

Esophageal perforation in a patient with lung cancer after administration of bevacizumab combined with radiotherapy and chemotherapy: A case report

QIANG JIA, YUN-LONG ZHOU, LAN-YING DUAN, HUI-CHAO LI and GAOWU HU

Department of Oncology, Jiangyou Second People's Hospital, Jiangyou, Mianyang, Sichuan 621701, P.R. China

Received July 23, 2025; Accepted September 25, 2025

DOI: 10.3892/ol.2025.15341

Abstract. The combination of bevacizumab and chemotherapy regimens has been widely recognized by international authoritative guidelines. However, although this treatment regimen has demonstrated a definite antitumor effect, its drug safety issues still require clinical attention. Notably, among the adverse reactions related to bevacizumab, esophageal perforation, as a serious complication that may endanger lives, has rarely been described in the literature in the field of lung cancer treatment. The present report describes a case of a rare complication of esophageal perforation that occurred during the treatment process in a patient with advanced lung adenocarcinoma who received bevacizumab combined with radiotherapy and chemotherapy. By systematically reviewing the clinical features, imaging evolution and treatment process of the present case, and assessing the occurrence mechanism, high-risk factors and treatment measures of esophageal perforation caused by bevacizumab in patients with lung cancer, the present study suggests that underlying gastrointestinal diseases can damage the esophageal mucosa, and that the combination of radiotherapy and chemotherapy can aggravate the damage and produce synergistic toxicity with the anti-angiogenic effect of bevacizumab to induce esophageal perforation. In conclusion, esophageal perforation is a rare adverse reaction and the risk of its occurrence is markedly increased when bevacizumab is combined with radiotherapy and chemotherapy. Therefore, high-risk factors need to be strictly evaluated before its use to optimize treatment decisions and enhance the ability to prevent and control serious complications.

Introduction

Bevacizumab is a recombinant humanized monoclonal antibody targeting vascular endothelial growth factor (VEGF). Numerous reports have shown that this drug exhibits significant efficacy in the treatment of various cancer types, including metastatic colorectal cancer, non-small cell lung cancer, hepatocellular carcinoma, cervical cancer and ovarian cancer. Bevacizumab can positively improve key indicators such as a patient's overall survival (OS) time, progression-free survival (PFS) time and objective response rate (ORR) (1-5). The core mechanism of action lies in the binding of bevacizumab to VEGF with high affinity, blocking the interaction between VEGF and receptors on the surface of endothelial cells, thereby effectively inhibiting tumor angiogenesis (6,7). Although this drug has demonstrated notable efficacy in clinical applications, its related adverse reactions cannot be ignored. A phase III clinical trial evaluated the safety of continued bevacizumab treatment in 245 breast cancer patients who experienced disease progression after receiving bevacizumab combined with chemotherapy. The most common grade 3 or higher adverse events were hypertension (13%), neutropenia (12%) and hand-foot syndrome (11%) (8). A phase II clinical trial evaluated the efficacy of adding bevacizumab to the cisplatin-paclitaxel treatment regimen in 150 patients with advanced cervical cancer. Among these, the most common grade 3/4 adverse events were neutropenia (25%), anemia (19%), hypertension (14%) and the occurrence of ≥ 1 perforation/fistula event (13%) (4). However, a literature search reveals that reports on esophageal perforation caused by bevacizumab during the treatment of lung cancer are extremely rare (9). The present report describes in detail the clinical diagnosis and treatment process of a patient with advanced lung cancer who developed esophageal perforation while receiving bevacizumab treatment, and systematically analyzes its occurrence mechanism and management strategies. The aim of the study is to provide references for clinical diagnosis and treatment, enhancing the awareness of and clinical management ability for this rare adverse reaction of the drug, and optimizing the risk early warning mechanism during the treatment process.

Case report

Disease diagnosis, treatment and development. The patient in the present case was a 67-year-old man, weighing 55 kg, with a history of chronic gastritis and a long-term smoking history.

Correspondence to: Professor Qiang Jia or Mr. Yun-Long Zhou, Department of Oncology, Jiangyou Second People's Hospital, 31 Juhui Road, Jiangyou, Mianyang, Sichuan 621701, P.R. China
E-mail: jaq7724@163.com
E-mail: workdragon@163.com

Key words: bevacizumab, tumor, lung cancer, esophageal perforation

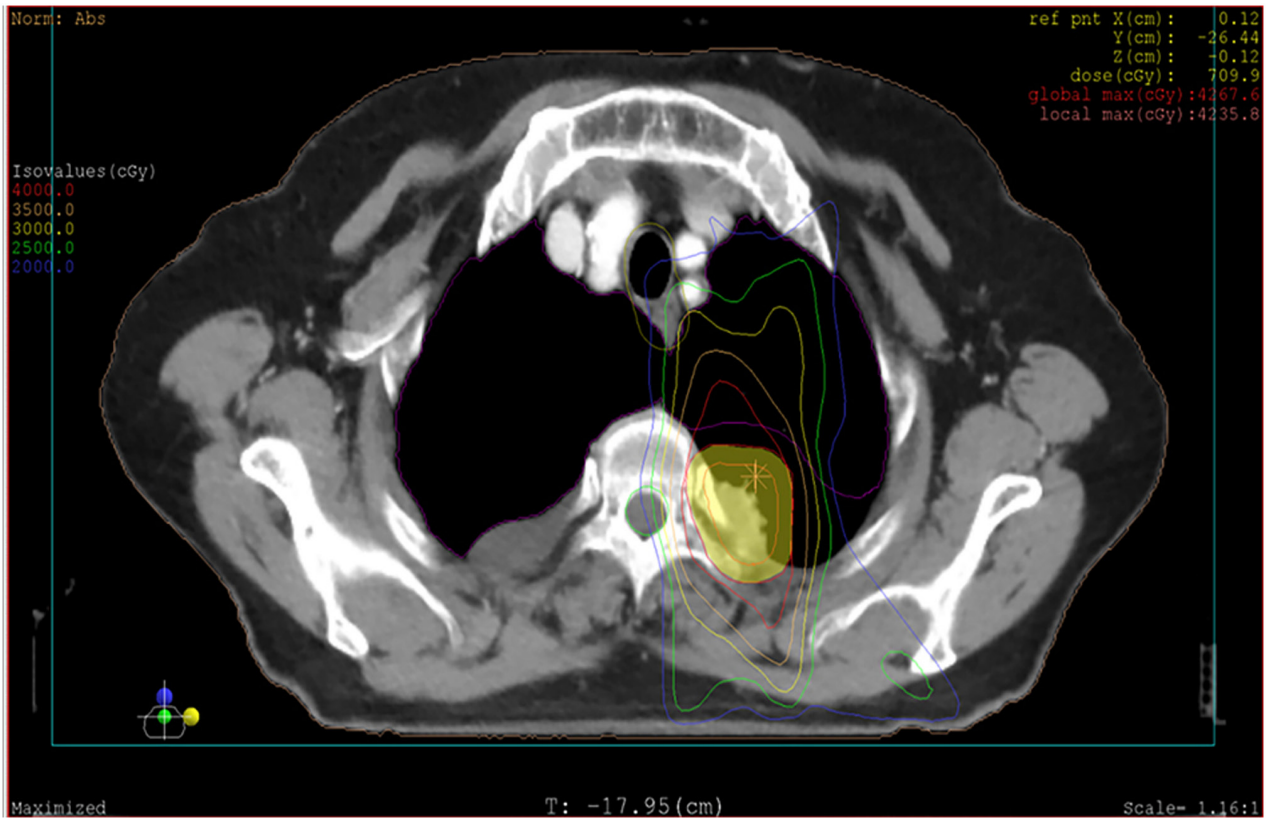


Figure 1. Isodose curve diagram showing the radiation dose distribution in the patient. Different colored curves each represent isodose lines, with doses measured in cGy; their specific values are as indicated in the 'Isovalues (cGy)' legend, which are 4000.0, 3500.0, 3000.0, 2500.0 and 2000.0 respectively. The yellow-shaded region in the diagram indicates the target volume receiving radiation. cGy, centigray.

In February 2023, the patient underwent a wedge resection of the right lung tumor at Taizhou First People's Hospital (Taizhou, China) due to a mass in the right lung. Postoperative pathology indicated lung adenocarcinoma with a staging of TxN3M1 [stage IV, with intrapulmonary metastasis; American Joint Committee on Cancer (10)]. Genetic testing results were negative, and no postoperative adjuvant antitumor treatment was administered. In April 2024 (14 months after the surgery), due to the delayed healing of the surgical incision, a chest CT reexamination revealed multiple metastatic lesions in both lungs and lymph node metastasis, and a 3-cm lesion in the upper lobe of the left lung was found. Therefore, radiofrequency ablation of the left lung lesion was performed under computed tomography (CT) guidance. Starting in April 2024, the patient received a chemotherapy regimen of 700 mg bevacizumab on day 1 + 0.8 g pemetrexed intravenous infusion on day 1 + 0.4 g carboplatin intravenous infusion on day 1, once every 3 weeks, for a total of 4 cycles. Moreover, in April 2024, palliative radiotherapy with intensity-modulated radiotherapy for the left lung mass was sequentially performed (95% planning target volume, 40 Gy in 20 fractions). The radiation isodose curve is presented in Fig. 1 (XIO planning system; version 4.8; Elekta AB). Grade I acute esophageal toxicity and grade I acute skin toxicity [Common Terminology Criteria for Adverse Events Version 5.0 (11)] were side effects of the radiotherapy. In August 2024, the dose of bevacizumab dose was adjusted to 800 mg, whilst the original chemotherapy regimen was maintained (5th cycle). The last treatment was in September 2024, and the efficacy evaluation revealed that

the disease was stable. In October 2024 (1 month after the last treatment), the patient experienced a cough, with expectoration of white sticky phlegm and shortness of breath without obvious incentives. The patient experienced pain in the right chest and hypochondrium when coughing, accompanied by dizziness, acid reflux, heartburn and a poor appetite. The patient then visited the Respiratory Department of Jiangyou Second People's Hospital (Jiangyou, Mianyang, China). In November 2024 (Fig. 2), a chest CT (Ingenuity Core 128; Philips Medical Systems, Inc.) revealed the following: i) Postoperative changes in the right lung accompanied by a mass shadow at the stump (no progression compared with the film from October 2024); ii) multiple nodules in both lungs (stable compared with October 2024); and iii) enlargement of the mediastinal lymph nodes. After 2 weeks of anti-infection treatment (2 g cefoperazone and sulbactam every 12 h + 0.4 g moxifloxacin every day; intravenous infusion, continuously for 7 days), preventive antifungal treatment (0.2 g voriconazole every 12 h for 2 weeks), bronchodilator treatment (0.2 g doxofylline every day for 2 weeks), glucocorticoid treatment (40 mg methylprednisolone every day for 2 weeks) and nutritional support treatment, the symptoms were relieved, and the patient was discharged from the hospital.

Esophageal perforation occurrence and management. In November 2024, the patient was admitted to Jiangyou Second People's Hospital again for a 6th cycle of chemotherapy (800 mg bevacizumab + the original chemotherapy regimen). After the treatment, the patient experienced a severe cough

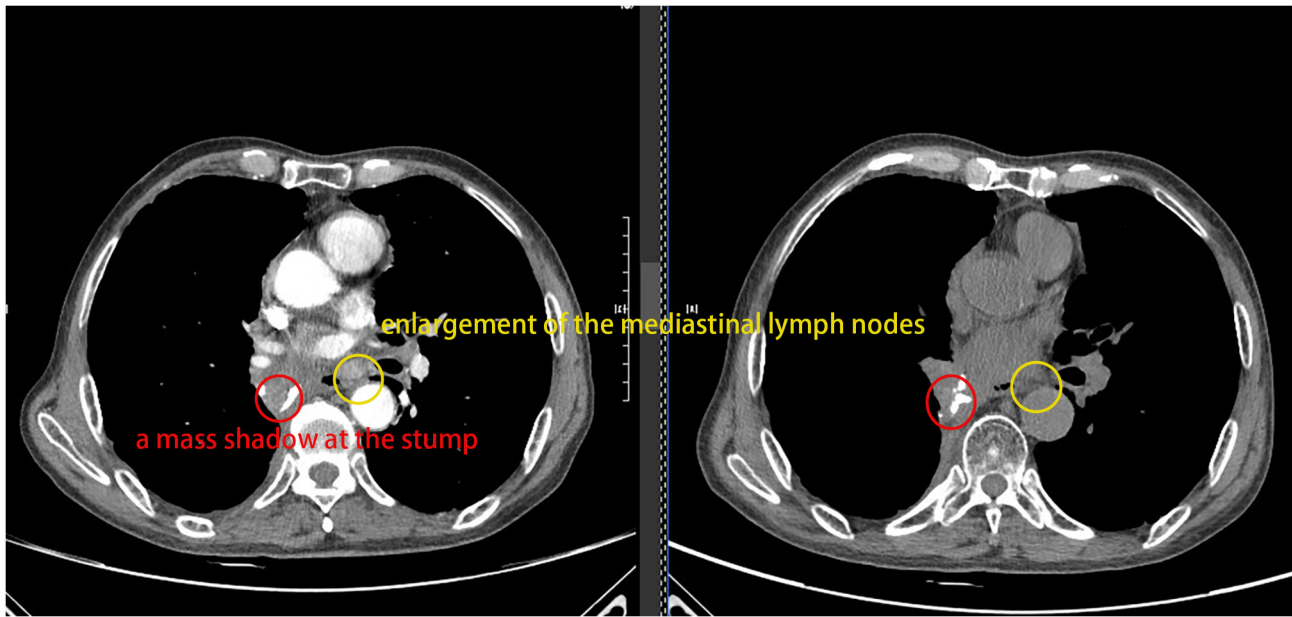


Figure 2. Clinical examination images. CT images of the patient from October 2024 (left) and November 2024 (right), respectively. By comparing these two images, it can be seen that there is no significant progressive change in the shape, size or other aspects of the mass-like shadow at the stump of the right lung after surgery (marked with a red circle); meanwhile, through observation of the CT images from October and November, the phenomenon of lymphadenopathy in the mediastinal region can be clearly observed (marked with a yellow circle).

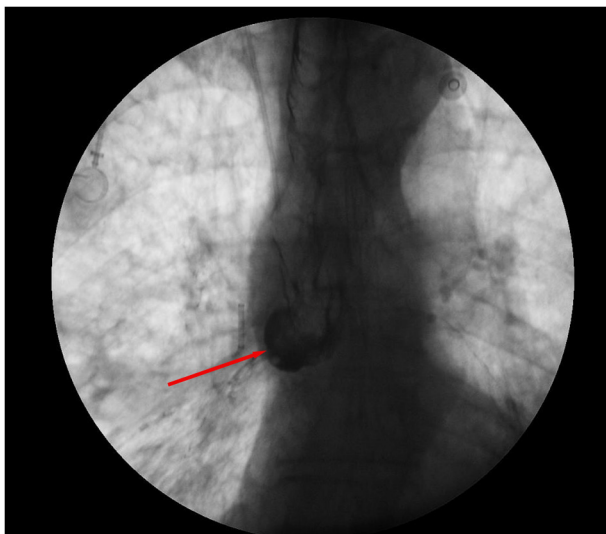


Figure 3. Esophagography performed with iohexol. The esophagus is not well visualized, with some of the contrast agent entering the trachea and resulting in partial opacification of the trachea. The image clearly shows a communication between the esophagus and the trachea (marked by the red arrow), thus confirming the diagnosis of tracheoesophageal fistula.

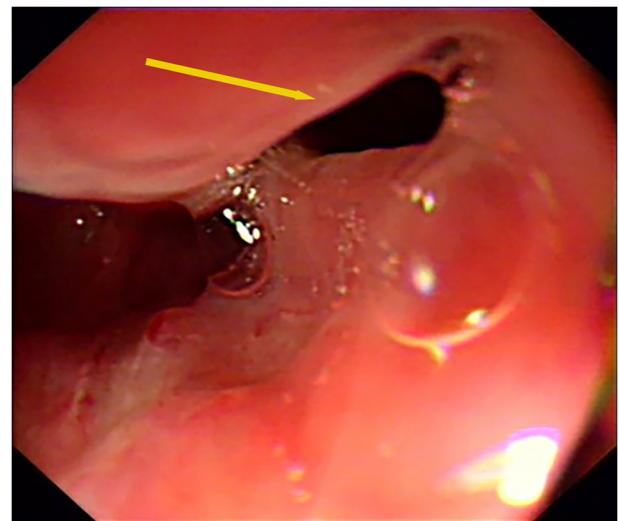


Figure 4. Gastroscopy. Gastroscopic image showing a fistula opening (marked by the yellow arrow) with a size of ~0.5x0.5 cm at the esophageal site, 35 cm from the incisors. This image was captured using narrow-band imaging technology in the A3 electronic staining mode, with an optical magnification of 1.0x, which clearly displays the fistula opening and the fine structure of the surrounding mucosal tissue.

accompanied by yellow sticky phlegm (which was difficult to expectorate), decreased exercise tolerance and gastrointestinal symptoms. In December 2024, *Aspergillus flavus* was detected by targeted next-generation sequencing (tNGS) of bronchoalveolar lavage fluid, and voriconazole (200 mg every 12 h for 40 days) was administered as an antifungal treatment. During the treatment period, a new choking cough after eating occurred. A total of 4 days later, both upper gastrointestinal contrast radiography (Fig. 3) (X-ray fluoroscopic diagnostic device; Ultimax-I; Canon Medical Systems Corporation) and

painless gastroscopy (Fig. 4) (X-ray fluoroscopic diagnostic device; Ultimax-I; Canon Medical Systems Corporation) confirmed a tracheoesophageal fistula in the middle esophagus (35 cm from the incisors). Therefore, 2 days later, esophageal covered stent implantation was performed under endoscopy (Fig. 5) (X-ray fluoroscopic diagnostic device; Ultimax-I; Canon Medical Systems Corporation). After the operation, parenteral nutrition and anti-infection management were administered (1 g meropenem every 8 h for 17 days). A total of 19 days after stent implantation, a reexamination revealed

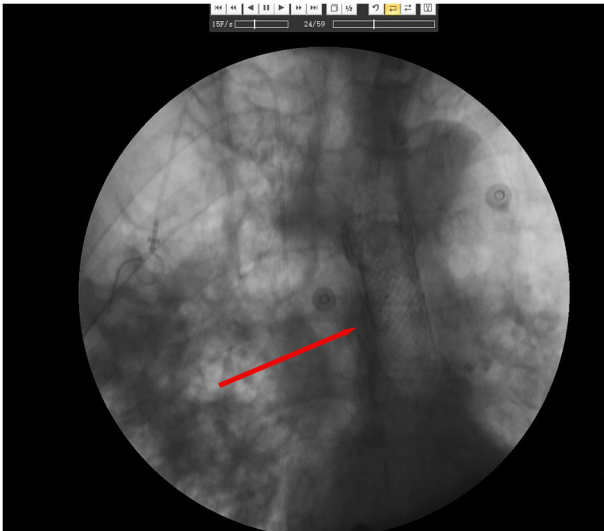


Figure 5. Fluoroscopic image of the esophagus. A stent is visible in the middle segment of the esophagus. The contrast agent flows relatively smoothly downward through the stented area (marked by the red arrow), which demonstrates that the esophagus remains patent after stent placement.

that the position of the stent was good, and the patient was discharged from the hospital after their condition gradually improved. Due to advanced malignant tumors complicated by cardiopulmonary and respiratory circulatory system failure, the patient was followed up until January 2025 when they passed away due to advanced lung cancer.

Discussion

The present report describes the case of a patient with advanced lung cancer who had a history of chronic gastritis. In the early stage, the patient received 4 cycles of chemotherapy with 700 mg bevacizumab combined with pemetrexed and carboplatin, as well as intensity-modulated radiotherapy (total dose of 40 Gy/20 fractions). Later, the dose of bevacizumab was adjusted to 800 mg + the original chemotherapy regimen. Esophageal perforation occurred during the 6th cycle of treatment. After comprehensive treatments, such as esophageal covered stent implantation under endoscopy, the condition of the patient improved in the short term.

From the results of the present report, combined with a literature analysis, we hypothesize that the pathogenesis is associated with the synergistic effect of multiple risk factors. The anti-angiogenic effect of bevacizumab as a key therapeutic drug, the duality of the vascular normalization effect and the toxic effect of bevacizumab are worthy of in-depth discussion. This drug blocks the phosphorylation of VEGFR-2 by binding to VEGF-A with high affinity, which inhibits tumor angiogenesis whilst also impairing the physiological vascular repair mechanism (12,13). Thawani *et al* (14) reported that even if patients did not receive local treatments (radiotherapy or surgery) and only used bevacizumab, it could also cause a tracheoesophageal fistula. When perforation occurred in the patients, the median dose of bevacizumab used was 733 mg, which was close to the median dose of 800 mg for the risk threshold of gastrointestinal perforation reported in the literature (15). The odds ratio was 2.8 ($P=0.03$), suggesting

that high-dose medication may be an important predisposing factor. ii) The synergistic damage effect of combined radiotherapy and chemotherapy is another risk factor. During the radiotherapy process for lung cancer, there is an association between the length of time after the completion of radiotherapy and the occurrence of esophageal fistula. According to previous studies, the time span from the end of radiotherapy to the appearance of esophageal fistula varies greatly. The condition may occur as soon as ~4 months after the end of radiotherapy (16) or as late as 21 months (17). Previous case reports by Nishie *et al* (18) and Wang *et al* (19) have indicated that during the treatment of lung cancer, esophageal perforation may be induced in patients who did not receive radiotherapy when treated with bevacizumab combined with chemotherapy. However, in the present case, the situation was more complex, as the patient not only received bevacizumab combined with chemotherapy but also sequentially underwent radiotherapy. Specifically, the mean esophageal dose of the patient was 18 Gy, and the maximum esophageal dose was 36 Gy. The mean dose at the location of the later esophageal perforation was 21 Gy, and the maximum esophageal dose was 33 Gy. Radiotherapy is likely to cause chronic inflammation and fibrosis of the esophageal mucosa (20). When the adverse effects caused by radiotherapy are superimposed on the anti-angiogenic effect of bevacizumab, the tolerance of tissues may be further weakened (21). Furthermore, the regimen of pemetrexed combined with carboplatin used in the patient in the present case may have exacerbated the damage to the esophageal mucosa (22). The *Aspergillus flavus* infection (confirmed by tNGS) that occurred in the patient later could have caused pulmonary inflammation and the severe cough (23,24). This may have increased the pressure on the esophageal wall through mechanical stress and become a direct predisposing factor for perforation (25). Spigel *et al* (26) performed two independent phase II clinical trials on 34 patients with small cell lung cancer (29 patients) and non-small cell lung cancer (5 patients). The research revealed that the combination of bevacizumab with radiotherapy and chemotherapy markedly increased the risk of a tracheoesophageal fistula in patients with lung cancer (incidence rate, 2.3 vs. 0.0%, respectively). The treatment regimen of the patient in the present case included the combination of bevacizumab with radiotherapy and chemotherapy, which may have increased the risk of tracheoesophageal fistula. Another risk factor associated with the pathogenesis of perforation is the superimposed impact of underlying diseases and predisposing factors. The previous chronic gastritis of the patient in the present case may have led to acid reflux, which could have chronically stimulated the esophageal mucosa to form chronic inflammation and reduce the resistance of local tissues (27). Zhou *et al* (15) performed a retrospective analysis of 8 cases of bevacizumab-related gastrointestinal perforation, reporting that 62.5% of the patients had underlying digestive tract diseases, which was consistent with the situation in the present case. Moreover, when the patient in the present case coughed, the intrathoracic pressure suddenly increased (up to 50-100 mmHg) (28,29), which may have caused damage to the weak areas of the esophageal wall (25). Especially when the mucosa has already been damaged by radiotherapy or drugs, it is easy for a full-thickness rupture to form and create a fistula.

In view of the serious consequences of tracheoesophageal fistula (the patient in the present case eventually died due to advanced cancer), the following management strategies should be considered when bevacizumab is used clinically: i) Screening of high-risk factors: Patient medical history should be collected in detail, with a focus on basic conditions such as the history of digestive tract diseases (such as chronic gastritis and ulcers), radiotherapy history and chronic cough. For patients who are due to receive bevacizumab combined with radiotherapy, the radiation dose received by the esophagus should be strictly evaluated. Furthermore, the superimposed use of high-dose drugs (such as ≥ 800 mg per time) plus radiotherapy and chemotherapy should be avoided if possible. ii) Baseline assessment and monitoring: For patients at moderate-to-high risk of esophageal perforation (such as those with combined radiotherapy, chemotherapy and bevacizumab, or those with a history of digestive tract diseases), gastroscopy is recommended before treatment (30) to exclude esophageal mucosal damage. During the treatment, swallowing functions (such as swallowing pain, a foreign body sensation and a choking cough) and respiratory symptoms (an aggravated cough and shortness of breath) should be closely monitored. When abnormalities occur, an esophageal fistula should be immediately screened for (upper gastrointestinal contrast radiography or endoscopy is preferred). iii) Principles of emergency treatment: Once a tracheoesophageal fistula is diagnosed, bevacizumab should be immediately stopped, fasting started, and anti-infection and nutritional support treatments should be administered. Minimally invasive methods such as endoscopic stent implantation should be prioritized to close the fistula and improve the quality of life of the patient.

In conclusion, we hypothesize that the esophageal perforation in the present case was the result of the synergistic effect of multiple factors, including drug dosage, radiation dose to the esophagus, esophageal damage caused by chemotherapy, underlying digestive tract diseases and mechanical stress damage. Clinically, individualized risk assessments for high-risk groups are needed, and treatment indications and dosages should be strictly controlled and combined with close symptom monitoring and imaging evaluations, in the hope of the early identification and management of this rare but potentially fatal complication.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

QJ, YLZ, and GWH were responsible for the conception and design of this study. QJ undertook the analysis and summary

of patient clinical data and drafted the initial manuscript. YLZ and GWH conducted rigorous revisions on important intellectual content of the manuscript (such as the relevance between the discussion section and literature) and provided critical comments. HCL and LYD were responsible for the acquisition of medical imaging data and collection of patient treatment records, participated in the preliminary analysis and interpretation of data, and also took part in manuscript review. QJ, YLZ, LYD, HCL and GWH confirm the authenticity of all the raw data and take responsibility for all aspects of the work, ensuring that any questions regarding the accuracy or integrity of any part of the work were appropriately investigated and resolved. All authors read and approved the final version of the manuscript and unanimously agreed that the manuscript could be published.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Informed consent for the publication of the manuscript was obtained from the patient's wife.

Competing interests

The authors declares that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, AI tools were used to improve the readability and language of the manuscript or to generate images, and subsequently, the authors revised and edited the content produced by the AI tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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