The Potential Role of Inflammation Associated with Interaction between Osteopontin and CD44 in a Case of Pulmonary Tumor Thrombotic Microangiopathy Caused by Breast Cancer

Akifumi Higashi¹, Yoshihiro Dohi¹, Naohiro Uraoka², Kazuhiro Sentani³, Sayuri Uga¹, Hiroki Kinoshita¹, Yoshiharu Sada¹, Toshiro Kitagawa¹, Takayuki Hidaka¹, Satoshi Kurisu¹, Hideya Yamamoto¹, Wataru Yasui² and Yasuki Kihara¹

Abstract

Pulmonary tumor thrombotic microangiopathy (PTTM) is a rare and fatal cancer-related complication. We herein present a case of PTTM that diagnosed antemortem by lung scintigraphy and pulmonary microvascular cytology. The patient was treated with steroid pulse therapy. Although her symptoms temporarily improved, she died of respiratory failure. An autopsy showed PTTM, and an immunohistochemical analysis revealed the expression of osteopontin and CD44 in macrophages that had migrated into the PTTM lesions. These findings suggest that inflammation associated with the interaction between osteopontin and CD44 may play an important role in PTTM.

Key words: pulmonary tumor thrombotic microangiopathy, pulmonary hypertension, osteopontin, CD44

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Introduction

Pulmonary tumor thrombotic microangiopathy (PTTM), which was first identified by von Herbay et al. in 1990, is a complication related to malignant tumors (1). PTTM is histologically characterized by microscopic tumor cell emboli, fibrocellular and fibromuscular intimal proliferation in the pulmonary small arteries and arterioles, and fibrin thrombi from the local activation of coagulation, which result in vascular stenosis (2, 3). Clinically, patients with PTTM present with pulmonary hypertension, right cardiac failure, and sudden death. We herein report a case of PTTM associated with breast cancer.

Case Report

The patient was a 66-year-old woman who had a history of dermatomyositis, drug-induced interstitial pneumonia, and superior vena cava thrombosis. She took steroids and anticoagulants orally. In 2010, left breast cancer was diagnosed, and a left mastectomy and axillary lymph node dissection were performed. She then underwent postoperative chemotherapy with paclitaxel, TS-1, and capecitabine. She regularly visited the clinic for follow-up. In July 2012, positron emission tomography/computed tomography (CT) and skin biopsy demonstrated metastases in the bilateral hilar lymph nodes, bone, and skin. In October 2012, she was admitted for exertional dyspnea and dry cough that had persisted for 1 month. On presentation, she was tachycardiac (105 bpm) and normotensive, and her oxygen saturation in room air was 93%. CT showed infiltrative shadows, septal thickening in the lung, and no evidence of pulmonary thromboembolism (data not shown). Transthoracic echocardiography indicated pulmonary hypertension with a D-shaped left ventricle and severe tricuspid regurgitation; the estimated gradient...
pressure was approximately 80 mmHg (Fig. 1a). Lung scintigraphy showed multiple subsegmental perfusion defects, which suggested microvascular disease (Fig. 1b). A right heart catheter showed pulmonary hypertension with a systolic pulmonary pressure of 74 mmHg, a mean pulmonary pressure of 47 mmHg, a pulmonary vascular resistance of 11.6 WU, and a pulmonary artery wedge pressure of 9 mmHg. Malignant cells that were found in the pulmonary microvascular cytology, and drawn through a wedged pulmonary catheter (Fig. 1c), showed PTTM. We started treatment for pulmonary hypertension and right heart failure with endothelin antagonists, a phosphodiesterase type 5 inhibitor, and diuretics. However, she developed a dry cough and hypoxia, and her urine volume decreased (approximately 3,000 mL/24 h). The favorable condition and focal hypercoagulability, resulting in luminal stenosis and obstruction in the small pulmonary arteries (1, 2, 4). We achieved a response that was confirmed by CT on the 26th hospital day demonstrated new irregular shadows (Fig. 1d). Computed tomography after steroid pulse therapy shows improvement of the shadows (e).

Discussion

PTTM is a rare condition that is observed in the autopsies of 0.9-3.3% of patients with malignant tumors. PTTM is histologically characterized by fibrocellular intimal proliferation and focal hypercoagulability, resulting in luminal stenosis and obstruction in the small pulmonary arteries (1, 2, 4). The most frequent primary site associated with PTTM is the stomach, followed by the lungs, breast, ovaries, bladder, and esophagus. The most common tissue type is adenocarcinoma, particularly mucinous or signet-ring cell carcinoma (1, 2, 5).

PTTM is associated with a poor prognosis and most cases are diagnosed at autopsy. In some cases, the antemortem
pathological diagnosis of PTTM is made by lung biopsy (6). In the present report, we reached an antemortem diagnosis by pulmonary microvascular cytology using samples that were drawn through a wedged pulmonary catheter. Pulmonary microvascular cytology is considered to be a useful alternative to lung biopsy for patients who are already presenting with either severe hemodynamic or respiratory distress (7).

Previous studies have suggested that the cytokines produced by tumor cells, such as platelet-derived growth factor, VEGF, tissue factor, and OPN, play important roles in the pathogenesis of PTTM. OPN promotes the adhesion, migration, and proliferation of cells, such as fibroblasts, vascular endothelial cells, and smooth muscle cells, integrins and CD44, which are OPN receptors (8). Takahashi et al. (9) reported a case of PTTM with OPN expression and suggested that the interaction of ανβ3 with OPN integrin is associated with fibrocellular intimal proliferation and thrombus formation. CD44 is a cell adhesion molecule, which contributes to inflammation, autoimmune diseases, angiogenesis, atherosclerosis, and tumor metastases. The overexpression of OPN and CD44 is correlated with the progression and metastasis of cancer (10). However, the interaction of OPN with CD44 is also considered to be associated with inflammatory processes, such as the chemotaxis and haptotaxis of T cells and macrophages (8). Several reports have demonstrated that the infiltration of inflammatory cells, such as T cells and macrophages, plays an important role in the pathogenesis of pulmonary hypertension (11). In the present case, the expression of OPN and CD44 was detected in tumor cells, as well as in the macrophages that had migrated into the PTTM lesions. Crawford et al. (12) reported that tumor-derived OPN inhibited the function of macrophages and enhanced the growth and survival of metastases, while host-derived OPN functioned as a macrophage chemoattractant. Our study suggests that recruitment of macrophages causes inflammation in the PTTM lesions, and that the interaction between OPN and CD44 might be responsible for not only the formation of metastases, but also for development of intimal proliferation and local inflammation.

Although no effective treatment for PTTM has been established, several reports have suggested that the prognosis of PTTM that is diagnosed at an early stage can be improved by systemic chemotherapy (6). Our patient’s symptoms were temporarily resolved with steroid pulse therapy. Local inflammation may play a major role in the development of PTTM, and anti-inflammatory treatments, such as steroid pulse therapy, might be useful. In PTTM, pulmonary

Figure 2. The immunohistochemical analysis of α-smooth muscle actin (α-SMA; a: original magnification ×10), CD68 (b: original magnification ×40), CD44 (c: original magnification ×40), and osteopontin (OPN; d: original magnification ×40) in serial sections of pulmonary tumor thrombotic microangiopathy (PTTM) lesions. Proliferating intimal cells were positive for α-SMA (a). CD68-positive macrophages were identified in PTTM lesions (b). CD68-positive macrophages were positive for CD44 (b, c; arrowheads). CD68-positive macrophages were also positive for OPN (b, d; arrows).
vasoconstriction, which may be induced by the migration of macrophages, would be limited by steroid therapy.

In summary, PTTM is a rare pulmonary complication related to malignant tumors. Clinically, PTTM is rapidly progressive and is associated with a poor prognosis. Pulmonary microvascular cytology may allow for its early diagnosis and treatment. Pulmonary vasoconstriction, which is caused by inflammation associated with an interaction between OPN and CD44, may therefore be a factor involved in the development of PTTM.

The authors state that they have no Conflict of Interest (COI).

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