Chronic Thromboembolic Pulmonary Hypertension Complicated with Homocystinuria

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Abstract

A 17-year-old boy with homocystinuria was found to have a systolic murmur during a routine examination. Echocardiography demonstrated pulmonary hypertension (PH), and computer tomography angiography showed pulmonary thrombi. Although 12-month anticoagulation treatment reduced the thrombotic material within the main branch, it failed to clear thrombotic materials in the left and right lobar branches. Two years later, the patient was admitted to our hospital due to a worsening of PH. Treatment with bosentan, sildenafil and beraprost, in addition to anti-coagulant therapy, did not improve his PH. Balloon pulmonary angioplasty (BPA) was performed to remove the pulmonary thrombi. BPA markedly improved the patient’s hemodynamics and exercise capacity. Close follow-up is scheduled to prevent any potential future thrombotic complications.

Key words: chronic thromboembolic pulmonary hypertension, homocystinuria, balloon pulmonary angioplasty


Introduction

Homocystinuria is a congenital metabolic disorder of methionine. The most frequent cause of homocystinuria is deficiency of the enzyme cystathionine $\beta$ synthase (1). Hyperhomocysteinemia due to methionine metabolic disorders is associated with various complications including skeletal, ophthalmic, mental and thrombovascular abnormalities. The reported prevalence of homocystinuria in Japan is 1 per 900,000 (2). Half of the patients with homocystinuria develop vascular events by age 30 years (3). We herein report a rare case of severe chronic thromboembolic pulmonary hypertension (CTEPH) associated with homocystinuria. The patient was effectively treated with balloon pulmonary angioplasty (BPA) in addition to medical therapy for pulmonary hypertension.

Case Report

A 17-year-old boy who was diagnosed with homocystinuria during a routine screening after birth was found to have a systolic murmur on a routine medical check-up. The patient visited the hospital periodically and was subsequently treated with oral betaine at the Pediatric Outpatient Department. Transthoracic echocardiography performed on August 2009 showed pulmonary hypertension (PH) [pulmonary artery pressure (PAP): 57/17 mmHg]. Computer tomography (CT) angiography showed thrombotic material within the main branch of the right pulmonary artery, branches of the right lower lobe, branches of the left lower lobe and left middle lobe, but not in the corresponding veins. Based on

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Figure 1. (A) Twelve-lead electrocardiogram recorded on the first admission shows right ventricular hypertrophy. (B) Chest radiograph on the first admission shows a mild right ventricular enlargement. (C) Short-axis view of transthoracic echocardiography on admission shows dilatation of the right heart cavities and a D-shaped left ventricle. (D, E) CT angiography on the first admission shows thrombotic materials within the branches of the right lower, left lower and middle lobes (arrows).

these findings, the patient was placed on anticoagulant therapy (warfarin). Transthoracic echocardiography performed in the Outpatient Department in April 2011 showed progression of PH. The patient was referred and admitted to our department for further management.

Although the patient had no shortness of breath, he was tachypneic during conversation (class III, New York Heart Association classification). His blood pressure was 130/80 mmHg, pulse rate was 90 beats/min and respiration rate was 18/min. The arterial oxygen saturation was 95% on room air. A physical examination showed jugular vein dilatation, a split S2 sound and a systolic murmur with Levine II/XI on the left sternal border between the second and third ribs. Electrocardiography showed a sinus rhythm (heart rate: 75 beats/min) and evidence of right ventricular hypertrophy (high-amplitude R waves in V1 and V2 leads, deep S wave in V5 lead; Fig. 1A). The chest X-ray showed a cardiothoracic ratio of 46% and mild enlargement of the right ventricle (Fig. 1B). Transthoracic echocardiography demonstrated dilatation of the right heart cavities, a D-shaped left ventricle (Fig. 1C) and progression of PH (PAP: 96/24 mmHg). Plasma total homocysteine and serum brain natriuretic peptide (BNP) levels were 123 μmol/L and 18.6 pg/mL, respectively. The coagulation screening and immune marker concentrations were unremarkable. CT angiography showed thrombotic material within the lobar branches bilaterally (Fig. 1D, E) but no venous thrombosis. Ventilation/perfusion scanning demonstrated diffuse perfusion deficits (Fig. 2D).

The definitive diagnosis was CTEPH. Bosentan, sildenafil and beraprost were added to the anti-coagulant therapy; however, this treatment failed to improve the patient’s PH. He underwent repeated BPA between June and December 2011 (Fig. 2A-C), which resulted in a reduction of the mean PAP from 59 to 23 mmHg and enhancement of the 6-minute walking test from 360 to 475 m approximately one year after the final BPA (Table). No complications occurred during or after BPA. Lung perfusion scintigraphy performed on November 2011 showed partial improvement of perfusion deficits (Fig. 2E).

Discussion

Patients with homocystinuria can develop various complications due to the associated hyperhomocysteinemia. Therefore, the goal of any treatment of homocystinuria is to lower the plasma homocysteine levels. Evidence suggests that pyridoxal phosphate supplementation, folate, betaine and vitamin B12 aid in the conversion of homocysteine to cysteine (4). Clinical evidence indicates that hyperhomocysteinemia is involved in the pro-thrombotic state and endothelial dysfunction, which may cause extensive vascular thrombosis (5-9). Therefore, the severe homocysteinemia observed in our patient (Fig. 3A) was considered to be the cause of his thrombotic complications. Importantly, our patient did not develop clear-cut acute pulmonary embolism. The thrombotic material within the main branch of the right pulmo-
monary artery in the first CT angiography (Fig. 3B) was non-occlusive, and no venous thrombosis was apparent. Based on these observations, it is possible that thrombosis of the pulmonary arteries was directly due to pulmonary endothelial dysfunction associated with severe homocysteinemia.

This is the first known report that describes the effective treatment of CTEPH associated with homocystinuria with BPA. CTEPH represents persistent pulmonary hypertension lasting more than six months caused by organized thrombi within the pulmonary artery. Pulmonary thromboendarterectomy (i.e., the mechanical removal of thrombi from within the pulmonary artery) is the most effective therapy for CTEPH (10). In inoperable cases or those with recurrent PH after pulmonary thromboendarterectomy, medical therapy and BPA should be considered (11). Previous reports described the effectiveness of medical therapies for CTEPH, such as pulmonary artery vasodilators (12), bosentan (13), sildenafil (14) and prostacyclin analog (15). BPA is also an effective and safe treatment especially for properly selected patients (16). In our patient, BPA was selected because it is...
In conclusion, BPA markedly improved the hemodynamics and exercise capacity of a CTEPH patient complicated with homocystinuria. The patient’s condition is currently being managed by oral betaine and medical therapy to prevent any potential future thrombotic complications.

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

Shinpei Ogawa and Tetsuji Katayama contributed equally to this work.

References