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Case Report

A case of granulocyte colony-stimulating factor producing lung adenocarcinoma with anaplastic lymphoma kinase gene rearrangements

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ABSTRACT

A 49-year-old woman was diagnosed with lung adenocarcinoma, stage IIIB, with increased leukocytes and neutrophils. Positron emission tomography showed dense uptake in right lung, but not in the bone marrow or bone. Biopsy revealed positive anaplastic lymphoma kinase (*ALK)* gene rearrangements. First-line ALK inhibitor, crizotinib, was used for 9 weeks and its effect was limited. Second-line ALK inhibitor did not show effect. Positive immunostaining and high serum granulocyte colony-stimulating factor (G-CSF) levels confirmed G-CSF-producing lung adenocarcinoma. The patient died after 4.5 months of diagnosis. This is the first reported case of G–CSF–producing lung cancer with *ALK* rearrangements.

1. Introduction

Granulocyte colony-stimulating factor (G-CSF) is a hematopoietic growth factor that promotes development, mobilization, and activation of neutrophils and their precursors [1]. G-CSF producing malignancies have been reported in various organs [2], however, they may even arise from unknown primary sites. These malignancies are highly aggressive and associated with poor prognosis, often leading to a short survival time [3].

Previous studies have indicated that the lung is the most frequent site of G-CSF-producing tumors [2,4]. The G-CSF producing tumor with anaplastic lymphoma kinase (*ALK*) gene rearrangements can be presented as a rare subset of non-small cell lung cancer [5,6]. Lung cancers with *ALK* gene rearrangements show a high sensitivity to small-molecule ALK inhibitors, and are associated with a good prognosis [7].

While rare, there have been several reported cases of G-CSF-producing tumors, particularly from Japan [8]. To the best of our knowledge, our case study is the first case of G-CSF producing lung cancer reported from Korea. Several oncologists have possibly encountered clinical situations in which cancer patients exhibit leukocytosis, which may be a result of G-CSF-producing lung cancer or other tumors. While cases of G-CSF producing lung adenocarcinoma are rare, to our knowledge, no reported cases have been associated with ALK gene rearrangements thus far. In this case report, we share our experience with a rare case of G-CSF-producing with *ALK*-positive lung adenocarcinoma. This case is important as it highlights the need for early recognition of G-CSF producing lung cancer early, which can aid in the development of an appropriate treatment regimen.

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2. Case presentation

A 49-year-old woman, non-smoker, presented to our hospital with cough that had persisted for several months. Her Eastern Cooperative Oncology Group performance status score was 1. She had no underlying diseases. Her chest radiograph showed a protruding mass over right cardiac border (Fig. 1A). Chest computed tomography (CT) showed a 7.6 cm large lung mass in the right middle lobe and a small amount of pleural effusion (Fig. 1B), and enlarged lymph nodes in the prevascular, right lower paratracheal, hilar, interlobar, and cardiophrenic areas. Bronchoscopy revealed a protruding mucosal lesion between the right middle lobar bronchus and the lower lobe basal segmental bronchus (Fig. 1C). A hypoechoic lesion was observed in the basal segment of the right lower lobe during radial probe endobronchial ultrasound (Fig. 1D).

Biopsy was performed on the mucosal lesion identified at the right lower lobe basal segmental bronchus. The mass was diagnosed as adenocarcinoma (Fig. 2A). Transbronchial needle aspiration and biopsy of the paratracheal lymph node revealed metastatic adenocarcinoma. A bone scan identified no evidence of bone metastasis. The positron emission tomography (PET) scan showed fluorine-18

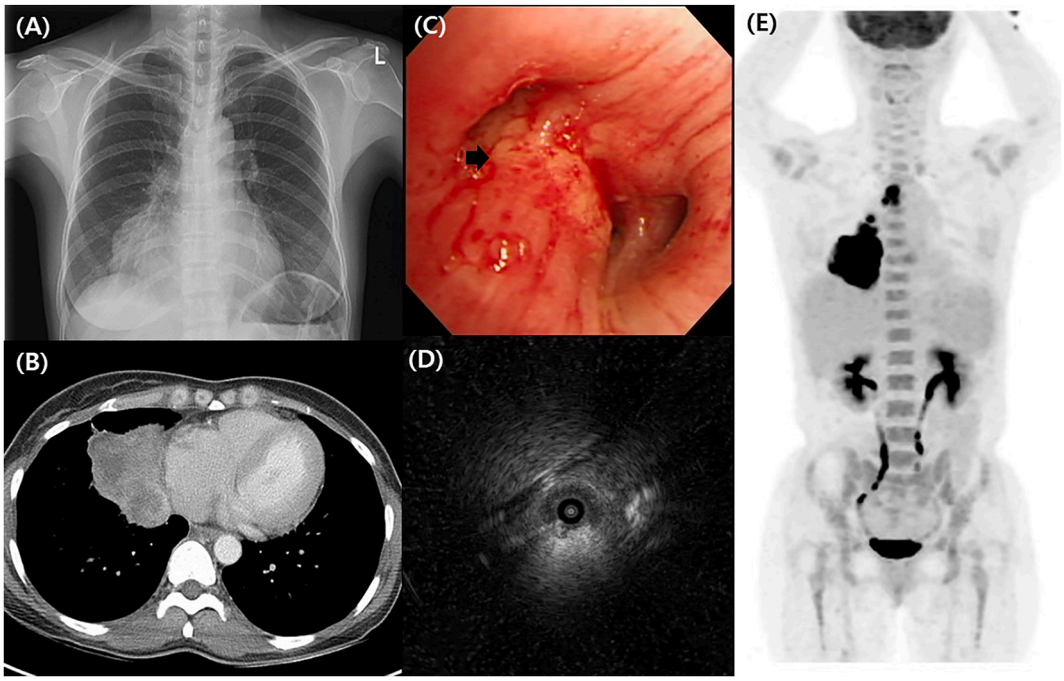

Fig. 1. Initial diagnosis. (A) The chest radiograph showed a protruding mass over the right cardiac border. (B) The chest CT showed a 7.6 cm sized huge mass in right middle lobe. (C) Bronchoscopy showing the protruding lesion at bronchus intermedius (black arrow). (D) Radial probe endobronchial ultrasound showed hypoechoic lesion in right lower lobe basal segment. (E) Findings of fluorine-18 fluorodeoxyglucose (^{18}F-FDG) PET-CT showed dense uptake of ^{18}F-FDG in the lung mass in the right middle lobe (maximum (standardized uptake value, [SUV]; SUVmax 35.86) and ^{18}F-FDG uptake in enlarged right paratracheal and hilar lymph nodes (SUVmax 11.16). The PET-CT did not show the FDG uptake in bone marrow or bone. CT, computed tomography; PET-CT, positron emission tomography-CT.

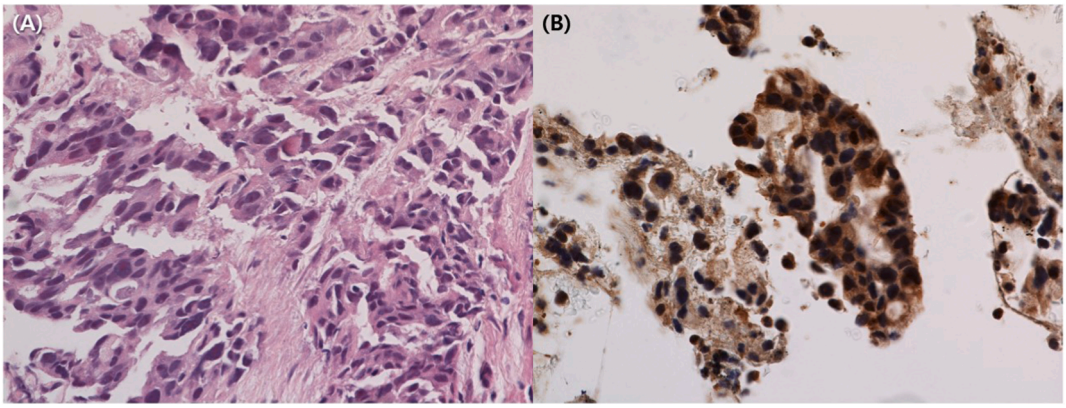

Fig. 2. Histopathologic findings of the lung mass. (A) Hematoxylin and eosin staining showed adenocarcinoma in the lung mass (× 400). (B) The immunohistochemical analysis for granulocyte colony-stimulating factor (G-CSF) antibody of the lung mass revealed positive results (anti-G-CSF antibody, abcam, Cambridge, UK) (× 400).

fluorodeoxyglucose (^{18}F-FDG) uptake in the obstructive mass lesion of the right middle lobar bronchus of the lung, with a maximum standardized uptake value (SUVmax) of 35.86. Additionally, there was ^{18}F-FDG uptake observed in the prevascular, right paratracheal and hilar lymph nodes at a SUVmax of 11.16 (Fig. 1E). There was no ^{18}F-FDG uptake in the bone marrow or bone. The clinical staging was confirmed as stage IIIB (T4N2M0) [9]. The epidermal growth factor receptor (EGFR) mutation was not found, and the programmed cell death-ligand 1(PD-L1) was expressed as 10% using Ventana SP263 assay (Roche, Ventana medical systems, inc., USA). A fluorescence in situ hybridization (FISH) test for *ALK* translocation was requested. The initial laboratory tests showed a WBC count of 36,500/μL with neutrophils (87.9%, 32,084/μL), a red blood cell count of 3.33 × 10^6/μL, and a platelet count of 552 × 10^3/μL. The patient had a hemoglobin value of 8.2 g/dL and a hematocrit of 25.9%. A peripheral blood smear showed a marked increase in WBC counts, however no immature cells were observed. Severe leukocytosis and neutrophilia indicated the possibility of G-CSF producing lung cancer, but there was no sign of abnormal hematopoiesis in the bone marrow, such as diffused uptake observed on ^{18}F-FDG PET-CT. Therefore, G-CSF producing lung cancer was not initially included in the diagnostic considerations.

As the first-line treatment, a combination of pemetrexed and cisplatin chemotherapy was administered. However, after just one cycle (3 weeks) of this treatment, an increase in lung mass size was observed on the chest CT (Fig. 3B). Blood tests revealed drastically elevated WBC count (61,300/μL) and neutrophilia (92%, 56,500/μL). Simultaneously, the *ALK*-FISH test result was positive. Therefore, crizotinib, an ALK-inhibitor, was prescribed for 6 weeks, and subsequently, the size of the lung mass decreased (Fig. 3C) within a month. WBC count (14,800/μL) and neutrophilia (78%, 11,500/μL) also improved. These effects lasted for 6 weeks. However, 9 weeks after initiation of crizotinib, the lung mass increased in size again (Fig. 3D). The number of WBC (62,100/μL) and neutrophilia (88%, 54,650/μL) worsened. Therefore, crizotinib was discontinued and alectinib, a drug for *ALK*-positive lung cancer treatment, was administered for 1 month. One month after the initiation of alectinib therapy, the lung mass continued to increase in size, as seen on imaging (refer to Fig. 2E). The patient's WBC count (68,700/μL) and neutrophilia (96%, 65,950/μL) persisted. The patient was administered one cycle of gemcitabine/vinorelbin combination chemotherapy, but the WBC count (94,000/μL) and neutrophilia (88%, 83,600/μL) were found to increase further. The clinical course of this patient, including the changes in the mass size and WBC count, is presented in Fig. 4. Due to the abnormal increase in the patient's WBC count a serum sample was taken and tested for G-CSF level using a Enzyme Immunoassay (EIA, Japan). The G-CSF level was found to be high, measuring at 591 pg/mL (reference value: 10.5–57.5 pg/mL). Immunohistochemistry staining of the tumor tissue with anti-G-CSF antibody showed a positive result (anti-G-CSF antibody, abcam, Cambridge, UK) (Fig. 2B). Next-Generation Sequencing was performed on the patient's tissue, and no mutations were found. The patient's condition rapidly deteriorated, and the lung cancer eventually progressed. Despite treatment attempts, the patient's high fever persisted, which was suspected to be a result of paraneoplastic syndrome caused by G-CSF secretion. Unfortunately, the patient eventually died due to hypoxia and a drop in blood pressure, 4.5 months after the initial diagnosis.

3. Discussion

To our knowledge, this is the first case report of G-CSF producing lung adenocarcinoma with *ALK* rearrangement.

G-CSF-producing tumors can be mistaken for other diseases due to sharing clinical symptoms with other conditions, such as infections, leukocytosis, an inflammatory reaction, and fever. Moreover, since the tumor size is usually large and may have a necrotic por-

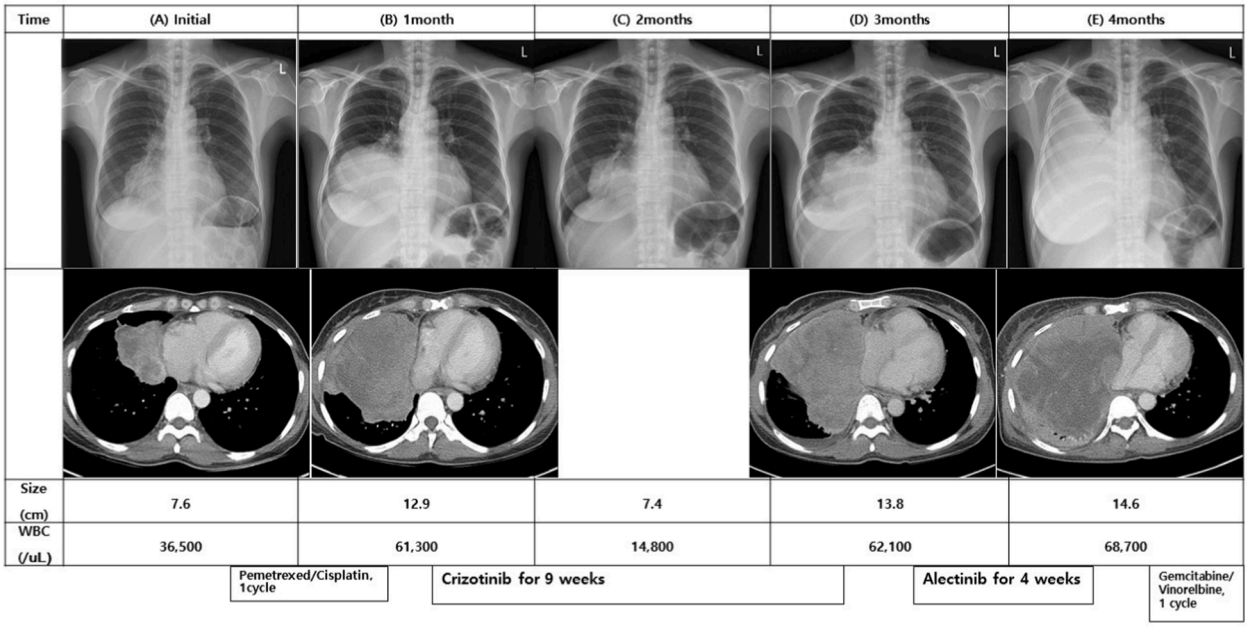

Fig. 3. Chest radiograph and computed tomography (CT) scans during the clinical course of the patient. These showed that the mass size was decreased after treatment of crizotinib (ALK-inhibitor), but after 2 months of crizotinib therapy, the mass size increased again. Other chemotherapy did not show any effect.

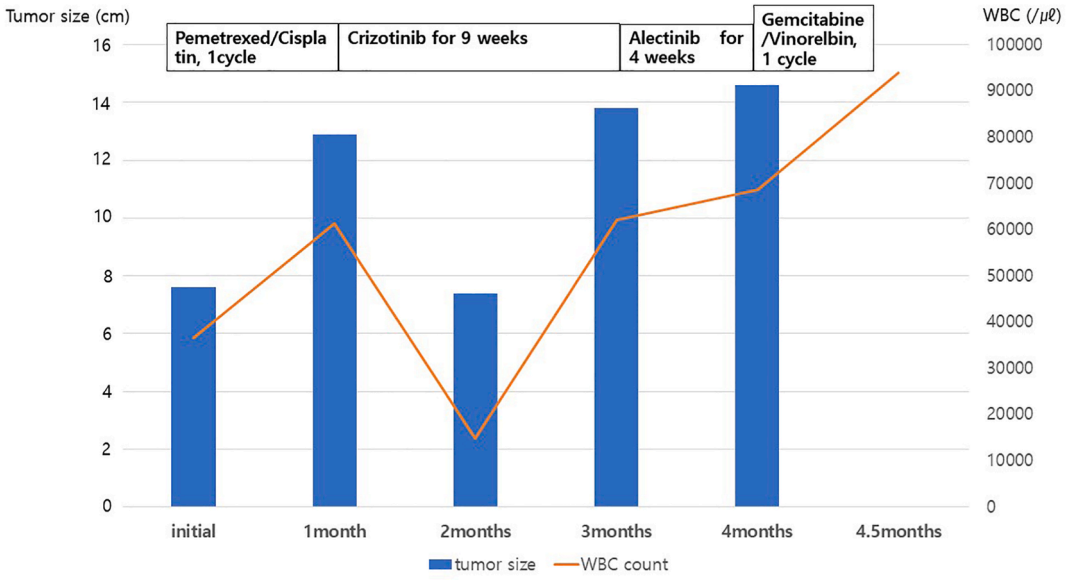

Fig. 4. Tumor size and white blood cell (WBC) counts over the clinical course of the patient. The tumor size together with WBC counts decreased after initial treatment with crizotinib (an ALK-inhibitor), but after 2 months of crizotinib administration, the mass size and WBC counts increased. The increase and decrease of the mass size and WBC counts were concomitant with each other.

tion inside the mass, tissue diagnosis may be delayed. For these reasons, an early diagnosis does not often occur, making it difficult to plan an appropriate treatment strategy. In this case, the possibility of a G-CSF-producing tumor was considered due to the continuous increase in leukocytes and neutrophils, and large mass size in the early stage. However, the diagnosis was delayed due to the time taken to obtain the results of the tests for G-CSF level. The delayed diagnosis of G-CSF-producing tumor in our patient's case was partly due to the unavailability of tests to check G-CSF levels in Korea, as abnormal levels had not been reported previously. In addition, the patient was concurrently diagnosed with *ALK*-positive lung cancer, and treatment with *ALK* targeting agents was expected to have a good response. While treatment with an ALK-inhibitor was initially effective, it was short lived, lasting only about 6 weeks. Subsequent treatment with another ALK-inhibitor also failed to produce positive outcomes.

G-CSF is a cytokine involved in the maturation of neutrophils. The lung is the most frequent site of G-CSF-producing tumors, followed by the stomach, thyroid, and liver. G-CSF-producing tumors are diagnosed by the following four criteria: an elevated WBC count in the peripheral blood, an elevated serum G-CSF level, G-CSF expression in the tumor tissue, and a reduction in the WBC count, or G-CSF expression in the serum following tumor resection or treatment [2]. Patients with G-CSF producing tumors experience high fever, leukocytosis, and elevated serum C-reactive protein. These findings are related not only to G-CSF, but also to several cytokines such as IL-6 [10]. These malignant tumors show an aggressive clinical course, and resistance to treatment [11]. In patients with G-CSF producing carcinoma, the tumors contain large necrotic masses, marked FDG uptake by the tumors, diffuse FDG uptake by the bone marrow, and increased FDG uptake in the spleen [8,12]. Although these patients have a poor prognosis, the treatment method has not been determined. If the tumor size is large and the WBC count is high, a G-CSF-producing tumor should be considered. In our case, leukocytosis and a large tumor mass were presented, however there was no FDG uptake in the bone marrow, suggesting that G-CSF production had not yet occurred at the time of diagnosis. Diffuse FDG uptake in the bone marrow may reflect increased metabolism and cellularity of red bone marrow in response to tumor-produced G-CSF [8,13]. Serum G-CSF level and WBC count have been found to be related to tumor progression and treatment response [4,8,14,15], making them useful markers for therapeutic effectiveness and recurrence in patients with G-CSF-producing tumors. In our case, leukocytosis and tumor size seem to show a significant correlation.

Studies have indicated that surgery can reduce symptoms and G-CSF levels in these patients [4,16]. However, surgery may not be feasible in many cases due to poor health condition and advanced stages of diseases at the time of diagnosis. A case report has described successful treatment of a patient with G-CSF producing lung cancer through radiotherapy [4]. In other cases, a combination of chemotherapy and radiation therapy has been reported to be effective [17], but chemotherapy alone does not appear to be as effective [4]. Furthermore, a case reported a patient with highly expressed PD-L1 and aberrant G-CSF production, where monotherapy with the anti-PD-1 antibody, pembrolizumab, was effective as the first-line of treatment [15]. A study of 13 cases of lung cancer with PD-L1 expression found that the effectiveness of pembrolizumab was limited, and the use of nivolumab as a second line treatment had no effect [18]. A case of G-CSF producing lung cancer that was positive for an activating EGFR mutation, showed successful results following radiotherapy, leading to a complete remission state that was maintained for 30 months. After recurrence of the lung cancer, that particular case was treated with the EGFR-tyrosine kinase inhibitor, afatinib, however there was no response [4]. In another case report involving G-CSF-producing squamous cell lung cancer, the tumor cells were found to be positive for c-ros oncogene 1 (ROS1) rearrangements, and the patient showed a positive response to surgery after neoadjuvant radiation and chemotherapy [19]. In the present case, pemetrexed/cisplatin chemotherapy was ineffective, whilst the ALK-inhibitor, crizotinib, showed limited effect. Second line ALK-inhibitor, alectinib also showed no effect. A phase 3 trial in advanced ALK-positive lung cancer that compared crizotinib to

chemotherapy (pemetrexed or docetaxel) [20], showed that the median progression-free survival was significantly different, with 7.7 months for crizotinib and 3.0 months for chemotherapy. The duration of response, from partial or complete response to progression or death, was 32.1 weeks for crizotinib and 24.4 weeks for chemotherapy. In this case, crizotinib showed a partial response at 1 month, but progressive disease occurred at 1.2 months after that. This suggests that the effect of crizotinib was not maintained and resistance to the drug appeared quickly. Pemetrexed and cisplatin, which were used as chemotherapy in this case, were not effective at all. The activity of chemotherapy has not been established in ALK-positive non-small cell lung cancer, although retrospective studies have suggested that ALK rearrangements might be associated with enhanced sensitivity to pemetrexed-based chemotherapy, with durations of response similar to those observed with crizotinib [21,22]. From a clinical perspective, surgical resection or radiation should be considered as an option in cases of diagnosed G-CSF-producing lung cancer. However, delayed diagnosis, and poor performance of the patients can make it difficult to implement other treatments.

4. Conclusion

This is the first reported case of G-CSF-producing ALK-positive lung adenocarcinoma. Since the ALK rearrangements were positive, ALK-inhibitors were initiated as targeted therapy, but their effect was limited, and the progression of the lung cancer could not be halted. A marked increase in the white blood cell count and a large lung mass size at the initial diagnosis can suggest G-CSF-producing lung cancer, and the white blood cell count can be used as a marker of the therapeutic effect of lung cancer.

Declaration of competing interest

The authors declare no conflicts of interest associated with this manuscript.

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