Imatinib Dramatically Improved Pulmonary Hypertension Caused by Pulmonary Tumor Thrombotic Microangiopathy (PTTM) Associated with Metastatic Breast Cancer

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Summary
Pulmonary tumor thrombotic microangiopathy (PTTM) is a rare malignancy-related respiratory complication, showing rapid progression of respiratory dysfunction and pulmonary hypertension (PH). Accumulating evidence suggests that imatinib, a platelet-derived growth factor (PDGF) receptor-tyrosine kinase inhibitor, might be effective and improve severe PH in patients with PTTM associated with gastric cancer. However, its efficacy in PTTM with breast cancer is generally believed as very limited. We experienced a rare case of PTTM associated with metastatic breast cancer, a rare case who were treated with imatinib, exhibiting significant improvement of respiratory dysfunction and PH.

Key words: Cardio-oncology, Heart failure, Malignancy

Imatinib is a small molecule drug that targets the PDGFR and KIT receptors. It is approved for the treatment of several malignancies, including chronic myeloid leukemia and gastrointestinal stromal tumors. In recent years, it has also been evaluated for its potential use in treating other malignancies, such as breast cancer and lung cancer.

Pulmonary Tumor Thrombotic Microangiopathy (PTTM) is a rare malignancy-related respiratory complication that was first described by Von Herbay et al.1 According to the reports of autopsy cases with carcinoma, the incidence of PTTM is 1.4%-3.3%.1,2 The most common histological type is adenocarcinoma and common origin is stomach, especially the mucinous, signet ring, and poorly differentiated subtypes.

Recent studies reported that imatinib treatment improved the survival and pulmonary hypertension (PH) in patients with PTTM associated with gastrointestinal cancer.3-5 However, there has been no report that imatinib was effective and prolonged survival period for more than several months in PTTM caused by breast cancer.

Here, we experienced and report a rare case of PTTM associated with metastatic breast cancer a rare case who were treated with imatinib, showing significant improvement of respiratory dysfunction and PH.

Case Report
A 42-year-old female patient was diagnosed as left breast cancer 6 years ago. She underwent lumpectomy and lymphadenectomy, followed by subsequent adjuvant chemotherapy, radiation therapy, and hormone therapy. However, distant metastasis was found in bones, lymph nodes, and pleura 3 years ago. The patient continued chemotherapy but had never experienced cardiovascular complications.

The patient experienced chronic sputum and cough from one month before the admission. Because the patient experienced acute progressing dyspnea within a few days, she was admitted to Hyogo Cancer Center (Japan) where she received cancer treatment. She exhibited hypoxia (SpO2 of 80% at room air), but chest computed tomography (CT) showed no specific findings of pulmonary embolism, infectious pneumonia, or interstitial pneumonia although she had received everolimus until one month ago. The oncologist immediately started steroid mini-pulse therapy (methylprednisolone 500 mg/day), targeting everolimus-induced interstitial pneumonia, but the patient’s respiratory condition kept getting worse. Transthoracic echocardiography performed at two days after the hospitalization exhibited right ventricular enlargement and significant PH. The oncologist suspected PTTM, and the patient was transferred to division of Cardiology, Kobe University Hospital (Japan) for further cardiac assessment and treatment.

On admission to our hospital, her body temperature was 36.7°C, blood pressure 112/74 mmHg, heart rate 108/minutes, respiratory rate 24/minute with O2 saturation 93% by oxygen mask (under O2 8 L/minutes), and New York Heart Association (NYHA) Classification was identified as class IV. Chest X-ray showed left pleural effusion, where pleurodesis was performed because of carcinomatous pleuritis. Electrocardiogram (ECG) exhibited T wave inversions in the right precordial leads (V1-4) and biphasic P wave in V1-2, indicating the presence of PH (Figure 1A, B).

On blood examination, inflammatory marker and re-
nal/liver tests exhibited within normal range. The blood coagulation tests showed a slightly hypercoagulative state (prothrombin time activity of 101.1%, prothrombin time international normalized ratio of 0.99, activated partial thromboplastin time of 25.3 seconds, D-dimer of 7.3 μg/mL (normal < 1 μg/mL), fibrinogen and fibrin degradation products of 14.6 μg/mL). Brain natriuretic peptide (BNP) level was elevated (438.95 pg/mL, normal 0-18.4 pg/mL).

Contrast-enhanced CT scan was performed, showing no visible pulmonary embolism. However, dual-energy CT (DECT) iodine map showed multiple small peripheral patchy areas of reduced blood flow (Figure 2A). Transthoracic echocardiogram (TTE) revealed normal left ventricular (LV) systolic function (LV ejection fraction, 55%), but significant enlargement of right ventricular and atrium, compressed D-shaped left ventricle (Figure 1C, D), and elevated tricuspid regurgitation pressure gradient (TRPG) of 45 mmHg was observed. On the second day, right heart catheterization was performed and confirmed significant PH (pulmonary artery pressure of 48/20/ (31) mmHg and cardiac index of 2.01 L/minute/m²). PCWP showed 10/10/ (7) mmHg, indicating no evident LV dysfunction. Pulmonary artery wedge blood sampling was performed for cytological examination to detect malignant cells, which turned out to be negative a week later.

Without waiting pathological diagnosis, we clinically diagnosed PTTM based on the following clinical findings, (1) history of metastatic breast cancer, (2) acute progression of respiratory failure with severe PH, (3) no specific CT findings of pulmonary embolism and chronic thromboembolic PH, and (4) multiple subsegmental peripheral perfusion defect.

Accumulating evidences suggest that imatinib, a platelet-derived growth factor (PDGF) receptor-tyrosine kinase inhibitor, might be effective and improve severe PH in patients with PTTM. Because this treatment was off-label, we immediately obtained approval from the ethics committee at Kobe University Hospital on the first day of admission and could start imatinib on the second day after the right heart catheterization.

Figure 1. Chest radiography, electrocardiography, and echocardiography. A: Chest X-ray showed left pleural effusion, where pleurodesis was performed because of carcinomatous pleuritis. B: Electrocardiogram (ECG) exhibited T wave inversions in the right precordial leads (V1-4) and biphasic P wave in V1-2, indicating the presence of PH. C, D: Transthoracic echocardiogram (TTE) revealed enlargement of right ventricle (C) and compressed D-shaped left ventricle (D).
Imatinib (200 mg once daily), tadalafil (phosphodiesterase 5 inhibitor, 20 mg once daily), and anticoagulation therapy (continuous infusion of heparin 10000-15000 U/day) were started on day 2 (Figure 3). After starting those treatments, serial TTE examination showed the disappearance of D-shaped left ventricle (Figure 4), and TRPG level was gradually reduced. Although chest X-ray shows persisted left pleural effusion (Figure 4), her respi-
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Figure 4. Chest radiography and echocardiography after treatment. A: Chest X-ray shows persisted left pleural effusion likely because carcinomatous pleuritis. B: Echocardiography shows no evidence of D-shaped left ventricle, indicating improved pulmonary hypertension.

ratory condition was dramatically improved. We added macitentan (endothelin receptor antagonist, 10 mg once daily) for further PH treatment on day 9. Although 8 L/minute oxygen was required at admission, she discharged on day 14 without oxygen treatment. The NYHA classification improved from IV to II, TRPG from 45-28 mmHg, and BNP from 439-51 pg/mL (Figure 3).

We decreased the dose of imatinib to 100 mg/day after discharge and continued tadalafil (20 mg/day), macitentan (10 mg/day), and rivaroxaban (15 m/day). DECT iodine map performed at one month after discharge showed significant improvement of pulmonary perfusion (Figure 2). She continued to receive the medications and did not show recurrence of PH. She died in her house due to progression of breast cancer about 3 months after the discharge.

Discussion

PTTM is a rare malignancy-related respiratory complication and was first described by Von Herbay, et al.1) Pathological features of PTTM are tumor cell microemboli and surrounding fibrocellular intimal proliferation in small pulmonary arteries and vein. Ultimately, vessel occlusion and hyperplasia cause PH. According to the reports of autopsy cases with carcinoma, the incidence of PTTM is 1.4%-3.3%.1,2) The most common histological type is adenocarcinoma and common origin is stomach, especially the mucinous, signet ring, and poorly differentiated subtypes. Other origins include lung, breast, colon, pancreas, and esophagus.3)

PTTM patients usually present with rapidly progressive dyspnea, hypoxia, and PH. Because of the extremely rapid worsening of respiratory failure, PTTM leads to death in a few days to a few weeks typically.4) An antemortem diagnosis of PTTM is rarely achieved.5)

The laboratory data often shows a hypercoagulative state, which seems to reflect the presence of tumor embolism as observed in this case. Chest CT scan is needed for excluding pulmonary embolism, lymphangitic carcinomatosis, and other diseases that can cause respiratory failure and PH. Chest CT findings in patients with PTTM are nonspecific, showing ground-glass opacity, consolidation, small nodules, and a tree-in-bud appearance.6)

Ventilation-perfusion scintigraphy usually shows multiple small peripheral subsegmental defects throughout the bilateral lungs. In our case, we performed DECT iodine map to evaluate pulmonary perfusion. In this case, DECT detected segmental multiple perfusion defect, and we successfully monitored the improvement of pulmonary perfusion after the imatinib treatment (Figure 2).

For the antemortem diagnosis of PTTM, the cytological examination is essential. However, lung biopsy may not be generally capable of unstable and progressive PTTM patients. Pulmonary artery wedge blood sampling with a Swan-Ganz catheter is also performed to detect malignant cells but is incapable of discriminating between PTTM and pulmonary tumor embolism. If sample is not wedged, circulating malignant cells from primary tumor can be contaminated.7)

Although there was no malignant cell in sampling blood in this case, likely owing to insufficient wedge blood aspiration, we clinically diagnosed PTTM based on the patient’s acutely progressive clinical course and the DECT perfusion findings. Considering that (1) diagnostic and technical limitations of wedged aspiration and (2) PTTM might acutely progress within days before we receive the pathological findings, we believe that our decision of clinical diagnosis of PTTM and starting imatinib without waiting for pathological report in this patient can be reasonable and justified.

The mechanism of PTTM is still unclear, but several previous studies revealed that cancer cells produced PDGF, vascular endothelial growth factor, tissue factor, and osteopontin, which induce fibrocellular intimal proliferation and local activation of coagulation.8) In the past report, PDGF is also implicated in pulmonary arterial hypertension, and imatinib (PDGF receptor-tyrosine kinase
inhibitor) has anti-proliferative and pro-apoptotic effects on pulmonary artery smooth muscle cells stimulated with PDGF in idiopathic PH.\textsuperscript{10}

Ogawa et al first reported the case of PTTM caused by gastrointestinal cancer with severe PH treated successfully with imatinib.\textsuperscript{11} Some cases of PTTM treated with imatinib were subsequently reported.\textsuperscript{3-5} Kubota, et al. reported the PTTM patients caused by gastric cancer with severe PH, which was not under control by bosentan and dobutamine, was improved by the addition of imatinib.\textsuperscript{3} However, there has been no report that imatinib was effective and prolonged survival period for more than several months in PTTM caused by breast cancer.

We measured the serum level of PDGF-BB in order to determine whether it can be used as a diagnostic marker of PTTM or could be a predictor of the therapeutic effects of imatinib. In this patient, the serum level of PDGF before imatinib administration was not significantly elevated (1101 pg/mL) and dramatically increased 10 days after the imatinib administration (6225 pg/mL). Although the molecular mechanism is unclear, increased serum level of PDGF-BB might indicate the upregulation of PDGF production owing to the blockade of PDGF signaling pathway by imatinib. Past reports show incompatible response of serum PDGF-BB level after the imatinib treatment in patients with PTTM.\textsuperscript{3,10} Ogawa, et al. reported that plasma levels of PDGF decreased in parallel with the amelioration of PH following the imatinib treatment.\textsuperscript{11} Contrary, Minatsuki, et al. reported that the serum level of PDGF-BB increased after starting imatinib and decreased after total gastrectomy and administration of adjuvant chemotherapy.\textsuperscript{5} It suggests that proliferating cancer cells are the primary source of PDGF-BB.\textsuperscript{5} Further studies are needed to determine whether the circulating PDGF level can be used as a predictor or a biomarker of the therapeutic effects.

Because anti-cancer drugs were not effective to inhibit multiple metastasis in this patient, we and oncologist did not resume chemotherapy. She was discharged home and spent the last three months with her family including small children. To the best of our knowledge, this is the first case of PTTM caused by metastatic breast cancer that imatinib significantly improved PH and prognosis.

However, we experienced and believe that early diagnosis of PTTM and prompt administration of imatinib will lead to a sufficiently meaningful extension of survival period in some patients, especially in young patients with PTTM. Because antemortem definitive diagnosis of PTTM by pathology is challenging and might lose a treatment chance, clinical diagnosis and prompt initiation of imatinib might be one of the strategies in patients with unstable PTTM.

**Disclosure**

**Conflicts of interest:** None.

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