Reversible osimertinib-associated heart failure mimicking cancer recurrence in *EGFR*-mutated non-small cell lung cancer after pneumonectomy: A case report

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Abstract. Osimertinib is a third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor widely used in patients with *EGFR* mutation-positive non-small cell lung cancer (NSCLC). Although generally well tolerated, clinically notable cardiovascular toxicities, including heart failure, have been recognized. The present study describes the case of a 77-year-old man who developed symptomatic heart failure 5 months after initiating osimertinib treatment for postoperative recurrence of NSCLC. The patient presented with dyspnea and right-sided pleural effusion, which was initially suspected to represent tumor progression. However, the pleural effusion was transudative and echocardiography revealed a marked reduction in left ventricular ejection fraction from 69 to 27%. Discontinuation of osimertinib and treatment for heart failure resulted in resolution of the pleural effusion and recovery of cardiac function. The present case highlights the importance of differentiating heart failure-related pleural effusion from tumor recurrence and indicates the need for careful monitoring of cardiac function during osimertinib therapy, particularly in patients with conditions that may compromise cardiopulmonary reserve, such as prior pneumonectomy or aortic stenosis.

Introduction

Osimertinib is a third-generation epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) widely used in patients with *EGFR* mutation-positive non-small cell lung cancer (NSCLC), particularly those harboring exon 19 deletions or exon 21 L858R mutations. In addition to its use as first-line therapy for advanced or recurrent disease (1), osimertinib has recently been employed as adjuvant therapy following surgical resection (2). Given its ability to prolong both recurrence-free and overall survival, osimertinib plays a central role in current treatment strategies. Moreover, given the often prolonged duration of osimertinib therapy, the management of adverse events is critical for maintaining treatment continuity and optimizing patient prognosis. Common adverse events associated with osimertinib include rash, diarrhea, interstitial lung disease, and QT interval prolongation (1). Recently, however, increasing attention has been focused on osimertinib-associated cardiovascular toxicities. Clinical trials have reported that approximately 5.5% of patients receiving osimertinib experienced a decrease in left ventricular ejection fraction (LVEF), whereas <1% developed symptomatic heart failure (3). Furthermore, although pleural effusion in patients with lung cancer often raises suspicion of tumor recurrence or malignant pleuritis, it may also result from non-malignant causes, such as heart failure, infection, or hypoalbuminemia. Therefore, interpreting pleural effusion as definitive evidence of recurrence may lead to unnecessary therapeutic interventions or missed opportunities for appropriate treatment. We herein report a case of symptomatic heart failure that developed during osimertinib treatment for postoperative recurrence following left pneumonectomy. A distinctive feature of this case was the presentation of osimertinib-associated heart failure as a new contralateral pleural effusion in a patient with potentially compromised cardiopulmonary reserve following left pneumonectomy, necessitating differentiation from tumor progression.

Case report

A 77-year-old man initially presented to another hospital with a cough in April 2024. He was a former smoker with a

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history of diabetes mellitus, hypertension (well controlled with amlodipine 5 mg), and mild aortic stenosis but no history of cardiovascular events, including angina. Chest radiography revealed an abnormal shadow in the left lower lung field, and biopsy findings led to a diagnosis of NSCLC. The patient was subsequently referred to the Department of Thoracic Surgery at Nara Medical University Hospital (Kashihara, Japan) for multidisciplinary treatment, including surgery, and underwent left pneumonectomy in July 2024. Histopathological examination revealed adenosquamous carcinoma composed of adenocarcinoma (85%) and squamous cell carcinoma (15%) (Fig. 1A). Immunohistochemical staining for thyroid transcription factor-1 and p40 supported the adenocarcinomatous and squamous differentiation, respectively (Fig. 1B and C). The pathological stage was pT4N1M0 (stage IIIA). Molecular profiling using the Oncomine Dx Target Test identified an *EGFR* exon 21 L858R mutation. The patient was subsequently referred to our department and admitted for postoperative adjuvant chemotherapy comprising two cycles of cisplatin plus vinorelbine, beginning in September 2024. Transthoracic echocardiography performed before the initiation of chemotherapy showed an LVEF of 69%, with normal biventricular size and wall motion. There were no findings suggestive of elevated left ventricular filling pressure, right ventricular dysfunction, or pulmonary hypertension. Mild aortic stenosis was noted. Serial echocardiographic findings are summarized in Table I. In October 2024, a brain metastasis was detected on magnetic resonance imaging, and stereotactic radiotherapy was initiated in November 2024. Treatment with the oral EGFR-TKI osimertinib (80 mg/day) was initiated in the same month. Blood tests showed a B-type natriuretic peptide (BNP) level of 57.0 pg/ml and a creatine kinase-MB (CK-MB) mass of <3 ng/ml. Serum potassium, magnesium, and corrected calcium levels were 3.7 mEq/l, 1.9 mg/dl, and 9.5 mg/dl, respectively, with no electrolyte abnormalities. In January 2025, routine outpatient blood testing revealed an elevated D-dimer level of 14.2 μg/ml. Lower-extremity venous ultrasonography performed in February 2025 revealed no evidence of deep vein thrombosis.

In March 2025, the patient developed nocturnal wheezing and presented for an unscheduled visit. Chest computed tomography (CT) revealed a new mild right-sided pleural effusion. Fluid in the left hemithorax had been present since the pneumonectomy and had remained unchanged since the early postoperative period. There were no findings suggestive of drug-induced lung injury, such as ground-glass opacity or reticulation, or evidence of local recurrence. Electrocardiography showed no significant ST-T changes. Given the small volume of the effusion and the high risk of pneumothorax, thoracentesis was deferred. Blood tests showed KL-6, SP-A, and SP-D levels of 182 U/ml, 26.8 ng/ml, and 42.7 ng/ml, respectively, all within the reference ranges. No overt thyroid dysfunction was observed (thyroid-stimulating hormone level, 5.02 μIU/ml; free thyroxine level, 1.39 ng/dl). As the pleural effusion subsequently increased, thoracentesis was performed in April 2025. The pleural fluid was pale yellow and slightly turbid. Biochemical analysis of the right pleural fluid revealed a total nucleated cell count of 189/μl, total protein level of 2.3 g/dl, albumin level of 1.4 g/dl, and lactate dehydrogenase (LDH) level of 66 U/l. The corresponding serum values were 7.2 g/dl for total protein and 181 U/l for LDH; the serum D-dimer level was 9.3 μg/ml. The pleural fluid-to-serum total protein and LDH ratios were 0.32 and 0.36, respectively. The upper limit of the institutional reference range for serum LDH was 222 U/l, and the pleural fluid LDH level was below 148 U/l, corresponding to two-thirds of this value. As none of the three components of Light's criteria were met, the effusion was classified as transudative. Bacterial culture was negative, and cytological examination revealed no malignant cells. Tumor-related markers in the right pleural fluid were as follows: carcinoembryonic antigen, 1.0 ng/ml; neuron-specific enolase, 1.2 ng/ml; adenosine deaminase, 11.2 U/l; and hyaluronic acid, 16 ng/ml. Subsequently, the patient developed worsening dyspnea and general fatigue, accompanied by nocturnal cyanosis of the lower extremities. Chest CT revealed a further increase in the right pleural effusion, along with an increase in the cardiothoracic ratio from 48.6% 2 months earlier to 51.7% (Fig. 2A and B). Therefore, osimertinib was discontinued, and the patient was admitted for further evaluation and symptom management.

On admission, the patient was alert, with an oxygen saturation of 99% on room air; however, his New York Heart Association (NYHA) functional class was III. Blood tests showed a white blood cell count of 4,400/μl, C-reactive protein (CRP) level of 0.31 mg/dl (institutional upper limit, 0.14 mg/dl), serum potassium level of 4.0 mEq/l, corrected calcium level of 9.4 mg/dl, creatinine level of 1.2 mg/dl, and estimated glomerular filtration rate of 45.7 ml/min/1.73 m^2. On hospital day 2, oral azosemide (30 mg/day) was initiated. Electrocardiography showed sinus rhythm with mild ST elevation in leads V2-V4 and a corrected QT (QTc) interval of 441 msec. Transthoracic echocardiography revealed a markedly reduced LVEF of 27%, compared with 69% 7 months earlier, with diffuse left ventricular hypokinesis. Left atrial enlargement was present, and the mitral inflow E/A ratio was 1.7. Moderate aortic stenosis was noted. Right ventricular size and wall motion were preserved. The tricuspid regurgitation pressure gradient (TRPG) had increased to 55 mmHg, indicating pulmonary hypertension, and the stroke volume index had decreased to 35 ml/m^2 (Table I). Blood tests revealed a BNP level of 2,880.6 pg/ml (Fig. 3). The cardiac troponin T level was mildly elevated at 0.032 ng/ml (institutional upper limit, 0.014 ng/ml), whereas the CK-MB mass was 4 ng/ml, within the normal range. By hospital day 3, the patient's symptoms had improved, and the right pleural effusion had decreased by day 6. Follow-up electrocardiography showed prolongation of the QTc interval to 525 msec; however, no palpitations, syncope, hemodynamic compromise, or clinically apparent arrhythmias were observed, and serum potassium and magnesium levels were within the normal ranges at that time. On day 9, oral spironolactone (12.5 mg/day) and oral enalapril maleate (2.5 mg/day) were initiated, and oral carvedilol (1.25 mg/day) was added on day 16. The patient's condition gradually stabilized, and he was discharged on day 19 with improvement in his NYHA functional class to I.

The serum potassium level was measured serially during hospitalization and remained largely within the normal range. The serum magnesium level, measured 2 months after discharge, was also normal. Myocardial scintigraphy performed after discharge showed no reduction in uptake at

Table I. Serial transthoracic echocardiographic findings before osimertinib initiation, at the onset of heart failure, and after treatment.

Parameter	Before osimertinib (2 months after pneumonectomy)	At heart failure (admission)	After treatment (3 months after discharge)
Left ventricle			
Left ventricular ejection fraction, %	69	27	58
Stroke volume index, ml/m^2	56	35	39
Regional wall motion	Normal	Diffuse severe hypokinesis	Normal
Diastolic function			
Mitral inflow E/A ratio	0.6	1.7	0.6
Average E/e′	11.3	32.4	14.3
Left atrial volume index, ml/m^2	28	41	16
Right ventricle and pulmonary circulation			
Right ventricular basal diameter, mm	27	29	29
Tricuspid annular plane systolic excursion, mm	20	18	19
Right ventricular fractional area change, %	36	Not determined	43
Tricuspid regurgitation pressure gradient, mmHg	16	55	25
Inferior vena cava diameter (expiration/inspiration), mm	12/4	11/3	9/4
Inferior vena cava resp. change, %	67	73	56
Valves			
Aortic valve area, cm_2	1.7	1.2	1.3
Aortic valve peak velocity, m/sec	2.5	2.2	2.3

Studies were performed before the initiation of osimertinib (September 2024, 2 months after left pneumonectomy), at the onset of heart failure (April 2025), and 3 months after discharge (July 2025). E/A, ratio of peak early (E) to late (A) diastolic transmitral flow velocity; E/e′, ratio of peak early diastolic transmitral flow velocity (E) to early diastolic mitral annular velocity (e′).

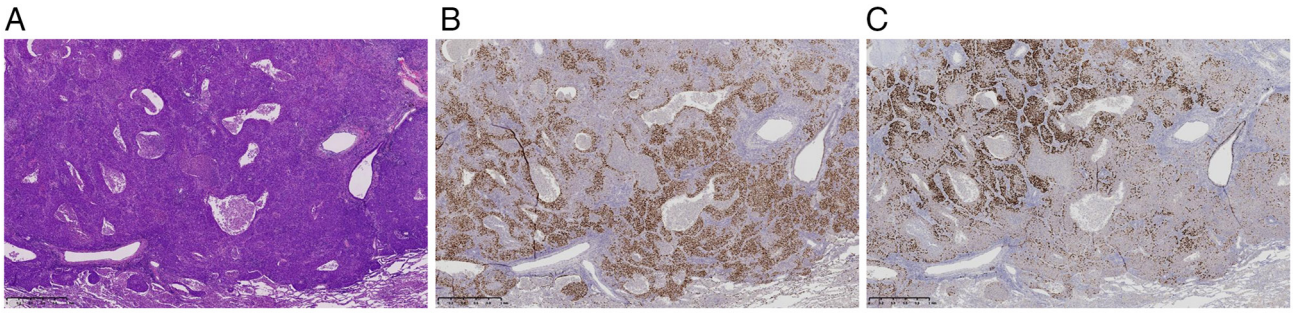

Figure 1. Histopathological and immunohistochemical findings. (A) Hematoxylin and eosin staining at x25 magnification showing adenosquamous carcinoma composed of adenocarcinoma (85%) and squamous cell carcinoma (15%). The tumor measured 90x80x60 mm. The pathological stage was pT4N1M0, with pleural invasion (pl2), lymphatic invasion (Ly1c, D2-40), and vascular invasion (V1c, EVG). (B) Immunohistochemical staining for thyroid transcription factor-1 at x25 magnification. (C) Immunohistochemical staining for p40 at x25 magnification.

rest or during stress, with neither fixed nor reversible defects, indicating no evidence of myocardial ischemia. Coronary angiography was not performed because of impaired renal function. Based on the clinical course and findings, the patient was diagnosed with osimertinib-associated symptomatic heart failure. In June 2025, the dose of carvedilol was gradually increased to 5 mg/day, and in July 2025, the dose of azosemide was reduced from 30 to 15 mg/day. Enalapril maleate was subsequently discontinued because of cough. The BNP level decreased to 81.4 pg/ml. Follow-up echocardiography in July 2025 (3 months after discharge) demonstrated recovery of the LVEF to 58%. Osimertinib

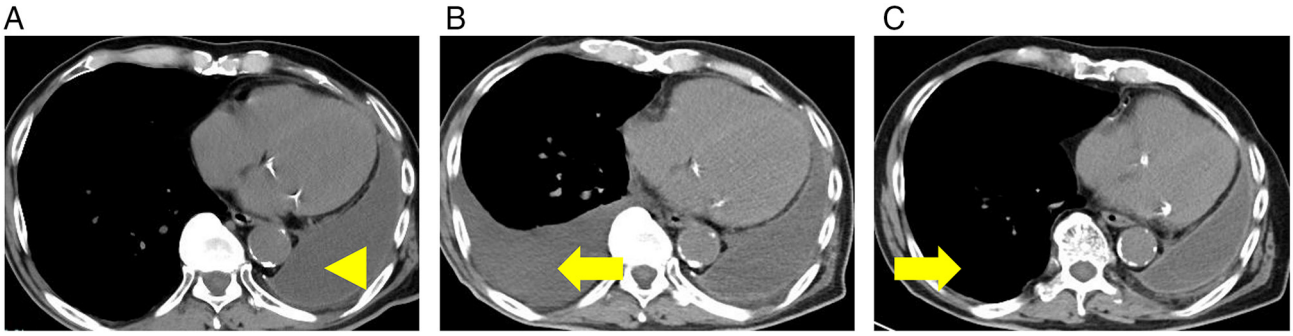

Figure 2. Serial chest CT findings. (A) CT in February 2025. The arrowhead indicates fluid in the left hemithorax, representing filling of the post-pneumonectomy space as a postoperative change rather than a pathological effusion; this finding had remained unchanged since the early postoperative period. (B) CT in April 2025 showing a right pleural effusion (arrow). (C) CT in September 2025 showing no reaccumulation of the right pleural effusion (arrow). CT, computed tomography.

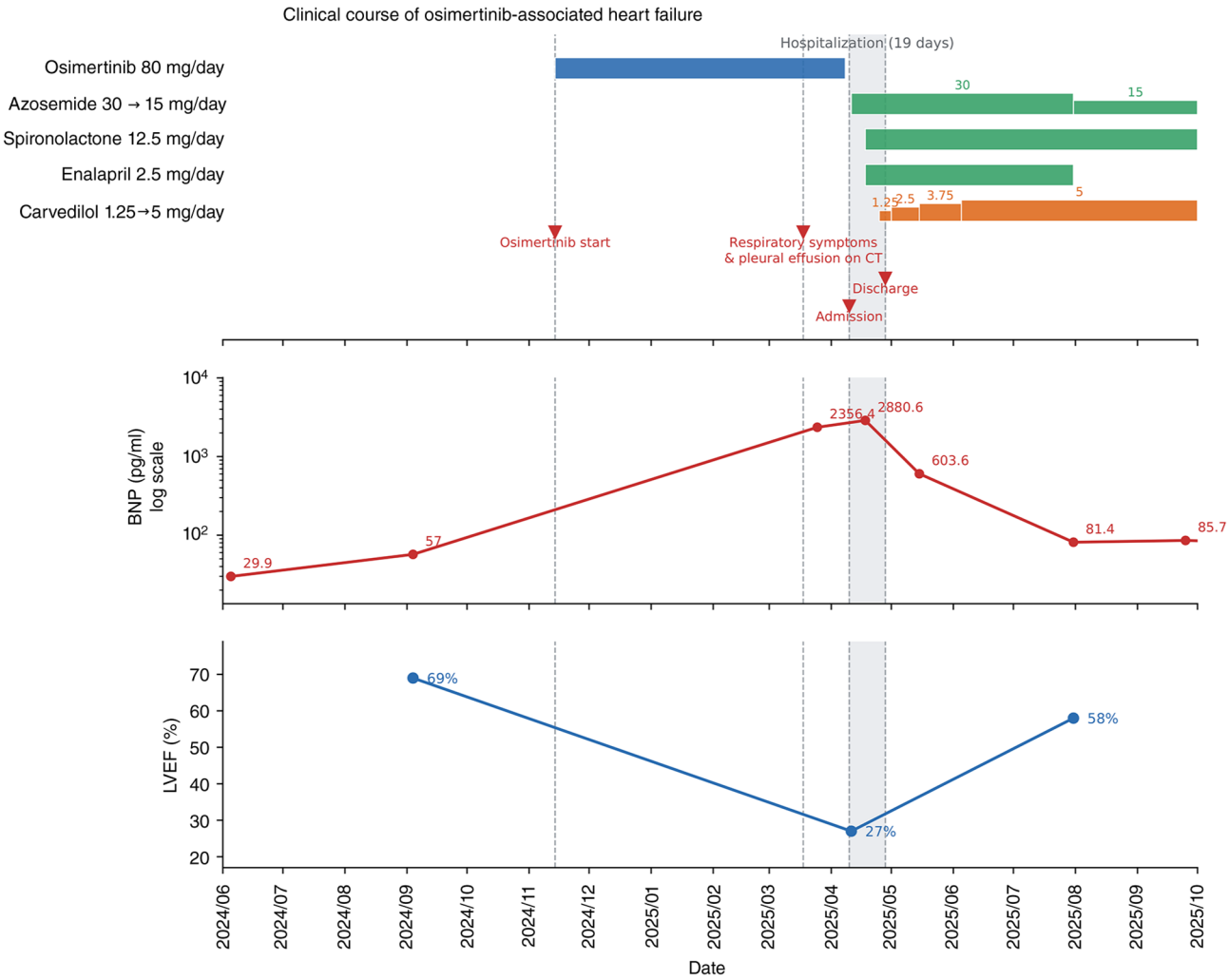

Figure 3. Serial changes in LVEF and BNP levels. The clinical course is shown, with the periods of osimertinib administration and hospitalization and the initiation of treatment for heart failure indicated on the time axis. Serial LVEF (%) and BNP (pg/ml) values are plotted. BNP, B-type natriuretic peptide; LVEF, left ventricular ejection fraction.

was not resumed. At that time, the brain metastasis had been controlled with stereotactic radiotherapy, and no measurable lesion requiring treatment was identified. The case was discussed at a departmental conference, where consensus was reached that observation was an acceptable option, provided that the risk of recurrence was fully explained. After discussion with the patient and his family, close observation with radiological follow-up was chosen in accordance with their preference. Follow-up CT performed in September 2025 showed no reaccumulation of the right pleural effusion

(Fig. 2C). No evident disease progression had been observed as of March 2026.

Discussion

Osimertinib is a third-generation EGFR-TKI developed to overcome T790M-mediated resistance while sparing wild-type EGFR owing to its mutation-selective profile (4). However, cardiovascular adverse events, including heart failure, have emerged as clinically significant concerns, although the underlying mechanisms remain incompletely understood (5). In this context, comparisons with first-generation EGFR-TKIs, such as gefitinib and erlotinib, which have not been clearly associated with cardiotoxicity, may be informative (6-8). Among first-generation EGFR-TKIs, gefitinib primarily targets EGFR and exhibits minimal inhibitory activity against HER2 (9), whereas preclinical studies have shown that osimertinib moderately inhibits HER2 phosphorylation (4). Furthermore, its active metabolite, AZ5104, exerts even greater inhibitory activity against HER2 than osimertinib itself (4). These findings indicate that osimertinib-induced cardiotoxicity may not be attributable solely to EGFR inhibition but may instead involve off-target effects on HER2. However, this hypothesis alone may not fully explain the observed clinical findings. Given that HER2 signaling plays a critical role in cardiomyocyte survival and homeostasis (10), similar cardiotoxic effects might be expected with afatinib, an irreversible inhibitor of both EGFR and HER2. Nevertheless, no clear clinical association between afatinib and overt heart failure has been observed (11). Conversely, reductions in LVEF and the development of heart failure have been reported with osimertinib at non-negligible frequencies (3). This discrepancy indicates that HER2 inhibition alone may not sufficiently explain the cardiotoxicity of osimertinib and that additional drug-specific mechanisms may be involved.

Recently, a drug-specific pathway that may account for this discrepancy has been reported. In a study using human induced pluripotent stem cell-derived cardiomyocytes and a murine model in which transverse aortic constriction was used to reproduce the hemodynamic stress experienced by patients with cancer, osimertinib was shown to reduce GATA4 phosphorylation, thereby suppressing *MYLK3* transcription and decreasing downstream MYL2 phosphorylation, resulting in sarcomere disarray and impaired contractility (12). GATA4 is a transcription factor that plays an important role in cardiac function and is not a member of the ErbB family; thus, the existence of such a HER2-independent pathway may explain why the cardiotoxicity of EGFR-TKIs does not necessarily parallel the degree of HER2 inhibition. Moreover, this mechanism involves transient sarcomere disruption rather than permanent cellular injury or pathological remodeling. The clinical course of our patient, in whom the elevation in cardiac troponin T levels was mild and the LVEF recovered from 27 to 58% after osimertinib discontinuation, may be compatible with this proposed mechanism; however, this mechanism cannot be established from the available clinical data. Additionally, osimertinib has been reported to impair ATP synthase (complex V) activity, resulting in decreased ATP production; therefore, mitochondrial dysfunction may also contribute to its cardiotoxicity (13).

In the present case, dyspnea and a new pleural effusion developed during osimertinib treatment following the detection of brain metastasis. The differential diagnosis of the newly developed pleural effusion included malignant effusion, heart failure, pulmonary embolism, infectious pleuritis, and hypoproteinemia. Pulmonary embolism was considered unlikely because lower-extremity venous ultrasonography revealed no deep vein thrombosis, the D-dimer level showed a decreasing trend, and the dyspnea followed a chronic course without chest pain or hypoxemia. CT pulmonary angiography was not performed, also considering the patient's impaired renal function. Infectious pleuritis was considered unlikely given the absence of fever or a significant elevation in inflammatory markers, together with negative pleural fluid cultures. Hypoproteinemia was excluded because the serum albumin level was preserved. Given the underlying lung cancer and the absence of a history of symptomatic heart failure, tumor progression was initially considered the most likely cause. However, CT revealed mild cardiomegaly, cytological examination of the pleural fluid showed no malignant cells, and the effusion was transudative. Furthermore, a marked reduction in LVEF was observed, leading to the diagnosis of heart failure-related pleural effusion. Discontinuation of osimertinib and initiation of treatment for heart failure resulted in resolution of the pleural effusion and improvement in LVEF.

The differential diagnosis of heart failure included drug-induced myocardial injury, ischemic heart disease, progression of aortic stenosis, takotsubo cardiomyopathy, and acute myocarditis. Although electrocardiography on admission showed mild ST elevation in leads V2-V4, this was not accompanied by reciprocal ST depression. Moreover, myocardial perfusion scintigraphy demonstrated neither fixed nor reversible defects, and cardiac function improved after osimertinib withdrawal. Based on this clinical course, ischemic heart disease was considered an unlikely cause of heart failure. Regarding the progression of aortic stenosis, the aortic valve area decreased to 1.2 cm^2 after the onset of heart failure symptoms (baseline, 1.7 cm^2); however, it remained essentially unchanged at 1.3 cm^2 after symptom improvement, and the peak aortic jet velocity did not increase from baseline (2.2 m/sec vs. 2.5 m/sec at baseline). Therefore, aortic stenosis was considered unlikely to have contributed substantially to the development of heart failure. Takotsubo cardiomyopathy was also considered unlikely because echocardiography showed diffuse left ventricular hypokinesis rather than regional wall motion abnormalities or apical ballooning, with no findings typical of this condition. Acute myocarditis was considered unlikely because there was no episode of fever or upper respiratory symptoms, the CRP level on admission was only mildly elevated, and the clinical course was chronic rather than acute.

Based on these differential findings, the temporal relationship with osimertinib administration, and the improvement in cardiac function after its discontinuation, a diagnosis of osimertinib-associated heart failure was made. However, multiple factors that may have compromised cardiovascular reserve coexisted in this patient, including advanced age, hypertension, diabetes mellitus, a history of smoking, aortic stenosis, prior cisplatin-based chemotherapy, and hemodynamic changes following pneumonectomy. The present report does not suggest that osimertinib caused myocardial injury

independently of these factors; rather, we consider that heart failure became clinically manifest in the setting of reduced cardiovascular reserve, as discussed below. Notably, as osimertinib withdrawal and the initiation of treatment for heart failure occurred in close succession, their respective contributions to the subsequent improvement in cardiac function cannot be evaluated separately.

Differentiating heart failure-related pleural effusion from tumor recurrence based solely on imaging findings can be challenging in clinical practice. In particular, after pneumonectomy, fluid may accumulate in the operated hemithorax as a postoperative change, further complicating the interpretation of imaging findings. Thoracentesis may therefore be necessary to differentiate tumor progression from congestive heart failure; however, when pleural effusion develops on the side of the sole functioning lung, the procedure must be performed with particular caution because of the risk of complications such as pneumothorax. Given that misdiagnosing tumor progression may delay appropriate management, the development of a new pleural effusion during osimertinib treatment should prompt clinicians to consider not only cancer recurrence but also heart failure and to perform a careful differential evaluation, including assessment of cardiac function and pleural fluid characteristics.

Next, we considered the factors that may have contributed to the severity of heart failure in the present case. In clinical trials, osimertinib-associated reductions in LVEF have been reported in approximately 5.5% of patients and symptomatic heart failure in less than 1% (3), with most cases not progressing to clinically overt cardiac events. In our patient, however, the LVEF decreased from 69 to 27%, and symptomatic heart failure corresponding to NYHA functional class III developed. The clinical course therefore differed from that typically described in previous reports. We examined patient-related background factors as possible explanations for this discrepancy.

Although osimertinib-associated heart failure is generally considered reversible (5), multiple factors are thought to contribute to its development. Previous studies have identified advanced age, pre-existing cardiac disease, combination chemotherapy, radiotherapy to the left chest, smoking, and hyperlipidemia as potential risk factors (14,15). Our patient had several of the aforementioned background factors, which may have exerted subclinical effects on cardiac function. Moreover, the patient had undergone pneumonectomy. To assess the potential contribution of pneumonectomy in this case, the origin of the pulmonary hypertension observed at the onset of heart failure must first be considered. At that time, the mitral inflow E/A ratio had increased from a baseline value of 0.6 to 1.7, suggesting elevated left ventricular filling pressure, while the stroke volume index had decreased from 56 to 35 ml/m^2. Conversely, the right ventricular basal diameter and tricuspid annular plane systolic excursion remained essentially unchanged, and neither the inferior vena cava diameter nor its respiratory variation showed changes suggestive of elevated right atrial pressure. Chronic precapillary pulmonary hypertension is frequently accompanied by right ventricular dilatation or hypertrophy; however, no right ventricular remodeling was observed in our patient. Therefore, the increase in TRPG to 55 mmHg was considered to predominantly reflect a postcapillary change associated with left ventricular dysfunction. In other words, the central pathophysiological feature was left ventricular systolic dysfunction rather than primary right heart failure, and the hemodynamic consequences of pneumonectomy alone are unlikely to account for the heart failure observed in this patient.

Nevertheless, pneumonectomy may have reduced cardiovascular reserve and thereby facilitated the clinical manifestation of heart failure. In a prospective evaluation conducted before and after pneumonectomy, pulmonary artery systolic pressure increased significantly at 6 months postoperatively, even in patients with normal preoperative pulmonary artery systolic pressure, right ventricular diameter, and LVEF (16). Similarly, a prospective 4-year follow-up study showed progressive increases in pulmonary artery systolic pressure and right ventricular diastolic diameter after pneumonectomy, whereas neither variable changed significantly after lobectomy, indicating that these changes may be specific to pneumonectomy (17). The pulmonary circulation is a low-resistance vascular bed that can accommodate increases in blood flow through vascular recruitment and distension with minimal increases in driving pressure. After pneumonectomy, the remaining lung can normally accommodate the entire resting pulmonary blood flow without an increase in pulmonary arterial pressure; however, there is a limit to the increase in blood flow that can be accommodated without a corresponding increase in pressure, and this limit is lower when the pulmonary vascular bed is affected by disease (18). Therefore, normal hemodynamic measurements at rest do not necessarily exclude the effects of pneumonectomy. Although the TRPG was normal at 16 mmHg 2 months after pneumonectomy in our patient, a latent reduction in cardiovascular reserve may have become clinically apparent when an additional hemodynamic burden was imposed. However, as this is a single-case observation, this interpretation remains hypothetical. Given the recent increase in the use of osimertinib as adjuvant therapy, awareness of its cardiovascular adverse events is becoming increasingly important. However, the cardiovascular safety of osimertinib in patients with a history of lung resection has not been systematically investigated and warrants further study.

In the present case, systemic therapy was not resumed after osimertinib discontinuation, and a policy of observation was adopted. Rechallenge with osimertinib was also considered; however, the anticipated risks were considered to outweigh the expected benefits. The risks were substantial. With only one functioning lung, the patient's respiratory reserve was limited, and during the present episode, pleural effusion accumulated on the right side, involving the sole functioning lung and potentially compromising ventilation. Recurrent heart failure under these circumstances could therefore be life-threatening rather than merely treatment-limiting. Similar concerns applied to switching to another EGFR-TKI or initiating cytotoxic chemotherapy. Conversely, the expected benefit of systemic therapy was uncertain. At the onset of heart failure, the brain metastasis, which represented oligorecurrence, had been controlled with stereotactic radiotherapy, and no other measurable lesion requiring treatment was identified. Systemic therapy would therefore have been administered without a measurable target for assessing treatment response. Furthermore, the brain metastasis had developed after two cycles of postoperative

adjuvant cisplatin-containing chemotherapy, making a meaningful response to platinum rechallenge unlikely. On this basis, the case was discussed at a departmental conference, where consensus was reached that observation was an acceptable option, provided that the risk of recurrence was fully explained. After discussion with the patient and his family, close observation with radiological follow-up was chosen in accordance with their preference. This approach did not represent abandonment of treatment; rather, the patient has been closely monitored to allow prompt initiation of systemic therapy should a lesion requiring treatment emerge.

If disease progression occurs in the future, the management strategy will need to be determined through multidisciplinary discussion between cardiologists and oncologists. As a guiding principle, current guidelines for HER2-targeted therapy state that treatment resumption should be considered in patients whose signs and symptoms of heart failure have resolved and whose LVEF has recovered to ≥40% (preferably ≥50%) and recommend frequent assessment using echocardiography and cardiac biomarkers for a defined period after treatment resumption (19). Our patient's LVEF recovered to 58%, suggesting that rechallenge could be considered based on these criteria. However, applying these recommendations to EGFR-TKIs represents an extrapolation from guidance for a different class of agents, and its validity has not been established. No evidence is currently available regarding the optimal management strategy following severe cardiac dysfunction such as that observed in the present case, and this issue warrants further investigation.

This report has some limitations. First, this is a single-case observation, and a causal relationship between osimertinib and heart failure cannot be established. Second, cardiac magnetic resonance imaging was not performed; therefore, myocardial tissue characteristics could not be assessed. This examination was not performed because acute myocarditis was not the leading clinical consideration and there were no findings suggestive of myocardial ischemia; nevertheless, it might have provided additional information for differentiating other non-ischemic myocardial diseases. Third, coronary angiography was not performed; therefore, asymptomatic coronary stenosis could not be anatomically excluded. Moreover, exercise testing was not performed, and cardiovascular reserve could not be directly assessed. In addition, baseline and serial cardiac troponin measurements were not available, limiting the assessment of the presence and temporal evolution of cardiomyocyte injury. Finally, the mechanisms discussed above are based on findings from cellular and animal models and cannot be confirmed in a single clinical case.

In conclusion, we report a case of reversible heart failure associated with osimertinib. This case highlights the importance of considering causes other than tumor progression when a new pleural effusion develops in a patient with lung cancer and of evaluating both pleural fluid characteristics and cardiac function. It also underscores the importance of careful cardiac monitoring during osimertinib therapy, particularly in patients with conditions that may compromise cardiopulmonary reserve, such as prior pneumonectomy or aortic stenosis. Further accumulation of cases is needed to clarify the potential relationship between a history of lung resection and osimertinib-associated heart failure.

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Availability of data and materials

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

Authors' contributions

HY conceptualized the manuscript. Data acquisition and interpretation were performed by HY, NH, RS, YY, MO, SO, HN, TK, YN, MaiT, MH and MasT. HY wrote the original draft. HY and MasT confirm the authenticity of all the raw data. HY, NH and MasT reviewed and edited the final manuscript. All authors read and approved the final manuscript, and agree to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was obtained from the patient for publication of this case report and the accompanying images. The patient was informed that all identifying information would be removed to ensure anonymity.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, AI tools ChatGPT (GPT-5.4, GPT-5.5, and GPT-5.6; OpenAI) were used to improve the readability and language of the manuscript, and subsequently, the authors revised and edited the content produced by the AI tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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