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# A Case of Middle Mediastinal Thymic Carcinoma with Pulmonary Cavitaion and Pneumothorax after Lenvatinib Administration

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## Abstract

A 58-year-old woman visited our hospital complaining of persistent cough for one month. Computed tomography (CT) confirmed a middle mediastinal tumor centered on the tracheal bifurcation. A diagnosis of middle mediastinum thymic carcinoma (cT4N2M0 Stage IVb stage) was made from the tissue when the right main bronchial stenosis was relieved, and progressive disease (PD) was diagnosed despite the administration of cytotoxic anticancer drugs and radiotherapy. Next, oral administration of lenvatinib, a multityrosine kinase inhibitor (TKI), was started, and the dose was reduced or discontinued for 4 months due to side effects. Although stable disease (SD) was maintained, the patient had coughing symptoms, and CT confirmed a ground-glass opacity in the right upper lobe. The patient was discontinued as a side effect of lenvatinib, but a right pneumothorax developed, the opacity worsened, and steroid pulse therapy was performed. Tegafur-gimeracil-oteracil potassium (TS-1) was started as an anticancer agent, and although the opacities in the lung field showed an improvement trend, the tumor worsened and she died 305 days after starting lenvatinib.

**Keywords:** Pulmonary cavitation; Lenvatinib; Thymic carcinoma

## Introduction

Thymic carcinoma is a rare tumor of the thymus, most commonly found in the anterior mediastinum, but rarely found in the middle mediastinum and below the carina. Furthermore, this time, although anticancer drugs similar to those for thymic carcinoma were administered, the patient developed PD, and after switching to lenvatinib, a multikinase inhibitor, she developed a pulmonary cavitary lesion in a relatively early stage and developed a right pneumothorax. To date, there have been no reports of pulmonary cavity formation during lenvatinib administration for thymic carcinoma.

## Case Report

A 58-year-old woman visited our hospital with a chief complaint of cough lasting for 1 month. CT showed a bifurcation tumor with mediastinal lymphadenopathy, and an image of stenosis of the right main bronchi was confirmed (Figure 1A, 1B).

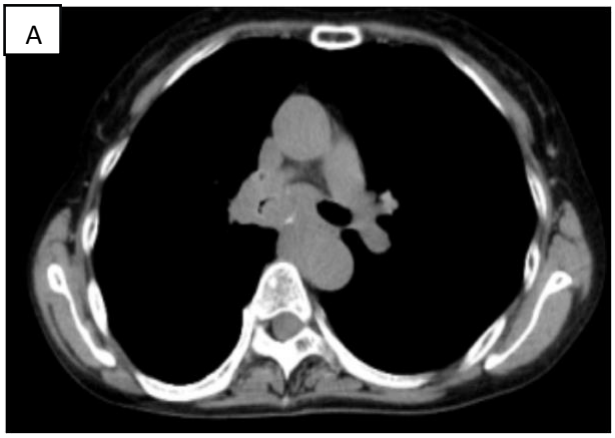


**Figure 1 A:** A tumor can be confirmed in the middle mediastinum centered on the tracheal bifurcation.

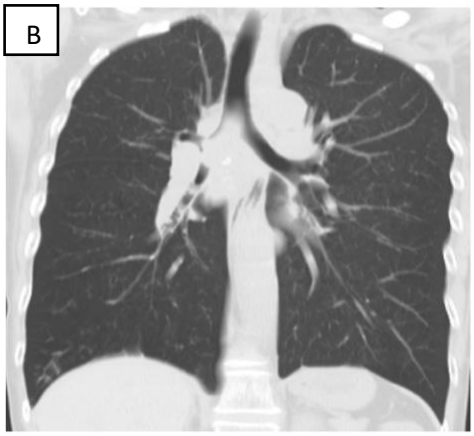


**Figure 1B:** The tumor narrows the bronchi from the right main bronchi to the right middle trunk.

A tumor was exposed at the site of tracheal stenosis, so the bronchial constriction was relieved using hot biopicy forceps and a cryo-apparatus, and a biopsy was performed from the same site. Microscopically, naked nucleus-like cells proliferated in a honeycomb pattern, and immunostaining was positive for p40, AE1/AE3, CK14, PAX8, and CD5. The tumor was diagnosed as thymic carcinoma pathological T4N2M0 stage IVb. For treatment, 4 courses of carboplatin (CBDCA) + paclitaxel (PTX) + 60 Gy radiotherapy were performed, and after that, recurrence was observed, so CBDCA + PTX was readministered for 8 courses. After that, the patient developed PD, and one course of CBDCA + amurubicin (AMR) was administered, but the toxicity was strong and ended with one course. Lenvatinib was then administered. After the start of administration, the tumor remained SD without growth, however, 4 months after administration, the cough worsened, and a CT scan revealed a cavitary lesion in the right upper lobe and ground-glass opacities on both sides (Table 1).

The WBC count increased to 15670 /μL, and the CRP level increased to 21.2mg/dL, so Antibiotic + methyl-prednisolone (mPSL) 40mg was administered, considering side effects of lenvatinib as the cause. The inflammatory response tended to improve, and the cavitary lesion remained unchanged. Multiple lymph node metastases, multiple liver metastases, and bilateral pleural effusions were exacerbated, and we assumed that thymic carcinoma was exacerbated, so the anticancer drug was changed from lenvatinib to TS-1. Severe herpes zoster occurred concurrently, although it is unknown whether the immunity was decreased due to administration of PSL, and PSL was temporarily discontinued and administration of an antiherpes drug was started. On the 124th day of lenvatinib administration, CT showed rapid deterioration of the cavitary lesion, right pleural effusion and right pneumothorax were observed, and a trocar was inserted. Many neutrophils were confirmed in the pleural effusion, and the WBC and CRP level were elevated to 13801/μL and 23.44mg/dL, suggesting pleurisy. The procalcitonin level was normal, and the pleural fluid culture was negative, so it was determined that pneumothorax and pleural effusion were caused by lenvatinib, and steroid pulse therapy (mPSL 1000mg) was started and tapered off (Table 1).

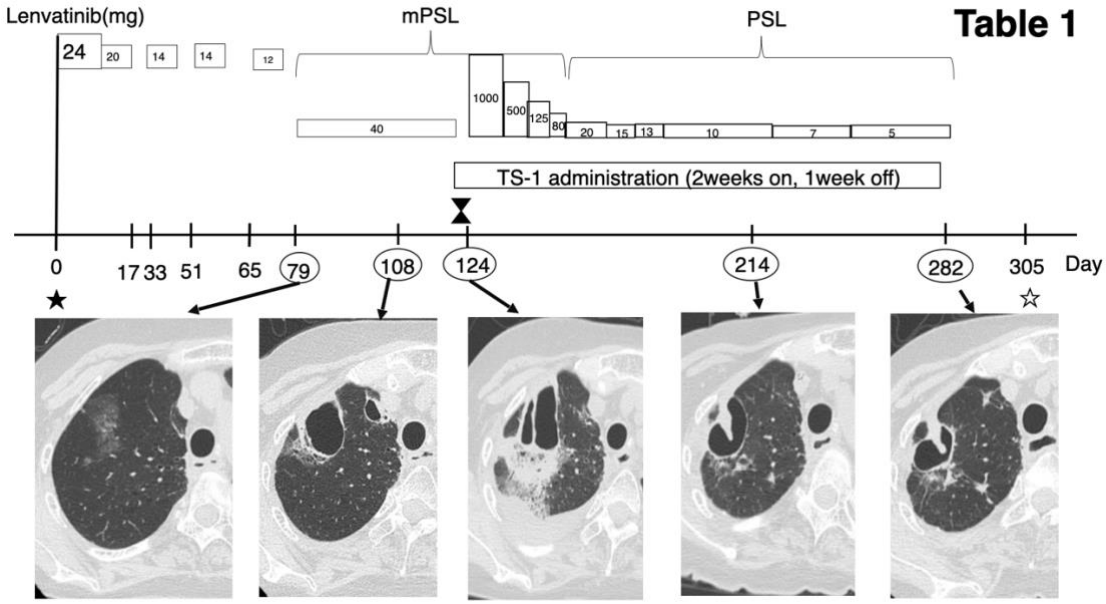


**Table 1:** Clinical course after administration of lenvatinib is shown. On the 79th day of administration, ground-glass opacities were observed in the lungs where metastatic lesions could not be confirmed, and then the ground-glass opacities spread. Steroid pulse therapy showed an improvement trend.

★: Lenvatinib start;⧗ : Severe shingles; ☆: Dead.

The ground-glass opacity around the cavitary lesion disappeared, and the thoracic drain was removed to improve the pneumothorax. Furthermore, tumor shrinkage was temporarily observed, mainly in the metastatic tumor, and the cavitary lesion also showed a gradual shrinkage trend. However, after the oral administration of TS-1, abdominal symptoms became stronger, and when the drug was discontinued, the tumor was aggravated. Due to deterioration of general condition, the patient died 305 days after the start of lenvatinib administration.

## Discussion

Thymic carcinoma accounts for only approximately 1% of all thymic tumors and occurs mostly in the anterior mediastinum. Vernon et al. previously reported only one case of thymic carcinoma that developed in the middle mediastinum below the tracheal bifurcation and is extremely rare [1].

Regarding the mechanism of development, there are reports of ectopic thymoma, and it has been suggested that the failure of the thymus to migrate to the superior anterior mediastinum during pulmonary development may result in ectopic thymus, which may lead to thymoma [2]. Thymic carcinoma is also presumed to have undergone malignant transformation under the ectopic thymus and become thymic carcinoma. Thymic carcinoma has a poor prognosis with a median survival of 14-49.4 months. Among the therapeutic agents, CBDCA + PTX administration has an average survival time of 22.7-49.4 months, with a 1-year survival rate of 85% and a 3-year survival rate of approximetely 60%, which is quite promising data [3], so it was administered in this case.

Lenvatinib, administered for tumor enlargement, is a multitargeted TKI, involved in tumor angiogenesis and tumor growth factors such as vascular endothelial growth factor (VEGF) receptor (VEGFR1-3), fibroblast growth factor (FGF) receptors (FGFR1-4), platelet-derived growth factor receptor (PDGFR) α, and stem cell factor receptor (KIT), rearranged during transfection proto-oncogene (RET). It inhibits receptor tyrosine kinases of the above factors and particularly inhibits the formation of vessel-like tubular structures of vascular endothelial cells induced by VEGF and FGF [4,5].

Regarding the administration of lenvatinib after platinum-based chemotherapy, the response rate was 38%, the partial response was 57%, and the reported side effects were hypertension (67.8%), diarrhea (59.4%), and fatigue (59%) [6]. In this case, fatigue, nausea, diarrhea, and numbness in the limbs were present. Lenvatinib was tapered off along with complaints of symptoms, and was eventually reduced to 12mg, but the tumor remained SD. Regarding other side effects, pulmonary cavity formation and pneumothorax occurred in this case, but pulmonary cavity formation with lenvtinib was reported in only 2 cases, and is a very rare complication. Yamasaki et al [7]. used lenvatinib in a case of metastatic lung tumor due to thyroid cancer, and reported that necrosis inside the metastatic lesion formed a cavity and led to pneumothorax. Toda [8] et al. used lenvatinib for thyroid cancer and metastatic lung tumors, but temporarily discontinued lenvatinib because the patient developed COVID-19 pneumonia. However, they reported a case with a cavitary lesion on the opposite side of the metastatic lesion 2 weeks after the onset of COVID-19 pneumonia. On the other hand, there are also reports that show only ground-glass opacities without cavitary lesions. Imakura et al [9]. reported 13 cases of interstitial pneumonia caused by lenvatinib, all of which were ground-glass opacities and infiltrative opacities. Lenvatinib mainly suppresses VEGF and FGF signals to normalize intratumoral venous networks and enhance antitumor effects. The rate of pulmonary cavitation caused by angiogenesis inhibitors has been reported to be approximately 24% [10], and both the checkvalve induced by tumor obstruction of the airway and the pulmonary infarct caused by angiogenesis inhibitors, including lenvatinib, are considered to be the mechanism of cavity formation. Most reports advocate that pulmonary cavitation mechanism [11].

However, in this case, no pulmonary metastases were confirmed at the site of cavity formation, and a ground-glass opacity appeared during oral administration of lenvatinib, and cavity formation occurred at the same site, resulting in pneumothorax (Table 1). In lungs with no metastases, as in the present case, the mechanism of cavity formation after ground-glass appearance and the mechanism of only ground-glass opacities in the case of Imakura et al, remain unexplained, and we look forward to future clarification.

## Author Contribution

**Akira Naomi:** Primary author of the manuscript, drafted and revised the paper.

**Ayumi Kurabe, Hujiwara Hideyuki, Yukari Sakurai, Yasuo Kohashi, Yukiko Yoneda, Yuka Kitamura, Yoshinobu Hattori and Yuji Saitou:** The attending doctors who treated the patient on admission. All authors read and approved the final manuscript.

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