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【 CASE REPORT 】

Retroperitoneal Metastasis, with Marked Fibrosis, of Lung Adenocarcinoma after Afatinib Treatment: An Autopsy Case Report

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Abstract:
A 73-year-old woman was admitted to our hospital for treatment of vomiting. Four months previously, she had been diagnosed with lung adenocarcinoma (cT3N3M1a stage IVA) and started receiving afatinib as first-line treatment. On admission, the primary tumor had shrunk, but abdominal computed tomography revealed a new retroperitoneal lesion causing duodenal obstruction and hydronephrosis. She underwent gastrojejunostomy, and a biopsy of the peritoneum revealed adenocarcinoma. She was treated with second-line chemotherapy but developed cerebral infarction and died 104 days after admission. An autopsy revealed marked fibrosis with scattered tumor cells in the retroperitoneum. The underlying mechanism of the metastasis is discussed.

Key words: lung adenocarcinoma, retroperitoneal metastasis, retroperitoneal fibrosis, hydronephrosis, EGFR mutation, transformation

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Introduction

Diffuse retroperitoneal metastasis of lung cancer is rare. We herein report a case of unique metastasis of lung adenocarcinoma that resembled retroperitoneal fibrosis.

Case Report

A 73-year-old woman was admitted to our hospital for treatment of nausea and vomiting of a few days' duration. Four months previously, she had been diagnosed with lung adenocarcinoma [Fig. 1; cytology from pericardial effusion, clinical T3N3M1a stage IVA; epidermal growth factor receptor (EGFR)-mutation positive; exon 19 deletion] in the right lower lung (Fig. 2). She had no history of malignancy, collagen disease, or recent infectious disease. She did not smoke tobacco and had no history of dust exposure. She was started on first-line afatinib 30 mg daily but soon developed diarrhea. After cessation of afatinib and resolution of the diarrhea, she was restarted on afatinib 20 mg daily.

On admission, chest radiography and computed tomography (CT) showed that the primary tumor had shrunk (Fig. 2); however, abdominal CT showed a new retroperitoneal lesion and right hydronephrosis. Contrast-enhanced CT and magnetic resonance imaging (MRI) (Fig. 3a) showed an area of poorly marginated soft-tissue density around the duodenum and inferior vena cava. Duodenal obstruction was revealed by an examination of the upper gastrointestinal tract (Fig. 4b), and she underwent gastrojejunostomy and a peritoneal biopsy. An analysis of the biopsy specimen revealed thyroid transcription-factor (TTF)-1 immunohistochemistry-positive, EGFR mutation-positive adenocarcinoma with exon 19 deletion (negative T790M), which was consistent with retroperitoneal metastasis of the lung adenocarcinoma (Fig. 3c, d). These findings suggested that the

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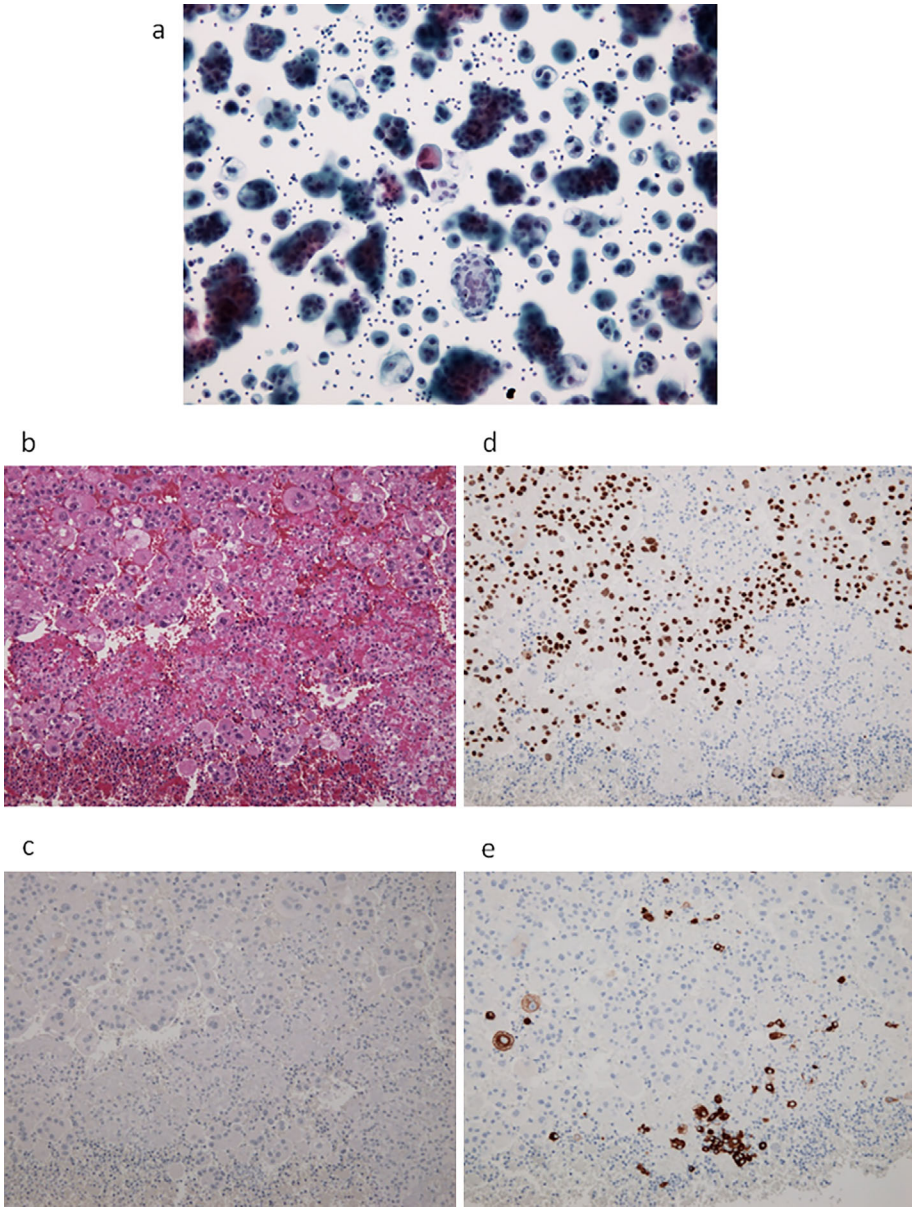

Figure 1. **Cytology from pericardial effusion (a). (b-e) Cell block immunohistochemistry. b. Hematoxylin and Eosin staining. c. No Napsin A staining was seen. d. TTF-1. E. CK5/6.**

duodenal obstruction was due to retroperitoneal metastasis. She was treated with second-line carboplatin (CBDCA)/pemetrexed (PEM) and CBDCA/PEM/bevacizumab (BV), one course at a time. However, she developed cerebral infarction 2 months after admission and ultimately died 104 days after admission.

An autopsy revealed right ureteral obstruction and hydronephrosis, which were caused by a markedly sclerotic lesion in the retroperitoneum. The lesion resembled retroperitoneal fibrosis and involved the pelvic organs. A microscopic examination revealed marked fibrosis and carcinoma cells scattered throughout the retroperitoneum (Fig. 4i). Microscopy showed that the tumor cells at the metastatic site (retroperitoneum) were poorly differentiated and differed greatly from those at the primary site (lung) (Fig. 4a). At the primary site, the tumor cells were mostly positive for Napsin A and TTF-1 and negative for CK5/6 (Fig. 4b-d); however, the opposite results were obtained in a minute portion of the moderately differentiated cells (Fig. 4f-h). Tumor cells at the metastatic site were negative for Napsin A and TTF-1 and partially positive for CK5/6 (Fig. 4j-l), thus resembling the minute portion in the primary site (Fig. 4f-h). Retrospective analyses revealed a small number of CK5/6-positive and TTF-1-negative cells in pericardial effusion (Fig. 1d, e). E-cadherin, the absence of which suggests epithelial-mesenchymal transition, was positive at the primary and metastatic sites. Vimentin, the expression of which indicates epithelial-mesenchymal transition, was negative at the primary and metastatic sites. None of the neuroendocrine markers (chromogranin A, synaptophysin, and CD56) were positively stained at either the primary or metastatic sites. Marked pericardial adhesion was accompanied by sclerosis, and tumor cells were present. Small foci of metastasis were found in the parathyroid gland. The systemic presence of

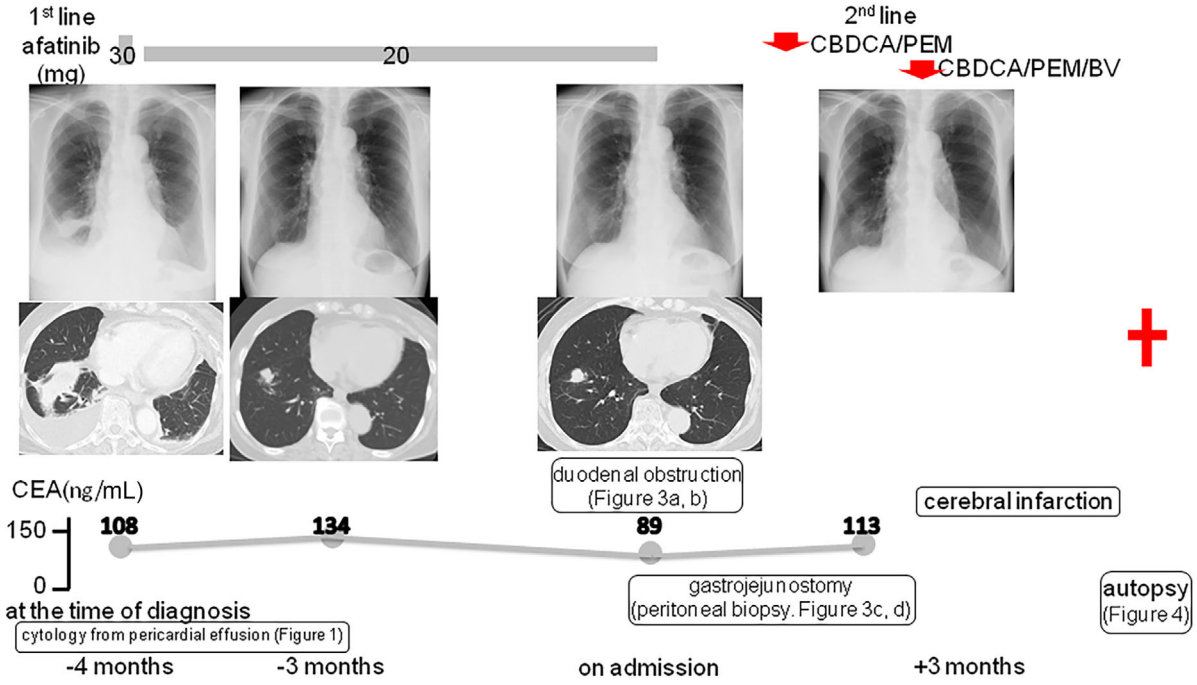

Figure 2. **A chest radiograph and CT on admission showing shrinkage of the primary tumor since the diagnosis.**

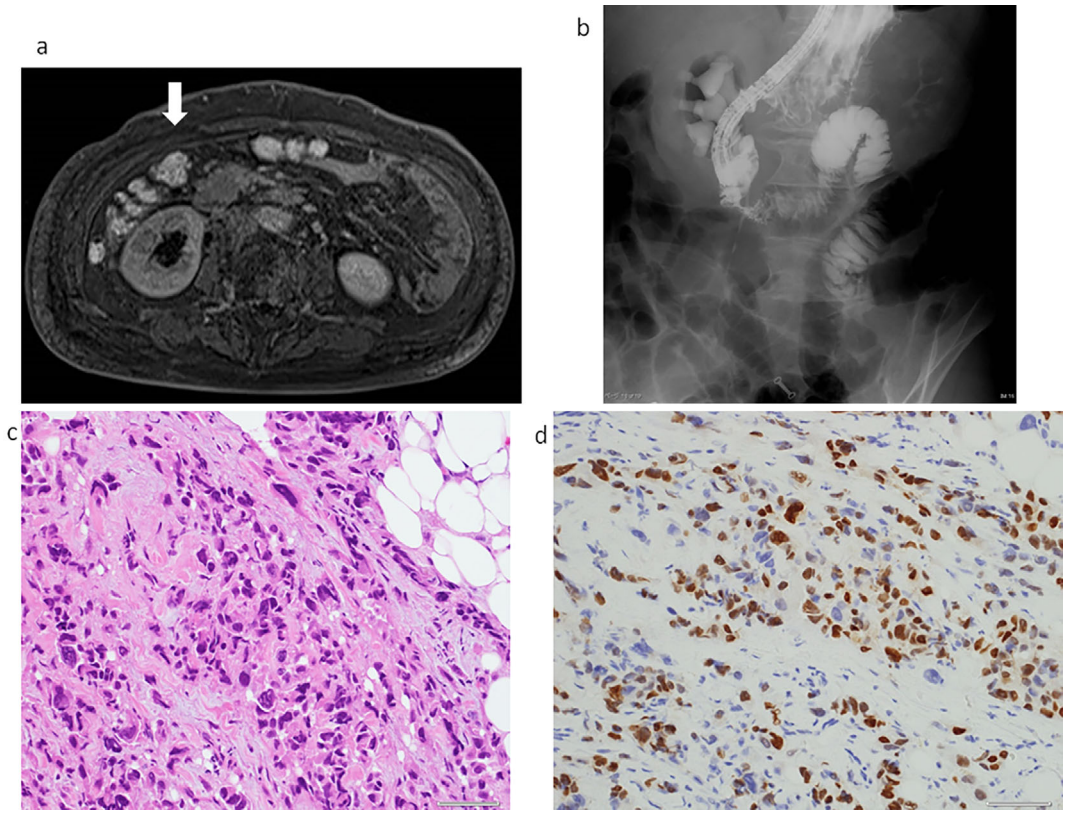

Figure 3. **(a) T1-weighted contrast-enhanced MRI showing poorly marginated soft tissue around the duodenum (white arrows) and right hydronephrosis. (b) An examination of the upper gastrointestinal tract showing duodenal obstruction. (c, d) Biopsy specimen of the peritoneum showing metastasis of poorly differentiated lung adenocarcinoma on Hematoxylin and Eosin staining (c) and TTF-1 immunohistochemistry (d).**

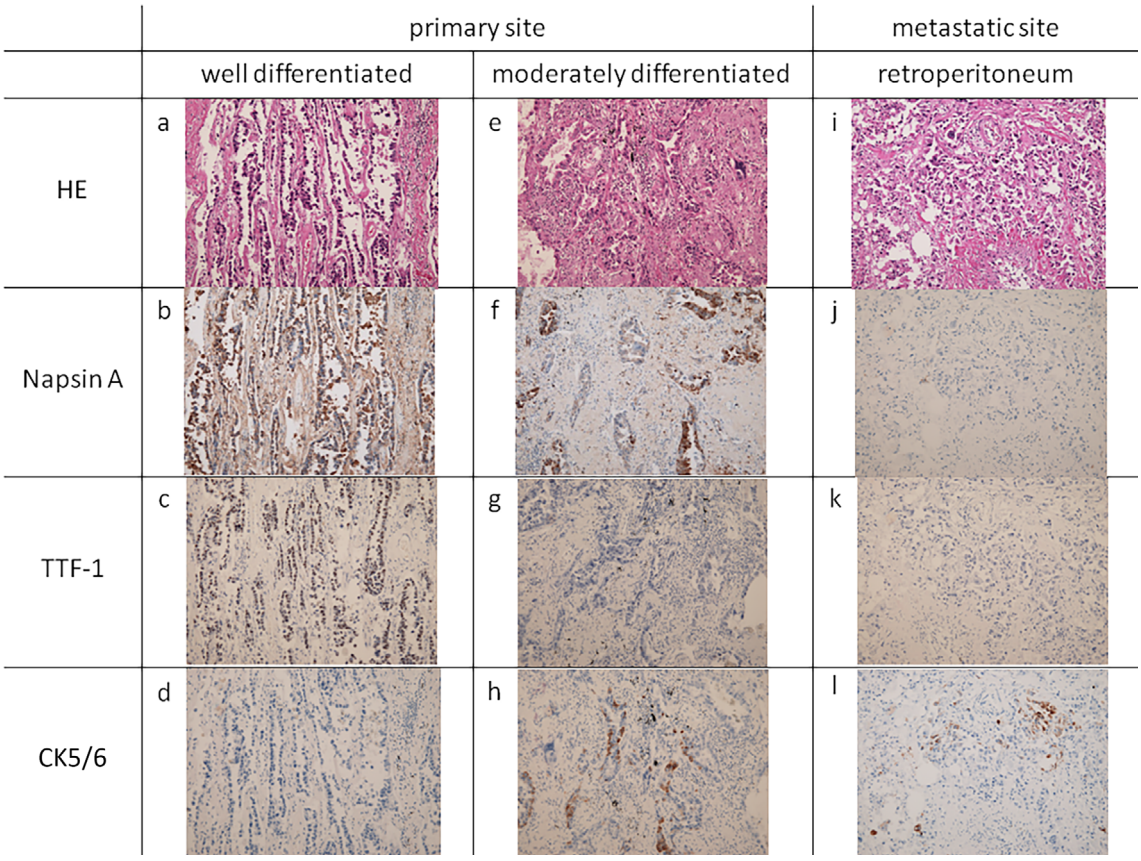

Figure 4. **Microscopic features of carcinoma at the autopsy; Hematoxylin and Eosin staining (a, e, i), immunohistochemistry for Napsin A (b, f, j), TTF-1 (c, g, k), and CK5/6 (d, h, l). (a-d) Well-differentiated adenocarcinoma at the primary site. (e-h) Moderately differentiated adenocarcinoma at the primary site. (i-l) Poorly differentiated carcinoma cells scattered among areas of marked fibrosis throughout the retroperitoneum. The immunohistochemical features at the metastatic site (j-l) were completely different from those in the well-differentiated cells at the primary site (b-d) but resembled the minute element in the moderately differentiated cells at the primary site (f-h).**

various stages of thrombi suggested that cerebral infarction had been caused by Trousseau syndrome.

Discussion

Lung cancer is the most common cause of cancer death worldwide in men and women. The brain is the most common site of lung cancer metastases, followed by the bones, liver, and adrenal glands (1). Retroperitoneal lung cancer metastasis that resembles retroperitoneal fibrosis and results in duodenal or urinary obstruction is extremely rare and is the subject of the present report.

More than two-thirds of cases of peritoneal fibrosis are idiopathic. Secondary retroperitoneal fibrosis is caused by drugs, infection, malignant disease, and connective tissue disease (2). Implicated malignant diseases include carcinoma of the colorectum, prostate, breast, and stomach, sarcomas, and lymphomas (3). Among patients with retroperitoneal metastasis from lung cancer, some have the mass-forming type (4), but it is rare for patients to have diffuse retroperitoneal metastasis mimicking retroperitoneal fibrosis presenting with poorly marginated soft tissue density around the aorta, as was seen in our patient. In the present case, a sclerotic lesion extended throughout the retroperitoneum, thereby obstructing or deforming several organs. To our knowledge, four cases of secondary retroperitoneal fibrosis of lung cancer have been reported (5-8). In some patients with carcinoid syndrome, retroperitoneal fibrosis reportedly develops because of a fibrogenic response to long-term secretion of vasoactive substances, such as serotonin and tachykinins (9). In the present case, tumor cells were scattered throughout the fibrotic lesion, so retroperitoneal lung cancer metastasis mimicking retroperitoneal fibrosis was diagnosed.

Almost all EGFR-mutant lung cancers develop resistance to EGFR-tyrosine kinase inhibitors (EGFR-TKIs). Several mechanisms have been identified, including development of an EGFR T790M mutation, hepatocyte growth factor overexpression, loss of phosphatase and tensin homolog expression, epithelial-mesenchymal transition, and transformation to small-cell carcinoma or squamous cell carcinoma (10-14). In the present case, the results of tests for neuroendocrine markers were negative at the retroperitoneal metastatic site, which suggested that transformation to small-cell lung can-

cer was unlikely. An EGFR T790M mutation was negative. E-cadherin was positive, and vimentin was negative at both the primary and metastatic sites, suggesting that epithelial-mesenchymal transition was unlikely. In this case, the marked histological and immunohistochemical changes at the metastatic sites (poor differentiation, loss of TTF-1 and Napsin A staining, and presence of CK5/6-positive cells) suggest two possible mechanisms: transformation to squamous cell carcinoma or emerging heterogeneity. There have been two reported cases of squamous cell carcinoma transformation after afatinib treatment (13, 14). In the present case, however, the presence of minute TTF-1-negative/Napsin A-negative/CK5/6-positive moderately differentiated adenocarcinoma on cytology at the diagnosis and at the primary site at the autopsy suggest emerging heterogeneity. The acquired (or emerging) phenotype may have triggered a fibrogenic response in this patient.

An analysis of other cases resistant to EGFR-TKI or CBDCA/PEM/BV may help identify the mechanism underlying this fibrogenic response.

The authors state that they have no Conflict of Interest (COI).

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