

Therapeutic Resistance in G-CSF Producing Lung Cancer With *EGFR* Mutation

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Abstract. *Background/Aim:* Granulocyte colony-stimulating factor (G-CSF)-producing neoplasms are relatively rare; however, little is known on the clinical features of G-CSF-producing lung cancer harboring activating epidermal growth factor receptor (EGFR) mutations. *Case Report:* A 66-year-old female was definitively diagnosed with G-CSF-producing lung cancer that was positive for EGFR mutations. She repeatedly received epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs), such as osimertinib and afatinib. However, she developed resistance to these molecular-targeting drugs within 2 to 3 months after immediate shrinkage. Thus, the patient was treated with chemoinmunotherapy including bevacizumab, and demonstrated a slight survival benefit. *Conclusion:* Overall, G-CSF-producing lung cancers positive for EGFR mutations were resistant to different treatment modalities. Clinicians should be attentive to the potential resistance of G-CSF-producing EGFR mutant lung cancer to EGFR-TKI therapy.

Granulocyte colony-stimulating factor (G-CSF) is a cytokine that promotes neutrophil production. The clinical features of G-CSF-producing neoplasms include neutrophilia without infection and chemotherapeutic resistance with a dismal

outcome (1, 2). However, little is known about the relationship between genetic alterations and G-CSF-producing lung cancers.

Epidermal growth factor receptor (EGFR) mutations have been identified as the major genetic alterations in patients with lung cancer (3), and EGFR-tyrosine kinase inhibitors (TKIs) are standard treatments for lung cancer that demonstrate high efficacy. Only one report has described the radiosensitivity of G-CSF-producing lung adenocarcinoma positive for an activating *EGFR* mutation (4). However, there is still no experience with EGFR tyrosine kinase inhibitors (TKI) in patients with G-CSF-producing lung cancers harboring *EGFR* mutations. Herein, we present a case of G-CSF-producing lung cancer with *EGFR* mutation in a patient who received EGFR-TKI treatment.

Case Report

A 66-year-old female without history of smoking complained of a cough and visited a hospital. Chest radiography revealed a mass shadow in the left upper lung field; therefore, the patient was referred to our Institution. Computed tomography (CT) revealed a primary tumor in the left upper lobe of the lung (Figure 1A), swelling of the left hilar lymph nodes (Figure 1B), and enlargement of both adrenal glands (Figure 1C). Two-deoxy-2-[fluorine-18]-fluoro-D-glucose positron emission tomography (¹⁸F-FDG PET) revealed increased accumulation in the primary tumor (Figure 2A), hilar lymph nodes (Figure 2B), and both adrenal glands (Figure 2C), consistent with the CT scan findings. Additionally, there was evidence of diffuse bone marrow accumulation (Figure 2D). Laboratory findings showed leukocyte levels at 26,000/ μ l, neutrocyte levels at 23,500/ μ l C-reactive protein (CRP) levels at 3.58 mg/dl, and serum G-CSF levels at 635 pg/ml (normal range, <39.0 pg/ml). Her physical examination revealed no notable changes. A definitive diagnosis by transbronchial biopsy revealed the histology of non-small cell lung cancer with cT2N1M1c

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Key Words: G-CSF, lung cancer, EGFR mutation.

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stage IVB. Immunohistochemical staining for G-CSF was substantially positive in the tumor specimens (Figure 3). Based on the high levels of serum G-CSF, leukocytes, and neutrophils, and diffuse ^{18}F -FDG uptake in the bone marrow, a definite diagnosis of a G-CSF-producing tumor was made. Molecular analyses including gene panel testing revealed an exon19 deletion and 90% programmed death ligand-1 (PD-L1) expression. Therefore, osimertinib at a dose of 80 mg/day was orally administered as the first-line treatment. The therapeutic course after first-line osimertinib treatment is shown in Figure 4. On day 12 after osimertinib administration, blood testing revealed a decreasing trend in leukocyte, neutrophil, and CRP levels, and chest radiography showed shrinkage of the primary tumor on day 28. On day 56, an increasing trend in leukocyte count and CRP was observed. We identified progressive disease (PD) after osimertinib treatment because of primary tumor enlargement on day 84. Therefore, the patient was treated with carboplatin, paclitaxel, bevacizumab, and atezolizumab following bevacizumab plus atezolizumab maintenance therapy as the second-line treatment on day 89. Leukocyte and CRP levels were markedly decreased, and there was evidence of shrinking of the primary tumor. On day 238, she demonstrated a significant increase in leukocyte and CRP levels, corresponding to the growth of the primary tumor, indicative of progressive disease (PD) despite combination chemotherapy. On day 238, afatinib was administered as a third-line treatment. Subsequently, leukocyte and CRP levels decreased, and stable disease of the primary tumor was observed on day 252. However, leukocyte and CRP levels increased over a short period. On day 266, the TKI was changed to gefitinib; however, the effect of the gefitinib could not be confirmed. Combination chemotherapy and immunotherapy were administered again on day 287. There was no recurrence after the treatment, and the patient continued to receive combination chemo-immunotherapy.

Discussion

G-CSF-producing tumors were first reported by Asano *et al.* in 1977 (1), and the following diagnostic criteria were proposed: 1) marked leukocytosis, mainly of mature neutrophils without a cause; 2) high serum G-CSF levels; 3) decreased leukocyte count and G-CSF levels due to tumor resection or treatment; and 4) evidence of G-CSF production in the tumor. In our case, these criteria were met. In addition, diffuse accumulation of ^{18}F -FDG in the bone marrow has been reported as a characteristic of G-CSF-producing tumors and has been effective in determining the diagnosis and treatment response in several reports, corresponding to the findings of our case (4, 5). However, the association between G-CSF-producing tumors and *EGFR* mutations is unclear, and there are few reports on their clinical characteristics. *In*

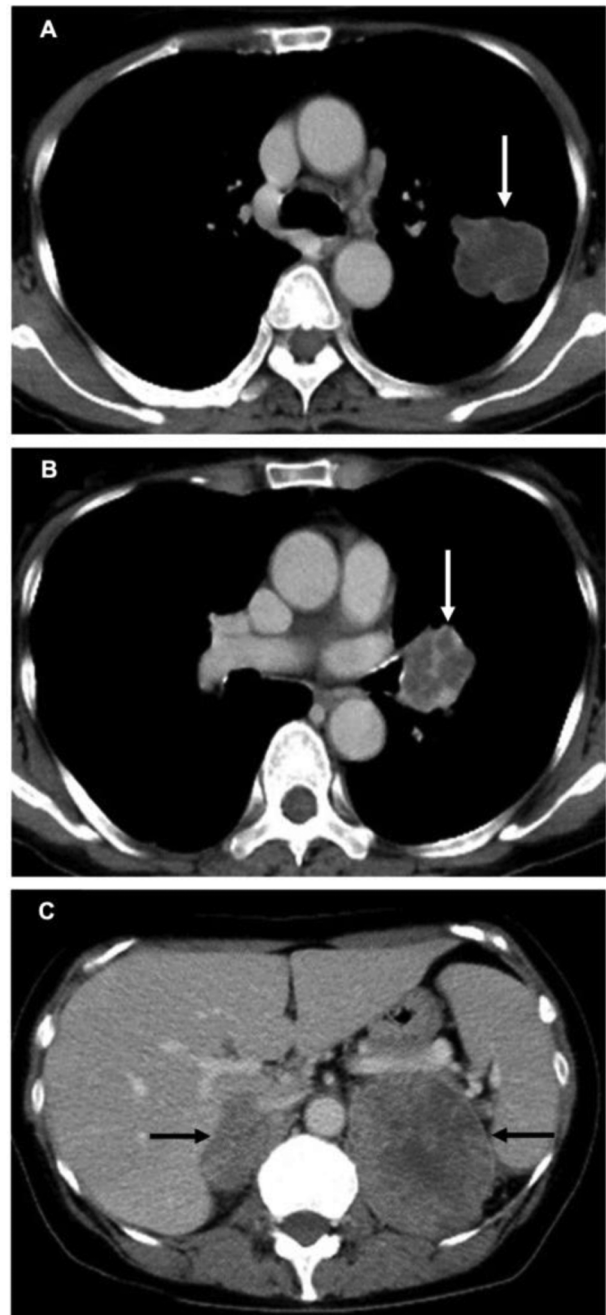


Figure 1. Chest CT at diagnosis showing a primary tumor in the left upper lobe of the lung (A) (white arrow), swelling of the left hilar lymph node (B) (white arrow), and enlargement of both adrenal glands (C) (black arrows). Low-density attenuation within individual tumor specimens reveals tumor necrosis. CT: Computed tomography.

vivo and *in vitro* studies have shown that *EGFR* regulates granulocyte/macrophage colony-stimulating factor (GM-CSF), which is required for differentiation into neutrophil colony-forming cells (6); however, its relationship with G-

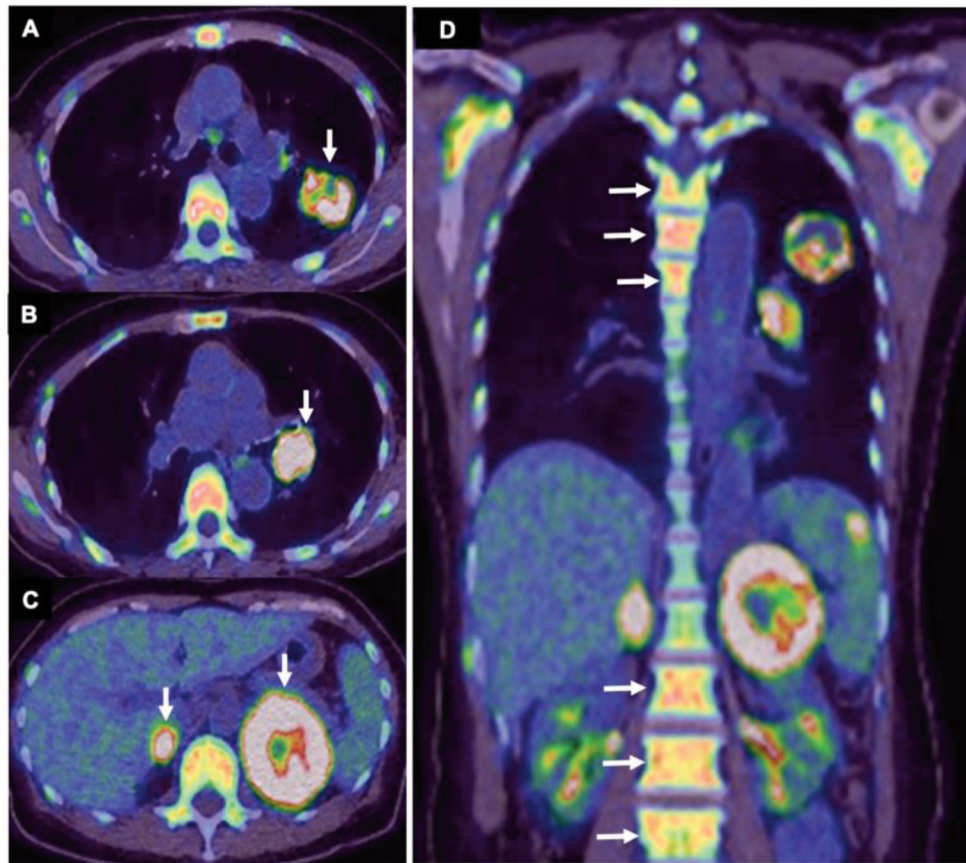


Figure 2. Sagittal view of ^{18}F -FDG PET imaging at diagnosis showing substantially elevated uptake of ^{18}F -FDG in the primary site of the left upper lobe of the lung (SUV_{max} of 20.8) (A) (white arrow), left hilar lymph node (SUV_{max} of 18.1) (B) (white arrow), and both adrenal glands (C) (white arrows). Coronal view of ^{18}F -FDG PET showing diffuse accumulation in the sternum, ribs, and bone marrow (D) (white arrows). ^{18}F -FDG PET: 2-deoxy-2-[fluorine-18]-fluoro-d-glucose positron emission tomography.

CSF is unclear. *EGFR* mutations are the most commonly detected genetic mutations in the Oriental population and may have been detected incidentally in G-CSF-producing tumors (3). In general, driver gene mutation-positive cases, including *EGFR* mutations, are characterized by low PD-L1 expression and tumor mutation burden (TMB) (7, 8). Additionally, the efficacy of immune checkpoint inhibitors (ICI) is poor in *EGFR* mutation-positive NSCLC (7, 8), and high PD-L1 expression is associated with early resistance to *EGFR*-TKIs (9). In contrast, Miyazaki *et al.* found a trend toward higher PD-L1 expression (>50%) (69.2%, 9 out of 13 patients) in G-CSF-producing tumors and reported that the objective response rate (ORR) and median overall survival (OS) of ICI monotherapy were 33.3% and 7.3 months, respectively, regardless of PD-L1 expression (2). Although the major population in their study had PD-L1 expression >50% (2), the therapeutic efficacy of ICI monotherapy seemed to be slightly lower than that of pembrolizumab monotherapy in G-CSF-non-producing lung cancer with PD-

L1 expression >50% (ORR, 46.1%; median OS: 26.6 months) (10). One reason for this discrepancy is the elevated levels of inflammatory cytokines in G-CSF-producing tumors (1, 2), resembling an immune environment that suppresses sensitivity to ICI (11). However, because of the different designs of both studies (2, 10), it may be difficult to compare the therapeutic efficacy of ICI treatment between G-CSF-producing and non-producing lung cancers.

In the present case, *EGFR*-TKIs induced resistance within 2 to 3 months of the immediate response. Although the high expression of PD-L1 (90%) is considered a potential resistance to *EGFR*-TKIs, the presence of the G-CSF-producing phenomenon may have led to early resistance to *EGFR*-TKIs. In contrast, chemoimmunotherapy resulted in a mild response in our case, with a progression-free survival of approximately 5 months. Overall, G-CSF-producing lung cancer may be resistant to *EGFR*-TKIs or chemoimmunotherapy, even if they have high PD-L1 expression and sensitive *EGFR* mutations. The relationship between the mechanism of G-CSF production

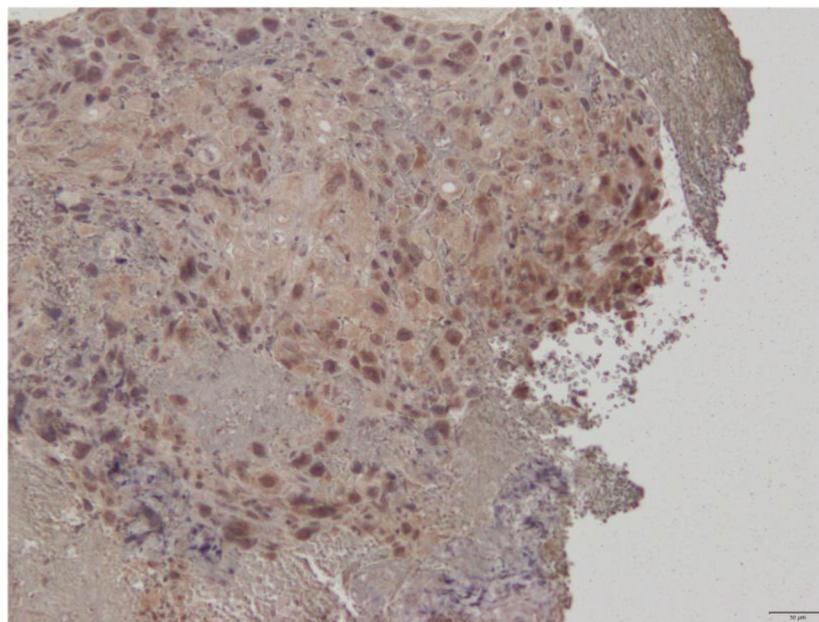


Figure 3. Immunohistochemical staining for G-CSF shows substantial positivity in the tumor specimens. An anti-human G-CSF mouse monoclonal antibody (1:100 dilution; clone 4-12-2; Immuno-Biological Laboratories Co., Ltd., Gunma, Japan) was used for immunohistochemistry. G-CSF: Granulocyte colony-stimulating factor.

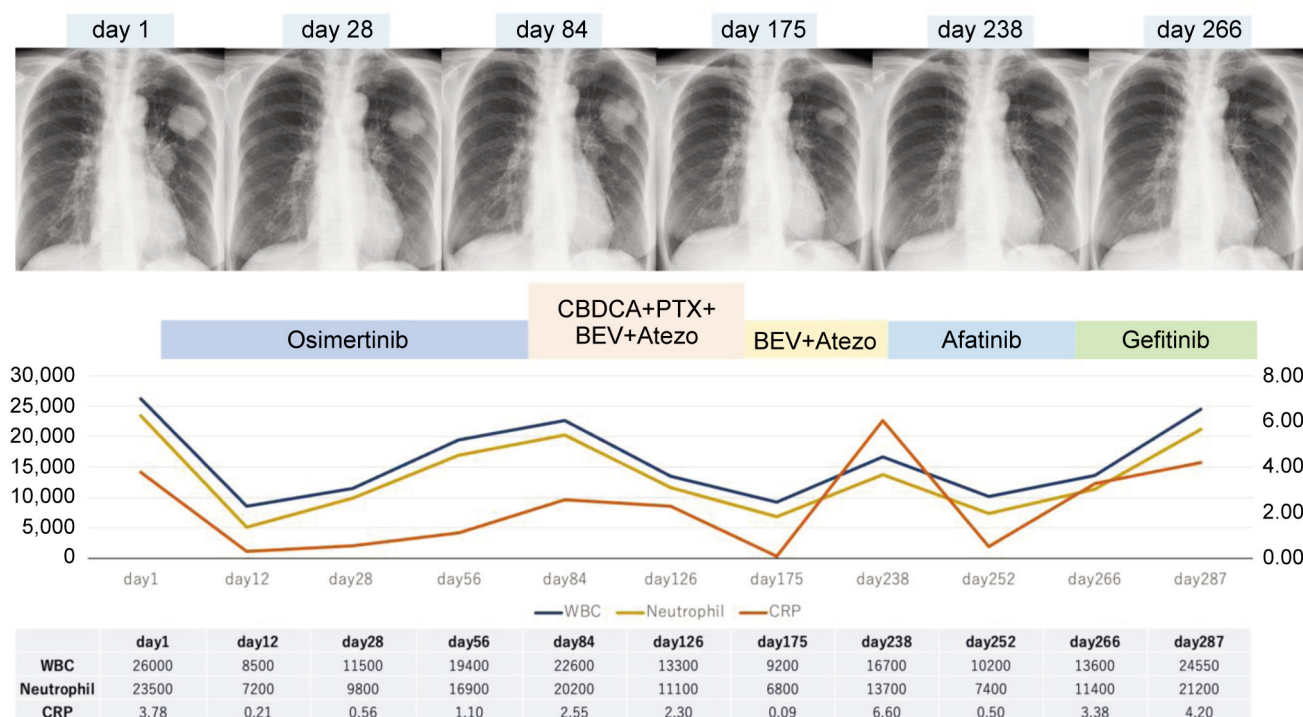


Figure 4. The therapeutic course after osimertinib treatment as first-line setting showing changes in images over time, course of treatment, and blood laboratory testing. Chest radiography showing baseline on day 1, shrinkage of primary site due to osimertinib on day 28, progressive disease on day 84, shrinkage of primary site due to chemo-immunotherapy on day 175, and, before afatinib administration on day 238 and gefitinib administration on day 266, respectively. Blood testing showing the trend of WBC, neutrophil, and CRP according to different treatment. CBDCA, Carboplatin; PTX, paclitaxel; BEV, bevacizumab; Atezo, atezolizumab; WBC, white blood cell; CRP, C-reactive protein.

and therapeutic resistance remains poorly understood. However, the discovery of a promising systemic treatment for G-CSF-producing tumors remains an important issue. Clinicians should consider the potential resistance of G-CSF-producing *EGFR* mutant lung cancer to EGFR-TKIs.

Conclusion

EGFR-TKIs imply clinically resistance to G-CSF-producing lung cancer with EGFR mutations. Chemoimmunotherapy is the most effective treatment, but offers a limited efficacy in G-CSF producing lung cancers harboring *EGFR* mutations.

Conflicts of Interest

The Authors have no conflicts of interest.

Authors' Contributions

KI and KK were involved in the conception of the study, as well as the drafting and critical revision of the article. HI, AS, KH, OY, and HK conducted the acquisition, analysis, and interpretation of the data and critical revision of the article.

Acknowledgements

The Authors would like to thank Ms Kozue Watanabe and Ms. Koko Kodaira in Saitama Medical University, Hidaka city, Japan for assistance in preparing the manuscript. We would like to thank Editage (www.editage.com) for English language editing.

Funding

This research received no specific grants from any funding agency in the public, commercial, or not-for-profit sectors.

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Received February 5, 2024

Revised March 24, 2024

Accepted April 5, 2024