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【 CASE REPORT 】

# Pulmonary Hypertension that Developed During Treatment for Hepatopulmonary Syndrome and Pulmonary Arteriovenous Malformation

Yumiko Ikubo[1], Hajime Kasai[1], Toshihiko Sugiura[1], Takahiko Saito[2], Hiroki Shoji[1], Seiichiro Sakao[1], Yasunori Kasahara[1,3], Nobuhiro Tanabe[1] and Koichiro Tatsumi[1]

**Abstract:**
Hepatopulmonary syndrome (HPS) and pulmonary arteriovenous malformation (PAVM) are hypoxemic diseases caused by right-to-left shunting but are rarely concomitant with pulmonary hypertension (PH). A 66-year-old woman with chronic hepatitis C was scheduled to undergo liver transplantation. She was referred to our department for hypoxia and an abnormal shadow in the right lung found on a preoperative examination. She was diagnosed with HPS and a PAVM in the right middle lobe. After liver transplantation, PH temporarily developed, but the pulmonary arterial pressure normalized after coil embolization. Combined HPS and PAVM may cause unique changes in pulmonary hemodynamics during treatment.

**Key words:** pulmonary hypertension, hepatopulmonary syndrome, pulmonary arteriovenous malformation, liver transplantation

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## Introduction

Hepatopulmonary syndrome (HPS) is a condition associated with advanced liver disease; it shows three main features: liver function abnormality, dilatation of capillaries in the lung (shunt), and hypoxemia (1). In patients with HPS, hypoxemia can improve after liver transplantation (2, 3). Pulmonary arteriovenous malformation (PAVM) is a blood vessel malformation that results in direct capillary-free communication between the pulmonary and systemic circulations; it is therefore an anatomic right-to-left shunt (4). It is rare for HPS to be accompanied by PAVM, and the pulmonary hemodynamics in such cases are unclear.

We herein report a case wherein pulmonary hypertension (PH) developed during the course of treatment for HPS and PAVM.

## Case Report

A 66-year-old woman was diagnosed with chronic hepatitis C 2 years before her current presentation. She developed cirrhotic hepatitis and was determined to require liver transplantation. She was scheduled to undergo living donor liver transplantation; however, she was referred to our department because of hypoxia and an abnormal shadow in the right lung that were found during a preoperative examination.

Her pulse oximetry was 93% on room air. She had icteric bulbar conjunctiva and swelling in her lower limbs, although she had no cutaneous telangiectasia. She had had a 40-pack/year smoking history between the ages of 20 and 60 and was a social drinker. The value of hepatitis C virus (HCV)-ribonucleic acid was 4.1 U/mL. As the liver function was severely reduced, antiviral therapy could not be administered. Therefore, only nutritional supporting agents were used to improve her general condition. An arterial blood gas analysis (BGA) on room air showed a partial pressure of ar-

[1]Department of Respirology, Graduate School of Medicine, Chiba University, Japan, [2]Department of Medicine, School of Medicine, Chiba University, Japan and [3]Department of Respiratory Medicine, Eastern Chiba Medical Center, Japan
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Correspondence to Dr. Hajime Kasai, daikasai6075@yahoo.co.jp

**Table 1. Laboratory Data before the Liver Transplantation.**

| Complete blood count | | Blood chemistry | | Blood Gas Analysis (Room Air) | |
|---|---|---|---|---|---|
| WBC | 3,400 /μL | AST | 39 U/L | pH | 7.47 |
| RBC | 353×10⁴ /μL | ALT | 28 U/L | $PaCO_2$ | 33.8 mmHg |
| HGB | 14.0 g/dL | LDH | 216 U/L | $PaO_2$ | 71.7 mmHg |
| HCT | 39.5 % | ALP | 373 U/L | A-$aDO_2$ | 38.0 mmHg |
| PLT | 69×10⁴ /μ | γ-GTP | 45 U/L | | |
| | | ChE | 120 U/L | | |
| Coagulation test | | T-BIL | 4.1 mg/dL | Child-Pugh score | 9 (Grade B) |
| APTT | 39.8 sec | ID-BIL | 0.8 mg/dL | MELD score | 17 |
| PT | 12.6 sec | TP | 6.7 g/dL | MELD-Na | 14 |
| PT activity | 74 % | ALB | 2.7 g/dL | | |
| PT-INR | 1.16 | UN | 23 mg/dL | | |
| | | CRE | 0.80 mg/dL | | |
| Immunology | | Na | 132 mmol/L | | |
| CRP | 1.3 mg/dL | K | 3.6 mmol/L | | |
| | | Cl | 103 mmol/L | | |
| | | $HbA_{1c}$ | 4.7 % | | |
| | | $NH_3$ | 96 μg/dL | | |

APTT: activated partial thromboplastin, PT: prothrombin time, PT-INR: PT international normalized ratio, PR3-ANCA: proteinase 3 antineutrophil cytoplasmic antibody, MPO-ANCA: myeloperoxidase-antineutrophil cytoplasmic antibody, MELD score: Model for End-Stage Liver Disease, GBM: glomerular basement membrane, HPF: high power field

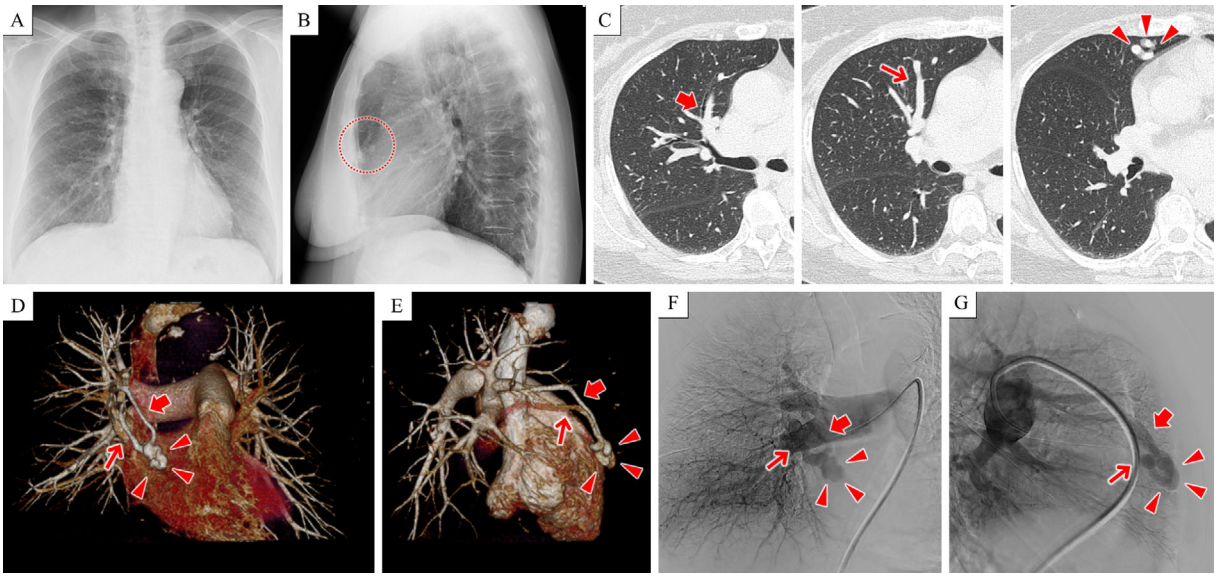


**Figure 1. (A, B) The left lateral view thoracic radiograph showed an abnormal shadow suspected to be pulmonary arteriovenous malformation (PAVM) (dotted circle), while the postero-anterior view showed no abnormal shadow. (C, D, E) Plain computed tomography (CT) showed the PAVM sac (triangle), feeding artery (arrow), and draining vein (thin arrow). (D, E, F) The front and right-side views on three-dimensional CT and pulmonary arteriography showed the PAVM sac (triangle), feeding artery (arrow), and draining vein (thin arrow). CT: computed tomography, PAVM: pulmonary arteriovenous malformation**

terial oxygen ($PaO_2$) of 71.7 mmHg and increased A-$aDO_2$ (38.0 mmHg) (Table 1).

Thoracic radiographs showed the presence of a PAVM in the right middle lobe (Fig. 1A and B). Enhanced computed tomography (CT) of the chest and three-dimensional reconstructed images revealed that the PAVM had one feeding artery and one draining vein with diameters of 3 and 4 mm, respectively. The sac was 8 mm in diameter (Fig. 1C-E). Abdominal CT revealed liver atrophy and a nodular surface, as well as splenomegaly without ascites (Fig. 2A). Enhanced CT of the abdomen and three-dimensional reconstructed images showed venous dilatation in the mucosa and submucosa

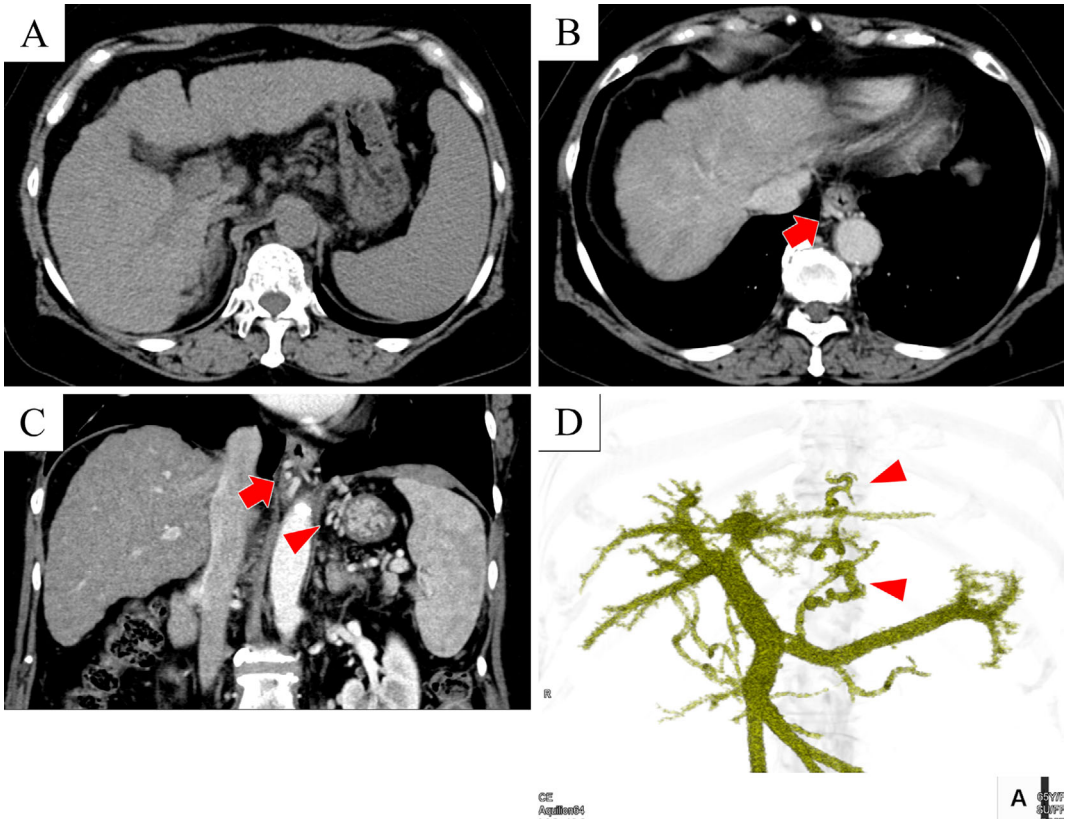


**Figure 2.** **Abdominal computed tomography (CT) revealed liver atrophy and nodular surface as well as splenomegaly without ascites (A). Enhanced CT of the abdomen and three-dimensional reconstructed images showed venous dilatation in the mucosa and submucosa of the lower esophagus (arrow) as well as the dilation and meandering of the left gastric veins (triangle) (B-D). CT: computed tomography**

of the lower esophagus and dilation and meandering of the left gastric veins (Fig. 2B-D). Gastrointestinal endoscopy showed an esophageal varix (Lm, F1, Cw, RC negative). Transthoracic echocardiography (TTE) showed dilatation of the left ventricle and atrium, and mild diastolic dysfunction of the left side of the heart. The grade of tricuspid regurgitation (TR) and mitral regurgitation was mild, and the pressure gradient of TR was 17 mmHg. Abdominal ultrasonography revealed that the portal blood flow had not increased, and the patient did not have portal hypertension. Lung perfusion scintigraphy yielded a shunt ratio of 19.2% (Fig. 3A). Right heart catheterization (RHC) revealed a normal mean pulmonary artery pressure of 12 mmHg, pulmonary arterial wedge pressure of 5 mmHg, pulmonary vascular resistance (PVR) of 1.55 Wood units, and cardiac index of 4.6 L/min/$m^2$ (Table 2). Angiography of the pulmonary artery revealed a PAVM in the right middle lobe (Fig. 1F and G). The shunt and hypoxemia were caused by HPS and PAVM. She subsequently underwent liver transplantation and recovered well from that surgery without any complications. Four months after liver transplantation, hepatoviral C reinfection of the graft (G2a) occurred. Sofosbuvir and ribavirin were then administered, and a sustained virological response was obtained.

Fourteen months after liver transplantation, she was admitted for coil embolization of PAVM. BGA in room air revealed a $PaO_2$ of 69.1 mmHg and A-a$DO_2$ of 28.6 mmHg. Lung perfusion scintigraphy yielded a shunt ratio of 10.7% (Fig. 3B). TTE showed improvement in the dilatation of the left ventricle, mild diastolic dysfunction of the left heart, and mild mitral regurgitation, although dilatation of the left atrium remained. RHC revealed a mean pulmonary arterial pressure of 26 mmHg. No complications occurred during or after coil embolization. The mean pulmonary arterial pressure did not increase during coil embolization and was 22 mmHg on 2 L/min oxygen inhalation after coil embolization (Table 2).

Six months after coil embolization for PAVM, a BGA on room air showed a $PaO_2$ of 87.5 mmHg and an A-a$DO_2$ of 11 mmHg. TTE showed improvement in the dilatation of the left atrium. Lung perfusion scintigraphy yielded a shunt ratio of 6.8% (Fig. 3C). RHC revealed a mean pulmonary artery pressure of 18 mmHg. Even at one year after coil embolization, the mean pulmonary artery pressure remained normal (Table 2).

## Discussion

The present case carries two notable clinical findings. First, HPS can be accompanied by PAVM and shows a re-

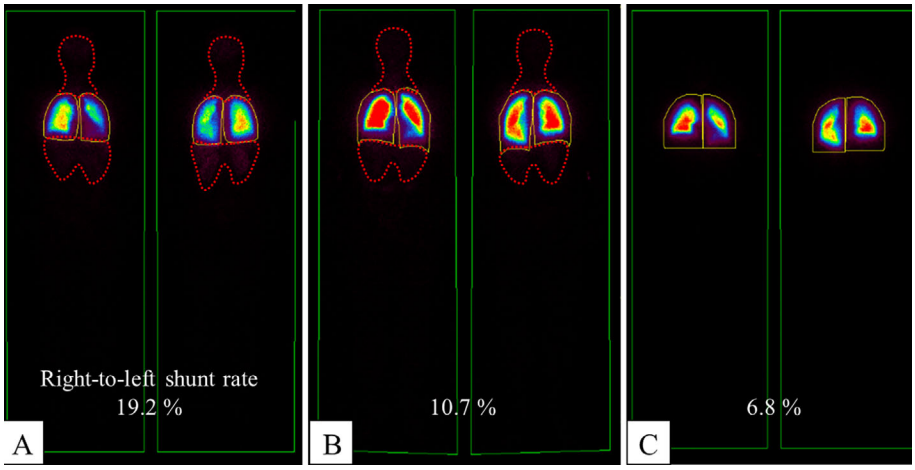


**Figure 3.** **Lung blood perfusion scintigraphy showed the accumulation in organs other than the lungs before and 14 months after liver transplantation (A, B). Twenty months after liver transplantation (six months after coil embolization), the accumulation in organs other than the lungs had disappeared.**

**Table 2.** **Pulmonary Hemodynamics from before Liver Transplantation until after Coil Embolization for Pulmonary Arteriovenous Malformation.**

| | Normal Range | Before liver transplantation (room air) | 14M after liver transplantation | | 20M after liver transplantation |
|---|---|---|---|---|---|
| | | | Before coil embolization (room air) | Immediately after coil embolization ($O_2$2L/min) | 6M after coil embolization (room air) |
| $PaO_2$ (mmHg, Room air) | | 71.7 | 69.1 | - | 87.5 |
| Systolic Pulmonary Arterial Pressure (mmHg) | 15-25 | 22 | 40 | 34 | 31 |
| Diastolic Pulmonary Arterial Pressure (mmHg) | 8-15 | 6 | 17 | 15 | 9 |
| Mean Pulmonary Arterial Pressure (mmHg) | <25 | 12 | 26 | 22 | 18 |
| Pulmonary Arterial Wedge Pressure (mmHg) | 3-13 | 5 | 13 | - | 7 |
| Pulmonary Vascular Resistance (Wood unit) | -3 | 1.55 | 3.75 | - | 3.61 |
| Cardiac Index (L/min/$m^2$) | 2.5-4.0 | 4.61 | 3.47 | 3.31 | 3.05 |

markable right-to-left shunt with hypoxia. Second, in a patient who has HPS and PAVM, hypoxemia may persist over the course of treatment, and the patient may develop PH.

In patients with HPS, vasodilator production in the liver increases and reaches the lungs. This causes the lung capillaries to dilate considerably, resulting in V/Q mismatch and hypoxemia. Although PAVM is sometimes reported to accompany HPS (5), there is a possibility that this PAVM may present as intra-pulmonary vasodilatation (IPVD), which is diffusely dilated pulmonary capillary (6). In contrast, original PAVM is a congenital vascular malformation caused by mesodermal angiogenesis failure and results in an abnormal shunt between the pulmonary arteries and veins. Multiple PAVMs are reported in 30% of cases; most cases of multiple PAVMs are related to hereditary hemorrhagic telangiectasia (HHT). In fact, HPS has not been listed as the causative disease of PAVM (4). In this case, because the shunt rate seen on lung blood perfusion scintigraphy was higher than that seen in a single PAVM (19.2%), we considered that our patient might also have HPS. In fact, the first RHC showed low PVR and high cardiac output, which was consistent with HPS. In addition, even after liver transplantation, hypoxemia persisted due to the shunt caused by a single PAVM. HPS and PAVM rarely merge, in which case, a large shunt can develop.

Patients with coexisting HPS and PAVM may also develop PH during the course of treatment. HPS and portal hypertension are the primary conditions affecting pulmonary hemodynamics in patients with liver cirrhosis. In such patients, both the vasodilator and vasoconstrictor, which are not metabolized in the liver, flow into the pulmonary artery, and whether or not HPS and portal hypertension merge depends on the balance between this vasodilator and vasoconstrictor (7). In contrast, HHT, a causative factor for PAVM, rarely complicates PH (8). In the present case, no increase in the portal blood flow was seen on abdominal ultrasonography in either the preoperative or postoperative phase. In addition, as the diagnostic criteria for HHT were not fulfilled in this case, we concluded that the patient did not have PH due to HHT. In this case, the patient showed a decrease in PVR from the shunt because of vasodilatation before surgery, although some amount of the vasoconstrictor

might be flowing into the pulmonary artery. This was primarily because of HPS and PAVM reducing the pulmonary arterial pressure and the shunt increasing the cardiac output. The PVR was low because of a combination of all of these factors. However, this high cardiac output state might induce shear stress in the pulmonary artery, which can cause pulmonary vascular remodeling. After liver transplantation, although vasodilatation due to HPS disappeared, pulmonary vascular remodeling may still remain. As a result, the PVR increased. Furthermore, although the cause is unknown, an increase in the pulmonary artery wedge pressure also appeared, resulting in PH. The pulmonary artery pressure ultimately decreased, presumably due to the normalization of the cardiac output as a result of coil embolization for PAVM and the improvement of pulmonary vascular remodeling.

Liver transplantation in patients with liver cirrhosis without PH does not affect pulmonary hemodynamics and normalizes the PVR (9). Furthermore, PH rarely occurs after liver transplantation in patients with HPS (10). This phenomenon may be caused by dysregulation of a shared vascular signaling pathway, which may lead to either pulmonary vasoconstriction or vasodilation or preferential binding of endothelin-1 to either the endothelin-1A or endothelin-1B receptor (11). In the present case, because the blood flow through the shunt of PAVM, which had low vascular resistance, was interrupted due to coil embolization, and the blood flowed into other pulmonary arteries, an increase in the PVR and exacerbation of PH were considered. Furthermore, PH did not recur during RHC at 20 months after liver transplantation (Table 2). This suggests that the treatment for PAVM might not have affected the development of PH after liver transplantation. However, PAVM may also show central nervous symptoms, such as paradoxical cerebral infarction (12). There was a risk of these complications occurring during the perioperative period. When this patient was referred to our department, the date of liver transplantation was confirmed. Despite explaining the risk of complications of PAVM in the perioperative period to the gastrointestinal surgeons and the patient, she expressed a desire to undergo early liver transplantation. Thus, liver transplantation preceded the treatment of PAVM. If PAVM treatment is performed first, there is no need to worry about PH exacerbation or complications due to PAVM during or after liver transplantation.

## Conclusion

The present case of HPS and PAVM in combination may have shown unique changes in the pulmonary hemodynamics during treatment. It is important to correctly understand the symptoms and pathology of both diseases in order to understand the pulmonary hemodynamics and provide appropriate treatment.

**The authors state that they have no Conflict of Interest (COI).**

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