IJAE
Vol. 123, n. 3: 263-276, 2018
ITALIAN JOURNAL OF ANATOMY AND EMBRYOLOGY

Research Article - Human Anatomy Case Report

Complete situs inversus: A variation in left-right asymmetry during embryogenesis

Suniti Pandey*, Shailendra Singh, Jigyasa Passey, Rahul Singh, Sushobhana, Raveena Singh, Namrata Jaiswal

Department of Anatomy, G.S.V.M. Medical College, Kanpur, Uttar Pradesh, India

Abstract

Complete situs inversus is a very rare anomaly featured with the total inversion of all abdominal and thoracic organs. During the normal embryonic development laterality (left-right-sidedness) is featured by a cascade of signal molecules and genes. Any disturbance in the establishment of normal anatomical left- right asymmetry during this period results in left-right axis malformations which may express as complete situs inversus, incomplete situs inversus or situs ambiguous. A cadaver was detected with complete situs inversus during the routine dissection in the Anatomy Department of G.S.V.M. Medical College, Kanpur, Uttar Pradesh, India. The anomaly is very rare and may not be diagnosed until later in life when people seek medical attention because of unrelated medical problem and undergo radiographic investigation. The cadaver was carefully dissected. The literature was reviewed concerning the underlying cause of the anomaly during the embryonic period and the clinical implications of the condition. Special emphasis was given to the genetic cause of the condition. A literature search was performed in Pubmed, Scopus, Web of Science and Google Scholar databases, including studies published up to March 2016, with no lower data limit.

Key words

Dextrocardia, heterotaxy, left-right axis, mirror image, situs inversus.

Introduction

Situs inversus is a rare anatomical anomaly referring to the mirror image of the abdominal and thoracic viscera. Growing evidence suggests that interference with normal genetic mechanisms and pathways for the establishment of left to right axis during embryogenesis may be responsible for most cases of this anomaly (Yokoyama et al.,1993). Humans establish anatomical left-right asymmetry before and during gastrulation in the embryonic period. Variation from this normal arrangement (situs solitus) results in heterotaxy, expressed either as randomization (situs ambiguus) or complete reversal (situs inversus) of normal organ position. Complete situs inversus is a rare syndrome, with overall frequency estimated at 1/10,000 births (Marta et al., 2003).

Situs inversus is further classified as situs inversus with levocardia and situs inversus with dextrocardia. In levocardia, the base-to-apex axis of heart points to the left, while in dextrocardia, the axis is reversed. Situs inversus occurs more commonly with dextrocardia than levocardia. Situs inversus with dextrocardia is also termed

* Corresponding author. E-mail: dr.suniti@yahoo.co.in

http://www.fupress.com/ijae
DOI: 10.13128/IJAE-25418

situs inversus totalis. Situs inversus with levocardia is rare, (1 in 2,000,000 of the general population), also known as "situs inversus incompletus" (Maldjian et al., 2007). Isolated dextrocardia is also referred as situs solitus with dextrocardia. Dextrocardia was first drawn by Leonardo da Vinci in 1452-1519 and recognized by Marco Severino in 1643. However, Mathew Baillie described the complete mirror-image reversal of the thoracic and abdominal organs in situs inversus after more than a century (Wilhelm, 2007).

A 3-5% incidence of congenital heart disease is observed in situs inversus with dextrocardia. It is usually associated with transposition of the great vessels and a right-sided aortic arch, atrial and ventricular septal defects, tetralogy of Fallot (Maldjian et al., 2007). The literature provides evidence that situs inversus is associated with multiple congenital defects namely, Kartagener syndrome, duodenal atresia, biliary atresia, gastroschisis along with vascular anomalies (Tonkin and Tonkin, 1982; Kamitani, 2005; Lee et al., 2006; Abdur-Rahman et al., 2007).

The situs inversus is typically diagnosed incidentally during diagnostic imaging for other conditions. It may be recognized first by using radiographic investigations or ultrasonogram. Electrocardiography reveals an inversion of the electrical waves from the heart and is the diagnostic measure of choice for dextrocardia. Computed tomography scanning is the preferred examination for the definitive diagnosis of situs inversus with dextrocardia (Tonkin and Tonkin, 1982). The condition is of clinical significance for the physician, who need to be aware of the possibility of situs inversus, as more common conditions will present uncharacteristically in this condition (appendicitis, for instance, will present as pain in the left lower quadrant) (Ngim et al., 2013).

Material and methods

This study is based on the dissection and observations made on a 70 year-old female cadaver in the Department of Anatomy, GSVM Medical College, Kanpur, Uttar Pradesh, India.; the cause of her death was myocardial infarction. The cadaver had dextrocardia, which was detected incidentally while doing a routine supervision of dissection of thorax region of 12 embalmed adult cadavers by first year MBBS students. The cadaver was further dissected by the departmental faculty using traditional methods and techniques. A complete digital photography log was kept during the dissection. The cadaver was diagnosed as a case of complete situs inversus, which is a very rare congenital anomaly. Such a case was not seen in the Department of Anatomy since past many years.

The study provided a better avenue for the students to understand the embryonic development and the process that brought about this congenital abnormality. The literature was reviewed for the genetic cause and clinical implications of the anomaly.

Results

The arrangement of the viscera in the cadaver was in general agreement with previous reports of situs inversus. Specifically, there was dextrocardia. The apex of the

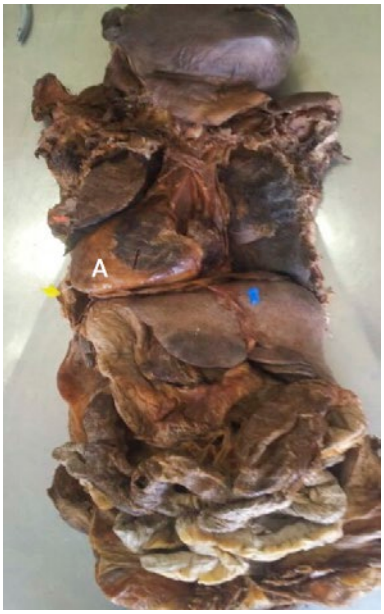

Figure 1. Cadaver showing dextrocardia with situs inversus: A- Apex of heart on the right side, right lung with cardiac notch, liver in the left hypochondrium (blue flag), stomach in the right hypochondrium, splenic flexure on the right side lower hepatic flexure on the left side.

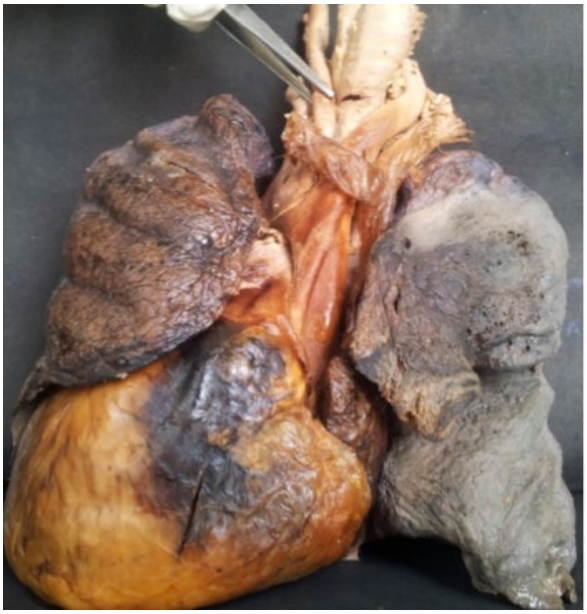

Figure 2. Heart- lung unit (anterior view), showing dextrocardia.

heart was directed toward the right side (Figures 1, 2). The heart was dissected. The ventricular wall thickness was measured with a digital vernier caliper. The right ventricular wall (morphological left ventricle) was 16.17 mm thick while the left ventricular wall (morphological right ventricle) was 5.84 mm thick.

There was transposition of great vessels with the ascending aorta arising from the right (morphological left) ventricle and pulmonary trunk from the left (morphological right) ventricle. The branches of aortic arch were transposed i.e starting from the heart, in the order of the right subclavian artery, right common carotid artery and brachiocephalic trunk which in turn divided into the left common carotid and left subclavian arteries. A probe was passed in the left common carotid artery which emerged through the right (morphological left) ventricle. The left sided superior vena cava and left sided inferior vena cava were present, draining in left (morphological right) atrium (Figure 3).

The right lung had one fissure and only two lobes with a prominent cardiac notch and lingula, and the left lung also had one fissure and only two lobes (Figures 2, 4).

The descending thoracic aorta was found on the right side of the thorax, where it pierced the right crus of the diaphragm at about the level of the 12th thoracic intervertebral disc. (Figure 4).

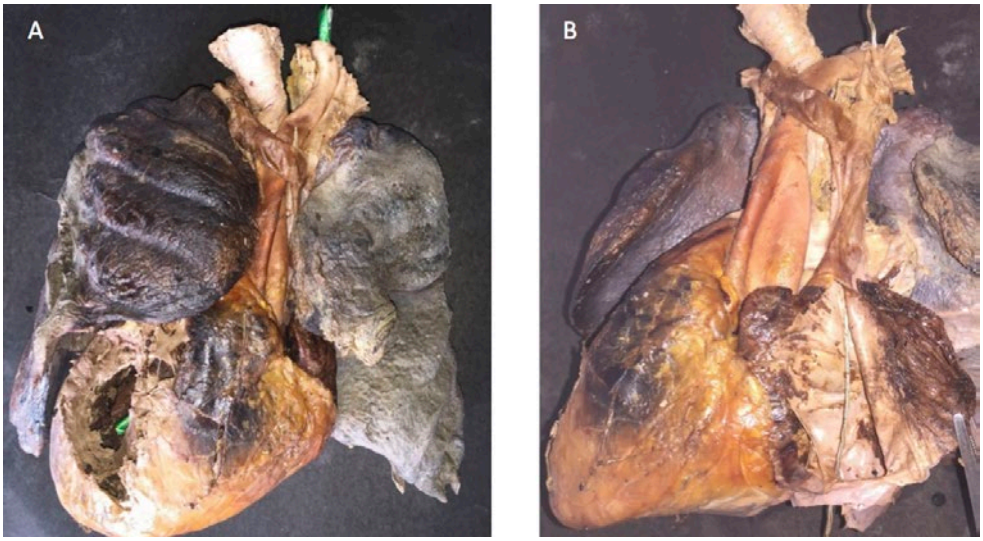

Figure 3. A. Aorta arising from the right (morphological left) ventricle: a probe (green) passed through left common carotid artery emerged through the right (morphological left) ventricle. The thickness of the right (morphological left) ventricular wall is visible. B. Left atrium (morphological right) is opened to show the internal surface.

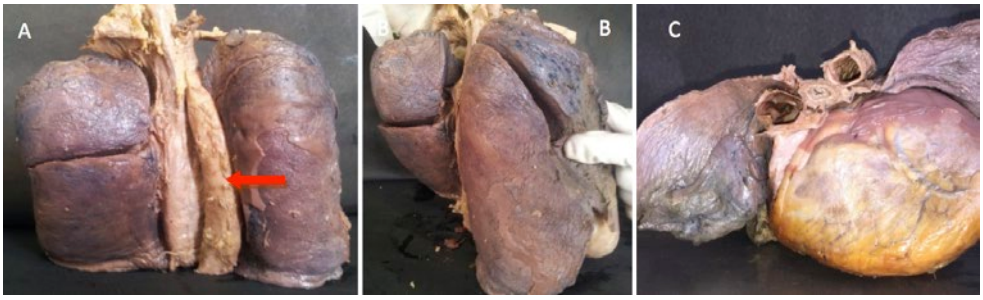

Figure 4. A. Descending thoracic aorta on right side (red arrow), left lung with one horizontal fissure (posterior view). B. Right lung with one oblique fissue and two lobes, left lung also with one horizontal fissure. C. Diaphragmatic surface showing lumen of inferior vena cava, oesophagus and aorta from left to right.

On further exploration of abdomen, the spleen was found to be located on the right side The spleen showed multiple splenic notches on the superior border, the most anterior one being the deepest (Figure 5).

There was dextrogastria with stomach on the right side, the first part of duodenum crossing the midline to the left and the C- loop on the left side (Figure 1, 6, 7).

The head of pancreas was on the left and the tail directed to the right (Figure 8). The pancreas was adherent to the posterior abdominal wall.

The liver and gallbladder were located on the left side (Figures 1, 9A). The mor-

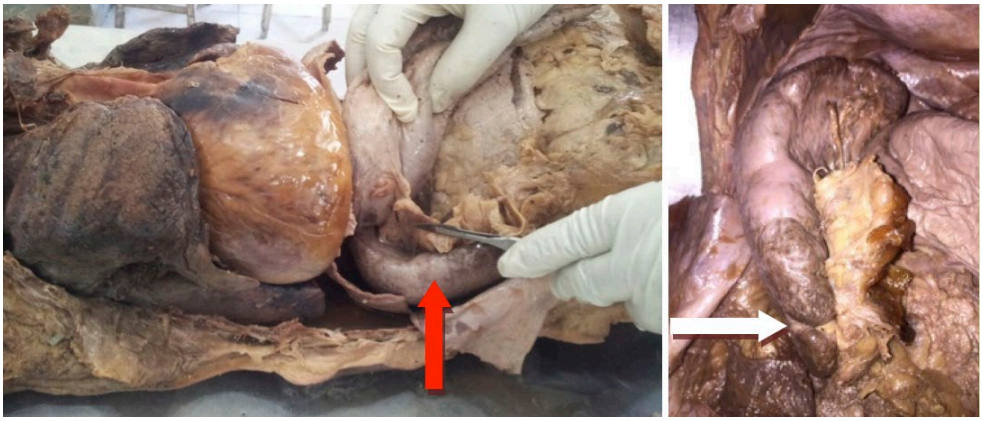

Figure 5. A. Spleen (arrow) in the right hypochondrium; B. Superior border of spleen showing multiple splenic notches, the anterior notch is deepest (arrow).

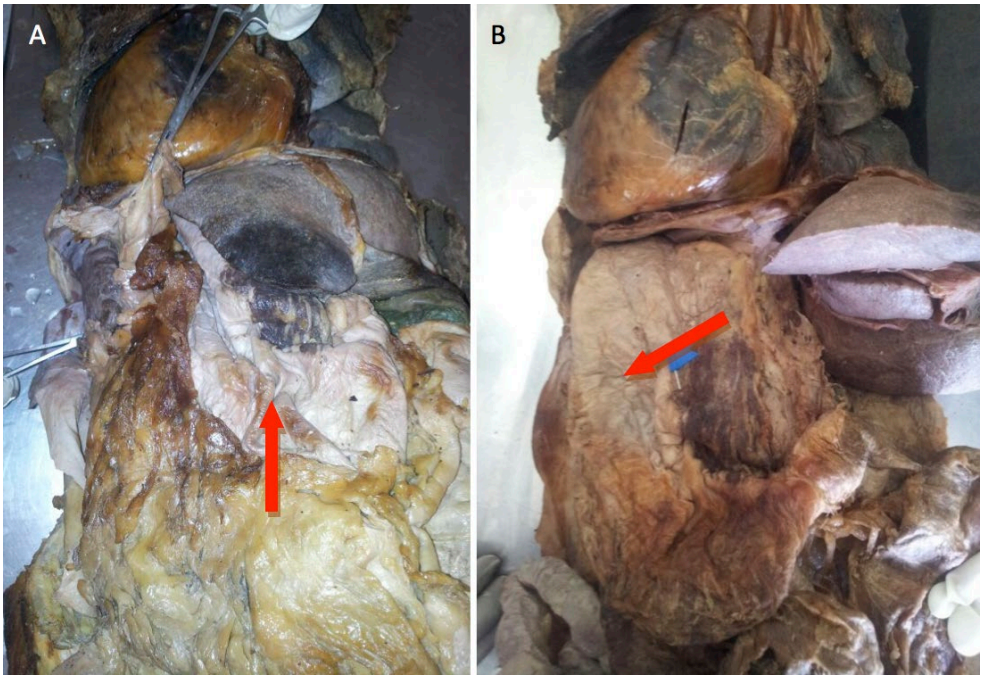

Figure 6. A. Stomach (arrow) in the right hypochondrium with greater omentum attached to the greater curvature. The spleen with multiple notches is also visible in the right hypochondrium. B. Stomach in the right hypochondrium with the lesser omentum attached to the lesser curvature (attachment of lesser omentum on liver divided and greater omentum removed).

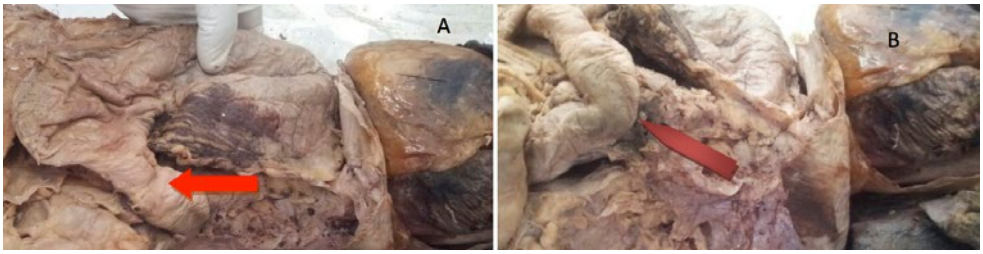

Figure 7. A. Stomach in the right hypochondrium with the lesser omentum attached to the lesser curvature; first part of duodenum (arrow) passing through the epigastrium to the left hypochondrium (supine position). B. First and second part of duodenum on the left side (arrow; liver removed).

Figure 8. Head of pancreas (long arrow) on the left side and tail (short arrow) at the hilum of spleen on the right side. The splenic artery is visible on the superior border of pancreas. Stomach and first part of duodenum everted with forceps.

phological right lobe of liver (normal) was present in the left hypochondrium while morphological left lobe was on the right side. The groove for the inferior vena cava was present on the posterior surface of the left lobe (the morphological right lobe; Figure 10).

The ascending colon, caecum and appendix were lodged on the left side (Figure 8) and the descending and sigmoid colon were on the right side (Figure 11). The splenic flexure was on right side and higher while hepatic flexure was on left side and lower.

Both kidneys were lobulated, presenting a polycystic appearance in cut section. (Figures 11, 12). The right renal artery was anterior to the right renal vein. An aberreant left renal artery, arising directly from aorta, was present. The left kidney had two left renal arteries, both arising directly from abdominal aorta. One left renal artery was anterior and another was posterior to the left renal vein. Both renal arteries divided in 2-3 branches before entering in the hilum of kidneys. The right renal vein was longer than left renal vein. The tributaries of the right renal vein were right ovar-

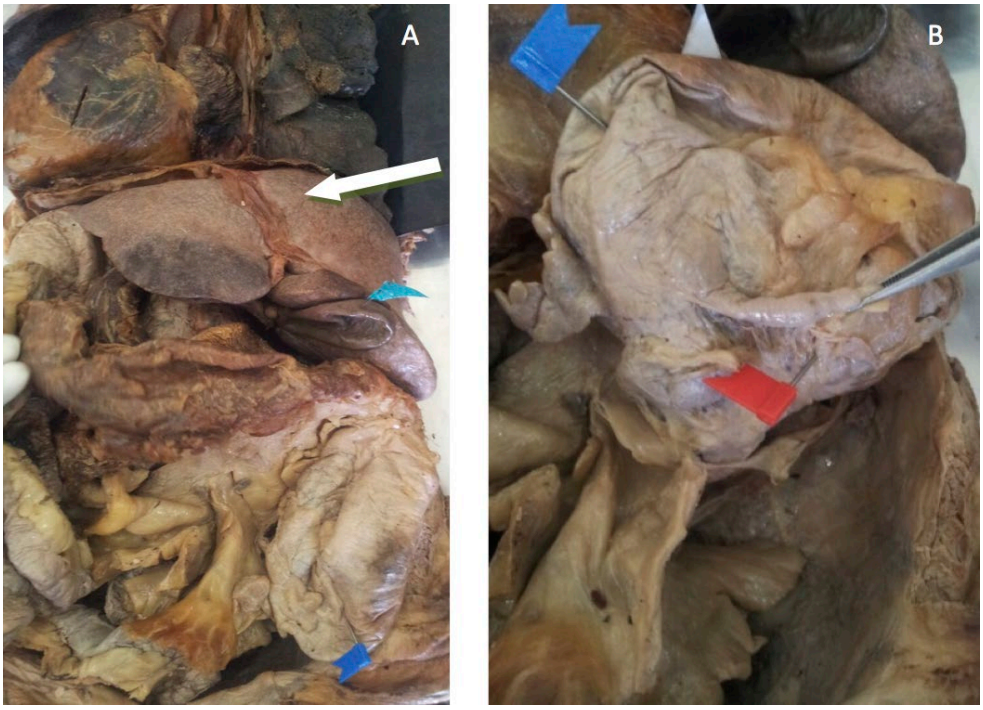

Figure 9. A. Liver (white arrow) and gall bladder (blue flag) in the left hypochondrium (blue flag), caecum and appendix in the left iliac fossa. B. Caecum (blue flag) and appendix in the left iliac fossa (held with forceps).

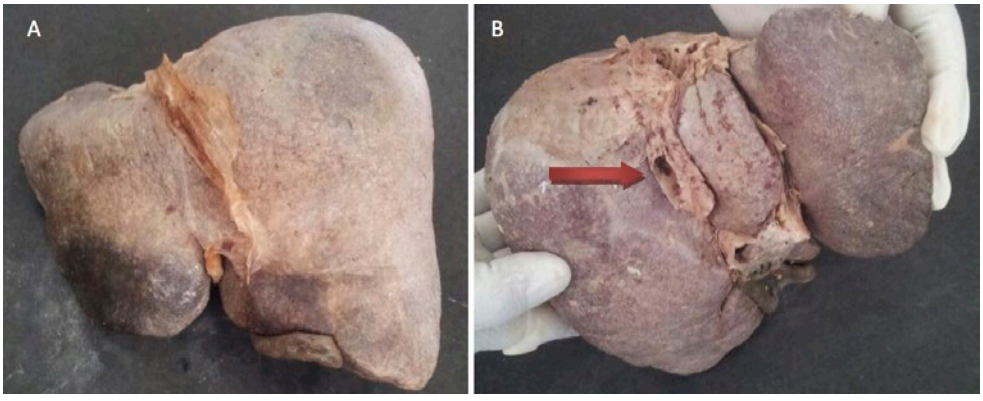

Figure 10. A. Liver (anterior surface) showing morphological right lobe as left lobe and morphological left lobe as right lobe. B. Liver (posterior surface) showing the groove for inferior vena cava (red arrow) on the posterior surface of the left lobe (morphological right lobe).

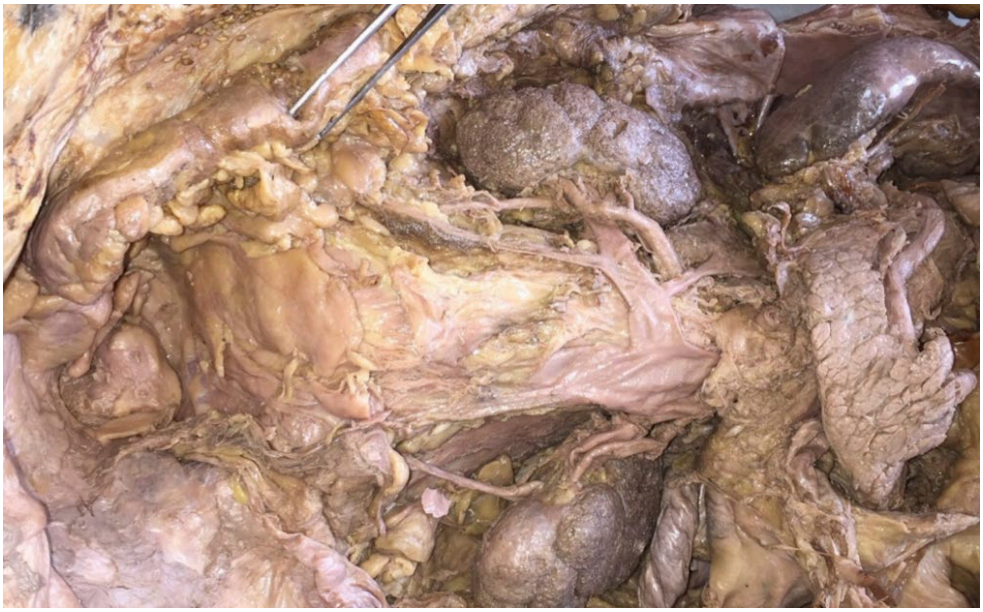

Figure 11. Sigmoid colon (held with forceps) in the right iliac fossa. Spleen in the right hypochondrium, pancreas and kidneys, both lobulated are also visible.

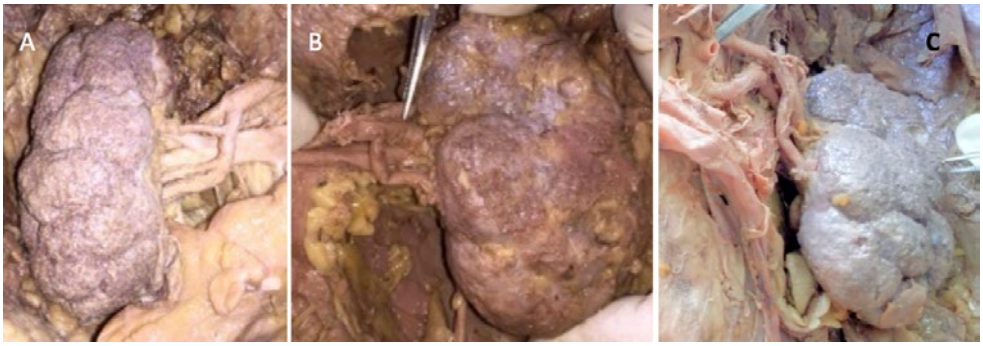

Figure 12. A. Lobulated right kidney with right renal artery anterior to vein. B. Lobulated left kidney with two left renal arteries. C. Two left renal arteries arising directly from abdominal aorta (one with cut lumen, another intact). Inferior vena cava, on the left side, is holded aside.

ian vein, right phrenic vein and right suprarenal vein. The inferior vena cava was on the left side and abdominal aorta was on the right side. The cut section of the kidney showed polycystic appearance (Figures 11, 12, 13).

While taking out the brain from this cadaver the confluence of venous sinuses was present on the right side. On gross examination the brain was normal. No asymmetry in terms of occipital and frontal petalia was evident.

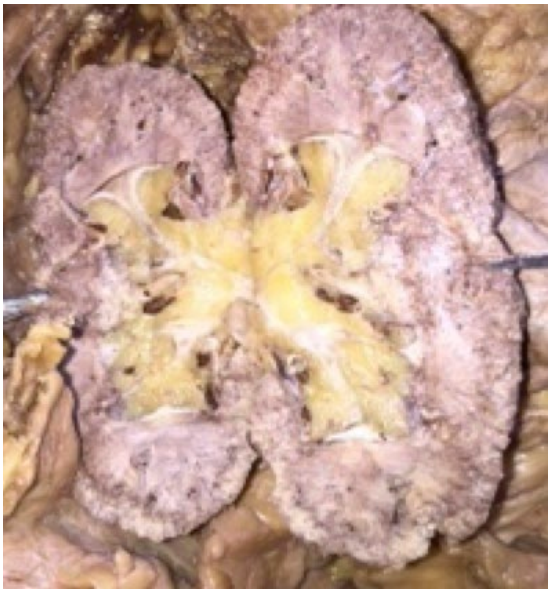

Figure 13. Section showing polycystic kidney.

Discussion

Situs inversus with dextrocardia is also termed situs inversus totalis because the heart and abdominal viscera are present as a mirror image of the normal anatomy (Maldjian, 2007). Situs inversus totalis has equal distribution in both gender (Marta et al., 2003; Tayeb et al., 2011). Situs inversus is usually inherited as an autosomal recessive condition but it may be inherited as X-linked disorder or may be found in identical mirror twins (Chib et al., 1977; McNamara et al. 2016). Monozygotic twinning may be associated with mirror image twins which result when the fertilized egg splits later in embryonic stage than normal timing around day 9-12. Mirroring, as a reflection of a biological polarization, can result in anatomical, functional, medical, or psychological mirror imaging. Mirror image twins exhibit reversed asymmetry. They can be opposites of each other in terms of dominant handedness, dental structure, asymmetrical features, and/or brain-hemisphere dominance. Even the facial and dermatoglyphic analysis reveal mirror-image smiles as well as fingerprint patterns. Heterotaxy, or situs inversus with almost identical mirror-image abdominal thoracic viscera has been reported in mirror-image twins. Situs inversus can be discordant when only one individual of a twin pair is the sufferer, in which case it is termed situs inversus specularis (Song et al. 2013).

When the anatomical left-right axis in the body is neither normal nor entirely reversed as a mirror-image, the phenotype is termed situs ambiguous or heterotaxy. Situs ambiguus describes an overall anatomical arrangement in which any structure with left-right asymmetry can be normal, completely reversed or neither. The situs ambiguous is classified as two primary subtypes (a) right isomerism, or asplenia syn-

drome or bilateral rightsidedness, and (b) left isomerism, or polysplenia syndrome in left isomerism, or polysplenia or bilateral left-sidedness (Sadler, 2013).

While making diagnosis of situs inversus totalis, the possibility of family history, mirroring and other similar conditions such as situs ambiguous and situs inversus incompletus are to be borne in mind which requires further investigations.

Recent studies with positional cloning have shown that a tightly regulated genetic cascade plays a crucial role in establishment of the three orthogonal body axes, anteroposterior (AP), dorsoventral (DV), and left-right (LR) takes place before and during the period of gastrulation (Sadler, 2013), prior to the appearance of morphological asymmetry. Conceptually, LR patterning is divided into three phases. in the first phase of LR patterning, an as-yet unknown mechanism must orient the LR axis with respect to the other two axes. The LR axis is probably specified after the AP and DV axes, and is determined with respect to them. The cascades of asymmetric gene expression form the middle phase of LR patterning. By inducing or repressing transcription of downstream asymmetric targets, they propagate signals among sub-populations of cells (such as node and lateral plate mesoderm), which eventually dictate sidedness for the organs undergoing asymmetric morphogenesis. In the final phase, individual organs utilize cell migration, differential proliferation, cytoskeletal organization, and other mechanisms to achieve asymmetries in their location or morphogenesis (Levin, 2005).

When the primitive streak appears, fibroblast growth factor 8 (FGF8) is secreted by cells in the node and primitive streak which induces expression of *Nodal*. Later, as the neural plate is established, FGF8 maintains *Nodal* expression in the lateral plate mesoderm, as well as left-right determination factor 2 (*LEFTY-2)*, and both of these genes upregulate Paired-like homeodomain transcription factor 2 (*PITX2)*, a homeobox and master gene for left- sidedness (Casey and Hackett 2000; Levin, 2005; Sadler, 2013). Its expression is repeated on the left side of the heart, stomach and gut primordial as these organs are assuming their normal asymmetrical body positions. If the gene is expressed ectopically, e.g. on the right side this abnormal expression results in laterality defects, including situs inversus and dextrocardia. Simultaneously, left-right determination factors *(LEFTY*) is expressed on the left side of the floor plate of the neural tube and may act as barrier to prevent left sided signals from crossing over. Sonic hedgehog *(SHH)* may also serve this role as a repressor for left sided gene expression on the right. The *Brachyury T* gene, encoding a transcription factor secreted by the notochord is also essential for expression of *Nodal, LEFTY-1* and *LEFTY2* (Casey and Hackett 2000; Wright 2001; Levin, 2005; Sadler, 2013).

Nodal is located on human chromosome 10q21–q23, where a de novo interstitial deletion has been detected in human left right axis malformation. Analysis of polymorphic microsatellites flanking human *NODAL* in the affected individual and her parents indicates that this gene is included within the deleted region. Further, cloning has proven effective in the identification of mutations in ZIC3, an X-linked zinc-finger transcription factor as one molecular genetic cause of human left right axis malformations. Zic genes are involved in (sonic) hedgehog signalling which are implicated in human left right axis specification (Casey, 1998). Importantly, the neurotransmitter serotonin (5HT) also plays a critical role in this signaling cascade that establishes laterality. 5HT is concentrated on the left side, probably because it is broken down by its enzyme monoamine oxidase (MAO) on the right. Mothers who take selective sero-

tonin reuptake inhibitors as antidepressants may give birth to children with laterality defects (Sadler, 2013).

Interestingly the cilia normally present on ventral surface of primitive node beat and create a gradient of *Nodal* toward the left may initiate the cascade or a signaling gradient established by gap junctions and small ion transport (proton–potassium pump -H+/K+-ATPase) may also have some role (Levin, 2002; Sadler, 2013). It has been reported that approximately 20% of patients with situs inversus have Kartagener syndrome, an abnormality affecting the respiratory cilia and often accompanied by infertility (Casey,1998; Wright, 2001; Abdur-Rahman, 2007). Affected individuals suffer from chronic respiratory tract infections and from a variable combination of infertility (in males), chronic ear infections and decreased or absent sense of smell. These problems arise as a result of defective cilia and flagella, hence the diagnosis immotile ciliary syndrome (ICS). The cilia are functionally abnormal and electron microscopy usually reveals absence or abnormalities of the dynein arms connecting the nine pairs of microtubules (Afzelius 1985). Mutation in the 82 exons of the gene DNAH11 (axonemal heavy chain dynein type 11) present on chromosome 7p21 has been held an underlying cause of ICS in patients with Kartagener syndrome with situs inversus (Bartoloni et al., 2002). In addition to kinesin and dynein, other proteins like inversin, polaris, polycystein- 2 have also been linked to asymmetry which have been interpreted to result from impaired ciliary function (Levin, 2005).

Glimpses into mechanisms of asymmetry were provided by a variety of drugs which cause defects in a LR asymmetric manner or randomize asymmetry. These drugs include cadmium (heavy metal), phenyl ephedrine (adrenergic agonist), retinoic acid (teratogen) and many others (Levin, 2005).

Thus many genes viz. *LEFTY, NODAL, HAND, ZIC3, SHH, ACVR2B, PITXZ* (Marta et al.,2003) are suspected to orchestrate the proper positioning and patterning of the organs in the body. Since a cascade of many genetic steps is required to produce situs inversus, the incidence is rare. However, a specific genetic cause of dextrocardia with situs inversus has not been identified.

In our case the age of the cadaver was 70 yrs and the cause of her death was myocardial infarction. It has been claimed that the situs inversus totalis is not associated with physiological difficulties so life expectancy of the persons with situs inversus totalis remains unaffected (Marta et al., 2003; Levin, 2005).

In the present case we found dextrocardia i.e the heart was situated in the right hemithorax with base apex axis pointing to the right. Rightward looping of the heart tube is the first embryological manifestation left-right asymmetric development The cardiac situs is determined by the location of the atria. The ventricles presented the L loop pattern where the right ventricle was situated posterior and to the left of left ventricle. In situs inversus the expression of HAND genes, dHAND for right and eHAND for left ventricle, is inverted (Marta et al.,2003) So the persons with situs inversus usually have dextrocardia (Yokoyama et al.,1993; Marta et al.,2003; Maldjian, 2007). 5-10% of cases of dextrocardia with situs inversus present congenital cardiac disease (Marta et al.,2003). In this case we found transposition of great vessels and a right sided aortic arch. Interatrial septum and interventricular septum were normal.

In the cadaver the right lung had only two lobes which could predispose for therespiratory disease. The left lung also had two lobes. Therefore left isomerism or bilateral left-sidedness was evident in lungs. Spleen too had multiple notches though pol-

ysplenia was not evident. Since mirror image reversal of all asymmetrical structures was evident in the cadaver so situs inversus totalis was diagnosed.

Complete situs inversus may form part of multiple malformational syndromes and is commonly associated with polysplenia and splenic malformations (Nawaz 2005; Lee,2006). In the present case the spleen was situated in the right hypochondrium. It showed multiple splenic notches on superior border, the most anterior one being the deepest indicating the embryological predisposition of polysplenia because of non fusion of all lobules.

In the present case both the kidneys were lobulated representing polycystic kidneys. Congenital polycystic kidney is inherited as autosomal recessive or autosomal dominant disease and is linked to mutations in genes that encode for cilia related proteins (Sadler 2013). The inv (inversion of embryonic turning) mutation may produce situs inversus and cyst formation in kidneys (Mochizuki et al., 1998). Therefore the lobulated kidneys in a case of situs inversus can be explained due to the mutation in the related genes. The ureters and urinary bladder were normal.

Vascular anomalies have been well reported to be present in cases with situs inversus (Kamitani, 2005; Kulesza, 2007). In the present case, two left renal arteries arising directly from abdominal aorta were present. The relationships of vessels at the hilum of both kidneys were also altered. The renal artery was anterior to renal vein on both sides. The left renal vein was in between the two left renal arteries. The right sided aorta and left sided superior vena cava and inferior vena cava can be explained as a result of left - right axis disturbance during embryonic development. The left aortic channel and the right superior and inferior venae cavae disappeared during fetal life while the right aortic channel, left superior vena cava and left supracardinal vein persisted resulting in left inferior vena cava (Kulesza et al., 2007). The confluence of venous sinuses in brain was also on the right side instead of left side as more commonly reported. This vascular anomaly could also have resulted as explained.

Gastrointestinal malrotation, more precisely 'intestinal rotation and fixation abnormalities' (IRFA), is also a manifestation of LRA malformations (Chang J et al., 1993). In the present cadaver the ascending colon, caecum and appendix were present on the left side and the descending and sigmoid colon were lodged on the right side. It is reported that the direction of rotation of gut is under the influence of the forces exerted by the adjacent organs on the intestine and its mesentery (Tonkin and Tonkin; 1982). So, liver on left side while stomach and spleen on right side could be the possibly interrelated with gastrointestinal reversal in the present case. The case was also at higher risk of developing acute volvulus since in such case the malrotation of gut and abnormal location of the caecum produces a narrow superior mesenteric vascular pedicle, as opposed to the normally broad based small bowel mesentery which predispose to subsequent midgut volvulus. It is recommended that the condition should be treated prophylactically by the laparoscopic Ladd procedure (Chang J et al., 1993) which requires mobilization of the right colon and caecum by division of Ladd bands, mobilization of the duodenum, division of adhesions around superior mesenteric artery to broaden the mesenteric base and an appendicectomy.

Conclusion

As the relationship between the organs is not changed, most people with situs inversus totalis have no medical symptoms or complications. Yet, they should wear a medical identification note to warn emergency medical persons that the patient's internal organs are reversed from normal so they can act accordingly, e.g. by listening for a heartbeat on the right rather than left side of the chest. The diagnosis of situs inversus is important due to the fact that failure to recognize reversed anatomy or an atypical history may result in surgical mishaps. Careful observation of the image labels in the radiographic investigations in a patient with situs inversus is a must before any surgery. Similarly, with advancement of medical sciences in the field of organ transplantation a very careful intra-operative evaluation of accepted organs during procurement from a donor with situs inversus is necessary on one hand and similar recognition of any abnormalities that can make implantation difficult or impossible in the recipient is essential. Genetic counseling may be helpful for the affected families. The patients or relatives at risk may be advised of the consequences of the disorder, the probability of its inheritance in progeny and the options open for management and family planning.

Acknowlegement

We are thankful to the soul of the body donor and the attendants of Dissection Hall, Dept. of Anatomy. The work was not funded by any agency. The authors have no conflict of interest to declare. We also gratefully acknowledge the Italian Society of Anatomy and Histology for financial support in the publication of this article.

References

Abdur Rahman L.O., Adeniran J.O., Taiwo J.O. (2007) Concurrent dextrogastria, reverse midgut rotation and intestinal atresia in a neonate. J. Indian Assoc. Paediatr Surg. 12: 228-230.

Afzelius B. (1985) The Immotile-Cilia Syndrome: a microtubule associated defect. CRC Crit. Rev. Biochem. 19: 63-87.

Bartoloni L., Blouin J.L., Pan Y., Gehriq C., Malti A.K., Scamuffa N., Rossier C., Jorissen M., Armengot M., Meeks M., Mitchison H.M., Chung E.M., Delozier- Blanchet C.D., Craigen W.J., Antonarakis S.E. (2002) Mutations in the DNAH11 (axonemal heavy chain dynein type11) gene cause one form of situs inversus totalis and most likely primary ciliary dyskinesia. Proc. Natl. Acad. Sci. U.S.A. 99:10282-10286.

Casey B., Hackett B.P. (2000) Left-right axis malformations in man and mouse. Curr. Op. Genet. Dev. 10: 257-261.

Casey B. (1998) Two rights make a wrong human left-right malformations Hum. Mol. Genet. 7): 1565.

Chang J., Brueckner M., Touloukian R.J. (1993) Intestinal rotation and fixation abnormalities in heterotaxia: early detection and management. J. Pediat. Surg. 28: 1281-1284.

Chib P., Grover D.N., Shahi B.N. (1977) Unusual occurrence of dextrocardia with situs inversus in succeeding generations of a family. J. Med. Genet. 14: 30-32.
Kamitani S., Tsutamoto Y., Hanasawa K., Tani T. (2005) Laparoscopic cholecystectomy in situs inversus totalis with "inferior" cystic artery: a case report. World J. Gastroenterol. 11: 5232-5234.
Kulesza J.R.J., Kalmey J.K., Dudas B., Buck W.R. (2007) Vascular anomalies in a case of situs inversus. Folia Morphol. 66: 69-73.
Lee S.E., Kim H.Y., Jung S.E., Lee S.C., Park K.W., Kim W.K. (2006) Situs anomalies and gastrointestinal abnormalities. J. Pediatr. Surg. 41: 1237-1242.
Levin M., Thorlin T., Robinson K.R., Nogi T., Mercola M. (2002) Asymmetries in H+/K+-ATPase and cell membrane potentials comprise a very early step in left–right patterning. Cell 111: 77-89.
Levin M. (2005) Left-right asymmetry in embryonic development: a comprehensive review. Mech. Dev. 122: 3-25.
Maldjian P.D., Saric M. (2007) Approach to dextrocardia in adults: review. AJR Am. J. Roentgenol. 188: S39-S49.
Marta M.J., Falcao L.M., Saavedra J.A., Ravara L. (2003) A case of complete situs inversus. Rev. Port. Cardiol. 22: 91-104.
McNamara H.C., Kane S.C., Craig J.M., Short R.V., Umstad M.P. (2016) A review of the mechanisms and evidence for typical and atypical twinning. Am. J. Obstet. Gynecol. 214: 172-191.
Mochizuki T., Saijoh Y., Tsuchiya K., Shirayoshi Y., Takai S., Taya C., Yonekawa H., Yamada K., Nihei H., Nakatsuji N., Overbeek P.A., Hamada H., Yokoyama T. (1998) Cloning of *inv*, a gene that controls left/right asymmetry and kidney development. Nature 395: 177-181.
Nawaz A., Matta H., Hamchou M., Jacobez A., Trad O., AI Salem A.H. (2005) Situs inversus abdominus in association with congenital duodenal obstruction: a report of two cases and review of literature. Pediatr. Surg. Int. 21: 589-592.
Ngim O., Adams L., Achaka A., Busari O., Rahaman O., Ukpabio I., Eduwem D. (2013) Left sided acute appendicitis with situs inversus totalis in a Nigerian male - a case report and review of literature. Internet J. Surg 30 (4) [5 pages]; on line at: https://print.ispub.com/api/0/ispub-article/14683, accessed August 11, 2018.
Sadler T.W. (2013) Langman's Medical embryology. 12th edition, Lippincott William and Wilkins. Pp. 52-57, 237.
Tayeb M., Khan M.F., Rauf F. (2011) Situs inversus totalis with perforated duodenal ulcer: a case report. J. Med. Case Rep. 5: 279.
Tonkin I.L., Tonkin A.K. (1982) Visceroatrial situs abnormalities: sonographic and computed tomographic appearance. AJR Am. J. Roentgenol. 138: 509-515.
Wilhelm A. (2007) Situs Inversus. eMedicine updated Nov 22, 2015; www.emedicine.com/radio/topic639.htm, accessed Dec 5, 2016.
Wright C.V. (2001) Mechanisms of left–right asymmetry: what's wright and what's left? Dev. Cell 1: 179-186.
Yokoyama T., Copeland N.G., Jenkins N.A., Montgomery C.A., Elder F.F., Overbeek PA (1993) Reversal of left-right asymmetry: a situs inversus mutation. Science 260: 679-682.