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Editorial

Pulmonary Tumor Thrombotic Microangiopathy: An Under-Recognized Potentially Fatal Cause of Pulmonary Hypertension

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With the increased incidence of cancer, recognizing and managing cancer-related complications have become imperative. Pulmonary tumor thrombotic microangiopathy (PTTM) is a rare, but potentially fatal, complication of cancer that usually presents as rapidly progressing dyspnea and unexplained pulmonary hypertension.[1] First described in 1990 by von Herbay et al., it is characterized by intimal hyperplasia of the pulmonary arterioles in response to microscopic tumor emboli attachment to the endothelium.[2] The resulting pulmonary hypertension is primarily due to histopathologic changes in the vasculature and secondary thrombosis, rather than direct vascular obstruction by the large tumor emboli.[3] Given its pathology, PTTM should be considered in patients with cancer in the following scenarios: 1) unexplained, rapidly progressive dyspnea, 2) presence of pulmonary hypertension on echocardiography without any apparent cause, and 3) absence of pulmonary arterial thrombus on chest computed tomography (CT). Further studies, such as perfusion scans, right heart catheterization, or lung biopsy, should be performed in these patients. However, these additional studies often cannot be performed because of the unstable clinical conditions. Moreover, unfamiliarity with the disease entity (e.g., when to suspect and how to evaluate suspected PTTM) hinders early diagnosis and timely management.

From this perspective, the study by Bak et al.[4] in the current issue of the Korean Circulation Journal is noteworthy. The authors elegantly described the clinical features and progression of suspected cases of PTTM. A total of 28 cases were collected over 10 years at a tertiary center. Among the 28 cases, PTTM was histologically confirmed in only one, which shows the difficulty in obtaining a confirmatory diagnosis by biopsy. In clinical practice, PTTM is primarily a tentative diagnosis made through a combination of clinical history, physical examination, echocardiographic and CT imaging, and laboratory examination in patients with cancer. In addition to PTTM being a diagnostic conundrum, this study showed that the clinical course of suspected PTTM is rapid and fatal. Most patients with New York Heart Association class 4 dyspnea or desaturation died within 1 week. The median time to death from right ventricular (RV) failure onset was only 3.8 days. All the patients with suspected PTTM died. Although chemotherapy delayed death, its effect was minimal.

Conflict of Interest
The authors have no financial conflicts of interest.

Data Sharing Statement
The data required to reproduce these findings cannot be shared due to that this article is an editorial.

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Diagnosis of PTTM is difficult unless there is a high degree of suspicion. Furthermore, its rapidly progressive nature results in PTTM diagnosis being made post-mortem. An important strength of this study is that it describes the characteristics of patients who were clinically diagnosed with PTTM ante-mortem. Patient characteristics, such as the type of cancer causing PTTM, echocardiographic and CT findings, and laboratory parameters, were similar to those of previous postmortem studies.[5)6)] These results suggest that PTTM should be suspected in patients with unexplained severe dyspnea out of proportion to the imaging findings, signs of pulmonary hypertension and RV failure, and laboratory findings of thrombocytopenia and disseminated intravascular coagulation (DIC), even before it is pathologically confirmed.

What are the implications of these findings in clinical practice? First, a clinico-diagnostic approach, such as the one described in this study, has the potential to detect PTTM easily and earlier in the disease course than with the current practices. Two post-mortem studies in random patients with carcinoma revealed that the histopathologic features of PTTM were found in 1.4% and 3.3% of cases.[2)6)] This implies that PTTM is currently underdiagnosed. Greater awareness of the imaging and echocardiographic findings of PTTM could lead to an increase in the diagnosis of this rare entity in patients with cancer with unexplained dyspnea. In addition, early diagnosis has the potential to change the clinical course of PTTM. Currently, PTTM if diagnosed late in the disease course of the disease, and critically ill conditions, such as hemodynamic instability, preclude the use of potentially effective therapy. In this study, similar to previous reports, patients with less severe symptoms at the time of diagnosis survived longer than those with severe symptoms.

Chronic thromboembolic pulmonary hypertension (CTEPH) should be considered as a differential diagnosis. CTEPH can develop in patients with cancer. Although CTEPH and PTTM share similar features (intimal proliferation-induced pulmonary hypertension with ventilation-perfusion mismatch), the major differences between the two diseases lie in their clinical course.[7)] CTEPH is a chronic disease, whereas PTTM progresses rapidly. Cough is more common in patients with PTTM than in those with CTEPH. Several of the CT and laboratory findings (DIC profiles including thrombocytopenia), which are presented in the current study are more in favor of PTTM (**Table 1**).

In this study, chemotherapy was associated with a significant improvement in survival. Does this imply that all patients with suspected PTTM should receive chemotherapy? First, there

Table 1. Features of PTTM and CTEPH

Parameters	PTTM	CTEPH
Clinical features		
Clinical presentation	Acute to subacute	Chronic
Dyspnea	Common	Common
Cough	Common	Less common
Radiologic features		
CT findings	Ground-glass opacities, nodules, mediastinal/hilar adenopathy, septal thickening	Mosaicism, wedge-shaped infarcts, organized, calcified thrombus, enlarged bronchial artery (collateral vessel formation)
Laboratory findings	DIC profile, hemolytic anemia, thrombocytopenia	Non-specific
Pathologic findings		
Thromboembolus	+	+
Fibrocellular intimal proliferation	+	+
Presence of tumor cells	+	−

CT = computed tomography; CTEPH = chronic pulmonary thromboembolism; DIC = disseminated intravascular coagulation; PTTM = pulmonary tumor thrombotic microangiopathy.
Modified from reference.[5)7)]

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may be a high possibility of survival bias. The authors did not specify the characteristics of the patients who received chemotherapy, such as symptom severity. However, it seems likely that they were in better condition than those who were not considered for chemotherapy. Second, the overall benefit observed was only modest; survival was prolonged by approximately seven days, which raises the question of its clinical relevance. However, several patients were able to discharge after chemotherapy. The data seem to suggest that the patients were relatively more stable and not in a state of cardiogenic shock, although RV failure and severe dyspnea were universally present. Therefore, identifying patients who could potentially respond to chemotherapy may be important. In addition, the authors did not specify whether the increased survival in these patients was due to improved RV function and pulmonary hypertension or due to other factors such as cancer status. Several studies have reported prolonged survival after administration of agents such as imatinib, bosentan, and sildenafil, possibly through lowered pulmonary arterial pressures.[8-10] Incidentally, this study included only a small number of patients who were being treated with agents for reducing pulmonary hypertension; no survival benefit associated with these agents was detected. Further studied are required to assess the mechanisms and efficacy of treatment options for PTTM.

In conclusion, this is an important and valuable paper describing the characteristics of patients diagnosed with PTTM ante-mortem in a large tertiary center. The study shows that PTTM diagnosis does not necessarily have to be made through biopsy. PTTM should be clinically suspected in patients with cancer with rapidly progressing RV dysfunction and pulmonary hypertension. Chemotherapy appears to be a promising treatment option for PTTM. However, additional studies are needed before it can be incorporated into clinical practice.

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