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WHEN IMMUNITY BACKFIRES: PEMBROLIZUMAB-INDUCED BILATERAL PNEUMOTHORAX IN A PATIENT WITH METASTATIC HPV-ASSOCIATED OROPHARYNGEAL CARCINOMA

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ABSTRACT

Background: Immune checkpoint inhibitors (ICIs) are standard therapy for recurrent or metastatic head and neck squamous cell carcinoma, but unleashing antitumour immunity can trigger immune-related adverse events (irAEs). Pneumothorax is a rare pulmonary complication compared with the more recognised ICI-associated pneumonitis.

Case report: A 67-year-old man with p16-positive, poorly differentiated oropharyngeal squamous cell carcinoma presented with progressive bilateral cervical lymphadenopathy and subsequently required tracheostomy and gastrostomy for upper-airway obstruction. Chemoradiation with weekly docetaxel was discontinued early due to severe mucositis. Restaging showed regression of the primary tumour but new and enlarging subpleural pulmonary nodules consistent with metastases. Pembrolizumab was initiated. Within days of the first infusion, the patient developed pleuritic chest pain and dyspnoea. Upright chest radiography demonstrated a large right pneumothorax, and a computed tomography scan revealed bilateral subpleural lesions with adjacent parenchymal abnormalities; a contralateral pneumothorax was also present. Bilateral chest tubes were placed with symptomatic improvement. In the absence of trauma, mechanical ventilation, known bullous disease, or infectious cavitation, an immune-mediated mechanism was considered most likely: rapid necrosis and cavitation of subpleural metastases creating alveolar–pleural fistulas. Given poor functional reserve and advanced disease, definitive pleurodesis was deferred and palliative care was engaged.

Conclusion: Acute pneumothorax—sometimes bilateral—can occur shortly after PD-1 inhibition, particularly in patients with subpleural metastatic disease. Clinicians should maintain a high index of suspicion when new respiratory symptoms arise soon after ICI initiation, obtain prompt imaging to distinguish pneumothorax from pneumonitis, and coordinate early multidisciplinary management to optimise outcomes and align treatment with patient goals.

KEYWORDS

Pembrolizumab, immune checkpoint inhibitor, pneumothorax, head and neck cancer, immune-related adverse event

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LEARNING POINTS

- Pneumothorax is a rare but reported pulmonary immune-related adverse event associated with PD-1/PD-L1 inhibitors; risk may be heightened by subpleural metastases undergoing immune-mediated necrosis/cavitation.
- New dyspnoea after checkpoint blockade warrants chest imaging for pneumothorax alongside evaluation for immune checkpoint inhibitor pneumonitis.
- Management should follow evidence-based pneumothorax guidelines and be individualized to performance status and goals of care.

INTRODUCTION

Immune-checkpoint inhibitors (ICIs) targeting PD-1/PD-L1 have reshaped the management of recurrent/metastatic head and neck squamous cell carcinoma (HNSCC), conferring meaningful survival benefits[1]. By reinvigorating antitumour T-cell activity, however, ICIs can precipitate immune-related adverse events (irAEs) across multiple organs[2,3]. In the lung, pneumonitis is the prototypical irAE and a key diagnostic consideration when new respiratory symptoms arise after treatment initiation[4,5]. Spontaneous pneumothorax is far less common but increasingly recognised in association with ICIs[6–8]. We report a distinctive presentation of pembrolizumab-associated, bilateral pneumothoraces occurring within days of the first infusion in a man with p16-positive oropharyngeal carcinoma and subpleural pulmonary metastases. Salient features include the very early onset after cycle 1, bilateral involvement, absence of alternate precipitants (trauma, mechanical ventilation, bullous disease, or infection), and imaging that demonstrated subpleural lesions with adjacent parenchymal change—collectively supporting a mechanism of rapid immune-mediated tumour necrosis and cavitation with alveolar–pleural fistula formation. Management required bilateral tube thoracostomy, while definitive pleurodesis was deferred in the context of limited physiological reserve and advanced disease. This case broadens the differential for early post-ICI dyspnoea beyond pneumonitis and underscores the need for prompt imaging and multidisciplinary planning when subpleural metastases are present.

CASE DESCRIPTION

A 67-year-old man with p16-positive, poorly differentiated HPV associated oropharyngeal squamous cell carcinoma initially presented with progressive bilateral cervical lymphadenopathy. Rapid tumour enlargement precipitated upper-airway obstruction requiring tracheostomy and percutaneous endoscopic gastrostomy. He underwent a 7-week course of radiotherapy with concurrent weekly docetaxel, which was discontinued early because of severe mucositis. Post-treatment imaging demonstrated marked regression of the primary tumour and cervical nodes but new and enlarging pulmonary nodules consistent with metastatic disease. Pembrolizumab was commenced with palliative intent.

Within several days of the first pembrolizumab infusion, the patient developed abrupt pleuritic chest pain and dyspnoea. An anteroposterior upright chest radiograph revealed bilateral pneumothoraces *(Fig. 1)*. Axial computed tomography confirmed the pneumothoraces *(Fig. 2)*. Baseline axial chest computed tomography (CT) scan demonstrated subpleural and intraparenchymal abnormalities in keeping with metastatic deposits *(Fig. 3)*. Initial laboratory studies were non-contributory; there was no clinical or microbiological evidence of infection. The patient had no recent trauma or exposure to positive-pressure ventilation, and there was no known history of bullous lung disease.

He underwent bilateral tube thoracostomy with prompt symptomatic improvement and radiographic re-expansion *(Fig. 4)*. Given limited physiological reserve and advanced disease, definitive pleurodesis was deferred following

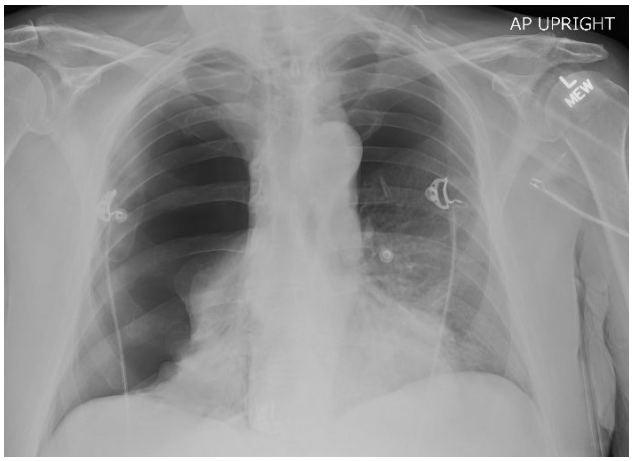


Figure 1. An anteroposterior upright chest radiograph revealed bilateral pneumothoraces.

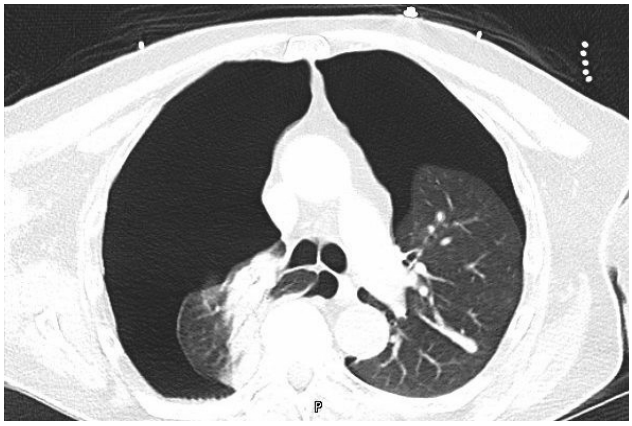


Figure 2. Axial computed tomography confirmed the pneumothoraces.

multidisciplinary discussion, and palliative care was engaged to align ongoing management with the patient's goals. The close temporal association with pembrolizumab initiation, the presence of subpleural metastatic lesions with interval parenchymal change, and the absence of alternative precipitants supported an immune-mediated mechanism, most plausibly rapid tumour necrosis and cavitation with formation of alveolar–pleural fistulae.

DISCUSSION

ICIs have improved survival in recurrent/metastatic HNSCC but introduce a spectrum of irAEs that frequently involve the lung parenchyma rather than the pleura[1–5]. Pneumonitis remains the prototypical pulmonary irAE; pleural complications are uncommon. Nevertheless, spontaneous pneumothorax has been increasingly described with PD-1/PD-L1 blockade, particularly in patients with subpleural metastases[6–8].

Our case adds several distinctive features to this emerging literature. First, temporality: bilateral pneumothoraces occurred within days of the first pembrolizumab infusion, earlier than typically reported. Second, distribution: baseline imaging demonstrated subpleural metastatic deposits with interval parenchymal change contiguous with the pleural surface at the time of presentation. Third, exclusion of alternative precipitating factors: there was no trauma, positive-pressure ventilation, known bullous disease, or microbiological evidence of infection. Taken together, these elements support a systemic immune mechanism rather than mechanical or infectious aetiologies.

Several pathophysiological pathways may underlie ICI-associated pneumothorax. The leading hypothesis—well aligned with our patient's clinicoradiological course—is immune-mediated necrosis and cavitation of subpleural metastases resulting in alveolar–pleural fistulae[6–8]. An alternative is parenchymal destruction secondary to ICI pneumonitis, whereby diffuse or focal inflammatory injury culminates in alveolar rupture and air leak[4,5]. In this case, the very early onset after cycle-1 pembrolizumab, bilateral involvement, and subpleural tumour geography most strongly favour the first mechanism.

This presentation carries important diagnostic implications. Early post-ICI dyspnoea and pleuritic pain are commonly attributed to pneumonitis; however, pneumothorax should be co-prioritised in the differential, especially when baseline imaging reveals subpleural disease. A low threshold for immediate chest radiography is warranted, with chest CT scan to define the extent of pneumothorax, identify fistulous tracts or cavitation, and characterise concomitant parenchymal irAEs. Prompt recognition is critical given the risk of rapid deterioration, including tension physiology.

Management should follow contemporary guidelines for spontaneous pneumothorax, recognising that most ICI-associated events in patients with underlying metastatic lung involvement meet criteria for secondary pneumothorax and often require tube thoracostomy rather than observation alone[9]. In our patient, bilateral tube thoracostomy produced rapid symptomatic improvement and radiographic re-expansion. Decisions regarding definitive pleurodesis or surgical intervention must balance recurrence risk (heightened with persistent subpleural disease) against performance status, anticipated cancer trajectory, and the patient's goals of care[9]. Multidisciplinary coordination among oncology, pulmonology, thoracic surgery, and palliative care is therefore essential.



Figure 3. Baseline axial chest CT demonstrated subpleural & intraparenchymal abnormalities in keeping with metastatic deposits.

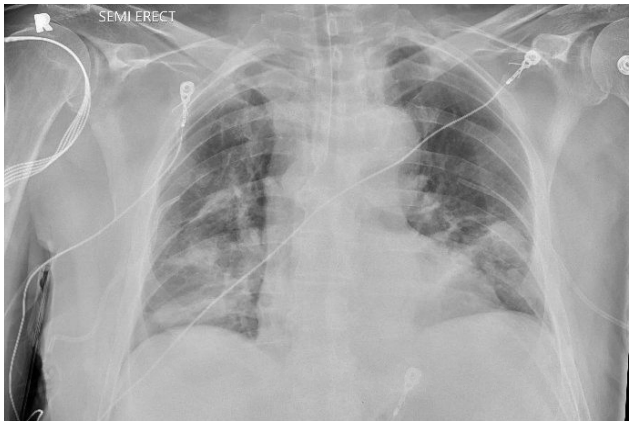


Figure 4. Bilateral tube thoracostomy with prompt symptomatic improvement and radiographic re-expansion.

From a preventive and counselling standpoint, clinicians should (i) review pre-ICI imaging for subpleural metastases as a potential risk marker, (ii) educate patients to report new chest pain or dyspnoea immediately after treatment initiation, and (iii) maintain expedited access to imaging and intervention. While these data do not justify withholding effective immunotherapy, they argue for heightened vigilance in anatomically high-risk settings.

Limitations include the absence of histopathological confirmation and the possibility that occult pneumonitis-mediated alveolar rupture contributed to the air leak. Prior radiotherapy and chemotherapy may also modulate tissue fragility. Even so, the temporal relationship, anatomic concordance with subpleural lesions, and lack of alternative precipitants make an ICI-triggered mechanism the most plausible explanation.

In summary, this case underscores that pneumothorax—

sometimes bilateral—can complicate PD-1 inhibition early in the treatment course, particularly when subpleural metastases are present. The findings support our conclusion that rapid, immune-mediated tumour necrosis with fistula formation is a plausible mechanism, and they reinforce guideline-concordant pleural management paired with early multidisciplinary discussion to align care with patient priorities[2,4–9].

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