Case report

G–CSF–producing left lung squamous cell carcinoma positive for ROS1 rearrangements completely resected after neoadjuvant radiation chemotherapy: A case report

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ABSTRACT

Granulocyte colony-stimulating factor (G-CSF) promotes neutrophil production. G–CSF–producing tumors have a feature of neutrophilia without infection, and most patients with G–CSF–producing tumors show an aggressive clinical course and poor prognosis. A 71-year-old woman was diagnosed with left lung cancer, cT4N1M0, stage IIIA. Severe neutrophilia and bone marrow uptake in 18-fluorodeoxyglucose-positron emission tomography suggested the possibility of G–CSF–producing lung cancer. Following neoadjuvant radiation chemotherapy, left lower lobectomy and left upper lobe partial resection were performed. According to pathology findings of the resected specimen, the patient was diagnosed with G–CSF–producing left lung squamous cell carcinoma. Moreover, genetic tests showed that the tumor cells were positive for c-ros oncogene 1 (ROS1) rearrangements. To our knowledge, this is the first reported case of G–CSF–producing lung cancer positive for ROS1 rearrangements, and complete resection was performed successfully after neoadjuvant radiation chemotherapy.

1. Introduction

Granulocyte colony-stimulating factor (G-CSF) is a hematopoietic cytokine that promotes neutrophil production. G–CSF–producing tumors are featured with neutrophilia without infection induced by overproducing G-CSF, and most patients with the tumors show an aggressive clinical course and poor prognosis [1,2].

We experienced a case of G–CSF–producing left lung squamous cell carcinoma, which showed severe neutrophilia and distinctive findings of 18-fluorodeoxyglucose-positron emission tomography (FDG-PET), completely resected after neoadjuvant radiation chemotherapy. Moreover, genetic tests after surgery revealed that the tumor cells were positive for c-ros oncogene 1 (ROS1) rearrangements. G–CSF–producing lung cancer positive for ROS1 rearrangements has never been reported before. Herein, we present this case along with some literature review.

Abbreviations: G-CSF, Granulocyte colony-stimulating factor; FDG-PET, 18-fluorodeoxyglucose-positron emission tomography; ROS1, C-ros oncogene 1; WBC, White blood cell; CRP, C-reactive protein; CT, Computed tomography; SUV_{max}, Maximum standardized uptake value; EGFR, Epidermal growth factor receptor; MST, Median survival time; TKI, Tyrosine kinase inhibitor.

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2. Case presentation

A 71-year-old woman presented with a cough for approximately 1 month. Her medical history included bladder cancer, atrial fibrillation, type 2 diabetes, and benign thyroid tumor. She smoked 10 cigarettes per day from age 25–40 years, so Brinkman index was 1500. Blood tests identified that a white blood cell (WBC) count elevated to 36,640/μL, with a neutrophil count of 32,180/μL and a mildly high C-reactive protein (CRP) level of 1.88 mg/dL. The counts of red blood cells and platelets were 430 × 10^6/μL and 335,000/μL respectively within normal range. The biochemical blood tests showed no noticeable abnormal findings. The serum concentration of cytookeratin 19 fragment also increased to 10.0 ng/mL. The serum level of G-CSF was not determined. Chest contrast-enhanced computed tomography (CT) revealed a 7.6 × 6.2 × 6.0 cm mass with uniform contrast effect in the left lower lobe of the lungs, infiltrating S2 from S6 as the main lesion (Fig. 1a). Lymphadenopathy of the left hilum and mediastinum was also detected, and invasion of the left pulmonary artery and descending aorta was suspected. FDG-PET showed elevated uptake in the mass in left lower lobe, with maximum standardized uptake value (SUVmax) of 17.8, and in the lymph node of the left hilum (Fig. 2a). Diffuse uptake in the bone marrow and localized uptake of the benign tumor in the right thyroid were also identified (Fig. 2b). A transbronchial biopsy was performed for the left lung tumor, and histological examination of the specimen revealed a squamous cell carcinoma. Lymph node metastasis and aortic invasion were suspected on chest CT; thus, the patient was diagnosed with left lung squamous cell carcinoma, cT4N1M0, stage IIIA. Severe leukocytosis and neutrophilia indicated the possibility of G-CSF-producing lung cancer, and abnormal hematopoiesis in the bone marrow appeared to be reflected in the diffuse uptake on FDG-PET. However, no physical characteristics were noted, such as a clubbed finger. The patient underwent neoadjuvant radiation chemotherapy to improve the chance of avoiding left pneumonectomy or combined resection of the aorta. The patient received 40 mg/m² paclitaxel and carboplatin dosed with an area under the concentration-time curve of 2 once a week for 6 weeks and concurrent radiation therapy 40 Gy in 20 fractions, which means 2 Gy per fraction.

The tumor demonstrated a remarkable response to radiation chemotherapy. Although the blood tests at the start of radiation chemotherapy revealed a WBC count of 61,500/μL and neutrophil count of 59,240/μL, blood tests after radiation chemotherapy revealed a markedly decreased WBC count of 3730/μL, with a neutrophil count of 2310/μL. On chest CT 11 days after the last neoadjuvant therapy, the tumor diameter in the left lower lobe shrank to 3.7 cm, and the size of the lymph nodes in the left hilum and mediastinum also diminished (Fig. 1b). FDG-PET nearly 1 month after the last neoadjuvant therapy revealed decreased uptake in the primary tumor, with SUVmax of 6.62, and the uptake in the bone marrow disappeared (Fig. 2c and d).

One month after the end of neoadjuvant therapy, left lower lobectomy and left upper lobe partial resection were performed, with posterior lateral thoracotomy at the 4th intercostal space. Left pulmonary artery plasty was required because of tumor invasion. Despite the absence of aortic invasion, combined resection of the left vagus nerve and parietal pleura was performed because an invasion was suspected. The duration of the operation was 281 min, and the amount of blood loss was 120 mL without blood transfusion. On histological examination, the tumor was 5.2 × 4.0 × 2.1 cm in size, and there were only a few residual atypical cells with nuclear swelling (Fig. 3a and b). Most of the tumor cells had degenerated, and response evaluation for neoadjuvant therapy was Ef.2. On pathological examination, there was no invasion to the parietal pleura, pulmonary arteries, lymph vessels, and blood vessels. Pleural effusion cytology was also negative. Thus, the patient was diagnosed with squamous cell carcinoma of the left lung, yp-T3N0M0, Stage IIB. The immunohistochemical analysis for the G-CSF antibody of the resected specimen was positive (Fig. 3c and d). Genetic tests revealed that the tumor cells were negative for an activating mutation of the epidermal growth factor receptor (EGFR) gene and positive for ROS1 rearrangements. The programmed death ligand 1 tumor proportion score was 30%. The patient was discharged to home 15 days after surgery. For nearly 1 year after surgery, the patient has been alive without any evidence of a tumor recurrence such as leukocytosis, neutrophilia, and abnormal imaging findings.

3. Discussion

In 1977, Asano et al. reported that the presence of G–CSF–producing tumors was proved by increased neutrophil production and elevated G-CSF activity in the blood of mice transplanted with tumor tissues of patients with lung cancer having neutrophilia [1]. Since then, G–CSF–producing tumors have been reported in various organs, such as the liver, kidney, and gallbladder; however, lungs are the most common as primary sites [2]. A study reported that nearly all cases of G–CSF–producing lung cancer are non-small cell cancer and

Fig. 1. Findings of chest computed tomography (CT) before and after neoadjuvant radiation chemotherapy. (a) Chest CT revealed a mass in the left lower lobe, infiltrating the left upper lobe. Invasion of the left pulmonary artery and the descending aorta was suspected. (b) Chest CT after neoadjuvant therapy showed a reduction in the size of the tumor in the left lung and lymph nodes of the left hilum and mediastinum.
Fig. 2. Findings of 18-fluorodeoxyglucose-positron emission tomography (FDG-PET) before and after neoadjuvant radiation chemotherapy (color required).
(a, b) FDG-PET showed elevated uptake in the mass in the left lower lobe and lymph nodes of the left hilum. There was also diffuse uptake in the bone marrow. (c, d) FDG-PET after neoadjuvant therapy revealed decreased uptake in the tumor in the left lower lobe and disappearance of the uptake in the bone marrow. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Fig. 3. Histological findings of the resected specimen (color required).
(a, b) Hematoxylin and eosin staining showed that most of left lung squamous cell carcinoma has degenerated and there were only a few residual tumor cells. (c, d) The immunohistochemical analysis for Granulocyte colony-stimulating factor antibody of the resected specimen revealed positive. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)
large-cell carcinoma is the most common [3].

Severe leukocytosis and neutrophilia are well known as clinical features of G-CSF–producing tumors; moreover, elevated CRP levels and high-grade fever are shown in various cases. These inflammatory manifestations are thought to be induced not by G-CSF itself but by other cytokines such as IL-6, which is often produced simultaneously. A study presented that debilitation caused by chronic inflammation resulted in a poor prognosis of G-CSF–producing tumors [4].

Although the diagnostic criteria for G-CSF–producing tumors are not strictly defined, in most past reports, it is described as (i) severe leukocytosis, (ii) elevated G-CSF activity in the blood, (iii) reduction in WBC count and G-CSF activity after treatments, and (iv) signs of G-CSF production in tumors [1]. During diagnoses, it is not necessarily required to fulfill all of four criteria. Even if (ii) the activity of G-CSF in the blood was not determined, the other three criteria were met, and this patient was diagnosed with G-CSF–producing lung cancer, also considering the clinical course.

Fortunately, neoadjuvant therapy had a remarkable therapeutic effect on this patient, and complete resection was achieved. However, there are no specific treatments for G-CSF–producing tumors, which are treated according to the primary site and histological type. Most of the tumors are undifferentiated or poorly differentiated and show an aggressive clinical course. In 69 patients with G-CSF–producing lung cancer, 57 died within 1 year, and the median survival time (MST) was 5 months according to the report by Mizuguchi et al. Of the 36 patients who underwent surgery, 20 had recurrence within 6 months. The MST in all surgical cases was 8 months [3]. They had a poor prognosis; however, there have been reports of patients after treatment who survive without recurrence for over 2 years, though rare [5,6].

In the present case, diffuse uptake in the bone marrow was observed in the first FDG-PET. Increased FDG uptake in the bone marrow without bone metastasis was previously reported in patients with G-CSF–producing tumors [7]. The same findings were described in patients who received G-CSF as an adjunct to chemotherapy [8]. This is thought to be because hematopoiesis promoted by G-CSF abnormally increases marrow glucose metabolism [7]. As for the uptake in the bone marrow of patients with G-CSF–producing tumors or on G-CSF administration, cautious interpretation is necessary to avoid misdiagnosing bone metastasis. In this case, the accumulation of FDG disappeared after treatment, and there have been other similar reports [7]. These cases suggest that the level of FDG uptake reflects treatment efficacy.

In this patient, the tumor tissue was positive for ROS1 rearrangements despite being a squamous cell carcinoma. ROS1 rearrangements are known as driver genes of lung cancer; moreover, its expression was identified in other cancers such as gastric cancer, colon cancer, and ovarian cancer [9]. Clinically, patients with lung cancer positive for this mutation tend to be younger and more likely to be never-smoker. ROS1 rearrangements are identified in 1% or 2% of non-small cell lung cancer [10]. Furthermore, most of them are non-squamous cell carcinoma, and squamous cell carcinoma accounts for only approximately 2% of lung cancer cases positive for ROS1 rearrangements [11]. Although G-CSF–producing lung cancer positive for EGFR gene mutations was reported previously [12], there have been no reports of G-CSF–producing lung cancer positive for ROS1 rearrangements, i.e., this is the first case. As mentioned above, there are no specific treatments for G-CSF–producing lung cancer. However, the efficacy of tyrosine kinase inhibitor (TKI) for lung cancer positive for ROS1 rearrangements was confirmed, and the objective response rate of crizotinib was 72% according to past research [11]. Although the patient has been alive without recurrence for nearly one year, a cautious follow up is still necessary. TKI such as crizotinib is considered when the tumor recurs in this case.

4. Conclusion

To the best of our knowledge, this is the first reported case of G-CSF–producing lung cancer with ROS1 rearrangements, and complete resection was performed successfully after neoadjuvant radiation chemotherapy.

Author contributions

Hironobu Samejima: Conceptualization, Writing- Original Draft, Naoko Ose: Conceptualization, Writing- Review & Editing, Supervision, Teiko Sakurai: Resources, Hideki Nagata: Resources, Eiichi Morii: Resources, Yasushi Shintani: Writing- Review & Editing.

Ethics approval and consent to participate

The study protocol was approved by the Ethical Review Board for Clinical Studies at Osaka University (control number 10026–3).

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Declaration of competing interest

None.

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