CANCER DIAGNOSIS & PROGNOSIS
3: 475-478 (2023) doi: 10.21873/cdp.10242

A Case of Tracheoesophageal Fistula in a Non-metastatic Site During Lenvatinib Treatment for Hepatocellular Carcinoma

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Abstract. *Background/Aim: We report a case of tracheoesophageal fistula at a non-metastatic site during lenvatinib treatment of hepatocellular carcinoma with multiple bone metastases. Case Report: A 58-year-old male patient was diagnosed with hepatocellular carcinoma with multiple bone metastases and was treated with atezolizumab-bevacizumab. However, as the bone metastasis progressed, palliative radiation therapy was administered to the third thoracic vertebra, and lenvatinib was administered as a second-line treatment. The patient was hospitalized for aspiration pneumonia five months later. Chest computed tomography and bronchoscopy revealed a 5 cm tracheoesophageal fistula located 3 cm cranial to the carina. We diagnosed a benign tracheoesophageal fistula due to lenvatinib because his previous CT scan showed no metastases at the site of the fistula, and we performed esophageal bypass surgery 4 weeks after discontinuation of the lenvatinib. Conclusion: To the best of our knowledge, this is the first case report of tracheoesophageal fistula at a nonmetastatic site during lenvatinib treatment for hepatocellular carcinoma.*

Tracheoesophageal fistulas (TEF) associated with malignant tumors have been reported to occur during the treatment of tumors directly contacting the trachea, such as lung, esophageal, or thyroid cancer (1-3), and ischemia of the tracheal membrane or inflammation due to anastomotic leakage after esophagectomy (4). However, they rarely occur at sites where no malignancy is present or where a nonsurgical procedure is performed on the tracheal membrane and esophagus.

Lenvatinib is an oral, multi-targeted tyrosine kinase inhibitor with activity against tyrosine kinases involved in tumor angiogenesis and malignancy (5). It is used to treat thyroid cancer and advanced or unresectable hepatocellular carcinoma (HCC). Here, we report a case of benign TEF that developed in the absence of a tumor in the trachea or esophagus after radiation therapy to the thoracic vertebrae and lenvatinib treatment for HCC with multiple bone metastases.

Case Report

A 58-year-old male patient was diagnosed with HCC with multiple bone metastases. Although treatment with atezolizumab and bevacizumab was initiated, computed tomography (CT) performed two months later showed progression of the bone metastases. He was treated with radiotherapy (39 Gy/13 fractions) for metastases to the third thoracic vertebra and lenvatinib as second-line therapy. He was hospitalized because of continuous coughing and belching five months later. A CT revealed aspiration pneumonia, and the border between the membranous tracheal wall and the anterior wall of the esophagus disappeared (Figure 1). Bronchoscopy showed a fistula 5 cm in size located on the tracheal membrane within 3 cm cranially of the tracheal bifurcation (Figure 2A and B). We diagnosed the patient with a benign TEF due to lenvatinib because his previous CT showed no cancer metastasis at the fistula site and planned an esophageal bypass surgery for TEF four weeks after discontinuation of lenvatinib. Surgery was performed with left single lung ventilation by inserting a

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Key Words: Tracheoesophageal fistula, lenvatinib, hepatocellular carcinoma, esophageal bypass.

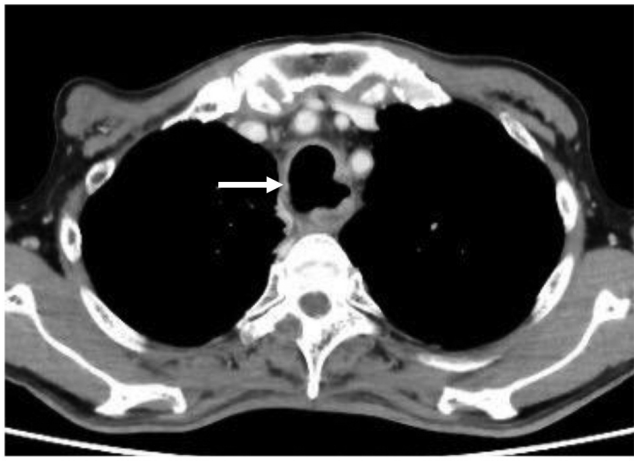

Figure 1. *A computed tomography, which was performed 5 months after lenvatinib treatment, shows a tracheoesophageal fistula (arrow).*

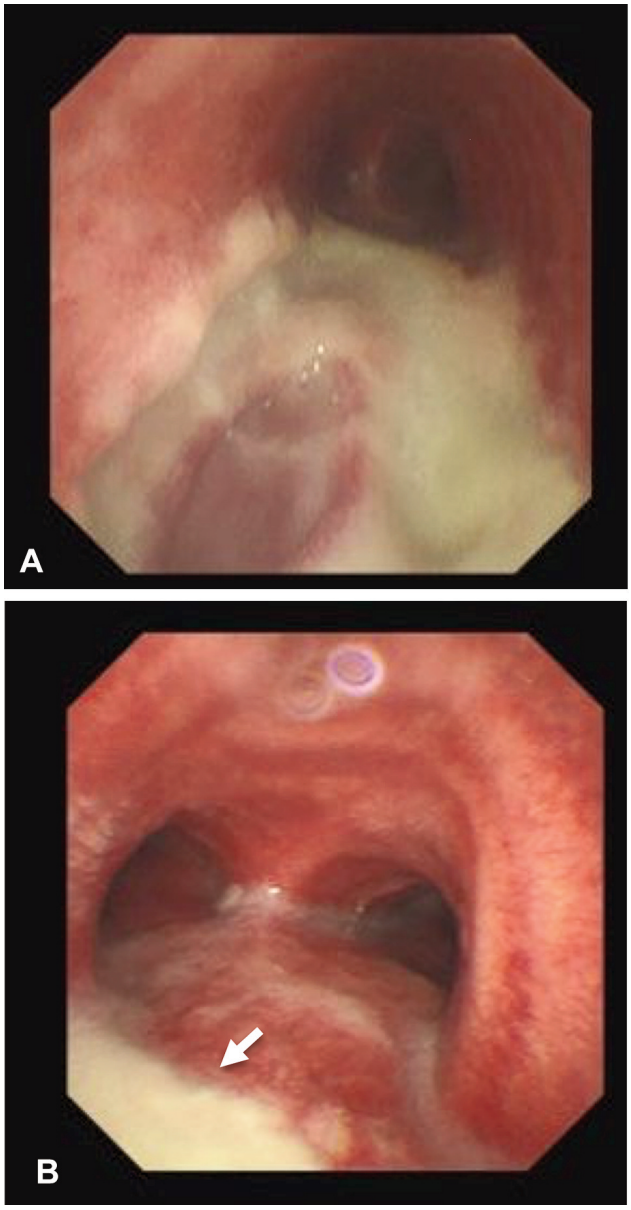

Figure 2. *Bronchoscopy findings. (A) The fistula is located on the tracheal membrane measuring 5cm in length. (B) The caudal end of the fistula (arrow) is located within 3 cm cranially to the tracheal bifurcation.*

tracheal tube into the left main bronchus under bronchoscopy guidance. A gastric tube was created and pulled up to the neck *via* the post-sternal route. Sufficient blood supply to the gastric tube was confirmed using near-infrared fluorescence imaging with indocyanine green (ICG), and esophagogastric tube reconstruction was performed. The postoperative course was uneventful, and the patient was discharged 25 days after surgery. One year after the surgery, the patient is still alive without any treatment for HCC.

Discussion

This is the first case report of TEF during lenvatinib therapy for HCC with multiple bone metastases. An online search using the keywords "lenvatinib", "tracheoesophageal fistula", and "hepatocellular carcinoma" revealed no reports similar to our case.

Lenvatinib is a multitargeted tyrosine kinase inhibitor that inhibits the vascular endothelial growth factor receptors 1-3, fibroblast growth factor receptors 1-4, and platelet-derived growth factor receptors, RET, and KIT (5), and cause several adverse events including hypertension, diarrhea, anorexia, hand-foot skin reaction, and hypothyroidism (6). Although gastrointestinal perforation or fistula formation during lenvatinib therapy has been reported as a serious adverse effect (7, 8), all reports of TEF associated with lenvatinib are for tracheoesophageal invasion of thyroid cancer (2, 3). The etiology of lenvatinib-associated gastrointestinal perforation or fistula is thought to be because the inhibitory effect of lenvatinib on angiogenesis may damage the structure and function of gastrointestinal vessels (9), induce arterial thromboembolism (10), and inhibit the healing of gastrointestinal ulcers and colonic diverticulitis, which in turn may lead to perforation (11). In our case, lenvatinib-induced inhibition of angiogenesis may have caused ischemia of the esophagus and trachea and the formation of the TEF. The history of radiation therapy is another potential cause of TEF formation. Although this case received only 39 Gy, the possibility of its influence cannot be completely ruled out since the radiation dose and number of fractions have been reported to have no effect on TEF formation (12).

The treatment of TEF depends on the patient's condition, and the TEF's etiology, size, and location. Kim *et al*. (13)

reported a management algorithm for acquired TEFs, according to which stenting was selected for malignant fistulas and stenting or surgery was selected for benign fistulas depending on the patient's condition. Although stenting is less invasive than esophageal bypass surgery, complications include stent migration, bleeding, and widening of the fistula; therefore, bypass surgery is the procedure of choice when a long-term prognosis is expected.

Various surgical treatment methods for TEF have been reported, ranging from curative closure to palliative bypass surgery (14-18). In our case, multiple bone metastases of HCC were stable after lenvatinib treatment; therefore, we believe that his prognosis was promising for more than one year. However, the size of the fistula was 5 cm. Therefore, we considered radical closure difficult and chose to perform bypass surgery. We also considered fistula closure with a stent difficult because of the size of the fistula and its proximity to the tracheal bifurcation. Concerned about the impaired blood flow and anastomotic leakage associated with lenvatinib's inhibitory effect on angiogenesis, the patient was given a 4-week rest period to avoid these complications. Additionally, sufficient blood flow to the reconstructed gastric tube can be evaluated using the ICG fluorescence method (19).

In conclusion, we encountered a rare case of TEF at a nonmetastatic site during lenvatinib treatment for HCC with multiple bone metastases, which was successfully managed by performing esophageal bypass. Attention should be paid to this severe complication in patients receiving lenvatinib and previous radiation therapy, even in the absence of tracheal and esophageal tumors. Further studies are needed to ensure the safe and effective treatment of such cases.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

KY, HK, KO performed the surgery, KY, HK concepted and wrote a draft of the manuscript, and TN, HM, MK edited, and SS supervised the study.

Acknowledgements

The Authors want to thank Editage (www.editage.com) for English language editing.

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Received May 15, 2023
Revised June 6, 2023
Accepted June 7, 2023