

Case Report

Lung cancers combined with venous thromboembolism: a case report

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Abstract: VTE, which is a paraneoplastic syndrome, is the second cause of deaths in patients with malignant tumors with a high mortality. VTE is especially common in patients with lung cancers. Two lung cancer patients with recurrent DVTs and PEs were admitted to our hospital recently. Review of these two patients was described as follows. Once a patient with malignancy had PE, difficulty of treatment increases and prognosis worsens. Thus, early diagnosis and prevention turn out to be obviously important.

Keywords: Venous thromboembolism, tumors

Introduction

Venous thromboembolism (VTE), a severe and life-threatening disease, consists of pulmonary embolism (PE) and deep vein thrombosis (DVT). As a common complication of malignant tumors, VTE, which is a paraneoplastic syndrome, is the second cause of deaths in patients with malignant tumors with a high mortality [1, 2].

VTE is especially common in patients with lung cancers, California Cancer Registries Research showed that incidence of DVT was 0.1%-0.4% in patients with lung cancer [3]. An biopsy research indicated that approximate half of patients with lung cancer developed histological thrombosis [4]. Two lung cancer patients with recurrent DVTs and PEs were admitted to our hospital recently. Review of these two patients was described as follows.

Case report

Case 1

The patient is a 63 years-old male, who is a retired worker. He was used to be healthy, without smoking, toxic gas inhalation history or dust exposure history. He was admitted due to recurrent hemoptysis for five months, intermittent

swelling in both lower extremities for two months, and pain in left upper extremity for one day. The patient had hemoptysis for no obvious reasons five months ago, manifesting blood-stained sputum, a short of breath after activities. Results of his enhanced chest CT showed there was a mass of 4.5*3.5 cm with an obscure boundary and an irregular shape in lower right lung; the mass was homogeneous enhanced after contrast injection; there were multiple lymphadenectasis in mediastinum; a filling defect was observed in lower right pulmonary artery trunk (**Figure 1**). Corresponding laboratory results were shown in **Table 1**. Thus, the patient was diagnosed with lower right lung cancer combined with pulmonary embolism in lower right artery. Then the patient was discharged after given low molecular heparin was given as an anticoagulant for two weeks. After discharge, he took low molecular heparin for anticoagulation continuously. Four months ago, pathology of pulmonary puncture biopsy indicated adenocarcinoma in another hospital. However, the patient refused a surgery and chemotherapy. Two months ago, the left extremity became swollen, combined with a significantly increased circumference. Ultrasound of lower extremities showed venous thromboembolism in right popliteal vein (**Figure 2A**). Thus, the patient was given 500000 IU/day of urokinase (7000 IU/Kg) for seven days. The symptoms of

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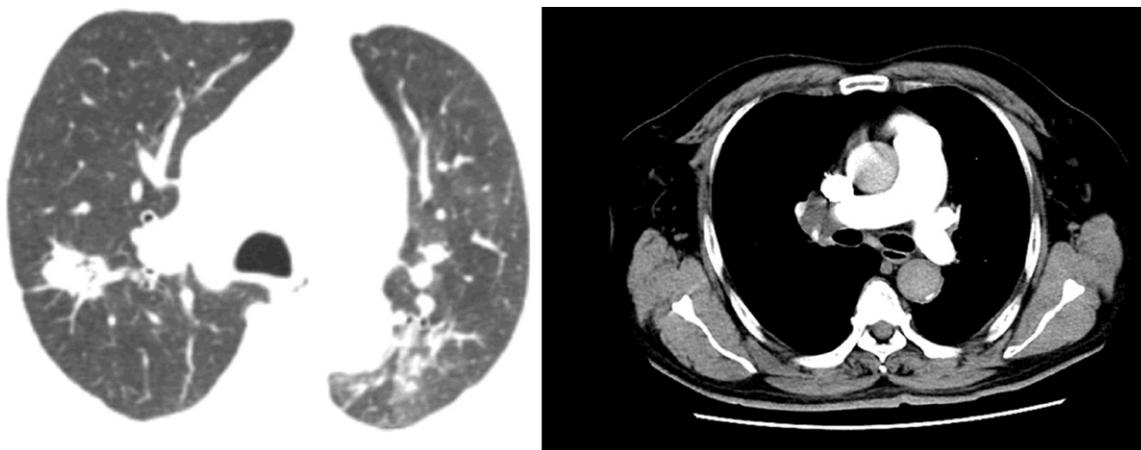


Figure 1. Results of enhanced chest CT showed a mass in lower right lung with pulmonary embolism in lower right artery.

Table 1. Laboratory results

Parameters	Value	Normal range	Parameters	Value	Normal range
WBC	4.9	4.3-9.8×10 ⁹ /L	IL-6	12.5	<5.9 pg/ml
PLT	147	125-350×10 ⁹ /L	IL-2R	350	223-710 U/ml
hs-CRP	79.5	<2.5 mg/L	Anticardiolipin antibody	Negative	Negative
PT	11	<12.1 s	CD3	65.8	50-84%
APTT	29	22.7-31.8 s	CD4	25	27-81%
INR	1.05		CD8	26.3	15-44%
Fb	2.89	2-4.5 g/L	NKCD16+CD56	22.3	7-40%
D-dimer	6.53	<1 mg/L	Integrin β2	98.9	71.1-95.8%

swelling then improved. Ultrasound of lower extremities was rechecked and still showed venous thromboembolism in right popliteal vein. After discharge, he was given long-term warfarin orally. INR was maintained at about 1.5. One month ago, the patient developed swelling in left lower extremity without a significantly increased circumference. And ultrasound of lower extremities showed incomplete embolism in left lower extremity (**Figure 2B**). The patient was given 400000 IU/day of urokinase for 10 days, and then was given increased warfarin. INR was adjusted to 2.5. One day ago, a pain occurred again in left upper extremity. Ultrasound of left upper extremity showed incomplete embolism in a superficial vein (**Figure 2C**).

Physical examinations: Body temperature was 36.7°C, and blood pressure was 130/80 mmHg. The patient has a conscious mind and a good mental state. He showed a mild anemic appearance without distension of jugular

vein. The lung respiratory sounds were clear, respiratory sounds of right lower lung were low, and no significant rhonchus or moist rales were heard. Boarder of heart did not enlarge. Heart rate was 75 beats/min. The heart rhythm was regular. No murmurs were heard. No significant swelling or tenderness was palpated in both lower extremities. A circumference of left lower extremity was 39 cm, and right 37 cm. Tenderness was positive in musculus gastrocnemius of left lower extremity. Pulses of both arteria dorsalis pedis were palpable. After admission, the patient was given 500000 IU/day of urokinase (7000 IU/Kg) for 10 days again. Then the symptoms improved. After discharge, the patient was given oral warfarin continuously. INR was recommended at 2.5.

Case 2

The second patient was a 62 years-old female. She was diagnosed with right lung adenocarci-

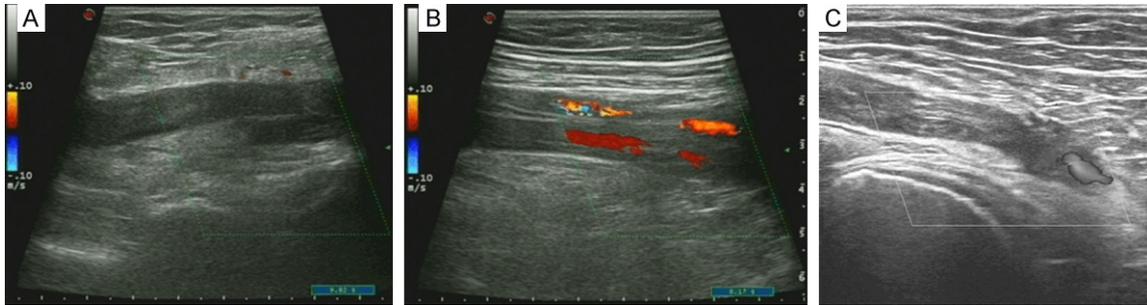


Figure 2. Results of ultrasound of lower limb blood vessels indicated venous thromboembolism in right popliteal vein (A); Results of ultrasound of lower limb blood vessels indicated venous thromboembolism with incomplete occlusion in left popliteal vein (B); Results of ultrasound of left upper limb blood vessels showed thromboembolism in a superficial vein of left upper limb (C).



Figure 3. Computed tomography angiography of pulmonary arteries indicated embolisms in two lower pulmonary arterial branches.

noma in situ in Shanghai Pulmonary Hospital and received wedge resection of lower lobe in on March 5th, 2015. After the surgery, symptoms of short of breath and chest tightness occurred in the patient. Computed tomography angiography (CTA) of pulmonary arteries indicated embolisms in two lower pulmonary arterial branches (**Figure 3**). After anticoagulation therapies were conducted in the patient, a second CTA was taken and showed no significant filling-defects in bilateral pulmonary arteries. The patient has a history of rheumatoid arthritis for 10 years and took methotrexate for a long term. Since 2010, she was diagnosed with coronary heart disease, acute myocardial infarction, and a double-vessel disease due to a continuous squeezing pain behind sternum. And the patient received repeating percutaneous coronary interventions (PCIs) and was implanted with five stents. After surgery, therapies of anticoagulation, anti-aggregation, dilation of coronary arteries were conducted in the patient. The patient has a history of hypertension for more than 20 years, with a high-

est hypertension of 150/100 mmHg. Zhenju Jiangya Tablet was taken to control the blood pressure with a good effect. Besides, the patient has a history of Diabetes Mellitus for three years, and acarbose was used to control blood sugar. The left eye of the patient was blind because of fundus hemorrhage 10 years ago. The patient denied histories of smoking, drinking and genetic diseases.

Physical examinations: Body temperature was 37°C, pulse was 90 beats/min, respiratory rate was 26 beats/min, and blood pressure was 110/70 mmHg. The patient has a poor mental state. He showed a mild anemic appearance. The left eye was blind. The patient presented no cyanosis or distension of jugular vein. A surgical scar was observed on lower right chest. The lung respiratory sounds were clear, respiratory sounds of right lower lung were low. Boarder of heart was normal. Heart rate was 90 beats/min. The heart rhythm was regular. P2 was not esthetic. No murmurs or pericardial friction sound were heard. Swan-neck deformities were observed in both hands. No swelling was palpated in both lower extremities. Cardiac ultrasonography indicated enlarged left ventricle with abnormal segmental left ventricular wall contraction activities, decreased left ventricular contraction activities, broadened pulmonary arteries of 28 mm with mild tricuspid regurgitation, normal systolic pulmonary artery pressure, and an ejection fraction of 0.47. Pulmonary perfusion imaging results showed reflective sparse distributions in posterior segment, lateral segment, and lateral basal segment in right lung. Corresponding laboratory results were shown in **Table 2**. A diagnose of pulmonary embolism was suspicious when

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Table 2. Laboratory results

Parameters	Value	Normal range	Parameters	Value	Normal range
WBC	6.8	4.3-9.8×10 ⁹ /L	IL-6	6.4	<5.9 pg/ml
PLT	342	125-350×10 ⁹ /L	IL-2R	284	223-710 U/ml
hs-CRP	3.9	<2.5 mg/L	Rheumatoid factors	1360	15.9I U/ml
PT	11.5	<12.1 s	CD3	71	50-84%
APTT	27	22.7-31.8 s	CD4	40.5	27-81%
INR	1.00		CD8	26.7	15-44%
Fb	4.27	2-4.5 g/L	NKCD16+CD56	20.8	7-40%
D-dimer	2.43	<1 mg/L	Integrin β2	98.6	71.1-95.8%
NT-pro-BNP	188.9	<100 pg/ml	TNF-α	12.8	<8.1 pg/ml

pulmonary ventilation imaging results were considered.

Diagnosis: The patient was diagnosed with pulmonary embolism, right lung adenocarcinoma in situ after surgery, coronary atherosclerotic heart disease, chronic anterior wall myocardial infarction after PCI, grade II cardiac function (NYHA), grade 2 hypertension in very high risk group, type 2 diabetes mellitus and rheumatoid arthritis. After definite diagnosis, the patient was then given oxygen, anticoagulants (low molecular heparin and clopidogrel), cardiotonic (digoxin), inhibitor of ventricular remodeling (metoprolol sustained-release tablet), and so on. After treatments, the symptoms improved. Patients were discharged after stabilization.

Discussion

In 1865, a French philosophy Armand Trousseau firstly reported a relationship between venous thrombus and tumor. Multiple articles reported that incidence of VTE in tumor patients are various from 4%-20%, which increased to 4-6 times of none tumor patients generally speaking [5, 6]. Pulmonary thrombi embolism is one of common complications and fatal causes in patients with malignant tumors, especially adenocarcinoma of lung tumors [7]. In 2009, Chuang et al. reported that genesis of VTE was related to not only cancer itself, but also risk factors like chemotherapy, perioperative period, tube in veins, immobilization, basic conditions etc. [8]. According to reports of Montreal, 2.2%-12% of tumor patients developed VTE two years before diagnoses of malignancies [9]. Unexplained VTE may be the first signal from malignant tumors. Mechanism of malignancies causing DVT is still unclear. Many researched indicated that it might be

related to hypercoagulability caused by tumors, abnormal malignant cells and anticoagulation system (decreased antithrombin and protein C system in tumor patients), and injuries of vessel walls caused by direct invasion and adhesion effects of tumor cells [10-12]. However, in this study, the first patient still developed recurrent venous thromboembolism under long-term anticoagulation, which is seldom reported at home and abroad. Many inflammatory markers have been confirmed to promote venous thromboembolism, and directly inhibit IL-6, IL-8, TNF-α and soluble P-selectin to reduce genesis and recurrence of VTE, and genesis of post-thrombotic syndrome. These two patients of this study had elevated IL-6, TNF-α, C-reactive protein as well as integrin β2. Integrins β2 (CD18), called leukocyte integrins, are mainly expressed on leukocytes. They can combine with different α subunits into leukocyte adhesion receptors, ligands of which are ICAM, iC3b, fibrinogen and so on [13-15]. Thus, it can be speculated that venous thromboembolism in patients with malignancies might be related to inflammations and immune dysfunctions, in which integrin β2 plays an important role in pathogenesis of VTE.

Conclusion

Once a patient with malignancy had PE, difficulty of treatment increases and prognosis worsens. Thus, early diagnosis and prevention turn out to be obviously important. Once patients with high risks developed unexplained dyspnea, chest pain, hemoptysis and hypoxemia, PE should be highly considered. As for suspicious VTE patients, an anticoagulation therapy should be conducted if there is no contraindication. It will be helpful for preventing and treating VTE patients to investigate how to

improve patients' immune status and to develop drugs inhibiting systemic inflammations.

Disclosure of conflict of interest

None.

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