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CASE REPORT

Pulmonary pleomorphic carcinoma: A case harboring *EGFR* mutation treated with EGFR-TKIs

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Abstract

Pulmonary pleomorphic carcinoma (PPC) is a very rare type of primary lung cancer with an aggressive clinical course. Few reports have documented therapeutic options for PPC with *EGFR* mutations. Herein, we report a case of PPC with *EGFR* mutation treated with EGFR-tyrosine kinase inhibitors (TKIs). A 65-year-old Japanese woman was diagnosed with stage IV lung adenocarcinoma with L858R point mutation in exon 21. Despite treatment with erlotinib, the patient died after two weeks as a result of rapid disease progression. Postmortem examination indicated that the thoracic tumors consisted primarily of spindle/sarcomatous components, while expression of the mutated *EGFR* protein was only observed in adenocarcinoma components. We speculate that the tumor was not driven by *EGFR* mutation. Clinicians should bear in mind the possibility of pleomorphic carcinoma if EGFR-TKI treatment fails to achieve a clinical response for adenocarcinoma harboring an activating *EGFR* mutation diagnosed on the basis of small biopsy specimens.

Introduction

EGFR mutation was discovered in 2004 as the first example of oncogene addiction in lung adenocarcinoma. EGFR-tyrosine kinase inhibitors (TKIs) have been shown to be effective against lung adenocarcinomas harboring *EGFR*-activating mutations.[1,2] Herein, we describe a case of pulmonary pleomorphic carcinoma (PPC) harboring an *EGFR* mutation treated with EGFR-TKIs.

Case report

A 65-year-old Japanese female non-smoker presented with a mass shadow that had been detected by chest radiography at a local clinic. Computed tomography (CT) revealed a 3 cm lesion in the right lower lung with no central necrosis and mediastinal lymphadenopathy extending to the contralateral side. Multiple metastases were observed in right pleural effusion, the adrenals, and bones (Fig 1). Transbronchial biopsy revealed primarily adenocarcinomatous cells with some spindle cells. Immunohistochemistry showed the cells to be diffusely positive for TTF-1 and Napsin A, but negative for vimentin. We diagnosed the primary tumor as adenocarcinoma, and detected a L858R point mutation in exon 21 by Cobas *EGFR* mutation assay (Roche Molecular Diagnostics Inc., South Branchburg, NJ, USA) (Fig 2). After 12 days of erlotinib treatment, the patient was admitted to our hospital because of dyspnea. CT revealed an increase of both pleural and cardiac effusion, and many subcutaneous metastases with acute renal injury and hypercalcemia. On day 15 of erlotinib treatment, the patient died as a result of aggressive tumor progression. An autopsy revealed that the thoracic masses consisted primarily of spindle/sarcomatous components, and immunohistochemistry showed the cells to be diffusely positive for vimentin. On the basis of these findings, we diagnosed the tumor as PPC (Fig 3).

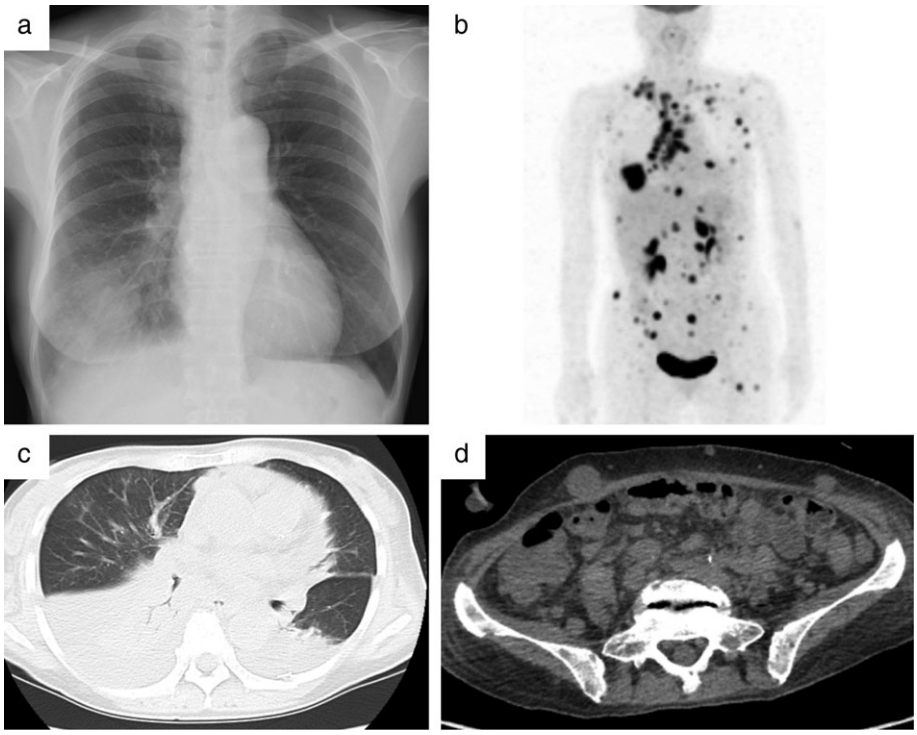

Figure 1 Imaging findings. (**a**) Radiograph showing the primary tumor located in the lower right lung field before treatment. (**b**) Positron emission tomography at diagnosis, showing that the lung cancer had spread to the entire body. (**c,d**) Computed tomography on admission showing bilateral malignant pleural effusions that had spread to the subcutis.

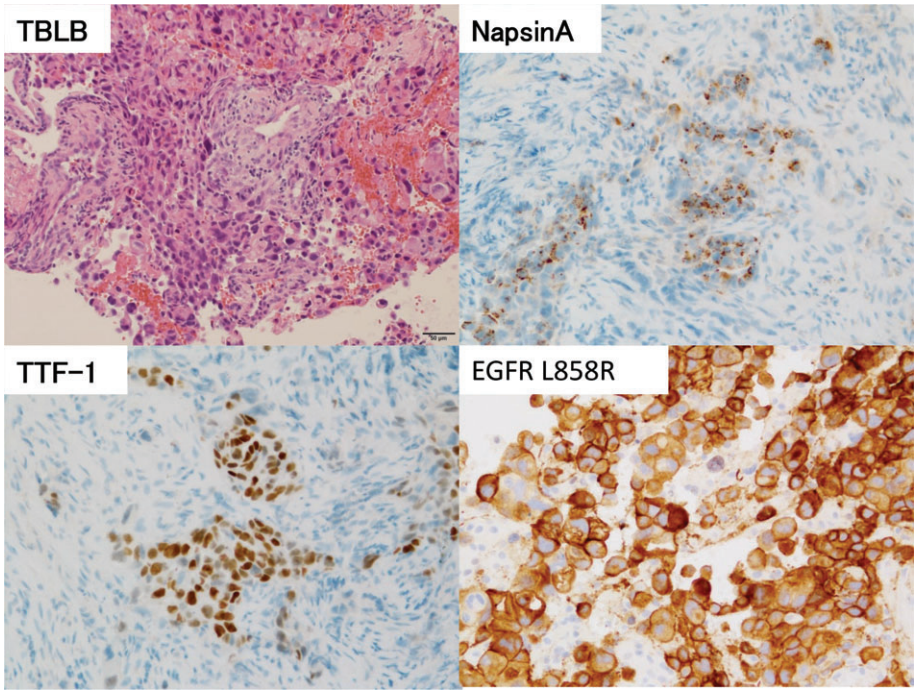

Figure 2 Pathological findings from a bronchoscopic transbronchial biopsy specimen. Microscopy shows that the tumor is an adenocarcinoma (hematoxylin & eosin staining). The adenocarcinoma component is positive for Napsin A and TTF-1, and positively stained with an antibody against mutated (L858R) *EGFR*.

Discussion

Pulmonary pleomorphic carcinoma is a very rare type of primary lung cancer, accounting for 0.1–1.6% of all malignant tumors of the lung.[3] PPC is defined as a poorly differentiated non-small cell lung cancer (NSCLC) containing spindle cells and/or giant cells, or a carcinoma that comprises spindle or giant cells alone, in at least 10% of the tumor.[4] It has an aggressive clinical course and can show resistance to chemotherapy, which is an actively

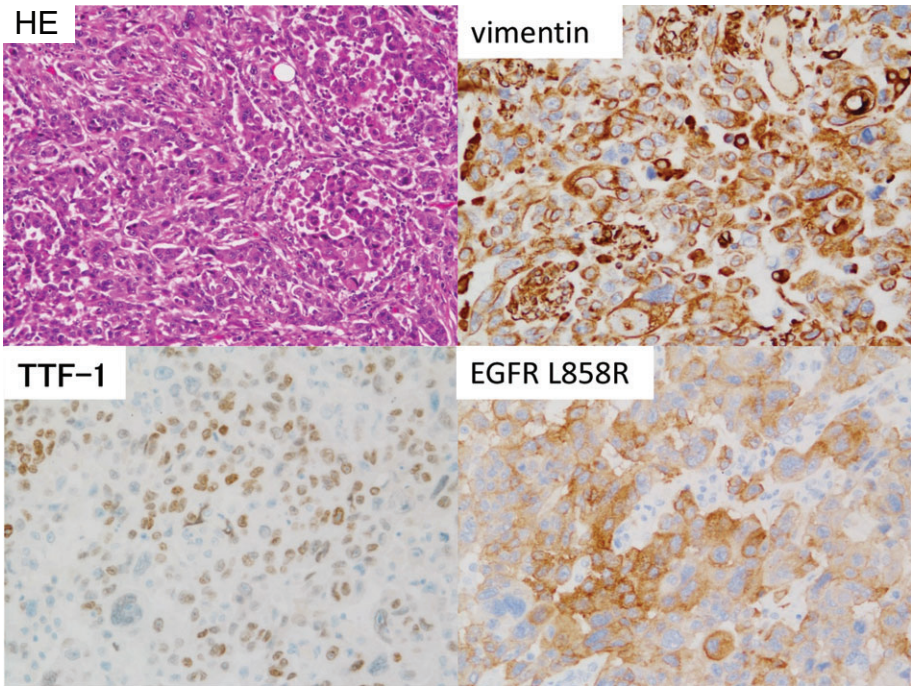

Figure 3 Pathological findings at autopsy. Microscopy shows mostly sarcomatous components (hematoxylin & eosin staining). The spindle/sarcomatous cells were positive for vimentin. Only the adenomatous component was positively stained for TTF-1 and the mutated (L858R) *EGFR*.

applied treatment for NSCLC.[5,6] The present case of PPC was unresponsive to EGFR-TKIs despite harboring an *EGFR* mutation.

Several researchers have reported that the frequency of PPC harboring *EGFR* mutations is approximately 15%.[6–9] However, it is still unclear whether EGFR-TKIs are active against this type of PPC. Tamura *et al.* reported a case of PPC expressing mutated EGFR protein in both the adenocarcinomatous and sarcomatoid components that showed a good response to gefitinib.[8] By contrast, Kaira *et al.* reported a case of PPC with L858R point mutation that did not respond to gefitinib.[6] In the latter case, expression of the mutated EGFR protein was detected in the adenocarcinomatous component, but not in the sarcomatoid component. Similarly, the present case of PPC, which expressed the mutated EGFR protein only in the adenocarcinomatous component, showed no response to EGFR-TKIs. We speculate that the *EGFR* mutation had not caused oncogene addiction in this case.

Pulmonary pleomorphic carcinoma shows distinctive heterogeneity, being composed of poorly differentiated NSCLC containing spindle cells and/or giant cells.[4] The molecular origin of PPC remains largely obscure. Lee *et al.* reported that 30 (49%) of 61 resected PPC cases had molecular alterations such as *EGFR*, *KRAS*, and c-kit, and amplification of *MET*.[7] Of these cases, eight had *EGFR* deletion in exon 19 and one had L858R mutation in exon 21. Furthermore, four cases also had c-kit mutation, and one had *KRAS* mutation with activating *EGFR* mutations. Another study detected *KRAS* mutations in 10 out of 110 PPC cases that occurred in never smokers.[9] Recently, *MET* skipping mutations were found in nine out of a series of 45 PPC cases.[10] We suggest that the biology of PPC, including driver gene alteration, should be investigated further.

In conclusion, we have described a case of PPC with *EGFR* mutation for which erlotinib was not effective. We speculate that the tumor was not driven by *EGFR* mutation. If adenocarcinoma harboring an activating *EGFR* mutation diagnosed from small biopsy specimens shows no clinical response to EGFR-TKI therapy, clinicians should consider the possibility that the tumor may be a pleomorphic carcinoma.

Disclosure

No authors report any conflict of interest.

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