CASE REPORT

Pulmonary embolism in a child with combined methylmalonic acidemia and homocystinuria

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INTRODUCTION

Pulmonary embolism is much less common in children than in adults. We encountered a 5-year-old girl with pulmonary embolism. She was finally diagnosed with combined methylmalonic acidemia and homocystinuria, which is a rare disease that could cause pulmonary embolism. Pulmonary embolism in our patient may be considered a case of in situ thrombosis of pulmonary arteries rather than classical thromboembolic pulmonary embolism. The clinical experience in this patient suggests that the possibility of metabolic disease should be considered when encountering pediatric pulmonary embolism.

CASE REPORT

A 5-year-old girl presented with a 2-month history of cyanosis. Her oxygen saturation was 88%–92% in room air. She had cyanosis of the lips and nail beds on exercise and a loud P2 on auscultation without rales or cardiac murmurs. Echocardiography showed moderate dilation of the right atrium and ventricle, with severe tricuspid and pulmonary valve regurgitation. Pulmonary hypertension (39 mmHg; pulmonary arterial pressure/ aortic pressure: 0.74, pre-oxygen inhalation; 0.62, post-oxygen inhalation was shown by cardiac catheterization. Computed tomography (CT) showed diffuse interstitial pneumonia with ground-grass centrilobular nodules (Figure 1) and a filling defect (Figure 2) secondary to the intraluminal presence of a thrombus after intravenous contrast injection. A full blood count showed macrocytic hyperchromic erythrocytes with a hemoglobin level of 81 g/L, mean corpuscular volume of 110.7 fL, and mean corpuscular hemoglobin concentration level of 37.9 pg. Vitamin B12 and folic acid levels were normal. Urinalysis showed protein 1+, blood 2+, and the red blood cell count ranged from 1–2 to 10–12/high power. The girl had slightly retarded intellectual development since birth, and had episodic seizures since 3 years of age. These seizures were controlled with antiepileptic treatment. Methylmalonic acidemia (MMA) and homocystinuria were confirmed by a plasma methylmalonic acid level of 0.0501(normal value: 0.001), and the plasma homocysteine (Hcy) level was 202.88 μmol/L (normal range: 1.98–12.8 μmol/L). Genetic analysis showed compound heterozygosity in the *MMACHC* gene (NM_015506) with c.609G>A and c.80A>G (both have been identified to be disease-causing genes[1]). Pulmonary embolism was treated with low molecular weight heparin and warfarin. Hydroxocobalamin, betaine, and levocarnitine were planned for long-term use. During follow-up after 3 months, the girl's symptom of cyanosis was relieved. Echocardiography showed a normal inner diameter of the right atrium and ventricle, while pulmonary arterial pressure had also decreased to a normal level. An enhanced CT scan showed a smaller filling defect compared with the last CT scan, but she still had diffuse interstitial pneumonia. She is still being followed up.

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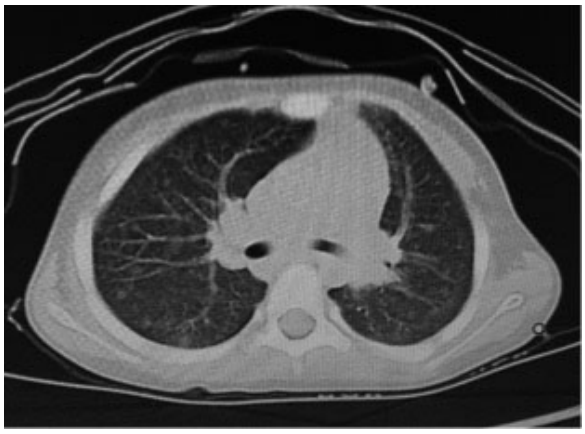

FIGURE 1 CT showed Diffuse interstitial pneumonia with ground-grass centrilobular nodules.

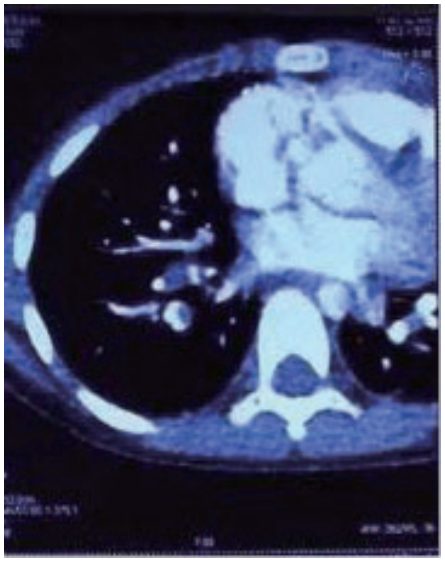

FIGURE 2 CT showed filling defect in right lower pulmonary artery after intravenous contrast injection.

DISCUSSION

MMA is a common organic acidemia, and is mainly due to metabolic disorders of methylmalonyl-CoA mutase or its coenzyme cobalamin (vitamin B12). Combined methylmalonic acidemia and homocystinuria is a subtype of MMA, and it includes three types, of cblC, cblD, and cblF. The most common type is cblC. Combined methylmalonic acidemia and homocystinuria, which belongs to autosomal recessive diseases, is caused by gene mutations located on chromosome 1p34. In our case, genetic analysis showed compound heterozygosity in the *MMACHC* gene (c.609G>A and c.80A>G), which is predominately reported in Chinese people. We made a final diagnosis of cblC disease.

The *MMACHC* gene mutation results in impaired intracellular synthesis of adenosylcobalamin and methylcobalamin, which are cofactors for methylmalonyl-CoA mutase and methionine synthase enzymes.[2] Elevated methylmalonic acid and Hcy levels with decreased methionine production are the biochemical hallmarks of combined methylmalonic acidemia and homocystinuria. In our case, the plasma methylmalonic acid level was 0.0501, which was almost 50 times higher than normal, while the plasma Hcy level was also higher than the normal level.

Elevated methylmalonic acid and Hcy levels cause multisystem damage, mainly including the neural system, kidney, and blood vessels. Approximately 90% of patients with cblC present with the severe, infantile, early-onset form of the disease. Characteristic clinical manifestations of cblC are encephalopathy (feeding difficulties and growth failure, developmental regression, seizures, and muscular hypotonia), anemia or thrombocytopenia, hemolytic uremic syndrome, visual inattention, and nystagmus.[3,4] Patients with late-onset cblC can present in any decade of life with progressive encephalopathy, subacute degeneration of the spinal cord, hemolytic uremic syndrome, pulmonary hypertension, and thromboembolic events.[5] These patients may previously be asymptomatic or have a history of learning or emotional difficulties, hematuria, proteinuria, anemia, or unexplained recurrent thrombosis.[6-8] The clinical classification of early-onset and late-onset disease can correlate with the genotype of patients.[9] In our case, the patient had late-onset presentation of slightly retarded intellectual development, onset of seizures after she was 3 years old, anemia, renal damage (proteinuria and hematuresis), diffuse interstitial pneumonia, severe pulmonary hypertension, and pulmonary embolism.

Pulmonary hypertension is a severe complication of combined methylmalonic acidemia and homocystinuria, especially the cblC type. Pulmonary hypertension often occurs in the late-onset type in male patients and can be the first and leading manifestation of MMA. A review of a group of patients with pulmonary hypertension and MMA showed that c.80A>G mutation of the *MMACHC* gene may be the related mutation of the MMA cblC type associated with pulmonary hypertension.[10] This gene mutation was also found in our patient.

Thromboembolic complications have only rarely been reported, but are an important cause for morbidity and mortality in patients with cblC disease. The pulmonary embolism observed in our case may have been a case of in situ thrombosis of the pulmonary arteries rather than classical thromboembolic pulmonary embolism. Severe pulmonary hypertension causes blood stasis and results in in situ thrombosis. Elevated plasma Hcy levels contribute to formation of pulmonary hypertension and pulmonary arterial thrombosis. According to a review, Hcy levels greater than 45 μmol/L are associated with development of vascular complications, and their severity may correlate

with increasing Hcy levels.[11] In our case, the Hcy level was as high as 202.88 μmol/L.

The treatment principles of MMA are to reduce generation of metabolic poisons and/or to accelerate their clearance. Hydroxocobalamin, betaine, and levocarnitine were planned for long-term use in our case. The prognosis of children with MMA mainly depends on the type of disease, the onset, and clinical compliance. Follow-up of our patient at 3 months showed a considerable positive effect after therapy, but long-term effects should still be further observed.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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