

# A Rare Complication after Adjuvant Atezolizumab Therapy for PD-L1-Positive Non-Small Cell Lung Cancer: A Case Report

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**How to cite this paper:** Futamata, T., Matsunaga, H., Yamashita, M., Imakiire, T., and Yoneda, S. (2026) A Rare Complication after Adjuvant Atezolizumab Therapy for PD-L1-Positive Non-Small Cell Lung Cancer: A Case Report. *Case Reports in Clinical Medicine*, 15, 229-234.  
<https://doi.org/10.4236/crcm.2026.156031>

**Received:** April 30, 2026

**Accepted:** May 30, 2026

**Published:** June 2, 2026

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## Abstract

In May 2022, atezolizumab, an immune checkpoint inhibitor (ICI), was approved as adjuvant therapy for PD-L1-positive non-small cell lung cancer (NSCLC). Following ICI administration, lymph node swelling due to drug-induced sarcoid-like reactions has been reported as a rare immune-related adverse event (irAE); however, it is difficult to distinguish from cancer recurrence or metastasis solely based on imaging findings. In this report, we present the case of a 76-year-old female who exhibited enlargement of an intrapulmonary nodule with abnormal accumulation on positron emission tomography-computed tomography (PET-CT) during adjuvant atezolizumab therapy. Suspecting lung cancer recurrence, a partial lung resection was performed; however, the final pathological diagnosis revealed normal lymph node swelling characterized primarily by lymphoid follicle formation without granulomas. This suggests the possibility that the lymph node swelling was caused by the excessive activation of lymphocytes, such as cytotoxic T lymphocytes (CTLs), associated with ICI administration. This suggests that CTL-driven reactive hyperplasia is a plausible hypothesis for the lymph node swelling associated with ICI administration, although causality cannot be definitively established from a single case. With the anticipated increase in patients receiving ICI therapy, the number of cases where it is difficult to distinguish between normal reactive lymph nodes and malignant tumors is expected to rise.

## Keywords

Atezolizumab, Non-Small Cell Lung Cancer, Immune-Related Adverse Events, Intrapulmonary Lymph Node Swelling, Case Report

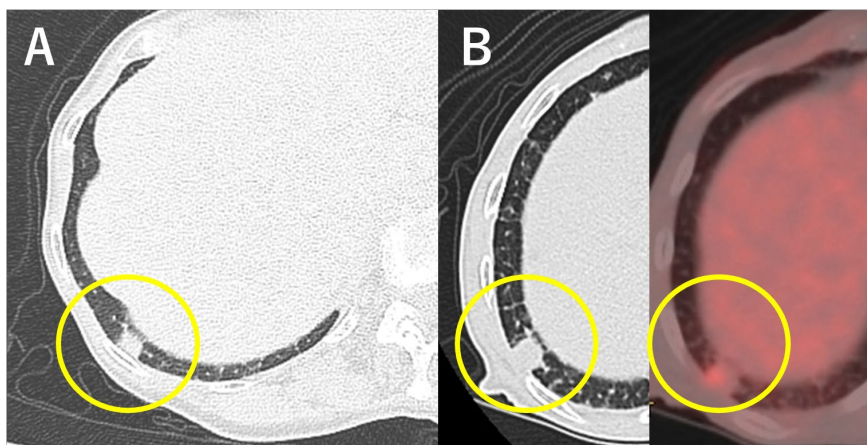
## 1. Introduction

ICIs play a crucial role in the treatment of NSCLC, and in May 2022, atezolizumab was approved as an adjuvant therapy for PD-L1-positive NSCLC. ICIs exert their antitumor effects by reactivating CTLs, which conversely can trigger various irAEs. Recently, drug-induced sarcoid-like reactions (DISR) accompanied by the formation of non-caseating granulomas have been sporadically reported as a rare complication following ICI administration. Such lymph node swelling is often accompanied by intense fluorodeoxyglucose (FDG) accumulation on PET-CT, making it extremely difficult to radiologically differentiate from recurrence of the primary disease or lymph node metastasis. Herein, we report a highly unusual case of a patient who received atezolizumab as an adjuvant therapy for PD-L1-positive lung adenocarcinoma. Although lung cancer recurrence was strongly suspected based on imaging, histopathological examination following surgical resection revealed the swelling of a normal lymph node without even a sarcoid-like reaction. We present this case along with a review of the relevant literature.

## 2. Case Presentation

A 76-year-old female presented to our hospital with the enlargement of an abnormal nodule in the right upper lobe on imaging. Her past medical history included hypertension, cervical cancer, cerebral aneurysm, pyelonephritis, colon polyps, and dementia. She had a smoking history of 5 to 6 cigarettes per day for approximately 56 years since the age of 20. In June 2022, the patient underwent a thoracoscopic right upper lobectomy and lymph node dissection for suspected right upper lobe lung cancer. The histopathological diagnosis was invasive non-mucinous adenocarcinoma, pT1bN2M0, Stage IIIA. The PD-L1 expression rate in the tumor tissue was high (70% - 90%), and the EGFR mutation was negative. As postoperative adjuvant chemotherapy, the patient received one course of CDDP and VNR therapy in July 2022, but the second course was cancelled due to renal impairment. Subsequently, adjuvant therapy with atezolizumab administered every three weeks was initiated three months after the surgery, in September 2022.

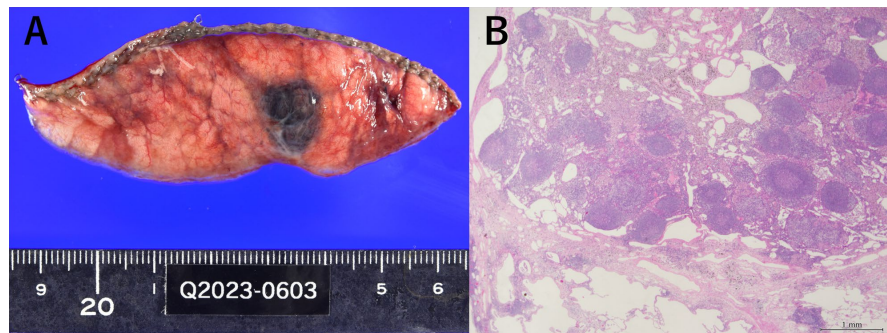
A small nodule in the right lower lobe had been present before the initial lobectomy. At that time, its baseline size was small, and it lacked highly suspicious features such as significant FDG uptake. Therefore, it was initially favored to be a benign intrapulmonary lymph node or an inflammatory change and was not targeted during the first surgery. However, in December 2022, after 3 months of atezolizumab administration, a chest CT revealed the enlargement of this right lower lobe nodule. A PET-CT scan performed in January 2023 showed further enlargement of the right lower lobe nodule with new mild abnormal accumulation (SUVmax of 2.75) (**Figure 1**), raising the suspicion of intrapulmonary recurrence. No obvious abnormal accumulation suggesting other lymph node metastases was pointed out.



**Figure 1.** Radiographic findings before and after atezolizumab treatment. (A) Non-contrast computed tomography (CT) before the initiation of atezolizumab, showing no significant FDG uptake on PET-CT (data not shown). (B) Follow-up non-contrast CT and PET-CT after 8 cycles of atezolizumab. The imaging reveals a newly developed lesion with an FDG uptake of SUVmax 2.75.

At the time the nodule enlargement was detected, the patient was afebrile and completely asymptomatic, without any respiratory symptoms such as cough or dyspnea. Tumor markers, including CEA (11.1 ng/mL), CYFRA (2.1 ng/mL), and ProGRP (86.8 pg/mL), were evaluated. There were no clinical or radiological signs of systemic sarcoidosis, such as uveitis or skin lesions, nor were there inflammatory markers or assessments suggesting active infections. Because the lesion was an intrapulmonary nodule, a bronchoscopic or percutaneous biopsy was deemed technically challenging and carried a high risk of yielding a false-negative or non-diagnostic result. Given the new abnormal FDG uptake strongly mimicking lung cancer recurrence, a video-assisted thoracoscopic surgery (VATS) partial resection of the right lower lobe was performed in March 2023 (after 8 courses of atezolizumab) to establish a definitive histopathological diagnosis and serve as a therapeutic excision. Intraoperative findings revealed a swollen intrapulmonary lymph node in the right lower lobe consistent with the preoperative CT, but no obvious tumor, pleural effusion, or disseminated nodules were observed elsewhere.

The partially resected lung contained a well-defined black nodular lesion with a maximum diameter of 1.5 cm (**Figure 2(A)**). Histologically, it was lymph node tissue with no evidence of malignancy or cancer metastasis. Furthermore, sarcoid-like reactions such as epithelioid cell granulomas were absent, and lymphoid follicle formation was predominant (**Figure 2(B)**). The resected lesion was considered to be normal lymph node swelling potentially caused by atezolizumab. Taking into account the patient's background, including the exacerbation of dementia, atezolizumab was discontinued postoperatively, and a policy of careful observation without treatment was adopted. To date, the patient has remained under watchful observation without any signs of cancer recurrence.



**Figure 2.** Pathological findings of the resected specimen. (A) Gross appearance: A well-circumscribed black nodular lesion with a maximum diameter of 1.5 cm is observed in the resected lung tissue. (B) Histological section (H&E staining): Microscopic examination shows predominant lymphoid follicle formation. There is no evidence of malignancy, infection, or sarcoid-like reaction (granuloma formation). (Scale bar: 1 mm).

### 3. Discussion

During the course of malignant tumors, it is known that sarcoid-like reactions (non-caseating granulomas) in regional lymph nodes occur in approximately 4% of patients due to immune responses to tumor antigens [1]-[3]. Recently, multiple cases have been reported where excessive immune responses triggered by treatment with anti-PD-1/PD-L1 antibodies, such as nivolumab and pembrolizumab—which reactivate CTLs—induce DISR [1] [4] [5]. Similar reports exist for atezolizumab. Recent peer-reviewed literature emphasizes that targeted therapies and immune checkpoint blockade can trigger an immune-stimulatory microenvironment leading to DISR and nodal pseudoprogession that radiologically mimic disease progression. As the use of these agents expands, awareness of benign reactive lymphadenopathy is becoming increasingly critical for oncologists and surgeons. It has been reported that there is no significant difference in the SUVmax values on PET-CT among sarcoidosis, sarcoid-like reactions, and malignant lymph node metastases, making it extremely difficult to differentiate these purely through diagnostic imaging [1] [6]. In the present case as well, lung cancer recurrence was suspected due to abnormal accumulation in the enlarged nodule on PET-CT, leading to the decision to perform surgical resection. However, a notable pathological feature of this case is that the resected swollen lymph node not only lacked malignant findings but also lacked any evidence of a “sarcoid-like reaction (granuloma formation)”. The pathological findings showed swelling of normal lymph node tissue predominantly with lymphoid follicle formation. As a possible mechanism for this, it is hypothesized that the administration of the ICI (atezolizumab) caused excessive activation and proliferation of lymphocytes, including CTLs, which led to the swelling of the regional lymph node itself without progressing to the step of a sarcoid-like reaction. However, a direct causal relationship cannot be definitively established from a single case report, and further accumulation of similar cases is necessary to fully confirm this pathogenesis. The clinical lesson demonstrated by this case is that when newly developed lymph node or nodule

enlargement is observed during ICI administration, one must consider the possibility of “swelling of a normal lymph node associated with increased lymphocytes”, in addition to “disease progression (recurrence/metastasis)” or “sarcoid-like reactions”. As the opportunities to use ICIs will increase in the future, it is highly likely that similar cases will be encountered. Because image differentiation currently has its limitations, the option of interrupting the medication temporarily to observe the clinical course—before immediately resorting to invasive biopsies or surgery—should be considered for safe management.

#### 4. Conclusions Ethics Statement

We experienced a rare case in which intrapulmonary lymph node swelling, which was radiologically difficult to differentiate from recurrence, occurred during adjuvant atezolizumab therapy for PD-L1-positive NSCLC, and was pathologically diagnosed as normal lymph node swelling without granuloma formation. When evaluating nodule and lymph node enlargement during ICI administration, it is necessary to make careful judgments, including the possibility of drug holidays (temporary discontinuation), keeping in mind the plausible hypothesis of benign lymph node swelling caused by an excessive immune response.

#### Ethics Statement

**Informed Consent** Written informed consent was obtained from the patient and her family for the publication of this case report and any accompanying images.

#### Acknowledgements

The authors would like to thank our colleagues for their insightful discussions and valuable comments throughout the development of this study.

#### Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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