Marked Response after One Cycle of Pembrolizumab Monotherapy for Non-small Cell Lung Cancer: A Case Report and Brief Review of the Literature

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Abstract

Introduction: To date, there have been few reports of Non-Small Cell Lung Cancer (NSCLC) cases where a single cycle of pembrolizumab monotherapy led to near-complete tumor resolution without any adverse events.

Case Presentation: A 57-year-old woman with clinical stage IVB NSCLC and high Programmed Cell Death ligand 1 (PD-L1) expression of 95% received first-line pembrolizumab monotherapy. After only one cycle of the therapy, she experienced a significant improvement in respiratory symptoms and showed a nearly complete tumor response on CT. To date, the patient has received 15 cycles of pembrolizumab and sustained a complete response without any immune or treatment-related adverse events for 15 months.

Conclusion: Our literature search yielded 11 similar case reports in addition to this report. According to them, the mechanism of such rapid tumor disappearance after pembrolizumab monotherapy remains unclear; however, close attention should be paid to fatal hemoptysis as a treatment-related adverse event, if the patient shows hilar or mediastinal lesions with suspected vascular invasion on baseline CT.

Keywords: Non-Small Cell Lung Cancer (NSCLC) • Pembrolizumab • Monotherapy • Marked response • Stage IV

Abbreviations: ICI: Immune Check-Point Inhibitor; NSCLC: Non-Small Cell Lung Cancer, PD-L1: Programmed Cell Death Ligand 1; irAE: immuno-related Adverse Event; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; CR: Complete Response; TLS: Tertiary Lymphoid Structure

Introduction

The results of the KEYNOTE-024 trial showed that pembrolizumab was associated with longer progression-free and overall survival than platinum-based combination chemotherapy in patients with previously untreated advanced Non-Small Cell Lung Cancer (NSCLC) and a Programmed Cell Death Ligand 1 (PD-L1) tumor proportion score ≥ 50% [1]. The histopathologic features of pathologic response to ICI may diverge from those reported for chemotherapy [2]. A spider plot of tumor burden changes on CT after first-line pembrolizumab monotherapy in 88 advanced NSCLC patients showed that 63% had a sustained reduction in tumor size. However, no patients showed a reduction of more than 60% within the first 8 weeks of treatment [3].

Immune-related Adverse Events (irAEs) involve inflammatory reactions against normal, healthy tissue that occur due to ICI-induced activation of the immune system. The irAEs may be severe or life-threatening, or lead to long-term toxicity. However, the occurrence of certain irAEs is associated with a survival benefit in patients with NSCLC expressing PD-L1 ≥ 50% receiving pembrolizumab [4].

As exceptional cases, there was reportedly a very rapid and marked response to pembrolizumab monotherapy in NSCLC patients [5-14]. In this study, we report a case of marked tumor shrinkage after a single cycle of pembrolizumab monotherapy, without any irAEs or shrinkage-related complications. We reviewed the literature to clarify the clinical and pathological features of similar cases.

Case Presentation

A 57-year-old Japanese woman was referred to the Department of Orthopedic Surgery of Kindai University Faculty of Medicine for pathological fracture of the left tibia on May 1, 2024. She underwent open reduction and internal fixation without cancer tissue resection for the fracture. She was a current smoker of 37 pack-years. From the beginning of April 2024, she had a persistent cough, and chest CT revealed a large mass extending from the right hilum to mediastinum fused with lymph node metastases, nearly obstructing the right main bronchus and compressing the pulmonary artery.

On May 7, 2024, endobronchial ultrasound-guided transbronchial needle aspiration revealed no histological evidence of glandular duct formation or mucous production, keratinization nor intercellular bridges on hematoxylin-eosin staining (Figure 1). Immunohistochemical staining of neoplastic cells was positive for CK7, weakly positive for p40 and SP-A, and negative for TTF-1, CK5/6, napsin A, synaptophysin, chromogranin A, CD56, and CK20. PD-L1 expression as measured by the 22C3 pharm DX assay (Dako, Agilent, Tokyo, JAPAN) was 95%. An Oncomine TM DX target test showed no genomic alteration of EGFR, ALK, RET, ROS1, BRAF, KRAS, or MET in the tumor sample. Immunohistochemically clear differentiation toward adenocarcinoma or squamous cell carcinoma was not revealed, being clinically defined as T4N3M1c, stage IVB, NSCLC (8th Edition).

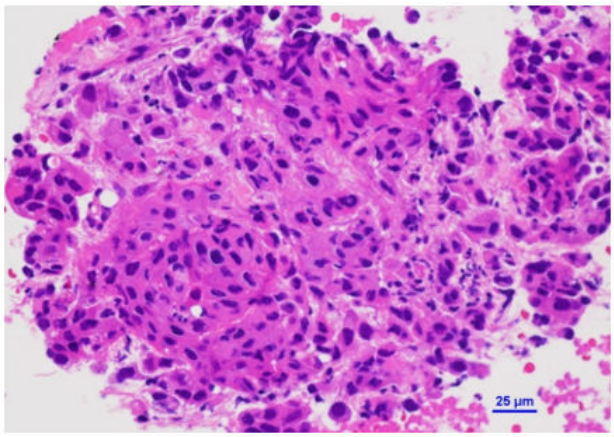

Figure 1. Hematoxylin and Eosin (HE) staining of a transbronchial biopsy specimen showing NSCLC without differentiating into squamous cell carcinoma or adenocarcinoma. Scale bars, 25 μm.

Then, due to family reasons, the patient was referred to Yao Municipal Hospital to undergo further systemic anticancer treatment. She was able to walk with crutches. Palpation revealed a 2 cm subcutaneous nodule showing a tendency to grow in the lower abdomen, suggesting subcutaneous metastasis. Chest auscultation revealed decreased right-sided breath sounds. She was mildly tachypneic, and pulse oximetry was 95% in room air.

Her white blood cell count was 9,7 × 10^3/μL (lymphocytes: 19.2%). Blood testing indicated elevated KL-6 of 1110 U/mL (reference range: <500 U/mL). Serum tumor markers were slightly high: CA19-9, 62.8 U/mL (reference range: <37.0 U/mL); SCC, 1.7 ng/mL (reference range: <1.5 ng/mL); NSE, 17.9 ng/mL (reference range: <16.3 ng/mL); CYFRA, 6.4 ng/mL (reference range: <3.5 ng/mL). CEA and Pro GRP levels were within normal limits. Her Eastern Cooperative Oncology Group performance status (ECOG-PS) score was 3.

Considering her PS and PD-L1 expression status, it was agreed that pembrolizumab monotherapy was preferable to combination chemo-immunotherapy [1]. At that time, there was concern that if the right main bronchus had been completely obstructed by tumor progression, the patient's respiratory condition might rapidly deteriorate. If the disease had progressed, palliative bronchial stenting and/or emergency radiation therapy would have been considered.

Pembrolizumab was started at a dose of 200 mg on June 21, 2024. Baseline contrast-enhanced CT taken on June 28, 2024 (Figure 2) showed a 6.8 × 5.4 cm right hilar mass that directly extended to the mediastinum, causing marked stenosis of the right main bronchus, and significant swelling of the pretracheal and subcarinal lymph nodes. The right pulmonary artery was markedly compressed by the tumor (Figure 2). Two subcutaneous metastases were noted in her back (Figure 2). On July 18, 2024, as the chest radiograph taken before the 2nd cycle of pembrolizumab showed marked shrinkage of the right hilar shadow, we added plain chest CT. As shown in Figure 2, marked shrinkage of the main tumor and subcutaneous metastases was identified. Her general condition has markedly improved (ECOG-PS of 1), and prophylactic radiation therapy was administered to the pathological fracture site of the left tibia. A contrast-enhanced CT scan performed on September 4, 2024, after completion of four cycles of pembrolizumab, showed a near Complete Response (CR) (Figure 2). Stenosis of the right main bronchus and vascular compression were completely resolved (Figure 2). At the start of ICI therapy in June 2024, the patient's body weight was 49 kg, indicating weight loss; however, by August 2025, after receiving 15 cycles of pembrolizumab, her weight had recovered to 55.9 kg, returning to her normal pre-illness level. The CR has been maintained as of August 2025 (Figure 2), during which no irAEs were observed and the ECOG-PS remained at 1.

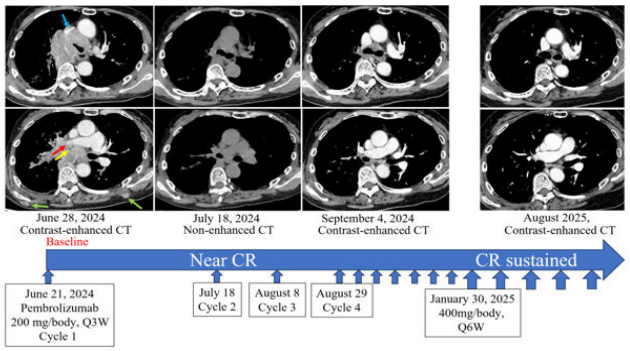

Figure 2. Clinical course.

Note: Baseline contrast-enhanced chest CT showing a 6.8 × 5.4 cm right hilar primary tumor with confluent mediastinal and hilar lymphadenopathy, and severe stenosis of the right main bronchus (yellow arrow). The right pulmonary artery (red arrow) and superior vena cava (blue arrow) was compressed by the tumor (red arrow). Two subcutaneous metastases (green arrows) were identified. A non-enhanced CT scan taken before the 2nd cycle of pembrolizumab shows marked shrinkage of both the primary tumor and the subcutaneous metastases.

Contrast-enhanced CT taken before the 4th cycle of pembrolizumab showing a near CR. Bronchial stenosis and compression to the pulmonary artery were completely resolved.

As of August 2025, a total of 16 cycles of pembrolizumab have been administered, and a CR has been maintained. CR: Complete Response.

Results and Discussion

We conducted baseline contrast enhanced CT (Figure 2) 7 days after the first cycle of pembrolizumab. When comparing the image with plain CT 20 days later, immediately before the 2nd cycle of pembrolizumab, a near CR was achieved for both the primary lesion and multiple subcutaneous metastases (Figure 2). A study using tissue specimens obtained before treatment revealed that NSCLC patients undergoing pembrolizumab treatment with favorable responses exhibited specific tumor characteristics, including larger proportions of viable tumor cells (smaller proportion of extracellular stroma), and increased tumor-infiltrating lymphocytes, indicating treatment effectiveness [15]. Histopathologic features on immune-mediated regression in NSCLC resection specimens are characterized by dense immune infiltrates with features of activation (Tertiary Lymphoid Structure (TLS), dense tumor infiltratinng lymphocytes infiltrates and plasma cells, granuloma formation), along with features of cell death (cholesterol clefts, interstitial foamy macrophages), and tissue repair/wound healing, such as neovascularization and new, proliferative fibrosis [2]. However, we found no reports describing how long it would take for the apoptotic cancer cells to undergo lysis and necrosis together with the tumor stroma, be removed by phagocytosis, and become invisible on images. The mechanism by which our patient's 6.8 cm-diameter tumor disappeared in just three weeks remains unknown. In addition, interviewing the patient revealed no episodes of the tumor or necrotic material being excreted via the airway.

We include a literature review involving 12 cases of pembrolizumab monotherapy as first-line treatment for patients with advanced NSCLC who showed a rapid and significant response, similar to our patient [5-14]. As summarized in Table 1, patients with a rapidly marked response to first-line pembrolizumab monotherapy were predominantly smokers, and had adenocarcinomas. All patients except the present case were male. All except one case (not described) had a PD-L1 expression rate of 50% or higher. Four of the 12 cases had a tumor originating from the peripheral lung and metastasizing to hilar and/or mediastinal lymph nodes closely contacting a great vessel or

bronchus. Of note, 2 of the 12 patients died suddenly of hemoptysis early after the first cycle of pembrolizumab administration [6,9], and another died of sudden hemoptysis at 28 weeks [10]. According to reports, in cases where tumor invasion into the pulmonary artery is suspected on pre-treatment contrast-enhanced CT, close attention should be paid to the risk of fatal hemoptysis when a significant response to pembrolizumab with rapid formation of cavitation, abscessation or necrosis in the tumor [6,10], or a deep and rapid tumor shrinkage is deemed responsible for the lethal hemorrhagic event [9]. In the present case, there was significant tumor shrinkage in a very short time, but the walls of the pulmonary artery, suspected to be infiltrated by the tumor (Figure 2), had recovered to a smooth appearance, and the bronchus buried by the tumor regained a normal shape on imaging (Figure 2). Thus, we assume that the fatal hemoptysis could have been avoided without forming a bronchopulmonary artery fistula.

Table 1. Reported cases of NSCLC with marked response to the first line pembrolizum ab monotherapy.

No.	First author, Year [Ref. no.]	Age (Years)/ Sex	Smoker	Histologic type/tumor location	Involved organs at hilum and mediastinum	Stage at initial diagnosis	PD-L1 expression (5%)	Cycle (s) of Pembrolizumab before evaluation	Response	irAE	Survival after start of treatment	Relevance
1	Hui Z, et al. 2015 [5]	73/male	Unknown	Squamous cell ca. (grade 3)/central type	Obstruction of the left bronchus.	IVA	Unknown	2	PR	Low grade fatigue, decreased apptit and vitiligo	4 months/ alive	Seven pre-existing thrombocytopenia. Combined autologous cytokine-induced killer cell therapy. No tumor recurrence after 5 cycles of pembrolizumab.
2	Artal-Cortes A, et al. 2018 [6]	64/male	Yes	Adenocarcinoma (grade 3)/ central type	Compressing and embracing the let PA.	IVB	80	1	Cavitation?	No	15 days/ dead	Massive hemoptysis from the tumor with central location.
3	Yamaura T, et al. 2018 [7]	79/male	Yes	Adenocarcinoma/ peripheral type	Left hilar lymph node invading the PA.	IIIA	95	1	CR	No	Unknown	Pesudo progression. Loss of *EGFR* gene mutation after TKI therapy.
4	McLoughlin EM, et al. 2019 [8]	60/male	Yes	Poorly diff. Ca./ central type	Obstructing the right mainstem bronchus.	IIIB	80	2	Near CR	No	Unknown	Switch to pembrolizumab because of no clinical response to emergent RT. *STK11* mutation.
5	Facchinetti F, et al. 2019 [9]	79/male	Yes	Adenocarcinoma (mucinous)/ central type	Invading the left PA.	IVA	50	1	Rapid disease shrinkage	No	5 days/ dead	Massive hemoptysis from the tumor with central location.
6	Wang R, et al. 2020 [10]	55/male	Yes	Adenocarcinoma/ central type	Giant mass lesion in the right lung with compression of the trachea and esophagus.	IV	60	4	PR	Grade-3 interstitial pneumonitis	28 weeks/ dead	Massive hemoptysis from the tumor with central location.

7	Kato M, et al. 2021 [11]	88/male	Unknown	Adenocarcinoma/ peripheral type	Right supraclavicular and mediastinal lymph node swelling.	IVA	70	1	Significant metabolic response on PET	Relapse of pre-existing organizing pneumonia	6 months/ alive	Pre-existing organizing pneumonia
8	Zhu X, et al. 2021 [12]	67/male	Unknown	Adenocarcinoma/ peripheral use	Right supraclavicular, mediastinal, and hilar lymph node swelling.	IV	80	1	PR	No severe irAEs	29 months/ alive	*SMARCA4*-deficient and *KRAS* co-mutation
9	Gohara K, et al. 2021 [13]	87/male	Yes	Adenocarcinoma (grade 3)/ central type	Large mass (7 cm) in the hilum lumped together with lymph nodes.	IIIB	90	2	PR	No	36 months/ alive	35 cycles of pembrolizumab. CR maintained after 9 cycles.
10	Gohara K, et al. 2021 [13]	63/male	Yes	Adenocarcinoma/ peripheral type	Right upper lobe mass. Hilar, mediastinal, and cervical lymph node swelling. Lymphangitic carcinomatosis.	IVB	70	2	PR	No	42 months/ alive	34 cycles of pembrolizumab. CR maintained after 12 cycles
11	Kondo Y, et al. 2022 [14]	79/male	Yes	Adenocarcinoma/ central type	Right middle lobe mass. Hilar and mediastinal lymph node swelling.	IIIC	100	1	Near-CR	Grade-3 hepatitis	18 months/ alive	80 mg/body of prednisolone with tapering and discontinuation. No tumor recurrence in absence of treatment.
12	Kodama K, et al. 2025 [present case]	57/female	Yes	NSCLC/ central type	6.8 cm hilar mass obstructing the right main bronchus and invading PA. Subcutaneous nodes.	IVB	95	1	Near-CR	No	15 months/ alive	No tumor recurrence after 15 cycles of pembrolizumab.

Note: PD-L1: Programmed Cell Death Ligand 1; irAEs: immune-related Adverse Events; PA: Pulmonary Artery; PR: Partial Response; CR: Complete Response; EGFR: Epidermal Growth Factor Receptor; TKI: Tyrosine Kinase Inhibitor; RT: Radiation Therapy, ARID1A: At-Rich Interaction Domain 1A; TMB: Tumor Mutation Burden; PET: Positron Emission Tomography; SMARCA4: SWI/SNF Related, Matrix Associated, Actin-Dependent Regulator of Chromatin, subfamily A, member 4, NSCLC: Non-Small Cell Lung Cancer

Based on a study with a large real-world cohort of NSCLC patients with PD-L1 expression ≥ 50%, the occurrence of irAEs may be a surrogate of clinical activity and improved outcomes in retrospective analysis [16]. However, the results of this literature review of 12 special cases of extremely rapid and marked tumor shrinkage did not provide a clear picture of the causal relationship between pembrolizumab efficacy and irAEs.

Conclusion

In conclusion, this case highlights that urgent intervention was prioritized to relieve the severe airway obstruction, which unexpectedly resulted in extremely rapid tumor regression. As a limitation, re-biopsy could not be performed, and therefore, cancer tissue was not available for further genetic analysis or for the investigation of its immune microenvironment. The mechanism underlying such rapid and dramatic tumor shrinkage remains unclear, especially in the absence of irAEs. Furthermore, when using ICIs in patients with centrally located, vessel-infiltrating tumors that strongly express PD-L1, careful clinical monitoring is warranted due to the potential risk of massive and fatal hemoptysis.

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Ethics Approval

This study was approved by the Institutional Review Board (IRB) of Yao Municipal Hospital Osaka, Japan (approval no. 041024-226).

Consent for Publication

We obtained written informed consent from the patient for the publication of this article.

Author Contributions

Ken Kodama: Conceptualization, data curation, writing – original draft, writing – review and editing, supervision. Toru Momozane: Investigation, resources, data curation. Hiroshi Takehara: Investigation, resources, validation. Junko Tanizaki: Investigation, methodology, resources. Kazuaki Sato: Data curation, visualization, supervision.

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Disclosure

The authors declare no conflicts of interest.

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