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Case Report

Unexpected Findings of Regulatory Factor X6 Gene Mutation and Severe Hepatic Macrovesicular Steatosis in a Neonate with Congenital Left Ventricle Diverticulum: A Case Report

Mohammad Reza Edraki[1], MD; Tara Taheri[2], MD; Mehran Fereidooni[2], MD; Hamid Amozgar[3], MD; Elham Dehghani[1], MD

[1]Cardiovascular Research Center, Shiraz University of Medical Sciences, Shiraz, Iran;
[2]Iranian Legal Medicine Research Centre, Legal Medicine Organization, Tehran, Iran;
[3]Neonatology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

Correspondence:
Elham Dehghani, MD;
602, Elizeh Building, 29th Alley, Mollasadra St., Ahmadabad Blvd., Postal code: 91736-95636, Mashhad, Iran
Tel: +98 51 38330169
Fax: +98 71 36474298
Email: dehghani.e1@gmail.com
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Abstract

Herein we present a case of a neonate with congenital left ventricular diverticulum (LVD), a rare anomaly, with an unusual course and unexpected findings. The neonate was born at 35 weeks in Namazi Hospital (Shiraz, Iran) and presented with a pulsatile umbilical mass immediately after birth. Based on multiple imaging modalities, the presence of a connection between the left ventricular apex and the umbilicus was confirmed. Percutaneous closure of LVD was unsuccessful. The patient's clinical course deteriorated after developing sepsis and multiorgan failure. The patient passed away before any corrective surgery could be performed. Unexpected findings in post-mortem evaluation were severe hepatic macrovesicular steatosis (suggestive of metabolic liver disease) and regulatory factor X6 (RFX6) heterozygous missense mutation in whole-exome sequencing.

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Keywords ● Diverticulum ● Pentalogy of Cantrell ● Ectopia cordis

What's Known

- Association of the congenital left ventricular diverticulum (LVD) with pentalogy of Cantrell syndrome were established.
- There is no reported association between congenital LVD and regulatory factor X6 (*RFX6*) gene mutation (Mitchell-Riley syndrome) or metabolic diseases.

What's New

- A case of a neonate with congenital LVD and RFX6 heterozygous missense mutation is presented.
- Post-mortem histological findings of the liver were highly suggestive of metabolic liver disease. Such an association has never been reported in patients with LVD.

Introduction

Congenital left ventricular diverticulum (LVD), a rare congenital cardiac disorder, is a contractile pouch originating from the left ventricular wall. Histologically, it contains all three layers of the heart, namely the endocardium, myocardium, and pericardium. LVDs are usually located in the apex of the left ventricle and are often asymptomatic. They can be isolated or accompanied by other congenital cardiac or non-cardiac abnormalities.[1-3]

Our literature search did not reveal any reported associations between congenital LVD and metabolic diseases or regulatory factor X6 (*FRX6*) gene mutation. Herein, we present an unusual case of congenital LVD in combination with an unexpected genetic mutation.

Case Presentation

In April 2019, a female neonate was born by caesarean section at 35 weeks gestation to a 28-year-old primigravid mother in Namazi Hospital affiliated with Shiraz University of Medical Sciences (Shiraz, Iran). Caesarean delivery was performed due

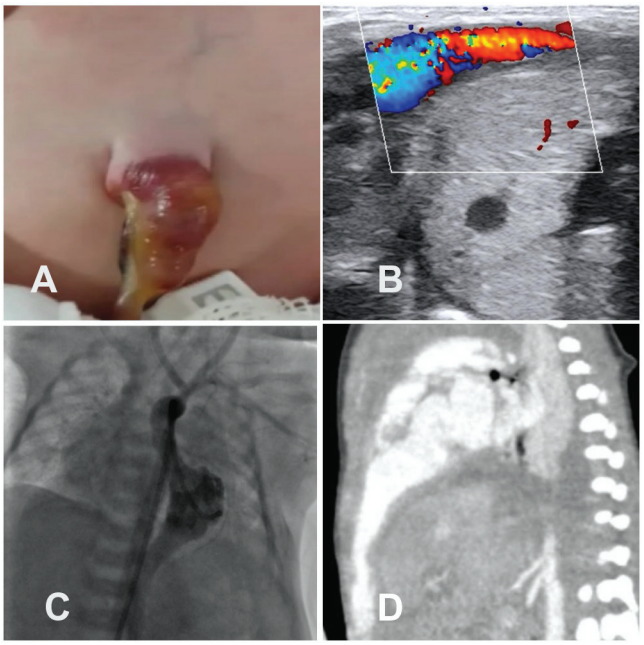

Figure 1: The tip of the left ventricular diverticulum presented as a pulsatile umbilicus (A). Color Doppler echocardiography of the patient shows the diverticulum immediately under the skin (B). Angiography of the left ventricle from the femoral artery reveals the connection between the diverticulum and the umbilicus (C). In this sagittal view of the chest and abdominal CT angiography, the extension of the diverticulum is better delineated (D).

to fetal distress following a nonstress test (NST). The parents were a young non-consanguineous couple, and the mother had an uncomplicated pregnancy. Prior to and during her pregnancy, she only took levothyroxine for hypothyroidism. The neonate had no apparent syndromic features. A large 30×25 mm pulsatile protruding mass in the midline, in the umbilical area, was noticed at birth (figure 1A), and a grade 3/6 pansystolic murmur was heard at the left lower sternal border. The patient was intubated due to tachypnea and respiratory distress that developed two days after birth. Other aspects of the neonate's physical examination were unremarkable.

Doppler ultrasonography of the periumbilical area showed a contractile muscular pouch from the umbilicus connected to the left ventricular apex (figure 1B). In addition, echocardiography revealed an LVD extending from the left ventricular apex to the umbilicus, one medium-sized mid-muscular, a small apical ventricular septal defect, a small atrial septal defect, a large patent ductus arteriosus, aberrant right subclavian artery, and cor triatriatum. The brain and abdominopelvic ultrasonography were unremarkable. Laboratory data, including complete blood count, renal and liver function tests, arterial blood gas; and screening tests for congenital hypothyroidism, phenylketonuria, and galactosemia were normal.

Heart failure therapy was initiated, and the neonate was scheduled for diagnostic and, if feasible, therapeutic angiography (to reduce volume overload and facilitate weaning from the ventilator). The angiographic evaluation confirmed the extension of the contractile LVD to the umbilicus (figure 1C). However, when inserting a Judkins right 5 catheters into the beginning of the diverticulum, the lumen was dissected (with no cardiovascular compromise), and the procedure was therefore terminated. A computed tomography (CT) angiography of the chest and abdomen was performed to evaluate the best surgical approach and to look for the anatomic delineation of the diaphragmatic and other midline defects. A large LVD was seen extending inferiorly through a 25 mm periumbilical defect in the anterior abdominal wall (figure 1D). The CT scan also revealed the presence of bilateral lung collapse and infiltration that contributed to the patient's respiratory distress.

Unfortunately, the patient's clinical condition deteriorated before any corrective surgical procedure could be performed after developing bilateral pneumothorax and fulminant sepsis leading to multi-organ failure and death (at the age of 12 days).

Apart from the LVD (figure 2A) and congenital cardiac defects, the important unexpected findings of the post-mortem evaluation were severe macrovesicular steatosis of the liver, mild to moderate cholestasis, and mild inter-hepatocytic fibrosis which were highly suggestive of a metabolic disease involving the liver (figure 2B).

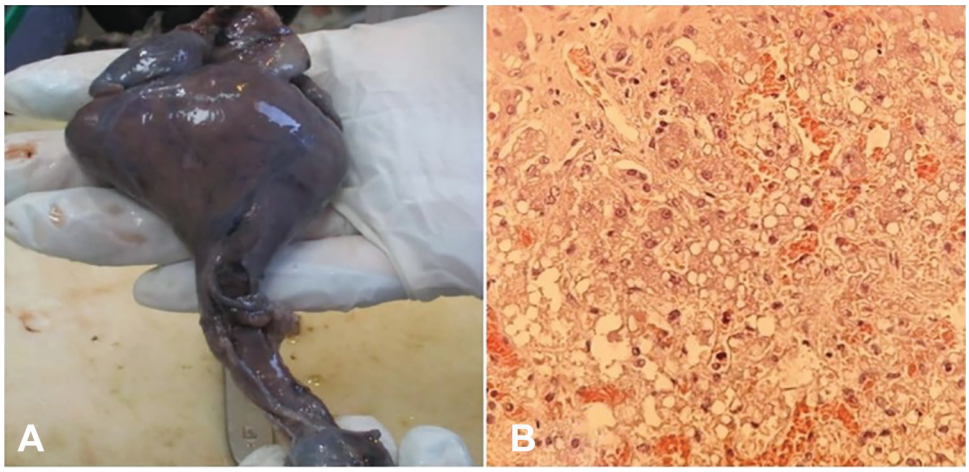

Figure 2: Post-mortem specimen of the patient's heart showing the extension of the left ventricular diverticulum (A). Post-mortem specimen of the liver showing macrovesicular steatosis and sinusoidal congestion of the hepatocytes (B).

Table 1: Properties of the detected mutation

Chromosome	Start	Details	SNP	CADD_phred
6	116928762	RFX6:NM173560: exon18: c. A2402G: p. Y801C	rs763236559	16.77

SNP: Single nucleotide polymorphisms; CADD_phred: Phred-style combined annotation-dependent depletion

Unfortunately, these findings were not identified with ultrasound or CT imaging when the patient was still alive but only detected as part of the post-mortem evaluation when a thorough metabolic evaluation was no longer possible. Therefore, post-mortem whole exome sequencing using Illumina next-generation sequencing was performed to further investigate any possible association between known mutations and abnormalities associated with metabolic diseases. Despite good coverage, we did not identify any pathogenic mutations related to the observed phenotype in the infant. However, a rare heterozygous missense mutation was detected in the *RFX6* (NM_173560:exon18:c. A2402G:p.Y801C) gene located on chromosome 6 (table 1).

The study was approved by the Ethics Committee of Shiraz University of Medical Sciences (IR.SUMS.MED.REC.1399.523). Written informed consent was obtained from the patient's father to publish this case report.

Discussion

Congenital LVD is a rare cardiac anomaly and is mainly asymptomatic. It is often detected incidentally in the third decade of life, although it can also occur from the antenatal period through late adulthood with various symptoms.[1-4] Failure of the primitive intra-embryonic mesoderm to differentiate into its splanchnic and somatic layers and inappropriate attachment of the primitive heart tube to the yolk sac are the most credible explanations for LVD.[1, 2] The main differential diagnosis of LVD is left ventricular aneurysm, which is a ventricular protuberance containing fibrous tissue with no organized myocardium, mainly akinetic or dyskinetic, and commonly located on the inferior surface of the heart.[2] A left ventricular aneurysm is generally larger than an LVD.[1] The prevalence of cardiac and extra-cardiac anomalies in patients with aneurysms is lower than in LVD, but the mortality is higher, especially due to congestive heart failure.[1]

In more than half of all cases, the LVD is located at the left ventricular apex, where detection with echocardiography is challenging.[1, 2] As reported, the overall incidence of abnormalities associated with the right ventricular diverticulum is much lower than LVD.[2] LVD can be isolated or occur as part of a constellation of abnormalities, such as the pentalogy of Cantrell, which includes the abdominal wall, diaphragm, sternum, inferior pericardial, and congenital heart defects. Of the latter, the most common are tetralogy of Fallot, tricuspid atresia, and ventricular septal defect.[2, 4, 5] In about one-third of all cases, the prevalence of the associated cardiac and non-cardiac anomalies is similar. Ventricular and atrial septal defects, coronary abnormalities, and cardiac malposition are the most common congenital cardiac defects. In addition, thoraco-abdominal wall defects (e.g., diaphragmatic defects, umbilical hernias, omphalocele, and caudal sternum abnormalities) are the most prevalent non-cardiac anomalies.[1, 3]

To the best of our knowledge, there are no

reports on LVD-associated metabolic diseases or any other hepatic histopathology as in our patient. Our histological findings in the liver (severe macrovesicular steatosis) were strongly suggestive of metabolic disease. However, since the patient had already passed away, we could not rely on the usual screening methods for metabolic diseases. The result of whole exome sequencing, performed to find the more common genetic abnormalities related to specific metabolic diseases, was also unexpected. Therefore, the rare heterozygous missense mutation detected in the *RFX6* gene may only be an incidental finding and not necessarily indicative of a cause-effect relationship. The only reported clinical features associated with this gene is Mitchell-Riley syndrome characterized by neonatal diabetes, pancreatic hypoplasia, intestinal atresia, gallbladder aplasia or hypoplasia, and jejunal atresia.[6] Except for occasional high blood glucose levels (200-300 mg/dl), most likely due to her critical condition, none of the above abnormalities were present in our patient. A substantial amount of research is required to fully investigate the association between a rare genetic defect and a rare congenital disease (e.g., LVD). However, we suggest performing a metabolic panel and genetic evaluation, at least, in the case of LVD presented in the early stage of life.

Rupture of the diverticulum, the main cause of death in LVD patients (75%), is much more frequent in the prenatal period and the first two years of life. The rupture is thought to be caused by an excessive elevation of systolic pressure inside the diverticulum.[1]

There are currently no guidelines regarding the therapeutic approach for asymptomatic LVD. However, due to a higher incidence of complications in the first years of life, some studies recommended surgical repair of the defect.[2,4] In the case of smaller defects, closure of the diverticulum using direct suturing is recommended. For defects larger than ≥2 cm, resection with patch closure is the accepted surgical method to prevent future complications in symptomatic cases.[1,2] A previous study reported percutaneous device closure of LVD in a 12-year-old female patient, i.e., closure of a non-apical 15×17 mm LVD with a narrow neck using a 12/10 mm ductus arteriosus occluder.[6] Another study reported transapical transcatheter closure of relapse LVD (after surgical closure) using a 16 mm atrial septal defect occluder.[7] Unfortunately, in the case of our patient, percutaneous closure of the diverticulum was not successful.

Conclusion

The unexpected histopathologic findings in the liver were highly suggestive of metabolic disease. In addition, the presence of a rare heterozygous missense mutation in the *RFX6* gene without the clinical features associated with this gene (Mitchell-Riley syndrome) may be a mere incidental finding. However, given the rarity of both, it is recommended to perform a metabolic panel and a genetic evaluation, at least, in the case of a large LVD presented in the early stage of life.

Authors' Contribution

MR.E, H.A, E.D: Performing the echocardiographic and angiographic procedures, medical and interventional planning and management, and direct involvement in clinical and imaging data collection and analysis; M.F, T.T: Performing post-mortem evaluation, comparing gross anatomic and microscopic tissue findings with the clinical and imaging data, reporting the unexpected abnormal findings in the liver tissue, and planning metabolic and genetic evaluation required for the suspected disorders based on the new findings; All authors actively participated in drafting, reviewing, and finalizing the manuscript. All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest: None declared.

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