Microangiopathic Hemolytic Anemia and Thrombocytopenia in a Child with Atrial Septal Defect and Pulmonary Hypertension

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SUZUKI, H., NAKASATO, M., SATO, S., YOKOYAMA, S., KATSUURA, M., YAMAKI, S. and HAYASAKA, K. *Microangiopathic Hemolytic Anemia and Thrombocytopenia in a Child with Atrial Septal Defect and Pulmonary Hypertension.* Tohoku J. Exp. Med., 1997, **181** (3), 379-384 —— Microangiopathic hemolytic anemia and thrombocytopenia have been reported in patients with primary pulmonary hypertension, but not in patients with congenital heart disease even if accompanied with pulmonary hypertension. We present a 7-year-old boy with atrial septal defect and pulmonary hypertension who developed microangiopathic hemolysis and thrombocytopenia. Microangiopathic hemolytic anemia and thrombocytopenia should be remarked as a complication in patients with congenital heart disease. —————— microangiopathic hemolytic anemia and thrombocytopenia; atrial septal defect; pulmonary hypertension

Microangiopathic hemolytic anemia and thrombocytopenia have been reported in some patients with primary pulmonary hypertension (Wang et al. 1965; Stuard et al. 1972; Paré et al. 1983; Jubelirer 1991). Although pulmonary hypertension occurs in patients with congenital heart disease, these complications have not been previously described. We describe a 7-year-old boy with atrial septal defect and pulmonary hypertension who developed microangiopathic hemolytic anemia and thrombocytopenia.

CASE REPORT

A 7-year-old boy presented with heart murmur at 11 days of age. A chest radiograph disclosed dextrocardia, cardiomegaly with pulmonary plethora and stomach on the right. Electrocardiogram showed coronary sinus rhythm and

right ventricular hypertrophy. Echocardiography demonstrated mirror-image dextrocardia, a large sinus venosus superior type atrial septal defect (15 mm in diameter at 4 months of age), and interruption of the inferior vena cava with hemiazygos continuation. The patient had recurrent respiratory infections and failure to thrive in infancy. Cardiac catheterization at 11 months of age showed severe pulmonary hypertension (peak pulmonary arterial pressure 69 mmHg). Mean pulmonary capillary wedge pressure was normal. There was no significant increase in oxygen saturation from the superior vena cava to the right atrium. Arterial oxygen saturation was 89% in room air and rose to 97% on inhalation of 100% oxygen, suggesting pulmonary venous desaturation. Pulmonary arteriolar resistance and pulmonary blood flow could not be calculated because of failure to advance the catheter into the pulmonary veins or the left atrium. The dye-dilution curves revealed a small left-to-right shunting not right-to-left at the atrial level. Pulmonary arteriography showed that the bronchial anatomy was that of situs inversus with a hyparterial bronchus on the right, an eparterial bronchus on the left. Angiocardiography demonstrated mirror-image dextrocardia {I, L, I}, an atrial septal defect without partial anomalous pulmonary venous connection and hemiazygous continuation of the interrupted inferior vena cava. Lung specimens obtained at 1 year of age showed marked medial hypertrophy and necrotizing arteritis in the small pulmonary arteries and arterioles (Fig. 1). There were no plexiform lesions. Yamaki's index of pulmonary vascular disease (Yamaki et al. 1987) was 2.5, indicating that surgical closure of the atrial septal defect would be inappropriate. He was treated with digoxin and furosemide, but cyanosis gradually appeared at the lips and fingers. At 6 years of age, he was recatheterized and pulmonary hypertension was confirmed (peak pressure 71 mmHg). Arterial oxygen saturation was 84% in room air, and rose to 92% on inhalation of 100% oxygen. Pulsed-Doppler echocardiographic examination showed bidirectional shunting at the atrial level. Examination of the blood showed a hemoglobin of 13.9 g/100 ml, a white blood cell count of 6.4×10^9/liter, a platelet count of 263×10^9/liter, and thrombin-antithrombin III complex of 59.4 μg/liter (normal range, <3.0 μg/liter). On smears of peripheral blood, the red cells were microcytic and hypochromic. Anticoagulant therapy with warfarin and home oxygen therapy were started.

At 7 years and 2 months of age, he complained of recurrent epistaxis and thrombocytopenia (54×10^9/liter) was noted. Epistaxis was not improved even after withdrawal of warfarin and the platelet count progressively reduced to 5×10^9/liter. He was hospitalized and bone marrow examination revealed an increased number of megakaryocytes and erythroid hyperplasia. Platelet-associated IgG in his serum was elevated to 72.9 ng/10^7 cells (normal range, 9.0–25.0 ng/10^7 cells). Intravenous immunoglobulin administration did not increase the platelet count. The hemoglobin value was 9.8 g/100 ml and he was given a transfusion of 2 units of packed red cells. He was referred to our hospital 7 days
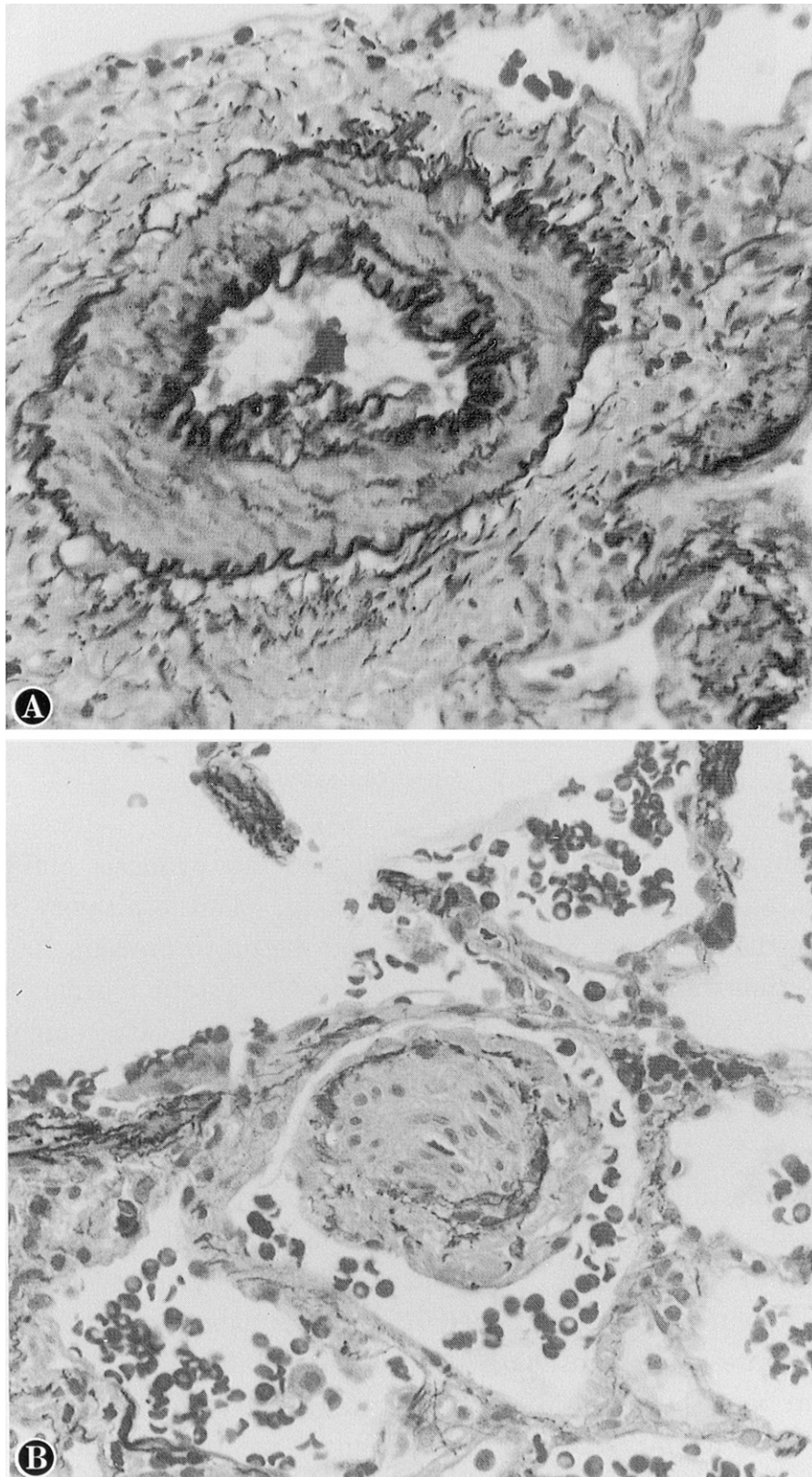
Fig. 1. (A) Small pulmonary artery with marked increase in the thickness of the media (Elastica-Goldner stain; original magnification ×200).
(B) Pulmonary arteriole with necrotizing arteritis demonstrating fibrinoid necrosis (Elastica-Goldner stain; original magnification ×200).

Fig. 2. Chest radiogram.

later.   On physical examination, he showed moderate cyanosis, clubbed fingers, and purpura and petechiae over the entire body.   The respiratory rate was 60 breaths/min, the heart rate 116 beats/min, and the blood pressure 106/40 mmHg. A gallop rhythm was present.   He had a grade 3/6 systolic murmur heard along the upper right sternal border, and an accentuated pulmonary component of the second heart sound.   The liver was palpable 1 cm below the left costal margin. Arterial oxygen saturation by pulse oximetry was 77% on 100% oxygen.   Chest radiogram (Fig. 2) showed cardiomegaly with a cardiothoracic ratio of 0.69 and pulmonary congestion.   Laboratory examination showed a white blood cell count of 7.0×10^9/liter with 72% neutrophils, a hemoglobin of 12.7 g/100 ml, and a platelet count of 14×10^9/liter.   The peripheral blood smear revealed fragmented cells.   The reticulocyte count was 6.5%.   Other laboratory findings were as follows: aspartate aminotransferase 49 IU/liter, lactate dehydrogenase 1,904 IU/ liter (normal range, 202 to 357 IU/liter), total bilirubin 3.2 mg/100 ml, direct bilirubin 0.7 mg/100 ml, serum urea nitrogen 27 mg/100 ml, and creatinine 0.5 mg/100 ml.   The direct Coombs' test and antinuclear antibody test were negative. The plasma fibrinogen, partial thromboplastin time, prothrombin time, and fibrinogen degradation products were normal.   Serum haptoglobin was below 12 mg/100 ml, and thrombin-antithrombin III complex was 9.3 μg/liter.   The urine was negative for protein and occult blood.   He received pulse doses of methyl-prednisolone, but showed no response.   The patient became more dyspneic and

died on the 7th hospital day. No postmortem examination was performed.

DISCUSSION

Atrial septal defect is one of the relatively common congenital heart defects. The sinus venosus superior type atrial septal defect, which is located just inferior to the entrance of the superior vena cava, constitutes 5 to 10% of atrial septal defects and is commonly associated with partial anomalous pulmonary venous connection (Porter et al. 1995). Young patients with isolated secundum or sinus venosus atrial septal defect usually have normal or slightly elevated pulmonary artery pressure and the development of pulmonary vascular disease is uncommon. However, a few patients developed pulmonary vascular disease soon after birth (Wagenvoort et al. 1961; Haworth 1983; Cherian et al. 1983). Wagenvoort et al. (1961) reported that the fetuses with atrial septal defect had medial hypertrophy in the pulmonary arterial tree. After birth, pulmonary vascular disease would deteriorate in such cases due to increased pulmonary blood flow caused by left-to-right shunting at the atrial level (Wagenvoort and Wagenvoort 1970; Haworth 1983). Our case presented congestive heart failure in infancy, and he was diagnosed as mirror-image dextrocardia {I, L, I}, an atrial septal defect without partial anomalous pulmonary venous connection and hemiazygous continuation of the interrupted inferior vena cava. He developed severe pulmonary vascular obstructive disease showing marked medial hypertrophy and necrotizing arteritis. Yamaki et al. (1987) reported that fibrinoid necrosis of the media due to angiitis was unusual in children with atrial septal defect. The patient seems to be an extremely rare case of atrial septal defect associated with pulmonary hypertension from birth.

The patient was also complicated with microangiopathic hemolytic anemia and thrombocytopenia. These complications have been reported in 8 cases with primary pulmonary hypertension characterized by severe pulmonary vascular obstructive disease (Wang et al. 1965; Stuard et al. 1972; Paré et al. 1983; Jubelirer 1991). It was considered that shear stress on blood cells came from the fibrin deposited in the plexiform lesions of the pulmonary microvasculature (Stuard et al. 1972; Paré et al. 1983; Jubelirer 1991). Plexiform lesions are composed of a complex network of small pulmonary arteries separated by proliferating endothelial cells (Pietra et al. 1989), which are observed in patients with primary pulmonary hypertension or Eisenmenger's syndrome. We could not detect plexiform lesions in the lung specimens obtained at 1 year of age and the autopsy was not available. Microangiopathic hemolysis and thrombocytopenia are usually associated with thrombotic thrombocytopenic purpura, hemolytic uremic syndrome or disseminated intravascular coagulation (Bithell 1993). However, the patient was not affected with these conditions. It is likely that plexiform lesions might be formed at final stage as pulmonary vascular disease and blood cells and platelets might be damaged in the pulmonary microvasculature.

To our knowledge, these complications have not been previously reported in patients with Eisenmenger's syndrome. We cannot deny the possibility that our case might have atrial septal defect and pronounced pulmonary vascular disease incidentally. Microangiopathic hemolytic anemia and thrombocytopenia should be remarked as a complication not only in patients with primary pulmonary hypertension, but also in patients with congenital heart disease.

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