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**Arteriovenous thrombotic events in a patient with advanced lung cancer following bevacizumab plus chemotherapy: A case report**

Kong Y *et al.* Arteriovenous thrombotic events occurred in NSCLC

## **Abstract**

### **BACKGROUND**

In driver-gene-negative non-small cell lung cancer patients who relapse following radical resection, combination chemotherapy using bevacizumab and a platinum-based dual drug is known to increase both progression-free and overall survival. Treatment initially includes bevacizumab, and if patients are able to tolerate it, bevacizumab can continue to be utilized until disease progression. Bevacizumab is a recombinant humanized monoclonal neutralizing antibody that acts against vascular endothelial growth factor (VEGF). Various anti-VEGF monoclonal antibodies, such as bevacizumab, can increase the risk of arterial thromboembolism. Current data indicate that the treatment of VEGF-target does not significantly increase the risk of venous thromboembolism events, except for bevacizumab.

### **CASE SUMMARY**

A 55-year-old man underwent radical resection for cancer of the right lung. Six months following surgery, multiple metastases were observed in his left lung. Subsequently, six cycles of bevacizumab combined with pemetrexed/carboplatin chemotherapy was given. Efficacy evaluation continued to be part relief according to RECIST 1.1 standards, and no noticeable adverse reactions were noted. After three cycles of maintenance therapy using a combination of bevacizumab and pemetrexed, the patient developed dizziness and dyspnea. The patient was diagnosed with acute cerebral infarction and pulmonary embolism following head magnetic resonance imaging, computed tomography angiography, and chest enhanced computed tomography scan. Although the patient received low-molecular-weight heparin anticoagulation and other treatment, the patient eventually died of respiratory failure one month later. This case report may offer some insight into fatal arteriovenous embolism, which has not been previously reported.

### **CONCLUSION**

Bevacizumab combined with chemotherapy may also increase the risk of arteriovenous thromboembolism. Accordingly, patients who receive angiogenesis inhibitor therapy should be carefully selected. Furthermore, close monitoring and timely intervention are necessary in order to reduce the risk of such toxicities.

**Key Words:** Cerebral infarction; Pulmonary embolism; Bevacizumab; Chemotherapy; Non-small cell lung cancer; Case report

Kong Y, Xu XC, Hong L. Arteriovenous thrombotic events in a patient with advanced lung cancer following bevacizumab plus chemotherapy: A case report. *World J Clin Cases* 2022; In press

**Core Tip:** This report describes a middle-aged man with post-operative recurrence of non-small cell lung cancer who developed cerebral infarction and pulmonary embolism six months after treatment with bevacizumab, which was given in combination with chemotherapy. Concurrent arteriovenous thrombosis continues to be rarely reported in literature. Bevacizumab in conjunction with chemotherapy may increase the risk of arteriovenous thromboembolism. As a result, patients who undergo treatment with angiogenesis inhibitors should be carefully selected, and close monitoring and timely interventions (such as low molecular weight heparin prophylactic anticoagulant therapy) are necessary in order to reduce the risk of arterial thromboembolism and venous thromboembolism.

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## **INTRODUCTION**

Bevacizumab is a monoclonal antibody that acts against vascular endothelial growth factor (VEGF). A wide range of drugs may be used in targeting the VEGF signaling pathway in the treatment of various solid tumors; however, a plethora of toxic effects have increasingly been discovered, which have been shown to be fatal in a small number of cases<sup>[1,2]</sup>. The increased incidence of potentially fatal arterial

thromboembolism (ATE), including transient ischemic attack, stroke, angina pectoris, and myocardial infarction, has been initially reported in advanced colorectal cancer, which was treated with a chemotherapy regimen containing bevacizumab, with the incidence of severe ATE being 4%-5%<sup>[3]</sup>. Some studies have revealed that bevacizumab can increase the risk of venous thromboembolism (VTE) in patients with cancer, however, inconsistent conclusions have been reported. Two meta-analyses that were conducted at the patient level have shown that, compared to patients solely receiving chemotherapy, the risk of VTE did not increase in patients who received bevacizumab plus chemotherapy<sup>[4]</sup>. Here, we describe a 55-year-old man who suffered from arteriovenous thrombosis after receiving bevacizumab in conjunction with intravenous chemotherapy.

### <sup>3</sup> **CASE PRESENTATION**

#### ***Chief complaints***

A 55-year-old man presented to our department with hemoptysis.

#### ***History of present illness***

The patient's chest computed tomography (CT) and positron emission tomography-CT demonstrated consolidation and thick-walled voids in the posterior and dorsal lobes of the right lung (Figures 1 and 2). Ultrasound bronchoscopy revealed the presence of adenocarcinoma. The patient then underwent radical resection for right lung cancer, after which postoperative pathology revealed central invasive adenocarcinoma (pT4N1M0, IIIA). Moreover, genetic testing revealed the following: <sup>2</sup>Epidermal growth factor receptor (-), anaplastic lymphoma kinase (-), ROS1 (-), Kirsten rat sarcoma/murine sarcoma viral oncogene homolog B1 (-), and programmed death 1 (-). Adjuvant chemotherapy was not provided following surgery in light of the patient's poor physical condition. Six months postoperatively, the patient's condition worsened, and a chest enhanced CT demonstrated enlarged mediastinal lymph nodes, diffuse nodules in the left lung, and left pleural effusion. Endobronchial ultrasound-guided

transbronchial lung biopsy was difficult to obtain and was not performed due to the presence of diffuse small lesions within the left lung. The patient subsequently received regimen chemotherapy with bevacizumab 400 mg d1 + pemetrexed 750 mg d1 + carboplatin 500 mg d1, q3w for six cycles. The curative effect was evaluated with part relief during chemotherapy according to RECIST 1.1 standards. The patient had no chemotherapy-related adverse reactions, including nausea and vomiting, and no bone marrow suppression, increased blood pressure, proteinuria, or bleeding. Bevacizumab 400 mg d1+pemetrexed 750 mg d1, q3w was then maintained for 3 cycles. Afterward, the patient developed dizziness with nausea and vomiting, for which magnetic resonance imaging (MRI) of the head displayed acute cerebral infarction in the right lateral ventricle (Figure 3A), CT angiography (CTA) of the head demonstrated local occlusion of the right superior cerebellar artery following bevacizumab combined with chemotherapy (Figure 3B). In addition, the patient experienced symptoms, such as progressive dyspnea and decreased blood oxygen saturation. D-2 increased 10-fold, and other blood coagulation function indexes were within normal range. Routine blood tests, C-reactive protein and procalcitonin levels were also within normal range. Chest enhanced CT revealed a filling defect of the right pulmonary artery (Figure 1), after which pulmonary embolism was diagnosed.

### ***History of past illness***

The patient had no history of hypertension, cardiovascular or cerebrovascular disease, and chronic kidney disease. He was a smoker for 30 years.

### ***Personal and family history***

There was no family history of lung cancer.

### ***Physical examination***

No breath sounds in his right lung and low breath sounds in his left lung. His heart examination showed no significant abnormality.

### ***Laboratory examinations***

Routine blood tests, C-reactive protein and procalcitonin levels were also within normal range. D-2 increased 10-fold, and other blood coagulation function indexes were within normal range.

### ***Imaging examinations***

MRI of the head displayed acute cerebral infarction in the right lateral ventricle (Figure 3A). CTA of the head demonstrated local occlusion of the right superior cerebellar artery following bevacizumab combined with chemotherapy (Figure 3B). Chest enhanced CT revealed a filling defect of the right pulmonary artery (Figure 1). Electrocardiogram (ECG) and color doppler echocardiography of the discussed patient showed no obvious abnormalities.

### **FINAL DIAGNOSIS**

Cerebral infarction and pulmonary embolism.

### **TREATMENT**

The patient developed distant metastatic disease and was unable to be cured; therefore, systemic treatment was the goal in his palliative care plan. Accordingly, treatment with bevacizumab was terminated, and aspirin (100 mg/d) + clopidogrel bisulfate tablets (75 mg/d) + atorvastatin (20 mg/d) + low molecular weight heparin (LMWH) (4100 IU/12 h) anticoagulation were provided. In addition, diuresis, drainage of pleural fluid and non-invasive ventilator therapy were performed.

### **OUTCOME AND FOLLOW-UP**

The patient died of respiratory failure one month later.

### **DISCUSSION**

Patients suffering from lung cancer are known to have the highest incidence of cerebral infarction among all existing cancer types. Previous studies have shown that cancer-related cerebral infarction may give rise to unique clinical manifestations, including increased D-2 levels and multiple cerebral infarctions distributed in the blood supply area of various arteries in the brain<sup>[5]</sup>. Its pathophysiological mechanism may be related to cancer cells directly invading the left atrium, leading to infiltrating endocarditis and hypercoagulable status<sup>[6]</sup>. ECG and color doppler echocardiography of the discussed patient showed no obvious abnormalities. The pathogenesis of more cancer-related cerebral infarctions remains unknown. MRI of the head is advantageous in detecting early cerebral infarction as it can accurately assess brain tissues at risk of infarction and exclude certain diseases that exhibit stroke-like characteristics, such as tumors. MRI of the head using diffusion imaging is better than CT, and neurovascular imaging is very important for acute ischemic stroke. Magnetic resonance angiography and CTA can be used to assess extracranial and intracranial large vessels in order to determine the presence of embolism or hypoperfusion in ischemic stroke as well as the potential source of the flow.

A variety of anti-angiogenic drugs, such as bevacizumab, are known to be associated with an increased risk of ATE<sup>[7]</sup>. However, it remains unclear whether these patients have an increased risk of VTE due to inconsistent research data. Patients receiving angiogenesis inhibitors have an increased risk of thromboembolism, for which its pathophysiology remains unclear<sup>[8]</sup>. The common hypothesis posits that tumor-associated endothelial cells are disturbed, which then transforms the endothelium from a natural anticoagulant state to a pro-thrombotic state. Afterward, systemic coagulation is activated, where such cancer patients are more prone to thromboembolism for underlying diseases. In addition, the VEGF pathway can regulate and protect endothelial cell function by inhibiting apoptosis and inflammation pathways. Endothelial dysfunction may expose phospholipids that can promote thrombosis and underlying stroma<sup>[9]</sup>. Recent studies have shown that the preventive application of antiplatelet and anticoagulant drugs can effectively reduce the incidence of thrombotic



events in cancer patients<sup>[10]</sup>. Lung cancer has a higher risk of VTE compared to that of other malignancies<sup>[11,12]</sup>. The mechanism of lung cancer with pulmonary embolism is complicated. Adenocarcinoma, advanced lung cancer, surgery, chemotherapy, and underlying co-morbidities serve as important high-risk factors. International guidelines recommend LMWH as first-line treatment in the management of tumor-related pulmonary embolism<sup>[13]</sup>. If patients with lung cancer and pulmonary embolism have no bleeding manifestations and are at a low risk of bleeding, novel oral anticoagulants can be considered instead of LMWH<sup>[14]</sup>. The anticoagulation time should be at least six months, while anticoagulation time should be prolonged or even given long-term depending on the situation<sup>[15]</sup>.

Certain lung cancer patients that are at a high risk of pulmonary embolism can benefit from preventive anticoagulation, which should be carefully evaluated in combination with the thrombosis risk assessment model and D-dimer levels. The prediction models used for VTE risk assessment of cancer patients include the Khorana score, PROTECHT score, COMPASS-CAT score and CONKO score. These models have been developed and validated in patients with ambulatory lung cancer<sup>[16]</sup>. Khorana score is currently the most validated chemotherapy-related VTE risk assessment model, which is a reliable model based on five clinical and laboratory parameters. It is suitable for the VTE risk assessment of patients undergoing lung cancer chemotherapy and can be used to customize anticoagulant thrombosis prevention in such patients<sup>[17]</sup>. However, The Khorana score may not be sensitive enough to identify high-risk lung cancer patients. Verso *et al*<sup>[18]</sup> has shown that the PROTECHT score is more advantageous than the Khorana score in distinguishing patients at high risk of VTE. Meanwhile, COMPASS-CAT score is able to accurately distinguish high-risk and low-risk VTE patients<sup>[19]</sup>. It is more sensitive in predicting the VTE risk of lung cancer patients compared to that of the Khorana, PROTECHT, and CONKO models and may be more suitable for thrombosis prevention in lung cancer patients receiving anti-tumor therapy, however, further verification is needed.

The patient reported in this study was suffering from advanced lung cancer and benefited from treatment with bevacizumab in conjunction with chemotherapy. The patient was in good physical condition and did not have hypertension or a history of cardiovascular or cerebrovascular diseases. Risk factors for deep vein thrombosis include hospitalization, indwelling deep vein catheters, and aggressive chemotherapy. Unfortunately, fatal arteriovenous thrombosis occurred during maintenance treatment with bevacizumab. Moreover, pleural effusion of the left lung increased during maintenance therapy, indicating that the patient had disease progression at the time of these thromboembolic events. Therefore, low-molecular-weight heparin anticoagulation, diuresis, drainage of pleural fluid, and non-invasive ventilator therapy was administered for the patient, however, the patient still developed shock and experienced a progressive decrease in blood oxygen saturation. The patient continued to suffer from uncontrollable respiratory failure and died after one month.

## **CONCLUSION**

This report is the first to discuss cerebral infarction and pulmonary embolism occurring in a patient with non-small cell lung cancer following treatment using bevacizumab combined with chemotherapy. Accordingly, the above drug combination may increase the risk of arteriovenous thromboembolism. However, its mechanism of occurrence remains unclear, and future studies are required to investigate the prevention and management of ATE and VTE associated with bevacizumab. In light of these findings, patients who receive angiogenesis inhibitor therapy should be carefully selected according to certain parameters, such as reasonable daily physical status, controlled blood pressure, and no severe cardiovascular events within 6-12 mo. Furthermore, close monitoring and timely intervention are necessary to reduce risk of toxicity.

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