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Case Report

Development of pulmonary arterial hypertension following long-term Qing-Dai use for ulcerative colitis

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ABSTRACT

A 20-year-old woman using Qing-Dai for about 7 years for intractable ulcerative colitis was admitted to the emergency room because of dyspnea and syncope following exertion. The patient was diagnosed with drug-induced pulmonary arterial hypertension (PAH). Discontinuation of Qing-Dai rapidly improved PAH symptoms. The REVEAL 2.0 risk score, which is useful for assessing the severity of PAH and predicting prognosis, improved from high risk (12) to low risk (4) within 10 days. Discontinuing long-term use of Qing-Dai can rapidly improve Qing-Dai-induced PAH.

Learning objective: Discontinuing the long-term use of Qing-Dai used for treating ulcerative colitis (UC) can rapidly improve Qing-Dai induced pulmonary arterial hypertension (PAH). REVEAL 2.0 risk score in patients who developed PAH due to Qing-Dai was useful for screening PAH in patients taking Qing-Dai for treatment of UC.

Introduction

Pulmonary arterial hypertension (PAH) is a rare and intractable disease characterized by increased pulmonary arterial pressure and pulmonary vascular resistance due to pulmonary microvascular obstruction, which can ultimately lead to heart failure and death [1,2].

The Chinese herbal medicine Qing-Dai (indigo naturalis) has been reported to be effective in inducing remission in patients with moderate ulcerative colitis (UC). However, there have been several studies that suggest a possible relationship between Qing-Dai and PAH development, and in 2016, the Japanese Ministry of Health, Labour and Welfare issued a warning about the risk of PAH during Qing-Dai use for treating UC [3].

In this report, we describe a case of Qing-Dai induced PAH in a young woman who presented with shortness of breath and syncope following long-term use of Qing-Dai for treating UC. We report the rapid timeframe for recovery and a significant change in REVEAL 2.0 risk score [4] following the discontinuation of Qing-Dai.

Case report

A 20-year-old woman suffered from UC for about 9 years and had been taking the Chinese herbal medicine Qing-Dai (3 g/day) for about 7 years and had shown improved UC symptoms. She had no noted history of autoimmune or other diseases besides UC. There was no family history of note. About 2 years previously, the patient noticed increased dyspnea after walking or climbing stairs. After fainting, the patient was admitted to Gifu Prefectural General Medical Center, Gifu, Japan.

Upon admission, the patient had a blood pressure of 110/70 mmHg, heart rate of 130 beats per minute, respiratory rate of 20 per minute, oxygen saturation of 99 % on room air, and temperature of 35.7 °C. Her body mass index was 21. Her GCS score was 15. A physical examination revealed normal jugular venous distension, clear lung sounds, increased IIp heart sounds, soft abdomen, and no lower extremity swelling.

Complete blood counts were almost normal. D-dimer showed 2.04 μg/dL. Serum chemistries showed aspartate aminotransferase: 58 IU/L, alanine aminotransferase 56 IU/L, C-reactive protein: 5.97 g/dL, N-terminal prohormone of brain natriuretic peptide (NT-pro BNP): 1002 pg/mL, troponin I: slightly positive. Atrial blood gas with the patient breathing room air revealed pH: 7.48, partial pressure of arterial carbon dioxide: 26.6 mmHg, partial pressure of arterial oxygen: 72.1 mmHg, hydrogen carbonate ion: 19.7 mmol/L. Human immunodeficiency virus testing revealed negative. In special antibody analysis, lupus anticoagulant and anticardiolipin antibodies were positive.

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Chest X-ray indicated that the right second arch was protruding (Fig. 1A-a). Electrocardiogram (ECG) showed sinus tachycardia and broad negative T waves in II, III, aVF, and V1–6 leads (Fig. 1B-a). Echocardiogram showed no obvious thrombus in the veins of the lower extremities. Tricuspid regurgitation pressure gradient (TRPG) was 79 mmHg, inferior vena cave diameter was 18 mm with respiratory fluctuations. Systolic right ventricular pressure was estimated to be 82 mmHg (Fig. 1C-a, b). The respiratory functional test was normal. Hilar mediastinal lymphadenopathy and mild interlobular septal thickening on simple chest computed tomography (CT), but no lobular central frosted shadows on lung high-resolution CT was evident. Additionally, no contrast loss area in the pulmonary artery on contrast-enhanced CT (Fig. 1D-a) and no decrease in pulmonary blood flow on pulmonary blood flow scintigraphy were indicated (Fig. 1D-b).

From right heart catheterization, mean pulmonary artery pressure (PAP) was 59 mmHg, mean pulmonary artery wedge pressure (PAWP) was 10 mmHg, and pulmonary vascular resistance (PVR) was 14.41 mmHg min/L. With nitric oxide loading, mean PAP was 52 mmHg, and mean PAWP was 12 mmHg (Table 1).

Enlargement of the right atrium and ventricle, and elevation of TRPG in the echocardiography suggested the presence of pulmonary hypertension. Previous reports of patients developing PAH after taking Qing-Dai as a treatment strategy for UC, indicated discontinuing Qing-Dai as a treatment option [5]. According to such reports, we decided to discontinue her taking Qing-Dai. Diuretics and inotropic agents were not used for treatment of PAH. Her symptoms of dyspnea rapidly improved after discontinuing Qing-Dai, and completely disappeared after 5 days. The patient was discharged on the 10th day of hospitalization.

According to the US Registry to Evaluate Early and Long-term PAH Disease Management risk score (REVEAL 2.0) [4], which is useful in assessing the severity and predicting the prognosis of PAH, the patient score was 12 (High risk) at the time of initial treatment but showed marked improvement with a score of 4 (Low risk) at the time of discharge. During hospitalization, NT-pro BNP improved from 1002 pg/ml to 267 pg/ml. As for the 6-minute walk, the patient could hardly walk at the time of admission, but during the course of the treatment, she was able to walk about 200 m. At discharge, she was able to walk 460 m.

Table 1
Right heart catheterization on admission to chronic phase.

On admission	Systolic	Diastolic	Mean	
PAP	87	42	59	mmHg
PAWP	10	9	10	mmHg
RVP	80	3	9	mmHg
RAP	10	7	6	mmHg
PAP after NO load	76	38	52	mmHg
PAWP after NO load	12	10	12	mmHg
PVR	14.41	wood units		
CO	5.69	L/min		
CI	3.77	L/min/m^2		
SV	69.1	ml		
Chronic phase	**Systolic**	**Diastolic**	**Mean**	
PAP	32	18	25	mmHg
PAWP	8	8	8	mmHg
RVP	33	3	18	mmHg
RAP	6	7	6	mmHg
PVR	3.26	wood units		
CO	5.21	L/min		
CI	3.30	L/min/m^2		

On admission, PAP and PVR were high. In Chronic phase (2 months after admission), she retested the right heart catheterization. Both PAP and PVR showed prominent improvement.
PAP, pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; NO, nitric oxide; RVP, right ventricle pressure; RAP, right atrium pressure; PVR, pulmonary vascular resistance; CO, cardiac output; CI, cardiac output index; SV, stroke volume.

In chronic phase after her symptoms improved, chest X-ray indicated that the right second arch enlargement was diminished (Fig. 1A-b). ECG showed improvement of broad negative T waves in widespread leads (Fig. 1B-b). In echocardiography D-shape was diminished and TRPG decreased from 79 mmHg to 10 mmHg (Fig. 1C-c, d). In right heart catheterization, PAP showed prominent improvement; from 87/42 (59) mmHg to 32/18 (25) mmHg (Table 1).

After discontinuation of Qing-Dai, the severity of UC was mild during hospitalization (Fig. 2). After that she started to take mesalazine instead of Qing-Dai, which she had used previously. UC did not deteriorate for a while. However, UC exacerbated again. Therefore, a specialist introduced her to steroids and adalimumab and UC went into remission.

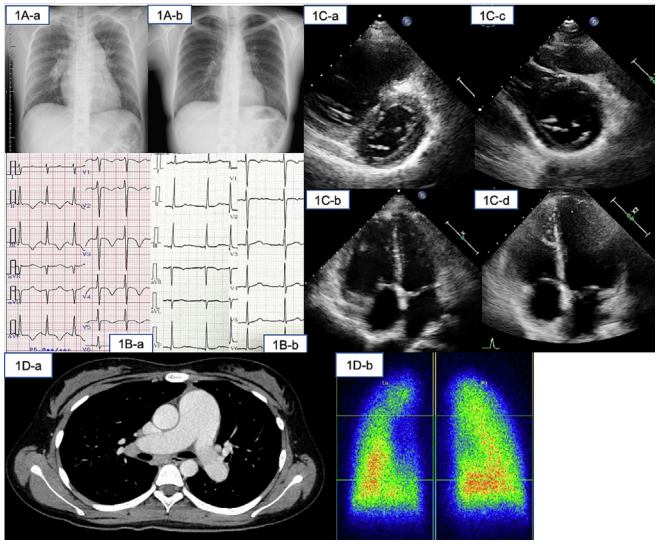
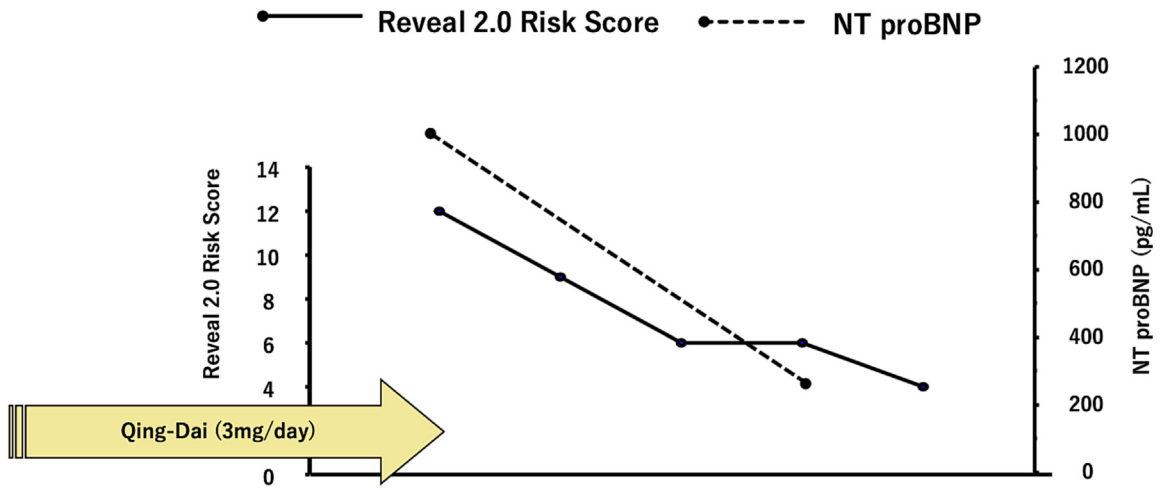


Fig. 1. (A) Chest X-ray photography. Chest X-ray photography indicated that the right second arch was protruding (a). After improvement, chest X-ray indicated that the right second arch enlargement was diminished (b). (B) Electrocardiogram showed sinus tachycardia and broad negative T waves in II, III, aVF, and V1–6 leads (a). After improvement, electrocardiogram showed improvement of broad negative T waves in widespread leads (b). (C) Echocardiogram showed obvious D-shape (a). Tricuspid regurgitation pressure gradient (TRPG) was 79 mmHg (b), inferior vena cave diameter was 18 mm with respiratory fluctuations. Systolic right ventricular pressure was estimated to be 82 mmHg. After improvement, D-shape was diminished and TRPG decreased from 79 mmHg to 10 mmHg (c, d). (D) Contrast-enhanced computed tomography and pulmonary blood flow scintigraphy. There was no contrast loss area in the pulmonary artery on contrast-enhanced computed tomography (a) and no decreased area in pulmonary blood flow on pulmonary blood flow scintigraphy (b).

Discussion

PAH is characterized by increased pulmonary arterial pressure and PVR due to pulmonary microvascular obstruction, a rare and intractable disease that eventually leads to right heart failure and death [1]. While Qing-Dai, a Chinese herbal medicine, has been used to treat UC [6], there have been several case reports suggesting a possible relationship between Qing-Dai and the development of PAH. Nagamura et al. reported that from a Japanese nationwide survey among 877 UC cases that took Qing-Dai, 11 of them developed PAH [7]. Based on these findings, "indigo and indirubin", the main ingredients of Qing-Dai, were classified as having a "Possible association" as a drug/toxin class related to PAH [8].

In this case, we proceeded with exclusionary diagnosis. In blood test analysis and special antibody findings, lupus anticoagulant and anticardiolipin antibodies were positive, but there was no contrast loss area in the pulmonary artery on contrast-enhanced CT and no decreased area in pulmonary blood flow on pulmonary blood flow scintigraphy. From blood tests and imaging findings we consulted autoimmune disease specialists, but they determined that these findings did not meet the diagnostic criteria of antiphospholipid antibody syndrome, chronic



	On admission	Day 3	Day 5	Day7	At discharge
Reveal 2.0 Score	12	9	6	6	4
NYHA WHO functional class	IV	III	I	I	I
Severity of UC	mild	mild	mild	mild	mild

Fig. 2. Time course after her hospitalization. Since there have been some reports of patients who developed pulmonary arterial hypertension (PAH) after taking Qing-Dai as a treatment of ulcerative colitis (UC), we decided to discontinue Qing-Dai because drug-induced PAH was considered. Her subjective symptoms improved after withdrawal of Qing-Dai, completely disappeared on the 5th day, and she was discharged on the 10th day of hospitalization. According to the Reveal 2.0 Risk Score, score of this patient was 12 at the time of admission, but showed marked improvement with a score of 4 at the time of discharge. N-terminal prohormone of brain natriuretic peptide (NT-pro BNP) also improved significantly. Her symptoms of UC were not deteriorated, and the severity of UC was mild through hospitalization.
NYHA, New York Heart Association.

thromboembolic pulmonary hypertension, and pulmonary embolism. Furthermore, her symptoms improved rapidly after discontinuation of Qing-Dai. Finally, this case was diagnosed as drug-induced PAH by taking Qing-Dai.

In previous reports, patients with PAH due to Qing-Dai ranged in age from 10 to 60 years and were sparsely gendered. Nagamura et al. noted that most patients who developed PAH by Qing-Dai had been taking it for more than 24 weeks, but there was no clear association with dosage (it was reported that intussusception by Qing-Dai occurred at a dose of 0.5–2.0 g/day) [7].

The REVEAL 2.0 risk score is useful in assessing the severity and predicting the prognosis of PAH [4]. In this case, the score was estimated to be 12 at the time of initial treatment (Fig. 2), indicative of a 5-year predicted survival rate of about 20 %. Misumi et al. reported that PAH induced by Qing-Dai may be reversible [5]. In this report, despite long-term in taking of Qing-Dai, symptoms of PAH disappeared quickly after discontinuation. The REVEAL 2.0 risk score also dramatically improved, suggesting that PAH induced by Qing-Dai is reversible.

Thus, we report rapid PAH improvement after discontinuation of Qing-Dai indicated by REVEAL 2.0 risk score decreasing from high risk (12) to low risk (4) in less than 10 days.

As in this case, some patients developed PAH after taking Qing-Dai for as long as 7 years, so patients taking Qing-Dai should be carefully monitored, and an algorithm for screening PAH in patients taking Qing-Dai is urgently needed. Although the REVEAL 2.0 risk score includes right heart catheterization and echocardiography in its evaluation items, it has many objective indicators that can be measured simply, such as symptoms and vital signs, and is easily accessible to co-medical staff other than physicians in daily clinical practice. Therefore, it may be used not only for evaluating the severity and prognosis of PAH, but also for the screening of PAH in patients taking Qing-Dai.

There are no reports of PAH caused by Qing-Dai in which subjective symptoms improved in a short time after discontinuation of Qing-Dai without using specific drugs for PAH treatment. The pathophysiology which symptoms of PAH rapidly improve after discontinuation of Qing-Dai has not been made clear. Recently, it was found that Qing-Dai contain large amounts of aryl hydrocarbon receptor (AhR) agonists, and Masaki et al. reported that AhR in pulmonary vascular endothelial cells is associated with the development of PAH [9]. Hiraide et al. also reported that activation of AhR increases the risk of developing PAH, while decreased AhR activity is associated with the development of UC [10]. It is necessary to clarify the pathogenesis of emergence of PAH by Qing-Dai and of rapid improvement of PAH after discontinuation.

Conclusion

We diagnosed drug-induced PAH in a young woman taking Qing-Dai for UC who presented with dyspnea and syncope on exertion. Her symptoms rapidly improved with the discontinuation of Qing-Dai, indicated by a marked improvement in REVEAL 2.0 risk score.

Patient permission/consent statement

Appropriate consent was obtained from the patient and her family.

Declaration of competing interest

The authors declare that there is no conflict of interest.

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