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Case Report

Long-term Follow-up of Qing-Dai–Induced Pulmonary Arterial Hypertension: A Case Series

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Qing-Dai, a Chinese herbal medicine, has been shown to have anti-inflammatory effects in refractory inflammatory bowel disease (IBD). However, pulmonary arterial hypertension (PAH) is one of the most serious side effects, and the long-term clinical course of Qing-Dai–induced PAH remains unknown. We present 2 patients with PAH, whose hemodynamics normalized after discontinuation of Qing-Dai and administration of pulmonary vasodilators. Notably, PAH relapsed following the discontinuation of vasodilators. This study suggests that regular checkups are necessary for patients with chronic Qing-Dai–induced PAH.

Patient 1

Presentation history

This study was approved by the Ethics Committees of Keio University Hospital and Kyorin University Hospital. Patient 1 was a 33-year-old woman who complained of shortness of breath upon exertion. Her vital signs at initial assessment were as follows: body temperature of 36.3°C, blood pressure of 108/64 mm Hg, and heart rate of 78 beats/min. Her symptoms were classified as World Health Organization Functional Class (WHO-FC) III. On auscultation, the pulmonary field was clear, a murmur of tricuspid valve regurgitation was heard, and P2 was enhanced in the left upper sternal border. No lower-extremity edema or jugular venous pressure elevation was observed.

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Medical history

Patient 1 developed ulcerative colitis at age16 years and had visited a gastroenterology department regularly. She had been taking the Chinese herbal medicine Qing-Dai (2 g/d) for 3.5 years as an effective treatment for ulcerative colitis.

Investigations

Chest radiography of patient 1 showed enlargement of the right pulmonary interlobar artery and the left pulmonary artery trunk (Fig. 1A). Echocardiography revealed ventricular septal compression during systole, an estimated pulmonary artery systolic pressure (PASP) of 68 mm Hg, and a tricuspid annular plane systolic excursion (TAPSE) of 20 mm (Fig. 1B). Electrocardiography revealed normal axial deviation and no criteria for right atrial enlargement in lead II. Negative T-waves were observed in the thoracic leads V1 to V3 (Fig. 1C). Laboratory tests revealed elevated serum levels of B-type natriuretic peptide (BNP; 30.3 pg/mL, normally < 18.4 pg/mL). No specific autoantibodies were detected. Her 6-minute walking test distance (6 MWTD) was 577 m. Right heart catheterization (RHC) showed a pulmonary artery pressure (PAP) of 74/26 mm Hg (mean, 44 mm Hg), a pulmonary vascular resistance (PVR) of 8.49 Wood units, a mean right atrial pressure (RAP) of 7 mm Hg, a mean pulmonary artery wedge pressure (PAWP) of 10 mm Hg, a cardiac output (CO) of 4.01 L/min, a cardiac index (CI) of 2.49 L/min per m^2, and a venous oxygen saturation (SvO2) of 68.3%. CO was calculated using the indirect Fick method, and the oxygen consumption was estimated as 125 mL O_2/min multiplied by body surface area. Oximetry did not reveal any left-to-right shunts. Lung perfusion scintigraphy and spirometry results were near normal.

Differential diagnosis

Based on the patient's medical history, Qing-Dai–induced PAH was the most likely diagnosis. The diseases associated

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Novel Teaching Points

- Follow-up in patients with PAH is important, even after normalization of hemodynamics.
- Qing-Dai intake has reversible and irreversible effects on development of PAH.

with the development of PAH were excluded as follows: connective tissue diseases by the blood testing of antibodies, and physical examinations; congenital heart diseases by echocardiography; and chronic thromboembolic diseases by a negative V/Q scan.

Management

The patient discontinued Qing-Dai intake after the diagnosis of PAH. One month later, the patient's symptoms and electrocardiographic findings remained unchanged. Thus, macitentan (10 mg/d) was administered, followed by riociguat (initial 1.0 mg, 3 times per day, titrated to 2.5 mg, 3 times per day). Her WHO-FC, chest radiograph (Fig. 1D), echocardiogram (Fig. 1E), and electrocardiogram (Fig. 1F) findings improved after 4 years of treatment. Echocardiography demonstrated an estimated PASP of 23 mm Hg and a TAPSE of 25 mm. Her 6MWTD was 596 m. Although a sufficient follow-up of hemodynamic measures could not be performed due to the COVID-19 pandemic, vasodilators for PAH were discontinued at the patient's request. However, approximately 6 months later, chest radiography (Fig. 1G), echocardiography (Fig. 1H), and electrocardiography (Fig. 1I) suggested PAH recurrence. Echocardiography demonstrated an estimated PASP of 45 mm Hg, and the TAPSE decreased to 21 mm. Her 6MWTD decreased to 510 m. RHC demonstrated a PAP of 31/15 mm Hg (mean, 21 mm Hg), PVR of 2.59 Wood units, a mean RAP of 5 mm Hg, a mean PAWP of 8 mm Hg, a CO of 5.01 L/min, a CI of 3.01 L/min per m^2, and SvO2 of 74.3%. Because she experienced shortness of breath on exertion, macitentan (10 mg/d) was resumed, and her symptoms and hemodynamics improved. One year after treatment initiation, echocardiography revealed an estimated PASP of 28 mm Hg, a TAPSE of 26 mm, and normal right ventricular function. The clinical course of patient 1 is shown in Figure 1J.

Patient 2

Presentation history

Patient 2, a 20-year-old man, was referred to our hospital due to complaints of dyspnea at rest. Upon assessment, the patient's symptoms were classified as WHO-FC IV. His vital signs at initial assessment were a body temperature of 36.8°C, blood pressure of 93/70 mm Hg, a heart rate of 110 beats/min, and a respiration rate of 16 breaths/min. The patient presented with a distended jugular vein and prominent hepatomegaly.

Medical history

Patient 2 had been diagnosed with and treated for ulcerative colitis at age 1 year. However, the diagnosis changed to Crohn's disease when he was age 17 years. He had taken Qing-Dai to stabilize his Crohn's disease for 6 months before the onset of shortness of breath occurred.

Investigations

Chest radiography revealed marked cardiac and pulmonary artery trunk enlargements (Fig. 2A). Echocardiography revealed dilatation of the right ventricle, a flattened interventricular septum, a high estimated PASP of 82 mm Hg, and pericardial effusion (Fig. 2B). The electrocardiogram showed large negative T-waves from V1 to V4, increased R-wave amplitudes in V1, and deep S-waves in the V5-V6 leads (Fig. 2C). Laboratory tests revealed an abnormal BNP level of 122.6 pg/mL. No specific autoantibodies were detected. RHC revealed severe pulmonary hypertension, with a PAP of 85/34 mm Hg (mean, 53 mm Hg), a PVR of 26.5 Wood units, a mean RAP of 17 mm Hg, a mean PAWP of 8 mm Hg, a CO of 1.70 L/min, a CI of 1.27 L/min per m^2, and an SvO2 of 33.4%. Oximetry did not reveal any left-to-right shunts. Lung perfusion scintigraphy results were near normal.

Differential diagnosis

The hemodynamic analysis satisfied the criteria for PAH. Given that the patient developed PAH after the Qing-Dai intake, Qing-Dai–induced PAH was the most likely diagnosis. Regarding the diseases associated with the development of PAH—congenital heart disease and chronic thromboembolic disease were excluded on the basis of the above investigations.

Management

The patient was administered dobutamine (2.0 μg/kg/min), tadalafil (40 mg/d), and intravenous epoprostenol infusion of up to 40 ng/kg/min for PAH treatment. After 1.5 years, RHC demonstrated a mean PAP of 17 mm Hg, a PVR of 1.39 Wood units, a mean RAP of 1 mm Hg, a mean PAWP of 6 mm Hg, a CO of 7.91 L/min, a CI of 5.21 L/min per m^2, and an SvO2 of 82%, suggesting a high output status. Moreover, the patient's skin flushing worsened. Thus, intravenous epoprostenol infusion was gradually reduced and discontinued. He also was directed to stop tadalafil intake because his hemodynamics, chest radiography (Fig. 2D), echocardiogram (Fig. 2E), and electrocardiogram (Fig. 2F) normalized after epoprostenol discontinuation. Echocardiography revealed an estimated PASP and TAPSE of 25 mm Hg and 22 mm, respectively. However, the patient was subsequently lost to follow-up while experiencing stable symptoms. Six years later, chest radiography (Fig. 2G), echocardiography (Fig. 2H), and electrocardiography (Fig. 2I) were performed as preoperative tests for cholecystectomy; the recurrence of severe pulmonary hypertension was observed. Echocardiography revealed a high estimated PASP of 77 mm Hg, and a low TAPSE of 16 mm, suggesting right ventricular dysfunction. Subsequent RHC demonstrated a mean PAP of 35 mm Hg, a PVR of 6.92 Wood units, a mean RAP of 1 mm Hg, a mean PAWP of 4 mm Hg, a CO of 4.54 L/min, a CI of 2.91 L/min per m^2, and an SvO2 of 70.6%, indicating PAH recurrence. The patient was prescribed macitentan (10 mg/d) and tadalafil (20 mg/d). Four months later, echocardiography showed an improved TAPSE of 21 mm. RHC showed a

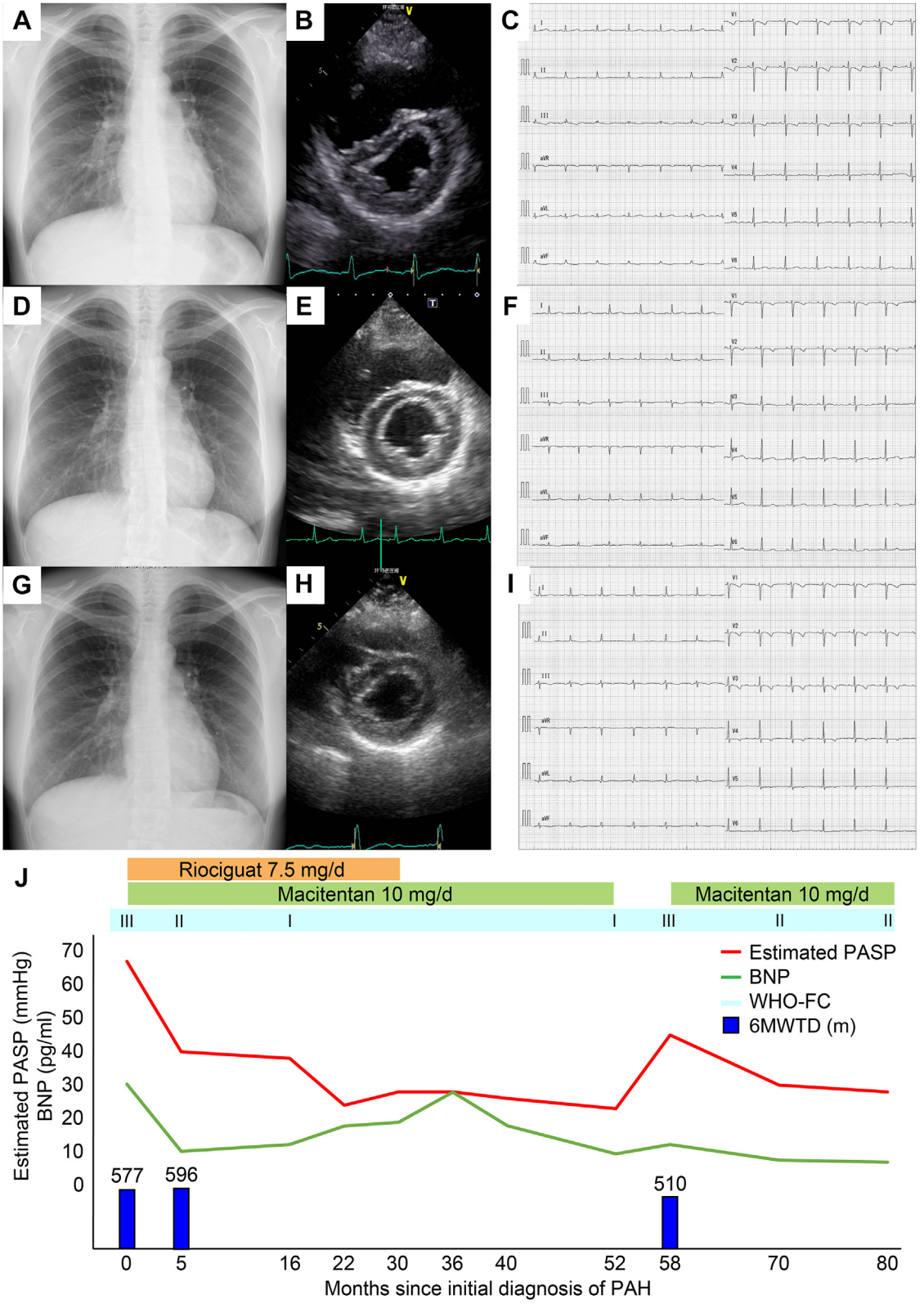

Figure 1. Imaging findings and clinical course of patient 1. Chest radiograph, echocardiogram (parasternal view, short axis), and electrocardiogram data (**A-C**) at initial diagnosis, (**D-F**) at discontinuation of vasodilators, and (**G-I**) at recurrence of pulmonary arterial hypertension. (**J**) Clinical course of patient 1. Estimated pulmonary arterial systolic pressure (PASP) was measured by echocardiogram. BNP, B-type natriuretic peptide; PAH, pulmonary arterial hypertension; WHO-FC, World Health Organization functional class; 6MWTD, 6-minute walking test distance.

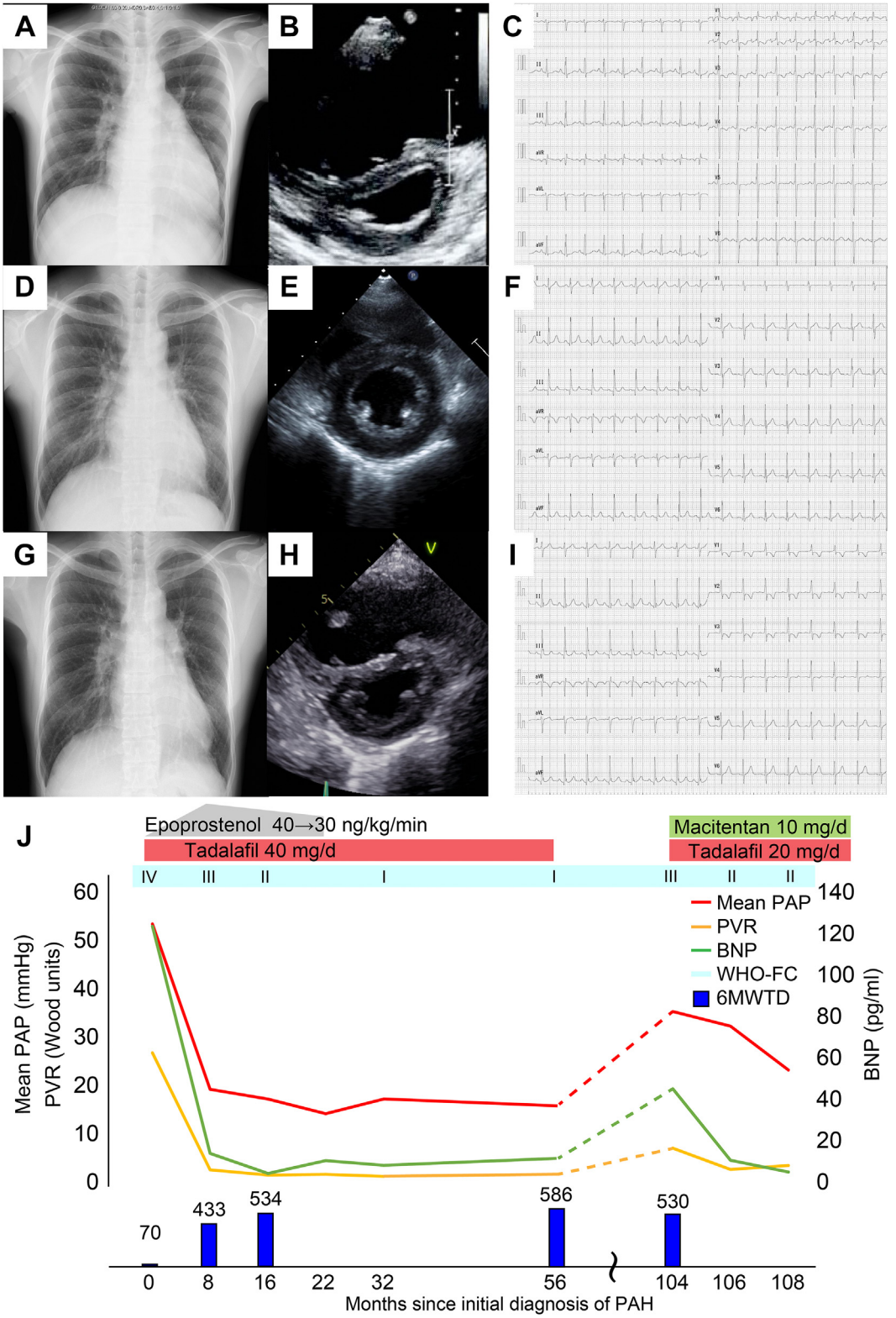

Figure 2. Imaging findings and clinical course of patient 2. Chest radiograph, echocardiogram (parasternal view, short axis), and electrocardiogram data (**A-C**) at initial diagnosis, (**D-F**) at discontinuation of vasodilators, and (**G-I**) at recurrence of pulmonary arterial hypertension (PAH). (**J**) Clinical course of patient 2. **Dashed lines** indicate the period during the loss to follow-up. BNP, B-type natriuretic peptide; PAP, pulmonary arterial pressure; PVR, pulmonary vascular resistance; WHO-FC, World Health Organization functional class; 6MWTD, 6-minute walking test distance.

reduced mean PAP of 23 mm Hg, a PVR of 3.37 Wood units, a mean RAP of 2 mm Hg, a mean PAWP of 4 mm Hg, a CO of 5.64 L/min, a CI of 3.77 L/min per m^2, and an SvO2 of 73.0%, indicating hemodynamic improvement. The clinical course of patient 2 is shown in Figure 2J.

Discussion

We encountered 2 cases of Qing-Dai—induced PAH that normalized after treatment with combination vasodilator therapy but relapsed several years after vasodilator discontinuation. The Chinese herbal medicine Qing-Dai has anti-inflammatory effects in refractory IBD. However, PAH is one of the most serious side effects of this medicine.[1] A nationwide survey in Japan found that 1.8% of 49,320 IBD patients were treated with Qing-Dai, and 1.2% (n = 11) of patients taking Qing-Dai for IBD developed PAH.[2] Furthermore, a prospective study demonstrated that the duration of the Qing-Dai intake period was associated with increased estimated PAP in IBD patients.[3]

Several studies have examined the mechanisms underlying Qing-Di—induced PAH. Qing-Dai contains a large number of aryl hydrocarbon receptor (AhR) ligands. AhR signal activation induces interleukin-22 synthesis by T helper 17 lymphocytes and promotes mucosal healing in the gut.[4] However, extreme AhR signaling in the lung may cause PAH via overproduction of vascular endothelial cells and narrowing of the lumen of pulmonary vessels.[5]

Previous reports on Qing-Dai—induced PAH have demonstrated marked improvements after the discontinuation of Qing-Dai and the administration of vasodilators for PAH; however, PAH recurrence has not been described.[6] Two causes of PAH recurrence have been proposed. First, prolonged administration of Qing-Dai may cause irreversible vascular remodelling, in addition to acute reversible vasoconstriction.[2] Chronic AhR signal activation, which is associated with cell proliferation and vascular inflammation,[5] may contribute to vascular injury and subsequent remodelling during long-term Qing-Dai treatment. Although vasodilators may provide temporary relief by improving vasoconstriction, the ongoing vascular injury may facilitate progressive vascular remodelling over time. Second, normal resting hemodynamics do not necessarily indicate that the pulmonary microvascular circulation is normal. In the present study, vasodilators were discontinued based on hemodynamic data at rest. Nevertheless, the pulmonary microcirculation still may have been damaged.

This case report has several limitations. First, vasodilator challenge tests were not performed at diagnosis. Vasodilator challenge is recommended by guidelines for drug- and toxin-related PAH, to identify patients who are responsive to vasodilators.[7] Second, hemodynamic assessment with RHC could not be performed before discontinuation of vasodilators in patient 1. Although the hemodynamic data of RHC were not compared, her symptoms, estimated PAP measured by echocardiography, serum BNP level, and 6MWTD worsened after the discontinuation of vasodilators, suggesting PAH recurrence. Third, in patient 1, the combination of macitentan and riociguat was initially used. In the current guideline, the combination of macitentan and tadalafil was recommended to the patients with PAH without cardiopulmonary comorbidities.[7] Finally, although the PAH medications were discontinued at the request of both patients, guidelines do not recommend discontinuation of pulmonary vasodilators in patients with drug-induced PAH.[7]

Conclusions

We report 2 cases of PAH recurrence after the discontinuation of Qing-Dai and pulmonary vasodilators. Reduction of pulmonary vasodilators in Qing-Dai—induced PAH should be performed with caution, and regular follow-up is vital even after normalization of hemodynamics.

Ethics Statement

This study was approved by the Ethics Committees of Keio University Hospital and Kyorin University Hospital.

Patient Consent

The authors confirm that a patient consent form has been obtained for this article.

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Disclosures

The authors have no conflicts of interest to disclose.

References

1. Nishio M, Hirooka K, Doi Y. Pulmonary arterial hypertension associated with the Chinese herb indigo naturalis for ulcerative colitis: It may be reversible. Gastroenterology 2018;155:577-8.
2. Naganuma M, Sugimoto S, Suzuki H, et al. Adverse events in patients with ulcerative colitis treated with indigo naturalis: a Japanese nationwide survey. J Gastroenterol 2019;54:891-6.
3. Orihara Y, Asakura M, Hida N, et al. Effect of oral Qing-Dai medication on pulmonary arterial pressure levels in patients with ulcerative colitis. Circ J 2020;84:1339-45.
4. Naganuma M. Treatment with indigo naturalis for inflammatory bowel disease and other immune diseases. Immunol Med 2019;42:16-21.
5. Hiraide T, Teratani T, Uemura S, et al. Pulmonary arterial hypertension caused by AhR signal activation protecting against colitis. Am J Respir Crit Care Med 2021;203:385-8.
6. Misumi K, Ogo T, Ueda J, et al. Development of pulmonary arterial hypertension in a patient treated with Qing-Dai (Chinese herbal medicine). Intern Med 2019;58:395-9.
7. Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J 2022;43:3618-731.