Autopsy Case Reports

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Classic form of hypoplastic left heart syndrome diagnosed post-natally: an autopsy report

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ABSTRACT

Hypoplastic left heart syndrome (HLHS) is a congenital heart disease, which, despite the current improved knowledge about its management and surgical treatment, is still associated with high mortality, especially in the early neonatal period and before the second stage of reconstruction surgery. The low rate of prenatal diagnosis and delayed diagnostic suspicion results in unsuccessful therapeutic intervention, even though the real impact of early diagnosis and intervention on mortality and quality of life of patients is still uncertain. Fortunately, this syndrome of challenging treatment is not that frequent. It involves a spectrum of obstructions to the blood flow within the left heart and is characterized by an inappropriate size of the left ventricle associated with a wide variety of valvular dysfunctions. Treatment ranges from heart transplantation to palliative surgical procedures. The authors describe a case of a newborn with HLHS, whose diagnosis was made after birth because of early respiratory failure. Despite the use of prostaglandin the newborn died. An autopsy was performed and the anatomical findings were described.

Keywords
Hypoplastic Left Heart Syndrome; Respiratory Insufficiency; Shock, Cardiogenic; Autopsy.

CASE REPORT

A male newborn with 38 weeks and 6 days of gestational age, weighing 3410 g with an Apgar score of 10/10/10, was born through an uneventful cephalic presentation vaginal delivery after an oxytocin-induced labor. The 31-year-old mother, gravida 5 and para 4, was previously healthy, had apparently normal prenatal consultations and follow-up. Congenital heart disease (CHD) was not diagnosed intra uterus. She had immunity for rubella and toxoplasmosis; serologies for hepatitis B and C, syphilis, and HIV were negative. Blood type was B^+, and the evaluation for irregular blood group antibodies was negative. Twenty-seven hours after birth the newborn presented marked respiratory failure with respiratory frequency of 98 respiratory movements per minute, intense respiratory labor with intercostal and subcostal retractions, tachycardia (pulse rate of

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170 beats per minute), capillary refill time of 7 seconds, room air oximetry of 85%, and small amplitude arterial pulses. In the Intensive Care Unit (ICU) mechanical ventilatory support, umbilical vein catheterization, fluid resuscitation, and administration of vasoactive drugs were undertaken, initially considering the hypothesis of septic shock. The outcome was unfavorable with metabolic acidosis. Hypotension was maintained despite the administration of vasoactive drugs; the upper limbs systolic pressure was higher than the lower limbs (75 × 54 mmHg). An echodopplercardiogram was performed and was compatible with left ventricle hypoplasia, reason why continuous intravenous prostaglandin was infused to assure the patency of ductus arteriosus and the establishment of an adequate retrograde shunt to the aortic arch and coronary arteries.

Further detailed echocardiography observed *situs solitus*, and showed hypoplastic aortic arch (2 mm caliber) showing retrograde blood flow; systemic and pulmonary venous drainage were apparently preserved. The mitral valve showed hypoplasia, and no communication between the left ventricle and the aortic arch was evidenced (aortic valve atresia). Ductus arteriosus was patent (4 mm) with bidirectional flow predominantly from the pulmonary artery to the aorta. The heart was enlarged, mainly due to the right chambers with hypokinesia of the right ventricle. The left ventricle was normal in size and thickness but was also hypokinetic. A left-to-right flow was observed due to a 5 mm restrictive atrial septal defect (ASD). A 6 mm interventricular communication provided a predominant left-to-right blood flow. The pericardium was normal. Figure 1 shows a schematic design of this case.

The newborn died on the third day of life due to cardiogenic shock and multiple organ failure secondary to CHD.

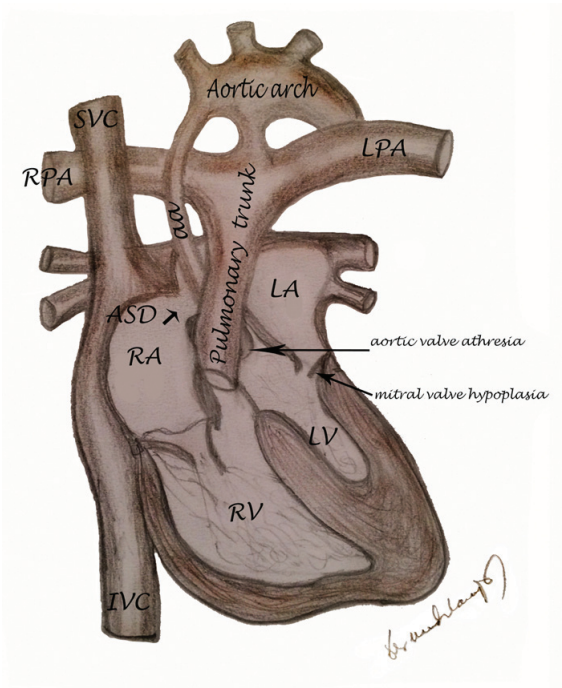

Figure 1. Schematic view of hypoplastic left heart syndrome. aa = aortic arch; ASD = atrial septal defect; IVC = inferior vena cava; LA = left atrium; LV = left ventricle; LPA = left pulmonary artery; RA = right atrium; RPA = right pulmonary artery; RV = right ventricle; SVC = superior vena cava.

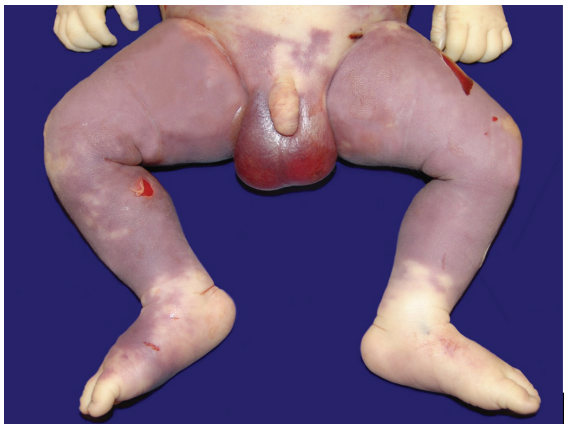

Figure 2. External examination showing cyanosis of the lower limbs and scrotum. Note focal areas of desquamation of the skin.

AUTOPSY FINDINGS

The ectoscopic examination showed a male neonate without external malformations. There were signs of anasarca and an intense cyanosis of the lower limbs and scrotum, with red-wine-stained skin and focal areas of desquamation (Figure 2).

At the opening of the thoracic cavity, the heart weighted 29.0 g (reference value [RV]: 17.7 g ± 5.4 g), and showed severe hypoplasia of the ascending aorta and aortic arch (Figure 3A), the internal diameter of which measured 1.0 mm; aortic valve atresia; large ductus arteriosus (measuring 7.0 mm) (Figure 3B); coarctation of the aorta with aortic isthmus measuring 2.5 mm; restrictive patent foramen ovale and additional ASD measuring 1.5 mm (Figure 3C); severe hypoplasia of the left ventricle with trabecular aspect and thick myocardium; hypoplasia of the mitral valve; and an enlarged right ventricle (Figure 3D).

On microscopic examination, the trabeculated aspect of the myocardium described on gross evaluation corresponded to numerous and deep spaces lined by endothelial cells, occasionally surrounded by fibrosis, compatible with ventriculocoronary connections (Figure 4).

On gross examination, the lungs showed congestion on the lower lobes (right lung = 36.0 g;

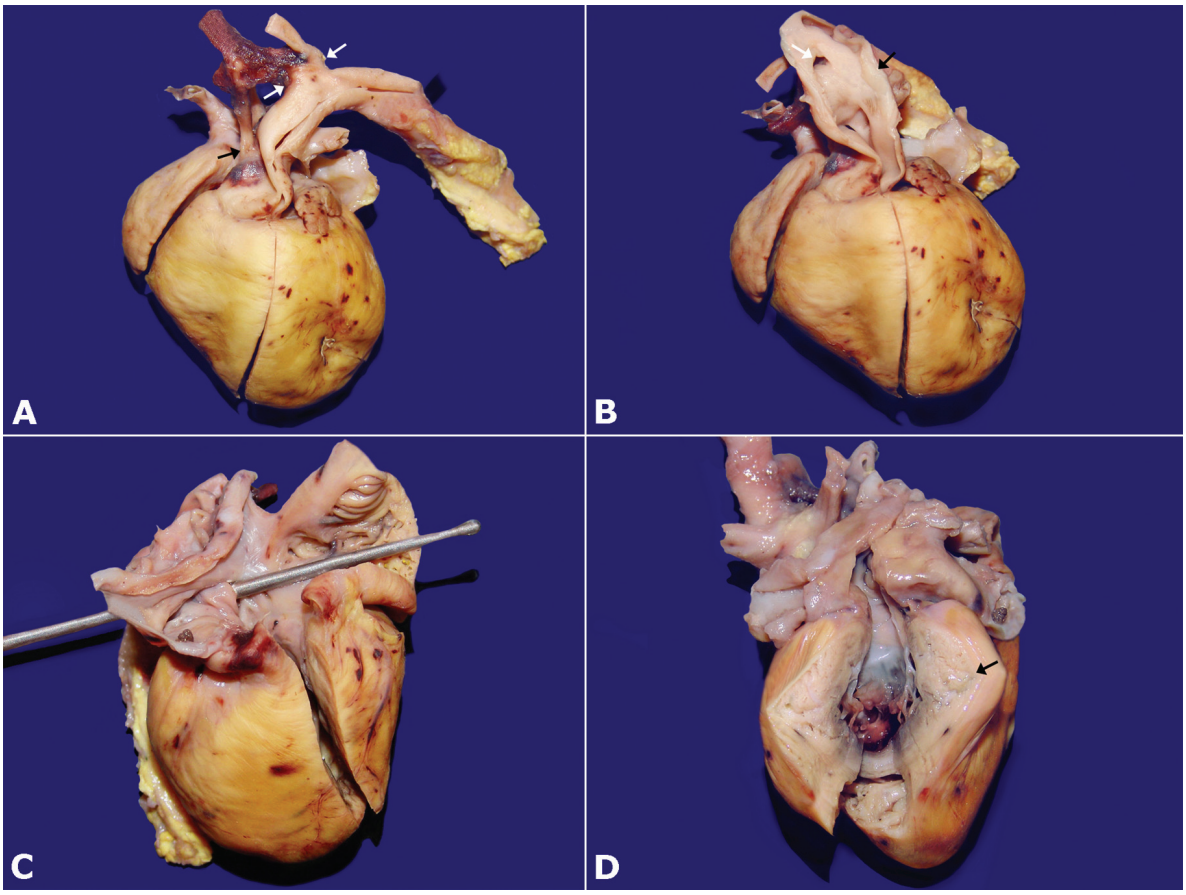

Figure 3. Gross examination of heart. **A -** The presence of severe hypoplasia of the ascending aorta and aortic arch (black arrow) and large ductus arteriosus (white arrows). **B -** Large ductus arteriosus (black arrow) communicating pulmonary artery with descending aorta and aortic isthmus (white arrow). **C -** Restrictive patent foramen ovale. **D -** Severe hypoplasia of left ventricle with trabeculated aspect and thick myocardium (black arrow), and hypoplasia of the mitral valve.

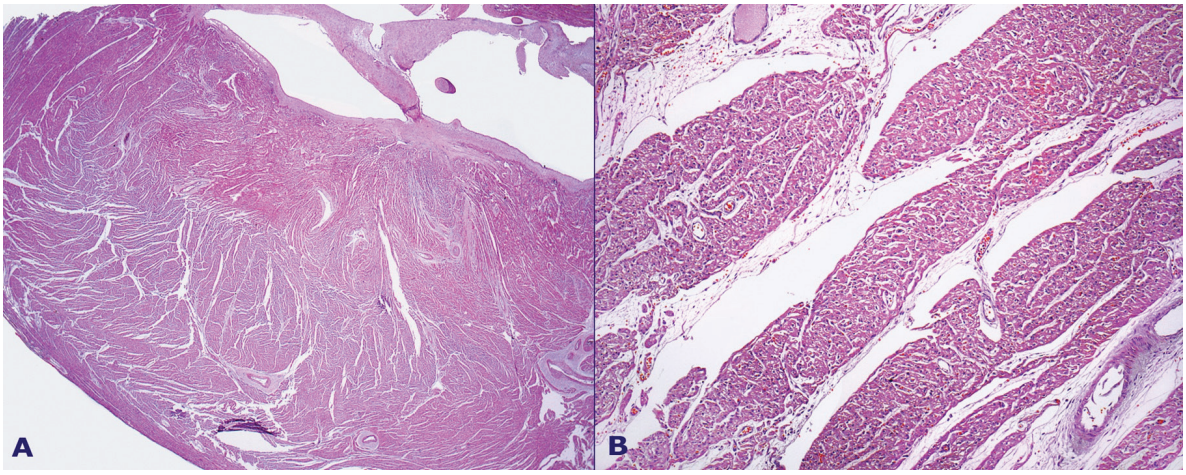

Figure 4. Photomicrography of the left ventricular myocardium. **A** and **B -** Note the presence of deep intertrabecular spaces between the myocardial fibers (H&E, 25X). B – (H&E, 100X).

left lung = 29.9 g [RV: 40.6 g ± 17.1 g—both lungs together]). The microscopic examination showed parenchyma in the alveolar stage of development with diffuse congestion of capillaries and areas of hemorrhage. In the alveolar lumen, there were scales and numerous neutrophils consistent with pneumonia (Figure 5).

On gross examination of the abdominal cavity, the viscera were congested. The liver was enlarged and weighed 169.8 g (RV: 113.5 g ± 34.7g); the cut surface showed diffuse congestion. The microscopic examination showed preserved portal tracts, severely congested and dilated hepatic sinusoids with foci of necrosis in the hepatic lobule, and the presence of hepatic extra medullary hematopoiesis (Figure 6).

The spleen was congested and enlarged, and weighted 16.8 g (RV: 9.5 g ± 3.5 g), and showed congestion of the red pulp on microscopic examination (Figure 7).

The right and left kidney weighed 18.7 g and 18.9 g, respectively (RV: 24.8 g ± 7.2 g for both kidneys). On cut surface, the kidneys showed diffuse congestion of the cortex and medulla compatible with acute tubular necrosis, which was confirmed on microscopy (Figure 8).

The cause of death was related to cardiogenic shock and restriction of pulmonary venous return, due to the restrictive character of the ASD.

The placenta was not sent for pathological examination.

DISCUSSION

CHDs are the most common group of malformations affecting fetuses and neonates. Prenatal detection is notably challenging because both the right and the left ventricular chambers are involved in the arterial systemic circulation (parallel circulation, which is different from the *in series* post-natal pattern).

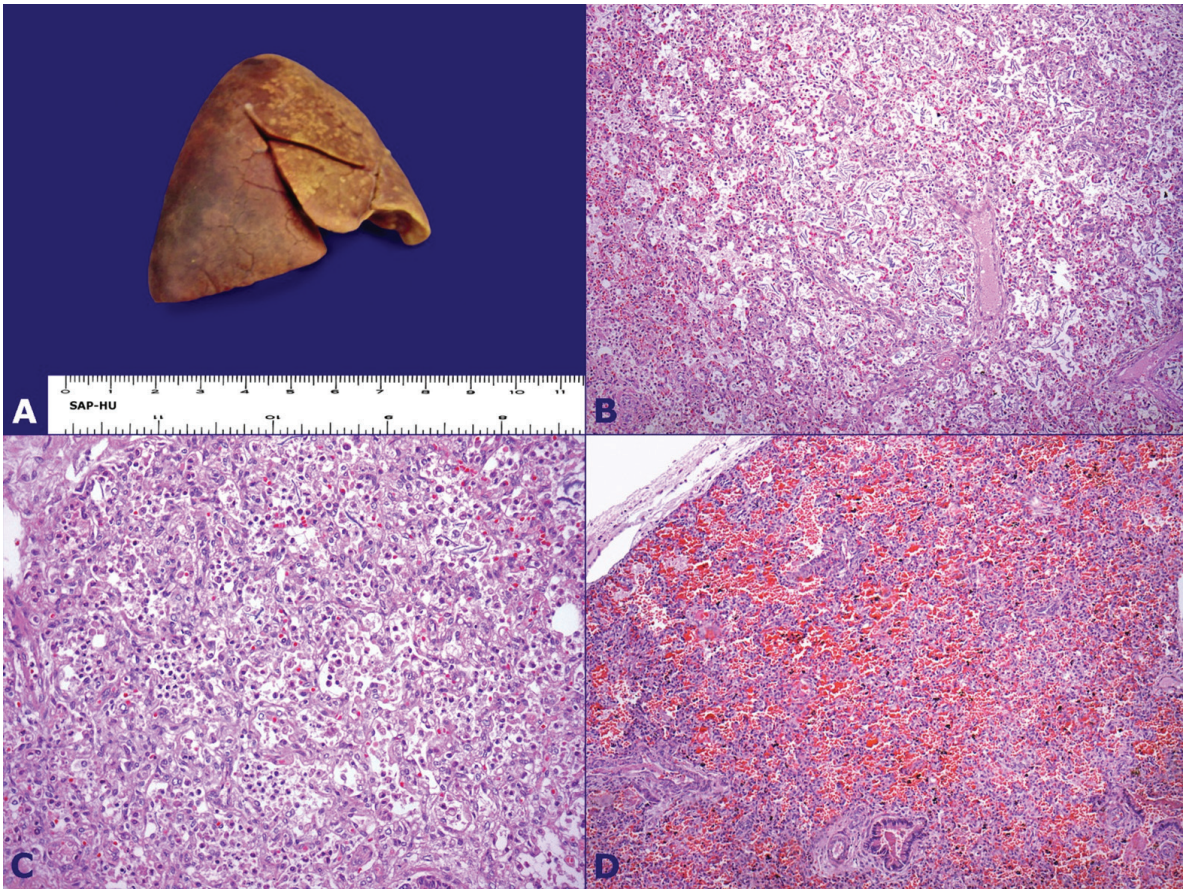

Figure 5. A - Gross examination of the right lung showing the congested lower lobe. Photomicrography of the lung (B–D); **B -** Pulmonary parenchyma in the alveolar stage of development showing cornea scales in the alveolar lumen (H&E, 100X); **C -** The presence of numerous neutrophils in the alveolar lumen (H&E, 200X); **D -** The presence of an area of alveolar hemorrhage (H&E, 100X).

Atrial and arterial shunts are present, and the placental circulation provides oxygenation and nutritional support for normal fetus development. The majority of fetuses with CHD do not exhibit signs of cardiac failure, because one side of the heart compensates for an abnormality on the other side.[1]

In 1851, Dr Bardeleben[2] first reported the description of the pathologic, pathophysiology, and clinical features of what was further coined as hypoplastic left-heart syndrome (HLHS) by Noonan and Nadas[3] in 1958—although, in 1952, Maurice Lev[4,5] had described a group of CHD characterized

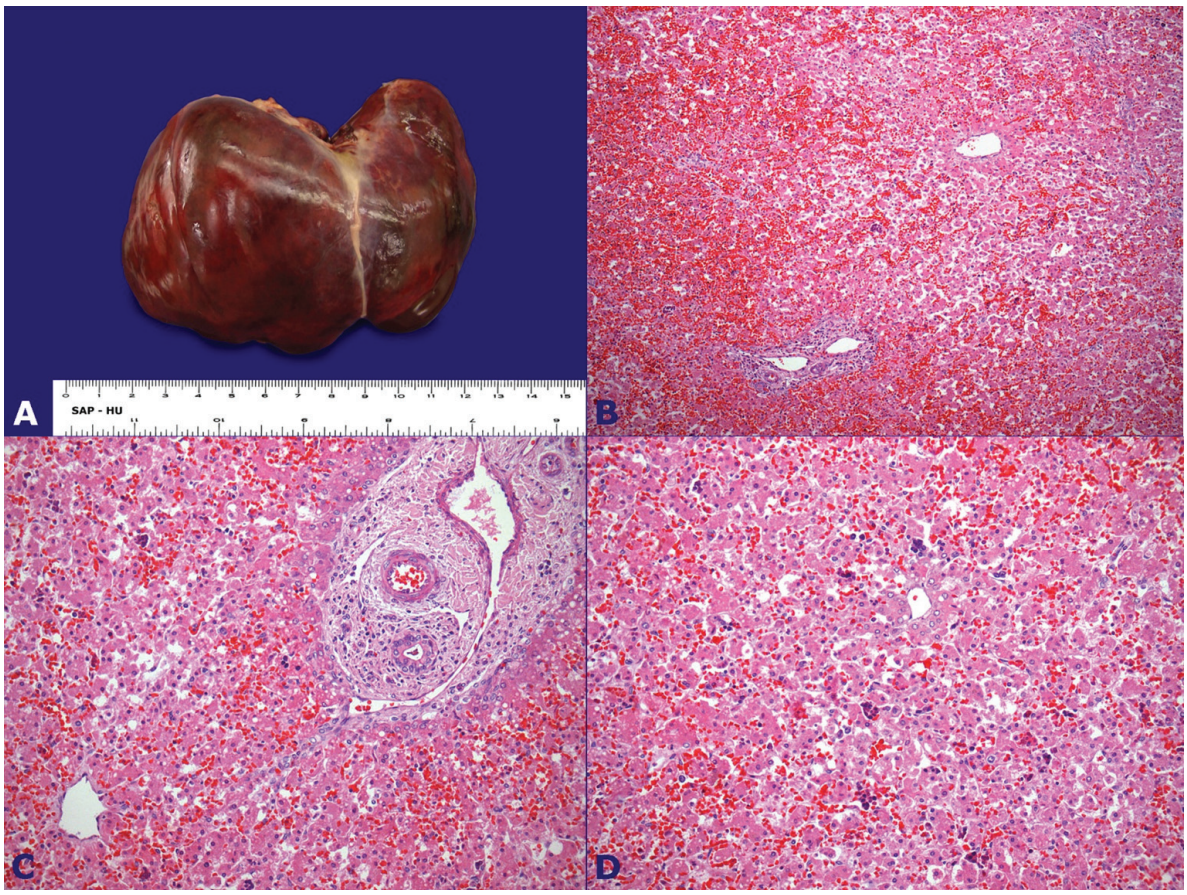

Figure 6. A - Gross examination of the liver showing a congested capsular surface. Photomicrography of the liver B–D); **B -** The presence of diffuse congestion of the hepatic sinusoids (H&E, 100X); **C -** Detail of a preserved portal tract and congested hepatic sinusoids with scattered hematopoietic cells (H&E, 200X); **D -** The presence of hematopoietic cells in the hepatic sinusoids (H&E, 200X).

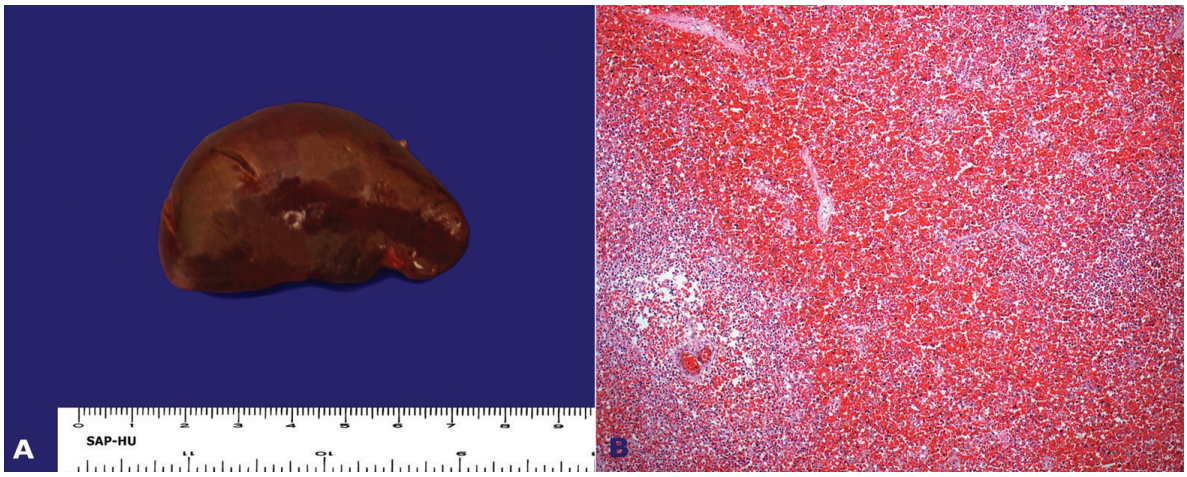

Figure 7. A - Gross examination of spleen showing a congested capsular surface; **B -** Photomicrography of the spleen showing congested red pulp (H&E, 100X).

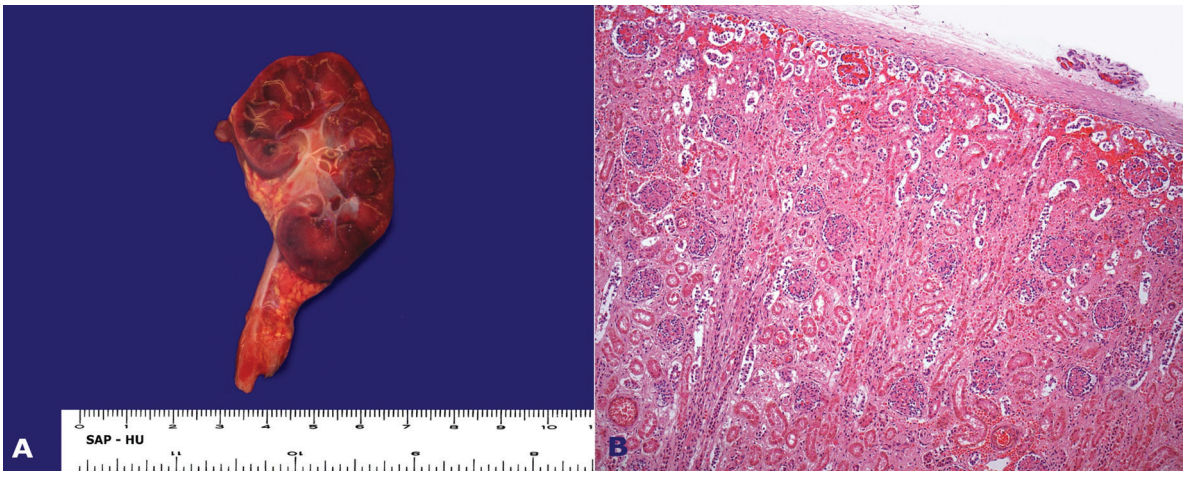

Figure 8. A - Gross examination of kidney showing a congested cortex and medullar parenchyma; **B -** Photomicrography of the kidney showing acute tubular necrosis and absence of the nephrogenic zone (H&E, 100X).

by the hypoplasia of the aortic tract complexes basically featuring hypoplasia of the left heart and hypertrophy of the right side of the heart. In 1966,[6] HLHS was characterized by varying grades of hypo development of the left ventricle associated with valvar abnormalities.[5] The incidence of HLHS ranges from 0.016% to 0.036% among all births, and corresponds to 3.8% of all CHD, the fourth most frequent during the first year of life. Without treatment this syndrome is fatal in 100% of cases with 95% of patients dying during the first month of life. HLHS is the most frequent cause of death by cardiopathy during the first week of life.[7] The etiology is still not well known, but it seems to be multifactorial involving the mother, the gestation, the genetics, and exposure to teratogenic agents.[6,8]

Anatomically, the syndrome involves a spectrum of obstructions to the blood flow within the left heart characterized by an inappropriate size of the left ventricle to support the systemic circulation associated with variable degrees of valvar obstructions.[9] Atresia or stenosis of the mitral and aortic valves, as well as hypoplasia of the aortic arch and ascending aorta, are the main described abnormalities. Aortic coarctation is also very frequent (around 45% in an anatomical series) and is significantly associated with an ascending aorta diameter lower than 3 mm.[10] The definition criteria for hypoplasia of the left ventricle are somewhat controversial.[11] Classification of HLHS may range from mild to severe cases requiring individualized therapy. The development of new clinical approaches and the upgrading of classic surgical techniques has been achieving better survival rates.[12,13]

Newborns with HLHS have only one functional ventricle. The cardiac output is maintained through the left-to-right atrial shunt and the patent of ductus arteriosus is associated with the high pulmonary vascular resistance, which provides systemic arterial flow from the right ventricle.

The detection of CHD, in general, depends on routine antenatal ultrasonographic abnormalities as well as the identification of risk factors for CHDs.[1,14] In this setting, the measurement of nuchal translucency (NT) during the eleventh and thirteenth gestational week is noteworthy. There is a correlation between the presence of CHD and NT over the 95th percentile; which are chromosomally normal in 44% of patients. Fetuses presenting TN greater than the 99th percentile (3.5 mm) have an incidence of 6-7% of CHD and are chromosomally normal in 20%.[8,15]

Other risks for CHD include abnormal karyotype; monochorionic twin pregnancy; fetal hydropsy; fetal arrhythmias; other extra cardiac abnormalities like congenital diaphragmatic hernia, duodenal atresia, and cystic hygroma; and suspicion of CHD on obstetric ultrasongraphy.[1] The maternal risks include the use of prostaglandins synthetase inhibitors containing medications like ibuprofen; teratogenic drugs like lithium and anticonvulsants; diabetes mellitus; infection by Parvovirus; diffuse connective tissue disease with positivity for antibodies anti-Ro and anti-La; history of CHD in first-grade relatives; and in vitro fertilization.[8]

Although it is important to recognize the risk factors, most cases of CHD occur in the low-risk

population, and early detection depends on fetal echocardiography mostly at the four-chambers view.[8] This echocardiography view, incorporated in obstetric anomaly screening, has some accuracy in detecting HLHS, tricuspid valve atresia, and atrial and ventricular septal defects, but transposition of the great arteries, tetralogy of Fallot, and common arterial trunk (truncus arteriosus), require the cardiac outflow to be accurately visualized with Doppler examination. In HLHS, the echodopplercardiogram is able to demonstrate hypoplastic, hypertrophic, and hypocontractile, left ventricle, atresia, or stenosis of the mitral or aortic valves, endocardial fibroelastosis, and aortic arch retrograde flow. Intra uterine diagnosis presents a positive predictive value of 95%. Fetal position, maternal body mass index, quality of equipment, and ultrasonographer's expertise will all reflect on the accuracy of the examination.[8]

The genetic origin of HLHS is not well defined; multiple loci have been related to this syndrome—among them the NKX2.5 on chromosome 5, 10q22, and 6q23. The HLHS may be associated with higher frequency in the other genetic abnormalities such as Turner syndrome (X0), Jacobsen syndrome (distal 11q deletion) and trisomies 13 and 18.

Clinical features vary according to the anatomical abnormalities, since the expected left ventricular and left valve malformations may be accompanied by other multiple lesions such as pulmonary vessels, tricuspid valve, pulmonary valve, ductus arteriosus, and interatrial and interventricular septa.[11]

Although antenatal diagnosis of HLHS has a marked impact in the survival expectancy, the majority of infants are term-newborns without prenatal diagnosis.[14] Clinical presentation usually starts when the ductus arteriosus closes, jeopardizing the systemic circulation and resulting in hypoxemia, tachycardia, cyanosis, acidosis, and cardiogenic shock. A subgroup of patients with HLHS (up to 6%), because of an intact interatrial septum and with some degree of restriction (up to 22%), decompensate soon after birth presenting hemodynamic instability, venous congestion, severe cyanosis, and acidosis. These patients show a higher morbimortality rate when compared with the other patients with this syndrome, and require an urgent interatrial communication intervention.[16]

Currently, 28% of HLHS cases are detected during pre-natal examination, and although all efforts were made to achieve this diagnosis, the mortality rate did not change.[8] In this regard, more evidence is required to evaluate the impact and the cost-benefit of intrauterine screening.[17] However, pre-natal diagnosis affords some benefits: it permits hospitalization in tertiary centers, and intervention in the early neonatal period, such as intensive care and surgery if necessary.[17-20] On the other hand, neurological morbidity reduces with pre-natal diagnosis, since specific treatment can be managed immediately after birth, such as atrial septostomy or surgical septectomy. Both interventions increase the septal defect and even can be realized before birth in those cases where the atrial septum does not show any primary defect.[21]

During the last few decades, the treatment of HLHS greatly improved after the use of prostaglandins, which prevent the ductus arteriosus closure.[20] Newborns should receive prostaglandin E1 in the labor room and ideally be referred to a tertiary specialized center.

HLHS patient survival depends on immediate maintenance of patency of the foramen *ovale* and the ductus arteriosus, since the systemic perfusion will depend on these shunts. Patency of the ductus arteriosus can be obtained initially and temporarily, with the continuous administration of prostaglandin E1, until the scheduled surgery. It is essential in HLHS that the presence of a non-restrictive ASD to assure an initial patient survival. When the ASD is not wide enough to permit an adequate left-to-right flow, the patient should be submitted to an atrial septostomy until the surgical procedure can be undertaken.

The treatment options include cardiac transplantation, pregnancy interruption, palliative heart surgery, and exclusive palliative care. However, the possibility of a surgical treatment raises an ethical dilemma. Palliative care or abortion is reserved for cases associated with other genetic syndromes, which do not have a long expectancy of life. A heart transplantation is the least frequent option because of the scarcity of donors in the neonatal period, the long-term immunosuppression side effects, and the high mortality rate. Currently, the three-stage palliative cardiac surgery, described by Norwood et al.,[22] has been the therapy of choice for most cases. Norwood et al.,[23] published the first case-series of

operations between 1979 and 1981 with favorable outcomes, and since then this operation has been improved and recommended.[24] The first stage, known as Norwood surgery, is undertaken after birth and consists of connecting the main pulmonary artery to the aortic arch, which was previously expanded, with a polytetrafluoroethylene (PTFE) graft, thus forming a new aorta. Pulmonary perfusion is maintained by a tubular PTFE graft anastomosed in the right subclavian and right pulmonary arteries.[5,24,25] Interatrial septal defect may be widened in this procedure. In 2003, Sano et al.[26,27] published modifications in the Norwood technique with outcome improvement. The second stage, the Glenn surgery, occurs between 2 and 10 months of age, and consists of replacement of the systemic-pulmonary shunt via a bidirectional cavopulmonary anastomosis. The third stage is completed with Fontan surgery (also called total cavopulmonary shunt), which is performed between 18 and 24 months of age.[27] The highest incidence of complications occur between the first and the second stages, usually represented by cardiogenic shock.[28]

During the 1980s, the survival rate during hospitalization after the surgery varied between 42% and 66%, and long-term survival ranged between 21% and 44%.[24] A Brazilian study conducted by Fantini et al.[7] showed immediate survival (from surgery until hospital discharge) of 80%, and 60% after 1 year of follow-up, in accordance with the literature where 1 month survival is reported to be between 72% and 60% after 1 year, and 54% after 5 years.

A new hybrid procedure has been recently used and is gradually replacing the Norwood surgery, which includes a surgical procedure and interventional radiology. It consists of surgically placed bands around the right and left pulmonary arteries, creating fixed pulmonary circulation resistance in an attempt to direct flow to the systemic circulation, followed by an interventional approach by placing a stent in the ductus arteriosus to maintain its patency and allow discontinuation of prostaglandin E1.[29-31] Many neonates require atrial septostomy or septectomy to ensure the free flow through the atrial septum.

Literature data on survival rates show an improvement during the last two decades[12] resulting from improvements in surgical techniques and perioperative care, but it is still worth noting that HLHS has a high morbidity and mortality.[28]

The case reported herein represents the most frequent form of HLHS. The pregnancy was considered of low risk for cardiac malformations and the prenatal follow-up was uneventful, although no data was available concerning the performance of obstetric and morphological ultrasonographic examinations. Therefore, in this case, the CHD diagnosis was made after birth, which greatly decreased the chance of survival. The interatrial septostomy was not undertaken in this patient because the diagnosis was delayed and early clinical instability with severe respiratory failure. The early diagnosis of HLHS and surgical preparation support at tertiary medical centers ensure a greater chance for survival in these patients.

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