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Pulmonary Hypertension in a Child with Juvenile-Type Autosomal Recessive Polycystic Kidney Disease

An 11 year-old girl, whose condition was diagnosed as juvenile-type autosomal recessive polycystic kidney disease (ARPKD) at five years of age, presented with chest pain and dyspnea that had developed suddenly two months previously. Two-dimensional echocardiography, Doppler study and cardiac catheterization confirmed pulmonary hypertension. The underlying mechanism of the diagnosis was not defined. Two and a half months after the onset of symptoms, the patient died of pulmonary hypertensive crisis. Careful regular checks of cardiopulmonary status using two-dimensional echocardiography and Doppler should be considered for the early detection of pulmonary hypertension even in an asymptomatic patient with juvenile-type ARPKD.

Key Words: *Hypertension, pulmonary; Kidney, polycystic, autosomal recessive; Liver cirrhosis*

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INTRODUCTION

Autosomal recessive polycystic kidney disease (ARPKD) is a rare, hereditary cystic disease of the liver and kidney. Its clinical spectrum varies widely, with most cases presenting in infancy. Blyth and Ockenden assumed that ARPKD could be divided into four different subtypes, distinguished by clinical symptoms and pathological finding (1). Juvenile groups who present the disease in childhood or adolescence tend to have predominantly hepatic findings and less obvious kidney manifestations. The progression of congenital hepatic fibrosis has been reported to result in biliary stasis, portal hypertension, hypersplenism and esophageal varices though hepatic failure has not been reported (2). The gene for autosomal recessive polycystic kidney disease has been localized by linkage analysis to chromosome 6p21-cen (3).

Pulmonary hypertension has been reported in cases of chronic liver disease and portal hypertension, and its prognosis is poor (4). Pulmonary hypertension appeared to be linked to portosystemic shunting by a cause-and-effect relationship. Though several putative mechanisms have been proposed for the increased pulmonary resistance in patients with portal and pulmonary hypertension, its mechanism is not clearly defined. Recently genetic locus for familial primary pulmonary hypertension has been reported to be mapped on chromosome 2q31-q32, which may contribute to reveal the precise pathogenesis of primary pulmonary hypertension (5).

We describe here a case of juvenile-type ARPKD in which the patient died of pulmonary hypertension.

CASE REPORT

An 11 year-old girl visited Seoul National University Children's Hospital due to chest pain and syncope that were brought on by exercise.

At five years of age, abdominal distension with hepatosplenomegaly was noted. The results of a liver function test were normal, and blood urea nitrogen and serum creatinine were in the normal range. Microscopic hematuria was noted. Abdominal sonography revealed polycystic lesions in both kidneys and dilated bile duct within the liver (Fig. 1). Liver biopsy disclosed hepatic fibrosis including portal widening fibrosis, bile duct proliferation, scattered bile plugging the bile duct and inflammatory cell infiltration (Fig. 2). Renal and liver function were in the normal range, and there was no history of cholestasis. Autosomal recessive polycystic kidney disease was diagnosed and the patient was followed up. At seven years and eight months of age, she presented with hematemesis. Gastrofiberscopy demonstrated hemorrhagic gastritis and varices of grade I with no evidence of recent bleed-

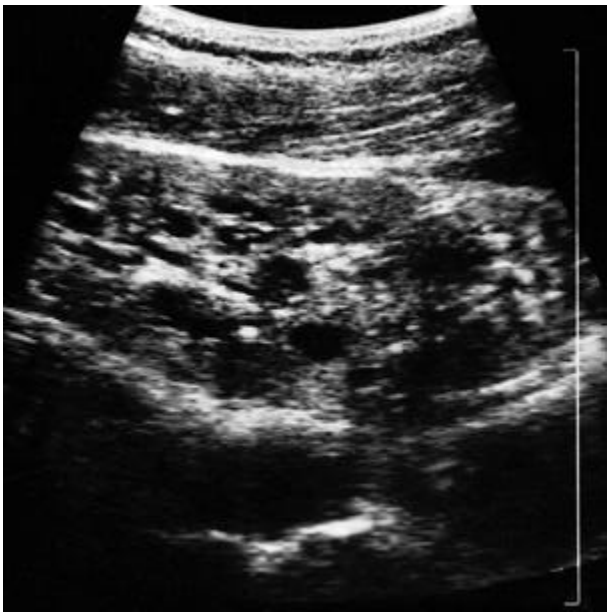

Fig. 1. Kidney sonongraphy demonstrated increased echogenicity of renal parenchyme with multiple small cysts in the right kidney.

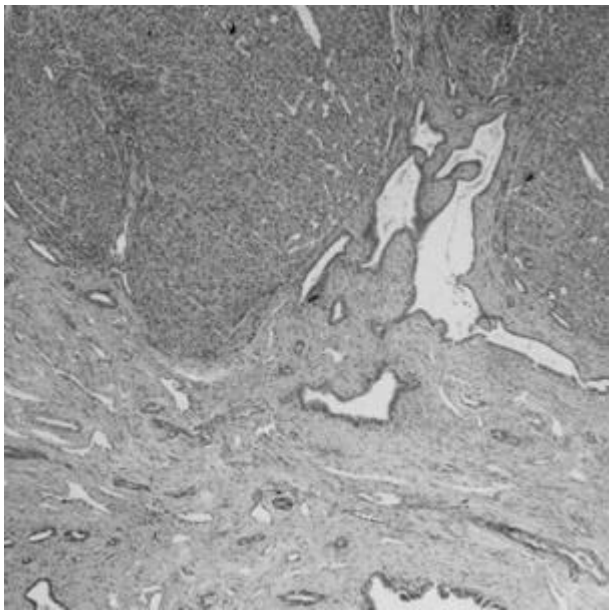

Fig. 2. Liver biopsy disclosed hepatic fibrosis including portal widening fibrosis, bile duct proliferation, scattered bile plugging in the bile duct and inflammatory cell infiltration (H&E, ×100).

ing. After then, hematemesis and/or melena developed at eight years one month and eight years eight months of age, but there was no evidence of variceal bleeding. She was then not followed up for two years. She was not taking oriental herb or other medication.

Two months prior to admission, while at school, the patient developed a syncopal attack of brief duration but soon recovered completely. Subsequently, however, she complained of palpitation and dizziness about twice a week, and her general condition gradually worsened.

Physical examination on admission indicated a blood pressure of 90/60 mmHg, a pulse rate of 128 beats per min, and a respiration rate of 24 per min. Her height was 134 cm (10-25 percentile), and weight was 27.5 kg (10-25 percentile). The conjunctiva was anemic, but the sclera was not icteric. Chest expansion was symmetric without retractions, and breathing sound was slightly coarse without rales. The heartbeat was regular with grade II ejection systolic murmur and grade I early diastolic murmur on the left upper sternal border. Increased P2 component of second heart sound was detected. Precordium was hyperactive. Her liver span was one finger' breadth below the right midclavicular margin, and her spleen span was two fingers' breadth below the left midclavicular margin. Her kidneys, however, were not enlarged. The results of physical examination were otherwise completely normal.

Chest X-ray showed an acute tapering pattern of pulmonary artery vasculature indicating pulmonary arterial hypertension. Hemoglobin was 7.5 g/dL; MCV, 74.7 fl; MCH, 23.4 pg; WBC, 9,200/μL; and platelet, 26,000/μL, results which indicated anemia and thrombocytopenia due to hypersplenism. The results of liver function test were normal. Serum creatinine concentration was 1.0 mg/dL, and urinalysis showed microscopic hematuria. Serum bicarbonate concentration decreased to 13 mmol/L and arterial CO_2 was 26 mmHg; results that were compatible with metabolic acidosis with respiratory compensation. Abdominal ultrasound demonstrated polycystic kidneys and a heterogenous echogenic liver. Two-dimensional echocardiography and Doppler study revealed a mild degree of tricuspid regurgitation at a velocity of 4.6 m/sec, mild pulmonary regurgitation with 4 m/sec; right ventricle, main pulmonary artery and its branches were large (Fig. 3). Lung perfusion scan with ^{99m}Tc-MAA showed no evidence of intrapulmonary shunt. Electroencephalography revealed no noticeable abnormalities. Magnetic resonance imaging demonstrated mild brain atrophy. Cardiac catheterization demonstrated severe pulmonary hypertension (right ventricle systolic and end diastolic pressure 100/5 mmHg; left pulmonary artery systolic, diastolic, mean 105/55/76 mmHg; left ventricle, 116/3 mmHg) and slight reduction of pulmonary artery pressure to 82/48/61 mmHg after the administration of high flow oxygen. No cardiac or pulmonary vascular anomalies were noted on pulmonary angiography. Idiopathic pulmonary hypertension with autosomal recessive polycystic kidney disease was eventually diagnosed and the patient was discharged without medication.

After discharge, she suffered from frequent attacks of

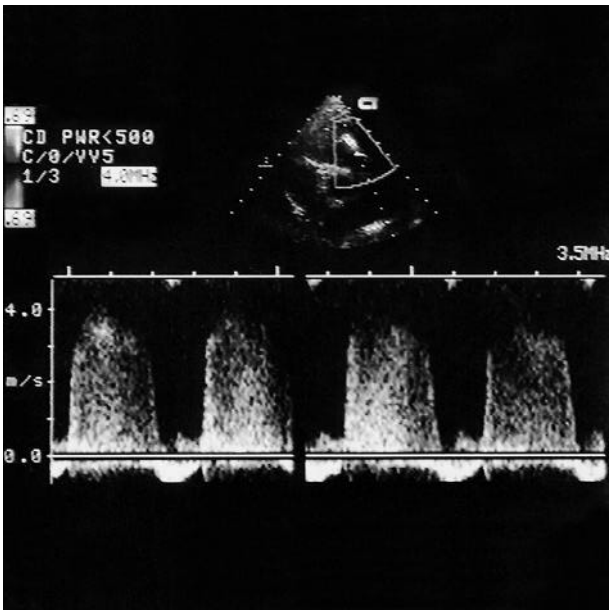

Fig. 3. Color and continuous wave Doppler study demonstrated a mild degree of pulmonary regurgitation at a velocity of 4 m/sec, indicating high pulmonary arterial pressure.

palpitation lasting 2-3 min, and these were followed by dyspnea, tachypnea and perspiration. She developed severe chest pain with dyspnea, followed by rigidity of the extremities, abdominal pain, and eyeball deviation and became unconscious. She died of pulmonary hypertensive crisis two and half months after the onset of symptoms. An autopsy was not performed.

DISCUSSION

Autosomal recessive polycystic kidney disease is characterized by bilateral enlargement of kidneys caused by generalized dilation of the collecting tubules. The disease is invariably associated with congenital hepatic fibrosis (6). Symptoms may develop at any time between birth and late adolescence. In patients whose disease develops at birth or during the neonatal period, renal disease is more common than liver involvement; in patients whose disease develops in childhood or adolescence, findings are mainly hepatic and less obvious kidney manifestations. The latter group requires medical attention because of complications arising from hepatic fibrosis. The liver is firm and splenomegaly is apparent. Hematemesis from bleeding esophageal varices is a frequent and distressing symptom as well as growth retardation. Anemia, leukopenia, and thrombocytopenia are frequent complications of hypersplenism (7). The prognosis of ARPKD is difficult to assess given the low incidence rate of the disorder and the variability in presentation.

In this case, the five-year-old patient presented with hepatic symptoms, and according to the classification of Blyth and Ockenden, her condition was juvenile-type ARPKD (1). During follow-up, there were three episodes of GI bleeding which were probably due to hemorrhagic gastritis, rather than esophageal varices. Erosive hemorrhagic gastritis on gastrofiberscopic examination was less compatible with portal hypertensive gastropathy, although not precluded. The results of gastrofiberscopic examination showed that esophageal varices secondary to portal hypertension was mild (grade I) and had not progressed. Nevertheless, pulmonary hypertension occurred suddenly three years and four months after detecting mild portal hypertension. It was thought that portal hypertension need not be surgically treated. Because cardiopulmonary complications such as pulmonary hypertension had not been considered to be clinically important during follow-up, cardiac status was not evaluated.

The first of possible mechanisms is portal hypertension. This, cirrhosis and acute liver failure may lead to complex changes in the pulmonary arterial bed, and these resulted in at least two clinically important and very distinct pulmonary vascular consequences; hepatopulmonary syndrome, and portopulmonary hypertension (4, 8). The latter may be the cause of pulmonary hypertension. The reasons of pulmonary hypertension in advanced liver disease are at least threefold; 1) a high flow phenomenon because of hyperdynamic circulation; 2) a volume phenomenon associated with possible cardiac manifestations of cirrhosis; and 3) vasoconstriction because of a spectrum of medial hypertrophy, intimal fibrosis, and classic plexogenic arteriopathy with or without thrombotic change. Only the third description should truly be considered portopulmonary hypertension and its frequency ranges from 1% to 4% of patients with advanced liver disease (9). There are several hypotheses to explain the association of pulmonary hypertension and portal hypertension: 1) thromboembolism through porto-systemic channels (10), 2) vasoactive substances normally metabolized by the liver, which enter the lungs through porto-systemic or portopulmonary channels (11), and 3) autoimmunity (12). The pulmonary vascular pathology in portopulmonary hypertension is considered indistinguishable from that seen in the primary pulmonary hypertension and right heart catheterization is essential for an accurate hemodynamic diagnosis (9). The time lag between the detection of portal hypertension and the manifestation of pulmonary hypertension varies from six months to 14 years (13). The risk of pulmonary hypertension has been shown to increase with increasing duration of portal hypertension (14). A report of three children with noncirrhotic extrahepatic portal hypertension described that progressive pulmonary hypertension developed despite

portal to systemic decompressive shunt (11). Also it was reported that a 25 years old female with noncirrhotic portal fibrosis who had underwent a splenorenal shunt presented with pulmonary hypertension ten years later (15). Surgical or spontaneous porto-systemic shunting in portal hypertension is an important risk factor for the development of pulmonary hypertension (14). Portal hypertension does not always lead to pulmonary hypertension but may cause hepatopulmonary syndrome (16). In a view of the relatively low incidence of pulmonary vascular disease among patients with portal hypertension, an additional factor of increased individual susceptibility of the pulmonary bed to a vasoconstrictor substance would seem to be required. Hepatic fibrosis in ARPKD finally results in portal hypertension that may cause not only esophageal variceal bleeding but also pulmonary hypertension. In this case, portal hypertension should be firstly considered a culprit for pulmonary hypertension. The difference between portal and variceal pressure varies widely, and there is not a close correlation between variceal and portal pressures. This makes it difficult, and even hazardous, to estimate portal pressure from endoscopic measurements of variceal pressure, especially in patients without previous variceal hemorrhage (17). So, mild degree of esophageal varices in this patient could not indicate that portal hypertension is mild and remain stationary. It is impossible in this case to accurately differentiate the etiologic mechanism. The pathogenetic mechanism of autosomal recessive polycystic kidney disease may be an additional susceptible factor. To our knowledge, there are no reports on clinical experience of ARPKD with pulmonary hypertension as well as molecular genetic data of it. Further molecular genetic study may help to disclose the mechanism of pulmonary hypertension in juvenile-type ARPKD.

Pulmonary hypertension in juvenile-type ARPKD is a rare complication, but because it is potentially fatal, early detection is essential. Cardiopulmonary status should be regularly assessed by two-dimensional echocardiography and Doppler study, if necessary, by cardiac catheterization even in an asymptomatic patient. Aggressive assessment of this kind could lead to treatment including surgery such as liver transplantation, and medical treatment for pulmonary hypertension.

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