

# Heterotaxy Syndrome in a Young Adult

Andres Abreu, DO, MS

Maria Luisa Nieto-Morales, MD, Ph.D

Margarita Fuentes, MD

## Abstract

Heterotaxy syndrome is found infrequently in the adult population. The syndrome is characterized by the presence of abnormal position of the viscera. If the patient does not present with cardiac anomalies incompatible with life, it can be asymptomatic, being diagnosed only incidentally in adulthood (5-10%). We present the case of a 36-year-old with heterotaxy syndrome who was diagnosed after presenting to the emergency department with symptoms of pulmonary thromboembolism. After several radiology diagnostic studies, we observed interruption of the inferior vena cava along its course to the level of the renal vein with subsequent dilatation of the azygous vein to the level of the superior vena cava. Polysplenia and drainage of suprahepatic veins directly into the right atrium was also noticed.

## Introduction

Situs anomalies are rare, complex, and confusing. Situs ambiguous, or heterotaxy, implies a disordered organ arrangement in the chest or abdomen. This unpredictable anatomy differs from the orderly arrangement of the truncal organs in either the typical anatomy (situs solitus) or the mirror image of it (situs inversus).

Situs anomalies present a diagnostic challenge to the radiologist. Attempts at classification are difficult and usually oversimplify cases, since many patients do not demonstrate the expected, classical findings. We believe it is essential to understand situs abnormalities and their appearances on radiologic studies in order to recognize which children are at increased risk of congenital heart disease, immune deficiency (due to splenic absence), and catastrophic volvulus with malrotation.

## Terminology

The term *situs* refers to the position of the atria and viscera relative to the midline. The atrium whose appendage is broad-based and receives blood from the inferior vena cava may best be called the *systemic* or *right atrium*. The atrium with the smaller, narrower appendage and that receives blood from the pulmonary veins is called the *pulmonary* or *left atrium*.

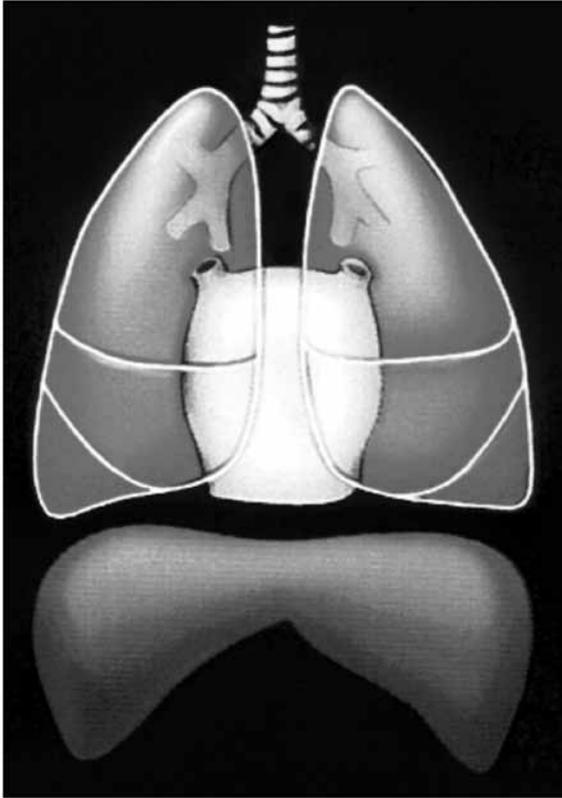
*Situs solitus* is the usual arrangement of organs and vessels within the body. The systemic atrium is on the right with a right-sided trilobed lung, liver, gallbladder, and inferior vena cava. The pulmonary atrium is on the left with a left-sided bilobed lung, stomach, single spleen, and aorta. The cardiac apex is on the left. The incidence of congenital heart disease in patients with situs solitus and levocardia is only 0.6%–0.8%.<sup>2</sup>

**Figure 1:** Polysplenia and Situs Inversus



*Situs inversus* (Fig 1) refers to an anatomic arrangement that is the mirror image of situs solitus. The systemic atrium is on the left with a left-sided trilobed lung, liver, gallbladder, and inferior vena cava. The pulmonary atrium is on the right with a right-sided bilobed lung, stomach, single spleen, and aorta. The cardiac apex is on the right. Situs inversus is seen in 0.01% of the population,<sup>2</sup> and the incidence of congenital heart disease in patients with situs inversus is 3%–5%.<sup>26</sup>

**Figure 2:** Asplenia – Right Sided Isomerism

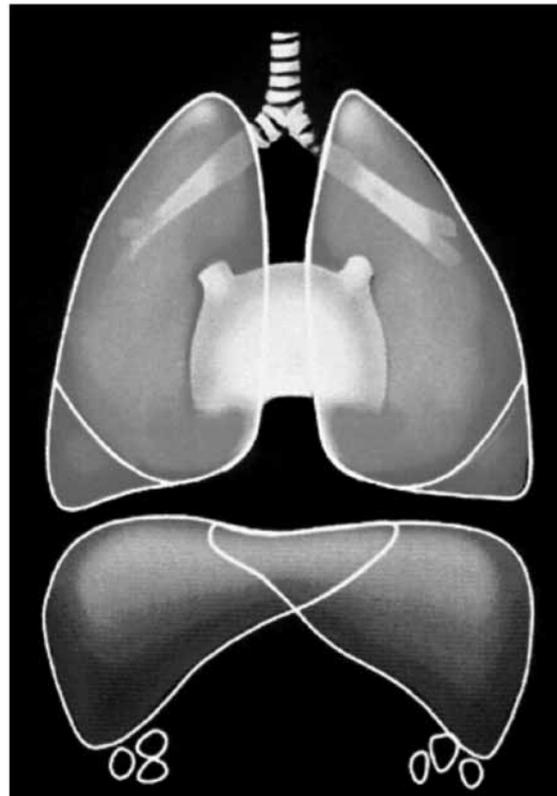


**Figure 5:** Asplenia with bilateral Minor Fissure and Trilobed lung

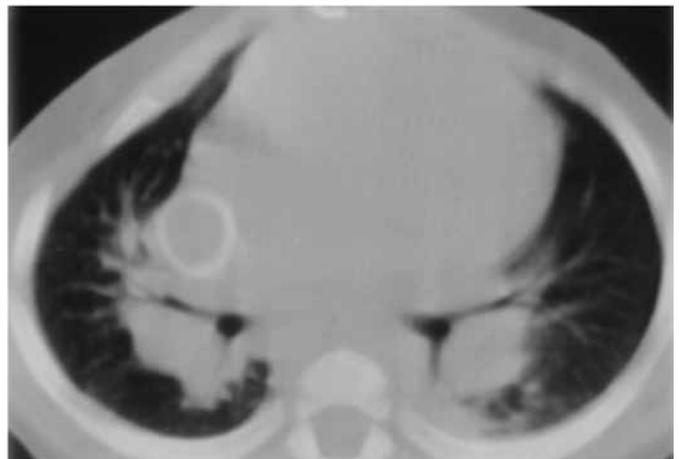


*Situs ambiguus*, or heterotaxy, refers to visceral malposition and dysmorphism associated with indeterminate atrial arrangement. This abnormal arrangement of body organs is different from the orderly arrangement seen in situs solitus or situs inversus. The incidence of congenital heart disease in patients with heterotaxy is very high, ranging from 50% to nearly 100%. In *asplenia* (right isomerism or bilateral right-sidedness), both lungs have three lobes and eparterial bronchi (Fig 2, 5).<sup>23</sup> The main bronchus is located superior to the ipsilateral main pulmonary artery on each side. In *polysplenia* (i.e., left isomerism or bilateral left-sidedness), both lungs have two lobes and hyparterial bronchi (Fig 3).<sup>23</sup> In this situation, the reverse is seen: The main bronchus passes inferior to the ipsilateral main pulmonary artery on each side (Fig 4, 6).

**Figure 3:** Polysplenia - Left Isomerism



**Figure 4:** Polysplenia with hyparterial bronchi and bilobed lung



**Figure 6:** Polysplenia with hyparterial bronchia and bilobed lung



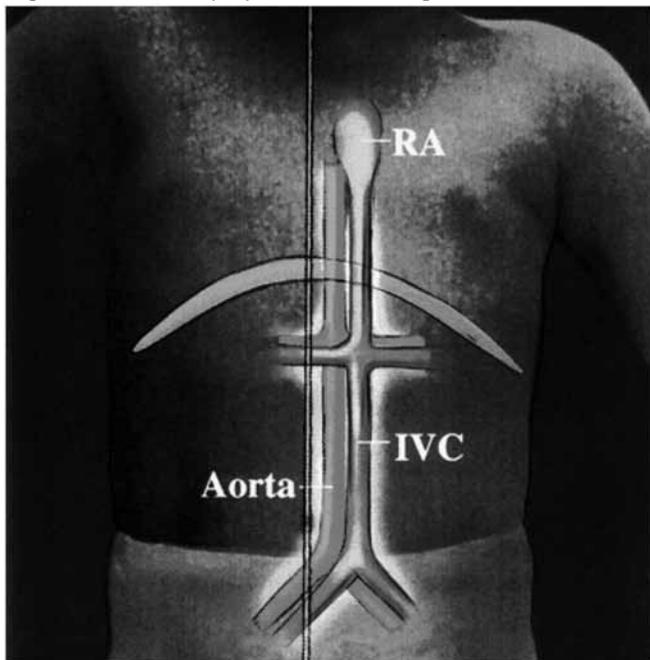
**Figure 7:** Interruption of Inferior Vena Cava with Azygous Continuation



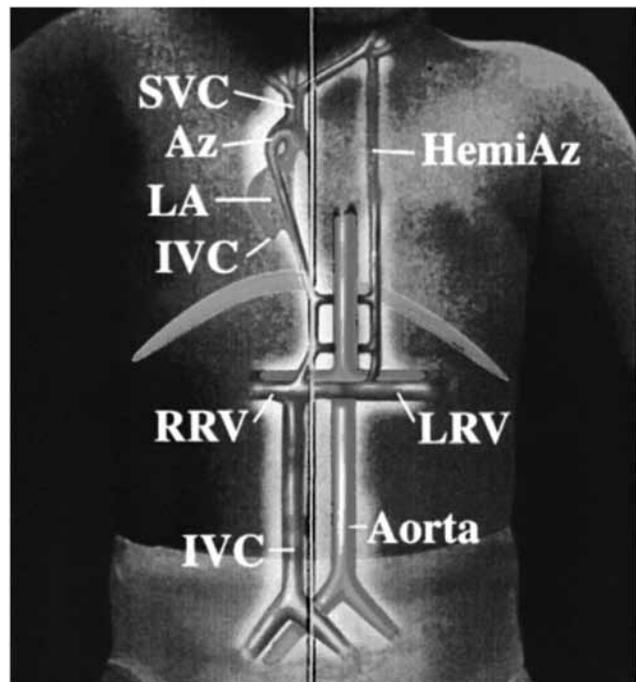
### Heterotaxy Syndrome with Asplenia

The designation of classic right isomerism or bilateral right-sidedness (Fig 2)<sup>23</sup> implies that the patient has bilateral trilobed lungs with bilateral minor fissures and eparterial bronchi, bilateral systemic atria, a centrally located liver, and a stomach in indeterminate position. The abdominal aorta and inferior vena cava would classically be located on the same side of the spine (Fig 9).

**Figure 9:** Heterotaxy Syndrome with Asplenia



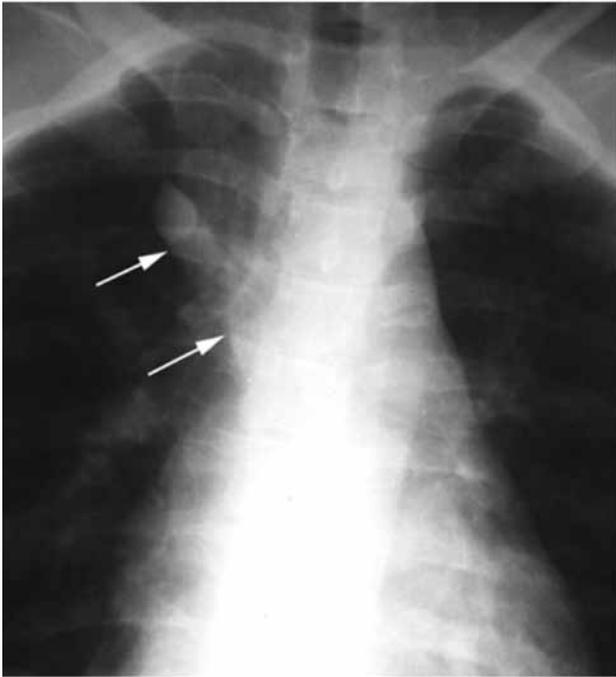
**Figure 8:** Polysplenia with interrupted IVC and azygous continuation.



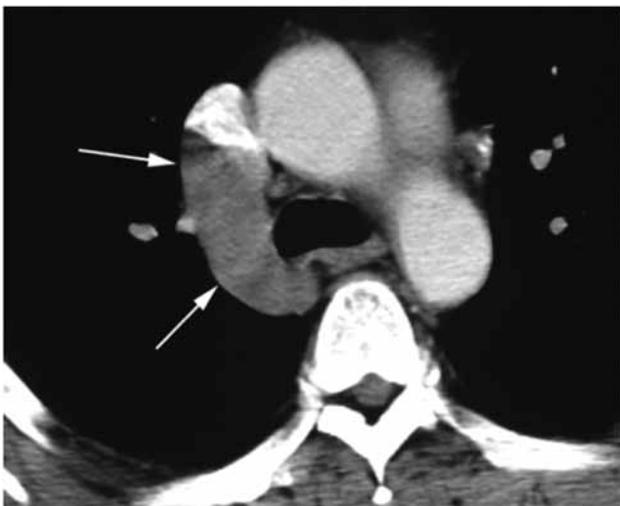
This syndrome occurs more frequently in males, and patients often present with cyanosis and severe respiratory distress. At chest radiography, the cardiac apex typically appears discordant from that of the stomach and liver. The stomach may also be midline and small (microgastria). Common cardiac malforma-

tions include a common atrioventricular canal, univentricular heart, transposition of the great arteries, and anomalous venous connections including total anomalous pulmonary venous return (seen in the majority of cases). The complex cardiac anomalies and abnormal immune status are closely linked to the understandably poor prognosis of this group of patients. Death occurs in the first year of life in up to 80% of cases.

**Figure 10:** Polysplenia with interrupted IVC and azygous continuation.



**Figure 11:** Polysplenia with interrupted IVC and azygous continuation.

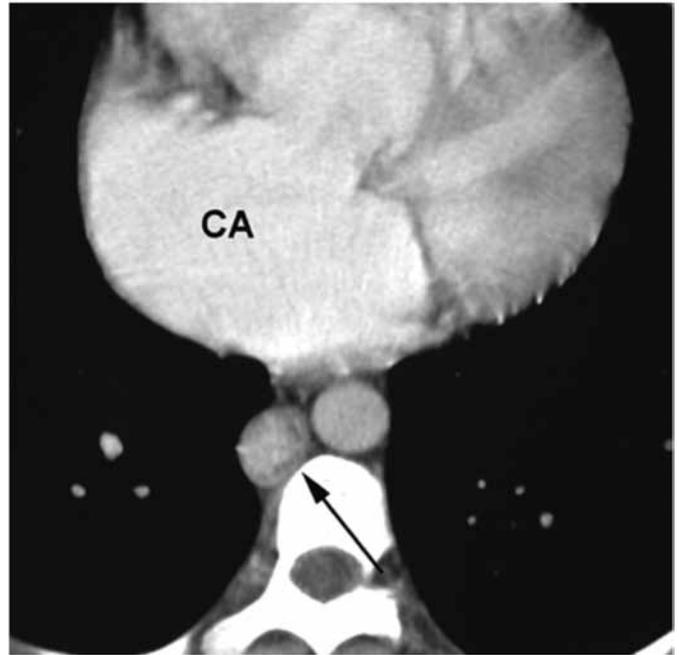


### Heterotaxy Syndrome with Polysplenia

Classic left isomerism or bilateral left-sidedness (Fig 3)<sup>23</sup> implies that patients have bilateral bilobed lungs, bilateral pulmonary atria, a centrally located liver, a stomach in indeterminate position, and multiple spleens. Interruption of the inferior vena

cava with azygous or hemiazygous continuation (Fig 7, 8, 10, 11, 12, 13)<sup>26</sup> may be suggested from the chest radiograph and is the most consistent finding seen in heterotaxy with polysplenia.

**Figure 12:** Polysplenia with interrupted IVC and azygous continuation



**Figure 13:** Polysplenia with interrupted IVC and azygous continuation



Polysplenia (Fig 14) is more common in females and has more variable clinical manifestations and prognosis. Fewer polysplenic patients (vs asplenic patients) present with cyanosis and more present with symptoms of congestive heart failure from left-to-right shunts. Absence of the inferior vena cava on the lateral chest radiograph and the azygous continuation on the frontal chest radiograph with discordance of the apex and abdominal viscera help suggest the diagnosis (Fig 10, 11, 12).<sup>26</sup> In general, cardiac anomalies are less common in polysplenic pa-

tients and not as complex as those in asplenic patients (the most common cardiac anomalies in this group are partial anomalous pulmonary venous return, atrial septal defect, and atrioventricular canal).

**Figure 14:** Polysplenia



**Figure 15:** Dextrocardia, right-sided stomach, left-sided liver



### Radiologic Evaluation

The critical structures to be evaluated with imaging in determining situs are (*a*) position of the atria; (*b*) position of venous drainage below the diaphragm relative to midline; (*c*) position of the aorta relative to midline; (*d*) position of the stomach and presence of malrotation; (*e*) position of the liver and gallbladder; (*f*) position of the cardiac apex; (*g*) presence, appearance, and number of spleens; and (*h*) presence of tri- or bilobed lungs, including presence or absence of bilateral minor fissures.

These anatomic structures may be evaluated with chest radiography, ultrasonography (US), CT, MR imaging, and angiocardiology, although the last study is now rarely necessary for diag-

nosis. With chest radiography, one can determine the presence or absence of normal situs (i.e., situs solitus). Normal situs is inferred when the aortic arch, cardiac apex, and stomach bubble are all located on the left. When these structures are positioned on the right or reversed, situs inversus is present (Fig 15). When any other situation is seen, an indeterminate situs or heterotaxy is inferred (Fig 16). The position of the atria may be inferred from the venous drainage below the diaphragm in a patient with situs solitus or situs inversus. However, in the presence of heterotaxy, even the echocardiographer may not be able to identify the appendages. The stomach may be displaced from its normal location directly under the hemidiaphragm by a bridging (midline) liver in either asplenic or polysplenic patients (Fig 17).

**Figure 16:** Indeterminate situs – stomach on left side



**Figure 17:** Levocardia, right-sided stomach bubble, and polysplenia side



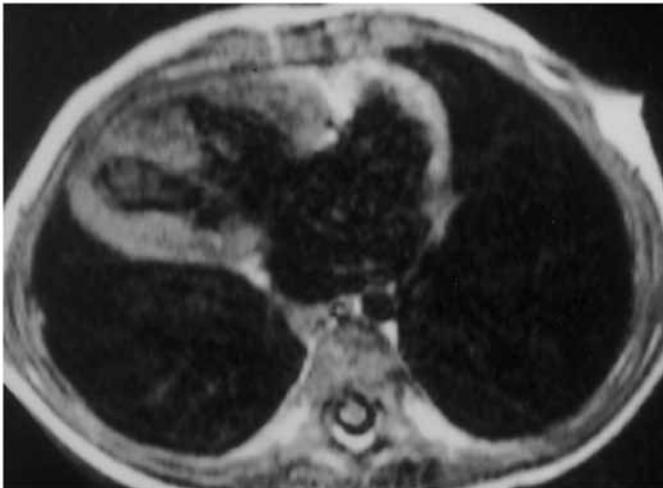
## Case Presentation

Modes of inheritance proposed for heterotaxy include autosomal dominant, autosomal recessive, and X-linked recessive. The last mode may help in part to explain the male preponderance of this syndrome. Overall, though, careful genetic study supports a multifactorial inheritance.<sup>2,3,4</sup>

The wide spectrum and variability of presentation of this syndrome is quite broad, and there is no single pathognomonic anomaly that can be cited.<sup>5,6</sup>

The wide spectrum of anomalies in the heterotaxy syndrome is explained by the variable duration of embryological causative factors during fetus development. A small portion of these patients present with cyanosis, while others present with symptoms of congestive heart failure with left to right shunt. The exact moment of embryological development of these anomalies is not known, but it is believed that it occurs at approximately 28 days of embryological development.<sup>7</sup> It is during this time period that the primitive heart and venous connections form. Disruption of this early embryologic event, when the cardiac chambers are incompletely septated, helps explain the preponderance of common atria, single ventricles, abnormal pulmonary venous connections, and conotruncal anomalies observed in heterotaxy syndrome (Fig 18).

**Figure 18:** Common Atrioventricular Canal with Common Atrium



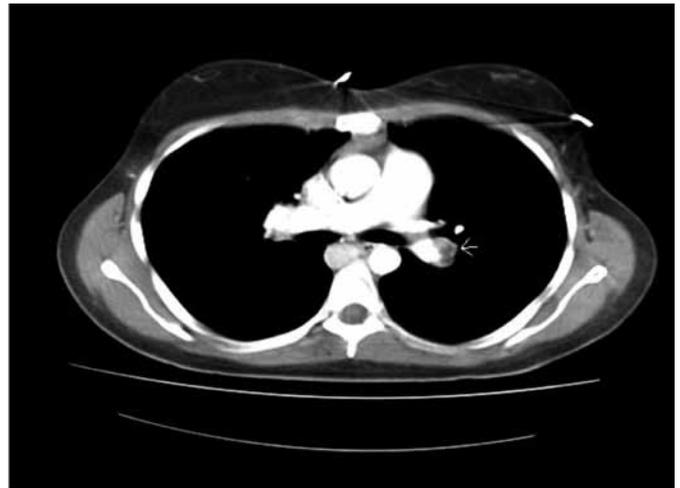
Only 40% of the affected population reaches two years of age, and most die before the age of five. Only 5-10% of these patients present with normal heart size or with minor cardiac anomalies which allowed the individual to reach adulthood without demonstrating any significant symptoms.<sup>8,9</sup>

Our 26 year old patient in this case study did not present with any significant clinical manifestations of heterotaxy, except for patent foramen ovale. In this case, the diagnosis of heterotaxy was an incidental one obtained when imaging studies were performed for other causes, in this case pulmonary embolism.

Our patient was admitted to the hospital due to symptoms of pulmonary thromboembolism (Fig 19). Prior to this case, there has only been one other case published in the literature with

similar clinical presentation. The presence of deep venous thrombosis in patients with heterotaxy is a more frequent finding than in the general population. It is for this reason that this entity must be considered in the differential diagnosis of deep venous thrombosis in patients younger than 30 years of age. Interruption of the inferior vena cava (Fig 8, 10, 11, 12, 13)<sup>26</sup> seen in patients with heterotaxy gives rise to an abnormal venous drainage of the lower extremity venous system that increases the risk of deep venous thrombosis,<sup>10,11</sup> and therefore pulmonary thromboembolism.<sup>26</sup> Similarly, an anomalous drainage of the splenic venous system into the azygous system predisposes to an increase in platelet aggregation, which also augments the risk of pulmonary thromboembolism.

**Figure 19:** Pulmonary embolism in left Main Pulmonary Artery



Our patient presented with a filling defect in the right main renal artery, which may have been the source of her pulmonary thromboembolism.

Polysplenia (Fig 1, 13, 14)<sup>26</sup> is another anomaly found in patients with heterotaxy syndrome. Multiple nonfunctioning splenules, ranging from five to 16, are seen, which are mostly located in the region of the greater curvature of the stomach. This latter finding is explained due to the embryological development of the spleen in the dorsal mesogastric region. In many cases, the abnormal position of the stomach is the only evidence of intestinal malrotation.

Bowel malrotation (Fig 20) is also found in heterotaxy syndrome. In a study performed by Ditchfield and Hutson on six pediatric patients with polysplenia,<sup>12</sup> all patients also had abnormalities related to bowel malrotation and midgut volvulus. Our patient did not present with any abdominal complaints. However, due to the known bowel abnormalities described in the literature, we recommended performing an upper gastrointestinal examination to exclude the possibility of bowel malrotation or other bowel anomalies.

The normal mesentery has a broad base of attachment, which extends from the Ligament of Treitz in the left upper abdomen to the ileocecal junction in the right lower abdomen. Patients presenting with complete or partial bowel malrotation often

have a thinner mesenteric base, which makes it more prone to the development of volvulus.

**Figure 20:** Malrotation with duodenum and Jejunum on patient's right side



As fluoroscopic upper gastrointestinal barium examination does not provide specific information to suggest which patients with malrotation are at risk for developing midgut volvulus, some institutions recommend performing preventive Ladd's surgical technique in these patients.<sup>13</sup> It is important to be aware of alteration in the position of vascular structures if a surgical procedure is to be performed in these patients.

It is estimated that intestinal and duodenal malrotation is diagnosed incidentally in approximately 0.2% of the population and only some cause symptoms in adulthood.<sup>12,13,14</sup> Barium enema studies on these patients often shows a malrotation of the ascending colon, but the cecum may demonstrate a normal position in more than 20% of these patients, which must be taken into consideration in order not to miss the diagnosis of malrotation.

Applegate et al. performed a study in ten patients with heterotaxy with polysplenia and noticed that the position of the aorta and stomach was variable, but the bowel malrotation was a constant finding.<sup>15</sup> In a study performed by Fulcher et al. on eight patients with heterotaxy, they remarked that in five out of seven patients with bowel malrotation the small bowel was localized primarily to the right and the colon to the left side of the abdomen. The stomach was located on the right side of the abdomen in three patients and to the left side in five patients.<sup>1</sup>

In a study performed by Galler et al. on 15 patients with polysplenia diagnosed in infancy, ten of these patients had either complete or incomplete bowel malrotation.

Our patient was diagnosed with inversion of the mesenteric vessels<sup>16</sup> (Fig 21). Although this finding is normally sufficient to diagnose bowel malrotation,<sup>8</sup> a recent study demonstrated bowel malrotation in only two out of eight patients with mesenteric vasculature inversion.<sup>9</sup> Vascular inversion, however, can also be seen in cases of abdominal masses or duodenal atresia. Zerlin et al. documented a case of bowel malrotation with midgut volvulus and normal position of the mesenteric vessels. This latter finding demonstrates that inversion of the mesenteric arteries and veins are not pathognomonic of bowel malrotation, because in some of these patients there may be a normal position of the mesenteric vessels.<sup>14</sup> An inverse relationship has also been described in which there is inversion in the position of mesenteric arteries and veins without malrotation. Because of the reasons stated above, mesenteric inversion is an important finding, which dictates a thorough evaluation of the bowel.

**Figure 21:** Midline Aorta and Left sided IVC



Bowel malrotation can be studied with fluoroscopic upper gastrointestinal examination and oral contrast CT examination, paying particular attention to the normal horizontal orientation of the third portion of the duodenum, the position of the ligament of Treitz, and the position of the small and large bowel with the small bowel on the right and large bowel on the left side of the abdomen in malrotation<sup>17</sup> (Fig 20).

In a study performed by C.K. Chon et al. to diagnose bowel malrotation by CT,<sup>18,19</sup> it concluded that only if there is inversion in position of the superior mesenteric vein and artery along with right-sided first and second jejunal branches can bowel malrotation be diagnosed with certainty. If bowel malrotation can be diagnosed with oral contrast CT, it is not necessary to perform upper GI examination. This can be done in cases in which the diagnosis is still in question after oral contrast CT.

Given that the development of the pancreas during embryogenesis is closely associated with duodenal jejunal rotation, it is not surprising that bowel malrotation is directly related with abnormal pancreatic morphology.<sup>13,20</sup> There is little reference

in the literature regarding the morphology of the pancreas in patients with polysplenia. In a study performed by Hatayama and Wells on six pediatric patients with polysplenia and other congenital anomalies, they described a short, thick pancreas. The presence of a short pancreas was mostly due to abnormal embryological development of the dorsal bud. In spite of the short size of the pancreas, the patients did not demonstrate any evidence of diabetes. The presence of abnormal morphology of both pancreas and spleen is due to the fact that both organs develop in the dorsal mesogastrium.<sup>21</sup>

If, after performing an endoscopic retrograde pancreatograph (ERCP) on a patient with polysplenia, only a short segment of the pancreatic duct opacifies, it is reasonable to conclude that this is due to the presence of a truncated pancreas rather than pancreatic divisum or pancreatic mass obstructing the pancreatic duct. Hader et al. demonstrated the presence of a short pancreas in adult patients with polysplenia. Oral contrast CT in our patient demonstrated the presence of a pancreas with absent body and tail. It is worth noting the presence of a preduodenal portal vein in these patients, which can interfere with the normal pancreatic development, thereby increasing the risks of pancreatic anomalies such as anular pancreas.<sup>8,22</sup> Knowing the existence of a preduodenal portal vein is important because of the risk of inadvertent injury during surgical procedures.

A bilobed lung is another type of malformation found in patients with polysplenia.

## Conclusion

Review of the literature, recent breakthroughs in embryologic understanding, and our own experience illustrate the complexity and spectrum of abnormalities seen in patients with the heterotaxic syndromes. We propose that the term **heterotaxy syndrome** be used to describe these patients and that the patient's individual anatomy be described, rather than using the classic but imprecise terms isomerism, asplenia, or polysplenia.

In our case, CT examination confirmed the findings of hypoplasia of the inferior vena cava with absence of the intrahepatic segment and direct continuation with the azygous venous systems, which, following polysplenia, is the most frequent finding found in heterotaxy.

We believe it is essential to understand situs abnormalities and their wide variety of appearances on radiologic studies. A more accurate classification approach to each patient with heterotaxy is the most practical way to recognize those children who are at increased risk of congenital heart disease, immune deficiency (splenic absence), and catastrophic volvulus with malrotation.

*Andres Abreu, DO, MS, is Radiology Medical Director, Dimensional Imaging Inc., Sarasota, Florida.*

*María Luisa Nieto-Morales, MD, PhD, is Staff Radiologist, Hospital Universitario Nuestra Señora de Candelaria, Santa Cruz de Tenerife, Spain.*

*Margarita Fuentes, MD, is Staff Radiologist, Hospital Universitario de Canarias, La Laguna, Spain.*

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