Liver transplantation in a patient with hereditary haemorrhagic telangiectasia and pulmonary hypertension

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Abstract

Hereditary haemorrhagic telangiectasia or Rendu-Osler-Weber syndrome is a systemic vascular disease with autosomal dominant inheritance, mucocutaneous telangiectasia, and repeated nasal bleeding due to vascular abnormalities. Hereditary haemorrhagic telangiectasia may occasionally lead to complications, including arteriovenous malformations and pulmonary hypertension. We present a case of a 52-year-old female patient with hereditary haemorrhagic telangiectasia who was referred to our hospital for treatment of pulmonary hypertension. She had been diagnosed with hereditary haemorrhagic telangiectasia during adolescence and was being followed up. Six months prior to presentation, she had undergone coil embolization for pulmonary haemorrhage due to pulmonary arteriovenous malformations. She was in World Health Organization functional class IV, with a mean of pulmonary arterial pressure of 38 mmHg, a pulmonary capillary wedge pressure of 10 mmHg, and a right atrial pressure of 22 mmHg. A contrast-enhanced computed tomography angiography showed large arteriovenous malformations in the liver. Right heart catheterization revealed an increase in oxygen saturation in the inferior vena cava between the supra- and infra-hepatic veins, low pulmonary vascular resistance, and high right atrial pressure. Hence, she was diagnosed with hereditary haemorrhagic telangiectasia with pulmonary hypertension due to major arteriovenous shunt resulting from arteriovenous malformations in the liver. Therefore, we considered liver transplantation as an essential treatment option. She underwent cadaveric liver transplantation after a year resulting in dramatic haemodynamic improvement to World Health Organization functional class I. Liver transplantation is a promising treatment in patients with hereditary haemorrhagic telangiectasia and pulmonary hypertension resulting from arteriovenous shunt caused by arteriovenous malformations in the liver.

Keywords

Rendu-Osler-Weber syndrome, arteriovenous malformation, pulmonary haemorrhage

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Case description

A 52-year-old female patient with hereditary haemorrhagic telangiectasia (HHT) presented with dyspnoea. She had been diagnosed with HHT with repeated nasal bleeding, mucocutaneous telangiectasia on tongue and nose, multiple arteriovenous malformations (AVMs) (lung and liver) and family history and was being followed up. One year before presentation, she had developed heart failure with lower limb oedema and was treated with diuretics at another hospital. She had also undergone coil embolization for pulmonary haemorrhage due to pulmonary AVMs at a general

hospital six months previously. However, she experienced persistent dyspnoea and was diagnosed with pulmonary hypertension (PH). Despite specific treatment of PH with bosentan, sildenafil, and dobutamine, no improvement was noted in her condition. Following this, she was referred to

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our centre, for specialised treatment of PH. She was in World Health Organization functional class IV and had dyspnoea at rest. Her oxygen saturation was 97% with high flow nasal oxygen support. We performed a right heart catheterization to assess her haemodynamic status. Her mean pulmonary arterial pressure was 38 mm Hg with a pulmonary capillary wedge pressure of 10 mmHg and a right atrial pressure of 22 mm Hg. Her cardiac output was 9.0 L/min,

(2)

and her pulmonary vascular resistance was 3.2 Wood units (Fig. 1a). Oxygen sampling by catheter revealed an increase in oxygen saturation in the inferior vena cava from 61 to 91% between the supra- and the infra-hepatic veins. As shown in Fig. 1b and c, a time-dependent change was observed in the morphology of the liver AVMs on computed tomography scans. The suspicion of extensive proliferation of AVMs was confirmed by contrast-enhanced computed

| Haemodynamic parameters | At patient transferred* | Before liver transplantation | After liver transplantation |
|---|----------------------------|---------------------------------|-----------------------------|
| Mean PCWP, mmHg | 9 | 15 | 2 |
| PAP, mmHg ⁺ | 60/26 (38) | 48/28 (34) | 30/17 (22) |
| Mean RAP, mmHg | 22 | 28 | 0 |
| Haemoglobin, g/dL | 11.5 | 9.1 | 11.7 |
| O ₂ consumption, mL/min | 161.4 | 155.9 | 145.1 |
| Aorta O ₂ saturation, % | 102.5 | 93.9 | 98.0 |
| Pulmonary artery O ₂ saturation, % | 89.6 | 75.2 | 76.2 |
| SVC and IVC O_2 saturation, % | 61.3 | 51.1 | NA |
| Cardiac output, L/min | 8.0 (2.5‡) | 6.7 (2.9‡) | 4.3 |
| Pulmonary vascular resistance, Wood unit | 3.6 | 2.8 | 4.8 |
| Qp/Qs | 1.0 (3.2‡) | 1.0 (2.3‡) | 1.0 |



Fig. 1. Haemodynamic data pre- and post-liver transplantation and arteriovenous malformations in the liver. A significant improvement in haemodynamic parameters was observed after liver transplantation compared to pre-transplant values (a). Compared with one year previously (b), low-density areas in the liver had enlarged on computed tomography scan indicating worsening of arteriovenous malformations (c). Contrast-enhanced computed tomography and angiography shows major shunt caused by arteriovenous malformations in the liver (d and e).

PH: pulmonary hypertension; PCWP: pulmonary capillary wedge pressure; PAP: pulmonary arterial pressure; RAP: right atrial pressure; O₂: oxygen; SVC: superior vena cava; IVC: inferior vena cava; Qp: pulmonary blood flow; Qs: systemic blood flow.

*Haemodynamic data were adjusted because right heart catheter in the referred patient was performed under oxygen inhalation and the continuous injection of dobutamine 3γ .

[†]PAP is presented as systolic/diastolic (mean) pulmonary artery pressure.

 3 Cardiac output is calculated using the average oxygen saturation in SVC and IVC, inferior to the hepatic vein as mixed venous oxygen saturation.

tomography angiography (Fig. 1d and e). Based on these findings and haemodynamic data, we considered the persistence of PH to be due to extreme arteriovenous shunt in the liver through the AVMs. Although previous study had reported that bevacizumab could be an effective treatment for HHT patients with liver AVMs, it was not approved in Japan.¹ Following discussions with hepatologists and transplant surgeons, we adjudged that liver transplantation (LT) was essential for the treatment of this condition. She was registered as an LT recipient, with a requirement for urgent LT. In the meantime, we considered that the high flow through the liver also results in elevated central mixed venous saturations that mimic those seen with atrial septal defects and other large intra-cardiac left-to-right shunts. Thereafter, we recalculated her haemodynamics using the average oxygen saturation in superior and inferior vena cava, inferior to the hepatic vein. By mixed venous oxygen saturation 61%, we estimated that her actual systemic output was reduced with 2.5 L/min. As per the results, we considered that more PH-specific therapy could increase her actual output and decrease her pulmonary arterial pressure that reduces her perioperative risk during LT, whereas it involved taking risks to increase AV shunt flow. Hence, we decided to switch PAH drug. Simultaneously, we also administered increasing diuretics to reduce any AV shunt flow. However, no significant improvement was observed in her condition even after the initiation of heart failure and PH-specific therapy (Fig. 1a). Eleven months after the initial presentation, she underwent a successful cadaveric LT. Intraoperative monitoring revealed a dramatic reduction in the central venous pressure from 21 to 4 mmHg after LT. Postoperative right heart catheterization revealed a remarkable haemodynamic improvement (Fig. 1a). Her symptoms improved to World Health Organization functional class I. She was continued on treatment with tadalafil and is being followed up regularly.

Discussion

In this case report, we describe the haemodynamic changes before and after specific treatment for PH and after LT in a patient with HHT. Detailed hemodynamic data were not presented in previous reports.^{2,3} HHT or Rendu-Osler-Weber syndrome is a systemic vascular disease leading to the formation of AVMs in the nose, mouth, brain, lungs, liver, gastrointestinal tract, and the skin.⁴ Various mutations in genes - such as ENG, encoding endoglin, and ACVRL1, encoding activin receptor-like kinase - are frequently associated with HHT. Such mutations are components of the receptor complexes for growth factors of the transforming growth factor superfamily. Hence, mediated angiogenic factors such as the vascular endothelial growth factor are believed to be involved in the expression of AVMs.^{1,4} A significant variation exists among patients in the AVM phenotype; however, the associated brain and pulmonary lesions lead to substantial morbidity and mortality. HHT is sometimes complicated with PH. There are some mechanisms for the development of PH in patients with HHT. PH commonly occurs due to a high output caused by AVMs in organs such as the liver, frequently complicated by left heart failure. Rarely, pulmonary arterial hypertension may be due to pulmonary vascular angiopathy.² In addition, HHT patients with the setting of liver cirrhosis and portal hypertension may cause portopulmonary hypertension. In our patient, major arteriovenous shunting was observed through AVMs in the liver with a mild increase in the pulmonary vascular resistance and left heart failure. Hence, we considered extensive shunt through AVMs in the liver to be the mechanism of causation of PH. Hence, LT was essential to treat PH associated with HHT in our patient.⁵ A previous report suggested that high pulmonary arterial pressure, especially >35 mm Hg, is a significant perioperative risk factor for LT in patients with portopulmonary hypertension.⁶ Fortunately, our patient did not have severe but moderate elevation in pulmonary arterial pressure, thus enabling successful LT. Although a significant improvement was noted in her clinical condition postoperatively, she requires careful follow-up for signs of worsening systemic vascular abnormality.

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Ethical approval

A written informed consent for publication was obtained from the patient.

Guarantor

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Contributorship

All authors meet the authorship guideline of contribution to this work.

Conflict of interest

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