A Case of Hypopituitarism Complicated by Non-Alcoholic Steatohepatitis and Severe Pulmonary Hypertension

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
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Patient: Female, 43-year-old
Final Diagnosis: Portopulmonary hypertension
Symptoms: Dyspnea
Medication: —
Clinical Procedure: —
Specialty: Critical Care Medicine • Medicine, General and Internal

Objective: Rare disease

Background: Pulmonary arterial hypertension (PAH), which is caused by increased pulmonary artery pressure, results in right-heart failure and presents with shortness of breath, chest pain, and syncope. PAH has idiopathic, heritable, and drug/toxin causes and is accompanied by other conditions, including connective tissue disease, congenital heart disease, and portal hypertension. Rarely, portal hypertension causes a type of PAH called portopulmonary hypertension (POPH). Portal hypertension can be triggered by liver cirrhosis, which can result from non-alcoholic steatohepatitis (NASH), a metabolic syndrome caused by hypopituitarism. Although an association between hypopituitarism and POPH has been suggested, few reports have described this relationship.

Case Report: A 43-year-old woman with hypopituitarism received hormone replacement therapy after partial hypothalamic resection at age 4 years. At age 32 years, she developed liver cirrhosis from NASH due to adult growth hormone (GH) deficiency. Despite restarting GH replacement therapy, she refused the required GH doses for economic reasons. She was hospitalized with abdominal pain and dyspnea and was found to have severe POPH. She received PAH-specific therapies, including endothelin receptor antagonist and prostacyclin analog. Pulmonary hypertension improved on day 3 of hospitalization while the cardiac index increased gradually. On day 12, her respiratory status rapidly worsened and percutaneous cardiopulmonary support was applied. On day 18, she died of multiple organ failure and disseminated intravascular coagulation despite intensive care management.

Conclusions: Severe PAH, particularly POPH, remains incurable despite the use of PAH-specific therapies and intensive care management. For hypopituitarism patients, careful observation, including of the cardiopulmonary system, can improve the prognosis after completing hormone replacement therapy.

MeSH Keywords: Hypertension, Portal • Hypertension, Pulmonary • Hypopituitarism • Prostaglandins I

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Background

Pulmonary hypertension is caused by the constriction or remodeling of the pulmonary artery, which leads to right-heart failure. One type of pulmonary hypertension is pulmonary arterial hypertension (PAH). Its hemodynamics are defined as a mean pulmonary arterial pressure (mPAP) exceeding 25 mmHg, a pulmonary capillary wedge pressure (PCWP) less than 15 mmHg, and a pulmonary vascular resistance greater than $240 \text{ dyne} \cdot \text{s} \cdot \text{cm}^{-5}$ by right-heart catheterization [1]. Although PAH occurs as a complication of other diseases, such as connective tissue disease, congenital heart disease, and portal hypertension, only 1% to 2% of patients with portal hypertension develop PAH, a condition known as portopulmonary hypertension (POPH) [2]. In addition to POPH, hepatopulmonary syndrome (HPS) is another important pathophysiological event in patients with liver cirrhosis. HPS is characterized by intrapulmonary vasodilation and impaired gas exchange, indicating a pathophysiology that differs from that of HPS [3].

PAH management was previously restricted to the use of diuretics, calcium channel blockers, and similar pharmaceutical approaches. Its prognosis was not favorable, with a 5-year life expectancy of just 34% [4]. However, the development of PAH-specific therapies has improved PAH outcomes and increased the survival rate [5]. Among PAH-specific therapies, the endothelin receptor antagonist macitentan reduces the production of calcium ions and inhibits vasoconstriction [3]. For patients with POPH, macitentan decreases the risk category for liver transplant mortality [6]. In contrast, the prostacyclin analog epoprostenol is a pulmonary artery vasodilator. Prostacyclin causes vasodilation and stimulates antiplatelet aggregation and the antiproliferative activity of vascular smooth muscle cells. Because the prostacyclin level is reduced in patients with PAH, administration of epoprostenol effectively improves their hemodynamics [7]. Furthermore, the dosing of epoprostenol should be increased carefully because the drug can induce hepatotoxicity and portal hypertension and increase blood flow via a portosystemic shunt, which would worsen the pathology of POPH [3]. Although there are some reports that epoprostenol ameliorates mPAP in patients with POPH, it has a negligible effect on portal hypertension. Thus, the management of severe POPH is still difficult [3,8].

Growth hormone (GH), a pituitary hormone, plays a significant role in lipid metabolism. It promotes the degradation and excretion of lipids and suppresses lipid synthesis; thus, GH deficiency is associated with the development of non-alcoholic steatohepatitis (NASH) [9]. The improvement of fatty liver by GH treatment in a 17-year-old boy with panhypopituitarism was reported in 1997 [10]. Subsequently, it was shown that GH supplementation also improved hepatic function in patients with NASH [11,12]. For NASH patients with hypopituitarism, GH replacement therapy would likely ameliorate hepatic function.

Case Report

The current case report concerns a 43-year-old woman with a height and weight of 157 cm and 83.6 kg, respectively (body mass index, 33.9 kg/m^2), and a history of hypothalamic hamartoma. After she underwent a partial hypothalamic resection at the age of 4 years, she developed panhypopituitarism and received hormone replacement therapy including thyroid hormone (levothyroxine), corticosteroid (hydrocortisone), and GH (somatotropin). When she underwent surgery for a slipped femoral epiphysis at the age of 13 years, decreased hepatic function (aspartate aminotransferase [AST], $195 \text{ U/}\mu\text{L}$; alanine transaminase [ALT], $169 \text{ U/}\mu\text{L}$) was noted, which was suspected to be due to fatty liver, based on the results of abdominal ultrasonography. After completing GH replacement therapy at the age of 17 years, the patient's hepatic function was monitored and she received medication such as glycyrrhizic acid to improve her hepatic function. At that time, GH replacement therapy was not generally recognized as being able to improve hepatic function.

At the age of 32 years, the patient was hospitalized for bleeding from esophageal varices. Hepatic biopsy revealed the presence of liver cirrhosis from NASH, namely, a burned-out type of NASH (Child-Pugh classification grade B). The level of growth hormone was 0.3 ng/mL (reference range, $0.5\text{--}2.7 \text{ ng/mL}$). GH plays a significant role in lipid metabolism and its deficiency causes NASH. It was revealed that the patient had developed adult GH deficiency and was restarted on hormone replacement therapy. In addition, she had pituitary amenorrhea and started taking estrogen (conjugated estrogen) and progesterone (hydroxyprogesterone) as Kaufmann therapy. However, she could not receive the indicated GH dosage for economic reasons.

At the age of 43 years, the patient presented to her local hospital with stomach pain. After hospitalization, she had difficulty moving because of dyspnea. The results of transthoracic echocardiography estimated pulmonary arterial pressure (PAP) and mean pulmonary arterial pressure (mPAP) values of $112/38 \text{ mmHg}$ and 45 mmHg , respectively, suggesting severe pulmonary hypertension. To manage her pulmonary hypertension, she was transferred to our hospital. She was conscious with a heart rate of 90 beats/min, systemic blood pressure of $132/101 \text{ mmHg}$, and SpO_2 of 90% under administration of 4 L of oxygen by face mask. A chest X-ray showed cardiac enlargement (cardiothoracic ratio, 65%) and pulmonary congestion (Figure 1). The transthoracic echocardiography results revealed mild pulmonary valve regurgitation and moderate tricuspid valve regurgitation and a D-shaped left ventricle compressed by a dilated right ventricle during the entire cardiac cycle. Right-heart catheterization determined a PAP of $118/55 \text{ mmHg}$, mPAP of 82 mmHg , pulmonary vascular resistance of $1405 \text{ dynes} \cdot \text{s} \cdot \text{m}^{-5}$, PCWP of 30 mmHg , and cardiac index of

Figure 1. Chest X-ray shows cardiac enlargement (arrowhead) and pulmonary congestion (arrow).

1.33 L/min/m². A previous report suggested that an increased PCWP should not rule out the diagnosis of POPH because left-heart failure accompanied by portal hypertension sometimes increases the PCWP [13]. The results indicated our patient had severe pulmonary hypertension and heart failure of Forrester's subset IV. Computed tomography (CT) revealed a rough surface and atrophy of the liver, splenomegaly, and the development of portal collateral circulation with ascites, indicating that her pulmonary hypertension was consistent with POPH (**Figure 2**). Pulmonary embolism was ruled out as the cause of pulmonary hypertension by CT. Child-Pugh classification was grade C (no hepatic encephalopathy, moderate ascites, bilirubin 6.3 mg/dL, albumin 3.5 g/dL, and PT 42%). Viral hepatitis and autoimmune hepatitis were excluded as causes of the patient's hepatic dysfunction based on tests for hepatitis viral antigen and antibodies and autoimmune antibodies such as anti-nuclear antibody (**Table 1A**).

To treat her pulmonary hypertension, the patient was administered the prostacyclin analog epoprostenol through a Swan-Ganz catheter. Epoprostenol was first administered at a dose of 0.199 ng/kg/min and the dosage was carefully increased by 0.15 to 0.5 ng/kg/min every 5 to 10 h. She was also administered 10 mg/d of the endothelin receptor antagonist macitentan, which decreases portal pressure by acting on hepatic stellate cells [3].

Due to the liver cirrhosis and splenomegaly, the patient had anemia (hemoglobin, 9.3 g/dL), a low platelet number (32 000/mL), and a coagulation abnormality (PT sec, 42%;

Figure 2. Abdominal image by computed tomography shows atrophy of right lobe and surface irregularity indicating liver cirrhosis (arrowhead) and pleural effusion (star) and ascites (double star).

PT-INR, 1.44) (**Table 1B**) and received a transfusion of blood products. A diuretic and continuous hemodiafiltration were applied to control the patient's hemodynamic state. For hormone replacement therapy, somatotropin injection was administered intermittently because it causes hypervolemia and increases peripheral blood resistance.

On day 3 of hospitalization, the patient's mPAP fell from 82 to a range of 56 to 63 mmHg on 1.34 ng/kg/min of epoprostenol, without hypotension. She had continual abdominal pain and her amylase level rose from 47 to 327 U/L (reference range, 46–136 U/L). An abdominal CT showed an enlarged pancreas and a peripheral dirty fat sign, indicating pancreatitis. The patient was revealed to have an enlarged gallbladder containing biliary sludge, which can obstruct the pancreatic duct and lead to acute pancreatitis. Protease inhibitors, 300 000 units/d of ulinastatin and 0.07 mg/kg/h of nafamostat mesilate, were administered.

On day 5, adverse effects of epoprostenol such as headache and diarrhea were recognized. Because the patient could tolerate the symptoms, the epoprostenol dose was carefully increased. She also showed jaundice and became drowsy, suggesting the development of hepatic encephalopathy. To ameliorate hepatic failure, the patient was given 600 mg/d of ursodeoxycholic acid and 500 mL/d of aminoleban. On day 11, her mPAP was still 57 to 64 mmHg and did not further decrease, even though the epoprostenol dose was increased to 6.173 ng/kg/min. Oral administration of 2.5 mg/d of the calcium blocker amlodipine was added to dilate the pulmonary artery.

On day 12, on 7.128 ng/kg/min of epoprostenol, the patient's cardiac index was 4.2 L/min/m², an approximate 3-fold increase

Table 1. (A) Laboratory data at administration in our hospital. (B) Changes over times in lipid metabolism.

(A)

RBC	443×10 ⁴ /ml	Na	139 mEq/L	Anti-nuclear antibody	–
WBC	9300/ml	K	4.2 mEq/L	Anti DNA antibody	–
Plt	3.2×10 ⁴ /ml	Cl	104 mEq/L	Anti-Sm antibody	–
Hb	9.3 g/dL	Ca	8.0 mEq/L	Anti-SS-A antibody	–
TP	6.2 g/dL	PT	42%	Anti-SS-B antibody	–
Alb	3.5 g/dL	PT-INR	1.44	Anti-Scl-70 antibody	–
T-Bil	6.3 mg/dL	APTT	37.4 sec	HBs antigen	–
D-Bil	1.51 mg/dL	BNP	2492 pg/mL	HBs antibody	–
				HbC antibody	–
				HCV antibody	–
Reference value					
AST	211 U/L	HbA1c (NGSP)	6.50%	IgG	1024 mg/dL 870–1700 mg/dL
ALT	88 U/L	BUN	34 mg/dL	IgA	358 mg/dL 110–410 mg/dL
LDH	1249 U/L	Cre	2.07 mg/dL	IgM	259 mg/dL 46–260 mg/dL
γ-GTP	26 U/L	CRP	5.38 mg/dL	CH50	30.7 U/mL 30–45 U/mL
AMY	47 U/L			C3	63 mg/dL 65–135 mg/dL
				C4	16 mg/dL 11–34 mg/dL

(B)

	Age 33	Age 43	Reference value
LDL-C	138 ↑	101	60–119 mg/dL
HDL-C	65	3.6 ↓	>40 mg/dL
T-Cho	221 ↑	155	140–199 mg/dL
TG		78	30–149 mg/dL
GH	0.18 ↓	0.65 ↓	0.66–3.68 ng/dL

compared with that at admission, indicating a hyperdynamic state with no further decreases in her mPAP (Figure 3). On day 15, she had respiratory distress and her cardiopulmonary congestion was worse as indicated by chest X-ray. Her systolic pressure decreased to a range of 40 to 50 mmHg, and 1.2 µg/kg/min of dopamine, 0.025 µg/kg/min of noradrenaline, and 0.07 µg/kg/min of adrenaline were administered. Although her hemodynamic state was regulated by continuous hemodiafiltration, hydration was difficult owing to her hypotension. In addition, she became almost unresponsive to diuretics.

On day 16, the patient's respiration rate had increased to 40 to 50 breaths/min. The partial pressure of oxygen (pO₂) in the arterial blood was 49 mmHg under administration of 10 L of oxygen by reservoir mask. After tracheal intubation, her oxygenation did not improve; her pO₂ was 54 mmHg under

mechanical ventilation with 100% O₂. Percutaneous cardiopulmonary support was immediately introduced. In accordance with her respiratory failure, hepatorenal failure (AST, 1130 U/µL; ALT, 6242 U/µL; and creatinine, 2.62 mg/dL) with acidosis (pH 7.29) and hyperkalemia (potassium, 5.9 mEq/L) developed. On day 17, her hepatic failure progressed rapidly (AST, 5200 U/µL; ALT, 18499 U/µL). Hypotension continued, despite an increase in the catecholamine dose and administration of 100 mg/d of hydrocortisone. Furthermore, she began bleeding from the nasal cavity and gastric tube. On day 18, the patient died of multiple organ failure and disseminated intravascular coagulation.

Figure 3. Changes over time in mean pulmonary arterial pressure (mPAP) and cardiac index (CI) with the administration of epoprostenol.

Discussion

Pituitary gland dysfunction has many possible triggers, which include congenital, traumatic, and tumorigenic causes. Pituitary hormone deficiency is treated with hormone replacement therapy. One such pituitary hormone, GH, suppresses the synthesis of lipids and promotes lipid degradation by activating hormone-sensitive lipase, which reduces triglyceride accumulation in hepatocytes. Indeed, NASH develops in mice deficient in Janus kinase-2, a component of the signaling pathway for the GH receptor. IGF-1, mainly produced in the liver through GH stimulation, reduces oxidative stress and fibrosis, which could also prevent the development of NASH. In patients with adult GH deficiency, these functions decline and NASH or liver cirrhosis can develop [9,14]. Thus, replacement of GH would likely improve hepatic function in these patients [11,12].

Liver cirrhosis leads to portal hypertension and collateral circulation. Such a hyperdynamic state induces shear stress of the pulmonary artery wall and remodeling of the pulmonary artery. In addition, the metabolism of vasoconstrictors such as endothelin and angiotensin and inflammatory substances such as interleukin-1 and -6 is decreased in liver cirrhosis, causing

constriction or inflammation of the pulmonary artery. These pathological changes induce the development of POPH [3]. Our patient had abdominal complications of cholecystitis and pancreatitis. The metabolism of inflammatory substances is decreased in liver cirrhosis, causing constriction or inflammation of the pulmonary artery. It is possible that a declined ability to metabolize elevated inflammatory cytokines would worsen pulmonary vascular constriction. This condition might account for our patient's acute decompensation.

A previous case report documented the development of hypopituitarism after radiation therapy of the sella turcica in a 17-year-old girl with Langerhans' cell histiocytosis [15]. She developed liver cirrhosis and POPH, which was not severe (PAP of 72/41 mmHg and mPAP of 41 mmHg, estimated by right-heart catheterization). Her condition was stabilized through treatment with the phosphodiesterase-5 inhibitor sildenafil and the inhalational prostacyclin analog iloprost. To our knowledge, there are very few reports of POPH complicated with hypopituitarism except for the above case and our patient. It is worth mentioning that, compared with the above case, our patient's condition was severe, to the extent that the PAP was nearly equivalent to the systemic pressure.

Importantly, POPH develops in very few patients with portal hypertension [2]. One report linked a genetic risk factor to the development of POPH [16]. Single nucleotide polymorphisms, such as those in estrogen receptor type I, aromatase, and phosphodiesterase 5 (PDE5), may account for the development of POPH. In particular, single nucleotide polymorphisms in PDE5 in patients with POPH is an interesting possibility. Nitric oxide acts on endothelial smooth muscle cells and produces cyclic guanosine monophosphate, a second messenger of nitric oxide, causing vasodilation. PDE5 plays an important role in the hemodynamics of the pulmonary artery through the degradation of cyclic guanosine monophosphate [3].

Although POPH is improved by PAH-specific therapies, they have little effect on portal hypertension. Therefore, the prognosis of POPH would not be greatly altered [8]. Liver transplantation is considered a fundamental treatment for POPH, and the mPAP should be less than 35 mmHg, using a vasodilator for transplantation. If the mPAP is greater than 45 mmHg, transplantation is not recommended owing to the perioperative risk. Alternatively, a vasodilator such as epoprostenol is recommended [17]. Because POPH is still an incurable disease, an earlier diagnosis and therapies including PAH-specific drugs and intensive care would significantly improve the prognosis. We emphasize the need for systemic examination, including of the cardiopulmonary system, even after the completion of hormone replacement therapy, and application hormone replacement therapy to prevent the progression of hepatic failure.

Conclusions

POPH induced by hypopituitarism is an uncommon and severe disease. Critical care management including PAH-specific therapies is necessary. GH replacement is important for preventing progression from NASH to liver cirrhosis in hypopituitarism and improving patient prognosis.

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Conflict of interest

None.