

Tracheoesophageal fistula associated with bevacizumab after thoracic radiotherapy in non-small cell lung cancer

A case report

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Abstract

Introduction: Tracheoesophageal Fistula (TF) is a rare complication of Bevacizumab. Thoracic radiotherapy may be a contributing factor to TF formation. To the best of our knowledge, we report the first case of Chinese patient with non-small cell lung cancer (NSCLC) who developed TF after completion of chemotherapy with bevacizumab and thoracic radiotherapy.

Patient concerns: A 54-year-old male patient was diagnosed with NSCLC. He received definitive thoracic radiotherapy with concurrent pemetrexed and cisplatin chemotherapy. Two months after the treatment, the disease progressed with enlargement of right inguinal lymph node and chemotherapy of docetaxel, carboplatin and bevacizumab was administered. Eighteen days after 4 cycles, the patient presented a sudden onset of acute cough after drinking.

Diagnosis: Esophageal barium swallow revealed a TF. Gastroscopy confirmed a fistula in the esophagus.

Interventions: A jejunal feeding tube was placed for nutrition for a month. After that a covered esophageal stent was placed in the esophagus.

Outcomes: At the 6-month follow-up visit, the patient recovered well and had not developed any complication related to the stent placement.

Conclusion: TF is a rare but life-threatening complication of bevacizumab. Careful observation is imperative for those patients who are administered bevacizumab, particularly in patients treated previously with thoracic radiotherapy.

Abbreviations: CT = computed tomography, NSCLC = non-small cell lung cancer, TF = tracheoesophageal fistula.

Keywords: bevacizumab, radiotherapy, tracheoesophageal fistula

1. Introduction

Bevacizumab, a chimeric hominization immunoglobulin G1 monoclonal antibody against vascular endothelial growth factor,

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can prevent the development of new blood vessels needed for tumor cells to grow. Bevacizumab, in combination with carboplatin and paclitaxel, is approved by the US Food and Drug Administration for the first-line treatment of patients with advanced/metastatic recurrent non-squamous non-small cell lung cancer (NSCLC).^[1] NCCN Guidelines^[2] recommends bevacizumab combining chemotherapy as initial systemic therapy options for advanced or metastatic non-squamous NSCLC. Tracheoesophageal fistula (TF), a rare but severe complication of bevacizumab, had been reported in patients from different countries. However, there have been no such reports of patients from China. We describe a 54-year-old male with history of thoracic radiotherapy who developed a TF 2 weeks after completion of 4 cycles of chemotherapy with bevacizumab.

2. Case report

A 54-year-old male was referred to local hospital with cough and expectoration in April 2018. Chest computed tomography (CT) revealed a mass in the left of the lung, with multiple mediastinal lymph node metastases (4L, 5 and 6 region). Endobronchial ultrasound-guided transbronchial needle aspiration result was consistent with adenocarcinoma. Staging evaluation in Cancer Hospital, Chinese Academy of Medical Sciences (Beijing, China) with CT, positron emission tomography- CT, and magnetic resonance imaging of the brain conformed stage IIIB (T3N2M0)

according to the UICC 7th edition TNM classification. The patient was given concurrent chemotherapy, consisting of 500 mg/m² pemetrexed and 75 mg/m² cisplatin on day 1 every 3 weeks for 2 cycles, and definitive thoracic radiotherapy of volumetric modulated arc therapy (95%PGTV 60.2Gy in 28 fractions, 95%GTV 50.4Gy in 28 fractions). The isodose lines of radiation dose distribution are showed in Figure 1. A CT scan of the chest indicated a partial response. Grade I esophageal toxicity, Grade II gastrointestinal toxicity, Grade I dermatological toxicity and Grade I myelotoxicity (Common Terminology Criteria for Adverse Events Version 4.0; CTCAE v4.0) were the side effects of the concurrent chemoradiotherapy.

However, 2 months after completing concurrent chemoradiotherapy, he developed progressive disease with enlargement of right inguinal lymph node. Biopsy of the inguinal lymph node was consistent with adenocarcinoma and the patient was administered docetaxel 75 mg/m² on day 1, carboplatin AUC 5 on day 2 plus bevacizumab 7.5 mg/kg on day 1 once every 3 weeks.

Eighteen days after 4 cycles, the patient presented a sudden onset of acute cough after drinking. Esophageal Barium meal revealed a TF. Gastroscopy showed an esophageal mucosa erosion to be 28 to 36 cm from the nostrils, in which a deep hole was observed (Fig. 2). Then a jejunal feeding tube was placed for nutrition (Fig. 3). Forty days after the placement, the patients suffered from lung infections by an unclosed TF and a covered esophageal stent was placed in the esophagus (Fig. 4). The TF was managed with stents. Until now, 6 months after the event of TF, the patient was still in follow-up care without any complication related to the stent placement.

3. Discussion

Bevacizumab, an anti-vascular endothelial growth factor receptor antibody, has been demonstrated to have activity against advanced or recurrent non-squamous NSCLC. A phase III study demonstrated that combination of Bevacizumab and chemotherapy of carboplatin and docetaxel can significantly improve patients' overall survival, progression free survival, and partial response rate.^[3] However, bevacizumab displays several side

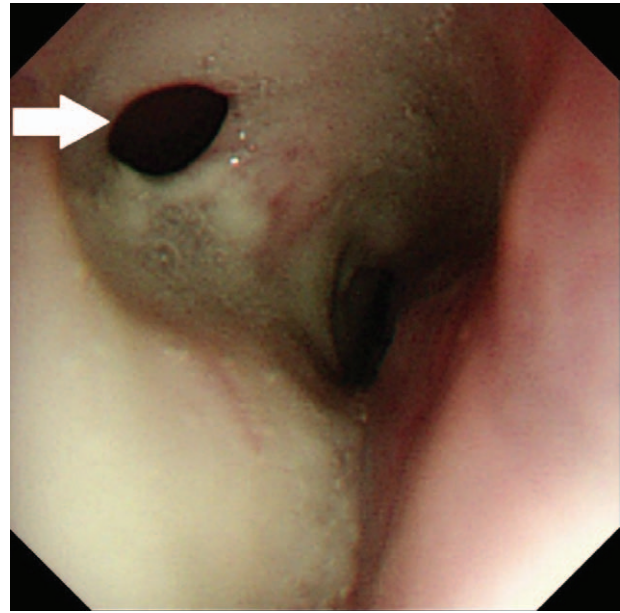


Figure 2. A tracheoesophageal fistula (white arrow) was observed by means of gastroscopy.

effects such as thromboembolism, hypertension, bleeding, proteinuria.^[4] Bevacizumab related TF is a rare but life-threatening complication which has been reported in the treatment of lung cancer. In a phase I/II trial of bevacizumab plus erlotinib for pancreatic cancer treatment, TF developed in one (2%) patients.^[5] Several literatures from different countries including Japan,^[6] American,^[7] Germany^[8] have reported the TF occurred after administering of bevacizumab. However, no such report of Chinese is available at this time. This is the first case of TF after administering of radiotherapy and bevacizumab for Chinese patient with NSCLC.

The mechanism of TF formation with bevacizumab is unknown, but it is hypothesized that impaired angiogenesis

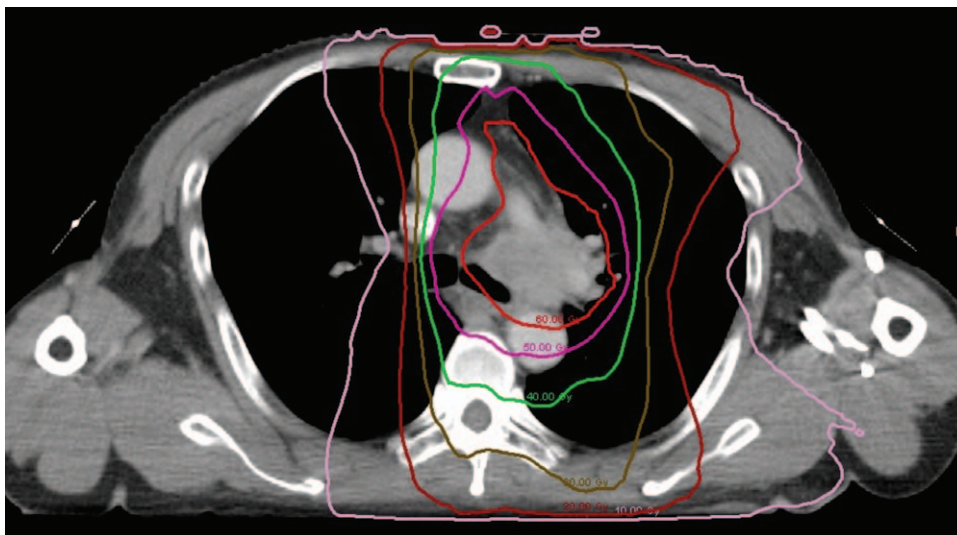


Figure 1. Isodose lines showing radiation dose distribution in a 54-yr-old male with stage IIIB non-small cell lung cancer.

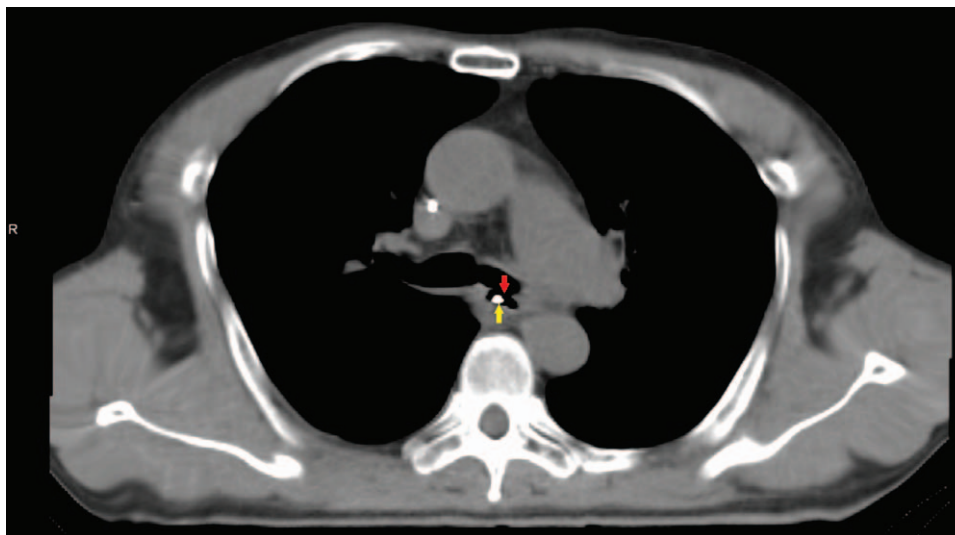


Figure 3. A chest computed tomography scan showed a tracheoesophageal fistula (red arrow) and jejunal feeding tube (yellow arrow).

leads to delayed wound healing. The predisposing factors suggested in previous reports for TF are tumor location,^[6] tracheoesophageal injury due to instrumentation, a history of thoracic radiotherapy.^[9]

Among all reports of TF, the time between the TF and radiotherapy in NSCLC is different, the shortest time is 2 months after the completion of radiotherapy^[10] and the longest time is 21 months.^[7] In our case, the patient suffered TF 5 months after the completion of radiotherapy. Acute esophageal toxicity is a common side effect of radiotherapy and predisposition for late TF. In a phase II clinical trial,^[9] all two patients of NSCLC who developed TF had a history of esophageal toxicity caused by radiotherapy.

In this case, volumetric modulated arc therapy technique, enabling better radiation dose conformality to the target volume

while simultaneously decreasing the dose to surrounding normal organs, was delivered. The mean esophageal dose was 26.0Gy, and the maximum esophageal dose was 62.2Gy, with an esophageal V50 of 32.4%. The mean dose in the location of later TF was 57.1Gy, the maximum dose was 61.8Gy, the minimum dose is 52.4Gy. And patient developed Grade I esophageal toxicity, Grade II gastrointestinal toxicity, Grade I dermatological toxicity and Grade I myelotoxicity during concurrent chemoradiotherapy.

TF is a rare but life-threatening complication of radiotherapy and bevacizumab in patients with NSCLC. Without early recognition and treatment, the patient would die of severe pulmonary infection. Gore et al. reported a case in which the unfortunate patient died of pneumonia caused by TF after the event.^[7]

The commonly recommended treatment options for TF are jejunal feeding tube placement, esophageal stent, or surgery.^[11] In our case, due to timely diagnosis and treatment of esophageal stent, he recovered well in follow-up care more than 6 months after these events.

Careful observation is imperative for those patients who are administered bevacizumab, particularly in patients treated previously with radiotherapy. If patients present with a sudden onset of acute cough after drinking and they are suspected to have TF, then stent placement or surgery should be the treatment of choice.

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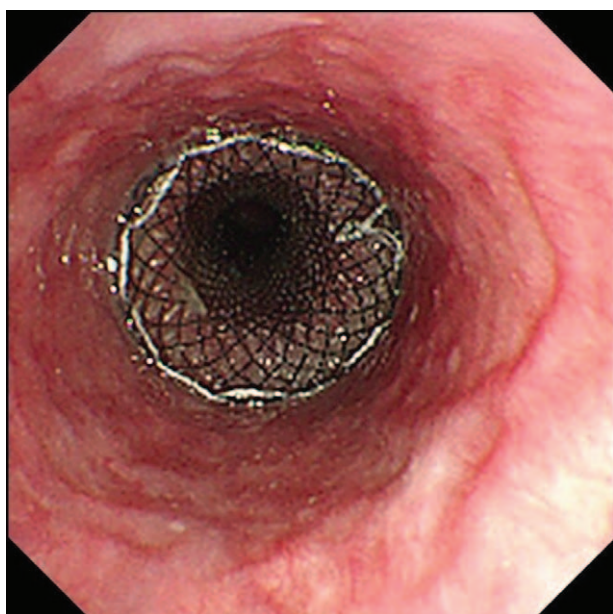


Figure 4. A covered esophageal stent in the esophagus.

References

- [1] Cohen MH, Gootenberg J, Keegan P, et al. FDA drug approval summary: bevacizumab (Avastin) plus Carboplatin and Paclitaxel as first-line treatment of advanced/metastatic recurrent nonsquamous non-small cell lung cancer. *Oncologist* 2007;12:713–8.
- [2] National Comprehensive Cancer Network. Non-Small Cell Lung Cancer (Version 5. 2019). http://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Access June 7, 2019.
- [3] Wang Y, Wang H, Jiang Y, et al. A randomized phase III study of combining erlotinib with bevacizumab and panitumumab versus erlotinib alone as second-line therapy for Chinese patients with non-small-cell lung cancer. *Biomed Pharmacother* 2017;89:875–9.
- [4] Crinò L, Dansin E, Garrido P, et al. Safety and efficacy of first-line bevacizumab-based therapy in advanced non-squamous non-small-cell lung cancer (SAiL, MO19390): a phase 4 study. *Lancet Oncol* 2010;11:733–40.
- [5] Socinski MA, Stinchcombe TE, Moore DT, et al. Incorporating bevacizumab and erlotinib in the combined-modality treatment of stage III non-small-cell lung cancer: results of a phase I/II trial. *J Clin Oncol* 2012;30:3953–9.
- [6] Nishie K, Yasuo M, Kitaguchi Y, et al. Bevacizumab-induced tracheoesophageal fistula in a patient suffering from lung cancer with bulky subcarinal lymph node: a case report. *Nagoya J Med Sci* 2018;80:129–34.
- [7] Gore E, Currey A, Choong N. Tracheoesophageal fistula associated with bevacizumab 21 months after completion of radiation therapy. *J Thorac Oncol* 2009;4:1590–1.
- [8] Schreiber J, Waldburg N. Bronchoesophageal fistula and fatal hemoptysis after bevacizumab-containing chemotherapy without radiation in lung cancer. *J Clin Oncol* 2012;30:e324.
- [9] Spigel DR, Hainsworth JD, Yardley DA, et al. Tracheoesophageal fistula formation in patients with lung cancer treated with chemoradiation and bevacizumab. *J Clin Oncol* 2010;28:43–8.
- [10] Goodgame B, Veeramachaneni N, Patterson A, et al. Tracheoesophageal fistula with bevacizumab after mediastinal radiation. *J Thorac Oncol* 2008;3:1080–1.
- [11] Steel GG, Hill RP, Peckham MJ. Combined radiotherapy–chemotherapy of Lewis lung carcinoma. *Int J Radiat Oncol* 1978;4:49–52.