American Journal of Case Reports

e-ISSN 1941-5923
© Am J Case Rep, 2021; 22: e933396
DOI: 10.12659/AJCR.933396

Received: 2021.06.01
Accepted: 2021.08.09
Available online: 2021.08.26
Published: 2021.10.04

Chronic Pleuritis and Recurrent Pleural Effusion After Atezolizumab for Small Cell Lung Cancer

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEF Julie Lin
ABCDEFG Bruce Fernando Sabath

Department of Pulmonary Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Corresponding Author: Bruce F. Sabath, e-mail: bsabath@mdanderson.org
Financial support: None declared
Conflict of interest: None declared

Patient: Female, 65-year-old
Final Diagnosis: Pleural effusion • small cell lung cancer
Symptoms: Shortness of breath
Medication: —
Clinical Procedure: —
Specialty: Pulmonology

Objective: Unknown etiology

Background: As use of immune checkpoint inhibitors consistently grows, so does knowledge of immune-related adverse events. Pleural complications from PD-L1 inhibitors such as atezolizumab have never been reported. We describe the first reported case of biopsy-proven pleuritis manifesting as recurrent pleural effusion in a patient treated with atezolizumab.

Case Report: A 66-year-old woman with history of extensive-stage small cell lung cancer presented with a new pleural effusion. She was previously treated with carboplatin, etoposide, and atezolizumab followed by atezolizumab maintenance, but this later was stopped due to pneumonitis. She had been on no systemic therapy for 6 months prior; radiation to the chest was completed 1 year earlier. Thoracentesis revealed an exudate with eosinophilia but no malignancy. She underwent medical thoracoscopy, which showed normal pleura with no evidence of radiation changes. Random pleural biopsies revealed only chronic pleuritis. Given normal-appearing pleura, radiation pleuritis was ruled out. It was felt that the chemotherapy had occurred too long ago to be a present cause of her pleuritis. As such, after extensive workup, the eosinophilic pleural effusion was felt to be due to pleuritis from atezolizumab. The effusion has ultimately recurred 5 times over 1 year, and cytology remains negative for malignancy.

Conclusions: Patients with prior cancer presenting with a new pleural effusion should undergo an extensive workup to evaluate for recurrence. When other causes have been ruled out, ongoing immune-related effects of immunotherapy should be considered. Pleural complications from PD-L1 inhibitors have not been reported; we present a possible case of chronic pleuritis and recurrent effusion due to atezolizumab.

Keywords: Immunotherapy • Pleural Effusion • Small Cell Lung Carcinoma • Atezolizumab

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/933396

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

Background

As immune checkpoint inhibitors are being increasingly used and investigated against various malignancies, we are learning more about their toxicity profiles, particularly immune-related adverse events. Pneumonitis causes lung parenchymal changes and is the most recognized pulmonary immune-related adverse event. Pulmonary complications from PD-1 inhibitors have been extensively described but adverse effects from PD-L1 inhibitors such as atezolizumab have not. Specifically, little is known about how PD-L1 inhibitors might affect the pleura and the pleural space. Here, we describe the first report ed case of biopsy-proven pleuritis manifesting as recurrent pleural effusion in a patient treated with atezolizumab.

Case Report

A 66-year-old woman with a history of extensive-stage small cell lung cancer presented to our clinic for evaluation of a new left-sided pleural effusion. She reported a 2-month history of progressive shortness of breath during which she was no longer able to exercise or perform household chores. She endorsed a dry cough when laying on her left side. She denied fevers, chills, night sweats, or weight loss. She had a prior 50 pack-year smoking history and quit 2 years earlier.

She had previously received systemic therapy with carboplatin, etoposide, and atezolizumab. After completing 4 cycles of this regimen, she had been on atezolizumab maintenance therapy but developed pneumonitis after 2 additional months of treatment; immunotherapy was therefore subsequently held. By the time of presentation to our clinic, she had been off of chemotherapy for 8 months and off of immunotherapy for 6 months. Radiation to the primary left upper lobe tumor and a cerebellar metastasis was completed 1 year prior to presentation.

Due to concern for recurrence of malignancy, she underwent a thoracentesis, with 750 mL of serous fluid removed. Pleural fluid analysis revealed a lymphocyte-predominant exudative effusion with eosinophilia (13%). Pleural fluid cytology revealed no malignant cells. Since the concern for malignant recurrence remained high, she underwent left-sided medical thoracoscopy. Inspection of the parietal pleura did not reveal any abnormalities, including no evidence of radiation changes (**Figure 1**). Random parietal pleural biopsies were taken, which revealed chronic pleuritis with reactive mesothelial hyperplasia and no tumor cells (**Figure 2**).

Given her completely normal-appearing pleura, radiation pleuritis was ruled out. It was felt that chemotherapy too long ago to be a present cause of her pleuritis. There was very low suspicion for pulmonary embolism given the normal right ventricle

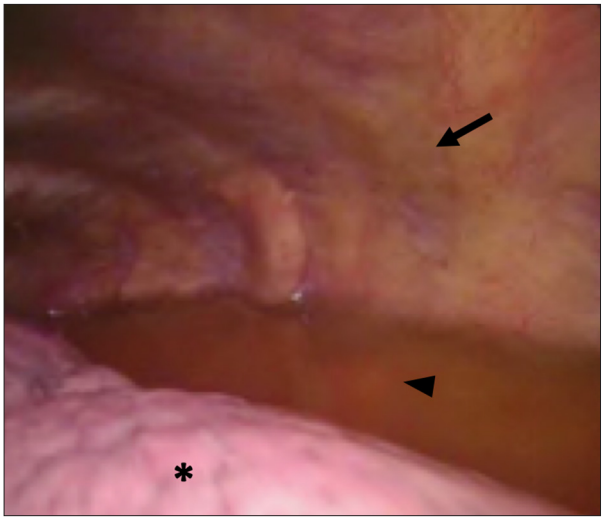

Figure 1. Normal-appearing parietal pleura (arrow) lining the anterior chest wall with serous effusion (arrowhead) and atelectatic left lung (*).

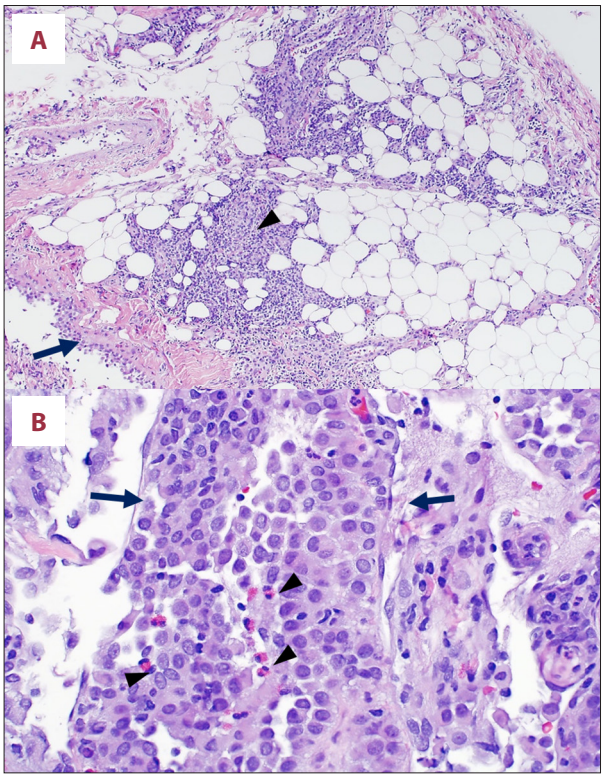

Figure 2. (**A**) H&E stain of parietal pleural biopsy showing lymphoid infiltration (arrowhead) and reactive mesothelial hyperplasia (arrow) consistent with chronic pleuritis (100×). (**B**) H&E stain of parietal pleural biopsy showing mesothelial hyperplasia (arrows) with eosinophilic infiltrate (arrowheads) (400×).

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

and tricuspid valve function on echocardiogram and resolution of symptoms with thoracentesis. As such, after extensive workup to rule out malignant recurrence and given the known ability of immunotherapy to have ongoing effects even after discontinuation, the eosinophilic pleural effusion was felt to be due to pleuritis from atezolizumab. The effusion eventually recurred and was drained again approximately 3 months later; in total, her effusion has been drained 5 times over 12 months, and cytology has remained negative for malignancy.

Discussion

Pulmonary toxicity related to immune checkpoint inhibitors has an overall incidence of 2-3% during cancer treatment [1,2]. Pneumonitis causes lung parenchymal changes and is the most recognized pulmonary immune-related adverse event. This is more commonly encountered with PD-1 or PD-L1 inhibitors than with cytotoxic T-lymphocyte antigen (CTLA)-4 inhibitors [3].

Less is known regarding how ICIs affect the pleura and pleural space. In the current literature, pleural effusions associated with ICIs are rarely encountered and have been reported with nivolumab use in case reports [3-6]. Socinski et al listed 1 case of pleurisy in a group of patients receiving combined atezolizumab, bevacizumab, paclitaxel, and carboplatin, but whether this referred simply to pain on inspiration and how this was diagnosed was not described [7]. To the best of our knowledge, this is the first case report of biopsy-proven pleuritis after atezolizumab.

Atezolizumab is a PD-L1 antibody that has been approved for use in metastatic non-small cell lung cancer, small cell lung cancer, and urothelial cancers [7]. In a meta-analysis comparing the safety profiles of ICIs, atezolizumab ranked among the safest in terms of incidence of overall adverse events compared to nivolumab, pembrolizumab, ipilimumab, and tremelimumab [8]. Pneumonitis associated with atezolizumab occurred in only 1% of cases [9]. Atezolizumab can cause a sarcoid-like reaction, but even large studies have not described pleural effusion as an adverse event [7,10,11].

Pleural effusion associated with immune checkpoint inhibitors is a diagnosis of exclusion. When patients with active or recent cancer develop a pleural effusion, initial management involves evaluation for malignant pleural involvement. In effusions with negative cytology after thoracentesis and high suspicion of malignancy, thoracoscopy with pleural biopsies should be performed next [12]. Nevertheless, in a study of thoracoscopy in patients with active malignancy and pleural effusion, the majority of patients did not have malignant pleural involvement but were deemed to have nonspecific pleuritis [13]. The effusion was then further subclassified based on clinical context and determined to be due to radiation, chemotherapy, or other etiologies. Radiation-induced pleuritis was accompanied by discolored, thickened pleura and often with a line of demarcation between normal and abnormal pleura that coincided with the radiation field. Chemotherapy-induced pleuritis usually occurred with agents known to cause effusion and relatively soon after therapy – at a mean time of 38 days after last treatment. In our case, given completely normal-appearing pleura, radiation-induced pleuritis was felt to be ruled out. Additionally, given the extended period of time since chemotherapy cessation (8 months), chemotherapy-induced pleuritis was also unlikely. As such, the remaining explanation for the effusion was atezolizumab. Of note, the patient had eosinophilia on her pleural fluid studies. In one study of drug-related effusions, 25% had eosinophilic effusions, supporting our belief that her effusion could be attributable to previous medical therapy [13]. Pulmonary embolism is a known cause of eosinophilic pleural effusions but suspicion was low in this case with a normal echocardiogram (normal right ventricular size and function with trace tricuspid regurgitation) and resolution of symptoms with each thoracentesis. Moreover, the repeated recurrence may be consistent with a prolonged immunotherapy effect. Chronic immune checkpoint inhibitor *pneumonitis* is a recently described entity (ICI pneumonitis that persists despite ICI cessation) [14,15]. In our case, we may additionally be observing the first reported case of chronic immune checkpoint inhibitor *pleuritis*.

Conclusions

Immune checkpoint inhibitors will be used more frequently as clinicians incorporate these therapies into cancer treatment regimens. With increased use, adverse events will be more frequently encountered and need to be better understood. We present the first case of chronic pleuritis with recurrent pleural effusion after atezolizumab to increase awareness for clinicians to recognize this as a potential etiology of pleural effusion. We propose that this is the first reported case of chronic immune checkpoint inhibitor pleuritis.

Declaration of Figures Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

References:

1. Brahmer JR, Lacchetti C, Thompson JA. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology clinical practice guideline summary. J Oncol Pract. 2018;14:247-49
2. Nishino M, Giobbie-Hurder A, Hatabu H, et al. Incidence of programmed cell seath 1 inhibitor – related pneumonitis in patients with advanced cancer: A systematic review and meta-analysis. JAMA Oncology. 2016;2:1607-16
3. Cadranel J, Canellas A, Matton L, et al. Pulmonary complications of immune checkpoint inhibitors in patients with nonsmall cell lung cancer. Eur Respir Rev. 2019;28:190058
4. Benn BS, Lombard CM, Krishna G. Nivolumab-induced granulomatous inflammation of the pleura. J Thorac Oncol. 2017;12:e100-e101
5. Kolla BC, Patel MR. Recurrent pleural effusions and cardiac tamponade as possible manifestations of pseudoprogression associated with nivolumab therapy – a report of two cases. J Immunother Cancer. 2016;4:80
6. Yanagihara T, Tanaka K, Ota K, et al. Tumor-infiltrating lymphocyte-mediated pleuritis followed by marked shrinkage of metastatic kidney cancer of the chest wall during nivolumab treatment. Ann Oncol. 2017;28:2038-39
7. Socinski MA, Jotte RM, Cappuzzo F, et al. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. N Engl J Med. 2018;378:2288-301
8. Xu C, Chen YP, Du XJ, et al. Comparative safety of immune checkpoint inhibitors in cancer: Systematic review and network meta-analysis. BMJ. 2018;363:k4226
9. Wang P-F, Chen Y, Song S-Y, et al. Immune-related adverse events associated with anti-PD-1/PD-L1 treatment for malignancies: A meta-analysis. Front Pharmacol. 2017;8:730
10. Mitchell MA, Hogan K, Amjadi K. Atezolizumab-induced sarcoid-like granulomatous reaction in a patient with urothelial cell carcinoma. Immunotherapy. 2018;10:1189-92
11. Horn L, Mansfield AS, Szczęsna A, et al. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. N Engl J Med. 2018;379:2220-29
12. Rahman NM, Ali NJ, Brown G, et al. Local anaesthetic thoracoscopy: British Thoracic Society Pleural Disease Guideline 2010. Thorax. 2010;65(Suppl. 2):ii54-60
13. Vakil E, Ost D, Vial MR, et al. Non-specific pleuritis in patients with active malignancy. Respirology. 2018;23:213-19
14. Naidoo J, Cottrell TR, Lipson EJ, et al. Chronic immune checkpoint inhibitor pneumonitis. J Immunother Cancer. 2020;8:e000840
15. Johnson DB, Taylor KB, Cohen JV, et al. Anti-PD-1-induced pneumonitis is associated with persistent imaging abnormalities in melanoma patients. Cancer Immunol Res. 2019;7:1755-59

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]