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Radiologic and autopsy findings in a case of fatal immune checkpoint inhibitor-associated pneumonitis☆

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ABSTRACT

Oncologists are increasingly managing drug-induced pneumonitis in lung cancer patients treated with PD-1/PD-L1 immune checkpoint inhibitors. To date only few studies on the topic have described both radiologic and pathologic findings in these patients. Here, we report a fatal case of immune checkpoint inhibitor-associated pneumonitis initially presenting with an organizing pneumonia, but who rapidly developed acute respiratory distress syndrome (confirmed histologically at the time of autopsy). As such, this case illustrates the need for clinicians to maintain a high index of suspicion for immune checkpoint inhibitor associated pneumonitis and have a low threshold to perform CT imaging in any symptomatic patient receiving checkpoint inhibition therapy.

Clinical practice points:

- Pneumonitis is a rare but potentially fatal complication of immune checkpoint inhibitors.
- Variety of radiographic and histopathologic patterns have been seen in immune checkpoint inhibitor-associated pneumonitis.
- Clinicians must maintain a high index of suspicion and have a low threshold to perform CT imaging in any symptomatic patient receiving checkpoint inhibition therapy.

Introduction

Pneumonitis is a rare and potentially fatal complication of treatment with immune checkpoint inhibitors [1,2]. Two to six percent of lung cancer patients on anti-PD-1 or anti-PD-L1 therapy have developed pneumonitis, only 2–3% grade 3–4 [1,3–7]. A meta-analysis of adverse events in 19 trials of lung cancer patients, who received either anti-PD-1 or anti-PD-L1 therapy, showed a higher incidence of pneumonitis from anti-PD-1 therapy with a higher proportion with grade 3–4, as well as all 7 deaths from pneumonitis occurring after anti-PD-1 [8]. Most reported cases detail radiographic and clinical changes though histopathologic findings are less well described. The most common radiographic presentation is organizing pneumonia (OP), though some patients present with acute interstitial pneumonia - acute respiratory distress syndrome (ARDS) or nonspecific interstitial pneumonia (NSIP) [9–12]. The largest series to date of immune checkpoint inhibitor induced pneumonitis contained eleven cases with limited histologic confirmation, demonstrating OP, diffuse alveolar damage, and/or cellular interstitial pneumonia [13]. The majority of patients who develop pneumonitis respond to steroids [11]. Here, we report a case of fatal pneumonitis secondary to immune checkpoint inhibitor therapy with histopathologic findings at autopsy.

Presentation of case

A 67-year-old white gentleman with a 50 pack-year tobacco history presents with recurrent, metastatic lung adenocarcinoma (wild-type for KRAS and EGFR, negative for ROS1 or ALK mutations) six months following definitive chemoradiation with Carboplatin/Pemetrexed. At the time of disease recurrence, immunohistochemical (IHC) testing for programmed death ligand 1 (PD-L1) expression (clone 22C3 pharmDx kit and Dako Automated Link 48 platform; Integrated Oncology/Lab Corp, New York, NY) demonstrated a tumor proportion score of 90% (Fig. 1), which is associated with an increased likelihood of a brisk and durable anti-cancer response [2]. The patient was treated with palliative pembrolizumab and experienced a complete response following the

☆ Consent: Written informed consent was obtained from the patient's next of kin for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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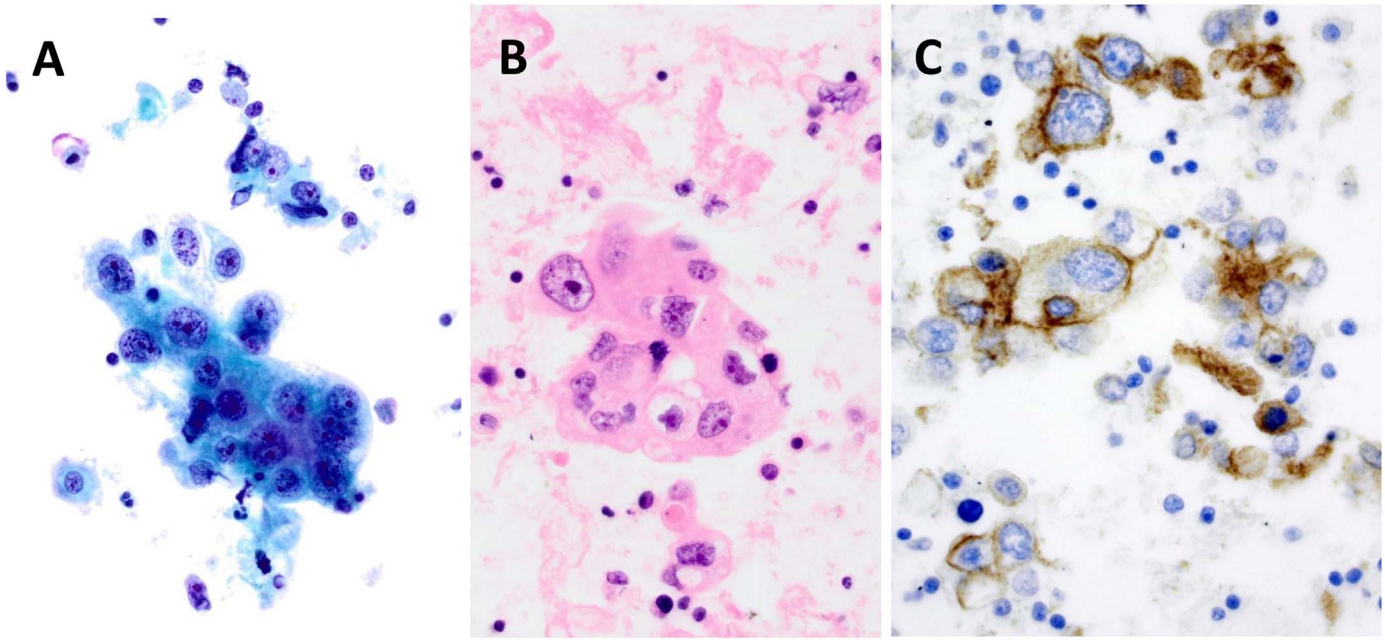

Fig. 1. Diagnostic specimen and PD-L1 IHC. A. Cytology specimen of subcarinal lymph node sampled via endobronchial ultrasound guided transbronchial needle aspirate (EBUS-TBNA) demonstrating metastatic lung adenocarcinoma (TTF-1 and Napsin-A positive, not shown). B. Corresponding cell block preparation of EBUS-TBNA aspirate from same node. C. IHC for PD-L1 (clone 22C3) demonstrated strong diffuse tumor staining.

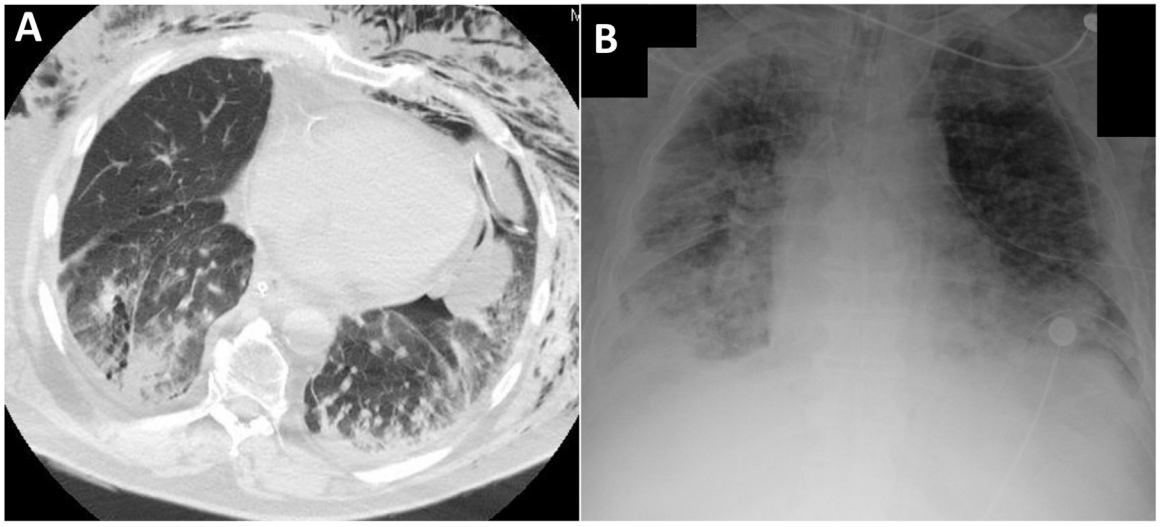

Fig. 2. Radiologic findings of pneumonitis. A. Initial computed tomography showing bilateral lower lobe opacities. B. Subsequent chest X-ray showing an acute respiratory distress syndrome (ARDS).

first 2 cycles of therapy. Five days following cycle 11 of pembrolizumab, he presented with acute dyspnea and chest pain. He was found to have a left tension pneumothorax and pneumomediastinum requiring intubation and mechanical ventilation. He subsequently developed fever and was empirically treated with broad-spectrum intravenous antibiotics for hospital-acquired pneumonia. A computed tomography (CT) scan (Fig. 2) showed extensive consolidation in the bilateral lower lobes on hospital day 3 and was treated for multifocal pneumonia. Microbiology specimens, including bronchoalveolar lavage and intubated sputum specimens, were negative. He remained ventilator-dependent despite broad-spectrum antibiotics and supportive care with progressively worsening bilateral opacities on chest x-ray indicative of acute respiratory distress syndrome (ARDS). He was unable to be safely transported for further imaging. He was initiated on daily IV methylprednisolone 1 mg/kg on hospital day 11 for suspected immunotherapy-mediated pneumonitis, but continued to decline. On HD 19, he died. At autopsy, there was a near complete pathologic treatment response with only microscopic viable tumor foci present. The lungs demonstrated diffuse bilateral consolidations with a dominant organizing pneumonia pattern, as well as focal areas of airspace fibrin indicative of more acute lung injury/diffuse alveolar damage (Fig. 3). All microbiologic cultures and special stains for microorganisms were negative.

Discussion

Detailed clinical, radiographic, and histopathologic reports classifying the spectrum of findings in patients with pneumonitis related to checkpoint inhibition therapy have been few to date. Furthermore, data regarding potential risk factors for developing pneumonitis is lacking, though prior smoking, previous chemotherapy with agents known to cause pulmonary toxicity, radiation to the chest and antecedent