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Case Report

VTE is the biophysical barrier preventing hematogenous metastasis of cancer cells: pathology of lung cancer tissue

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Abstract: Venous thromboembolism (VTE) forms when the filamentous mesh structure is filled with blood cells (mainly erythrocyte). It is the biophysical barrier that blocks hematogenous metastasis of cancer cells. However, only a few related cases have been reported to date. We here present two cases of lung adenocarcinoma with VTE, to explore the morphological characteristics of this barrier.

Keywords: Venous thromboembolism, lung cancer, metastasis

Introduction

Malignant tumor is a risk factor of VTE. Incidence of VTE in malignant tumor patients is 4 to 7 times higher than in non-malignant tumor patients [1-3]. Risk of VTE in metastasis malignant tumor patients is 5-13 times higher than in non-metastasis patients [4-6]. VTE is the second cause of death in patients with malignant tumor [3, 4, 7].

Lung cancer has the highest incidence and mortality among all malignant tumors. It is also one of the highest incidences of VTE. The main pathological types of lung cancer are adenocarcinoma and squamous carcinoma. We previously reported VTE originated from balance function collapse of systemic immune cells [8], and VTE is the intravenous defense mechanism triggered by alien antigen cells. It has been reported that fibrinogen is the main composition of VTE [9, 10]. Thrombosis core protein-integrin receptor β2, β3 subunits combines with ligands such as fibrinogen, constituting the filamentous mesh structure, and blood cells are stagnated in the structure, thus venous red thrombosis forms. Immunohistochemistry study of bowel cancer pathology showed that VTE might be the inevitable outcome of the malignant tumor proliferation period [11]. In this study, we report postoperative pathological of lung cancer and morphological characteristics of tumor intravenous emboli formation.

Case report

Two patients with lung adenocarcinoma were selected. A 61-year-old male patient with CT diagnosis of lung cancer with mediastinal lymph node metastasis and preoperative clinical diagnosis of right lung cancer with lymph node metastasis in hilus of lung, was performed right pneumonectomy. Postoperative pathological examination showed a 4.0*2.0*1.5 cm gray mass, and two pieces of gray nodules were 2 cm apart from the mass, 1.5*1.0*1.0 cm and 1.3*1.0*0.5 cm, respectively. Pathologic diagnosis: right lung invasive adenocarcinoma (entity mainly associated with mucus product subtype); 6/7 cancer metastasis in lymph node; postoperative TNM staging at T2aN2M0. A 57-year-old female patient with CT diagnosis of lung cancer with mediastinal lymph node metastasis was performed right lower lung cancer resection. Postoperative pathological examination showed a 4.5*3.5*3.5 cm mass. Pathological diagnosis: lower right lung invasive adenocarcinoma (entity adenocarcinoma with

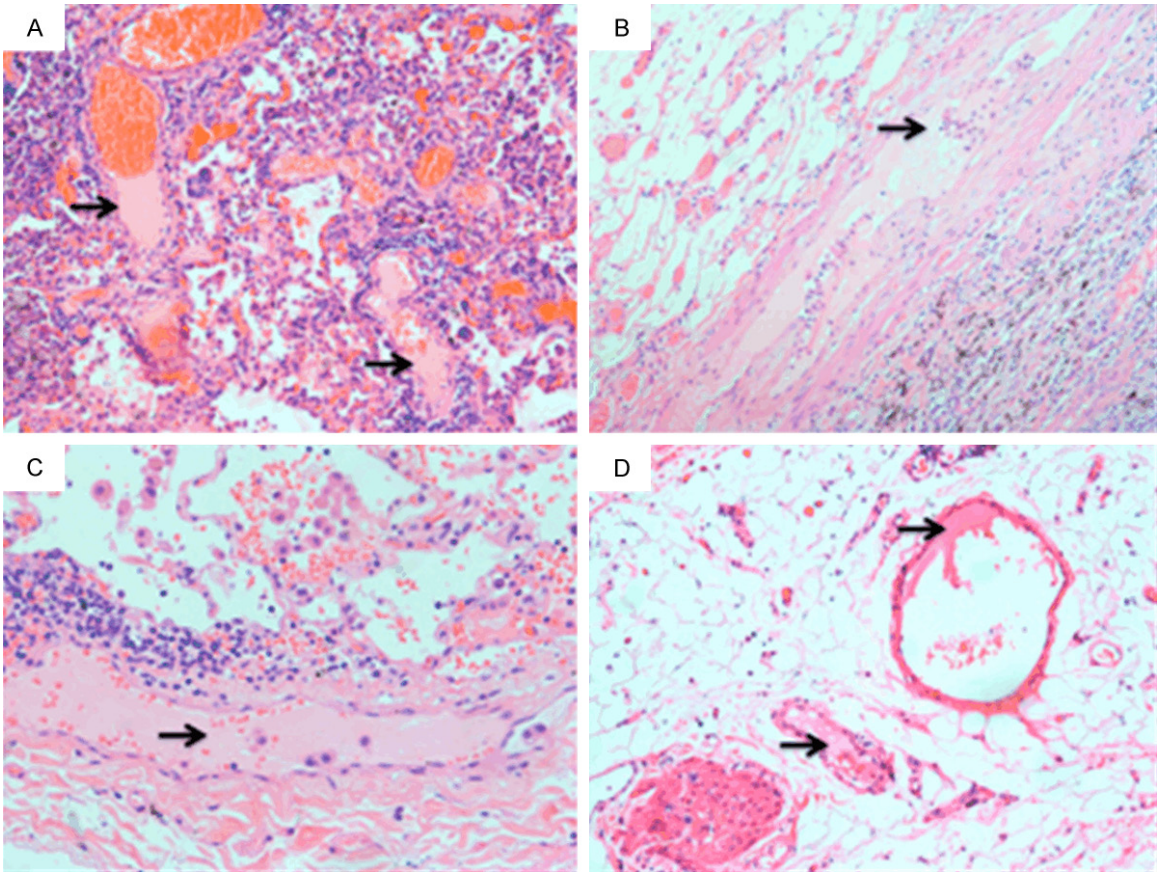

Figure 1. Arrows in (A-D) indicate acidophilic fibrin/fibrinogen, which is pink with HE staining: There is intravenous fibrin/fibrinogen depositionin (A-D), which is indicated by the arrows. Blood cells such as red blood cells can be observed in fibrin/fibrinogen deposition veins. Fibrin/fibrinogen is connected to the vein intima (D). (A) HE×200, (B) HE×100, (C) HE×200, (D) HE×100.

mucus secretion (70%), papillary type 20%, gland bubble type (10%)); extensive vascular tumor emboli formation; inside lung metastasis invasion of the upper and lower leaves; no cancer invasion in pleural; 8/9 cancer metastasis of bronchi lymph node; postoperative TNM staging at T2aN1M0.

Hematoxylin eosin (HE) staining

Postoperative tissue specimens of 2 cases were fixed by 10% formalin solution, embedded by paraffin, and serial sectioned at 4 um thick, then stained by HE.

Result showed that there was fibrin deposition in the venules in and around lung cancer tissue, and some deposition even filled the lumen. There was filamentous mesh structure in the fibrin. The structure blocked blood cells such as red blood cells, thus small thrombosis formed. The fibrin deposition was linked to blood vessel walls (**Figure 1**).

Fibrin/fibrinogen deposition in venule was presented as filamentous mesh structure, and was connected to the vascular intima. Cancer cells were blocked by fibrin/fibrinogen filamentous mesh structure, and the blocked cancer cells in the structure grew like nests and tumor emboli formed (**Figure 2**).

Discussion

Intravenous tumor emboli in lung cancer tissues in this paper were diagnosed under the microscope after surgery, while no tumor embolus was found in clinical preoperative and CT imaging examination, indicating that tumor embolus is latent.

There is intravenous fibrin/fibrinogen deposition, and filamentous mesh structure formed by which in lung cancer tissue (**Figure 1A-D**). The filamentous mesh structure blocks cancer cells, thus preventing the metastasis of cancer cells.

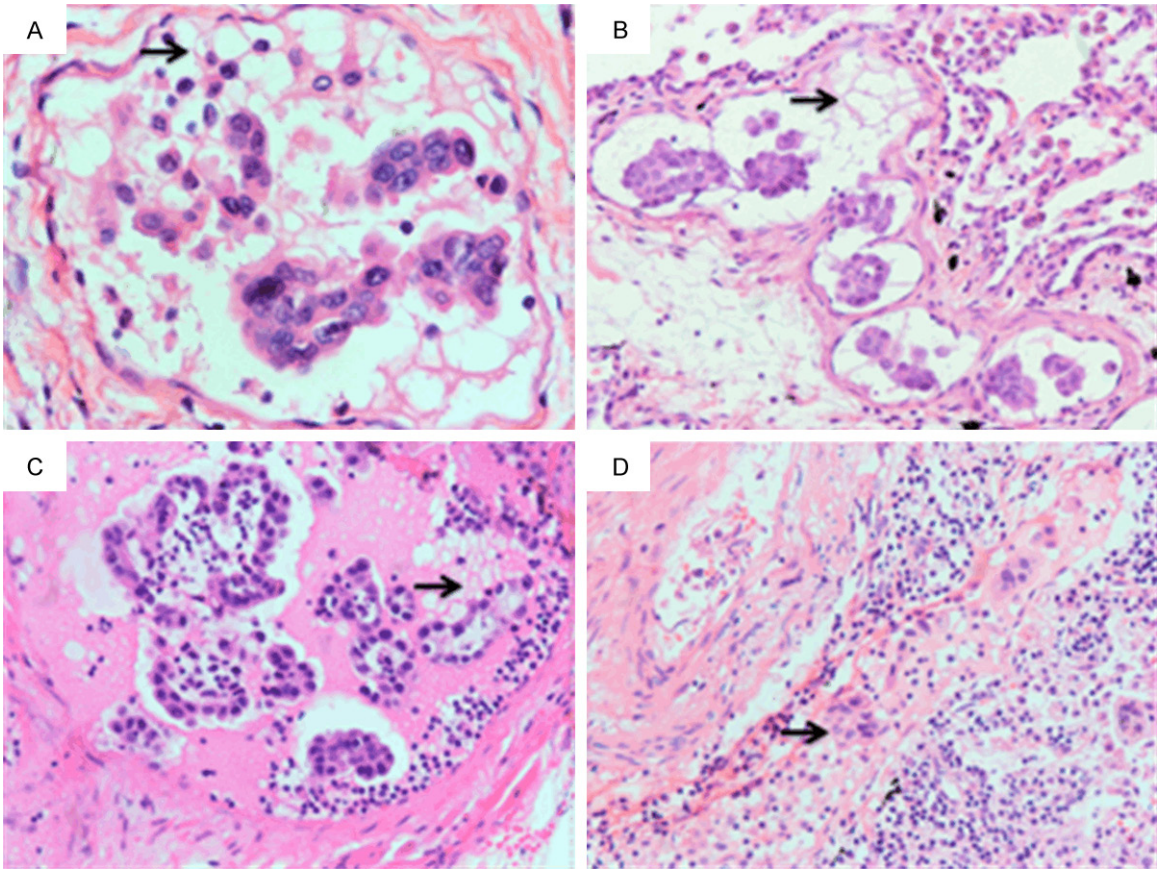

Figure 2. A. Cross-section of the vein. There is fibrin/fibrinogen filamentous mesh structure, trachychromatic nucleuses packaged by fibrin/fibrinogen, and various shapes of the nests of cancer cells. HE×400; B. Intravenous fibrin/fibrinogen filamentous mesh structure is linked with vascular intima. The nucleuses of nests of cancer cells are trachychromatic (arrow). HE×200; C. Venous cavity is filled with fibrin/fibrinogen filamentous mesh structure, and nests of cancer cells can be observed. HE×200; D. There is fibrin/fibrinogen filamentous mesh structure in intravenous profile. The nucleuses of nests of cancer cells are trachychromatic (arrow). HE×100.

Fibrinogen deposition transfers into fibrin, forming the barrier to prevent cancer cells from metastasizing in the surrounding of cancer cells. It has been confirmed that fibrin exists in primary lung cancer and metastatic carcinoma using electron microscopy and immunochemistry. Fibrin can wrap primary tumor cells, inhibit tumor cells from escaping, and also produce stable skeleton structure in the extracellular matrix of tumor [12]. Intravenous fibrinogen in cancer tissue generates filamentous mesh structure, which constructs another barrier preventing cancer cells from metastasizing. The barrier is the expression of physical defense function. The filamentous mesh structure can prevent hematogenous metastasis of cancer cells, and also prevent the reverse flow of blood cells. When the filamentous structure is filled with blood cells (mainly erythrocyte), VTE occurs, and the filamentous mesh structure transfers from defense to disease.

The proliferation of cancer cells is faster than the growth speed of small vessels, thus ischemic necrosis tends to happen, which is characterized by vascular permeability increase and small blood vessels damage. Malignant tumor invades small vessels (mainly small veins), causing the small vessels burst and the metastasis of cancer cells. VTE constitutes the biological physical barrier blocking the hematogenous metastasis of cancer cells. Results in this paper are consistent with the immunohistochemistry study of colorectal cancer pathology that we previously reported [11]: VTE is the biological physical barrier preventing hematogenous metastasis of cancer cells. Therefore, VTE can be considered as the inevitable outcome in the cancer cell proliferation period.

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Disclosure of conflict of interest

None.

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