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A Case of Combined Small-cell Carcinoma and Adenocarcinoma of the Lung With *EGFR* Exon 19 Deletion Identified *via* Liquid Genomic Profiling

YOHEI FUKUDA[1,2], KOSUKE HASHIMOTO[2], KYOICHI KAIRA[2], ATSUTO MOURI[2], REINA ISHII[2], NAOHITO HASHIMOTO[2], YU MIURA[2], AYAKO SHIONO[2], OU YAMAGUCHI[2], HISAO IMAI[2] and HIROSHI KAGAMU[2]

[1]Department of Clinical Training Center, International Medical Center, Saitama Medical University, Saitama, Japan;
[2]Department of Respiratory Medicine, International Medical Center, Saitama Medical University, Saitama, Japan

Abstract

Background/Aim: Mixed histological lung cancers, such as combined small-cell carcinoma (SCLC) and adenocarcinoma, are rare and often present diagnostic and therapeutic challenges due to intratumoral heterogeneity. In such cases, conventional tissue biopsies may fail to detect key genetic alterations, especially when sampling is limited or affected by tumor evolution. Liquid biopsy has emerged as a complementary approach capable of capturing broader genomic information in a non-invasive manner.

Case Report: We describe a 73-year-old woman with metastatic lung cancer initially diagnosed as *EGFR* wild-type adenocarcinoma via tissue biopsy. The patient underwent multiple lines of therapy, including immune checkpoint inhibitors and cytotoxic chemotherapy. Over time, the histology shifted, and repeat biopsy identified small-cell carcinoma. Due to the tumor's evolving nature and limited biopsy accessibility, a liquid biopsy using FoundationOne Liquid CDx was performed. This identified an *EGFR* exon 19 deletion (T751_A755del) that had not been detected in prior tissue analyses. Targeted therapy with osimertinib was initiated as fifth-line treatment, resulting in temporary disease stabilization and reduction in tumor markers.

Conclusion: This case illustrates the clinical value of liquid biopsy in detecting actionable mutations in patients with mixed histological lung cancers where tissue-based testing is inconclusive. Liquid biopsy enabled a personalized therapeutic approach without the need for further invasive procedures. Such strategies may be essential in managing histologically and genomically heterogeneous tumors.

Keywords: Combined small-cell carcinoma and adenocarcinoma, EGFR, FoundationOne Liquid CDx, liquid biopsy.

Kosuke Hashimoto, Department of Respiratory Medicine, International Medical Center, Saitama Medical University, 1397-1 Yamane, Hidaka, Saitama 350-1298, Japan. E-mail: hkosuke@saitama-med.ac.jp

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Introduction

Approximately 5% of *EGFR* mutation-positive non-small cell lung cancers (NSCLCs) transform into small-cell lung cancers (SCLCs) (1). Adenocarcinoma components are occasionally observed in resected SCLC tissue (2). Although treatment protocols for NSCLC and SCLC are well established, guidelines are lacking for mixed histological subtypes.

Conventional biopsy techniques, including transbronchial lung biopsy (TBLB) and computed tomography (CT)-guided biopsy, are limited by sampling error and tumor heterogeneity. Liquid biopsy has emerged as a complementary approach offering non-invasiveness and broader genetic insight (3, 4). Histological variation between primary and metastatic lesions further complicates diagnosis, particularly in combined histology tumors (5, 6).

Here, we report a case in which liquid genomic profiling identified an actionable *EGFR* mutation in a patient with histologically confirmed adenocarcinoma and SCLC, enabling the administration of fifth-line targeted therapy. The patient provided written informed consent for publication.

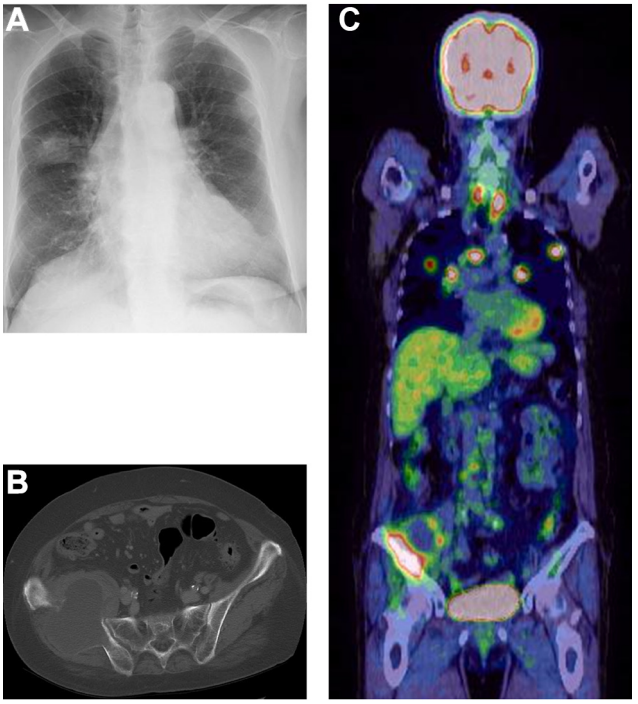

Figure 1. *Initial imaging findings. A) Chest radiograph showing bilateral lung masses. B) Contrast-enhanced computed tomography (CT) indicating a large mass in the right iliac bone. C) Positron emission tomography (PET)-CT demonstrating widespread metastases in both lungs, mediastinum, and iliac bone.*

Case Report

A 73-year-old woman with a smoking history presented with right iliac pain. CT revealed a right upper lobe lung mass and multiple metastatic lesions. Her performance status was 1. Blood tests showed elevated alkaline phosphatase (730 mg) and tumor markers, including cytokeratin 19 fragment (CYFRA), carcinoembryonic antigen (CEA), cancer antigen 15-3 (CA15-3), and cancer antigen19-9 (CA19-9), with levels of 29.1 mg/ml, 816.2 ng/ml, 176.8 U/ml, and 259.3 U/ml, respectively. Pro-gastrin-releasing peptide (Pro-GRP) was within the normal range (49.2 pg/ml).

CT-guided biopsy of the iliac lesion indicated metastatic lung adenocarcinoma. Immunohistochemistry supported pulmonary origin. Imaging showed bilateral lung tumors, mediastinal/hilar lymphadenopathy, and distant metastases. Initial genetic testing revealed stage IVB EGFR wild-type adenocarcinoma. Anaplastic lymphoma kinase (ALK) immunohistochemistry (IHC) was scored as 0, ROS proto-oncogene 1 (ROS1) was negative, and programmed death-ligand 1 (PD-L1) tumor proportion score (TPS) was 5% (Figure 1).

The patient received ipilimumab plus nivolumab as first-line therapy, resulting in partial symptom relief and regression of iliac metastasis. After four months, CT revealed progression of lung lesions, while lymph nodes remained stable. Repeat TBLB of lung tissue revealed small-cell carcinoma with neuroendocrine marker negativity. Diagnosis was revised to combined SCLC and adenocarcinoma.

She underwent second-line treatment with carboplatin, etoposide, and durvalumab, maintaining disease control for eight months. Third-line carboplatin

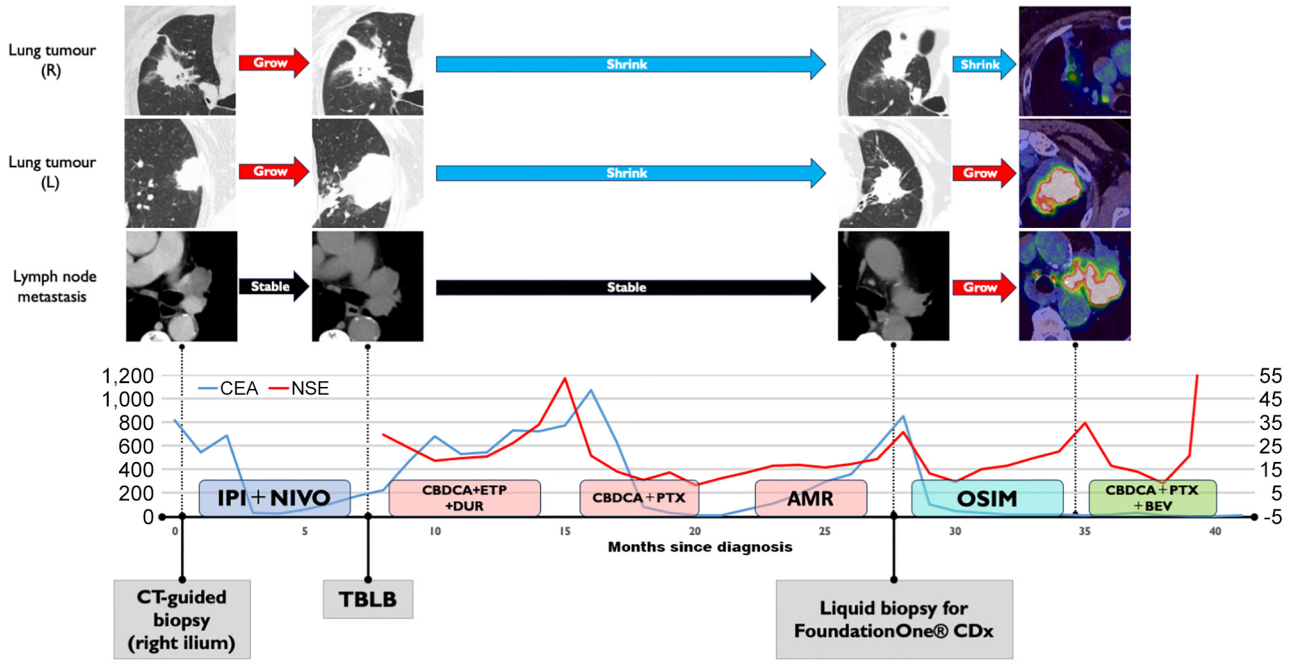

Figure 2. *Treatment course and biomarker trends. Treatment progression and fluctuations in carcinoembryonic antigen (CEA) and neuron-specific enolase (NSE) levels are illustrated. IPI: Ipilimumab; NIVO: nivolumab; CBDCA: carboplatin; ETP: etoposide; DUR: durvalumab; PTX: paclitaxel; AMR: amrubicin; OSIM: osimertinib; BEV: bevacizumab; ATZ: atezolizumab; TBLB: transbronchial lung biopsy; CT: computed tomography.*

plus paclitaxel lasted six months. Upon elevation of neuron-specific enolase (NSE), amrubicin was introduced (fourth-line) and stabilized the disease for four months.

Due to inter-tumoral histologic diversity, multiplex liquid biopsy (FoundationOne Liquid CDx) was performed and identified an EGFR exon 19 deletion (T751_A755del) previously undetected. Osimertinib (fifth-line) temporarily reduced tumor markers and achieved disease stability for 6.5 months. Sixth-line therapy with carboplatin, paclitaxel, bevacizumab, and atezolizumab was administered for five months, after which the patient transitioned to palliative care. The treatment timeline is illustrated in Figure 2.

Discussion

This case highlights both spatial and temporal tumor heterogeneity. The patient harbored coexisting adenocarcinoma and SCLC with site-dependent variation. Repeated tissue biopsies were impractical due to invasiveness. Liquid biopsy allowed comprehensive genomic profiling across tumor sites.

Similar cases typically involve SCLC transformation from *EGFR*-mutated adenocarcinoma. Hiura *et al.* (6) described histologic shifts linked to fluctuations in tumor markers. Their report required invasive biopsy due to negative cytology. In contrast, our case utilized liquid biopsy to avoid additional invasive procedures and detect a therapeutically relevant mutation.

Whether this represents a true mixed tumor or synchronous malignancies is unclear. Nonetheless, early detection of both components via tissue and liquid biopsies supported tailored treatment. Moreover, this case demonstrates the superiority of multiplex over single-plex genetic testing in detecting rare *EGFR* mutations. In a previous study, multiplex analysis identified mutations missed by single-gene tests (7).

Liquid biopsy enabled the identification of an actionable mutation and spared the patient from further

invasive diagnostics. It proved essential in this case of mixed histology and may be valuable in similar complex presentations.

Conclusion

Liquid genomic profiling with FoundationOne Liquid CDx successfully detected an EGFR exon 19 deletion in a patient with coexisting adenocarcinoma and SCLC. Liquid biopsy offers a non-invasive alternative for identifying actionable mutations in mixed histology lung cancers.

Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

Authors' Contributions

Y.F. conceived and designed the study, acquired clinical data, and drafted the manuscript. K.H. and K.K. interpreted the data, revised the manuscript critically for important intellectual content, and supervised the project. All Authors read and approved the final version of the manuscript.

Artificial Intelligence (AI) Disclosure

During the preparation of this manuscript, a large language model (GPT-4o, OpenAI) was used solely for language editing and stylistic improvements in select paragraphs. No sections involving the generation, analysis, or interpretation of research data were produced by generative AI. All scientific content was created and verified by the authors. Furthermore, no figures or visual data were generated or modified using generative AI or machine learning–based image enhancement tools.

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