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Case report

Heritable pulmonary arterial hypertension complicated by multiple pulmonary arteriovenous malformations

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ABSTRACT

Heritable pulmonary arterial hypertension (HPAH) is a type of familial pulmonary arterial hypertension, while pulmonary arteriovenous malformations (PAVMs) are abnormal communications between pulmonary arteries and veins that occur frequently in patients with hereditary hemorrhagic telangiectasia (HHT). A 21-year-old woman on continuing medication for HPAH was hospitalized. She had been diagnosed with HPAH at age 4 years and had been receiving epoprostenol infusion from age of 9 years. Although lung perfusion scintigraphy showed a shunt fraction of 18.9% at age of 19 years, the cause of the shunt was unclear. At the time of the present hospitalization, enhanced computed tomography (CT) of the chest and four-dimensional reconstructed images revealed multiple abnormal communications between the peripheral pulmonary arteries and veins. Furthermore, right heart catheterization revealed an elevated mean pulmonary arterial pressure. Wedged angiography of the pulmonary artery of the right lower lobe revealed several PAVMs. Multiple PAVMs and suspected HHT with HPAH was diagnosed. The possibility of PAVMs should be considered even in patients with HPAH. Moreover, evaluation of the shunt fraction by lung perfusion scintigraphy and morphological examination of PAVM by contrast-enhanced CT may facilitate PAVM detection in patients with HPAH

1. Introduction

Heritable pulmonary arterial hypertension (HPAH) is a form of familial pulmonary arterial hypertension. Bone morphogenetic protein receptor-II (*BMPR2*) gene mutations are associated with 80% of HPAH cases [1]. Rarely, mutations to activin A receptor type II-like kinase 1, endoglin, caveolin-1, potassium channel subfamily K, and member 3 genes have also been reported [2].

Pulmonary arteriovenous malformations (PAVMs) are associated with abnormal communications between pulmonary arteries and veins [3]. The incidence of PAVMs is 3 per 150,000 and occurs more frequently in patients with hereditary hemorrhagic telangiectasia (HHT) [4,5]. Limited reports on HPAH complicated by PAVMs have also been reported [6]. In those cases, the pulmonary hemodynamics were unclear. We present a case of HPAH complicated by multiple PAVMs.

2. Case presentation

A 21-year-old woman was referred to our hospital for treatment continuation of HPAH. Her father had recurrent hemoptysis and died of pulmonary hypertension (PH) at the age of 41 years, while her sister also died of the same disease at the age of 4 years. Owing to a family history of PH, the patient had been followed up since birth. At the age of 4 years, she was diagnosed with HPAH with a *BMPR2* gene mutation. Subsequently, she has been treated with various pulmonary vasodilators and continuous intravenous injection of epoprostenol from the age of 9 years. The dose of epoprostenol was subsequently increased and maintained at 18.8 ng/kg/min from the age of 11 years. Although lung perfusion scintigraphy showed a shunt fraction of 18.9% 2 years before the first visit to our institution, the shunt's etiology had yet to be determined. According to the World Health Organization Functional Classification, her symptoms were class 2 at the time of referral.

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Ambrisentan and tadalafil were administered because of the elevated pulmonary arterial pressure. The doses of these two drugs were progressively increased, while the epoprostenol regimen remained unchanged. Six months after the initial visit, she was hospitalized for evaluation of pulmonary hemodynamics. Her symptoms were stable with nasal cannula oxygenation at 2 L/min. Ambrisentan (5 mg), tadalafil (20 mg daily), and epoprostenol (18.8 ng/kg/min) were administered. Upon examination, her tongue and bilateral dorsal forearms showed telangiectatic skin lesions. Her workup revealed arterial blood gas analysis on room air with a partial pressure of oxygen of 62.3 mmHg and increased alveolar-arterial oxygen gradient (40.82 mmHg). Chest radiography showed mild cardiac enlargement and dilated bilateral pulmonary arteries (Fig. 1). Transthoracic echocardiography showed mild tricuspid regurgitation and mitral regurgitation, a 69.6-mmHg pressure gradient of tricuspid regurgitation, and no obvious shunt disease. Lung perfusion scintigraphy yielded a shunt fraction of 16.4% (Fig. 2). Contrast-enhanced chest computed tomography (CT) and four-dimensional reconstructed images revealed several abnormal communications between the peripheral pulmonary arteries and veins (Fig. 3A–C). Right heart catheterization revealed a high mean pulmonary artery pressure (53 mmHg), pulmonary vascular resistance (7.84 Wood units), and cardiac index (4.32 L/min/m^2 in room air) (Table 1). Wedge pulmonary arteriography of the right lower lobe pulmonary artery revealed several PAVMs (Fig. 4).

She was diagnosed with multiple PAVMs along with HPAH. Although HHT was suspected due to the PAVMs and mucocutaneous telangiectasia, her family history of HHT was unknown. Therefore, she was diagnosed with possible HHT based on the Curacao criteria [7]. The treatment strategy was to gradually increase epoprostenol dosage to the maximum tolerable dose because of the high pulmonary artery pressure. After 7 months, the epoprostenol dose was at 27.1 ng/kg/min. Lung perfusion scintigraphy yielded a shunt fraction of 13.4%. Repeat right heart catheterization showed a pulmonary artery pressure of 55 mmHg, pulmonary vascular resistance of 7.15 Wood units, and a cardiac index of 5.08 L/min/m^2 on room air (Table 1). Both adverse events associated with high-dose epoprostenol and PAVM complications were absent.

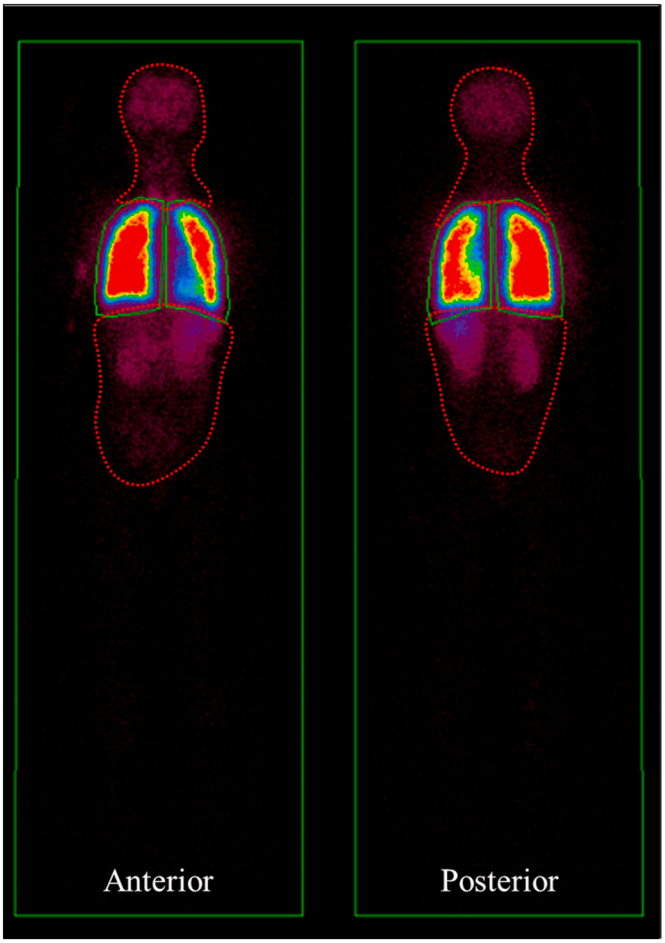

Fig. 2. Pulmonary perfusion scintigraphy shows accumulation in the brain and kidneys, in addition to the lungs, suggesting the presence of right-to-left shunts (dotted area). The shunt fraction was 16.4%.

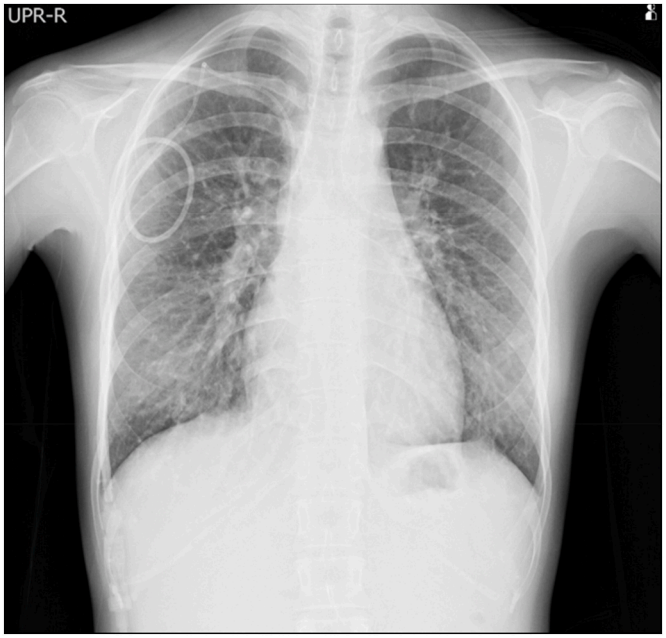

Fig. 1. Chest radiograph shows increased cardiac ratio, dilated pulmonary arteries, and ground-glass opacities in bilateral lung fields. An extracorporeal catheter for epoprostenol infusion is inserted into the right subclavian vein.

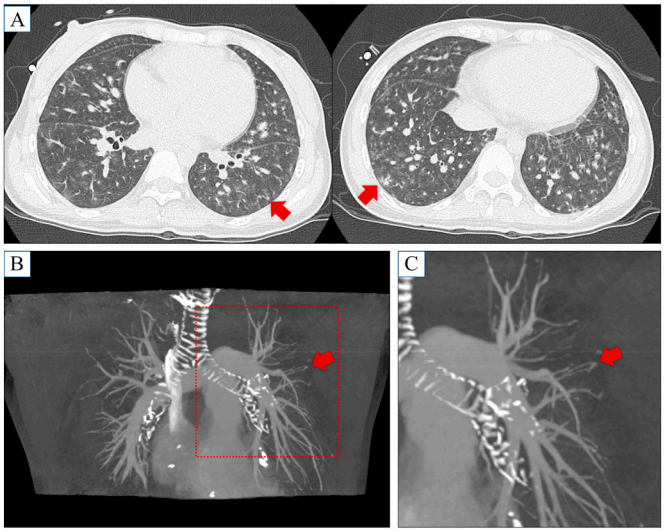

Fig. 3. Enhanced chest computed tomography (CT) shows diffuse anastomoses of peripheral pulmonary arteries and veins. Small pulmonary arteriovenous malformations are found in both lungs (arrow) (A). Four-dimensional reconstructed enhanced chest CT scans reveal multiple abnormal communications between the peripheral pulmonary arteries and veins (arrow) (B, C).

Table 1
Pulmonary hemodynamics upon initial examination at our hospital and 7 months after epoprostenol dose increase.

	Normal Range	Initial examination Epoprostenol 18.8 ng/kg/min		7 months after Epoprostenol 27.1 ng/kg/min (room air)
		(room air)	(O_2 2L/min)	
PaO_2 (mmHg, Room air)		62.3	–	57
Systolic Pulmonary Arterial Pressure (mmHg)	15–25	77	76	78
Diastolic Pulmonary Arterial Pressure (mmHg)	8–15	34	29	37
Mean Pulmonary Arterial Pressure (mmHg)	<25	53	49	55
Pulmonary Arterial Wedge Pressure (mmHg)	3–13	11	–	11
Pulmonary Vascular Resistance (Wood units)	~3	7.84	7.58	7.15
Cardiac Index (L/min/m^2)	2.5–4.0	4.32	4.04	5.08

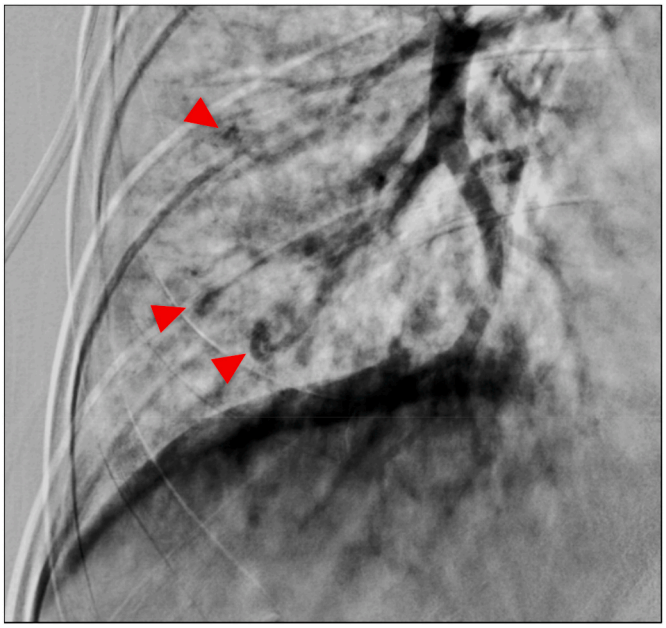

Fig. 4. Wedge pulmonary arteriography of the right lower lobe's pulmonary artery revealed several pulmonary arteriovenous malformations (triangle).

3. Discussion

This report includes notable clinical findings. First, HPAH can be complicated with PAVMs, although HPAH and PAVMs are both rare diseases. Second, PAVMs may occur during the clinical course of HPAH; evaluation of PAVMs by lung perfusion scintigraphy or enhanced CT is useful in such cases. Third, the hemodynamics of pulmonary arterial hypertension (PAH) associated with PAVMs can be complex and require careful correction.

HPAH and HHT share common mutations and hence, may co-exist. One report described 2 (6.3%) PAVMs in 32 PAH patients who underwent selective pulmonary angiography before epoprostenol administration [8]. This report showed a higher incidence than the general population (3/150,000) [4]. HHT is a major cause of PAVMs, and 70% of PAVMs are associated with HHT [5]. PAH is an important complication of HHT. While the exact prevalence of PAH in HHT patients is unknown, 13% of patients with HHT have associated PH [9,10]. HPAH and HHT share a common gene mutation in the transforming growth factor-beta (TGF-β) signaling pathway [11]. Thus, PAVMs could theoretically co-exist with HPAH. Some cases of PH and PAVMs have been reported in families with HHT [12], although their co-existence is limited even within the same family [12]. Therefore, factors other than genetic mutations might be involved. In one case report on a patient with combined BMPR2-positive idiopathic PAH (IPAH) and PAVM [13], the family history was unclear, and the patient did not meet the diagnostic criteria for HPAH and HHT [7]. Our case also did not meet the diagnostic criteria for HHT. HHT would be associated with *BMPR2* mutation [14]. If our patient's father and sister had pulmonary hypertension due to HHT, our case would have a family history of HHT and meet the diagnostic criteria for definite HHT. However, no detailed information of her family who died due to PH was available, and it was not possible to evaluate whether they had clinical symptoms that were suggestive of HHT. Although mutations other than *BMPR2* have not been assessed, TGF-β mutations have been considered in this context. PAH associated with HHT has a poorer prognosis than PAH alone [15]. In both HPAH and PAVM, the complications should be closely monitored.

HPAH patients may develop PAVMs during the course of the treatment; thus, lung perfusion scintigraphy and CT monitoring are recommended. Generally, pulmonary arteriography is not recommended for PAH cases because of the high risk of complications [16]. In addition, HPAH patients with a pathogenic *BMPR2* variant develop PH at a younger age [17,18] and undergo diagnostic catheterization approximately 10 years earlier than those without confirmed *BMPR2* deficiency [19]. CT is not frequently performed because of the risk of radiation exposure. Therefore, PAVMs may be overlooked in patients with HPAH. In PAH patients, scintigraphy should be performed at the time of diagnosis to exclude chronic thromboembolic PH. Even in cases of suspected HPAH, scintigraphy should focus on the shunt and the ventilatory blood-flow imbalance. Our patient was initially diagnosed with HPAH and received treatment specific to the disease. However, pulmonary perfusion scintigraphy revealed a high right-to-left shunt fraction, leading us to suspect a co-existing shunt-related disease. Four-dimensional CT, which can visualize small PAVMs, revealed multiple PAVMs. Furthermore, wedge pulmonary arteriography confirmed PAVM. Four-dimensional CT scans can identify PAVMs in PAH patients in whom pulmonary angiography is not recommended. On the other hand, pulmonary perfusion scintigraphy should be considered because PAVMs may become apparent during the course of HPAH; four-dimensional CT may also be useful.

Patients with concomitant PAH and PAVM have complicated hemodynamics, and treatment needs to be planned accordingly. PAVMs exhibit low vascular resistance and high cardiac output [20,21]. High cardiac output and shunt-related hypoxemia can increase pulmonary artery pressure. Conversely, the low vascular resistance of PAVM can reduce pulmonary artery pressure. It is difficult to determine how PAVMs affect pulmonary hemodynamics. Furthermore, pulmonary vasodilators may cause PAVM expansion and exacerbate hypoxemia. Increasing the dose of pulmonary vasodilators can lead to hypoxemia via PAVM dilation. The development of shunts associated with PAVM progression may further increase the cardiac output and pulmonary artery pressure. In patients with *BMPR2*-positive IPAH with co-existing PAVM and an unclear family history, pulmonary vasodilators were shown to improve the pulmonary artery pressure and pulmonary vascular resistance. However, the shunt fraction was increased, and oxygenation was deteriorated [13]. In our case, there was no history of worsening hypoxemia, suggesting no obvious deterioration of PAVMs by the administration of pulmonary vasodilators. Moreover, pulmonary vascular

resistance decreased, cardiac output increased, and shunt fraction improved along with incremental increases in epoprostenol dose. The reason may be that vasodilatory therapy results in a relative increase in the normal pulmonary vascular bed. However, epoprostenol may have a greater effect on abnormal blood vessels, requiring careful treatment adjustment.

4. Conclusion

HPAH and PAVMs may co-exist, making it necessary to consider the possibility of PAVMs in HPAH patients. PAVMs may become apparent during the course of HPAH; measurement of the right-to-left shunt fraction by lung perfusion scintigraphy and morphological evaluation by contrast-enhanced CT are useful for the assessment of PAVM.

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Declarations of competing interest

None.

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