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Original Article

Venous thromboembolism is a product in proliferation of cancer cells

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Abstract: The pathogenesis of venous thromboembolism (VTE) in patients with cancer is related to the destruction of small veins and the intravenous formation of filamentous mesh-like structure by fibrinogen. The filamentous mesh-like filter can block hematogenous metastasis of cancer cells and also can stagnate blood cells, leading to venous thrombosis. Cancer cells have characteristics of malignancy and fast proliferation, and ischemic necrosis frequently occurs, and small veins were invaded and damaged. The formation of filamentous mesh-like structure has defense function and also may cause the occurrence of VTE. VTE is a product of the proliferation process of malignant cells.

Keywords: Venous thromboembolism, cancer, filter

Introduction

Venous thromboembolism (VTE) including deep vein thrombosis (DVT) and pulmonary embolism (PE) is a globally common disease with high prevalence. Malignancy is one of risk factors of VTE. The prevalence of VTE in patients with malignancy is 4-7 times higher than that of patients without malignancy [1, 2]; the survival time of malignancy patients with concomitant VTE is also 2-3 times shorter than that of malignancy patients without VTE [3]. There is evidence showing that about 10-25% of patients with idiopathic VTE as initial symptoms were diagnosed as malignancy within 2 years, and most of them are diagnosed as malignancy within 6 months. Moreover, the incidence of VTE is increased by 4 times after confirmed diagnosis of malignancy [4]. VTE is not only a common complication of malignancies, but the second cause of cancer related death [5]. Why have malignancy patients had a high incidence of VTE? The reason is still unclear.

Case report

An 83-year-old male received surgical intervention due to adenocarcinoma of the sigmoid colon. An 84-year old male underwent surgical intervention due to gastric cancer. HE staining and immunohistochemistry for fibrinogen (rabbit anti-human fibrinogen antibody [ab34269] abcam, 1:100) were performed to observe the cancer cells and tissues.

In the acute venous thrombus, the filamentous mesh-like structure formed by dark brown fibrinogens was identical to the filamentous mesh-like structure in the veins of cancers (**Figure 1**). This suggests that the pathogenesis of VTE in patients with cancer is related to the destruction of small veins and the intravenous formation of filamentous mesh-like structure by fibrinogen.

Our study showed the exudation of a large amount of red blood cells and a large amount of fibrinogens deposit in cancer tissues (**Figures 2**, **3**). These suggest the cancer tissues damage small veins and/or increase in vascular permeability, which are characterized by hemorrhagic inflammation and fibrous inflammation. The small veins contain filamentous mesh-like structure formed by fibrinogens in which cancer cells were found. This structure significantly interfered with the migration of cancer cells.

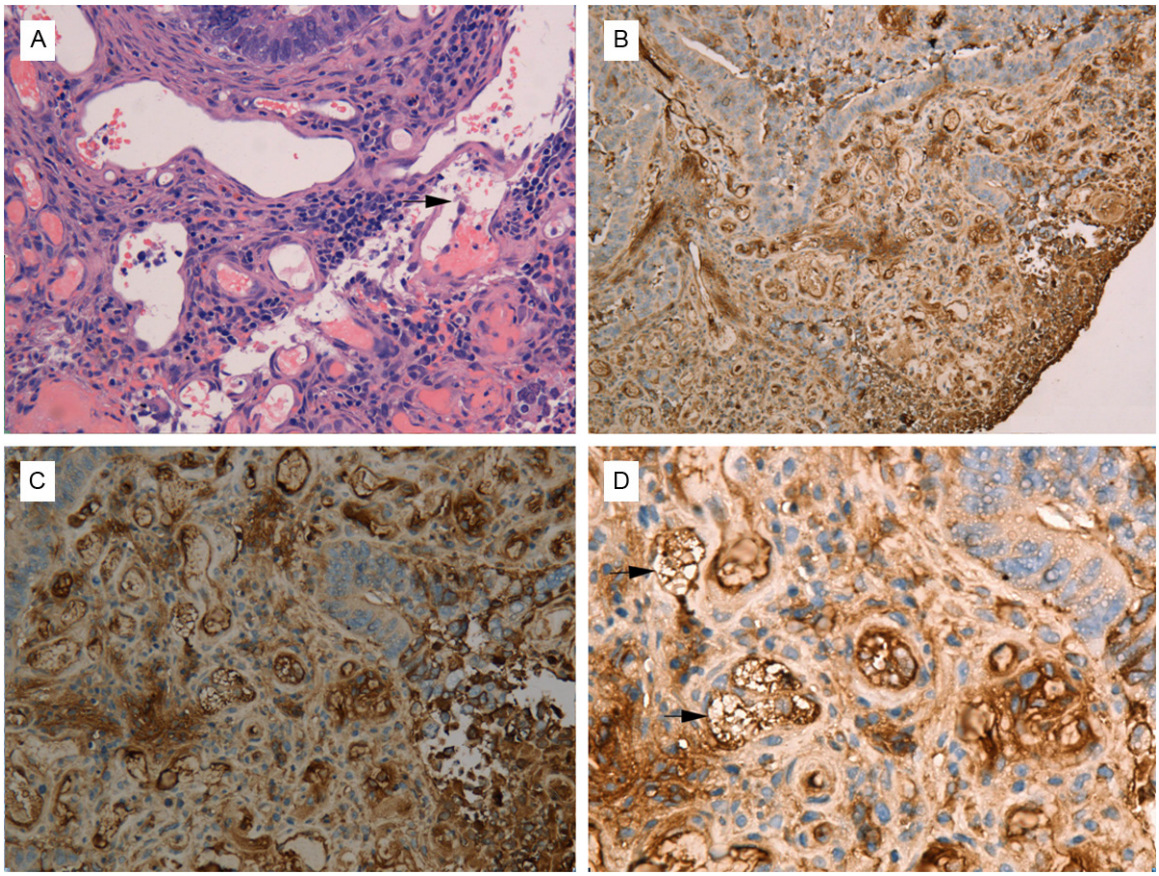

Figure 1. A. Necrosis, granulation tissues, angiogenesis of capillaries and small veins in sigmoid colon adenocarcinoma; →disruption of small veins, and red blood cells and eosinophilic protein-like substances in venous vessels (HE, ×200). B. Immunohistochemistry showed dark brown fibrinogens deposited in venous wall (×200). C. Dark brown fibrinogens deposited around cancer tissues (×200). D. →, Dark brown fibrinogens in veins formed mesh-like structure (×400).

Discussion

Fibrinogens convert to fibrins and deposit around cancer cells to form a barrier to block metastasis of cancer cells, which inhibit the migration of cancer cells. Electric microscopy and immunohistochemistry demonstrated the presence of fibrin in the primary cancer and metastatic cancer. These fibrins capsulated the primary cancer cells to inhibit the escape of cancer cells. In addition, these fibrinogens also formed stable skeleton in the extracellular matrix of cancer cells [6]. In the cancer, the intravenous fibrinogen formed mesh-like structure which becomes a barrier inhibiting the migration of cancer cells. The mesh-like structure not only inhibits the hematogenous metastasis of cancer cells, but blocks the back-flow of blood cells. The red blood cell dominant blood cells filling the mesh-like structure may cause VTE, which indicates the shift from defense to the opposite side.

Our previous study showed the main protein component of acute venous thrombi was fibrinogen [7]. Fibrinogens and fibrins constitute mesh-like structure, which becomes a nested-like filter in the veins (**Figure 3C**). The blood cells stay in the filter forming red thrombi (**Figure 3D**). The intravenous mesh-like structure in cancer tissues was consistent with the mesh-like structure in the venous red thrombi, as demonstrated by morphological examination and immunohistochemistry.

The proliferation of cancer cells is usually faster than the growth of small blood vessels. Thus, the cancer is susceptible to ischemic necrosis, which is characterized by increase in vascular permeability and disruption of small blood vessels. The malignant tumor may invade the small blood vessels (mainly the small veins), which may also destroy the small vessels. Autopsy of patients with malignancies showed 50% of patients developed concomitant VTE [8]. We

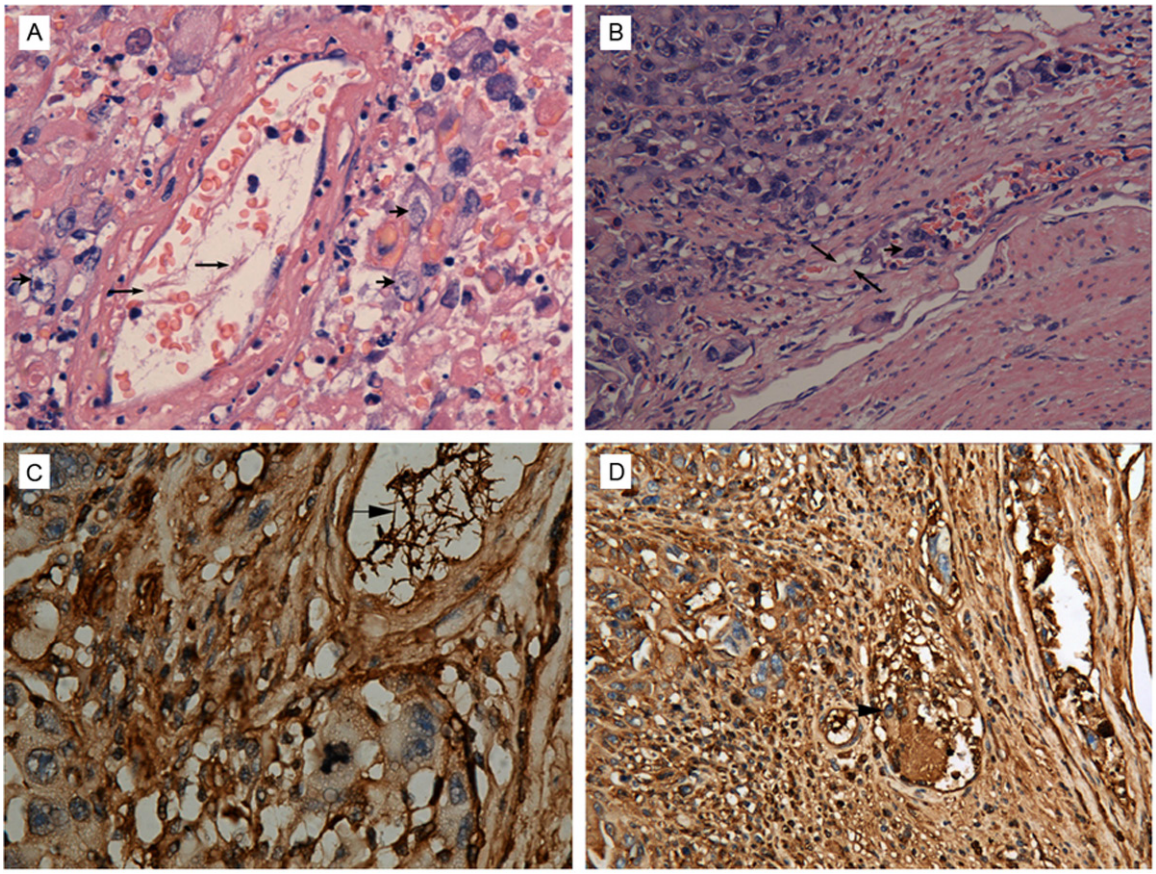

Figure 2. A. Necrotic region in poorly differentiated gastric carcinoma presented with exudation of a large number of red blood cells. →red blood cells and eosinophilic filamentous protein-like substances in veins; →cancer cells with nuclear atypia surrounding veins (HE, ×400); B. Dark brown fibrinogens in cancer tissues; →cancer embolus in veins (HE, ×200). C. Filamentous mesh-like dark brown fibrinogens in veins of cancer tissues (×400); D. Dark brown fibrinogens formed mesh-like structure which interfered with hematogenous metastasis of cancer cells (×200).

speculated that the prevalence of VTE in malignancy patients was higher than 50%. The morphological characteristics of proliferative cancer cells increase the risk for VTE in cancer patients, but the VTE may not be identified in early phase.

About 10-25% of VTE patients are diagnosed as malignancy within 2 years after diagnosis of VTE. Thus, patients with VTE of unknown cause might be candidates of occult cancer with VTE as a first symptom [8, 9]. This is of important significance for the diagnosis of cancer. On one hand, the cancerous VTE and non-cancerous VTE patients have obvious differences in the treatment, risk for VTE recurrence and survival time; on the other hand, malignant tumor may be diagnosed in an early phase due to the occurrence of VTE as an alarm, which promotes early diagnosis. On the basis of above findings, the National Institute for Health and Clinical Excellence in England developed a CG144 guideline in 2012 which recommends the screening of malignant tumors in patients older than 40 years and with idiopathic VTE [9]. Roekshana regarded it as a milestone in the prevention and treatment of VTE [8].

Malignancy patients with concomitant VTE have identical nature in the occurrence of VTE to the occult cancer patients with VTE as an initial symptom. In these patients, VTE serves as a product in the proliferation process of cancer cells and a result of focal fibrous inflammation after the disruption of small veins in cancers.

Acknowledgements

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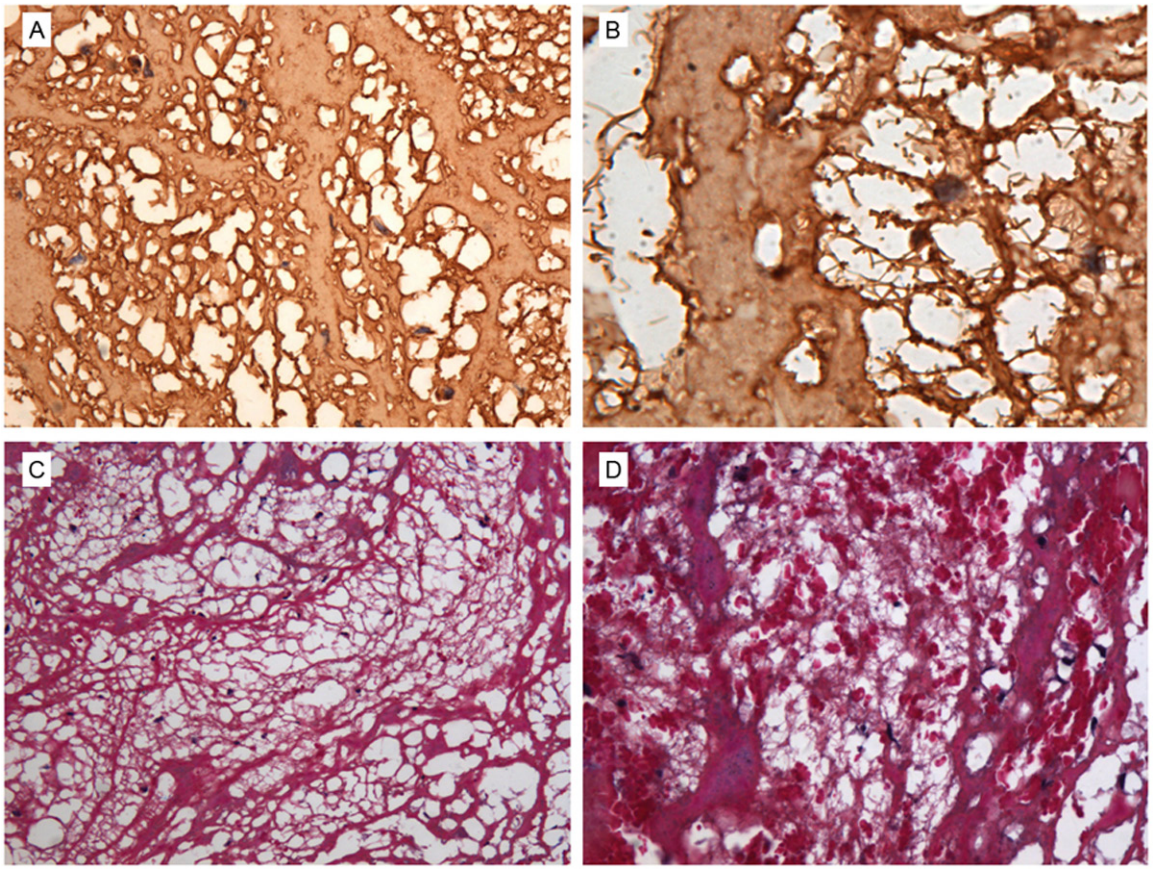

Figure 3. A. Immunohistochemistry for fibrinogens in acute venous thrombus. Dark brown fibrinogens formed filamentous mesh-like structure (×400). B. Amplification of filamentous mesh-like structure (×1000). C. Masson staining of thrombus (×400), and filamentous mesh-like structure as a venous filter. D. Red blood cells in filamentous mesh-like structure (Masson staining, ×400), and formation of red thrombus.

Disclosure of conflict of interest

There is no conflict of interest to disclose.

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