances such as diacetyl or ammonia, and a variety of other exposures.[12] In addition, bronchiolitis obliterans is the most common manifestation of lung allograft rejection after lung transplantation and graft-versus-host disease of the lung after hematopoietic cell transplantation.[12,17] Pulmonary function testing is key for the diagnosis of bronchiolitis. In lung transplant patients, bronchiolitis obliterans syndrome (BOS) is defined by a 20% decline in the forced expiratory volume in 1 second (FEV₁) from baseline values.[16] Pulmonary function testing typically shows a decrease in the FEV₁/forced vital capacity ratio and an increase in residual volume, particularly with relation to the total lung capacity. FEV₁ typically does not improve with beta-agonist bronchodilator therapy. Chest radiographs typically do not show abnormalities, but high-resolution computed tomography (HRCT) imaging can show areas of mosaic attenuation in the lung parenchyma, particularly on expiratory imaging, and peripheral cylindrical bronchiectasis.[12] Importantly, these HRCT findings are not sensitive and are only moderately specific for the diagnosis of bronchiolitis.[19] Histopathologic approaches to diagnosis of BOS are also challenging; the yield of transbronchial biopsy is low,[20] while open lung biopsy is associated with increased morbidity.[21] Furthermore, a pathological diagnosis of obliterative bronchiolitis correlates poorly with clinical findings in cases of BOS that occurs outside of lung transplantation.[22] Therefore, the diagnosis is typically made on the basis of pulmonary function testing, as in this case. We did not evaluate for autoimmune etiologies of bronchiolitis, as this is typically not performed unless patients exhibit other symptoms consistent with autoimmune diseases, and bronchiolitis in this setting is typically associated with long-standing disease.[23]

Treatment varies depending on the etiology of bronchiolitis. For example, macrolides are typically used in BOS after rheumatoid arthritis,[23] while the mainstays of therapy after hematopoietic cell transplantation are inhaled corticosteroids.[24-26] In this case, we continued therapy with inhaled corticosteroids and started therapy with macrolides, but we did not achieve improvements in her symptoms. We suspect that the lack of improvement was due to the delay in therapy as her symptoms were unnoticed due to her comorbid conditions. She did have some improvement with hypertonic saline, which we routinely prescribe in patients with bronchiolitis due to its efficacy and safety.[27] After our evaluation, she chose to have subsequent testing done closer to her home for convenience. Three years after our initial evaluation, she remains alive despite metastatic disease at the time of treatment with immunotherapy. Although we do not have data on whether her tumor was PD-L1 positive, this highlights the remarkable therapeutic potential of immunotherapy agents.

In conclusion, we report the first case of bronchiolitis obliterans after combination immune checkpoint inhibitor therapy with pembrolizumab and ipilimumab. Pulmonary function screening after cancer immunotherapy may be beneficial to detect early cases of bronchiolitis or pneumonitis.

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Conflicts of interest

The authors declared no conflicts of interest.

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