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Editorial

Importance of differential diagnosis of pulmonary hypertension

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Recent progress in the treatment of pulmonary hypertension has been remarkable over the past 2 decades. Three different pathways have been proposed to be involved in the pathogenesis of pulmonary arterial hypertension (PAH) and targeted drugs modifying each pathway have been developed. The diagnostic algorithm is shown and a treatment algorithm, including these PAH-targeted drugs, is recommended in the latest guidelines for the diagnosis and treatment of pulmonary hypertension [1]. More cases have been diagnosed and treated with these drugs as a consequence of wider recognition of pulmonary hypertension. However, the drugs have been proven to be effective only for treatment of PAH, which is classified as Group 1 in the guidelines [1]. Therefore, the use of PAH-targeted drugs is not approved for other groups of pulmonary hypertension because there is little evidence to prove that those drugs are effective in diseases other than Group 1 PAH.

In this issue of *Journal of Cardiology Cases*, Naito et al. report a case of pulmonary hypertension associated with intravascular lymphomatosis (IVL) [2]. The patient was 75 years old at diagnosis and had a high pulmonary capillary wedge pressure. They first diagnosed the patient with idiopathic PAH combined with pulmonary hypertension owing to left-sided heart disease (Group 2), and treated the patient with upfront combination therapy. After initiation of PAH-targeted therapies, the patient did not show improvement and 1 month later, IVL was diagnosed based on atypical cells detected in peripheral blood. After initiation of chemotherapy to treat IVL, pulmonary hypertension was also improved.

IVL is a rare form of lymphoma which was described for the first time in 1959 as angioendotheliomatosis [3]. IVL is characterized by proliferation of malignant cells within the lumen of small blood vessels. The development of symptoms is assumed to be caused by emboli or blood flow disturbance due to obstruction of vessels by tumor cells. Although the central nervous system or skin is frequently affected, the lung is also reported to be commonly affected. The lung is involved in approximately 60% of cases of IVL at autopsy, irrespective of the presentation of respiratory symptoms [4]. The prognosis of patients who are diagnosed antemortem is usually poor, with only 5 months median survival time [5]. Combination chemotherapy sometimes leads to complete remission and long-term survival in cases of IVL [6].

Several cases of pulmonary hypertension caused by IVL have been reported [7–9]. Although IVL was not pathologically confirmed in the present case described by Naito et al., pulmonary hypertension might have been caused by invasion of IVL into the pulmonary arteries. Chemotherapy might have been effective in eliminating lymphoma cells in those pulmonary arteries and ultimately could have led to amelioration of pulmonary hypertension. In this case, pulmonary hypertension would be categorized as Group 5 [1], which is not what the authors originally diagnosed, PAH. Group 5 comprises a heterogeneous collection of diseases with uncertain and multifactorial pathogenetic mechanisms leading to pulmonary hypertension, including hematological, systemic, metabolic, and other rare disorders. Considering the common involvement of the lungs by IVL and the fact that some patients with IVL can be treated with combination chemotherapy, pulmonary hypertension secondary to IVL may be reversible. IVL should be considered in the differential diagnosis of pulmonary hypertension.

The patient presented by Naito et al. was elderly as a patient with idiopathic PAH, which was originally reported to occur predominantly in younger women [10]. Of course, age at diagnosis is not the only factor for ruling out the diagnosis of idiopathic PAH. In fact, in countries with an aging population, idiopathic PAH is reported to be frequently diagnosed in elderly patients [11]. Elderly patients are described to respond less well to medical therapy and have a higher age-adjusted mortality compared with younger patients [11]. The reason for this finding is unknown. Pulmonary hypertension, which is first considered as idiopathic, can be secondary to other hidden causes, which were not diagnosed yet, similar to the clinical course of the patient presented by Naito et al. The possibility of malignancy should be considered in elderly patients manifesting pulmonary hypertension because they are at the peak age of onset of malignancy. Pulmonary tumor thrombotic microangiopathy related to malignancy should also be considered as a differential diagnosis of pulmonary hypertension [12].

The lesson learned from this case by Naito et al. is that an accurate diagnosis is essential for treating patients with pulmonary hypertension. Their patient did not respond to PAH-targeted drugs, but to chemotherapy instead, which targeted IVL, possibly causing pulmonary hypertension. Naito et al. carefully followed up their patient after initiation of PAH-targeted therapy, and this was important for successful diagnosis and treatment. The diagnosis of PAH always needs to be ensured because they are not approved for treating pulmonary hypertension other than PAH. In particular,

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upfront combination therapy is not yet proven to be better than sequential combination therapy in PAH [13]. To avoid delays in final diagnosis and adequate treatment, we should keep our eyes wide open for a sign that leads to a final diagnosis, even after a temporary diagnosis of PAH is made and treatment is initiated. For those patients who have an inadequate clinical response on follow-up, the initial diagnosis should be reconsidered. If there are any unusual findings, necessary examinations should be performed to make an accurate diagnosis. Otherwise, treating patients with pulmonary hypertension due to underlying disorders with PAH-targeted drugs could lead to an unfavorable clinical course of patients with high healthcare costs.

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