Lung squamous cell carcinoma with metastases in the left atrium and left ventricle responds to treatment with immunotherapy: A case report

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Received July 11, 2024; Accepted October 15, 2024

DOI: 10.3892/ol.2024.14826

Abstract. Tumor metastasis is a phenomenon in which tumor cells grow in distant organs far from their primary site and is the final and most lethal manifestation of cancer. Most patients with cancer succumb to metastatic disease, not primary tumors. The occurrence of cardiac metastases is rare, but any primary tumor can potentially metastasize to the heart. The present report describes a 71-year-old male with stage IV lung squamous cell carcinoma who was diagnosed with cardiac metastases. These were identified as pedicled structures in the left atrium and left ventricle via echocardiography and positron emission tomography/computed tomography (PET/CT) prior to curative therapy. PET/CT imaging confirmed increased uptake of the tracer in these regions, indicating malignancy. Given the high expression of programmed cell death-ligand 1, the patient was treated with sintilimab immunotherapy. Despite a transient increase in liver function markers during treatment, the patient completed eight cycles of immunotherapy. Notably, both the primary lung tumor and cardiac metastases were markedly reduced in size, indicating a positive therapeutic response. The present case underscores the potential efficacy of immunotherapy in the management of cardiac metastases originating from lung cancer.

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Key words: lung squamous cell carcinoma, cardiac metastasis, left atrium and left ventricular secondary metastases, immunotherapy, immune-mediated hepatitis

Introduction

Tumor metastasis to secondary organs, in addition to the primary malignant tumor, is a major cause of death. Although tumor cells can invade any organ in the body, secondary malignant tumors in the heart are rare, with few cases having been reported to date. A 35-year single-center autopsy study showed that 61 of 1294 (4.7%) were true heart metastases from solid cancer (1). Approximately 10% of patients with cancer develop cardiac metastases, which are often associated with a poor prognosis (2). Lung cancer is one of the most prevalent malignancies globally and the leading cause of cancer-related deaths, responsible for 18.0% of all cancer fatalities (3). A 2020 global population-based study showed that 20% of lung cancer cases were squamous cell carcinomas (4). Lung squamous cell carcinoma is a common type of non-small cell lung cancer, the survival rates of which have improved due to advancements in immunotherapy. Tumor immunotherapy is primarily divided into cellular immunotherapy and immune checkpoint inhibitor (ICI) therapy. ICIs mainly function by inhibiting the immune evasion of tumor cells and are widely applied in the treatment of lung cancer. Current ICIs include PD-1 inhibitors, PD-L1 inhibitors, and CTLA-4 inhibitors. A real-world study has indicated that among patients receiving immunotherapy combined with chemotherapy, the median overall survival (OS) for squamous non-small cell lung cancer (NSCLC) patients is 10.6 months (95% CI, 9.3-11.8); median OS for squamous NSCLC patients undergoing monotherapy with immunotherapy is 11.3 months (95% CI, 9.8-12.8) (5). Phase II/III clinical studies have confirmed the safety and efficacy of PD-L1 inhibitors, including atezolizumab, pembrolizumab and nivolumab, in the second-line treatment of advanced lung squamous cell carcinoma (6-9). In addition to its remarkable efficacy in the second-line treatment of non-small cell lung cancer (NSCLC), ICIs also show promising survival benefit data as first-line treatments for metastatic NSCLC with high PD-L1 expression (TPS ≥50%) and negative mutation genes. In the KEYNOTE 024 study, Pembrolizumab alone was significantly more effective than

standard chemotherapy in patients with PD-L1 expression ≥50% of patients in advanced NSCLC with first-line treatment, with a median OS of 26.3 months vs. 13.4 months (HR: 0.62, 95% CI, 0.48~0.81) (10). Nevertheless, there is insufficient evidence to demonstrate the efficacy of immunotherapy in the treatment of cardiac metastases. To the best of our knowledge, the present case report is the first documented instance of primary lung cancer with secondary malignancies in the left atrium and left ventricle. In addition, the response of the case to immunotherapy is described.

Case report

In November 2023, a 71-year-old male patient presented to the China-Japan Friendship Hospital (Beijing, China), with a 2-month history of intermittent cough and chest pain, accompanied by fever and hemoptysis. Chest computed tomography (CT) revealed a perihilar mass in the lower lobe of the right lung, extending into the pulmonary arteriovenous structures and the left atrium (Fig. 1A). The patient underwent fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT, which identified right lung cancer with multiple lymph node metastases as well as hypermetabolic foci in the left atrium and left ventricle of the heart (Fig. 1B). The high FDG uptake revealed by the PET/CT results confirmed the malignancy of the cardiac tumors, supporting the diagnosis of metastatic disease. Transthoracic echocardiography also can show a slightly higher echoic mass attached to the atrial septum at the base of the proximal anterior mitral valve in the left atrium, and a slightly higher echo group attached in the middle of the left ventricular posterior septum (Fig. 1C and D). At this point, the patient was diagnosed with stage IV NSCLC.

The patient exhibited no heart-related symptoms, and an electrocardiogram (ECG) revealed a normal sinus rhythm. A subsequent biopsy via fiberoptic bronchoscopy confirmed lung squamous cell carcinoma (Fig. 2A); morphology and immunohistochemistry were consistent with squamous cell carcinoma, and necrosis was visible in the focal area. Due to the low incidence of genetic mutations in lung squamous cell carcinoma, current guidelines, including European Society for Medical Oncology (11), the American Society of Clinical Oncology (ASCO) (12) and the National Comprehensive Cancer Network (NCCN) (13), do not recommend routine genetic testing for all cases, classifying it as a level II recommendation. Moreover, the patient had financial limitations. Therefore, molecular testing was not performed. Immunohistochemistry revealed that the tumor exhibited a high level of programmed cell death-ligand 1 (PD-L1) expression, with a tumor proportion score (TPS) of ~80% (Fig. 2B). According to the ASCO (12), NCCN (13), and the Chinese Society of Clinical Oncology (CSCO) (14) guidelines, immunotherapy alone is recommended for patients with lung cancer who have a PD-L1 TPS of ≥50% and a performance status of 0 or 1, which indicates the patient is capable of normal movement or experiences fatigue during strenuous exercise and physical exertion. The patient has a performance status of 0. The CTONG1901 study demonstrated that sintilimab is effective and well-tolerated in patients with advanced NSCLC, regardless of PD-L1 expression levels, and exhibits similar efficacy and safety to pembrolizumab (15). Additionally, considering the economic burden on patients, sintilimab is more appropriate for this patient. Therefore, sintilimab (200 mg every 3 weeks) was administered to the patient as the selected immunotherapy.

The patient had a history of good health, with no known hypertension, coronary heart disease or cardiomyopathy. A comprehensive assessment was performed, including detailed inquiries about cardiac-associated symptoms and a physical examination. The pre-treatment evaluations also included blood tests to assess cardiac enzyme levels, electrocardiography and echocardiography. However, cardiac MRI was not performed due to the financial limitations of the patient. The patient reported no discomfort, and all cardiac examination results were normal. After two cycles of immunotherapy, echocardiography showed the disappearance of the left atrial metastasis and a slight reduction in the left ventricular metastasis (Fig. 3). Furthermore, the lung mass demonstrated a marked response, with a clear reduction in size.

At this time, the patient was found to have elevated alanine transaminase (ALT) and aspartate transaminase (AST) levels, which were ~3-fold the upper limit of normal. This raised the suspicion of immune-mediated hepatitis (IMH), rated as grade 2 according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 (16), prompting a switch to paclitaxel plus cisplatin chemotherapy. Subsequently, following protection of the liver with glutathione and magnesium isoglycyrrhizinate, and without the administration of additional treatments such as glucocorticoids, the ALT and AST levels were normalized. Considering the long history of alcohol use by the patient and the exclusion of other chronic liver diseases, it is hypothesized that the transient liver injury may have been medication-induced, occurring in the context of alcoholic liver disease. Following the exclusion of organic liver damage, liver function was regularly monitored and remained normal during the subsequent two cycles of chemotherapy. Given the favorable response to immunotherapy, the treatment was resumed and cycles 3-8 were completed. Throughout the treatment, the liver function remained stable within normal limits, and ultrasound and CT examinations showed no abnormalities.

As of July 2024, the patient had completed 8 cycles of immunotherapy and 2 rounds of chemotherapy. The chest CT scan showed a steady reduction in the pulmonary lesion (Fig. 4), while the metastatic focus in the left ventricle remained unchanged. The patient was comprehensively reassessed every 3 months, which involved examination with CT scans of the chest and abdomen, ECG and echocardiograms. Furthermore, a brain MRI was conducted every 6 months. To date, the patient has reported no discomfort, and no evidence of ischemic infarction has been detected in other organs. Immunotherapy continues to provide clear clinical benefits.

Discussion

Nearly all primary tumors are able to metastasize to the heart. Frequent sources of cardiac metastases include malignant melanoma, lymphoma and lung cancer, and the most common route of metastasis to the heart is lymphatic spread to the epicardium and pericardium (17). However, other mechanisms, including direct extension and hematogenous dissemination, can also occur (18). Metastasis involving the endocardium and heart chambers is rare (19), and often

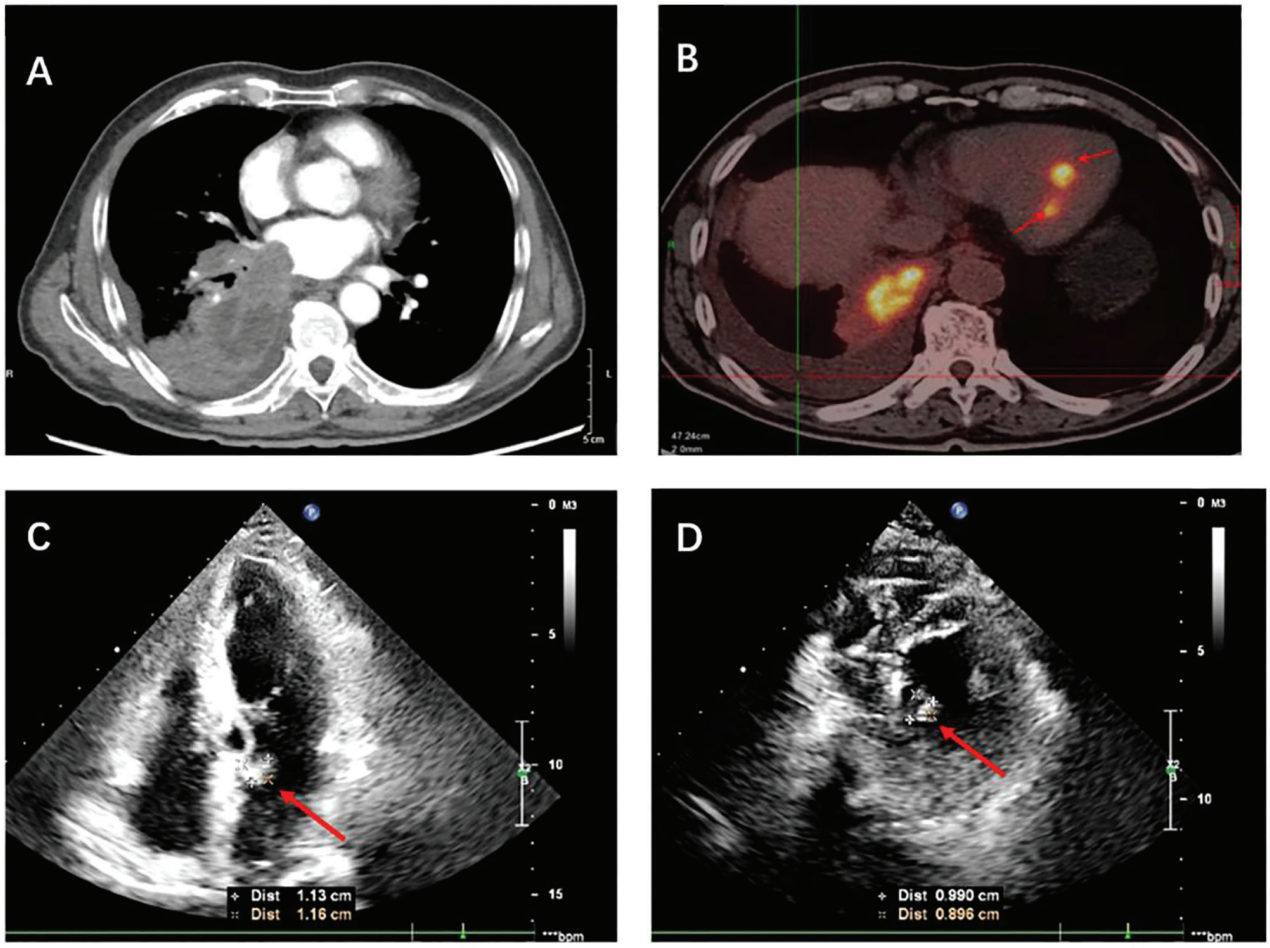

Figure 1. Perihilar and cardiac masses before treatment. (A) Chest CT shows a 10.5x7.6-cm parahilar mass in the lower lobe of the right lung, invading the pulmonary arteriovenous mass and left atrium. (B) Positron emission tomography/CT scan shows two radioactive concentrations of foci in the left heart chamber, with maximum standard uptake values of 8.9 and 6.3. (C) Transthoracic echocardiography shows an echogenic mass measuring ~1.1x1.2 cm attached to the atrial septum at the base of the proximal anterior mitral valve in the left atrium and (D) an echogenic mass measuring ~1.0x0.5 cm attached in the middle of the left ventricular posterior septum. CT, computed tomography.

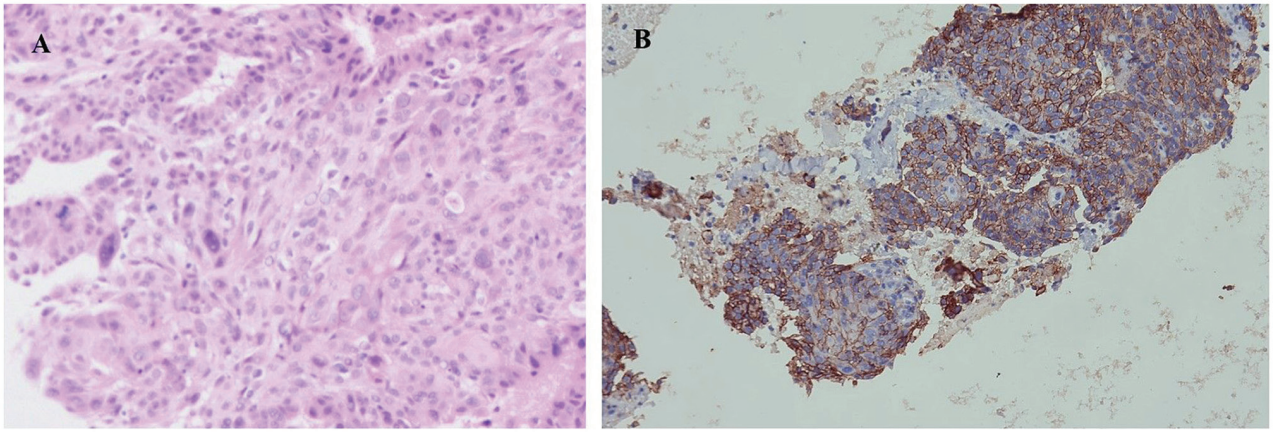

Figure 2. Pathological staining images. (A) Hematoxylin and eosin staining of the biopsy confirms the diagnosis of lung squamous cell carcinoma with 400x magnification. (B) Immunohistochemical staining shows high expression of programmed cell death-ligand, with a tumor proportion score of ~80% with 200x magnification.

undetectable before autopsy. To the best of our knowledge, there have been no previous reports of simultaneous metastasis to both the left ventricle and left atrium. Lung cancer most commonly metastasizes to the brain, bones, lymph nodes and liver (20), with cardiac invasion being rarely reported (21).

In the present case, tumor cells from the lung had invaded the left atrium directly through the pulmonary veins and

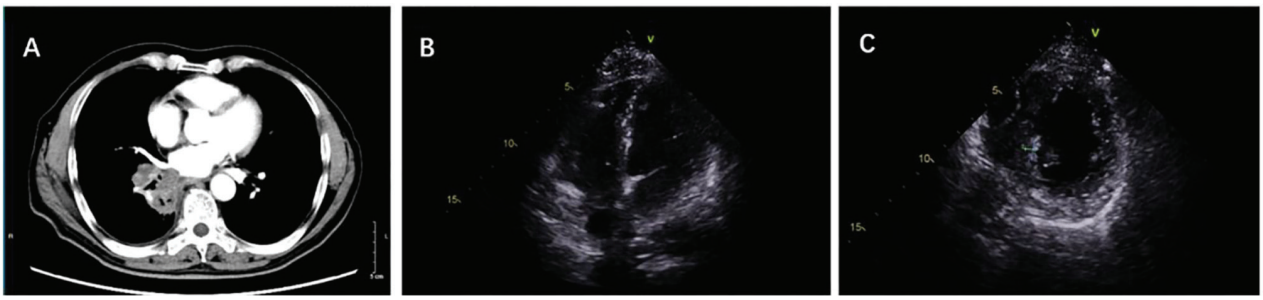

Figure 3. Primary tumor and metastases after two cycles of immunotherapy. (A) Chest computed tomography shows that the irregularly shaped parahilar mass in the lower lobe of the right lung invading the pulmonary veins and left atrium was markedly reduced in size to ~4.5x3.3 cm. (B) Transthoracic echocardiography showed no abnormal echo in the left atrium and (C) echogenic mass measuring ~0.8x0.5 cm attached to the middle of the posterior septum in the left ventricle.

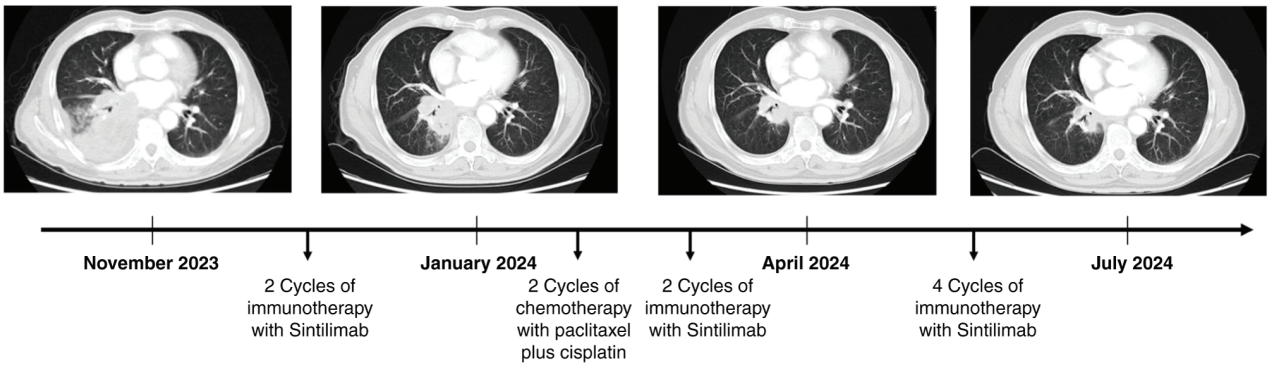

Figure 4. Treatment process of the lung mass and computed tomography images at various stages of treatment.

through hematogenous metastasis. This is the most direct and challenging method of metastasis. Given the pumping function of the left heart, it is not easy to contemplate that tumor cells would be able to enter the left atrium through the pulmonary veins in the midst of turbulent blood flow. Furthermore, if tumor cells manage to enter the left atrium, they would then need to pass through the mitral valve into the left ventricle and successfully implant in the endocardium. Following two rounds of immunotherapy using sintilimab, the primary lung tumor was markedly reduced in size, and the tumor tissue that had spread to the pulmonary veins and left atrium had completely disappeared. This outcome indirectly demonstrates that the cardiac metastasis occurred via hematogenous spread. Consequently, following active treatment of the primary mass, the cardiac metastases responded well to therapy.

In the present case, the secondary cardiac tumors rapidly diminished or disappeared due to high responsiveness to immunotherapy. However, this response carries a risk of hematogenous metastasis due to the likelihood that tumor cells will enter the bloodstream. Tumors in the left ventricle are particularly prone to spreading through the bloodstream to various organs, including critical ones such as the brain and kidneys, which are vulnerable to tumor embolism. While examination results did not show any evidence of ischemic infarction caused by tumor embolism in the systemic organs of the present case, this risk requires close monitoring in future treatments.

Research indicates that immune-related adverse events (irAEs) might be a positive prognostic marker in patients with lung cancer and may potentially improve treatment outcomes (22). However, the decision to resume immune checkpoint inhibitor (ICI) therapy after the resolution of irAEs is clinically challenging, due to uncertainties concerning the safety and benefits of such retreatment. According to current guidelines (23,24), ICI therapy should be paused for patients with a 2-grade elevation in transaminase levels (3-5-fold the normal value) until levels return to grade 1 or baseline based on the CTCAE. For IMH of grade ≥4, the permanent discontinuation of ICI therapy is recommended. However, it has been suggested that for patients with grade 3 or 4 immune hepatitis, appropriate interventions such as glucocorticoids may enable the resumption of ICI therapy to be considered once liver function improves to grade ≤1, depending on the overall condition, risk assessment and judgment of the patient by the physician (25). A clinical study (26) found that among patients irAE with no prior treatment response, those who resumed immunotherapy experienced longer progression-free survival and overall survival times than those whose immunotherapy was discontinued, indicating potential benefits from retreatment. In the present case, the patient showed a positive response after two cycles of immunotherapy, indicating that immunotherapy was a suitable treatment. Therefore, after the careful monitoring and follow-up of liver function, the decision was made to restart immunotherapy to provide continued survival benefits. It is recommended that the resumption of ICIs should be guided by the clinical background and specific requirements of the patient.

Currently, the primary approach to managing secondary cardiac tumors is effectively treating the tumor itself. ICIs have been demonstrated to be an effective therapy for lung cancer and are recommended as the first treatment for lung squamous cell carcinoma in ASCO, NCCN and CSCO (12-14). However,

clinical data to support the safety and efficacy of first-line ICIs in patients with cardiac malignancies are lacking, and the treatment risk is also unknown.

Although the present patient presented with IMH, no serious symptoms of toxicity or adverse effects, including heart-associated issues, were observed. Given that immunotherapy operates through mechanisms distinct from the direct cytotoxic effects of traditional chemotherapy, it is crucial to monitor and manage adverse effects on organs other than those targeted by the therapy as well as to assess its effectiveness.

In conclusion, immunotherapy shows promise in the treatment of cardiac metastases secondary to malignant tumors, as demonstrated by the positive response in the present case of lung squamous cell carcinoma. Despite the rarity of such cases and the limited evidence from clinical trials, the present case highlights the potential for immunotherapy to offer clear therapeutic benefits and improve the quality of life of the patient. The findings may serve as a valuable reference to guide the treatment approach in similar cases.

Acknowledgements

Not applicable.

Funding

This study was supported by Capital's Funds for Health Improvement and Research (grant no. 2022-2-4065), National High-Level Hospital Clinical Research Funding (grant no. 2022-NHLHCRF-LX-02-0111).

Availability of data and materials

The data generated in the present may be requested from the corresponding author.

Authors' contributions

YS and YZ participated in study design, and wrote the original manuscript draft. YY and HL obtained medical images and analyzed patient data. SL analyzed pathological images and made the diagnosis. HC was involved in drafting the manuscript, revising it critically for important intellectual content, data analysis and gave final approval of the version to be published. ZL and RL were involved in data collection, drafting the manuscript and confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

The patient provided written informed consent for publication of the case details and accompanying images.

Competing interests

The authors declare that they have no competing interests.

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