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Editorial

Pulmonary arterial hypertension due to pulmonary veno-occlusive disease in systemic sclerosis: Importance of early diagnosis and cautious use of pulmonary vasodilator therapy

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Pulmonary veno-occlusive disease;
Systemic sclerosis;
High resolution computed tomography;
Epoprostenol

Pulmonary arterial hypertension (PAH) is a serious and life-threatening condition characterized by pulmonary vascular remodeling leading to increased pulmonary arterial pressure and subsequent right ventricular failure and death. It can be idiopathic (IPAH), heritable, and caused by various underlying conditions including connective tissue diseases, mostly systemic sclerosis (SSc; scleroderma) [1]. Significant advancements in the field of PAH with regard to genetic, molecular, and cellular mechanisms have been made over the past quarter of a century, which have led to a number of targeted therapies acting on distinct pathways and have improved the symptoms, exercise capacity, and possibly prognosis in patients with PAH. Pulmonary veno-occlusive disease (PVOD) is a rare form of PAH accounting for 5—10% of initially diagnosed IPAH, and pathologically characterized by fibrotic obliteration of predominantly the venules and small veins in the interlobular septa of the pulmonary vasculature sparing the larger veins [2,3]. Although PVOD shares similar clinical presentation, genetic background, and hemodynamic characteristics with PAH, the prognosis is worse compared with IPAH and severe pulmonary edema can develop with a novel PAH-specific therapy [4]. PVOD is classified in a separate but related group of PAH as Group 1′ together with pulmonary capillary hemangiomatosis (PCH) [1].

SSc is a connective tissue disease of unknown etiology characterized by microvasculopathy, progressive fibrosis of the skin and various internal organs, and immune abnormality. SSc-associated PAH (SSc-PAH) caused by immune related vasculitis of the pulmonary vasculature and secondary to interstitial lung disease and left-sided heart failure mainly by diastolic dysfunction due to left ventricular fibrosis, occurs in 7—12% of patients with SSc. Compared with IPAH, SSc-PAH has a significantly inferior response to PAH-specific therapy and much worse prognosis and is the leading cause of death together with pulmonary fibrosis in SSc [5]. As life-threatening acute pulmonary edema is reported as a complication of vasoactive treatment in SSc-PAH as for PVOD, venular remodeling may similarly characterize SSc-PAH. Overbeek analyzed lung tissues from 8 patients with SSc-PAH, and all had both arterial and venous remodeling and 4 out of 8 patients displayed a PVOD-like pattern [6]. Another study showed 6 out of 8 patients with connective tissue disease-associated PAH (CTD-PAH), including all 4 patients with SSc-PAH, had PVOD-like lesions in their lung specimens [7]. Fibrous remodeling within pulmonary veins and venules may develop by altered fibrous reaction patterns, one of which is an altered transforming growth factor-β pathway signaling, of the post-capillary vasculature [8].

A recent report by Tada et al. [9] in the *Journal of Cardiology Cases* described a typical case of SSc-PAH due to PVOD and gives us the important message to take care of the patients with these conditions. They described a 55-year-old female with SSc-PAH introduced

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for treatment with intravenous epoprostenol because of the worsening symptoms even after aggressive treatment with pulmonary vasodilators, including oral prostaglandin, endothelin receptor antagonists, and phosphodiesterase 5 inhibitors at a prior medical facility. After administration of intravenous epoprostenol, pulmonary edema appeared dose-dependently and the presence of PVOD was suspected at that time. High resolution computed tomography (HRCT) of the chest showed septal line thickening and centrilobular ground-glass opacities which are relatively specific findings of PVOD. Along with reduction of epoprostenol infusion her pulmonary edema disappeared gradually. She refused to have a lung transplantation and died 4 months later after the introduction of intravenous epoprostenol therapy. A histological examination revealed severe stenosis and occlusion of pulmonary veinules and small veins as well as pulmonary arterial and capillary components. This report suggests that early diagnosis of PVOD is important to avoid a vicious effect like acute pulmonary edema as a result of PAH-specific vasodilator therapy.

The definite diagnosis of PVOD, however, needs histopathological confirmation of a wide spread fibrous intimal proliferation predominantly involved in the pulmonary venules and small veins by surgical lung biopsy, but lung biopsy is not recommended in patients with PAH because of associated significant risk. Alternatively, integrated assessment of clinical backgrounds like a higher male/female ratio and higher tobacco exposure in PVOD compared with IPAH, and noninvasive examination may be helpful [10]. Patients with PVOD show significantly lower resting partial pressure of arterial oxygen (PaO_2), a lower nadir arterial oxygen saturation (SaO_2) during 6 min walk test, and a lower single-breath diffusing capacity for carbon monoxide (DLCO) compared with patients with IPAH [2,3,10]. HRCT of the chest is an important diagnostic imaging modality to evaluate suspected PVOD. Beside the findings of hemodynamic consequences of PAH like central pulmonary arterial enlargement, right ventricular hypertrophy and dilatation, and bowing of the interventricular septum, normal sized left-sided cardiac chambers and main pulmonary veins are seen. A triad of diffuse ground-glass opacification, especially in centrilobular distribution, septal line thickening, and enlargement of mediastinal lymph node are highly suggestive findings of PVOD in patients with suspected PAH [10,11]. These findings reflect the increasing hydrostatic pressure in pulmonary capillary and the pulmonary venules or small veins component, and congestion of the lymphatic flow without the left-sided heart disease. Bronchoalveolar lavage (BAL) by bronchoscopy may be helpful for diagnosing PVOD. Significantly increased numbers of hemosiderin-laden macrophages are seen and there is higher average Gold score, which means occult alveolar hemorrhage is relatively common in PVOD [12]. However, bronchoscopy is a relatively invasive technique with an unacceptably high rate of complications and not recommended in patients with this condition.

Although right heart catheterization is an important modality to confirm the diagnosis of pulmonary hypertension by a mean pulmonary arterial pressure (PAP) more than 25 mmHg, and estimate the severity of hemodynamic disorder, it cannot distinguish PVOD from PAH, because measured pulmonary capillary wedge pressure (PCWP) values are normal range (less than 15 mmHg) in PVOD, and there are characteristic findings of precapillary pulmonary hypertension, even though anatomical obstruction in PVOD is predominantly at postcapillary sites. This discrepancy is caused by the way of measuring the PCWP. The site of the wedged catheter with inflated balloon is at relatively large branches of the pulmonary arteries, and the measured pressure at that site reflects the pressure at counterpart of the same size of pulmonary veins, which have no obstruction and normal pressure [2,3].

Despite discoveries of new specific PAH therapies, such as intravenous prostacyclin, prognosis of PVOD remains poor and currently lung or combined heart—lung transplantation seems the only therapeutic alternative to bring a durable clinical improvement and a possible survival benefit. Therefore, early referral for transplant evaluation is recommended. The waiting time for transplantation, however, may exceed a limited expected survival in PVOD. Although a life-threatening acute pulmonary edema caused by PAH-specific vasodilator therapy in PVOD is notable, a cautious use of continuous intravenous epoprostenol at low dose ranges and slow dose increases with high-dose diuretics improved clinical and hemodynamic parameters in PVOD at 3—4 months without commonly causing pulmonary edema, and may be a useful bridge to urgent lung transplantation [13]. Successful management using single drug regimens of bosentan (a non-selective endothelin antagonist) and sildenafil (a selective inhibitor of phosphdiesterase type-5) in rare cases of PVOD have been described. But a potential increased risk of acute pulmonary edema restricted the use of these drugs at the specialized expert center. Even though first-line monotherapy is not complicated with pulmonary edema, use of combinations of PAH-specific agents in a goal-oriented strategy should be undertaken with caution in PVOD [14]. Although treatment with the platelet-derived growth factor receptor inhibitor imatinib, which has anti-proliferative effects on pulmonary vascular smooth muscle cells, resulted in rapid clinical improvement and decrease of ground-glass opacities and septal thickening on HRCT in PVOD [15], imatinib still has an experimental status and should not be used outside reference centers. Successful outcomes of immunosuppressive therapies for PAH complicated with sarcoidosis, systemic lupus erythematosus, and mixed connective tissue disease have been reported but no significant effects were seen in SSc-PAH. Conventional general measures, limitation of physical activity, supplemental oxygen, vaccinations to prevent pneumococcal pneumonia and influenza, smoking cessation, warfarin anticoagulation with caution due to occult alveolar hemorrhage, and effective contraception for child-bearing females, may be recommended. Montani from the French Referral Center for Pulmonary Hypertension offers a realistic algorithm for managing PVOD at the present time (Fig. 1) [3].

Despite the advent of novel PAH-specific therapies, prognosis of PVOD is still dismal. Early diagnosis of PVOD with the noninvasive modalities in patients with suspected PAH, especially SSc-PAH, before trying vasodilator therapies and cautious use of some PAH-specific therapies as a bridge to lung transplantation may be the acceptable measures to manage PVOD currently.