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Lenvatinib for poorly differentiated carcinoma of the anterior mediastinum

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ABSTRACT

We describe a Case of a 74-year-old Japanese man with poorly differentiated carcinoma of the anterior mediastinum. The patient underwent anterior mediastinal tumor resection through median sternotomy. The tumor, 7.0 × 5.0 cm, had invaded surrounding tissues (pericardium, right lung, right and left brachiocephalic veins, and superior vena cava). Complete resection of the tumor was not performed. One month after the operation, the patient developed multiple pulmonary metastases, right pleural dissemination, and carcinomatous pleurisy. He was treated with lenvatinib, a novel multi-kinase inhibitor, to which the metastasis responded favorably. This case reports ~~for the first time~~ the clinical usefulness of lenvatinib for poorly differentiated carcinoma of the anterior mediastinum. Management of side effects by several methods, including suspending use of medication on weekends (called a weekends-off strategy), is another strong argument to continue lenvatinib administration.

1. Introduction

Mediastinal masses are caused by a variety of cysts and tumors, and etiologies differ according to patient age and by location of the masses (anterior, middle, or posterior mediastinum). The anterior mediastinum is the most common location for mediastinal masses in adults. Various diagnoses of anterior mediastinal masses include: thymoma, thymic carcinoma, teratoma, germ cell tumor, lymphoma, hemangioma, lipoma, liposarcoma, sarcoma, etc. [1]. However, even with thorough pathological examinations, it is sometimes challenging to determine the origin of the tumor. Cancer grades classify tumors based upon their degree of differentiation. Many tumors are classified as well-differentiated, moderately differentiated, or poorly differentiated (undifferentiated). In general, poorly differentiated carcinomas spread and metastasize more readily than well-differentiated or moderately differentiated ones. We describe a Case of poorly differentiated carcinoma of the anterior mediastinum, which spread and metastasized very rapidly, and which was successfully treated with lenvatinib, a novel multi-kinase inhibitor.

1.1. Case presentation

A 74-year-old man was referred to Hamanomachi Hospital for anterior chest pain. His medical history included chronic heart failure due to an old myocardial infarction with post-stent intervention 11 years earlier and chronic kidney disease. Chest computed tomography (CT) showed a bifurcated, multinodular mass having a maximum diameter of 6.0 cm with coarse internal calcification in the anterior mediastinum (Fig. 1A). The surrounding anterior mediastinal adipose tissue was opacified, and a right pleural effusion was also present (Fig. 1A). Increased levels of C-reactive protein (CRP) (3.87 mg/dL) and white blood cell count of 111 × 10^2/μL were noted. Based on these findings, teratoma rupture or thymoma with infarction was initially suspected, and he was treated with levofloxacin and acetaminophen. An anterior mediastinal tumor resection was scheduled, pending improvement of the inflammation.

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One month later, although his chest pain had disappeared, a follow-up CT revealed progression of the anterior mediastinal mass (Fig. 1B). Based on the rapid progression of the mass, malignancy was highly suspected. The patient subsequently underwent anterior mediastinal tumor resection through median sternotomy. The tumor had invaded the surrounding tissues (pericardium, right lung, right and left brachiocephalic veins, and superior vena cava). The middle lobe of right lung was partially resected since the tumor had invaded that. Intraoperative pathological diagnosis showed that it was a malignant tumor with highly aggressive potential. Moreover, the tumor seemed to perforate the right thoracic cavity before surgery and recurrent pleural dissemination after surgery was highly expected. Therefore, complete resection of the tumor was not performed, so as to avoid a high risk of serious bleeding.

Grossly, it was a 7.0 × 5.0 cm cystic mass, including fullness to necrosis, extending from the thymus to the lung. The circumferential surface was grayish-white and contained hemorrhagic and necrotic material. Histologically, there was diffuse proliferation of epithelioid tumor with high N/C ratio and hyperchromatic nuclei (Fig. 2A). Spindle-shaped tumor cells were also seen (Fig. 2B). Numerous mitotic figures (7–13/HPF) and necrosis were present. Elastica van Gieson staining showed numerous venous invasions (Fig. 2C). No component of mature teratoma or another germ cell tumor was seen. Tumor cells were positive for an epithelial marker, CAM5.2 (Fig. 2D), and partially positive for AE1AE3 (Fig. 2E), but negative for thymic carcinoma markers (CD5 and c-kit) (Fig. 2F), lymphocytic markers (CD3, CD20, CD30), mesothelial markers (D2-40 and calretinin), and melanocytic markers (HMB45 and melanA). Markers for p63 and p40 were negative, which excluded nuclear protein in testis (NUT) carcinoma. Tumor cells were positive for BRG1, which excluded SMARCA4-deficient thoracic tumor. There was no gene rearrangement examined by fluorescence *in situ* hybridization (FISH) for Capicua Transcriptional Repressor (CIC), which excluded CIC-rearranged sarcoma.

Based on its location, we initially assumed that this carcinoma originated from the thymus. We were, however, unable to make a diagnosis of thymic carcinoma by its staining patterns. In conclusion, the patient was diagnosed with poorly differentiated carcinoma of the anterior mediastinum. Driver mutations (*EGFR, ALK1, ROS1*, and *BRAF*) were all negative, when analyzed with an Oncomine Dx Target Test Multi-CDx system.

One month after the operation, a third chest CT revealed multiple pulmonary metastases, pleural dissemination on the right diaphragm, and mediastinum lymphadenopathy. There were soft tissue shadows at drain insertion sites on the right chest wall, indicating dissemination into the chest wall. The patient was diagnosed with multiple metastases, and he was admitted to the Department of Respiratory Medicine.

On admission, two months after the operation, he developed a massive right pleural effusion, which was confirmed cytologically as a malignant pleural effusion. He underwent thoracic drainage and pleurodesis using talc. A fourth chest CT revealed progression of pulmonary metastasis and pleural dissemination (Fig. 3A). Considering his medical conditions (chronic heart failure: 43% ejection fraction, paroxysmal atrial fibrillation, and chronic kidney disease: creatinine clearance rate of 45 mL/min), he was initiated with 14 mg of lenvatinib orally once daily, as first-line chemotherapy (Fig. 4). At initiation, serum levels of TSH (3.02 μIU/mL, normal: 0.27–4.2), freeT4 (0.98 ng/dL, normal 1.0–1.8), cortisol (13.9 μg/dL, normal: 7.07–19.6), and ACTH (20.9 pg/mL, normal: 7.2–63.3) were within normal ranges. On day 3 after lenvatinib initiation, he was treated with candesartan, followed by candesartan and amlodipine due to developing hypertension. On day 5 after lenvatinib initiation, he developed fatigue (grade 3) and exacerbation of chronic heart failure. On day 6, lenvatinib was transiently discontinued. He was referred to the Department of Cardiovascular Medicine and was initiated with eplerenone and furosemide (Fig. 4). On day 8, he responded well to the diuretics and his symptoms improved. Chest X-ray imaging on day 8 showed evidence of tumor shrinkage. He was then restarted with 10 mg of lenvatinib, suspending administration of the drug on weekends [2]. On day 12, he developed persistent atrial fibrillation and was treated with bepridil. By day 13, his physical condition had improved and the lenvatinib dose was increased to 14 mg. He was discharged on day 21. On day 28 at the outpatient clinic, a follow-up

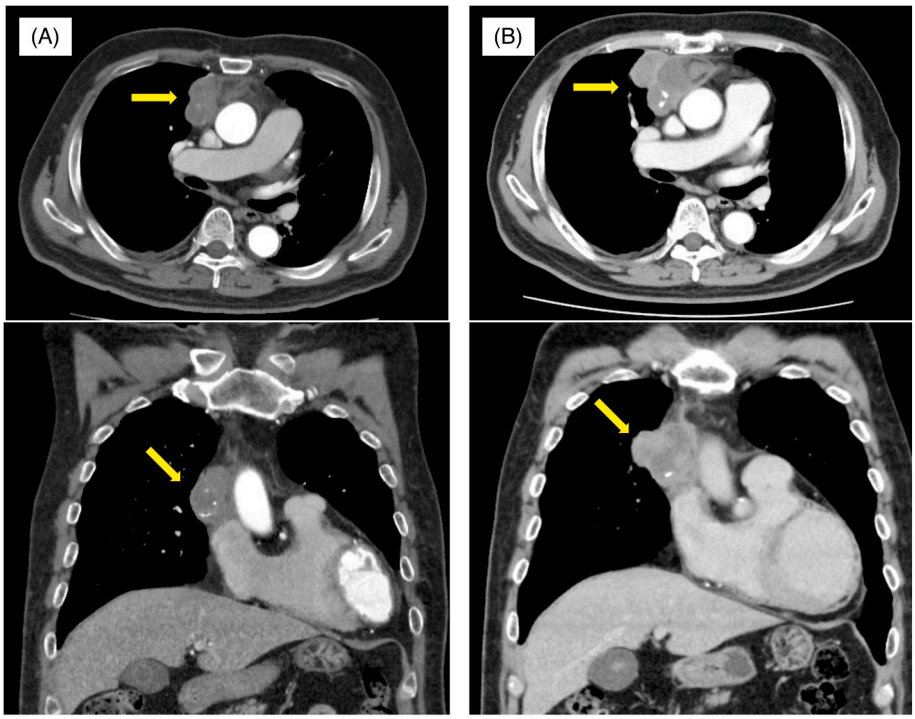

Fig. 1. Chest CT images of the patient before surgery. (A) Contrast-enhanced CT images of the chest at the initial visit. A bifurcated, multinodular mass with a maximum diameter of 60 mm and coarse internal calcification in the anterior mediastinum (arrows) was noted. (B) The anterior mass rapidly progressed one month after the first visit.

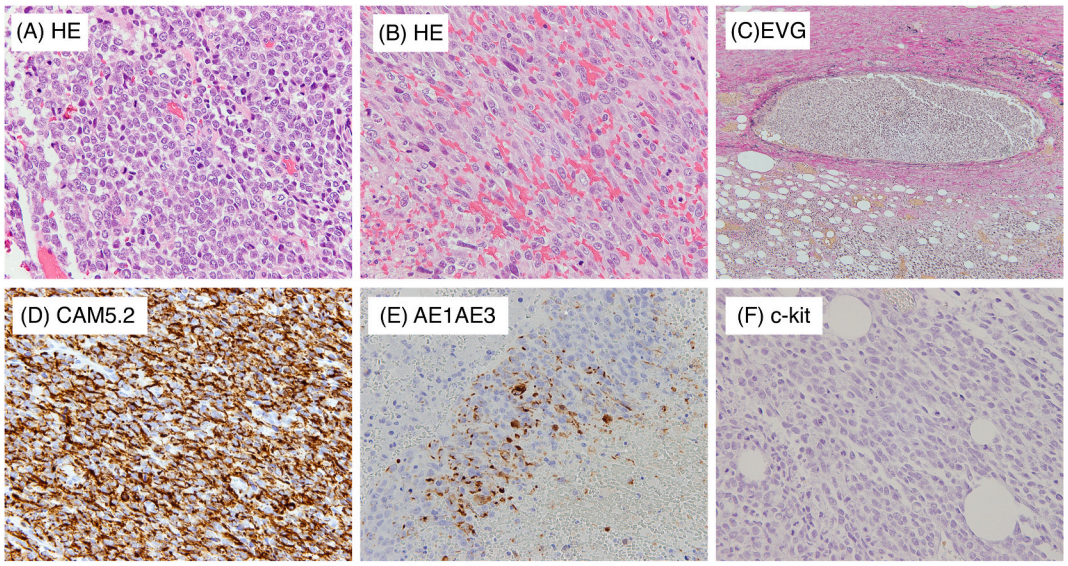

Fig. 2. Pathological examination of the tumor. (A) (B) Hematoxylin and eosin staining. (C) Elastica van Gieson staining showed numerous venous invasions of tumor cells. (D) CAM5.2 staining, (E) AE1AE3 staining, (F) c-kit staining. Magnification: (A),(B),(D),(E),(F) × 400, (C) × 100.

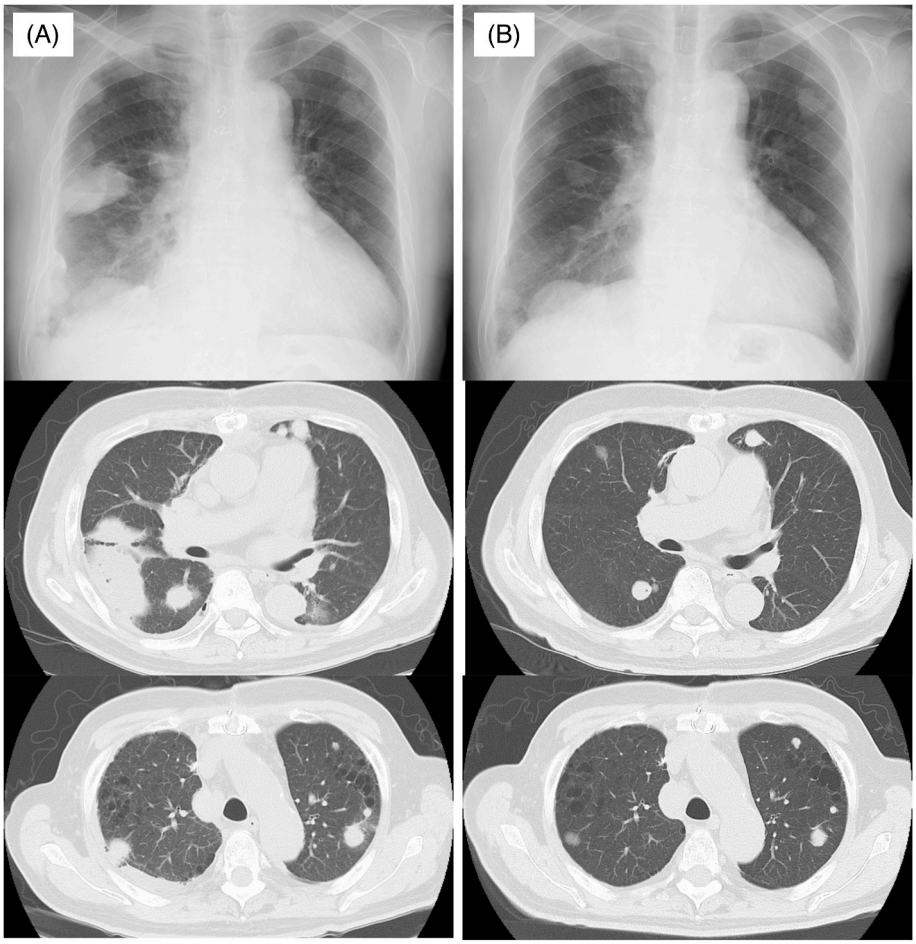

Fig. 3. Chest CT and X-ray images before and after lenvatinib treatment. (A) Chest CT and X-ray images (A) before and (B) 28 days after lenvatinib treatment.

chest CT (Fig. 3B) revealed a partial shrinkage of multiple lung metastases and pleural dissemination evaluated as a stable disease (SD). He has been treated with lenvatinib since then.

2. Discussion

Lenvatinib is a novel multi-kinase inhibitor for vascular endothelial growth factor receptor (VEGFR), fibroblast growth factor receptor

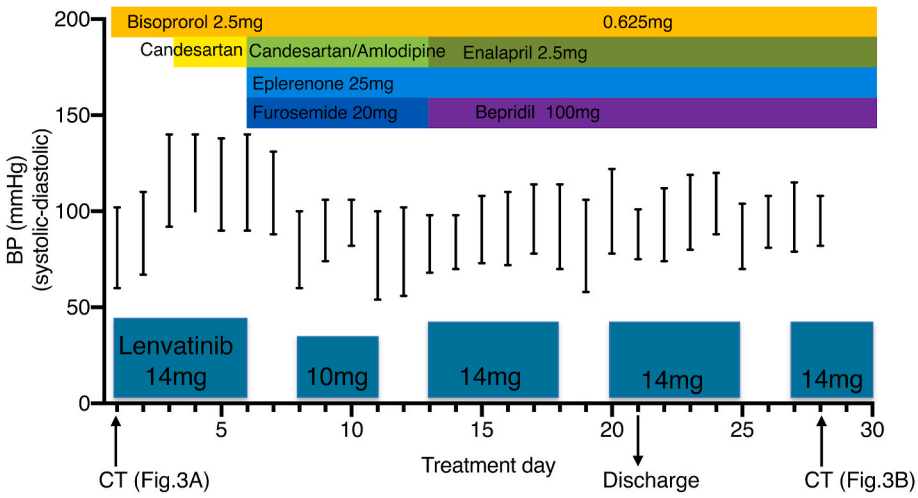

Fig. 4. Clinical course of the patient. The patient was initiated with 14 mg of lenvatinib. On day 3 after lenvatinib initiation, he was treated with candesartan, followed by candesartan and amlodipine due to developing hypertension. On day 5 after lenvatinib initiation, he developed fatigue (grade 3) and exacerbation of chronic heart failure. On day 6, lenvatinib was transiently discontinued. He was initiated with eplerenone and furosemide. On day 8, he responded well to the diuretics and his symptoms improved. He was then restarted with 10 mg of lenvatinib, suspending administration of the drug on weekends. On day 12, he developed persistent atrial fibrillation and was treated with bepridil. On day 13, the lenvatinib dose was increased to 14 mg. He was discharged on day 21. On day 28 at the outpatient clinic, a follow-up chest CT revealed a partial shrinkage of multiple lung metastases and pleural dissemination. He has been treated with lenvatinib since then.

(FGFR), platelet-derived growth factor receptor α (PDGFα), and c-Kit, which has shown anti-tumor activity in several cancer types [3,4]. Lenvatinib has been approved for treatment of thyroid cancer and hepatocellular cancer in several countries, including Japan and the U.S. Recently, a multicenter, single-arm, phase 2 trial (REMORA) was conducted, examining lenvatinib for patients with advanced thymic carcinoma [5]. All patients had received at least one platinum-based chemotherapy. Patients received lenvatinib orally once daily at a starting dose of 24 mg until disease progression or occurrence of unacceptable adverse events. The objective response rate was 38% and the disease control rate was 95% during the median follow-up period of 15.5 months [5]. Based on the results of this clinical trial, on March 23rd, 2021, lenvatinib was approved for treatment of unresectable thymic carcinoma in Japan, ahead of any other country.

The patient developed pleural dissemination and malignant pleural effusion. High VEGF levels are reported in malignant pleural effusions with different cancer origins, and VEGF signals have pathogenic roles in developing malignant pleural effusions [6–9]. Bevacizumab, a humanized anti-VEGF monoclonal antibody, added to a standard therapy is preferable for patients with non-small lung cancer with malignant pleural effusion [10,11]. We speculated that lenvatinib could also be effective for this patient with malignant pleural effusion, since lenvatinib targets VEGF signals. Moreover, the rapid growth of the tumor suggested upregulated various growth factors, which might be targeted by lenvatinib. From these points of view, we decided to use lenvatinib as the first-line chemotherapy.

Considering his medical condition, we prescribed 14 mg of lenvatinib as an initial dose, which is two steps below the highest recommended dose. Nevertheless, the patient developed fatigue (grade 3) and exacerbation of chronic heart failure. Iwamoto et al. reported that a weekends-off strategy (five days on/two days off administration) significantly prolonged the drug administration period and survival in patients with unresectable hepatocellular carcinoma, by reducing adverse events such as fatigue [2]. The thyroid and adrenal glands are prone to anti-angiogenic agents, and hypothyroidism and hypoadrenocorticism are correlated with fatigue related to anti-angiogenic drugs [12–14]. Indeed, 12% of patients showed decreased free T4 levels, and 60% of patients showed elevated TSH levels after lenvatinib treatment. Further, 39% of patients showed decreased cortisol levels after lenvatinib treatment [2]. Weekends-off administration contributed to recovery of vascularity in the thyroid and adrenal glands in a mouse model, thus reducing fatigue and other side effects [2]. This Case report emphasizes the importance of adverse event management, including use of a weekends-off strategy, especially for patients with several medical conditions when prescribing lenvatinib.

Patient consent for publication

Written, informed consent was obtained from the patient.

Conflicts of interest

All authors of the manuscript declare that they have no conflicts of interest.

Declaration of competing interest

All authors of the manuscript declare that there are no conflicts of interest.

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