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Pulmonary Hypertension in a Patient With Congenital Heart Defects and Heterotaxy Syndrome

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Background: Heterotaxy syndrome, also called isomerism, is a condition in which abdominal and thoracic organs are located in abnormal body positions. Pulmonary hypertension (PHTN) is an uncommon clinical feature of heterotaxy syndrome.

Case Report: We describe the case of a 26-year-old male who developed PHTN as a rare manifestation of heterotaxy syndrome. To our knowledge, PHTN has never been reported as a prominent clinical feature in a patient with heterotaxy syndome and congenital cardiac abnormalities.

Conclusion: It is important for the clinician to be aware of potentially serious consequences of PHTN in the setting of heterotaxy syndrome.

Keywords: *Heterotaxy syndrome, hypertension–pulmonary, isomerism*

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INTRODUCTION

Heterotaxy syndrome, also called isomerism, is a condition in which abdominal and thoracic organs are located in abnormal body positions. The condition results from abnormal rotation around the left-right axis during the embryonic period of development. Heterotaxy syndrome can be further divided into left and right isomerism. Left isomerism is generally characterized by less severe cardiac defects than right isomerism, 2 bilobed lungs, and polysplenia. Right isomerism is characterized by more severe cardiac defects than left isomerism, 2 trilobed lungs, and asplenia. The prognosis is poor for patients with cardiac defects: the 1-year mortality rate is >85% in patients with asplenia and >50% in patients with polysplenia.[1]

Nearly all infants with right isomerism have a pulmonary outflow obstruction.[2] They often present at birth with cyanosis because of a large right-to-left shunt exacerbated by the pulmonary outflow obstruction. Many cases are diagnosed antenatally by a late second trimester ultrasound.

Patients with left isomerism may be asymptomatic at birth because they generally have mild structural cardiac defects and no significant pulmonary outflow obstruction. However, they may present with cardiac conduction deficits, jaundice from biliary atresia, or bowel obstruction because of malrotation of the gut.

Pulmonary hypertension (PHTN) is an uncommon clinical feature of heterotaxy syndrome. PHTN has been previously reported as a presenting manifestation of heterotaxy syndrome in an adult without cardiac structural abnormalities.[3] We present the case of a patient with heterotaxy syndrome and congenital cardiac abnormalities who developed PHTN.

CASE REPORT

A 26-year-old male who was diagnosed as a fetus with heterotaxy syndrome with multiple structural cardiac defects presented to the hospital with shortness of breath. Anatomical abnormalities related to his heterotaxy syndrome included double outlet right ventricle with complete atrioventricular septal defect (Rastelli type A), asplenia, pulmonary atresia, interrupted abdominal inferior vena cava with right azygos continuation to the right superior vena cava, and hepatic veins forming a confluence that drained to the left atrium. Additionally, the patient had anomalous pulmonary venous return to a pulmonary venous confluence that lay posterior to the left atrium and drained in a cephalad direction via a vertical vein, ultimately making unobstructed connection with the innominate vein-right superior vena cava junction.

Furthermore, the patient's left aortic arch had 3 major aortopulmonary collaterals off the descending aorta: 1 serving the entire right lung, 1 serving the left lower lobe, and 1 serving the left upper lobe. This patient had had 3 previous surgical interventions, including unifocalization and an aortopulmonary shunt procedure at the ages of 9 months and 24 months, respectively. At age 17, he underwent a palliative Rastelli procedure in which a pulmonary or aortic homograft conduit is placed to relieve pulmonary obstruction in a double outlet right ventricle with

pulmonary stenosis. The patient also had had 4 previous catheterizations performed with no interventions noted.

During this admission, echocardiogram (EKG) revealed elevated pulmonary artery pressure with mild right ventricular hypertrophy. The right ventricular outflow tract had no obstructions. The conduits connecting the right ventricle to the pulmonary artery were patent with no stenosis. The pulmonary pressures obtained through right heart catheterization 6 months prior had been normal. To confirm the diagnosis of PHTN, right heart catheterization was repeated, revealing elevated pulmonary artery pressure at 71/38 mmHg with a mean of 51 mmHg and elevated pulmonary vascular resistance of 4.9 Wood units. The pulmonary capillary wedge pressure was within normal range, and the vasoreactivity test was negative. The patient was started on bosentan for management of PHTN.

DISCUSSION

Heterotaxy syndrome is associated with many structural malformations. The principal malformations involve the cardiovascular system, the spleen, the lungs, and the gastrointestinal system. The most significant malformations affecting prognosis are the degree of congenital heart disease (CHD) and the presence or absence of the spleen. The 1-year survival rate of patients with heterotaxy syndrome with CHD and asplenia is only 15% compared to approximately 50% in patients with CHD with polysplenia.[2] The most common congenital cardiovascular defects in patients with heterotaxy syndrome are atrioventricular septal defects, ventricular septal defects, pulmonary stenosis, pulmonary atresia, bilateral superior vena cava, double outlet ventricles, anomalous venous return, transposition of the great vessels, and patent ductus arteriosus.[4-6]

Given the higher incidence of pulmonary outflow tract obstruction and resulting right-to-left shunting in patients with right isomerism, cyanosis most often manifests at birth.[1,6] Some patients without obvious cyanosis are diagnosed during routine examinations when a systolic murmur is heard. Very few patients present with abdominal pain and vomiting because of an obstruction caused by small bowel malrotation.

With the success of corrective surgery for congenital heart defects, it is important to identify the other clinical features and complications of the syndrome that present later in life. PHTN is a rare clinical feature of heterotaxy syndrome. To our knowledge, our patient is only the second reported case of PHTN in an adult with heterotaxy syndrome. Our patient fit the right isomerism category of heterotaxy syndrome. He had asplenia, right-sided cardiac malformations, and pulmonary atresia.

With regard to the etiology of the patient's PHTN, we ruled out left-sided heart disease as a contributing factor based on the normal pulmonary capillary wedge pressure, and obstruction of the central pulmonary arteries and conduits was ruled out by EKG.

We know little about the long-term hemodynamic effects of conduits on pulmonary vasculature. One study recorded hemodynamic data collected in patients with pulmonary atresia/ventricular septal defect/major aortopulmonary collateral arteries immediately after they underwent complete repair with conduits.[1] After 4.5 years, on average, the same patients came back for conduit repairs, and hemodynamic data were collected again before the conduit repairs. No significant changes in right ventricular pressure were recorded after patients underwent complete repair with conduit placement compared to when they returned for conduit repair.[7] These results suggest that the pulmonary vasculature stays relatively constant after conduit replacement. Thus, the patent conduit in our patient is not likely to have contributed to the new-onset PHTN.

Chronic hypoxemia is a potential contributing factor. Our patient's baseline oxygen saturation was usually close to 85%. However, chronic hypoxemia-induced vasoconstriction seems to be unlikely in our patient given the relatively rapid onset of his PHTN. His EKG 6 months prior to presentation was normal. Because our patient had had chronic hypoxemia for 26 years, hypoxemia is not likely to have caused such drastic changes during a 6-month time span.

Left-to-right shunts are important causes of PHTN in patients with congenital heart defects. Our patient had a small ventricular septal defect that had been left unrepaired. The ventricular septal defect probably did not play a significant role because of the relatively rapid onset of his PHTN.

Other factors contributing to PHTN in heterotaxy syndrome include portosystemic shunts and asplenia. Portopulmonary hypertension is PHTN associated with portal hypertension. The exact mechanism of portopulmonary hypertension is unknown. One theory suggests that vasoactive substances normally metabolized by the liver bypass liver metabolism through portosystemic shunts.[8] These vasoactive substances include endothelin, vasoactive intestinal peptide, serotonin, and thromboxane A2. Endothelin is a well-known pulmonary vascular constrictor, and elevated levels of endothelin have been reported in patients with liver cirrhosis.[9] Bosentan, an endothelin 1 antagonist, is particularly effective in treating portopulmonary hypertension. In our study, survival rates of patients with portopulmonary hypertension were higher in those treated with bosentan compared to iloprost, a synthetic analog of prostacylin.[10] Our patient responded favorably to bosentan, indicating the possibility that a portosystemic shunt may have caused his PHTN. Patients with heterotaxy syndrome have liver abnormalities such as a midline liver. In particular, patients with right isomerism have many venous malformations that further elevate the possibility of portosystemic shunts in heterotaxy syndrome.

PHTN in heterotaxy syndrome might be related to asplenia. One theory states that patients with asplenia or hyposplenia cannot filter thrombocytes and erythrocytes adequately, increasing the risk of thromboembolism and resulting PHTN.[10] A case series and case-control study showed higher rates of asplenia in patients with PHTN compared to patients without PHTN.[11] The same study showed abundant thrombotic lesions in the lungs of patients with asplenia and PHTN. The patient with one other reported case of PHTN in heterotaxy syndrome also had hyposplenism with elevated levels of Howell-Jolly bodies.[3] Our patient had asplenia and secondary polycythemia, likely because of chronic hypoxemia, with recorded hemoglobin as high as 24.6 g/dL and hematocrit of 70.1%.

PHTN is a rare manifestation of heterotaxy syndrome that to our knowledge has never been reported as a prominent

clinical feature in a patient with congenital cardiac abnormalities. PHTN may arise in heterotaxy syndrome because of left-to-right shunts, portosystemic shunts, and the consequences of asplenia.

CONCLUSION

It is important for clinicians to be aware of heterotaxy syndrome in adults and its rare manifestations such as PHTN. More cases similar to ours may be reported in the future as the advancement of corrective cardiac surgery increases the life span of these patients well into adulthood.

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