Case Report

Situs Inversus Totalis and Ultrastructure of Respiratory Cilia: Report of a Cadaveric Case

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Situs inversus totalis is the complete reversal of positions of major thoracic and abdominal organs. The present study reports the reversed structures and histology of the epithelium of bronchus of a female cadaver, 87 years of age, which was found during the dissection in a medical course of gross anatomy. Opening the thoracic cage, the apex of heart was projected to the right side (dextrocardia) while the right and left lungs were alternated. Intra-abdominal organs were also completely alternated, as the liver situated on the left while spleen on the right and the same as the abdominal intestinal tract. The superior and inferior vena cavae located on the left side and drained blood into the left atrium. The azygos vein was on the right. The histology of the epithelium of bronchus and the transmission electron microscopy of the cilium ultrastructure were normal. Cardiac displacement seems to be associated with malrotation of the heart tube leads to dextrocardia and causes the inversion of positions of the thoracic and abdominal organs. The incidence of situs inversus totalis is approximately 1: 10,000 and may be associated with primary ciliary dyskinesia (PCD) which refers to the dysfunction of cilia. PCD is also known as Kartagener syndrome (KS) which is characterized by situs inversus, bronchiectasis, chronic sinusitis and infertility, KS represents 20-25% of situs inversus totalis. However, in the present study, the histology and ultrastructure of cilia appear normal.

Keywords: *Situs inversus totalis, Dextrocardia, Cilia, Primary ciliary dyskinesia (PCD)*

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Situs inversus is a congenital anomaly condition in which the major thoracic and abdominal viscerae are reversed, or mirrored, from their normal positions[1-3]. The organs are simply transposed through the sagittal plane[4,5]. The heart locates on the right side of the thorax, the stomach, spleen and descending colon are on the right side of the abdomen while the liver, gall bladder ascending colon and appendix are on the left side. The left lung is trilobed and the right lung bilobed. The blood vessels, nerves, lymphatics and the intestines are also transposed[6]. Its incidence is reported to be one in 10,000 of the normal population[7] and are often picked up when physicians, using a stethoscope and hear the heart sounds on the right side. To confirm the diagnosis of situs inversus, imaging studies such as MRI, CT or ultrasound are suggested. The one with situs inversus totalis can survive a healthy long life as normal but problems occur during operative procedures, especially during laparoscopic operations. The mirror image of laparoscopic view creates unfamiliarity for surgeons and the instruments were designed for right-handed operators. Up to now, many cases of laparoscopic cholecystectomy, common bile duct exploration and appendectomy in situs inversus totalis were reported[8].

Situs inversus can be classified further into situs inversus with levocardia or situs inversus with dextrocardia[8,9]. Isolated dextrocardia is also termed situs solitus (normal anatomical position) with dextrocardia. Therefore, the abnormal position of the heart is not always accompanied by displacement of other viscerae. Situs inversus with dextrocardia is also termed situs inversus totalis (SIT) because the cardiac position and abdominal viscerae are mirrored image with normal.

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Situs inversus totalis is reported to be closely associated with primary ciliary dyskinesia (PCD)[10,11]. PCD, also known as Katagener syndrome (KS), is characterized by situs inversus totalis, bronchiectasis and chronic sinus infections because of abnormal cilia. Cilia are responsible for clearing mucous from the lung and the dysfunction of cilia causes increased susceptibility to lung infections. These patients may also present infertility secondarily to immotile spermatozoa or dysfunction of uterine tube cilia[12-14]. Incidences of ectopic pregnancy are increased due to defective movement of the cilia in the uterine tube. Hydrocephalus and enlargement of the brain ventricles have also been reported[15]. The ependymal lining the brain ventricles is also ciliated epithelium and the impair ciliary activity leads to the blockage of the cerebral aqueduct is one cause of hydrocephalus[16]. However, there is no summation about the association of situs inversus totalis with PCD that play roles in infertility and chronic sinusitis[17].

The present report is designed to investigate the position of all major organs and structures within the thoracic, abdominal and pelvic cavities, histology and ultrastructure of cilia in ciliated organs of a case of situs inversus totalis to establish the association of PCD and situs inversus totalis conditions.

Case Report

One female cadaver, 87 years of age, provided by the Department of Anatomy, Faculty of Medicine Siriraj Hospital, Mahidol University had been previously dissected by the second year medical students in a standard anatomical laboratory course in 2008. After opening the thoracic wall, the thoracic viscerae were all reversed in mirror fashion. The heart situated on the right with inversion of position of the cardiac cavities (Fig. 1). The arch of aorta was right sided and the SVC was on the left. The right lung had two lobes (upper and lower) whereas the left lung had three lobes (upper, middle and lower) (Fig. 2). The trachea bifurcated into the main bronchi which the left one was more vertical course. The azygos vein and the thoracic duct were on the right. The pulmonary veins opened into the right atrium while the SVC, IVC and the coronary sinus opened into the left atrium. The bicuspid valve was on the right while the tricuspid valve was on the left (Fig. 3, 4).

The abdominal organs were also reversed (Fig. 5). The liver and gall bladder were on the left hypochondrium while the greater part of stomach was oriented to the right side of the midline in right hypochondrium. The spleen was normal in shape and situated on the right as well as the pancreatic tail (Fig. 6). All intestinal parts were reversed such as the ascending colon and appendix were on the left while the descending part was on the right.

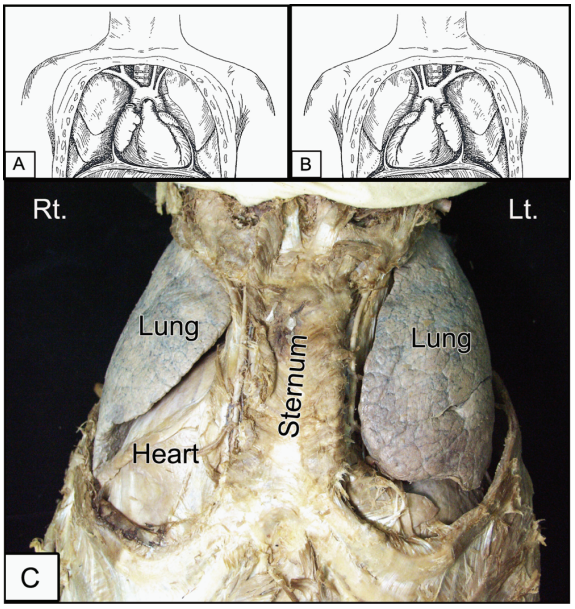

Fig. 1 The position of the heart was reversed in the mirror fashion compared with normal position. A) diagram of normal position, B) diagram of thoracic cavity of situs inversus totalis, C) Photograph of thoracic organs with sternum intact, the heart pointed to the right side while right lung was bilobed and left lung was trilobed

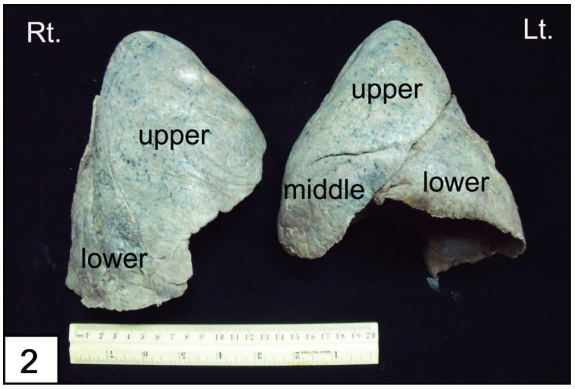

Fig. 2 Photograph of lungs. The right lung exhibited two lobes (upper, lower) and the left lung revealed three lobes (upper, middle, lower)

The variations were also presented in the arterial and venous supplies, such as the coeliac trunk which had three main branches, gastric, splenic and common hepatic arteries. The gastric branch ascended for a short distance, ran to the right, along the lesser curvature and terminated by anastomosing with the common hepatic branch. The splenic artery arose from the coeliac trunk and ran to the right along the upper border of the body and tail of pancreas. The superior mesenteric artery arose about 1 cm below the coeliac trunk and the inferior mesenteric artery arose 3-4 cm above the aortic bifurcation and gave right-sided colic artery and sigmoid artery.

The bronchus walls were observed both light and transmission electron microscopies aimed at the ciliated epithelium. Histology of bronchus was normally composed of 4 tunics. The epithelial lining consisted of pseudostratified ciliated columnar epithelium (Fig. 7) with goblet cell rested on the basement membrane. Light microscopy of cilia revealed the normal intact cilia. Under transmission electron microscopy of bronchus epithelium, cilia were the luminal surface projections of the cells. They were 0.25 mm in diameter and varied in length from 5-10 mm (Fig. 8, 9). The longitudinal sections of cilia were cylindrical and each contained 2-3 microtubules. At the base, the axoneme inserted into the cell apex called

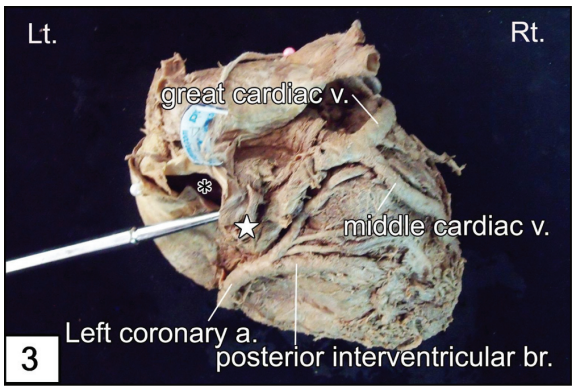

Fig. 3 Photograph of posterior view of the heart showed the left atrium. The orifice of coronary sinus (white star) opened between the orifice of IVC (asterisk) and the left atrioventricular vein. The main veins which contribute to the formation of the coronary sinuses were the great cardiac vein and middle cardiac vein

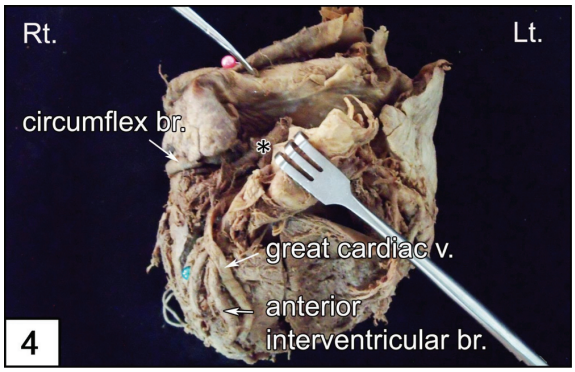

Fig. 4 Photograph of external morphologies of the heart showed the vessels which supplied the heart. The right coronary artery (asterisk) divided into an anterior interventricular branch accompanied with great cardiac vein and a circumflex branch

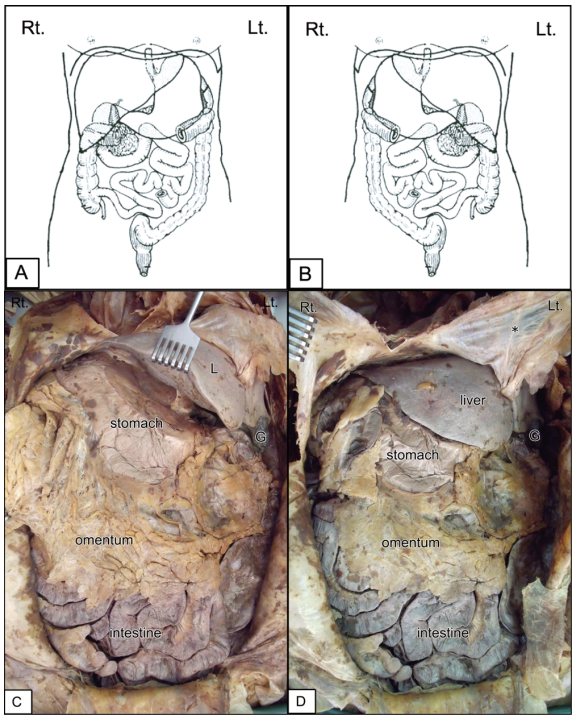

Fig. 5 Photograph of anterior view of abdomen (C, D). The positions of abdominal organs were also inverted. The liver (L) was roughly pyramidal in shape, with its base on the left and its apex directed to the right. The gall bladder (G) was laid on left hypochondrium where as greater part of stomach was oriented to right of midline. A) diagram of the normal, B) diagram of the abdomen of the situs inversus, C), D) abdominal organs after opening the abdominal wall, liver on the left and stomach on the right

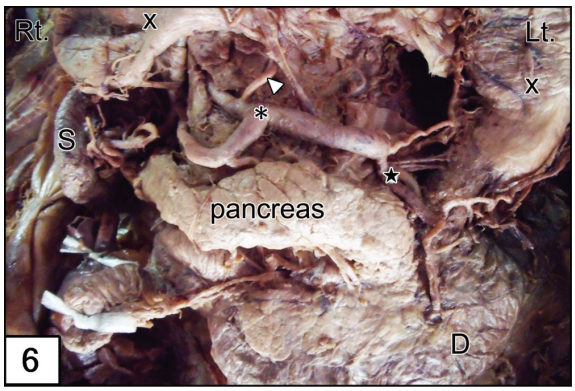

Fig. 6 Photograph of the anterior view of abdomen. The spleen was normal shape and situated in the right hypochondrium (S). The stomach was cut (X). The coeliac trunk (asterisk) divided into three branches. D, duodenum; Right, gastric artery (white arrow head); gastroduodenal artery (black star)

Fig. 8 TEM micrograph of the bronchus in situs inversus totalis at the higher magnification of the longitudinal section of the cilia which were cylindrical. Each cilium was found 2-3 microtubules. The cilia measured 0.25 μm in diameter and vary in length from 5 to 10 μm x22,000 bar = 0.5 μm

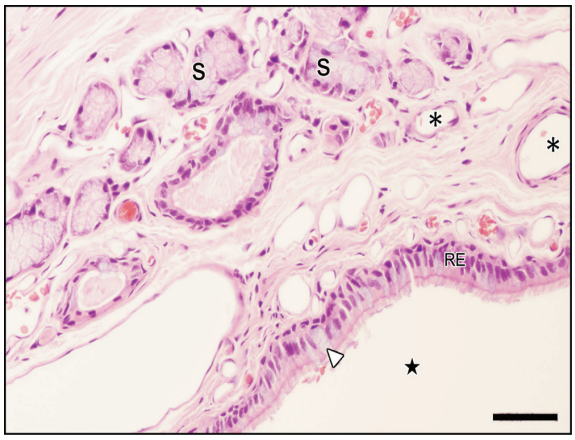

Fig. 7 Light micrograph of the bronchus in situs inversus totalis showing the respiratory epithelium (RE) with goblet cells (white arrowhead) lines the lumen (black star). The connective tissue of the lamina propria contained diffuse lymphoid tissue, blood vessel (asterisks). In submucosa, contained mixed seromucous glands (S). x200 bar = 20 μm

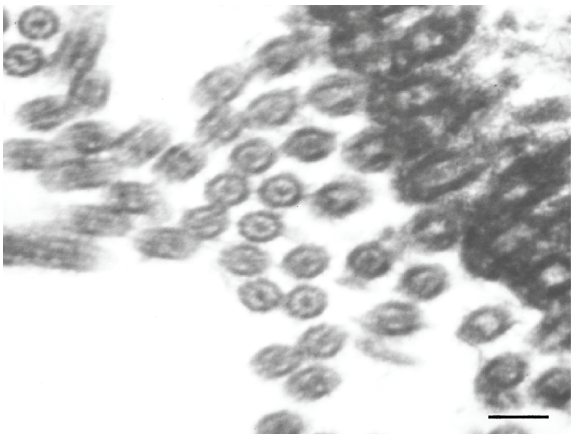

Fig. 9 TEM micrograph of the bronchus in situs inversus totalis The cross-sectioned cilia were circular. Each cilium was bounded by evagination of the luminal plasma membrane and contained a central core called the axoneme consisting of 20 microtubules arranged as a central pair surrounded by nine peripheral doublets. x 25,500 bar = 0.5 μm

basal bodies. The arrangement of microtubules was identical to the centriole (nine triplets). The cross-sections were circular, each cilium was bound by the plasma membrane, contained a central core of 20 microtubules arranged as a central pair surrounded by nine peripheral doublets and showed no difference from the normal ciliary ultrastructure.

Discussion

Establishment of the body axes such as right-left and dorsoventral, occurs during or before the process of gastrulation[18]. The unpaired organs of the thorax and abdomen begin their development at the midline and eventually lateralize to their adult positions, while the paired large blood vessels begin

as symmetrical-paired structures and subsequently fuse together. The lungs are paired structures, originally symmetry but later develop clearly right-left morphologically difference[19-21].

Malrotations of the organs result from the abnormal process of right-left axis specification. Right-left malrotations result in mirror-image reversal of all asymmetrical structures which is also called situs inversus. Analysis of familial cases of situs inversus suggested variable modes of transmission, autosomal dominant, autosomal recessive as well as x-linked. Gene mutations are also caused by right-left axis malrotation, such as sonic hedgehog (SHH) and fibroblast growth factor (FGF)[22]. Familial cases of situs inversus were reported to be associated with immotile cilia syndrome (ICS), an autosomal recessive, resulted in chronic upper respiratory tract infections, bronchiectasis, deafness and infertility. This syndrome is associated with the production of an abnormal form of dynein[23,24], a protein involved in ciliary motility. It was also confirmed that dynein is involved in the determination of right left rotation[25-29].

Moreover, there was also reports in mouse model lacking the novel ciliary protein Pcdp 1[14], homologous mice die perinatally from severe hydrocephalus, while mice of other background accumulated mucous in the sinus and also infertile. Mutant sperm lack mature flagella, repiratory epithelium present cilia but beating abnormal[30]. At the embryonic stage, the first organ showing lateralization is the rotation of the heart tube to the right. Abnormal rotation of the heart tube to the left leads to dextrocardia, which eventually causes inversion of thoracic organs and may also involve the abdominal organs. Many studies reported the transforming growth factor beta (TGFb) factor involves in looping of the heart tube[31].

The cilia structure observed by light and transmission electron microscopic studies of the presented case appears normal, as the luminal surface projections of the cells. They were 0.25 mm in diameter and vary in length from 5-10 mm. The longitudinally sectioned cilium was cylindrical while the cross-sectioned appears circular contains axoneme consists of microtubules arranged as normal general plan. This cadaver, therefore, had normal cilia structure and may also have normal function and activity. However, the authors could not conclude that the presented cadaver had absolutely no defective ciliary activity because the movement of a cilium depends on its central shaft or axonene and also their associated proteins.

Conclusion

The present study reports a cadaveric case of situs inversus totalis which includes the inversion of all main thoracic and abdominal organs. This case may not be associated with PCD as have been previously reported in many cases, according to the personal history. Present study of the cilia of the epithelial cell of bronchus by light and transmission electron microscopies also revealed normal ciliary structure. Therefore, situs inversus totalis may be or may not be associated with the abnormal function of the cilia.

Potential conflicts of interest

None.

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Situs inversus totalis และลักษณะจุลทรรศน์อิเล็กตรอนของซีเลีย: รายงานอาจารย์ใหญ่ 1 ราย

จันทิมา รุ่งเรืองชัย, วนิดา ณรงค์ศักดิ์, วาสนา ผลากรกุล, ยาดาฤดี วิรวุฒิ, เกษร ศรีเปารยะ, โกศล รุ่งเรืองชัย

Situs inversus totalis เป็นภาวะที่มีการสลับข้างของอวัยวะภายในช่องอกและช่องท้อง จากซ้ายเป็นขวาและขวาเป็นซ้าย รายงานฉบับนี้เกี่ยวกับการสลับซ้ายขวาของอวัยวะภายในทั้งหมดพบในอาจารย์ใหญ่ เพศหญิง อายุ 87 ปี ของภาควิชากายวิภาคศาสตร์ คณะแพทยศาสตร์ศิริราชพยาบาล มหาวิทยาลัยมหิดล เมื่อเปิดผนังช่องอกพบว่าปลายหัวใจชี้ไปทางด้านขวาเรียกว่า dextrocardia ปอดทั้งสองข้างสลับกัน โดยปอดขวามี 2 กลีบ และปอดซ้ายมี 3 กลีบ อวัยวะในช่องท้องสลับข้างกันทั้งหมด เสมือนภาพในกระจกเงากล่าวคือ กระเพาะอยู่ทางขวา ตับอยู่ทางซ้าย ปลายตับอ่อนชี้ไปทางขวา ม้ามอยู่ทางขวา ลำไส้ใหญ่ขาขึ้น และไส้ติ่งอยู่ทางซ้าย ลำไส้ใหญ่ขาลงอยู่ทางขวา SVC และ IVC อยู่ทางซ้ายทั้งเทเข้าสู่ เอเทรียมช่องซ้าย เมื่อหาความสัมพันธ์ระหว่าง situs inversus totalis กับลักษณะโครงสร้างของซีเลีย โดยใช้กล้องจุลทรรศน์แบบแสง และกล้องจุลทรรศน์อิเล็กตรอน ศึกษาจากเซลล์เยื่อบุผิวทางเดินหายใจของอาจารย์ใหญ่รายนี้พบว่า โครงสร้างของซีเลียปกติดีแม้เป็นเนื้อเยื่อจากอาจารย์ใหญ่ การกลับข้างของหัวใจเกิดจากการหมุนผิดปกติของท่อหัวใจขณะเป็นตัวอ่อนในครรภ์ ประมาณต้นสัปดาห์ที่ 4 เป็นผลให้เกิด dextrocardia และอาจเป็นต้นเหตุให้อวัยวะอื่น ๆ กลับซ้ายขวาไปด้วยหรือไม่ก็ได้ เชื่อว่าเกิดจากปัจจัยทางพันธุกรรม มีอุบัติการณ์ประมาณ 1:10,000 และอาจเกี่ยวข้องกับโรคอันเกิดจากการเคลื่อนไหวของซีเลียผิดปกติ ที่เรียกว่า primary ciliary dyskinesia (PCD) หรือ Kartagener syndrome (KS) ประกอบด้วย situs inversus, bronchiectasis และไซนัสอักเสบเรื้อรัง รวมทั้งอาจมีผลต่อระบบสืบพันธุ์ทำให้มีบุตรยาก มีผู้รายงานว่า Kartagener syndrome มีความสัมพันธ์กับ situs inversus ถึง 20-25% อย่างไรก็ตามจากการศึกษาครั้งนี้ไม่พบความผิดปกติทางโครงสร้างของซีเลีย แต่เห็นสมควรต้องรายงานเนื่องจากเป็นการพบ situs inversus totalis เป็นครั้งแรกในอาจารย์ใหญ่ไม่เคยมีผู้รายงานมาก่อน