Heritable pulmonary arterial hypertension complicated by multiple pulmonary arteriovenous malformations

Takahiro Arano a, Takuro Imamoto a, Rika Suda a, Hajime Kasai a,∗, Toshihiko Sugiura a, c, Ayako Shigeta b, Keiko Yamamoto a, Jun Nagata a, c, Seiichiro Sakao a, Nobuhiro Tanabe a, c, Koichiro Tatsumi a

a Department of Respiratology, Graduate School of Medicine, Chiba University, Chiba, Japan
b Health Professional Development Center, Chiba University Hospital, Chiba, Japan
c Department of Respiratory Medicine, Chibaken Saiseikai Narashino Hospital, Narashino, Japan

ARTICLE INFO

Keywords:
Heritable pulmonary arterial hypertension
Pulmonary arteriovenous malformation
Hereditary hemorrhagic telangiectasia
Enhanced computed tomography

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, endothelin, 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.

* Corresponding author. Department of Respiratology, Graduate School of Medicine, Chiba University, Chiba, Japan.
E-mail address: daikasai6075@yahoo.co.jp (H. Kasai).

https://doi.org/10.1016/j.rmcr.2021.101352
Received 27 August 2020; Received in revised form 8 December 2020; Accepted 13 January 2021
Available online 19 January 2021
2213-0071/© 2021 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license
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/m² 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/m² on room air (Table 1). Both adverse events associated with high-dose epoprostenol and PAVM complications were absent.

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. 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. 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).
hypertension (PAH) associated with PAVMs can be complex and require useful in such cases. Third, the hemodynamics of pulmonary arterial complicated with PAVMs, although HPAH and PAVMs are both rare went selective pulmonary angiography before epoprostenol selective pulmonary angiography before epoprostenol.

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

| Normal Range | Initial examination | 7 months after epoprostenol 27.1 ng/kg/min (room air) |
|--------------|---------------------|------------------------------------------------------|
|              | Epoprostenol 18.8 ng/kg/min | (O_2 air) 2L/min |
| PaO_2 (mmHg, Room air) | 62.3 | 57 |
| Systolic Pulmonary Arterial Pressure (mmHg) | 15-25 | 77 |
| Diastolic Pulmonary Arterial Pressure (mmHg) | 8-15 | 34 |
| Mean Pulmonary Arterial Pressure (mmHg) | <25 | 53 |
| Pulmonary Arterial Wedge Pressure (mmHg) | 3-13 | 11 |
| Pulmonary Vascular Resistance (Wood units) | –3 | 7.84 |
| Cardiac Index (L/min/m²) | 2.5-4.0 | 4.32 |

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 possibility of PAVMs in HPAH patients. PAVMs may become apparent, improving along with incremental increases in epoprostenol dose. The resistance decreased, cardiac output increased, and shunt fraction decreased, cardiac output increased, and shunt fraction decreased.

References

[1] J.P. Fessel, J.E. Loyd, E.D. Austin, The genetics of pulmonary arterial hypertension in the post-BMPR2 era, Pulm. Circ. 1 (2011) 305–319, https://doi.org/10.4103/2045-8932.87299, 2008/06/26. (Accessed 6 December 2011).

[2] C.G. Elliott, Genetics of pulmonary arterial hypertension, Clin. Chest Med. 34 (2013) 651–663, https://doi.org/10.1016/j.ccm.2013.08.003, (Accessed 26 November 2013).

[3] C.L. Shovlin, Pulmonary arteriovenous malformations, Am. J. Respir. Crit. Care Med. 190 (2014) 1217–1228, https://doi.org/10.1164/rcrm.201407-1254CL. (Accessed 25 November 2014).

[4] R.D. Sloan, R.N. Cooley, Congenital pulmonary arteriovenous aneurysm, Am. J. Roentgenol. Radial Ther. Nucl. Med. 70 (1953) 183–210. (Accessed 1 August 1953).

[5] J.R. Gossage, G. Kanj, Pulmonary arteriovenous malformations. A state of the art review, Am. J. Respir. Crit. Care Med. 158 (1998) 643–661, https://doi.org/10.1164/ajrccm.158.2.9711041. (Accessed 12 August 1998).

[6] V.M. Vorselaars, S. Velthuis, R.J. Snijder, et al., Pulmonary hypertension in hereditary haemorrhagic telangiectasia, World J. Cardiol. 7 (2015) 230–237, https://doi.org/10.4330/wjc.v7.i5.230. (Accessed 28 May 2015).

[7] C.L. Shovlin, A.E. Guttmacher, E. Buscarini, et al., Diagnostic criteria for hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome), Am. J. Med. Genet. 91 (2000) 66-67, https://doi.org/10.1002/1096-8628(20000306)91:1-66::aid-ajmg12-3.0.co;2-p. (Accessed 6 April 2000).

[8] M. Sakuma, J. Demachi, J. Nawata, et al., Epoprostenol infusion therapy changes angiographic findings of pulmonary arteries in patients with idiopathic pulmonary arterial hypertension, Circ. J. Off. Jpn. Circul. Soc. 72 (2008) 1147–1151, https://doi.org/10.1253/circj.72.1147. (Accessed 26 June 2008).

[9] M. Chizingga, A.A. Rudikovskaia, K. Henderson, et al., Pulmonary hypertension prevalence and prognosis in a cohort of patients with hereditary haemorrhagic telangiectasia undergoing embolization of pulmonary arteriovenous malformations, Am. J. Respir. Crit. Care Med. 196 (2017) 1353–1356, https://doi. org/10.1164/rcrm.201702-0267LE. (Accessed 5 April 2017).

[10] M.E. Faughnan, J.T. Granston, L.H. Young, The pulmonary vascular bed of hereditary haemorrhagic telangiectasia, Eur. Respir. J. 33 (2009) 1186–1194, https://doi.org/10.1183/09031996.00061308. (Accessed 2 May 2009).

[11] V.M.M. Vorselaars, A.E. Hosman, C.J.J. Westermann, et al., Pulmonary arterial hypertension and hereditary haemorrhagic telangiectasia, Int. J. Mol. Sci. 19 (2018) 2018/10-20, https://doi.org/10.3390/ijms19103203.

[12] L.B. Smoot, D. Odler, D.B. McElhinney, et al., Clinical features of pulmonary arterial hypertension in young people with an ALK1 mutation and hereditary haemorrhagic telangiectasia, Arch. Dis. Child. 94 (2009) 506–511, https://doi.org/10.1136/adc.2009.175302. (Accessed 10 April 2009).

[13] T. Handa, Y. Okano, N. Nakashii, et al., BMPR2 gene mutation in pulmonary arteriovenous malformation and pulmonary hypertension: a case report, Resp. Investig. 52 (2014) 195–198, https://doi.org/10.1016/j.resinv.2013.08.003. (Accessed 24 May 2014).

[14] C.M. Rigelsky, C. Jennings, R. Lehtonen, et al., BMPR2 mutation in a patient with pulmonary arterial hypertension and suspected hereditary haemorrhagic telangiectasia, Am. J. Med. Genet. 146A (2006) 2551–2556, https://doi.org/10.1002/ajmg.a.32468. (Accessed 17 September 2008).

[15] B. Girerd, D. Montani, E. Coutel, et al., Clinical outcomes of pulmonary arterial hypertension in patients carrying an ACVRL1 (ALK1) mutation, Am. J. Respir. Crit. Care Med. 181 (2010) 851–861, https://doi.org/10.1164/rccm.200908-1246OC. (Accessed 9 January 2010).

[16] S.R. Mills, D.C. Jackson, R.A. Older, et al., The incidence, etiologies, and avoidance of complications of pulmonary angiography in a large series, Radiology 136 (1980) 295–299, https://doi.org/10.1148/radiology.136.2.7403505. (Accessed 1 August 1980).

[17] B. Girerd, D. Montani, M. Eyries, et al., Absence of influence of gender and BMPR2 mutation type on clinical phenotypes of pulmonary arterial hypertension, Respir. Res. 11 (2010), https://doi.org/10.1186/1465-9921-11-75, 75.. (Accessed 11 June 2010).

[18] N. Pfarr, J. Szamalek-Hoegg, C. Fischer, et al., Hemodynamic and clinical onset in patients with hereditary pulmonary arterial hypertension and BMPR2 mutations, Respir. Res. 12 (2011), https://doi.org/10.1186/1465-9921-12-99, 99.. (Accessed 2 August 2011).

[19] R.D. Machado, L. Southgate, C.A. Eichstaedt, et al., Pulmonary arterial hypertension: a current perspective on established and emerging molecular genetic defects, Hum. Mutat. 36 (2015) 1113–1127, https://doi.org/10.1002/humu.22904. (Accessed 22 September 2015).

[20] S. Velthuis, E. Buscarini, M.W.F. van Gent, et al., Grade of pulmonary right-to-left shunt on contrast echocardiography and cerebral complications: a striking association, Chest 144 (2013) 542–548, https://doi.org/10.1378/chest.12-1599, (Accessed 23 February 2013).

[21] M.K. Whyte, J.M. Hughes, J.E. Jackson, et al., Cardiopulmonary response to exercise in patients with intrapulmonary vascular shunts, J. Appl. Physiol. 75 (1993) 321–328, https://doi.org/10.1152/jappl1993.75.1.321. (Accessed 1 July 1993).