Detection of EGFR T790M Mutation in Pericardial Effusion from a Non-Small Cell Lung Cancer Patient with Erlotinib Therapy

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**Key Words**
Cardiac tamponade · Pericardial effusion · Epidermal growth factor receptor mutation · Non-small cell lung cancer · T790M

**Abstract**
We report the case of a Japanese male with epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI)-sensitive lung adenocarcinoma, who had an EGFR mutation and presented in the emergency department with acute cardiac tamponade as the recurrence during EGFR-TKI therapy. We could detect a second mutation, T790M in exon 20 in the pericardial effusion. This is the first report to detect the resistant mutation T790M in pericardial effusion. We suggest that the pericardial effusion may therefore be useful as surrogate tissue for detecting EGFR mutation.

**Introduction**
Malignant pericardial effusion is a common complication of advanced cancers. Cardiac tamponade is a severe complication of lung cancer. The hemodynamic effects of pericardial fluid accumulation are the result of increased intrapericardial pressure, leading to impaired diastolic filling and a low cardiac stroke volume, which is potentially life-threatening.

It is known that non-small cell lung cancer (NSCLC) patients harboring epidermal growth factor receptor (EGFR) mutations are responsive to EGFR tyrosine kinase inhibitors (EGFR-TKIs) such as gefitinib and erlotinib [1, 2]. EGFR-TKIs have been found to have a significant impact in NSCLC patients with EGFR mutations [1–3].
Several prospective trials have shown the tumor response rates to gefitinib therapy to be approximately 75% in patients with tumors harboring EGFR mutations [4–6]. However, despite the initial dramatic tumor shrinkage, the tumors of most patients subsequently become resistant to EGFR-TKIs and eventually relapse. The most frequent recurrence site is the central nervous system. We herein report the case of a patient with recurrence-related carcinomatous pericarditis arising from a secondary resistant mutation, T790M, that could be detected in the pericardial effusion.

Case Report

A 75-year-old Japanese male was admitted to our hospital complaining of lumbago, which had persisted for one month. He was an ex-smoker, and had type II diabetes, hypertension and ileus. Chest computed tomography (CT) revealed a 37-mm diameter mass lesion in the left lower lobe of his lung. The histological diagnosis of the transbronchial biopsy specimen was adenocarcinoma (fig. 1a). We diagnosed the patient to have lung cancer with multiple bone metastases, brain metastasis, and liver metastasis (cT2aN0M1b, stage IV). After the patient provided informed consent, we analyzed the specimen obtained from the TBLB for EGFR mutations. The analysis identified an 18-base pair deletion in exon 19 (fig. 1b). The patient was treated with cisplatin and pemetrexed as a first-line chemotherapy; however, after one cycle of the treatment, he developed paralysis of his left leg, and this symptom was rapidly progressive. Therefore, an emergency operation was performed for posterior lumbar interbody fusion. As second-line chemotherapy, the patient was started on 150 mg/day erlotinib. One month later, the size of both the primary lesion and the bone metastases were found to have decreased.

Three months later, he developed dyspnea at rest and edema. Furthermore, he had severe dyspnea and orthopnea, with a resting heart rate of 160–170 beats/min and a blood pressure of 63/43 mm Hg. His temperature was 36.8°C, and his arterial oxygen saturation was 88.0% on room air. A physical examination revealed distant heart sounds and a significantly distended internal jugular vein to the jaw level. An electrocardiogram revealed sinus tachycardia and borderline low-voltage QRS complexes. Chest radiographs showed cardiomegaly with an increased cardiothoracic ratio and bilateral pleural effusion (fig. 2a). A CT scan of the chest revealed a large pericardial effusion (fig. 2b). An emergency echocardiogram confirmed the presence of a large pericardial effusion, together with evidence of diastolic collapse of the right atrium, ventricle and left atrium, consistent with cardiac tamponade (fig. 2c).

The patient underwent pericardiocentesis of 520 ml of malignant sanguineous fluid, and placement of a pericardial drain, while having removed 1,100 ml of sanguineous fluid, in which adenocarcinoma was detected (fig. 3a). EGFR mutation analysis was performed in this pericardial effusion, and both the 18-base pair deletion in exon 19 and a second mutation, T790M in exon 20, were detected (fig. 3b and c). The patient temporarily recovered from the state of shock and survived for one month after drainage. He could not undergo further chemotherapy because his general condition had worsened. He died due to progressive disease five months after the original diagnosis. No autopsy was performed.

Discussion

In our case, two points are highlighted. One is that the recurrence manifested as cardiac tamponade due to the presence of malignant pericardial effusion of NSCLC after erlotinib therapy.

In a large retrospective analysis of autopsies with confirmed primary malignancies, metastases to the heart and pericardium were present in 10% of patients [7]. Lung cancer is the most frequent cause of malignant pericardial effusion, accounting for approximately 47–74% of cases, and adenocarcinoma was the most frequent
histological type associated with the condition [8]. On the other hand, only approximately 2.5% of lung cancer patients develop carcinomatous pericarditis [9]. In this case, the patient had an EGFR mutation with an 18-base pair deletion, and initially had a good response to treatment with an EGFR-TKI.

The central nervous system is a frequent site of disease recurrence in patients with NSCLC after an initial response to EGFR-TKIs [10]. However, cardiac tamponade due to carcinomatous pericarditis as the recurrence site has not been reported previously for patients treated with EGFR-TKIs such as gefitinib or erlotinib. Therefore, we consider that we have herein reported an extremely rare case of an unusual metastatic recurrence site.

The mechanism of metastasis to the heart, like that to other organs, can be by direct contiguous growth, hematogeneous dissemination, or vascular growth along the vena cava, pulmonary veins, or lymphatic channels. The pericardial fluid collection is thought to result from the lymphatic obstruction of fluid from the pericardial sac [11]. In this case, it was thought to be caused by hematogeneous dissemination, since a chest CT scan showed no mediastinal lymph node invasion.

One of the most interesting findings of this case was the fact that the pericardial effusion acted as a surrogate tissue. DNA in pleural effusion fluid and cerebrospinal fluid, as well as serum DNA, can be used to detect EGFR mutations, and it has been known that these samples can show evidence of EGFR mutations [12–14]. However, it was unknown whether other samples, including pericardial effusion, could be useful for detecting EGFR mutations. To our knowledge, this is the first report to detect the resistant mutation T790M in pericardial effusion.

Cardiac tamponade caused by carcinomatous pericarditis is a potentially life-threatening complication, and is a medical emergency caused by fluid accumulation around the cardiac chambers that influence cardiac output. Therefore, it is very difficult to obtain a sufficient tumor sample by a transbronchial tumor biopsy in such a case.

We suggest that the EGFR mutation status in the pericardial effusion may therefore be useful as a predictor of the response to EGFR-TKIs for the patients with pericardial tamponade as the first manifestation [15]. Further validation with a large number of cases will be needed to confirm that the detection of EGFR mutations in pericardial effusion can be used to predict the response of the cancer to treatment.

Disclosure Statement

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Fig. 1. a Pathological findings. The tissue obtained by transbronchial biopsy revealed poorly differentiated adenocarcinoma. b A representation of the direct DNA sequencing for PCR products including the deletions in exon 19 of the EGFR. The deletion ranged from codon 747 to 753, including 18 base pairs of nucleotides (TAAGAGAAGCAACATCTC). The black vertical bars indicate deletion sites.

Fig. 2. a A chest radiograph showing an enlarged cardiac silhouette with diffuse vascular congestion, indicating cardiac tamponade. b A chest CT scan demonstrating pericardial effusion with cardiac tamponade. c An echocardiogram (four-chamber view) showing a large circumferential pericardial effusion (PE) with diastolic collapse of three chambers of the right atrium (RA), the right ventricle (RV), and the left atrium (LA).
Fig. 3. a Cytological preparation from the pericardial effusion showing pleomorphic nuclei and prominent nucleoli, consistent with adenocarcinoma, similar to the specimen obtained from the primary lesion. b We performed a mutational analysis of the exon 19 deletion with DNA from the pericardial effusion. The presence of the exon 19 deletion was confirmed by a common fragment analysis using polymerase chain reaction (PCR). The PCR products were analyzed on an ABI PRISM instrument. The two shorter segments, of 154.7 and 136.9, respectively, showed a deletion mutation. c The T790M mutation was detected by the Cycleave real-time quantitative PCR technique with a T790M-specific probe and a wild-type probe. Each Ct point of the wild-type and mutant sequence was 29.58 and 34.86 cycles.

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