Case Report Rapport de cas

Situs inversus totalis associated with subaortic stenosis, restrictive ventricular septal defect, and tricuspid dysplasia in an adult dog

Diego Piantedosi, Laura Cortese, Leonardo Meomartino, Antonio Di Loria, Paolo Ciaramella

Abstract — A rare association between *situs inversus totalis* (SIT), restrictive ventricular septal defect, severe subaortic stenosis, and tricuspid dysplasia was observed in an adult mixed-breed dog. Primary ciliary dyskinesia and Kartagener's syndrome were excluded. After 15 mo the dog died suddenly. The association between SIT and congenital heart diseases is discussed.

Résumé — *Situs inversus totalis* associé à une sténose sous-aortique, à une malformation septale diastolique restrictive et à une dysplasie tricuspide chez un chien adulte. Une rare association entre *situs inversus totalis* (SIT), une malformation septale diastolique restrictive, une sténose sous-aortique grave et une dysplasie tricuspide a été observée chez un chien de race croisée adulte. La dyskinésie ciliaire primaire et le syndrome de Kartagener ont été exclus. Après 15 mois, le chien est mort soudainement. L'association entre SIT et les maladies cardiaques congénitales est discutée.

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A 4-year-old, 15-kg, intact-male, mixed-breed dog, with a history of a single syncopal episode was referred to the Cardiology Service of the Veterinary Medicine Faculty of Naples for the evaluation of a heart murmur, that had been diagnosed several months earlier.

Case description

Upon presentation, the appearance of mucous membranes and the capillary refill time (2 s) were normal. No respiratory abnormalities were observed. Cardiac examination revealed a holosystolic, crescendo-decrescendo, grade 5/6 murmur, located over all landmark areas of cardiac auscultation, but loudest on the right side of the thorax over the 4th intercostal space at the costochondral junction. Other clinical findings were a stronger cardiac impulse, visible only on the right side of the thorax, a palpable thrill, and a weak arterial pulse (143 beats/min). Distension of the jugular veins and peripheral edema were not evident. Systolic and diastolic arterial blood pressures measured by an oscillometric method were within normal ranges. Results of a complete blood cell count and a routine serum biochemistry profile were within the normal ranges.

Department of Veterinary Clinical Sciences, Internal Medicine Division (Piantedosi, Cortese, Di Loria, Ciaramella); Radiology Veterinary Centre (Meomartino); University of Naples Federico II, Via F. Delpino 1, 80137 Naples, Italy.

Address all correspondence to Prof. Paolo Ciaramella; e-mail: paociara@unina.it

The electrocardiogram revealed a normal sinus rhythm, heart rate of 150 beats/min, and a biventricular enlargement pattern with a right shift of mean electrical axis (+160°). In the limb lead I the QRS complex and the P-wave were negative. A mirror image of the normal pattern in the precordial chest leads [CV6LL (V_2) and CV6LU (V_4)] was also evident (Figure 1).

Echocardiography was performed using the standardized right- and left-sided approach. The 2-dimensional echocardiographic images obtained from right and left parasternal standard views appeared inverted, suggesting an abnormal position of the heart in the thorax. The 2-dimensional examination showed a moderate myocardial concentric hypertrophy of the left ventricle and a mild left atrial dilation (LA/Ao ratio: 1.72) (normal value: < 1.6) (1). Small hyperechoic areas in the papillary muscles were evident. A fixed discrete endocardial thickening which extended circumferentially around the left ventricular outflow tract was observed (Figure 2A). The left semilunar cusp was thick and elongated (Figure 2B). Aortic post-stenotic dilation was also evident. No abnormalities were detected at the level of the right side of the heart.

Continuous wave Doppler recorded a turbulent high-velocity systolic blood flow through the left ventricular outflow tract (peak velocity: 554 cm/s; peak pressure gradient: 123 mmHg) (normal peak velocity value: < 170 cm/s) (1). Color-flow Doppler mapping demonstrated a mild tricuspid and aortic regurgitation, not considered hemodynamically significant. M-mode measurements showed a preserved left ventricular systolic function with an increased shortening fraction (SF) and ejection fraction (EF) (SF: 47.7 %; EF: 79.6 %) (SF normal value: 25% to 40 %; EF normal value: 50% to 65 %) (1), associated with an exaggerated septal and free-wall motion. A membranous interventricular septal defect (VSD) with a

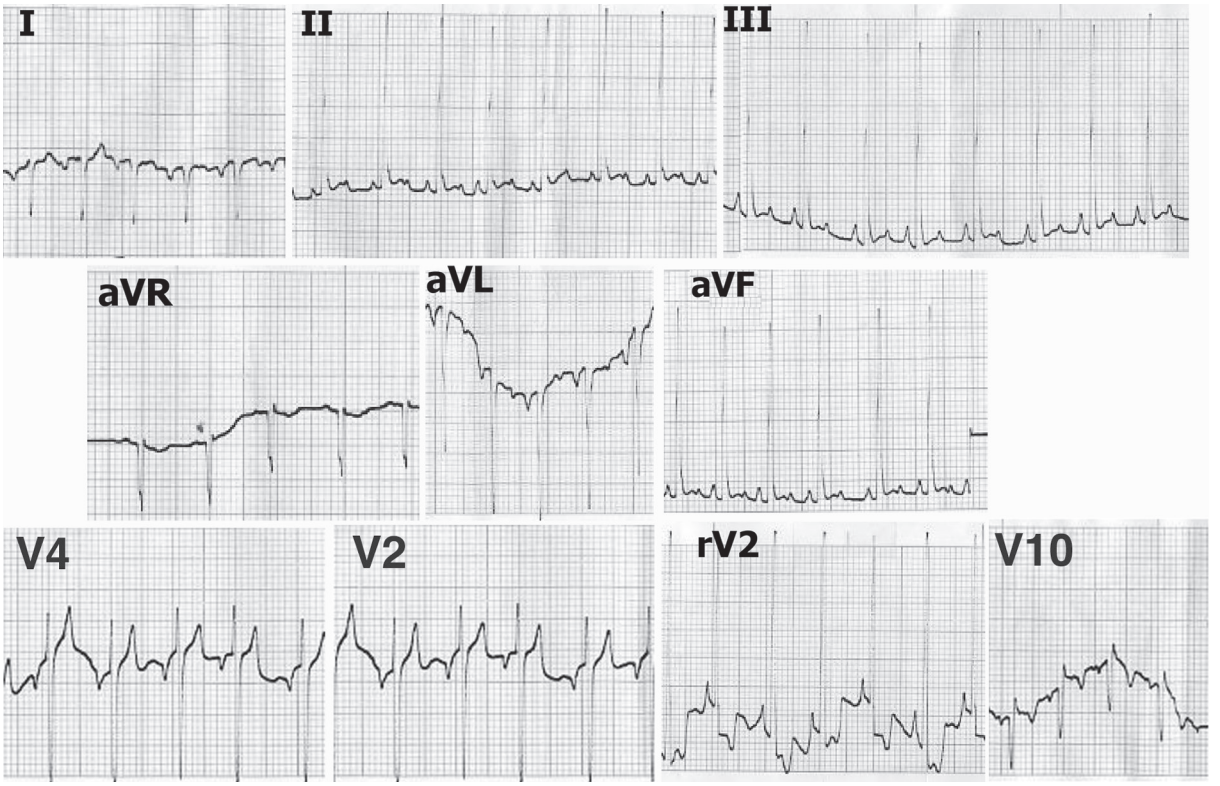

Figure 1. Six-lead standard ECG (I, II, III, aVR, aVL, aVF) – 25 mm/s – 10 mm/1mV – Heart rate: 150 bpm – Mean electric axis: +160°. The increased R-wave amplitude (> 2.5 mV) in limb leads II, III, and aVF is suggestive of left ventricular enlargement. The rightward shift of mean electrical axis, deep S waves in precordial chest leads CV6LU (V_4), and CV6LL (V_2), tall R-waves in precordial chest lead CV_5RL (rV2) are normally indicative of right ventricular enlargement.

diameter of 4 mm just under the tricuspid valve on the right side of the heart was observed (Figures 2B, 2C). The VSD had a post-stenotic location between the subaortic fibrous ring and the aortic cusps. Continuous Doppler interrogation through the defect revealed a high-velocity jet (peak velocity: 587 cm/s; peak pressure gradient: 138 mmHg) consistent with a small restrictive VSD with left to right shunting. A systolic blood flow velocity within the pulmonary outflow tract close to the upper limit of the normal range was also evident (peak velocity: 150 cm/s; peak pressure gradient: 9.93 mmHg) (normal peak velocity value: < 150 cm/s) (1). The echocardiographic findings were consistent with severe subaortic stenosis (SAS), aortic cusp dysplasia, restrictive VSD with left to right shunting, mild tricuspid and aortic insufficiency together with dextrocardia.

A new ECG performed with reversal of electrode placement, revealed a normal mean electrical axis (+60°) and only mild features of left ventricular enlargement. A 24-hour Holter electrocardiography showed several periods of sinoatrial arrests, but no malignant ventricular arrhythmias.

Lateral left-to-right, right-to-left and dorso-ventral thoracic radiographs showed an inversion of the cardiac aspect with the apex of the heart located to the right of mid-line, confirming the presence of dextrocardia (Figure 3A). The cardiac silhouette was rounded and enlarged [vertebral heart sum (VHS) = 12 v] (2). The caudal vena cava was on the left side of the spine and the diaphragmatic crura showed an inverted array. A vascular lung pattern was observed, characterized by mild dilation of pulmonary vessels. Bronchiectasis was not evident. Lateral and ventro-dorsal radiographs of the abdomen revealed that the gastric fundus and the head of the spleen were located within the right quadrant, and the left kidney was more cranial than the right (Figure 3B).

Chest computed tomography (CT), besides the dextrocardia, showed a complete inversion of the lung lobes and of the great vessels, and the right diaphragmatic bronchus compressed by the atrium (Figure 4). Abdominal CT demonstrated a total inversion of the abdominal organs and vessels. Skull CT did not show any anomalies. The nasal cavities and tympanic bullae were normal.

On the basis of the clinical and imaging findings a diagnosis of *situs inversus totalis* associated with congenital cardiac defects was made. In order to rule out the association of SIT and primary ciliary dyskinesia (PCD), or Kartagener's syndrome (KS), several endoscopic-guided biopsies of the bronchial epithelium were performed under general anesthesia. Specimens were fixed in 4% formaldehyde and 2.5% glutaraldehyde for light and transmission electron microscopy, respectively. The histopathological examination revealed a normal mucous epithelium and transmission electron microscopy showed normal ultrastructure of the cross-sectioned cilia. The dog was treated with propranolol (Inderal, AstraZeneca, Milan, Italy), 0.5 mg/kg body weight (BW), PO, q8h.

During a 10-month follow-up no syncopal episodes occurred and serial echocardiographic examinations did not show significant hemodynamic changes. After 15 mo from the first

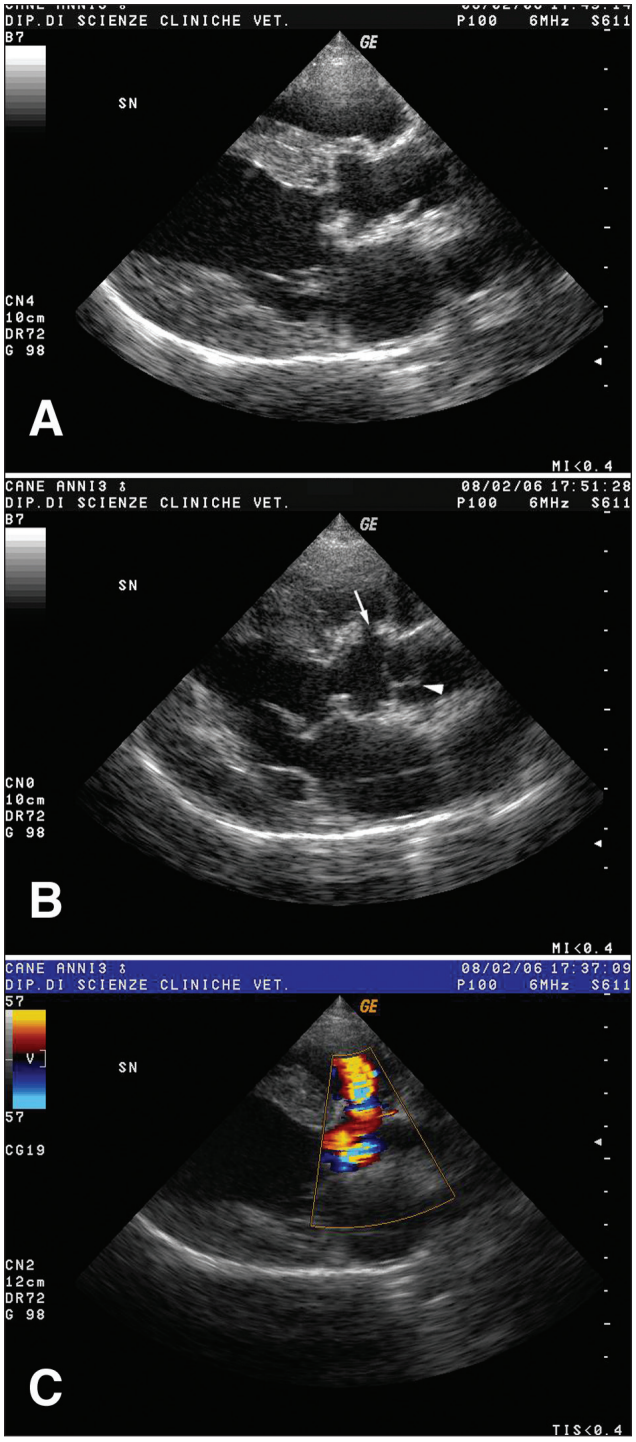

Figure 2. The 2-dimensional echocardiographic images obtained from the right and left parasternal standard views were inverted. Long-axis view of the left ventricular outflow tract recorded from the left apical parasternal location. **A** – A fixed discrete obstruction of the left ventricular out-flow tract is evident. **B** – A ventricular septal defect (4 mm) is evident at the septal base just below the aortic semilunar cusps (arrow). The left semilunar cusp is elongated (arrowhead). **C** – Color-flow doppler shows left to right shunting through the ventricular septal defect.

presentation, and 30 d following the last clinical check, the dog died suddenly in association with gastro-enteric disturbances, characterized by profuse diarrhea and vomiting.

A full postmortem examination was performed. The gross pathology findings of the heart were consistent with those previously identified on echocardiogram, radiographs, and CT. The tricuspid valve had only 2 cusps and a mild degree of tricuspid dysplasia was also evident, with the septal leaflet thick and incompletely developed. The chordae tendineae were also thick and short. Histopathology showed focal areas of myocardial fibrosis in the papillary muscles and subendocardial regions of the left ventricle associated with coronary arterial changes, gastric hyperemia, catarrhal enteritis, and moderate interstitial nephritis.

Discussion

This report describes a rare case of SIT in combination with a number of cardiac defects in an adult dog. *Situs inversus totalis* is a rare congenital malformation with complete reversal of organ placement within the body, producing an anatomical mirror-image of normal placement. The normal distribution of all the organs is described as *situs solitus.* In humans, SIT occurs in approximately 2 out of 10 000 live births and there is no gender predisposition (3). In individuals with SIT the primitive loop in the embryo moves in the reverse direction of its normal rotation for an altered ciliary movement, causing displacement of organs. Fifty percent of human patients with PCD have SIT (3). This clinical condition, characterized by the triad of signs consisting of rhinosinusitis, bronchiectasis, and SIT, is a subset of PCD known as Kartagener's syndrome. In humans the role of numerous genes with dominant and recessive inheritance in asymmetric development is under investigation. In the canine species there is little epidemiological data about SIT. In the veterinary literature SIT has been described several times as a part of KS or in association with various degrees of PCD (4–6). These dogs had severe respiratory abnormalities and short survival times. In our case there was no respiratory involvement, similar to 1 unique case previously described by Hough et al (7). Edwards et al (8) hypothesized an autosomal recessive mode of inheritance in a colony of English springer spaniel dogs with immotile-cilia syndrome, but there are no extensive genetic studies in dogs. It is likely that genetic defects and physiopathological mechanisms similar to humans also occur in dogs.

The pathogenetic mechanisms of SIT in the absence of abnormal ciliary movement are unclear. Experimental evidence showed that asymmetric gene expression during embryo development was involved in defects of laterality (9).

There is little data about concurrent SIT and congenital heart defects in dogs. In canine species SAS, VSD, and tricuspid dysplasia (TD) represent common congenital defects (SAS 35%; VSD 12.3%; TD 12%), but their association is rare (0.6%) (10). In humans, the estimated incidence of congenital heart diseases among individuals with SIT is low, ranging from 2% to 5% (3). Isolated dextrocardia without complete *situs inversus* is less common in humans (2 out of 20 000 live births) (11), but the association with congenital heart disease is high and up to 90% (3). In most cases congenital cardiac defects associated with SIT, or isolated dextrocardia, are complex and carry a poor prognosis (transposition of great arteries, double-outlet right ventricle, single ventricle, pulmonary atresia) (11). To the

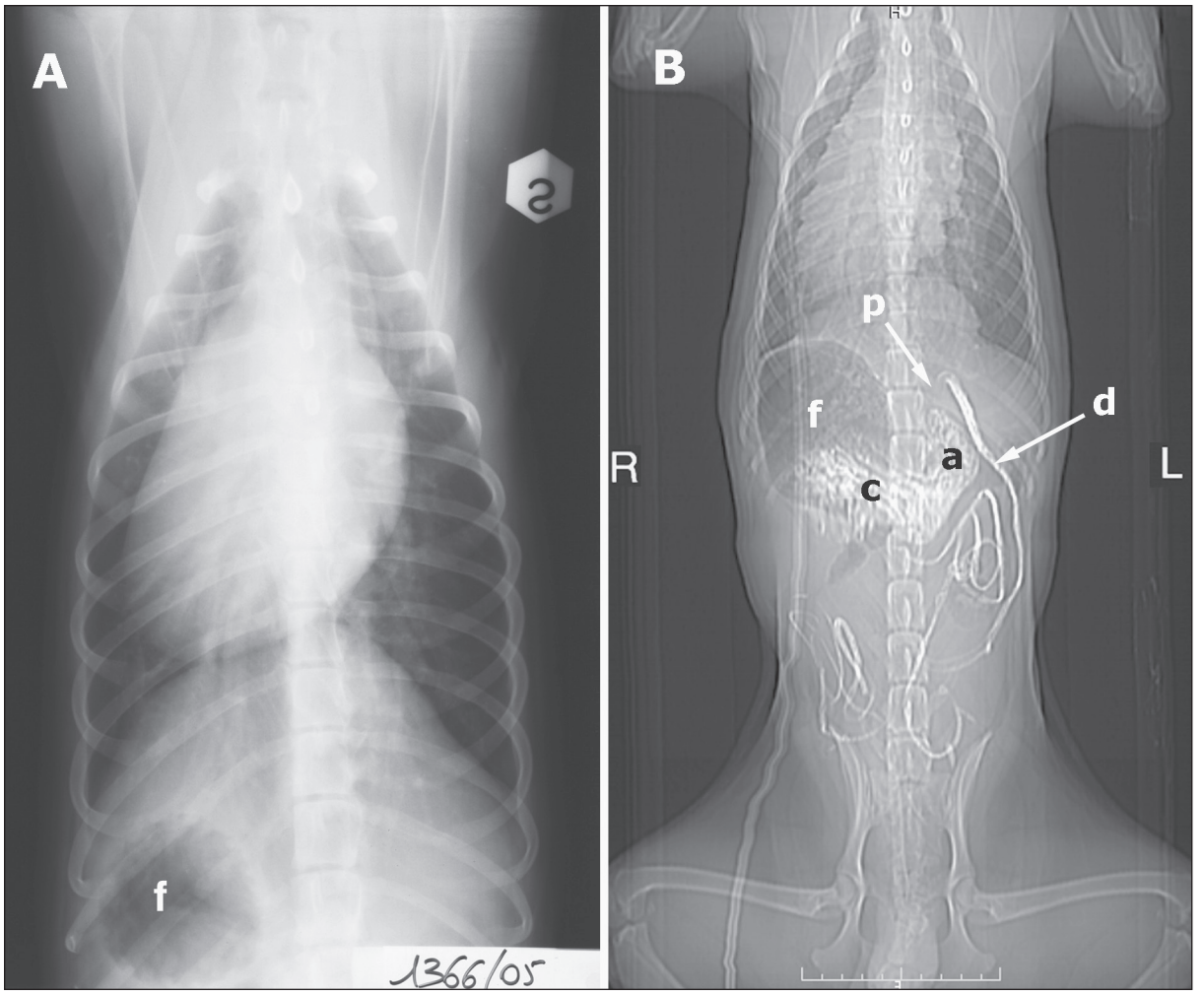

Figure 3. **A** – Thorax, dorso-ventral radiograph showing that the cardiac silhouette appears inverted and there is a left-sided enlargement (VHS 12 v). Mild dilation of the pulmonary vessels is evident. The fundus of the stomach (f) is on the right side. **B** – CT scout view of the entire body, after barium sulfate administration: there is a complete inversion of the gastro-intestinal arrangement (a – antrum; c – corpus; d – duodenum; f – fundus; p – pylorus).

authors' knowledge, the present case is the first report of SIT with concurrent SAS, VSD, aortic and tricuspid dysplasia in an adult dog without KS or PCD.

Reichler et al (12) described a case of a 9-month-old golden retriever bitch with PCD in combination with SIT, SAS, TD, and hydrocephalus with a poor prognosis. In the present case the absence of respiratory abnormalities due to normal mucociliary clearance, and the small-sized VSD characterized by no volume overload of the right ventricle, could explain the relatively favorable prognosis observed. In fact, despite the congenital cardiac defects and the syncopal episode, the dog did not show clinical signs of congestive heart failure during the follow-up. Although cardiac remodelling with myocardial fibrosis can be a consequence of severe SAS, it is not unusual for a dog with SAS to live for several years without developing congestive heart failure. Nevertheless a proportion of dogs with severe SAS will succumb to sudden cardiac death, presumably as a result of malignant arrhythmia (13).

The peak velocity measured through the defect by Doppler examination was lower than would be expected with the severity of the SAS and the resultant high left ventricular chamber systolic pressure. This low velocity is explained by the post-stenotic location of the VSD. The finding of left atrial enlargement can be explained by the left to right shunting of the VSD, probably in combination with the hemodynamic changes due to the severe SAS. The mild increase in the blood velocity across the pulmonic valve can be accounted for by the excess blood volume shunted through the VSD and flowing across a fixed orifice.

The cause of sudden death in this dog is not known. It is possible that the combination of subclinical renal failure due to interstitial nephritis and electrolytic imbalance secondary to the gastro-enteric disorders contributed to the dog's death. In any case, although this dog did not develop any symptoms after the first presentation, sudden death is a well-known complication with severe left ventricular outflow tract obstruction as a result of malignant ventricular arrhythmias.

A β-adrenergic blocking agent was employed in an attempt to prevent the arrhythmic effect of circulating catecholamines on the myocardium, a potential cause of sudden death. Furthermore, this anti-arrhythmic drug could have prevented myocardial ischemia, reducing myocardial oxygen demand and increasing coronary perfusion.

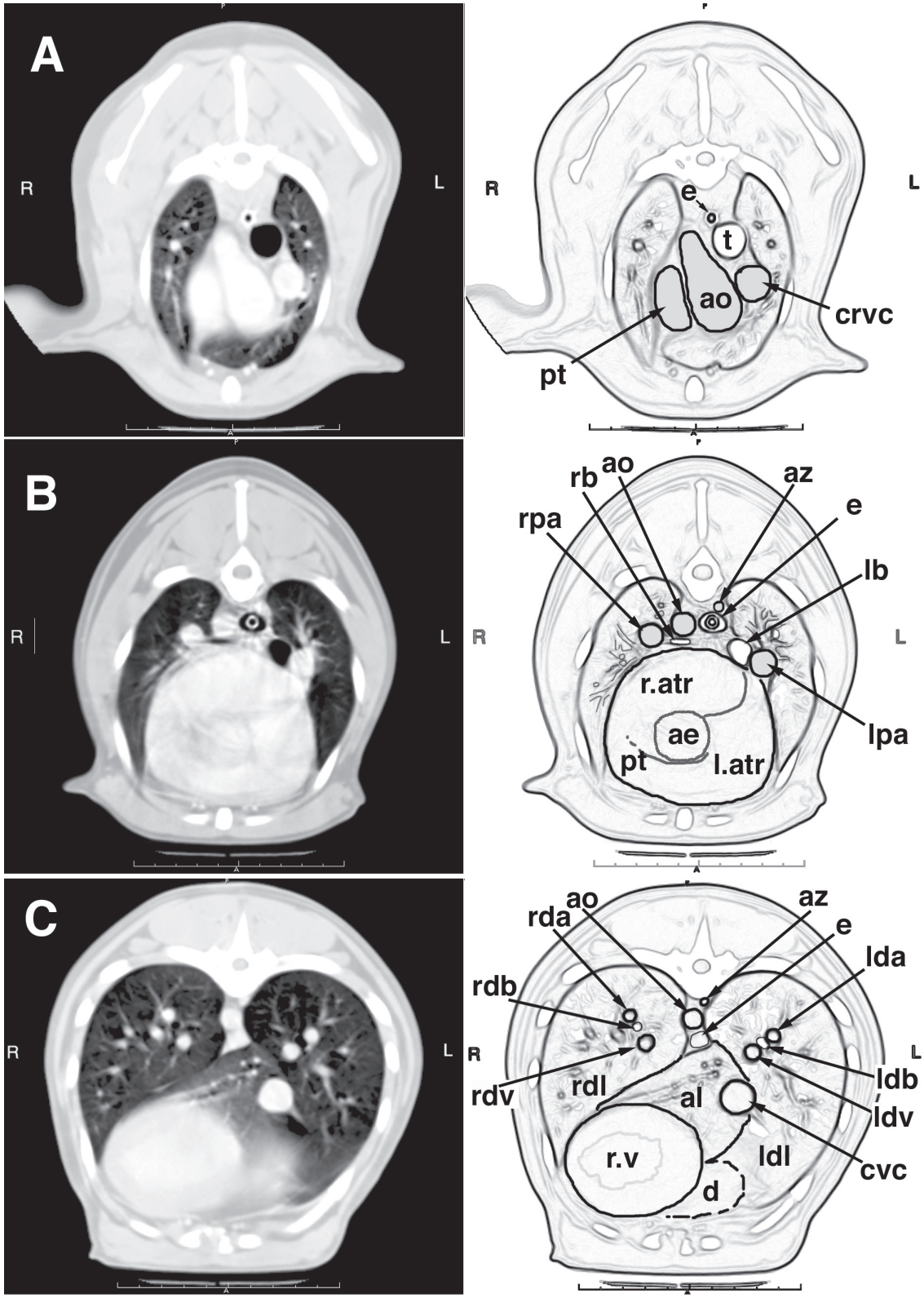

Figure 4. Thorax, CT scans after iodinated contrast administration. **A** – passing through the heart base: there is a complete inversion of the great vessels and mediastinal organ arrangement. **B** – passing through the atria and aortic root: the right bronchus is compressed between the right atrium and the aorta. **C** – passing through the cardiac apex: the caudal lung lobes are inverted and cardiac apex is on the right side. There is a dilation of the caudal vena cava and the diaphragmatic pulmonary veins (Legends: ao – aorta or aortic arch; ar – aortic root; al – accessory pulmonary lobe; az – azygos vein; cvc – caudal vena cava; crvc – cranial vena cava; d – diaphragm; e – esophagus; l.atr – left atrium; lb – left principal bronchus; lda – left diaphragmatic artery; ldb – left diaphragmatic bronchus; ldl – left diaphragmatic pulmonary lobe; ldv – left diaphragmatic vein; p t – pulmonary trunk; r.atr – right atrium; rb – right principal bronchus; rda – right diaphragmatic artery; rdb – right diaphragmatic bronchus; rdl – right diaphragmatic pulmonary lobe; rdv – right diaphragmatic vein; rpa – right pulmonary artery; r.v – right ventricle; t – trachea).

The findings of biventricular enlargement on the first ECG were misleading and the electrocardiographic standard patterns of dextrocardia are not established in dogs. In humans with dextrocardia the most pertinent findings on ECG are the global negativity in limb lead I (negative P-wave, QRS complex, and T-wave) and the reversed trend in amplitude of the QRS complex of the precordial chest leads. In a normal ECG there is a gradual increase in the amplitude of the R-wave from precordial leads V_1 to V_6, while in dextrocardia the QRS amplitude progression is reversed (14). In our case the negative P-wave and QRS complex in lead I, the right shift of mean electrical axis, the mirror-image pattern obtained in the precordial leads, similarly to humans, are consistent with dextrocardia, after ruling out ECG lead misplacements or the presence of right ventricular enlargement.

In conclusion, in canine species SIT is usually combined with KS or PCD. The occurrence of this organ malposition in association with cardiac malformations is rare. However, when SIT is diagnosed other congenital cardiac abnormalities should be ruled out, and a thorough respiratory examination should be performed to formulate an accurate prognosis.

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