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TEACHING CASES

Pulmonary tumor thrombotic microangiopathy caused by an ovarian cancer expressing tissue factor and vascular endothelial growth factor

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Abstract

Pulmonary tumor thrombotic microangiopathy (PTTM) is a rare clinicopathologic entity causing severe pulmonary hypertension, right-side heart failure, and sudden death. Its histologic features include widespread tumor emboli of the small arteries and arterioles of the lung, associated with thrombus formation and fibrocellular and fibromuscular intimal proliferation. The most frequent causative neoplasm for PTTM is gastric cancer, but lesions in other organs, including the ovary, have been occasionally identified as primary causes. Detailed molecular mechanisms underlying PTTM remain unclear, but some studies have suggested that tissue factor (TF) and vascular endothelial growth factor (VEGF) expressed by tumor cells may be involved in the pathogenesis for cases of gastric cancer. However, little is known about these molecules in PTTM caused by neoplasms of non-gastric origin.

Here, we report the autopsy findings of a 42-year-old woman with ovarian cancer showing positive immunoreactivity for both TF and VEGF who died suddenly of PTTM. The present case provides support for the conclusion that these factors may be involved in the pathogenesis of PTTM, independent of the causal neoplasm.

Keywords: Pulmonary tumor thrombotic microangiopathy; Vascular endothelial growth factor; Tissue factor; Ovarian cancer; Sudden death

Introduction

Pulmonary tumor thrombotic microangiopathy (PTTM) is a rare clinicopathologic entity that may cause severe pulmonary hypertension, right-side heart failure, and sudden death. Its histologic features include widespread tumor emboli of small arteries and arterioles of the lung associated with thrombus formation and fibrocellular and fibromuscular intimal proliferation [28]. A number of clinicopathologic features have attracted attention [6]: (1) the most common neoplasm associated with PTTM is adenocarcinoma, especially of poorly differentiated type, (2) the most frequent primary site is the stomach, (3) not only old, but also young persons are affected, and (4) antemortem diagnosis is very difficult.

Tumor emboli in PTTM do not occlude the vessels directly but activate the coagulation system, leading to the lesional complexes mentioned above [21]. Although the number of reported cases with PTTM is increasing [2–7,9,11–17,19–23,28,29], detailed molecular mechanisms of PTTM remain elusive. However, a number of studies have demonstrated expression of tissue factor (TF) and/or vascular endothelial growth factor (VEGF) by tumor cells in PTTM cases [6,20,22,23]. In addition, VEGF is known to be regulated by TF [1,8,25] and to

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play a pathogenetic role in the development of various forms of pulmonary hypertension [10,18,26]. In a case of PTTM documented by Miyano et al. [20], normalization of the serum level of VEGF after antitumor chemotherapy resulted in a favorable clinical outcome. The evidence thus indicates that these factors, in particular VEGF, may play important roles in the pathogenesis of PTTM. Although their expression has been demonstrated in gastric cancer cases, little information is available for the neoplasms of non-gastric origin.

Here, we report an autopsy case of a 42-year-old woman with a history of ovarian cancer presenting with sudden death. The autopsy revealed PTTM together with macroscopic pulmonary thromoboembolism, and ovarian cancer was found to be positive for TF and VEGF immunohistochemically.

Case report

A 39-year-old Japanese woman developed a left ovarian tumor, and bilateral adnexectomy with hysterectomy was performed in 2001. Pathologic examination revealed a clear cell adenocarcinoma of the left ovary. After the surgery, chemotherapy with paclitaxel and carboplatin was conducted, and she remained in good condition for 14 months. In January 2003, however, she exhibited ascites, and chemotherapy with the same regimen was conducted after clinical diagnosis of cancer relapse. Multiple intra-abdominal masses became apparent, and the diagnosis of peritonitis carcinomatosa was rendered in November 2003. In January 2004, at the age of 42, she called by herself, complaining of mild fever and nausea and left a message that she intended to visit our hospital. However, she was found in a state of cardiopulmonary arrest 40 min later and was transferred to our hospital. Cardiopulmonary resuscitation was not successful. A postmortem examination was performed 15 h after death.

Materials and methods

Formalin-fixed, paraffin-embedded tissue sections were routinely stained with hematoxylin–eosin and elastica van Gieson where appropriate. Immunohistochemistry was performed on formalin-fixed, paraffin-embedded tissue sections with antibodies against VEGF (sc-152; dilution 1:400, Santa Cruz Biotechnology, Santa Crus, CA, USA) and TF (dilution 1:100; American Diagnostica, Stamford, CT, USA) using a DAKO ChemMate Envision kit (DakoCytomation, Copenhagen, Denmark). Autoclave antigen retrieval was carried out for the TF immunostaining.

Pathologic findings

The surgically resected left ovary featured a multicystic tumor, including a solid part, measuring $23 \times 14 \times 10$ cm, showing hemorrhage and necrosis. Microscopically, the tumor exhibited both tubular and

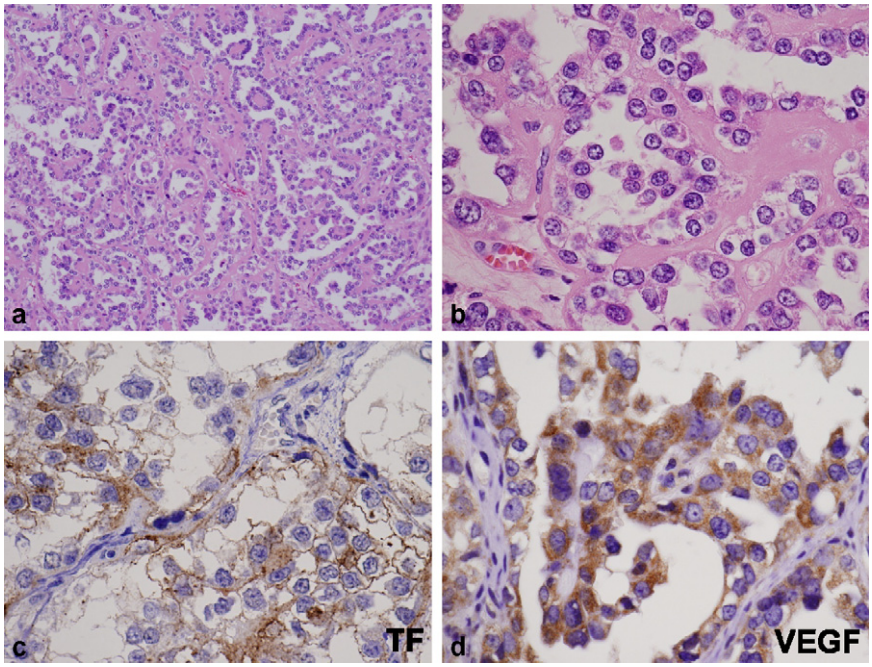

Fig. 1. Microscopic findings for the left ovarian tumor. The clear cell adenocarcinoma with characteristic hobnail cells demonstrates tubular and papillary structures (a, hematoxylin–eosin, original magnification $\times 100$). Clear cells and hobnail cells are supported by hyalinized stroma (b, hematoxylin–eosin, original magnification $\times 400$). Cancer cells are immunohistochemically positive for tissue factor (c, original magnification $\times 400$) and vascular endothelial growth factor (d, original magnification $\times 400$).