Platelet-Derived Growth Factor Receptor-Tyrosine Kinase Inhibitor, Imatinib, Is Effective for Treating Pulmonary Hypertension Induced by Pulmonary Tumor Thrombotic Microangiopathy

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SUMMARY

Pulmonary hypertension (PH) induced by pulmonary tumor thrombotic microangiopathy (PTTM) can be fatal because its rapid progression confounds diagnosis, and it is difficult to control with therapy. Here we describe a woman with symptomatic PTTM-PH accompanying gastric cancer that was suspected from perfusion scintigraphy. PTTM-PH was diagnosed by gastroesophageal endoscopy and lung biopsy after partial control of PH using the platelet-derived growth factor (PDGF) receptor (PDGFR) tyrosine kinase inhibitor, imatinib. Treatment with sildenafil and ambrisentan further decreased PH, and she underwent total gastrectomy followed by adjuvant TS-1 chemotherapy. PH did not recur before her death from metastasis. Postmortem histopathology showed recanalized pulmonary arteries where the embolized cancer masses disappeared. PDGF-A, -B, and PDGFR-α, β expression was detected in cancer cells and proliferating pulmonary vascular endothelial cells. Thus, PTTM-PH was successfully controlled using a combination of imatinib, drugs to treat pulmonary arterial hypertension, and cancer management. (Int Heart J 2015; 56: 245-248)

Key words : Circulatory disturbance, Cancer, Treatment

Pulmonary tumor thrombotic microangiopathy (PTTM) is an uncommon disease and sometimes accompanies pulmonary hypertension (PTTM-PH). PTTM-PH is directly caused by multiple microthrombi of cancer cells surrounded by fibrotic intimal cell proliferation and/or indirectly due to vascular remodeling mediated by growth factors such as platelet-derived growth factor (PDGF), vascular endothelial growth factor, and osteopontin that are released by cancer cells. Because PTTM-PH progresses rapidly, it is rarely diagnosed before autopsy. Therefore, PTTM-PH is not managed, and patients survive 1–3 months after symptoms appear.

CASE REPORT

In September 2011, a 64-year-old woman was admitted to our hospital with the main complaints of persistent cough, progressing dyspnea, and a 10-kg weight loss during the previous 3 months. Because the electrocardiogram showed right axis deviation and right ventricle hypertrophy (Figure 1A) and echocardiography revealed a markedly elevated right ventricular systolic pressure (85 mmHg) and a significantly dilated right ventricle with a counter-compressed left ventricle (Figure 1C), she was diagnosed with pulmonary hypertension (PH) and immediately admitted. A pulmonary perfusion scintigram showed diffuse and peripheral perfusion defects (Figure 2A) indicating diffuse micro-occlusions of pulmonary arteries (PA). Neither contrast-computed tomography nor pulmonary arteriogram detected a thrombus. Right heart catheterization confirmed severe PH (Figure 3), suggesting PTTM-PH.

Gastroesophageal endoscopy detected early gastric cancer that was characterized as a poorly differentiated adenocarcinoma involving signet-ring cells. After PH was controlled using imatinib (Figure 3), video-assisted thoracic surgery was performed to acquire a lung biopsy. Histopathology revealed that a considerable number of the small PA were occluded by gastric cancer cells (GCC) and organized tissue that included proliferating vascular intimal cells (Figure 4A). While PH was further controlled with sildenafil and ambrisentan combined with imatinib, she underwent total gastrectomy followed by adjuvant chemotherapy with TS-1 (Figure 3). In January 2012, her hemodynamic parameters were normal, including arterial oxygen-saturation (Figure 3) and the diffuse pulmonary perfusion defects (Figure 2B). The abnormal electrocardiogram...
Figure 1. Electrocardiogram and Echocardiogram. A, B: The electrocardiogram at admission (A) shows right axis deviation and right ventricle hypertrophy. At discharge, these findings were normalized (B). C, D: The short-axis view of the echocardiogram at admission (C) demonstrates dilatation of a right ventricle with a counter-compressed left ventricle. These findings were not seen at discharge (D).

Figure 2. Pulmonary Perfusion Scintigraphy. A: Pulmonary perfusion scintigram shows diffuse peripheral perfusion defects, suggesting diffuse and peripheral occlusions at the level of the small PA. B: Pulmonary perfusion defects are undetectable in the scintigram performed after hemodynamic normalization, suggesting reperfusion of the occluded PA.

Figure 3. Clinical course during hospitalization. The initial and sequential administration of tadalafil and imatinib decreased mean pulmonary arterial pressure (mPAP) and pulmonary vascular resistance (PVR). Although administration of tadalafil was discontinued due to congestion suspected from the results of X-ray, mPAP was maintained below 40 mmHg in the presence of imatinib. The sequential addition of sildenafil and ambrisentan further decreased mPAP and PVR with improved arterial oxygen saturation (SaO2). This allowed us to perform total gastrectomy followed by the adjuvant chemotherapy with TS-1. The serum level of PDGF-BB increased until total gastrectomy and administration of adjuvant chemotherapy, suggesting that proliferating cancer cells were the primary source of PDGF-BB. On January 30, 2012, the serum levels of brain natriuretic peptide and PDGF-BB were rather high, but the hemodynamic parameters and SaO2 level were normalized. SvO2: mixed venous oxygen saturation.
and echocardiogram findings were also normalized (Figure 1B and D). She was discharged and periodically visited our hospital as an outpatient. However, she died of systemic metastasis on September 18, 2012.

**DISCUSSION**

In cardiovascular disease, common causes of rapid progressing dyspnea are heart failure due to acute coronary syndrome, pulmonary embolism and worsening of chronic heart failure. Amniotic fluid embolism and eosinophilic myocarditis were previously reported as rare but important causes.

PTTM can also induce rapid progressive dyspnea. Furthermore, not all patients with PTTM are proven to have a malignant tumor at admission like this case. It is quite rare, however, and an early diagnosis is very important for rescue.

PTTM is detected in 3.3\% of autopsies of patients with carcinoma. The key to our diagnosis was a perfusion scintigram showing diffuse and peripheral perfusion defects (Figure 2A). Because Von Herbay, et al reported that PTTM-PH is most frequently caused by gastric cancer, we decided to perform gastroesophageal endoscopy. PTTM-PH is typically uncontrollable. The authors of several pathological studies suggest that PDGF secreted from tumor cells is associated with vascular remodeling in PTTM-PH, and that PDGF is secreted because of the endothelial damage induced by attachment of tumor thrombi. Moreover, PDGF-regulated expression of osteopontin is associated with fibrosis, neointima formation, and PA occlusion. Taken together, these findings suggested to us that inhibition of PDGF or PDGFR improves PTTM-PH. On the other hand, imatinib has been reported to be effective in patients with pulmonary arterial hypertension, and our own studies showed that imatinib treatment reduced serum levels of PDGF-BB in patients with pulmonary arterial hypertension, as reported in the patient with PTTM-PH by Ogawa, et al. However, our patient’s serum level of PDGF-BB increased until she underwent total gastrectomy and received adjuvant chemotherapy (Figure 3).

From the immunohistochemistry results, we conclude that PDGF-A and -B may primarily originate from the GCC in PA (Figure 4D and E) and the stomach (Supplemental Figure 1B and C). Positive staining using the anti-phospho-PDGFR-α of the vascular endothelial cells and the GCC in the PA and the stomach indicates that PDGF signaling was likely activated through autocrine and paracrine mechanisms, which were unlikely to have been inhibited by circulating imatinib (Figure 4F, Supplemental Figure 1D). Administration of imatinib and other PH drugs and suppression of GCC-proliferation by TS-1 resulted in normalization of hemodynamics, the lung perfusion scintigram, and arterial oxygen saturation. Histological analysis and comparison of the biopsy with the autopsy revealed recanalization of the previously occluded small PA (Figure 4A and 4H), which most likely occurred during the clinical course. We attribute this to the elimination of embolized cancer cells. In addition, the rate of normal vasculature was increased in the autopsy samples, which was most likely attributable to reverse remodeling of the intimal cell proliferation (Supplemental Figure 2). Both phenomena mainly contribute to a decrease in the mean value of the luminal stenotic rate of the PA. Because PH did not recur, the present case suggests the first strategy effective for treating PTTM-PH.
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DISCLOSURE

Conflict of interest: No conflict of interest exists for the specified authors.

REFERENCES


SUPPLEMENTAL FILES

Supplemental Table I, II
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