Scientific Publications

Case Report

Global Journal of Medical Case Reports, 2026, 6, 6788
www.scipublications.com/journal/gjmcr
DOI: 10.31586/gjmcr.2026.6788

Neonatal Presentation of Ivemark Syndrome with Asplenia: A Case Report and Review of the Literature

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Abstract: Heterotaxy syndrome comprises a group of congenital anomalies resulting from disrupted left–right axis patterning during embryonic development, leading to an abnormal arrangement of the thoracic and abdominal organs [1]. It is a rare condition, with an estimated prevalence of approximately 1 per 10,000 live births, and is frequently associated with complex congenital heart defects, making it a life-threatening disorder with significant morbidity and mortality [1]. Clinically, heterotaxy syndrome is classified into right atrial isomerism (Ivemark syndrome) and left atrial isomerism. Ivemark syndrome represents the most severe form and is primarily characterized by asplenia, complex cardiovascular anomalies, and abnormal positioning of the thoracoabdominal organs [2]. In this condition, paired organs exhibit right-sided morphology bilaterally, commonly accompanied by functionally univentricular physiology, extensive septal defects, dextrocardia, and extracardiac malformations such as intestinal malrotation and congenital absence of the spleen [2,3]. Asplenia is a hallmark feature that markedly increases susceptibility to overwhelming bacterial infections, while the associated congenital heart defects account for the high morbidity and mortality observed during the neonatal period [2]. Herein, we report the case of a male neonate with clinical and imaging findings consistent with Ivemark syndrome who experienced a rapidly progressive and fatal clinical course during the first week of life. A comprehensive review of the available literature identified only a limited number of published cases and scarce documented evidence. Therefore, this case report is supported primarily by the currently available international literature.

Keywords: Ivemark Syndrome, Heterotaxy Syndrome, Asplenia Syndrome, Case Reports

How to cite this paper:
Estefania, L. E. A., Alejandra, M. A. M., Fiorella, B. T. T., Estefania, C. E. A., Majerly, M. B. B., Domenica, A. M. P., Andrés, V. B. C., & Franchesca, A. M. M. (2026). Neonatal Presentation of Ivemark Syndrome with Asplenia: A Case Report and Review of the Literature. *Global Journal of Medical Case Reports*, *6*(1), 15-29. DOI: 10.31586/gjmcr.2026.6788

Academic Editor:
Ravi Kumar Chittoria

Received: June 11, 2026
Revised: July 20, 2026
Accepted: August 28, 2026
Published: August 31, 2026

1. Introduction

To facilitate a better understanding of this condition, it is essential to review several fundamental concepts underlying the anatomical and physiological abnormalities involved. **Situs solitus** refers to the normal arrangement and asymmetry of the thoracic and abdominal organs [1]. **Situs inversus** describes a mirror-image reversal of the thoracic and abdominal viscera while preserving normal organ function [1]. **Situs ambiguus**, commonly referred to in clinical practice as **heterotaxy syndrome**, is characterized by an indeterminate or disorganized arrangement of the thoracic and abdominal organs [1]. Finally, **isomerism** refers to a condition in which normally asymmetric organs, including

the lungs, heart, and intestines, develop symmetrical morphological features on both sides of the body [1].

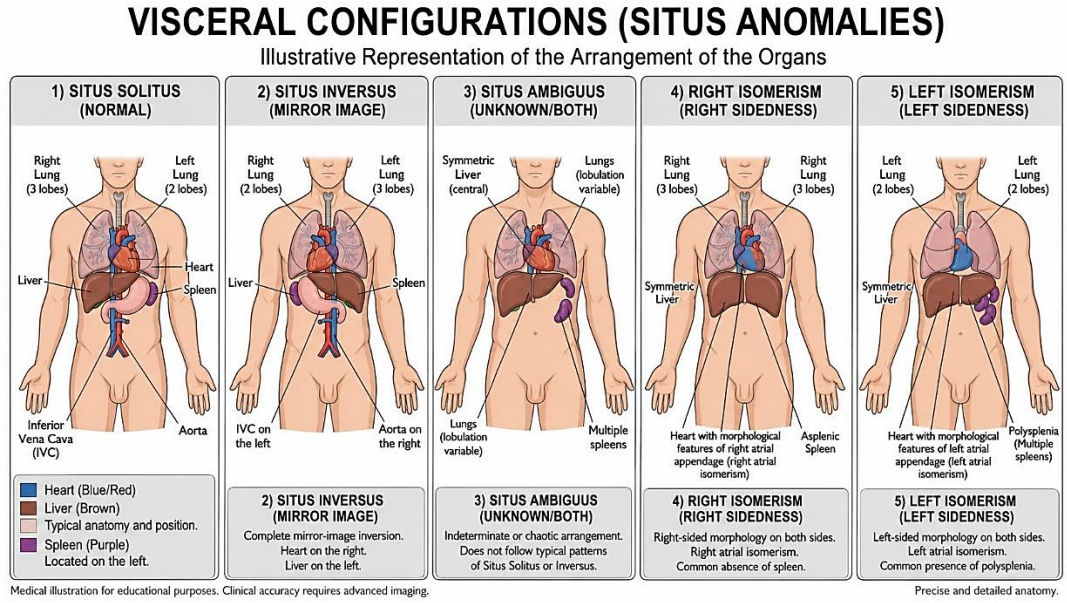

Figure 1. Illustrative comparison of the main human visceral arrangements (situs).

1.1. Classification

Heterotaxy syndrome is primarily classified into two major subtypes according to the morphological symmetry of the atrial appendage [1-3].

1.2. Right Atrial Appendage Isomerism (RAAI)

Also referred to as right atrial isomerism, asplenia syndrome, or Ivemark syndrome [1-4]. Both atrial appendages exhibit the morphological features of the right atrium, characterized by a broad-based triangular or pyramidal shape. The crista terminalis is well developed, and the pectinate muscles extend throughout the parietal wall toward the tricuspid valve vestibule [1,3]. This subtype is characterized by bilateral right atria, a midline symmetric liver, and trilobed lungs [1,2,4]. It is frequently associated with total anomalous pulmonary venous connection (TAPVC) [1]. Complete absence of the spleen (asplenia) is the typical finding; however, in approximately 10–15% of patients, splenic tissue may be present but functionally impaired [1,2,4] *(Figure 2)*.

1.3. Left Atrial Appendage Isomerism (LAAI)

Also known as left atrial isomerism or polysplenia syndrome [1-4]. It is characterized by elongated, narrow, and finger-like atrial appendages with left atrial morphology, accompanied by bilobed lungs [1,4]. Multiple small spleens (polysplenia) are typically present [1,2,4]. Approximately 80% of patients exhibit interruption of the inferior vena cava with azygos vein continuation, a characteristic vascular anomaly of this subtype *(Figure 3)*.

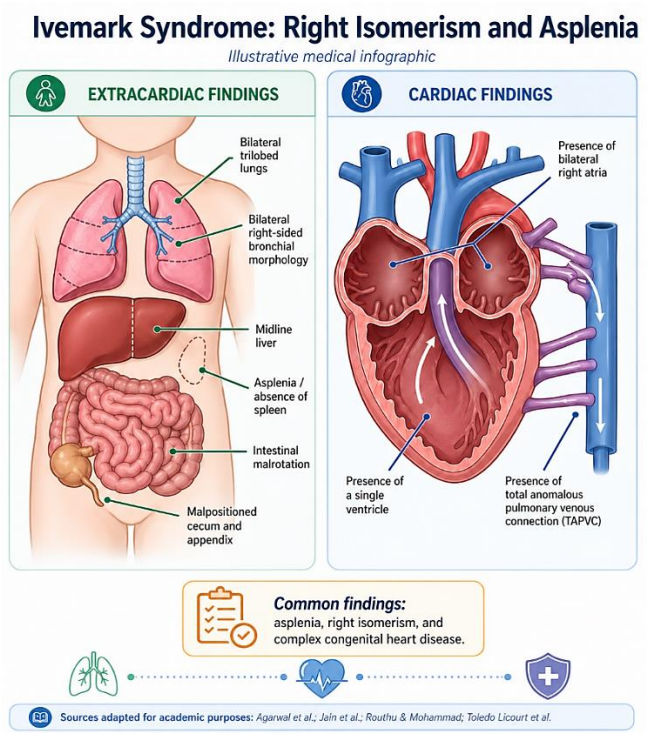

Figure 2. Medical infographic illustrating Right Atrial Isomerism (RAI) (Ivemark Syndrome).

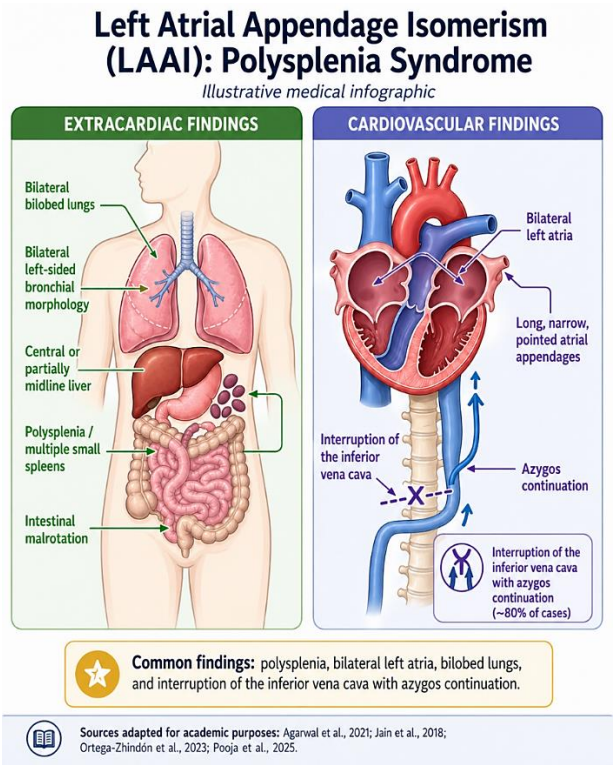

Figure 3. Medical infographic illustrating Left Atrial Isomerism (LAI) (Polysplenia Syndrome) with dextrocardia in a neonate.

1.4. Epidemiology

Heterotaxy syndrome is a rare congenital disorder, with a reported incidence ranging from 0.81 per 10,000 live births to approximately 1 per 10,000 live births [6]. The incidence

of right atrial isomerism (Ivemark syndrome) is even lower, ranging from 1 per 10,000 to 1 per 40,000 live births, whereas left atrial isomerism is relatively more common, with reported incidences between 1 per 10,000 and 1 per 20,000 live births [4].

Cardiovascular malformations are present in more than 80% of patients with heterotaxy syndrome [5]. In a cohort of patients with congenital heart disease, laterality defects accounted for 1.1% of all cases, of which 0.7% were classified as situs ambiguous [7]. Furthermore, laterality defects are significantly more frequent among patients with complex congenital heart disease (5.4%) than in those with simple cardiac defects (0.4%) [7].

The sex distribution of heterotaxy syndrome remains controversial. Some studies have reported a male predominance in right atrial isomerism and a female predominance in left atrial isomerism, whereas others have found no significant sex-related differences [4,6]. In addition, rare familial cases have been associated with pathogenic variants in the ZIC3 gene, located on the X chromosome. These account for fewer than 3–5% of all reported cases and predominantly affect male patients [5,7].

Heterotaxy syndrome may be diagnosed during the prenatal, neonatal, or postnatal period, depending on the severity of the associated malformations. Prenatal detection is frequently achieved through routine obstetric ultrasonography and can be confirmed by fetal echocardiography as early as the 16th week of gestation [5,8,9]. Although two-dimensional ultrasonography is useful for the initial evaluation, fetal echocardiography combined with color Doppler imaging provides a more comprehensive assessment by identifying abnormal blood flow patterns and anomalous venous connections [9,10]. Nevertheless, some affected fetuses may remain undetected despite apparently normal prenatal ultrasound examinations [4].

The prognosis largely depends on the complexity of the associated congenital anomalies. Severe forms of heterotaxy have been associated with mortality rates of up to 69% [4], exceeding 85% in patients with asplenia syndrome (right atrial isomerism) and 50% in those with polysplenia syndrome (left atrial isomerism) [6]

1.5. Embryology, Physiology, and Pathophysiology of Heterotaxy Syndrome (Ivemark Syndrome)

During the earliest stages of embryonic development, the embryo exhibits bilateral symmetry. Therefore, the establishment of the left–right body axis is a critical developmental event, as it determines the normal asymmetrical arrangement of the thoracic and abdominal organs [11,13].

During embryogenesis, left–right axis specification is initiated at the embryonic node, where bilateral symmetry is first broken [12]. At this stage, nodal cells undergo cell-cycle quiescence, a process regulated by the bone morphogenetic protein (BMP) signaling pathway through the activin A receptor type 1 (ACVR1). This signaling cascade promotes the formation of both motile and sensory cilia. Coordinated clockwise rotation of the motile cilia generates a leftward flow of extracellular fluid, known as nodal flow, which serves as the initial biomechanical cue for establishing embryonic laterality [11,12].

Nodal flow directs morphogenetic signaling molecules toward the left lateral plate mesoderm (LPM), where a highly conserved genetic cascade involving NODAL, LEFTY, and PITX2 is activated. These genes play a pivotal role in regulating the asymmetric morphogenesis of the heart and other thoracoabdominal organs.

Depending on the integrity of this developmental process, three major patterns of visceral arrangement may arise: situs solitus, situs inversus, and situs ambiguus (heterotaxy syndrome) [11].

Disruption of left–right axis formation may result from molecular or genetic abnormalities affecting this signaling cascade. Several genes have been implicated, including NODAL, FOXH1, ACVR2B, and SMAD2, which regulate left–right axis determination; ZIC3, the principal gene associated with X-linked heterotaxy; DNAH5,

DNAH11, and KIF3B, which impair ciliary motility and nodal flow; and FOXJ1, RFX3, and NOTO, all of which are essential for normal ciliogenesis. Pathogenic variants in these genes may lead to immotile or dysfunctional cilia, ultimately disrupting normal left–right patterning [11, 13] (Figure 4).

Consequently, situs ambiguus (heterotaxy syndrome) develops when nodal flow is either improperly generated or incorrectly interpreted, resulting in abnormal activation of the NODAL–LEFTY–PITX2 signaling pathway and, ultimately, an abnormal arrangement of the thoracic and abdominal organs [12]. Furthermore, heterotaxy syndrome is frequently associated with ciliopathies, particularly primary ciliary dyskinesia, in which ciliary dysfunction simultaneously impairs embryonic laterality and mucociliary clearance of the respiratory tract [13].

Overall, heterotaxy syndrome results from abnormalities in ciliary formation or motility, defective nodal flow, and disruption of the genetic pathways governing left–right axis specification. These developmental defects ultimately lead to abnormal thoracoabdominal organ arrangement and the broad spectrum of anatomical and clinical manifestations characteristic of this disorder.

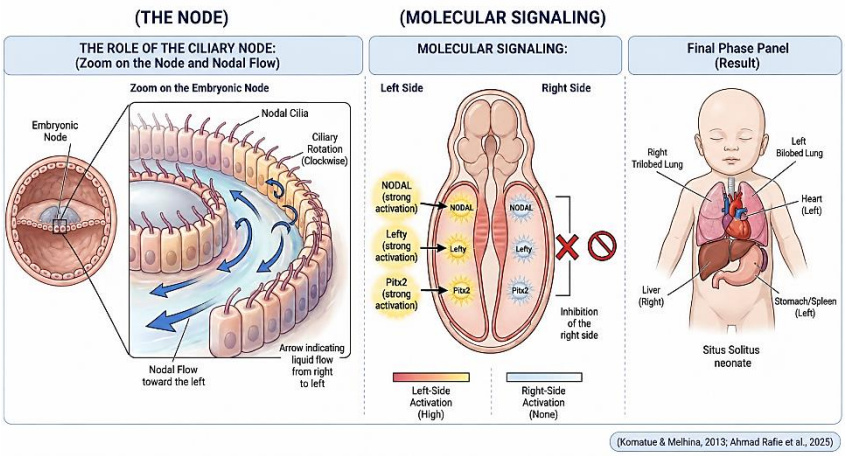

Figure 4. Medical infographic illustrating the normal embryonic development of left–right body axis specification.

2. Case Report

We report the case of a male neonate born to a 24-year-old primigravida mother, an agricultural worker who self-identified as Mestizo, had completed basic education, and was single. She had no previous pregnancies or history of miscarriage. Paternal information was unavailable because the mother was unable to provide it. The mother had no relevant personal, surgical, or family medical history and reported no known drug or food allergies. She denied tobacco use (active or passive), alcohol consumption, illicit drug use, or exposure to domestic violence throughout pregnancy. She attended seven prenatal care visits at a primary healthcare center near her residence. According to the prenatal records, maternal weight gain was appropriate, vital signs remained within normal limits, fetal movements were consistently present, and fetal heart rate was normal throughout follow-up. No episodes of vaginal bleeding were reported, and the MAMA score remained 0 during all prenatal assessments. Three obstetric ultrasound examinations were performed. The first was conducted between 11 and 13 weeks of gestation, whereas the gestational age at the second and third examinations was not specified in the medical records. All three ultrasounds were reported as apparently normal. Regarding immunization, the mother received two doses of the COVID-19 vaccine, one dose of the seasonal influenza vaccine, and tetanus vaccination during the eighth month of pregnancy. There was no documented history of preconception rubella

vaccination. Prenatal infectious disease screening was unremarkable. Serological testing for toxoplasmosis was negative. HIV screening was performed both before and after 20 weeks of gestation, yielding negative results on both occasions. Likewise, syphilis screening was negative at 18 weeks and again at 31 weeks of gestation. No screening tests were performed for Chagas disease or group B Streptococcus, whereas malaria screening was not indicated because of the epidemiological setting.

Maternal blood typing revealed O Rh-negative status. However, the medical records did not document the administration of anti-D immunoglobulin, the standard prophylactic intervention to prevent Rh alloimmunization. Consequently, it could not be confirmed whether this preventive measure had been administered.

Routine laboratory investigations showed a hemoglobin level below 11 g/dL before 20 weeks of gestation, for which the patient received iron and folic acid supplementation. Subsequent evaluations demonstrated correction of the anemia, with a hemoglobin concentration of 14 g/dL. Metabolic screening revealed fasting plasma glucose levels of 80 mg/dL before 20 weeks and 84.8 mg/dL after 30 weeks of gestation, both within the normal reference range.

Pregnancy was uneventful during the first and second trimesters. During the third trimester, the mother developed a urinary tract infection, which was successfully treated with nitrofurantoin.

2.1. Perinatal History

The patient was a full-term male neonate with a gestational age of 40 weeks, as determined by the Capurro assessment. He was delivered by cesarean section because of severe oligohydramnios and uterine tachysystole associated with fetal distress. The mother was unable to accurately recall the duration of membrane rupture before delivery.

The cesarean delivery was uneventful; however, a markedly reduced volume of amniotic fluid was noted intraoperatively. On April 7, 2025, at 11:16 a.m., a male neonate was delivered with Apgar scores of 8 and 9 at 1 and 5 minutes, respectively. Birth weight was 3,165 g, appropriate for gestational age, with a length of 49.4 cm and a head circumference of 35.5 cm. No neonatal resuscitation was required.

2.2. Initial Clinical Course at the Referring Hospital

Within the first hours of life, the infant developed cyanosis during feeding, accompanied by oxygen desaturation but without signs of respiratory distress. Supplemental oxygen was therefore initiated via nasal cannula.

At 24 hours of life, an initial complete blood count demonstrated a trend toward leukopenia, with a white blood cell count of 4,680/μL, while C-reactive protein (CRP) remained within the normal range. A chest radiograph was subsequently obtained and raised the first suspicion of dextrocardia (*Figure 5*). Based on these findings, a pediatric cardiology consultation was requested, and the patient was referred to a tertiary care center for further diagnostic evaluation.

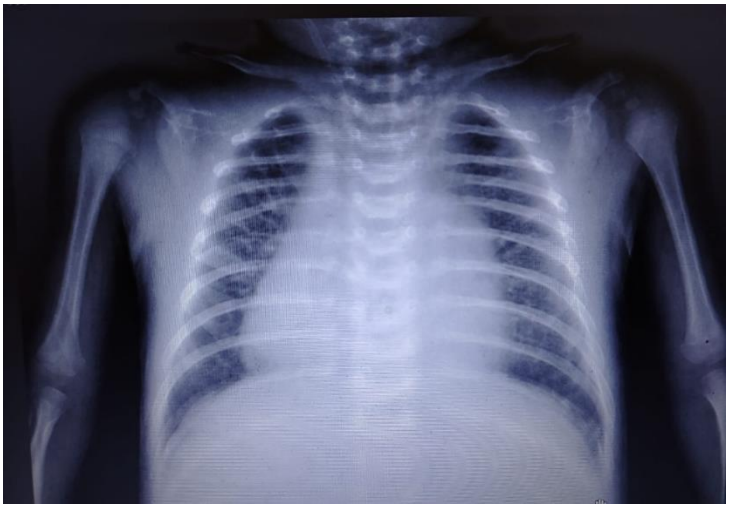

Figure 5. Anteroposterior (AP) chest and abdominal radiograph of a neonate.

The cardiac silhouette is enlarged, with the cardiac apex displaced toward the right hemithorax, consistent with dextrocardia. The lung fields appear symmetrically arranged. A centrally located radiopaque structure is identified in the lower portion of both lung fields, corresponding to a midline liver. Collectively, these radiographic findings are suggestive of abnormal visceral laterality, consistent with heterotaxy syndrome.

2.3. Clinical Deterioration and Transfer

At 72 hours of life (April 10, 2025), while hospitalized at a secondary-level hospital, the infant developed recurrent episodes of cyanosis triggered by crying, with oxygen saturation dropping to 50%, accompanied by hypotonia and an axillary temperature of 36.7°C, without apparent signs of respiratory distress. Initial stabilization measures were implemented; however, given the severity of the clinical deterioration, a Code Red neonatal transfer was activated at 74 hours of life, and the patient was urgently referred to a tertiary care center. During transport, the neonate was placed in a closed incubator and received supplemental oxygen via nasal cannula.

2.4. Hospital Admission and Initial Clinical Assessment

At 77 hours of life, the patient was admitted to the Emergency Department of a tertiary referral hospital. Initial evaluation by the pediatric team revealed a sleeping neonate who was responsive to stimulation, with normotensive fontanelles and equal, reactive pupils. Respiratory examination demonstrated mild subcostal retractions, preserved bilateral air entry, and no adventitious breath sounds. Cardiovascular examination revealed no audible heart murmurs, a heart rate of 143 beats/min, and an oxygen saturation of 70% while receiving supplemental oxygen through a nasal cannula. Based on these findings, the Neonatology Service was consulted, and the patient was immediately admitted to the Neonatal Intensive Care Unit (NICU).

2.5. Therapeutic Management in the Neonatal Intensive Care Unit

Upon NICU admission, the neonate was active and responsive to stimulation, with appropriate muscle tone but poor peripheral perfusion, evidenced by a capillary refill time of 3–4 seconds. Oxygen saturation reached 85% at rest but abruptly decreased to below 50% during crying episodes, accompanied by hypotonia and pallor, requiring continuous supplemental oxygen. Respiratory examination demonstrated mild intercostal retractions, preserved bilateral air entry, and no additional breath sounds. The respiratory rate was 50 breaths/min, corresponding to a Silverman–Andersen score of 1–2, indicating mild respiratory distress. Cardiovascular examination revealed a regular

cardiac rhythm without murmurs, while the cardiac apex was auscultated in the right hemithorax, consistent with dextrocardia. The abdomen was soft and mildly distended, with preserved bowel sounds and no palpable organomegaly. A mummified umbilical cord with a patent umbilical vessel was noted. Initial arterial blood gas analysis revealed the following values: pH 7.35, $PaCO_2$ 38.2 mmHg, PaO_2 23.9 mmHg, sodium 147 mmol/L, potassium 5.4 mmol/L, chloride 115 mmol/L, ionized calcium 1.13 mmol/L, hematocrit 59.9%, lactate 3.3 mmol/L, base excess −4.1 mmol/L, bicarbonate 19.9 mmol/L, and calculated osmolality 296.3 mOsm/kg *(Table 1)*. These findings were consistent with severe type I hypoxemic respiratory failure in the setting of a suspected cyanotic congenital heart disease, accompanied by compensated respiratory alkalosis.

Given the severity of the hypoxemia, continuous fentanyl infusion was initiated at 2 μg/kg/h, followed by invasive mechanical ventilation using the SIPPV mode, with the following initial settings: peak inspiratory pressure (PIP) 21 cmH_2O, positive end-expiratory pressure (PEEP) 6 cmH_2O, respiratory rate 50 breaths/min, and FiO_2 100%, maintaining oxygen saturation between 75% and 80%. Peripheral venous access was initially attempted but proved unsuccessful. Consequently, an umbilical venous catheter was placed to ensure prompt administration of medications and fluids. On the fourth day of life, this was replaced by a left axillary central venous catheter, which served as the definitive vascular access.

Throughout hospitalization, the patient required continuous inotropic support with high-dose dobutamine (8–10 μg/kg/min). Upon NICU admission, prostaglandin E1 was initiated at 0.1 μg/kg/min and maintained for 72 hours, followed by gradual tapering and discontinuation after partial improvement in systemic oxygen saturation.

Supportive therapy also included maintenance intravenous fluids, with a glucose infusion rate of 5–8 mg/kg/min, in addition to calcium gluconate (300 mg/kg/day). Given the need for invasive mechanical ventilation, central venous catheterization, and multiple unsuccessful peripheral venous access attempts, empirical intravenous antimicrobial therapy was initiated with ampicillin (50 mg/kg/dose), gentamicin (4 mg/kg/day), and fluconazole (5 mg/kg/day).

Arterial Blood Gas Analysis: The initial arterial blood gas analysis demonstrated severe type I hypoxemic respiratory failure, evidenced by a markedly reduced PaO_2 of 23.9 mmHg, while $PaCO_2$ remained within the normal range, indicating that the primary abnormality was impaired oxygenation rather than carbon dioxide retention. In addition, the elevated lactate concentration and mild negative base excess suggested the early development of metabolic consequences secondary to tissue hypoxia. Based on these findings, invasive mechanical ventilation was initiated using the SIPPV mode (PIP 21 cmH_2O, PEEP 6 cmH_2O, respiratory rate 50 breaths/min, FiO_2 100%) to improve the patient's severe hypoxemia. Four hours later, at 77 hours of life, a second arterial blood gas analysis demonstrated a modest improvement, with PaO_2 increasing to 35.4 mmHg, lactate decreasing to 2.6 mmol/L, and partial correction of the base excess. Nevertheless, oxygenation remained critically impaired, and the patient continued to meet criteria for type I hypoxemic respiratory failure. Based on this partial response, ventilatory support was adjusted by reducing the FiO_2 to 60%, while maintaining oxygen saturation between 75% and 80%.

2.6. Laboratory Investigations

At 77 hours of life, comprehensive laboratory testing was performed. The Transfusion Medicine Department determined the infant's blood type to be O Rh-positive, and the direct antiglobulin (Coombs) test was negative. The complete blood count demonstrated a normal total leukocyte count ($11.77 \times 10^3/\mu L$), with mild monocytosis ($1.81 \times 10^3/\mu L$) and the presence of immature circulating cells ($0.51 \times 10^3/\mu L$). Although these findings did not support the diagnosis of infection, they were considered compatible with a physiological stress response. Red blood cell indices revealed a hemoglobin

concentration of 18 g/dL and a hematocrit of 50.9%, excluding both neonatal anemia and polycythemia. Therefore, the patient's profound hypoxemia was attributed to the underlying congenital cardiopulmonary abnormality rather than impaired oxygen-carrying capacity.

The platelet count remained within the normal range (391 × 10^3/μL), with no evidence of thrombocytopenia or consumptive coagulopathy, indicating the absence of significant hematological abnormalities that could account for the patient's severe clinical condition. Serum biochemistry revealed an elevated blood urea nitrogen level (55.6 mg/dL), whereas serum creatinine remained normal (0.82 mg/dL), arguing against acute kidney injury. These findings were considered suggestive of prerenal azotemia, likely secondary to systemic hypoperfusion associated with severe hypoxemia and hemodynamic compromise. Electrolyte analysis demonstrated mild hypernatremia (148 mmol/L), mild hyperkalemia (5.78 mmol/L), and hyperchloremia (112 mmol/L), while the serum calcium concentration (9.3 mg/dL) remained within the normal reference range. High-sensitivity C-reactive protein (0.34 mg/dL) was not elevated, indicating the absence of a significant systemic inflammatory response at the time of admission. Total bilirubin was 6.77 mg/dL, with a direct bilirubin concentration of 0.51 mg/dL and an indirect bilirubin concentration of 6.26 mg/dL, findings consistent with physiological neonatal jaundice and not suggestive of neonatal hemolysis, as there was neither a rapid increase nor critically elevated indirect bilirubin levels during the first 24 hours of life. Cardiac biomarkers revealed an elevated B-type natriuretic peptide (BNP) concentration of 277.29 pg/mL, suggesting cardiac volume and pressure overload in the setting of congenital heart disease. In contrast, cardiac troponin I (0.03 ng/mL) and creatine kinase-MB (22 ng/mL) showed no evidence of acute myocardial injury. Procalcitonin (0.44 ng/mL) was within a range that did not support bacterial sepsis as the primary cause of the patient's clinical deterioration.

Overall, these laboratory findings were consistent with a critically ill neonate with structural congenital heart disease resulting in severe hemodynamic compromise, without laboratory evidence of bacterial sepsis, significant systemic inflammation, or infectious multiorgan dysfunction at the time of admission.

2.7. Coagulation Profile

Serial coagulation studies demonstrated significant changes over a relatively short interval of approximately 4 hours. During this period, the prothrombin time (PT) increased from 12.0 to 15.5 seconds, the international normalized ratio (INR) rose from 1.10 to 1.45, and prothrombin activity declined from 86.2% to 50.5%. In contrast, the activated partial thromboplastin time (aPTT) remained within the normal range, increasing only minimally from 36.2 to 36.7 seconds.

These findings suggest that systemic hypoperfusion may have caused transient impairment of hepatic synthetic function, resulting in reduced production of vitamin K-dependent coagulation factors. However, severe coagulopathy or disseminated intravascular coagulation (DIC) was considered unlikely, as the platelet count remained normal and the aPTT was not prolonged. This pattern was therefore interpreted as an early coagulation disturbance secondary to critical illness rather than overt consumptive coagulopathy.

Echocardiography and Cardiac Findings: On the fourth day of life, the patient remained in critical condition, requiring invasive mechanical ventilation, inotropic support, and prostaglandin infusion. An echocardiographic evaluation was performed by the Pediatric Cardiology Department at a tertiary care hospital, revealing situs inversus, dextrocardia, a 4.13 mm ostium primum atrial septal defect with right-to-left shunt, mitral valve atresia, a 13.2 mm ventricular septal defect with bidirectional shunting, a single right ventricular morphology, truncus arteriosus, and interatrial communication, findings consistent with a complex congenital heart disease (Figures 6, 7, 8).

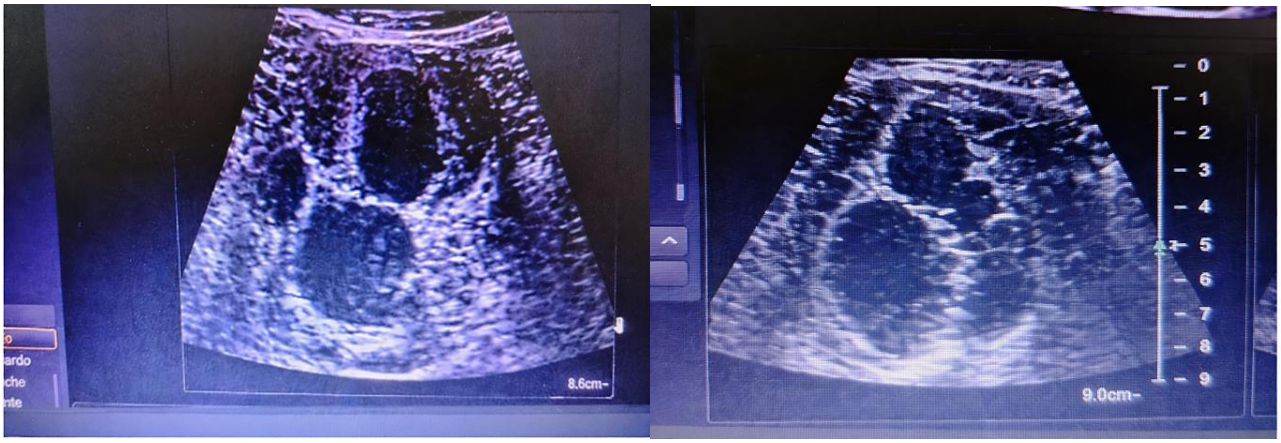

Figure 6. During the same evaluation, an abdominal ultrasound was performed to correlate the findings and guide the diagnosis toward a specific type of visceral heterotaxy. The study revealed a centrally located liver, absence of the spleen, intestinal malrotation, and right-sided gastric curvature, findings suggestive of visceral heterotaxy with features consistent with right atrial isomerism (Ivemark syndrome).

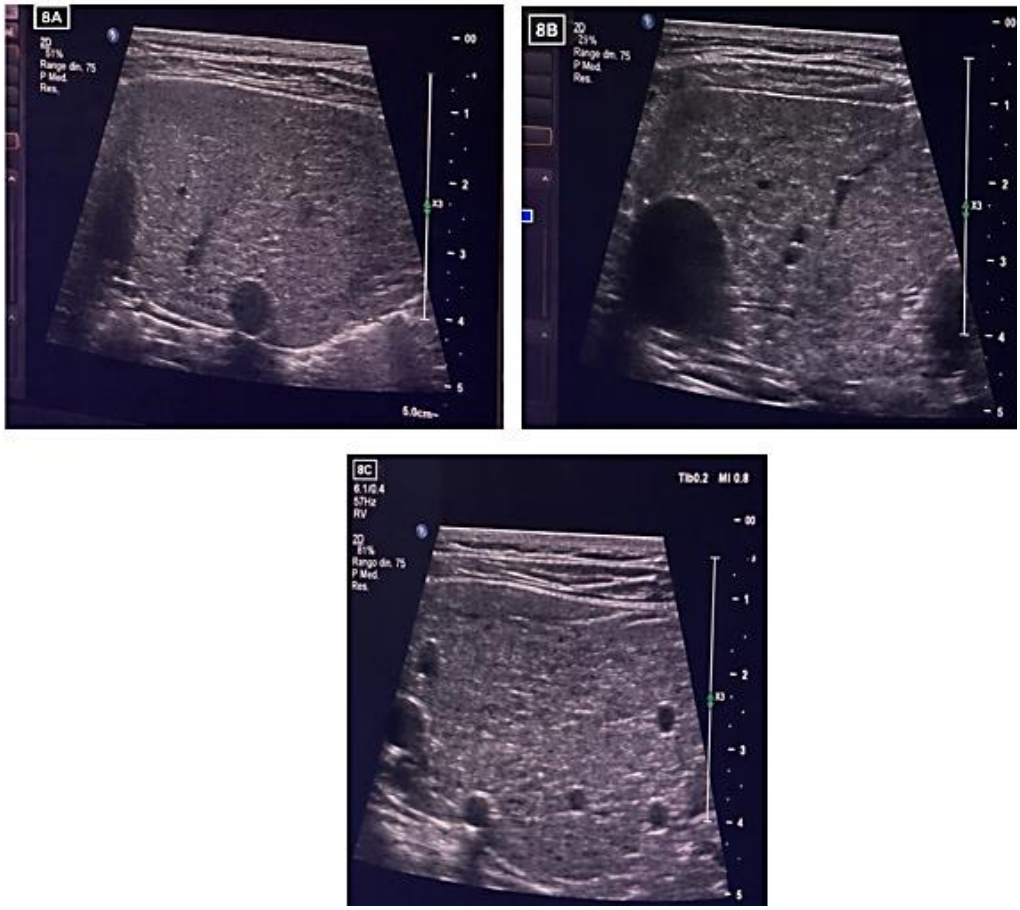

Figure 7. Neonatal abdominal ultrasound showing a prominent liver with a more central position than usual. The spleen was not identified in the left upper quadrant, findings suggestive of asplenia in the context of heterotaxy syndrome.

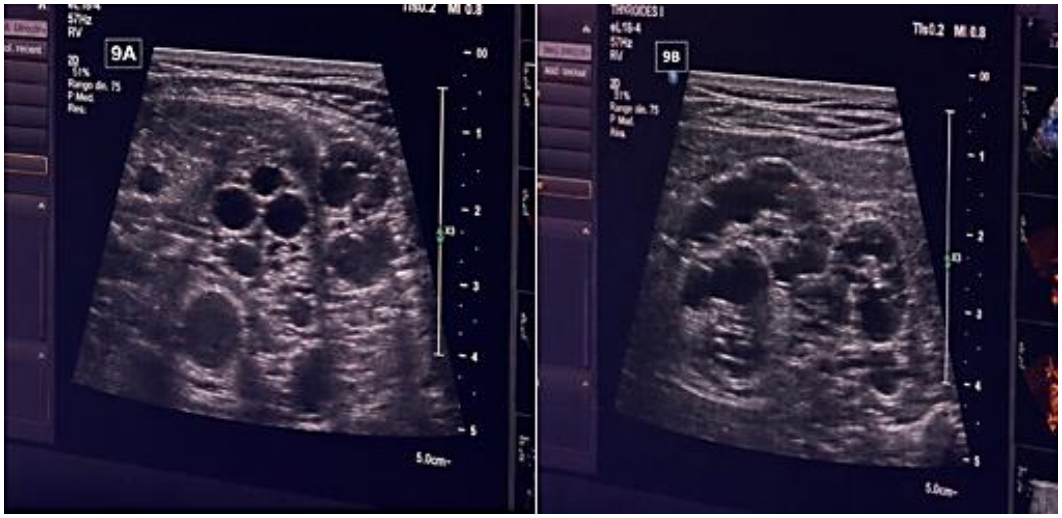

Figure 8. Neonatal abdominal ultrasound demonstrating disorganized distribution of intestinal loops, with an abnormal anatomical relationship compared with normal findings, suggesting intestinal malrotation associated with laterality abnormalities.

2.8. Evolution and Outcome

On the fourth day of life, after the completion of the imaging studies, the diagnosis of Ivemark syndrome was confirmed, a condition that explained the patient's unfavorable clinical course. Due to the complexity of the internal organ malformations and the multisystem involvement, the condition was considered to have a very poor prognosis. In this context, curative therapeutic interventions were not initiated; instead, the management focused on life-support measures and palliative care strategies.

Between the fifth and sixth days of life, the patient remained on invasive mechanical ventilation, with a fraction of inspired oxygen (FiO_2) of 70% and oxygen saturations as low as 56%. During this period, progressive reduction of dobutamine and prostaglandin doses was initiated. On the seventh day of life, inotropic support was discontinued. Subsequently, the patient developed sustained bradycardia with a heart rate of 36 beats per minute, followed by bradypnea and complete oxygen desaturation. Cardiopulmonary resuscitation maneuvers were not performed due to the extremely poor prognosis and the underlying condition considered incompatible with prolonged survival. The patient died at 11:21 a.m., and the outcome was communicated to the mother.

Finally, the certified causes of death established by the medical team corresponded to a primary pathophysiological condition of cardiogenic shock, in the context of a complex congenital heart disease compatible with hypoplastic left heart syndrome, associated with asplenia and heterotaxy. The clinical course was characterized by severe hypoxemia and multiorgan failure, representing a clinical picture consistent with Ivemark syndrome.

3. Discussion

Heterotaxy is a rare congenital condition characterized by abnormalities in the lateralization of thoracoabdominal organs, with an estimated incidence of approximately 1 per 10,000 live births. Within this spectrum, right atrial isomerism or Ivemark syndrome represents one of the most severe forms and is considerably less frequent, with an estimated incidence ranging from 1 per 10,000 to 1 per 40,000 births [4]. Its clinical relevance lies in its strong association with complex congenital heart defects and the absence of functional splenic tissue, a condition associated with neonatal mortality rates exceeding 85% [6]. The severity of this disorder was evident in the present case, as the

patient developed multiple organ failures during the first week of life, ultimately determining survival.

The patient's findings, including asplenia, dextrocardia, intestinal malrotation, and complex congenital heart disease, are consistent with an early disturbance in embryonic lateralization. According to current literature, these abnormalities originate during the third week of gestation, during visceral lateralization, when disruption of the Nodal/Lefty/Pitx2 signaling pathway occurs due to structural or functional defects in the embryonic cilia of the node [11,12].

Prenatal suspicion of this syndrome can be established through obstetric ultrasound from approximately 14 weeks of gestation, by identifying abnormal cardiac and gastric positioning, or from week 16 through a more detailed assessment of cardiac anomalies [8,9]. In this patient, despite the mother completing seven prenatal visits and undergoing the imaging studies requested during obstetric evaluation, abnormalities were not detected in the three performed two-dimensional ultrasounds. This highlights that apparently adequate prenatal care does not always exclude complex laterality disorders. Therefore, strengthening the identification of ultrasound warning signs is essential to ensure timely referral for specialized studies, such as fetal echocardiography.

The absence of prenatal detection may be explained by the limitations of routine obstetric ultrasound when not complemented by specialized fetal assessment. Certain structures, including the spleen, pulmonary lobulation, and bronchial anatomy, cannot always be accurately evaluated during fetal life.[9] Additionally, ultrasonography has been reported to have approximately 50% sensitivity and 90% specificity for assessing structures such as the spleen, heart, lungs, and liver, which helps explain why complex malformations may remain undetected during prenatal follow-up [10].

At birth, the patient was delivered with an Apgar score of 8/9, without the need for immediate resuscitation. This apparently stable initial presentation may have delayed the early suspicion of complex congenital heart disease, as clinical manifestations became more evident over the following hours. Initially, the patient developed cyanosis during feeding and desaturation without clear signs of respiratory distress. Subsequently, at 72 hours of life, he presented with crying-induced cyanotic episodes, with oxygen saturations as low as 50%, associated with hypotonia and pallor. Previous studies have indicated that neonatal clinical suspicion is based on the presence of respiratory, cardiovascular, or gastrointestinal manifestations, which may follow a progressive and severe course [1, 2, 5, 7].

The arterial blood gas analysis revealed that the patient presented with type I respiratory failure (hypoxemic respiratory failure), without carbon dioxide retention. This indicated that the primary problem was not ventilatory failure but rather impaired oxygenation. In this case, persistent hypoxemia was explained by the presence of complex congenital heart disease associated with a single ventricle and pulmonary blood flow obstruction, abnormalities that contributed to the severity of the clinical progression and are consistent with findings described by Jain et al [4]. Likewise, previous reports indicate that these patients may present with neonatal cyanosis and severe hypoxia with low oxygen saturation levels from the first hours of life [1, 4, 6].Therefore, persistent oxygen saturation values between 75% and 80% despite ventilatory support should be interpreted within the context of complex cyanotic congenital heart disease rather than as an isolated failure of respiratory management.

During the diagnostic evaluation, multiple imaging studies were performed, allowing integration of clinical findings with anatomical abnormalities. Chest radiography raised suspicion of dextrocardia and abnormal situs, whereas echocardiography provided a more detailed characterization of the cardiac defect, demonstrating dextrocardia, mitral valve atresia, a large ventricular septal defect, a single right ventricular morphology, truncus arteriosus, and septal communications. Abdominal ultrasound identified extracardiac abnormalities, including a centrally positioned liver,

absence of the spleen, intestinal malrotation, and right-sided gastric curvature. These findings correspond to those described in patients with Ivemark syndrome and are consistent with current evidence, which establishes that diagnosis requires confirmation of situs type, classification of isomerism, and evaluation through complementary studies such as neonatal echocardiography, abdominal ultrasound, chest radiography, computed tomography, or magnetic resonance imaging, depending on availability and clinical complexity [1, 4, 5, 9].

Furthermore, previous studies have reported that 73% to 100% of patients with right atrial isomerism present with single-ventricle physiology, which is directly related to the cardiac findings observed in this patient [1,4,6].

One limitation of this case was the absence of genetic testing and evaluation for Howell–Jolly bodies to document functional asplenia. The literature indicates that Howell–Jolly bodies may support the diagnosis of functional asplenia, while genetic studies can identify mutations associated with laterality defects [1,2,5–7]. However, in this patient, the clinical and imaging findings were sufficient to support the diagnosis.

Laboratory findings also contributed to understanding the systemic impact of the condition. The complete blood count showed no anemia, polycythemia, or thrombocytopenia that could independently explain the severe hypoxemia. Blood chemistry revealed elevated urea levels with preserved creatinine, which may suggest transient renal hypoperfusion in the context of impaired perfusion and hemodynamic compromise. Coagulation studies demonstrated progressive prolongation of prothrombin time (PT), increased INR, and decreased prothrombin activity, while activated partial thromboplastin time (aPTT) remained within normal ranges. These findings may reflect secondary functional alterations related to the critical clinical condition, without sufficient evidence to establish overt renal failure or disseminated intravascular coagulation.

The management approach was consistent with current recommendations, as neonates with right atrial isomerism and complex congenital heart disease require initial stabilization measures, including oxygen therapy, fluid management, and continuous monitoring [2,4,5]. In this patient, the requirement for invasive mechanical ventilation, prostaglandin E1 infusion, and dobutamine reflected the severity of cardiovascular and respiratory compromise. Prostaglandin E1 was initiated due to suspicion of ductus-dependent cyanotic congenital heart disease, as it maintains ductal patency and serves as a bridge therapy until potential definitive surgical intervention can be considered [4,5,14]. Although this intervention resulted in initial stabilization, the response was transient, reflecting minimal functional reserve and the severity of the cardiac anatomy.

Similarly, dobutamine administration was related to hemodynamic instability, as inotropic agents are used to maintain adequate cardiac output in patients with ventricular dysfunction or cardiovascular compromise [3, 4, 14].

In the therapeutic context, a non-curative management approach was selected, based on life support and palliative care measures, a decision consistent with the severity of the clinical condition. Surgical repair in patients with single-ventricle physiology requires multiple staged procedures, including the Norwood, Glenn, and Fontan operations; however, due to the complexity of the vascular abnormalities and the multisystem involvement present in this newborn, surgical intervention was not considered a feasible option because of the extremely high operative risk. Moreover, survival following these procedures remains limited, even under optimal clinical conditions [14].

The literature indicates that some neonates with right atrial isomerism may present with extremely complex malformations that preclude viable surgical intervention. Therefore, a palliative approach aims to alleviate symptoms, optimize quality of life, and provide family-centered support during decision-making processes [2, 4, 5, 14]. In the present case, the coexistence of multiple severe congenital abnormalities established a highly unfavorable prognosis.

Finally, this case describes a clinical presentation consistent with right atrial isomerism or Ivemark syndrome and fulfills the characteristic features reported in the literature. The unfavorable evolution leading to death was comparable to outcomes described in patients with similarly complex anatomical abnormalities, who are not always candidates for palliative surgical interventions. Disease severity is primarily determined by the complexity of the congenital heart disease and the extent of multiorgan involvement. In this patient, both factors were present from the early clinical course, including persistent severe hypoxemia, impaired perfusion, the need for invasive mechanical ventilation, inotropic support, coagulation abnormalities, and progressive deterioration.

Therefore, the association of asplenia, intestinal malrotation, and complex congenital heart disease resulted in an extremely poor prognosis, consistent with previous reports of critically ill neonates with severe Ivemark syndrome [2, 4, 5, 14].

4. Strengths and Limitations

This clinical case report presents several strengths and limitations that should be considered during its interpretation. Among its strengths is the detailed description of the patient's clinical progression, allowing a comprehensive understanding of the chronological sequence of events, from prenatal history to the final outcome. Additionally, the management provided in the intensive care unit was described in detail, including ventilatory support, pharmacological therapies, imaging evaluation, and palliative care measures, reflecting an approach appropriate for the severity of the condition.

Another important strength is the diagnostic conclusion, which was achieved through the integration of radiographic, echocardiographic, and laboratory findings. These evaluations allowed the identification of significant cardiovascular and systemic compromise, supporting the diagnosis of Ivemark syndrome, a rare disorder with substantial clinical relevance. From an ethical perspective, this case highlights the recognition of the patient's poor prognosis and the decision to prioritize supportive care and palliative management according to the severity and expected outcome.

Conversely, several limitations should be acknowledged. One major limitation was the absence of an appropriate prenatal diagnosis, which prevented early planning of neonatal management in a specialized referral center with greater resources, trained personnel, and advanced diagnostic capabilities.

Another relevant limitation was the initial underrecognition of the severity of the patient's manifestations. Early symptoms were managed with routine supplemental oxygen therapy without an initial suspicion of an underlying laterality disorder or ductus-dependent congenital heart disease. This factor, combined with delayed referral to a higher-complexity center, may have affected the opportunity for timely specialized management. Due to the circumstances surrounding this case, genetic testing and complete family history evaluation were unavailable, particularly because paternal information could not be obtained. These aspects are important in the assessment of rare congenital disorders, especially considering that their pathogenesis is directly associated with genetic alterations. Therefore, the absence of this information limited a deeper etiological evaluation. Nevertheless, the findings highlight the complexity of Ivemark syndrome and the existing challenges in both prenatal and neonatal diagnosis of this condition.

5. Conclusion

Ivemark syndrome represents one of the greatest challenges in neonatal clinical practice due to its association with severe congenital malformations, multisystem involvement, and high mortality rates. The present case correlates closely with findings reported in the scientific literature, fulfilling the characteristic features of right atrial

isomerism, including male predominance, asplenia, dextrocardia, intestinal malrotation, and single-ventricle physiology. These findings support the pathophysiological concept of an early embryological disturbance resulting in loss of normal body asymmetry and the development of right-sided anatomical characteristics on both sides.

Furthermore, this case highlights the discrepancy that may exist between theoretical diagnostic expectations and real-world clinical practice. Despite adequate prenatal follow-up and reportedly normal obstetric ultrasounds, structural abnormalities were not identified during fetal life. This delayed diagnosis and limited the possibility of timely referral to a higher-complexity center from birth.

Although rare, this case is consistent with previous reports describing neonatal mortality rates exceeding 85% among patients with asplenia-associated heterotaxy. In this context, the patient's outcome, characterized by severe hypoxemia, hemodynamic instability, and multiorgan failure, demonstrates the extreme severity of this condition, even after intensive therapeutic interventions, including prostaglandin infusion, mechanical ventilation, and inotropic support, due to the limited functional capacity of the cardiac anatomy in these newborns.

Similarly, this case demonstrates that although complex surgical strategies may exist, not all patients are candidates for intervention due to the severity of anatomical abnormalities and multisystem compromise. Consequently, a palliative approach may be appropriate in selected cases, focusing on symptom relief, proportional life support, and prioritization of neonatal comfort and family-centered care.

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