CHEST

A 2-Year-Old Boy With Hypoxemia, Pulmonary Hypertension, and Digital Clubbing

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CASE PRESENTATION: A 2-year-old boy was referred to the Ankara University School of Medicine Children's Hospital with a history of recurrent respiratory distress and cyanosis since birth. His medical history was significant for premature birth at 31 weeks via cesarean section, as an infant of a diabetic mother. There was no parental consanguinity. He was hospitalized in the neonatal ICU after birth because of respiratory distress. After receiving invasive mechanical ventilation for 4 days, noninvasive mechanical ventilation and oxygen therapy were given gradually. As a result of further investigations, he received a diagnosis of situs inversus totalis and pulmonary hypertension. He was discharged on postnatal day 53 without supplemental oxygen therapy or treatment for pulmonary hypertension. Up to the age of 2 years, the patient had a history of multiple admissions to hospital for respiratory distress, lower respiratory tract infection, and cyanosis as an inpatient and outpatient. After starting to walk, shortness of breath and coughing occurred with effort.

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Physical Examination Findings

On admission, the patient was afebrile with a heart rate of 120 beats/min; respiratory rate, 28 breaths/min; and BP, 80/50 mm Hg. He had central cyanosis and digital clubbing with resting oxygen saturation of 80% in room air. His respiratory sounds were normal, but increased heart sounds were heard in the right precordium with a 2/6 systolic murmur with regular rhythm. No retraction or thoracic deformities were observed. There was no jugular venous distension, hepatosplenomegaly, or peripheral edema. Results of the rest of the physical examination were normal.

Laboratory Findings

Pa_{O_2} and Pa_{CO_2} were 48 and 42 mm Hg, respectively, and peripheral oxyhemoglobin saturation was 83%. His hemoglobin level was 9.7 g/dL; WBC count, 13.1 $\times$ 10^9/L; and platelet level, 294 $\times$ 10^9/L. The results of liver and renal function tests were normal. His brain natriuretic peptide level was 113 pg/mL; serum iron level, 17 µg/dL; and ferritin level, 3 µg/L. His orthodeoxia test result was negative.

A chest radiograph revealed dextrocardia, right-sided stomach bubble, and normal lung parenchyma. Echocardiography detected mirror dextrocardia, absence of the hepatic segment of the inferior vena cava (IVC), and presence of azygos continuation of systemic veins. Contrast echocardiography showed no intrapulmonary shunting. Cardiac catheterization was performed, and the mean pulmonary artery pressure was measured as 40 mm Hg.

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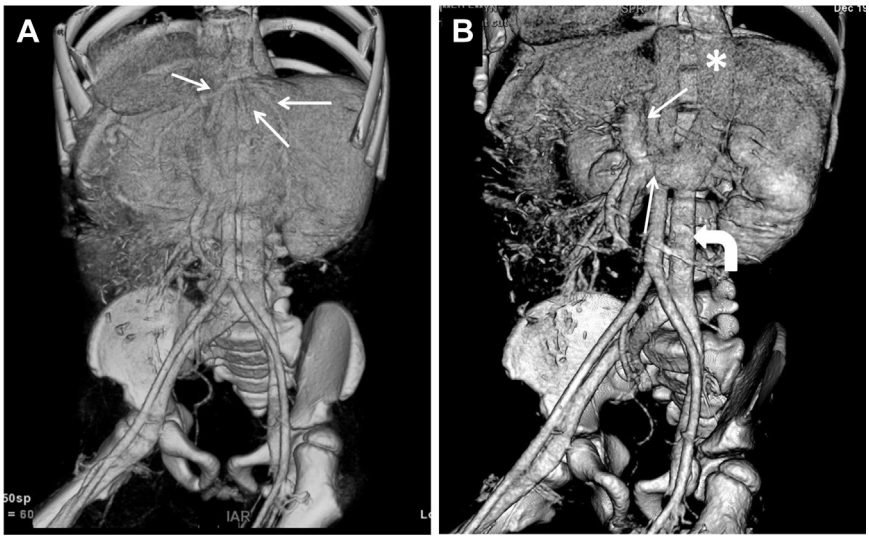


Figure 1 – *Situs inversus totalis. A, Virtual reality three-dimensional CT image of hepatic veins (arrows) draining into the atrium via a short suprahepatic inferior vena cava. B, Hepatic and infrahepatic segments of the inferior vena cava are absent. The portal venous system (straight arrows) joins with the left-sided vena cava like a systemic vein (curved arrow) and continues as an azygos system (asterisk).*

CT angiography of the thorax and abdomen detected situs inversus totalis with a very short IVC draining hepatic veins and opening to the right atrium, and a dilated azygos system connecting to the superior vena cava. The superior mesenteric vein (SMV) and splenic vein (SV) joined to form an end-to-side shunt and showed azygos continuity (Fig 1). Hypoplasia of the portal vein (PV), which was associated with the SMV before the SV-SMV junction, was detected. Polysplenia was observed (Fig 2). No parenchymal lung or liver abnormality was detected.

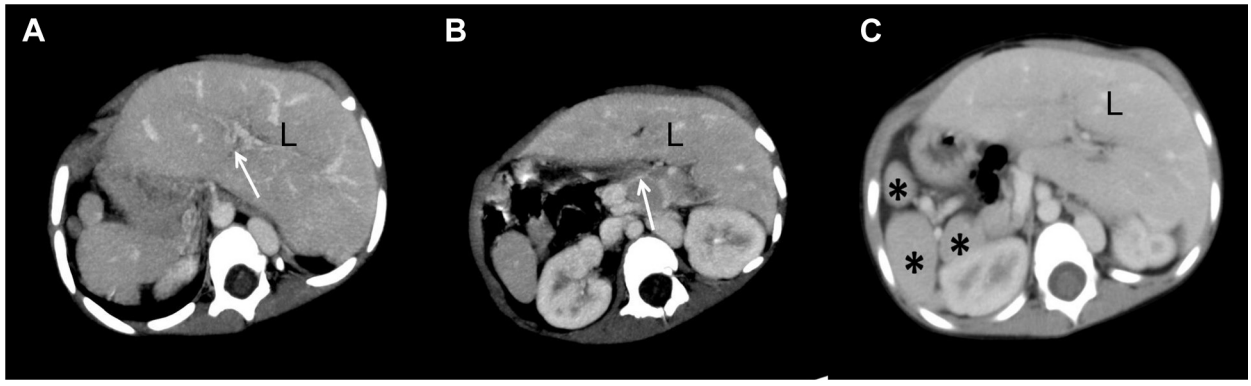


Figure 2 – *Situs inversus totalis. A and B, Virtual reality three-dimensional CT images show the small portal vein at the hilum connecting with the superior mesenteric vein (arrows). C, Multiple splenules (asterisks) on the right, as part of the syndrome. L = liver.*

What is the diagnosis?

Diagnosis: Congenital extrahepatic portosystemic shunt (Abernethy malformation) type II

Discussion

Congenital extrahepatic portosystemic shunt (CEPS), also known as an Abernethy malformation, is a rare malformation that was first described by Abernethy in 1793, and classified by Morgan and Superina in 1994 into two types. Type I CEPS is characterized by the absence of intrahepatic PV branches with an end-to-side portacaval shunt. It has also been classified into type Ia, in which the SV and SMV drain separately into a systemic vein, and type Ib, in which the SV and SMV join to form a common trunk that drains into a systemic vein. In type II CEPS, intrahepatic PV radicles are present; however, there is partial diversion of the portal blood into a systemic vein through a side-to-side shunt. The type I malformation occurs mostly in children and is more often associated with other malformations and complications than is type II.

The cardinal and vitelline venous systems are responsible, in uterine life, for the formation of the systemic and portal venous systems. Incomplete involution of the vitelline venous system results in various types of portosystemic shunts. Developmental caval vein anomalies such as interrupted IVC, double IVC, and azygous and hemiazygous continuation may also coexist with portal venous anomalies because the development of the IVC and PV are known to be interlinked to each other.

Heterotaxy with polysplenia has been described in conjunction with CEPS, although it is not well known. One of the most common lesions of heterotaxy syndrome is absence of the intrahepatic IVC with azygos or hemiazygos continuation. Patients with CEPS have been reported to develop pulmonary complications such as pulmonary hypertension (PHT) and hepatopulmonary syndrome (HPS). The clinical findings of these two complications include cyanosis, hypoxemia, and dyspnea.

PHT is defined as elevated pulmonary artery pressure with a mean of $>$ 20 mm Hg according to the new World Health Organization symposium guidelines. The mechanism by which PHT develops is thought to be related to vasoconstrictive and proliferative substances that bypass the liver without metabolism and act on the pulmonary vasculature, thus leading to hypertension. The increased pulmonary blood flow may also produce excessive shear stress, which leads to endothelial injury and dysfunction with vasoconstriction and progressive vascular remodeling. Heart disease association or hepatic involvement is not required for the development of PHT. Therefore, PHT-related CEPS can be considered as due to unclear causes according to the World Health Organization classification (group 5).

Another accompanying pulmonary pathology in CEPS is HPS. HPS is characterized by intrapulmonary vascular dilations that result in right-to-left shunting. There are three hypotheses that may explain the mechanism of HPS development in the setting of CEPS. The first hypothesis is that elevation of endothelin-1 levels, which upregulate nitric oxide (NO) production in the lungs, generates HPS by continuously stimulating NO synthase. Second, hepatic products necessary for pulmonary vasomotor control are decreased by hepatic venous flow reduction. According to the last hypothesis, translocation of gut bacteria activating alveolar macrophages results in an increase in inducible NO synthase. Therefore, endotoxin elevation because of bacterial translocation and the high concentration of endothelin-1 in the shunt blood cause vasodilation and angiogenesis in the pulmonary vascular bed. This leads to ventilation-perfusion mismatching, diffusion limitation of oxygen exchange, and arteriovenous shunting.

The specific pathophysiologic mechanism of digital clubbing remains unknown. One of the hypotheses is that potential vasodilators bypass the liver in the presence of portacaval shunt and bypass the lungs in the presence of HPS without metabolism. This situation causes an increase in blood flow and results in changes in the vascular connective tissue under the nail bed. Hypoxia may also activate local vasodilators, which increase blood flow to the distal portion of the digits.

Nodular hepatic lesions, such as in regenerative nodular hyperplasia, focal nodular hyperplasia, hepatic adenoma, and hepatocellular carcinoma, have been reported in patients with CEPS. These tumors are considered to result from an abnormal hepatocellular response to impairment of the portal venous supply and compensatory increases in hepatic arterial flow. They may increase in number and size during follow-up and become stable or even decrease after shunt closure.

Although quite rare, in a patient with a *PKHD1* mutation, CEPS associated with Caroli's syndrome was also reported. Caroli's syndrome is defined as a

combination of Caroli's disease (nonobstructive saccular intrahepatic bile duct dilation) and congenital hepatic fibrosis and/or kidney cysts. The underlying pathogenic mechanism of the association of two types of malformation is uncertain; however, as in the patient, it would be beneficial to consider this syndrome in patients with ciliopathy and potentially developing liver disease.

In CEPS type II, early shunt closure is considered to prevent and/or resolve complications and symptoms. Thus, long-term follow-up for associated complications is essential in patients with CEPS, especially if they do not undergo shunt correction in CEPS type II.

Clinical Course

The patient was diagnosed as having PHT and situs inversus totalis, and was admitted to our hospital with hypoxemia and digital clubbing. We attempted to exclude HPS in spite of the possibility of concomitant liver disease with situs inversus totalis. His liver function test results and contrast echocardiography were normal, and orthodeoxia was not detected. Abdominal CT angiography imaging detected PV hypoplasia with an end-to-side portacaval shunt and normal liver parenchyma. He received a diagnosis of CEPS type II, and it was understood that this shunt was the etiology of the digital clubbing and PHT, which caused hypoxemia in this patient. Supplemental oxygen therapy and treatment for PHT were started. For the presence of heterotaxy with polysplenia, the patient should have been evaluated for primary ciliary dyskinesia, a ciliopathy disorder; however, neither genetic analysis nor electron microscopy examination of nasal or bronchial cilia could be done. Shunt closure was planned but the patient was lost to follow-up.

Clinical Pearls

1. *CEPS, also known as Abernethy malformation, is a rare vascular malformation in which portal blood is shunted partially or completely into the systemic circulation via abnormal communication of the portal system.*
2. *CEPS should be considered in patients who present with unexplained hypoxemia, especially with clubbing and HPS without hepatic dysfunction, primary PHT, or nodular hepatic lesions.*
3. *Early diagnosis and treatment are essential for preventing or even resolving complications associated with CEPS.*

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Suggested Readings

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