CASE REPORT

RJME Romanian Journal of Morphology & Embryology http://www.rjme.ro/

Embryological and morphological insights into diagnosing cardiac anatomy in heterotaxy syndrome

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Abstract

Aim: The aim of this study was to highlight the hypothesis that embryological development and morphological aspects necessitate a comprehensive analysis of all situses and a detailed description of each anomaly, rather than attempting to force the malformation into the rigid categories of heterotaxy syndrome (HS) – left or right isomerism. This hypothesis is supported by describing the anatomy of a complex patient with multiple laterality defects resulting in multiple cardiac and organ malformations. *Case presentation*: The unique aspect of the presented patient's morphological diagnosis lies in the presence of a leftward heart loop with an unusual shape and direction, with the right ventricle (RV) positioned posterosuperior to the left ventricle (LV). This configuration suggests congenitally corrected transposition of the great arteries, although it deviates from the typical presentation. Additionally, there is an arrest in the development of other embryonic structures, including an atrioventricular septal defect (AVSD) with asymmetric ventricles, hypoplasia of the left-sided morphological RV, and malposition of the great arteries, with the aorta positioned anteriorly and to the right of the stenotic pulmonary artery. There is also another important inconsistency: the atrial situs is *solitus* within the context of HS, accompanied by left bronchial isomerism, polysplenia, interrupted inferior vena cava, and bilateral superior vena cavae. *Conclusions*: In our patient's case, the segmental analysis revealed a rare morphological cardiac anatomy. Understanding both normal and pathological embryological cardiac development, and correlating it with the current morphological anatomy, was crucial in ensuring the correct diagnosis and treatment for our patient.

Keywords: embryology, morphology, heterotaxy syndrome, congenital heart defect.

Introduction

Heterotaxy syndrome (HS) is a group of congenital conditions characterized by abnormal left–right asymmetry in the development of internal organs [1]. During normal embryonic development, organs are arranged asymmetrically, with the liver on the right, heart and spleen on the left, and other organs positioned on specific sides of the body. In HS, this normal asymmetry is disrupted, resulting in the misplacement and malformation of the organs. Two primary forms of HS or isomerism exist: left and right. Left isomerism, also called polysplenia syndrome, is the form in which both sides of the body exhibit structures that are normally found on the left, such as multiple spleens instead of a single spleen. The heart may have abnormal connections or position in the chest, and the lungs may present irregular bronchial patterns in the form of bilateral bifurcating hyparterial bronchus [2]. Right isomerism, also called asplenia syndrome, is characterized by multiple right-sided organ structures and typically an absence of spleen (asplenia) with bilateral trifurcating eparterial bronchus. It is often associated with more severe cardiac malformations and other organ abnormalities [2].

HS almost always leads to complex abnormalities of organs, resulting in significant public health challenges [3]. These may require surgical intervention, ongoing management and monitoring. The severity of the condition depends on which organs are affected and the nature of the associated malformations. Key features of HS include cardiac malformations, such as transposition of the great arteries, atrioventricular septal defect (AVSD) or double outlet right ventricle (RV); abnormalities in the positioning of other organs, including the bronchia, liver, stomach, and intestines; *situs inversus* or situs ambiguous, where organ placement deviates from the typical left–right arrangement, for example, the heart may be located on the right side instead of the left, or organs may be arranged in an unpredictable pattern [4].

HS is commonly associated with genetic mutations that disrupt the signaling pathways responsible for establishing left–right asymmetry during embryonic development. The *Nodal* gene, along with other genes involved in laterality, plays a crucial role in this process [1, 5]. At the cellular level, the role of *Nodal* and related genes is to initiate and primarily regulate asymmetry, encoded in the cells of each organ through organ-specific random generators of asymmetry. The various pathological variants of *Nodal* gene direct the right–left body axis, leading to diverse and heterogeneous asymmetries in the organs, which do not adhere to the usual left–right symmetry [5].

Understanding HS requires a comprehensive knowledge of cardiac embryogenesis. The presence of HS serves as a clue about the early stages of cardiac development, when

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asymmetric laterality either occurs normally or becomes pathological. The fetal or postnatal diagnosis is a complex process. It is not sufficient to diagnose left or right isomerism based solely on the status of the atria or spleen; all organs' abnormalities must be corroborated in order to establish a diagnosis [6].

Aim

The aim of this study was to underline that embryological development necessitates a comprehensive analysis of anatomy at all situses and a detailed description of each anomaly, rather than attempting to force the malformation into a rigid category of left or right isomerism. The hypothesis is sustained by describing the anatomy of one complex patient with multiple laterality defects resulting in cardiac and organs malformations.

Case presentation

Patient diagnosis

A 5-year-old boy was referred to our Department of Pediatric Cardiology at the Emergency Institute for Cardiovascular Diseases and Heart Transplant, Târgu Mureş, Romania, for specialized diagnosis and treatment.

To establish a correct diagnosis, clinical investigations, including electrocardiogram (ECG) and echocardiography, were combined with imaging techniques such as chest X-ray, computed tomography (CT) scan and cardiac catheterization. The echocardiography was performed by pediatric cardiologists. Three independent doctors conducted the scans and formulated conclusions, with the final diagnosis being reached after consultation among the specialists. The chest X-ray and a thoraco-abdominal contrast-enhanced CT scan were carried out in the Department of Radiology and interpreted by the cardiac radiologist. Cardiac catheterization was required to obtain specific anatomical details and to assess the patient's hemodynamic status. It was performed in the catheterization laboratory of the above-mentioned institution by a collaborative team of pediatric and adult cardiologists.

The patient was a 5-year-and-5-month-old child who was diagnosed with a complex cyanotic congenital heart defect during the neonatal period but was lost to follow-up thereafter due to poor family compliance. Upon presentation at our Unit, clinical examination revealed mucosal and skin cyanosis (peripheral blood oxygen saturation of 75%), clubbing, a grade IV/VI left parasternal systolic murmur, growth deficiency, and marked physical activity limitation.

Multiple tests and scans were needed in order to establish the correct and complete diagnosis for the patient. The ECG showed sinus rhythm alternating with atrial rhythm, with no conduction disturbances or other arrhythmias detected during the 24-hour Holter monitoring (Figure 1).

Figure 1 – ***Holter electrocardiogram (ECG) monitoring of the patient showing an atrial rhythm.***

The transthoracic (Figure 2, A–D) and transesophageal (Figure 3, A–D) echocardiography revealed a functional univentricular heart with the following anatomical features. At the abdominal level, the patient presented *situs ambiguus*, with the aorta and azygos vein on the same side of the spine, aorta located anteriorly and azygos vein posteriorly; no inferior vena cava was observed at abdominal level. The systemic venous return deviated significantly from the normal pathway: the inferior vena cava was interrupted at the abdominal level, and blood was conducted through the azygos continuation into the atrium situated on the right side of the heart. There were two superior vena cavae, right draining into the right-sided atrium and left draining into the coronary sinus. The hepatic veins opened separately into the right-sided atrium. The pulmonary veins opened separately into the left-sided atrium, without obstruction.

At the atrial level, there was a large *ostium primum*-type atrial septal defect, resulting in a functional single atrium. The atrioventricular (AV) junction consisted of a common AV valve, which had its insertion on the ventricular septum and also on papillary muscles located on the anterior and posterior ventricular walls. The valve was significantly regurgitant. The ventricular level consisted of one large ventricle located anteriorly and to the right, with LV morphology (non-trabeculated myocardium, no moderator band present). The other ventricle was hypoplastic and filled with blood through a muscular septal defect located in the inlet region and extending into the outlet region. This arrangement at the ventricular level is called ventricular inversion.

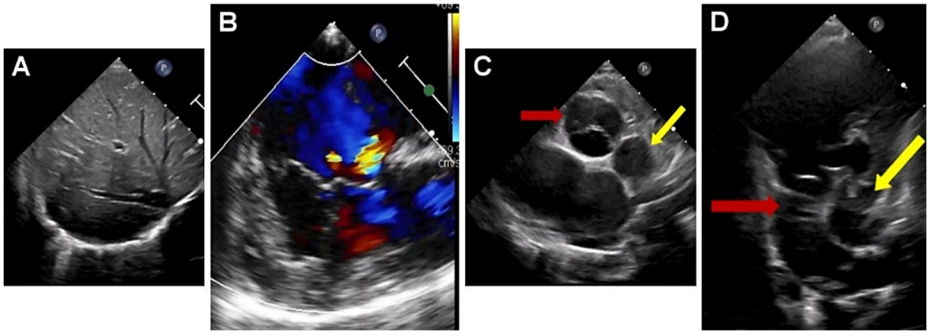

Figure 2 – ***Transthoracic echocardiography: (A) Hepatic veins opening into the RA (identified by their echogenic walls); (B) AV valve with significant regurgitation; (C) Tricuspid aortic valve (red arrow) and bicuspid pulmonary valve (yellow arrow); (D) Aorta arising from the large ventricle (red arrow) and pulmonary artery arising from the hypoplastic ventricle (yellow arrow). AV: Atrioventricular; RA: Right atrium.***

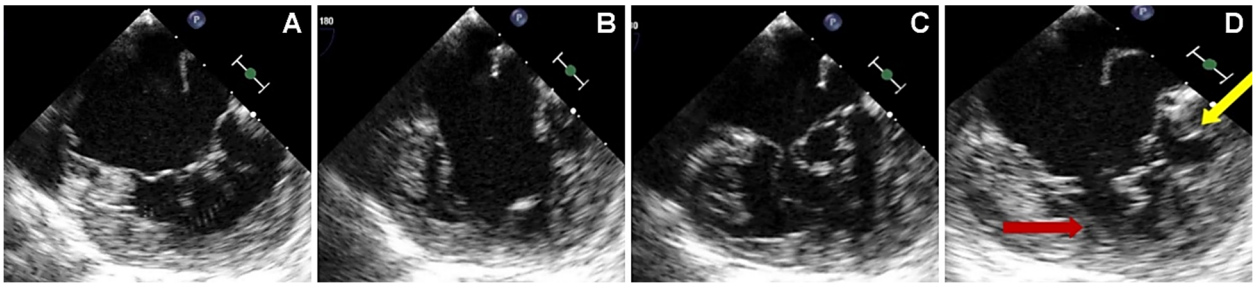

Figure 3 – ***Transesophageal echocardiography: (A) Two atria with a large inlet atrial septal defect and a closed AV valve; (B) AV valve open, with a large inlet ventricular septal defect; (C) AV valve inserted on the ventricular septum as well as on the lateral walls of the ventricle; (D) One large ventricle (red arrow), separated from a small ventricle (yellow arrow) by an inlet muscular ventricular septal defect. AV: Atrioventricular.***

Regarding the outflow tracts, the great arteries were transposed, with the aorta originating anteriorly and to the right from the large ventricle, and the pulmonary artery located posteriorly and to the left, arising from the hypoplastic ventricle. Subpulmonic stenosis was seen, secondary to the deviation of the conal septum. The aortic valve was tricuspid and had mild regurgitation. The ascending aorta was dilated. A bicuspid pulmonary valve was observed, and the pulmonary artery gave rise to well-sized pulmonary arteries. One large aorto-pulmonary collateral vessel or persistent *ductus arteriosus* (DA) was seen.

Chest X-ray revealed left bronchial isomerism, with the main bronchus bifurcating into two main branches in the right and also left lung, a normal position of the heart, a normal cardiothoracic index, and normal pulmonary perfusion (Figure 4, A and B).

Thoraco-abdominal contrast-enhanced CT scan revealed supplementary details about the patient's anatomy (Figure 5, A–C): ambiguous abdominal situs with multiple spleens, the stomach on the left, the liver on the right, and a left-sided thoracic aorta continuing into a median-positioned abdominal aorta; atrial *situs solitus* with the atrium located on the right exhibiting right atrial features (a triangular right atrial appendage and the presence of the *crista terminalis*) while the atrium located on the left was exhibiting left atrial features (a narrow left atrial appendage); ambiguous thoracic situs with left bronchial isomerism.

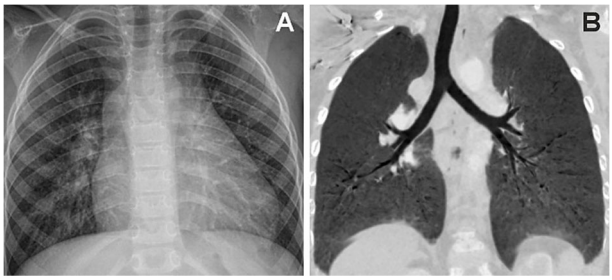

Figure 4 – ***(A) Chest X-ray showing left bronchial isomerism, with the main bronchus bifurcating into two main branches on both sides (left and right); (B) Computed tomography (CT) scan showing the same left bronchial isomerism, with a bilateral left-sided pattern of bronchopulmonary relationships, long and more horizontal bilateral bronchi, a distal first bifurcation of the bronchi, and bilobed lungs.***

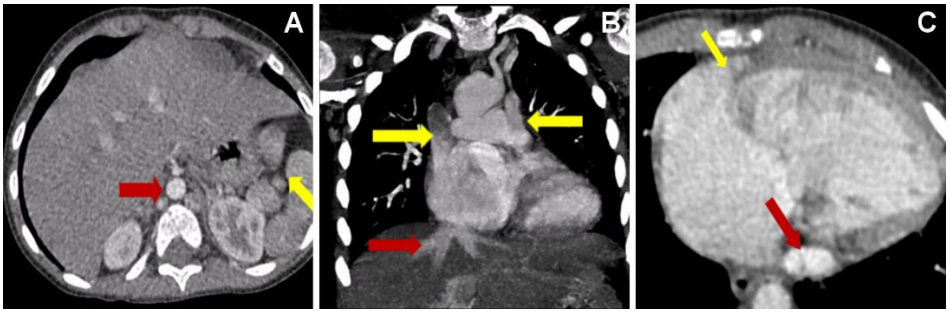

Figure 5 – ***CT scans: (A) Abdominal CT scan showing polysplenia (yellow arrow), a large liver, and a medially situated abdominal aorta (red arrow); (B) Thoracic CT scan showing bilateral superior vena cavae (yellow arrows) and hepatic veins draining directly into the RA (red arrow); (C) Thoracic CT scan showing atrial situs solitus: the RA with a morphological right appendage (yellow arrow), and the left atrium with a morphological left appendage (red arrow). CT: Computed tomography; RA: Right atrium.***

Cardiac catheterization provided additional details for the diagnosis. The patient had an interrupted inferior vena cava with azygos and hemiazygos continuity. He had bilateral superior vena cavae, without an innominate vein. Small veno-venous collateral vessels were identified, one from the right superior vena cava and one from the left superior vena cava. One common AV valve with significant regurgitation opened onto the ventricular cavity. The functional single ventricle appeared to be a right-sided left systemic ventricle, with normal contractile function. There was subvalvular pulmonary stenosis, with a peak-to-peak gradient of 39 mmHg, with protective role for the pulmonary circulation. Pulmonary circulation hemodynamics showed favorable values for performing a partial cavopulmonary connection (mean pulmonary artery pressure of 7 mmHg, pulmonary vascular resistance of 1.45 UW/m^2). The pulmonary vascular bed was well developed, without stenosis. Three medium-sized aorto-pulmonary collateral vessels and several smaller ones were present, along with what is likely a small central aorto-pulmonary connection resembling a persistent DA.

The complex morphological features of our patient and the methods used for diagnosis are summarized in Table 1 following a segmental approach of cardiovascular anatomy. The final morphological diagnosis of the patient was an unbalanced AVSD with a right-sided single morphological left ventricle (LV), congenitally corrected transposition of the great vessels with malposition of the great arteries, in the context of HS.

Table 1 – ***Summary of patient's morphological features and methods used for diagnosis***

Level	Patient's morphology	Diagnosis method
1. Thoraco-abdominal situs		
Thoracic situs	Situs ambiguous: bilateral hyparterial bronchus (left bronchial isomerism)	Chest X-ray, thoracic CT scan, cardiac catheterization
Abdominal situs	Situs ambiguous: left isomerism (polysplenia, interrupted inferior vena cava)	Echocardiography, abdominal CT scan, cardiac catheterization
2. Cardiac position	Levocardia	Chest X-ray, echocardiography, thoracic CT scan, cardiac catheterization
3. Segment by segment analysis		
Venous return	Systemic – disrupted: interrupted inferior vena cava continued by azygos and hemiazygos veins, two superior vena cava without an innominate vein Pulmonic – normal	Echocardiography, thoracic and abdominal CT scan, cardiac catheterization
Atrial situs and atria	*Situs solitus* *Ostium primum* atrial septal defect	Echocardiography, thoracic CT scan, cardiac catheterization
AV level	Common AV valve	Echocardiography, thoracic CT scan, cardiac catheterization
Ventricular level	Unbalanced AVSD Ventricular inversion with dominant LV and hypoplastic RV Muscular ventricular septal defect (extension from inlet to outlet)	Echocardiography, thoracic CT scan, Cardiac catheterization
Ventricular outflows and great arteries	Discordant ventriculo-arterial alignments: transposed great arteries Congenital corrected transposition of great arteries Sub-pulmonary stenosis	Echocardiography, thoracic CT scan, cardiac catheterization
Relationship between semilunar valves	Transposed: aortic valve anterior and to the right, pulmonary valve posterior and to the left	Echocardiography, thoracic CT scan, cardiac catheterization
4. Associated anomalies	Persistent ductus arteriosus Small venovenous collateral vessels Three medium-sized aorto-pulmonary collateral arterial vessels	Echocardiography, thoracic CT scan, cardiac catheterization

AV: Atrioventricular; AVSD: Atrioventricular septal defect; CT: Computed tomography; LV: Left ventricle; RV: Right ventricle.

Patient treatment and outcome

After the diagnosis was established, the patient underwent primary univentricular correction at five years and seven months of age, with a Kawashima procedure involving two superior bidirectional cavo-pulmonary anastomoses. The post-surgical recovery was favorable, with a blood oxygen saturation of 85% and proper functioning of the Kawashima anastomosis. His condition remained stable at the one-year follow-up.

Discussions

Embryological insights

The literature describes heterotaxic syndrome as one of the most striking forms of laterality defects as Houyel & Meilhac published in their paper [7]. According to Desgrange *et al.* [8], the rightward looping of the heart primordium is the first sign of asymmetric organogenesis. For many years, it was believed that *Nodal* gene signaling generated left–right asymmetry throughout the embryo. However, Desgrange *et al.* [8] demonstrated that there are organ-specific patterns and that the heart has a random generator of asymmetry, independent of *Nodal* gene, with specific laterality precursors contained in cardiac cells. *Nodal* gene's role is to initiate asymmetry in certain organs, such as the atria, lungs, and spleen, but it is primarily involved in regulating left–right asymmetries by determining the direction and shaping the cardiac loop [9].

Houyel & Meilhac [7] further highlighted that the pathogenic variants of *Nodal* gene exhibit variable clinical expressions in HS and congenital heart disease (CHD), including conditions like transposition of the great arteries, double outlet RV and AVSD. The understanding that each organ has its own generator of asymmetry, coordinated by *Nodal* gene and other laterality genes, helps in explaining partial randomization and also why the breakdown of normal laterality does not result in *situs inversus totalis* (a simple mirror image of the normal body plan). Instead, it leads to heterogeneous symmetry in the organs that do not follow typical left–right symmetry [10].

Historically, the classification of HS has been developed after morphological studies and was based on spleen status and atrial morphology [11, 12], distinguishing two types: right isomerism (asplenia syndrome) and left isomerism (polysplenia syndrome). Furtherer, Jacobs *et al.* [12] and also Uemura *et al.* [13] expanded the knowledge on the relationship between atrial situs and bronchial situs. More recently, upon embryological studies emerged, the guideline of the *International Society for Nomenclature of Paediatric and Congenital Heart Disease* (ISNPCHD) recommended evaluating the situs of each organ, including broncho-pulmonary relationships, atrial appendage arrangement, splenic status, and systemic and pulmonary venous connections, to accurately define laterality and HS [14].

However, Yim *et al.* [4] and also Houyel & Meilhac [7] demonstrated that diagnosing left or right isomerism based on atrial appendage arrangement and pectinate muscle morphology remains difficult, even with advanced imaging techniques like CT scans and magnetic resonance imaging, because embryological development is very complex and does not always follow specific models. They proposed

avoiding binary categorization (left or right) and instead describing each organ morphology using appropriate paraclinical investigations [4, 7]. It is also important to note that patients with *situs ambiguus* who deviate from conventional classifications, in at least 20% of cases cannot be categorized into left or right isomerism [1].

HS is commonly associated with congenital corrected transposition of the great vessels and asymmetric AVSD. Normally, during embryological life, an AV cushion develops and gives birth to the interventricular and interatrial septa, converging under spatial signaling and genetic influence. In HS, the abnormal looping of the embryo heart is often followed by an arrest in development during the convergence stage, leading to asymmetric AVSD [15], with various stages of incomplete septation and wedging that explain the variability in the malposition of the great arteries.

Morphological insights

In clinical practice, heterotaxia is often diagnosed by identifying anomalies in left–right axis asymmetry in organs other than the heart, such as polysplenia, digestive anomalies, and pulmonary radiographic findings. Cardiac evaluation through echocardiography should focus on signs of interrupted vena cava, pulmonary or systemic venous return anomalies, AVSD and through ECG complete bundle-branch block, as these may point to HS. It is essential to investigate the bronchopulmonary relationship, atrial appendage arrangement, systemic and pulmonary venous connections, splenic status, liver and stomach position, the presence of portal veins, biliary structures, colonic flexure, and provide appropriate extra-thoracic treatment if necessary [16].

The unique aspect of our patient's morphological diagnosis lies in the presence of a leftward heart loop with an unusual shape and direction, with the RV positioned posterosuperior to the LV. This configuration results in a morphology suggestive of congenitally corrected transposition of the great arteries, albeit deviating from the typical presentation, along with an arrest in the development of other embryonic structures. These include an AVSD with asymmetric ventricles, hypoplasia of the left-sided morphological RV, and malposition of the great arteries, with the aorta anterior and to the right of the stenotic pulmonary artery. There is an inconsistency in the atrial *situs solitus* within the context of heterotaxic syndrome, accompanied by left bronchial isomerism, polysplenia, interrupted inferior vena cava, and bilateral superior vena cavae. The literature describes how polysplenia syndrome (left isomerism) is associated with more heterogeneous right–left axis anomalies compared to right isomerism [12]. Additionally, cardiac malformations such as congenitally corrected transposition of the great arteries, AVSD, single ventricle, and pulmonary stenosis are often seen in right isomerism [4, 7].

A key diagnostic challenge was the patient's age (five years), as hemodynamic pressures and volumes significantly influence the remodeling of cardiac cavities over time. A few other challenges were encountered in establishing the morphological diagnosis.

Atrial segment: Normal or isomerism morphology?

In the case of our patient, the atrial appendages were arranged in the usual manner. The CT scan revealed normal atrial situs, with the right atrium on the right side, accompanied by the right atrial appendage and the presence of the *crista terminalis*. The left atrium was located on the left, with the left atrial appendage. Due to poor quality of the CT scan, the pectinate muscles could not be identified. On the ECG, the rhythm alternated between sinus rhythm and atrial rhythm. The atrial arrangement is important due to the fact that it can affect the usual location of the cardiac pacemaker which can be the sinus node or other group of cells [17] and also due to the fact that it has surgical implication in hearts with isomeric atrial appendages [18].

AV connections: Is there an AVSD present or an atretic AV valve?

The presence of an *ostium primum* atrial defect, along with a large interventricular inlet–outlet septal defect and a single AV valve, led to the diagnosis of an AVSD with ventricular asymmetry and a hypoplastic RV. The single AV valve had two main leaflets and a small posterior leaflet, which was challenging to identify with transthoracic echocardiography but was more clearly visualized with transesophageal echocardiography. The steps involved in the AV septation process are complex and prone to errors in some hearts like in our patient case [19].

Morphology of the single ventricle: Is it a right or left ventricle?

The single ventricle observed had a morphology consistent with a LV, characterized by a smooth appearance and two papillary muscles on the lateral ventricular wall. This LV was located on the right side of the heart, a condition known as ventricular inversion (corrected transposition of the great arteries). However, the thoracic position of the heart remained normal, with the cardiac apex pointing to the left, indicating levocardia. Ventricular morphology plays a critical role in understanding surgical anatomy and determining the most suitable procedure for definitive uni- or biventricular repair [20].

Outlets: Double or single outlet ventricle?

Inlet ventricular septal defect extended into the outlet, and the infundibular septum deviation contributed to subpulmonary dynamic stenosis. The pulmonary artery exited above the hypoplastic RV, but the aorta emerged from the dominant LV. The great vessels were malposed, with the aorta located anteriorly and to the right of the pulmonary artery, presenting an annular mismatch and asymmetry. The tricuspid aortic valve was larger than the bicuspid pulmonary valve. The failure of normal rotation of the outflow tracts may be the underlying cause of major forms of CHD like in our patient case [21].

Heterotaxy: Left or right isomerism?

According to the *ISNPCHD* [14], heterotaxic syndromes are classified into left or right isomerism based on atrial situs, bronchial situs, cardiac and spleen morphology. In our case, the CT scan identified normal atrial situs, left bronchial isomerism, polysplenia, two superior vena cavae, and an interrupted inferior vena cava. This constellation of findings is consistent with incomplete left isomerism, where the cardiac abnormalities breach the usual classification. In the case of our patient, the atrial appendages were arranged in the usual manner. Therefore, the heart itself was

not "heterotaxic". However, the lungs and abdominal organs exhibited an abnormal arrangement along the left–right axis of the body. Thus, when considering the patient as a whole, he displayed characteristics of "heterotaxy". This dilemma was described also in a case published by de Bellaing *et al.* [22].

In the case of a complex congenital cardiac defect, it is important to describe each segment individually, without trying to force it into an inflexible category of HS (left or right). Revisiting embryogenesis allowed us to track the lesions and identify additional, less evident lesions in both cardiac and extracardiac situs. Moreover, understanding embryological development helps prevent diagnostic errors and aids in understanding the patient's pathophysiology and hemodynamics. To provide an accurate diagnosis, segmental analysis recommended by Anderson & Shirali [23] and Van Praagh [24] is a valuable tool. The heterogeneous heterotaxia features observed in our patient exemplify recent findings in heterotaxy patient' series [4, 7, 25], confirming the need for a thorough assessment of malformations at every level to achieve a complete diagnosis and informed management strategy. This case underscores the importance of understanding both normal and pathological embryological development in correlation with the current morphological anatomy to reach an accurate diagnosis and optimize patient care. These were the key factors that supported accurate diagnosis and treatment in our patient. As Anderson *et al.* [6] said, in today's world, publishing the details of individual cases has become progressively more challenging. This is unfortunate, as valuable insights are often gained from these experiences.

Prenatal diagnosis of HS through fetal ultrasonography does not enhance survival in patients with palliative single ventricle pathway [26]. Faced with the challenge of diagnosing the morphology of an unoperated univentricular heart in a 5-year-old boy, it was necessary to understand embryological development and both normal and pathological aspects in order to provide an accurate diagnosis, as well as appropriate medical management and surgical treatment for the patient. The optimal care of children with HS requires a team of experienced specialists working together to deliver compassionate, standardized, and evidence-based care [27].

Conclusions

In our patient's case, the segmental analysis revealed a rare morphological cardiac anatomy. Understanding both normal and pathological embryological cardiac development, and correlating it with the current morphological anatomy, was a key factor in ensuring the correct diagnosis and treatment for our patients.

Conflict of interests

The authors declare that they have no conflict of interests.

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Received: May 5, 2025

Accepted: July 31, 2026