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A 79-Year-Old Woman With Stage IIIB Lung Squamous Cell Carcinoma Presenting With Late-Onset Durvalumab-Associated Myocarditis Requiring Differentiation From Pericardial Invasion

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

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Patient: Female, 79-year-old
Final Diagnosis: Durvalumab-associated myocarditis
Symptoms: Cardiomegaly • dyspnea
Clinical Procedure: —
Specialty: Cardiology • Oncology • Pulmonology
Objective: Unusual clinical course

Background: Durvalumab is a humanized monoclonal antibody and immune checkpoint inhibitor used for the treatment of advanced non-small cell lung cancer. Myocarditis, particularly in late-onset cases, is a rare but serious adverse event associated with durvalumab. This report describes a 79-year-old woman with non-small cell lung cancer who developed late-onset myocarditis requiring differentiation from direct pericardial invasion.

Case Report: A 79-year-old woman with stage IIIB lung squamous cell carcinoma developed myocarditis after 11 cycles of durvalumab maintenance therapy (5 months after initiation) following chemoradiation. She presented with reduced cardiac function, pericardial effusion, and elevated high-sensitivity troponin T, initially raising concern for pericardial invasion because the primary tumor was in direct contact with the myocardium. Urgent myocardial biopsy confirmed immune checkpoint inhibitor-related myocarditis, showing mononuclear lymphocyte and macrophage infiltration. Her condition improved after discontinuation of durvalumab and initiation of high-dose corticosteroids and intravenous immunoglobulin. Cardiac function recovered within 3 weeks, and biomarkers normalized. Notably, she has maintained a complete oncologic response for more than four years without further cancer treatment or recurrence of myocarditis, suggesting a durable antitumor effect despite early discontinuation of immunotherapy.

Conclusions: This case highlights the diagnostic challenge of distinguishing immune checkpoint inhibitor-induced myocarditis from direct cardiac invasion in patients with lung cancer, particularly in late-onset presentations. Early myocardial biopsy enabled prompt diagnosis and treatment, leading to a favorable long-term outcome. Careful cardiac monitoring is essential, and immune-related adverse events should be considered even when tumor invasion is suspected.

Keywords: Myocarditis • Neoplasms
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Introduction

Immune checkpoint inhibitors (ICIs) are integral to the pharmacologic management of lung cancer, as reflected in current treatment guidelines. By inhibiting immunosuppressive signaling pathways originating from antigen-presenting cells and tumor cells, ICIs maintain T-cell activation and promote antitumor immune responses [1]. As a result, unlike conventional cytotoxic anticancer agents, ICIs are associated with a diverse spectrum of immune-related adverse events (irAEs). Among these, myocarditis—although rare—has a high mortality rate once diagnosed, necessitating prompt recognition and treatment [2].

At present, 8 ICIs have received approval for use in lung cancer therapy. Compared with more frequently observed irAEs, such as thyroid or hepatic dysfunction, myocarditis is relatively uncommon. Myocarditis is an inflammatory disorder of the myocardium that can be triggered by malignancy, viral infection, autoimmune processes, drugs, or eosinophilia [3,4]. Histopathologically, it is categorized as eosinophilic, lymphocytic, giant cell, granulomatous, or pleomorphic, depending on the predominant cellular infiltrate within the myocardium.

Durvalumab is a human IgG1 monoclonal antibody targeting programmed death-ligand 1 (PD-L1) and is approved as consolidation therapy following concurrent chemoradiotherapy (CCRT) for stage III non-small cell lung cancer, based on the PACIFIC regimen [5]. In addition to its established role in lung cancer, its indications have recently been expanded to other malignancies, including liver cancer, biliary tract cancer, endometrial cancer, bladder cancer, and small cell lung cancer [6].

Although generally well tolerated, durvalumab can cause irAEs, including pneumonitis, thyroid dysfunction, hepatitis, colitis, and, rarely, myocarditis [7]. The incidence of ICI-associated myocarditis is estimated at 0.27% to 1.14%, although reports specifically involving durvalumab remain limited [8-10]. Several similar cases of durvalumab-associated myocarditis, including late-onset presentations, have been reported, such as those described by Maetani et al [11] and Khreisat et al [12]. These reports highlight the diagnostic challenges and potential severity of this adverse event.

This report describes the case of a 79-year-old woman with advanced squamous cell carcinoma of the lung who developed myocarditis following durvalumab treatment, requiring myocardial biopsy for definitive diagnosis.

Case Report

A 79-year-old woman with a >50 pack-year smoking history and hypertension, but no history of diabetes mellitus, dyslipidemia, or family history of coronary artery disease, was diagnosed with stage IIIB (T3N2M0) lung squamous cell carcinoma. No actionable driver mutations were identified, and the patient's PD-L1 tumor proportion score was <1%. With a performance status of 0, she was started on CCRT followed by PD-L1 inhibitor therapy.

She underwent 2 cycles of carboplatin combined with tegafur/gimeracil/oteracil (S-1) and received 50 Gy of thoracic radiation, followed by bi-weekly durvalumab. Because chest computed tomography (CT) demonstrated direct contact between the tumor and the heart, periodic echocardiographic monitoring was performed (**Figure 1A, 1B**).

After 11 cycles of durvalumab (5 months after initiation), routine follow-up echocardiography revealed a significant decline in left ventricular ejection fraction to approximately 30% by visual estimation, with diffuse hypokinesis and pericardial effusion. CT showed circumferential pericardial effusion and right-sided pleural effusion (**Figure 1C**). Electrocardiogram (ECG) revealed sinus tachycardia, generalized low voltage across all limb and chest leads, T-wave inversions in the anterior leads, and a QS complex pattern in V1-V2, which differed significantly from her previous ECG (**Figure 2A, 2B**).

On emergency admission, the patient was afebrile, with a blood pressure of 145/91 mmHg, heart rate of 107 beats/min, respiratory rate of 20 breaths/min, and oxygen saturation of 97% on room air. Laboratory evaluation revealed elevated markers of myocardial injury, including NT-proBNP (2064.0 pg/mL), high-sensitivity cardiac troponin T (hs-cTn; 0.663 ng/mL), and creatine kinase-myocardial band (CK-MB; 18.9 ng/mL).

Given the tumor's proximity to the heart, both pericardial invasion by lung cancer and durvalumab-induced myocarditis were considered. To establish a definitive diagnosis, urgent myocardial biopsy was performed on the day of admission. Histological examination revealed mononuclear lymphocyte and macrophage infiltration consistent with ICI-associated myocarditis, with no malignant cells identified (**Figure 3A-3C**). Coronary angiography was simultaneously performed, revealing normal coronary arteries. Although the creatine kinase (CK) level (322 IU/L) was mildly elevated, the patient exhibited no muscle weakness, such as respiratory fatigue or dysphagia, during her clinical course. Furthermore, neither myositis nor a myasthenia gravis-like syndrome was associated with the myocarditis.

High-dose methylprednisolone (1000 mg daily for 3 days) and intravenous immunoglobulin (IVIG; 400 mg/kg for 5 days) were initiated immediately following the endomyocardial biopsy. A beta-blocker (carvedilol 2.5 mg) and an angiotensin-converting enzyme inhibitor (enalapril 2.5 mg) were also initiated for diuretic and cardioprotective purposes. Oral prednisolone

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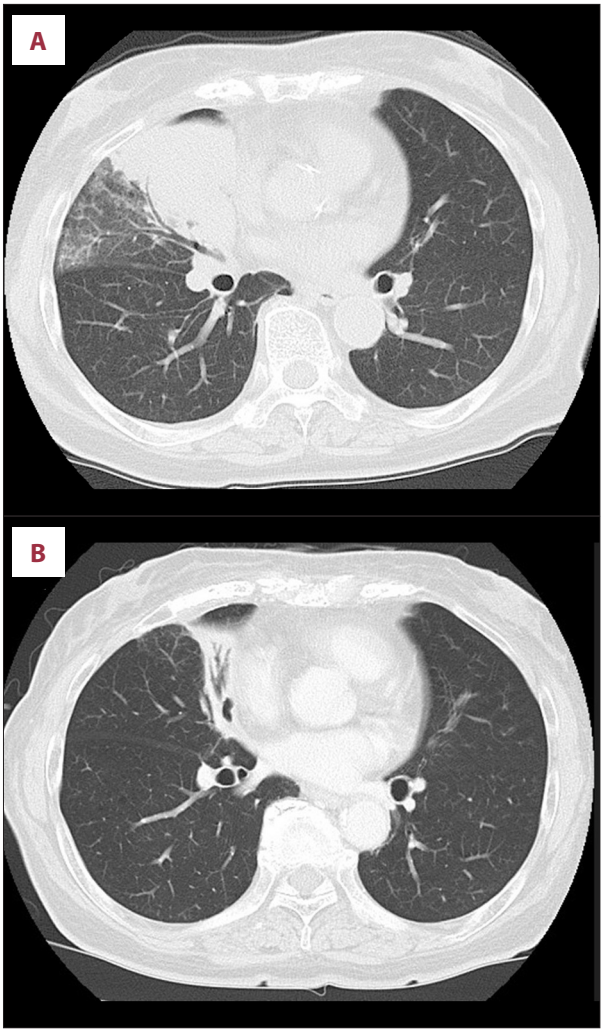

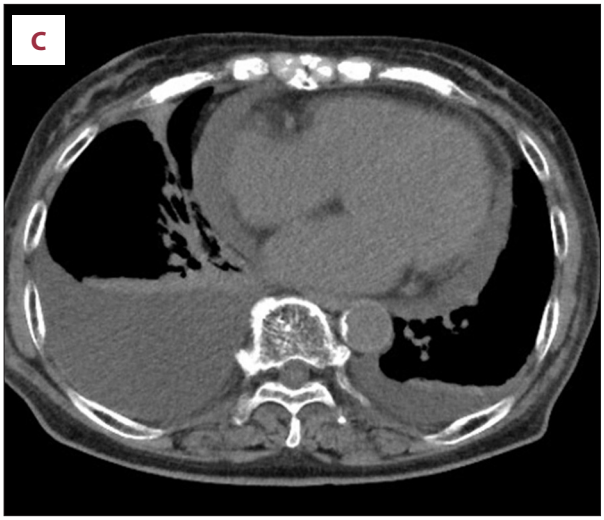

Figure 1. (**A**) Chest CT at diagnosis (April/202X): A large tumor is observed in contact with the pericardium, although CT alone cannot determine whether myocardial invasion is present. (**B**) Chest CT after concurrent chemoradiotherapy (CCRT) (September/202X): The tumor has shrunk, and only a small shadow remains after CCRT was performed; this indicates a therapeutic effect of CCRT. (**C**) Chest CT at the onset of myocarditis as an irAE (May/202X+1): circumferential pericardial effusion and predominantly right-sided pleural effusion are observed.

(1 mg/kg) was initiated and subsequently tapered by 5 mg each week. After 1 week, levels of hs-cTn (0.327 ng/mL), CK-MB (3.8 IU/L), and CK (65 IU/L) had declined; however, NT-proBNP levels did not exhibit a corresponding reduction. Clinical improvement in myocarditis was observed following discontinuation of durvalumab and initiation of steroid therapy.

After 3 weeks, echocardiography demonstrated recovery of left ventricular ejection fraction to approximately 50% by visual assessment, normalization of wall motion, and near-complete resolution of the pericardial effusion. Since discharge, she has experienced no evidence of cardiac decline or lung cancer relapse for over 4 years, without the need for additional anticancer treatment.

Discussion

We report a rare case of late-onset durvalumab-associated myocarditis in an older adult patient, which required differentiation from pericardial invasion by lung squamous cell carcinoma. Although myocarditis is an uncommon irAE, its reported mortality rate remains high [13], underscoring the importance of early recognition and prompt intervention. The underlying mechanism of ICI-induced myocarditis has not been fully elucidated; however, excessive activation of T lymphocytes is thought to play a central role. Histopathological findings typically include infiltration of $CD8^+$ lymphocytes and $CD68^+$ macrophages [14], consistent with the findings in our patient. While the overall incidence of cardiac irAEs is low (0.27% to 1.14%) [8-10], their severity warrants careful monitoring, particularly in older adults.

Although myocarditis generally occurs within the first 3 months after ICI initiation [10,13], several reports have described late-onset cases [11,15,16]. In our patient, myocarditis developed 5 months after starting durvalumab. Myocardial invasion by cancer was initially suspected because the primary lung tumor was in direct contact with the myocardium. However, previous reports, including that by Zamami et al, have suggested that ICI-related myocarditis may be more frequent in older adults [17], and late-onset irAEs have also been documented [11,12]. These reports describe late-onset ICI-related myocarditis and underscore the importance of continued clinical surveillance. Although our case also was late-onset irAE, chest CT demonstrated direct tumor–cardiac contact, prompting

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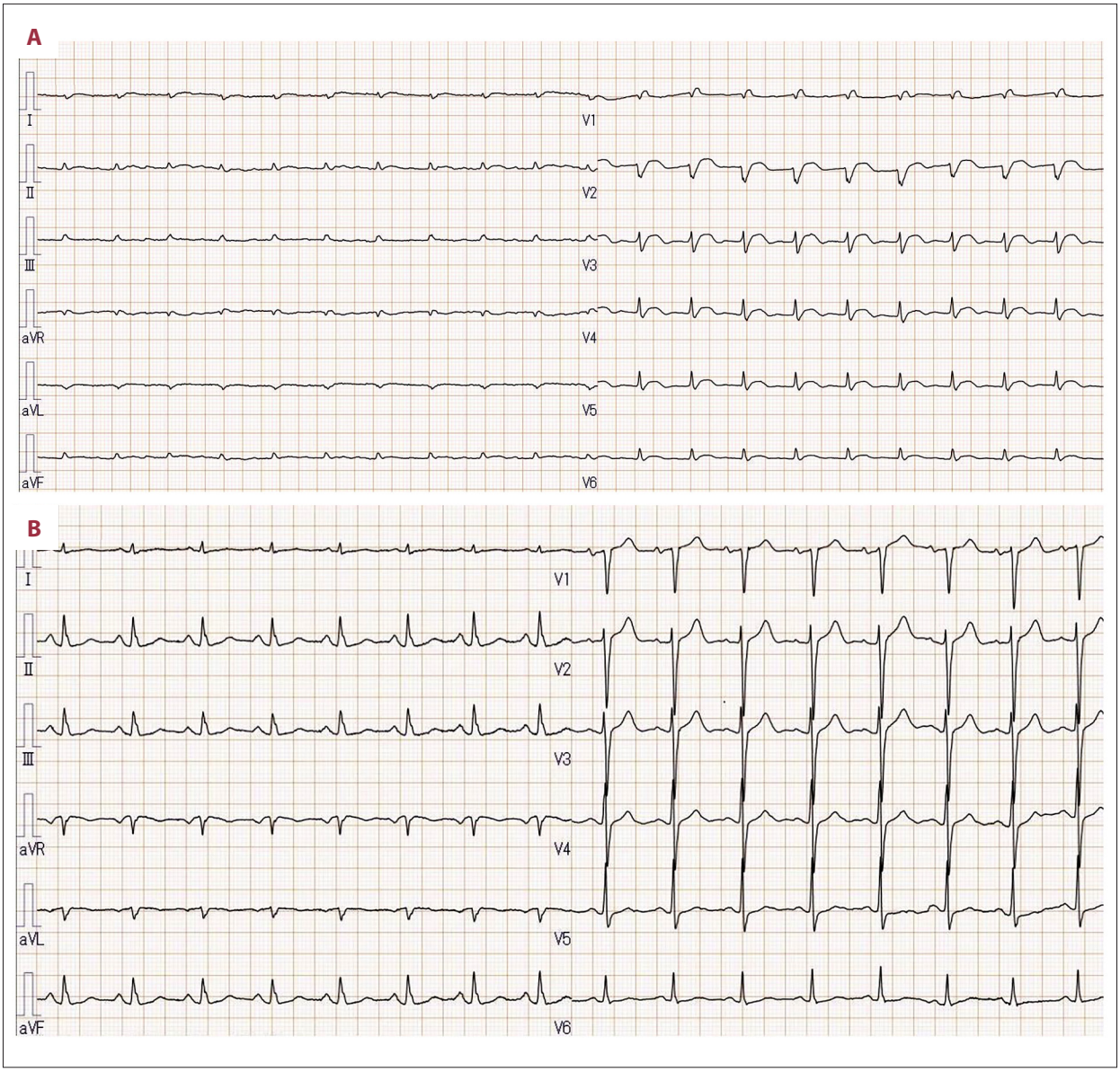

Figure 2. (**A**) Electrocardiogram after concurrent chemoradiotherapy (CCRT): sinus rhythm within normal limits. (**B**) Electrocardiogram at the onset of myocarditis as an irAE: findings include sinus tachycardia, low voltage in all limb and chest leads, T-wave inversion in anterior leads, and a V1-V2 QS pattern.

regular echocardiographic monitoring. This approach allowed us to perform a myocardial biopsy on the day of presentation, facilitating a prompt and definitive diagnosis and enabling timely initiation of therapy. These considerations prompted us to perform an urgent myocardial biopsy on the day of admission, which enabled a definitive diagnosis and timely treatment.

Biomarkers such as troponin, CK, and ECG abnormalities are useful for detecting cardiac irAEs [18,19]; in our case, hs-cTn and CK-MB decreased in parallel with clinical improvement. However, these biomarkers can also be elevated in cases of myocardial invasion by cancer, thereby limiting their diagnostic specificity. Therefore, when feasible, myocardial biopsy should be performed promptly. In institutions where myocardial biopsy is difficult to perform, cardiac MRI or FDG-PET can serve as alternative diagnostic modalities [20-22]. With respect to treatment, high-dose corticosteroids remain the standard of care for ICI-induced myocarditis. Although evidence supporting the use of IVIG is limited [23], its immunomodulatory effects may be beneficial, as suggested in this case. Although this patient ultimately improved with early therapeutic intervention, the myocarditis was a severe irAE.

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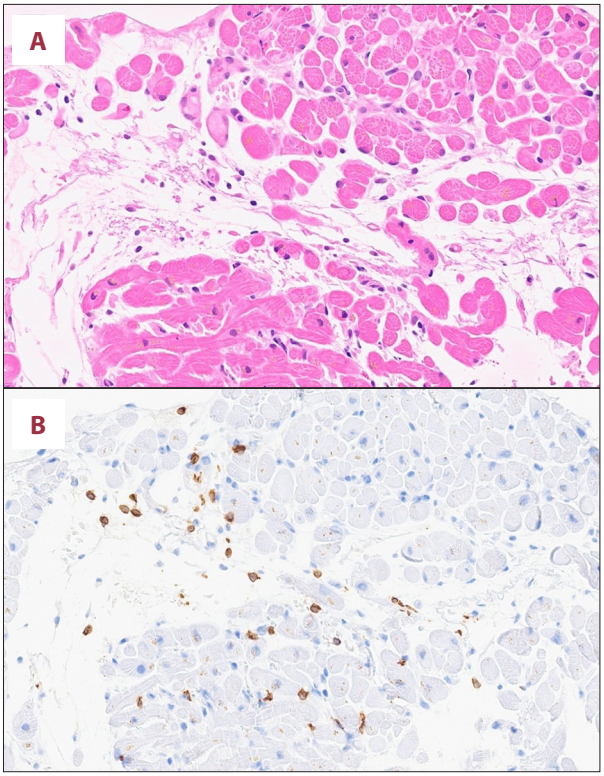

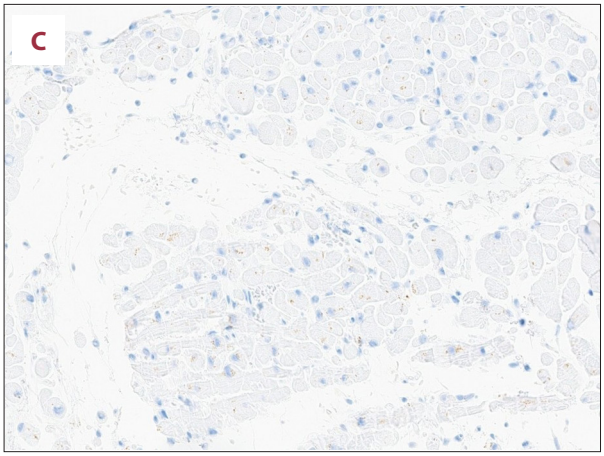

Figure 3. Myocardial biopsy demonstrating lymphocytic and macrophage infiltration without evidence of malignant cells, supporting the diagnosis of myocarditis and excluding myocardial invasion. (**A**) Hematoxylin–eosin staining and immunohistochemistry ((**B**) CD3, (**C**) CD20); original magnification ×200. Immunostaining revealed an inflammatory infiltrate predominantly composed of CD3-positive T cells. These cells were distributed within the myocardium, involving the subendocardial and myocardial fibers as well as the perivascular regions. CD20-positive B-cell infiltration was minimal. The findings were consistent with a T-cell–predominant lymphocytic infiltrate.

Previous studies have suggested that patients who develop severe irAEs may experience more favorable antitumor responses [24-26]. Given the limited clinical evidence on PD-L1 inhibitor–associated myocarditis, this case provides valuable insight into the diagnosis, management, and long-term prognosis of this rare but serious event.

Conclusions

This case highlights the diagnostic challenges of distinguishing ICI-induced myocarditis from myocardial invasion by lung cancer, particularly in older adults and in late-onset presentations. In our patient, prompt myocardial biopsy enabled early and definitive diagnosis, allowing timely initiation of immunosuppressive therapy and resulting in a favorable clinical course. Despite receiving durvalumab for only 5 months, the patient has maintained a complete response for more than 4 years.

Institution Where Work Was Done

Toho University Ohashi Medical Center, Tokyo, Japan.

Informed Consent

Written informed consent for publication was obtained from the patient.

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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.

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