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# Incomplete tracheal duplication associated with severe unilateral lung hypoplasia

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**Abstract**
A rare case of incomplete tracheal duplication with severe unilateral lung hypoplasia is presented. Photo-documentation of the gross post-mortem specimens is presented so that the anatomical aspects of this unusual anomaly can be recognized and appreciated. Clinical information is presented in the hope that successful premorbid identification of potential complications of this anomaly could be made by future physicians. To our knowledge, this is the first reported case of pathologically-confirmed duplication of the trachea.

**Key words: Trachea, Duplication; Lung; hypoplasia**

## Case report

A male infant was delivered by Caesarean section at a gestational age of 38 weeks and six days to a 32-year-old primagravida. The pregnancy was uncomplicated except for prolonged spontaneous rupture of membranes at 34 hours prior to delivery. APGAR scores were 8 and 8 at one and five minutes, respectively. Birthweight was 4000 grams. Marked respiratory distress and acute hypoxaemia developed shortly after birth. The cord blood gas indicated severe hypoxaemia. Satisfactory oxygen saturations were subsequently achieved after intubation with a 3.5 mm endotracheal tube (ETT), administration of surfactant, and high-frequency ventilation. A right pneumothorax developed, for which a chest tube was inserted. Chest X-ray, and ultrasonography demonstrated absence of the left lung with no evidence of diaphragmatic hernia. Echocardiography suggested only pulmonary hypertension. By the third day the $FiO_2$ was decreased to 21 per cent. Subsequently, worsening oxygen and ventilatory requirements developed. Extubation and re-intubation was attempted, suspecting endotracheal tube obstruction despite an apparently adequate ETT position by chest X-ray. A 3.5 mm endotracheal tube was passed easily below the vocal folds, yet chest wall movement was poor. Jet and oscillatory high frequency ventilation were tried unsuccessfully. Episodes of 'frozen chest' were exacerbated by neuromuscular blockade, which was reversed. Bedside flexible bronchoscopy via the endotracheal tube showed no obstruction beyond the endotracheal tube. What appeared to be a carina seemed to be of a normal configuration.

On the fifth day of life, in spite of ventilatory support, the infant's respiratory state worsened, and he was started on nitric oxide and transferred to the extra-corporeal membrane oxygenation (ECMO) centre of our institution. His condition deteriorated precipitously upon arrival, with persisting poor chest wall movement. Despite aggressive resuscitation efforts he expired.

A post-mortem genetics consultation noted the presence of several minor dysmorphic features, including tall forehead, short nose with depressed nasal bridge, long philtrum and small penis. Coupled with pulmonary hypoplasia, these features suggested the possibility of the deletion 22q11 syndrome. A peripheral blood karyotype was normal, 46, XY. A fluorescent in situ hybridization (FISH) study for deletion 22q11 was attempted on frozen fibroblasts but failed when the fibroblasts could not be revived. No other genetic diagnoses were suggested.

An autopsy six hours after death revealed incomplete tracheal duplication (Figure 1) and grossly abnormal tracheal cartilages. The left lung was severely hypoplastic and exhibited no evidence of lobation. The left pulmonary artery was also hypoplastic, while the left pulmonary veins were absent (Figure 2). Except for the absence of lobation, the right lung appeared grossly normal. The cardiovascular system was normal, aside from right ventricular hypertrophy.

Post-mortem endoscopy of the ex-vivo laryngotracheal-mediastinal contents was completed with a rigid 3.5 mm Hopkins' rod. The supraglottic, glottic, and subglottic anatomy appeared normal. The tracheal cartilages appeared incompletely formed and haphazardly arrayed. A bifurcation was noted 2.5 cm below the level of the vocal folds (normal tracheal length in a term infant is approximately 6 cm). No true carina was identified. The diameter of the right and left main 'tracheal' segments admitted a 2.5 mm endotracheal tube to 4 cm and 3 cm below the level of the vocal folds, respectively. Neither the left main tracheal segment, while externally larger than the right, nor the right, would admit a 3.5 mm ETT. The left segment was significantly hypoplastic with a small patent lumen. The common tracheal pars membranous was normal in appearance with no tracheo-esophageal communications found.

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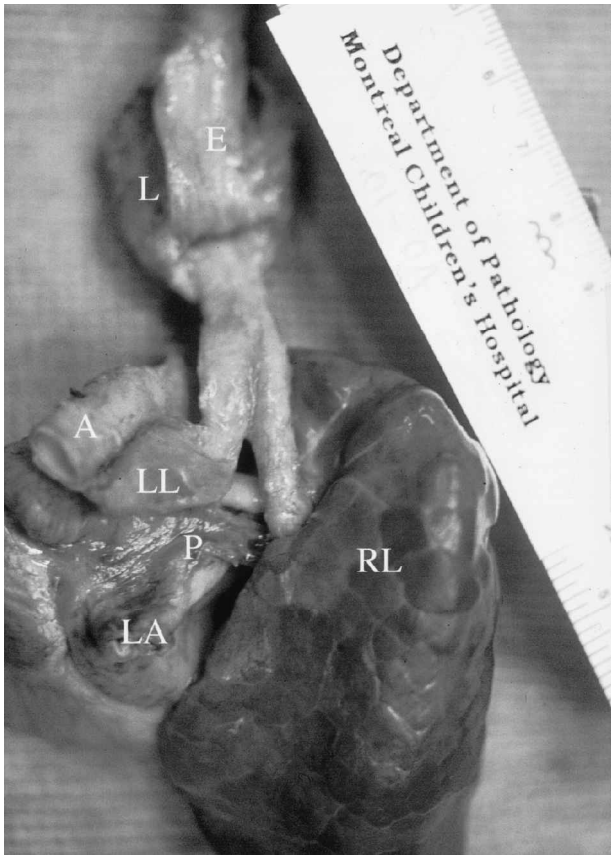


FIG. 1

Posterior view of the ex-vivo laryngotracheomediastinal contents. E oesophagus (cut and superiorly reflected), L larynx, A aortic arch (cut), P right pulmonary vessels, LA left atrium, LL (hypoplastic) left, and RL right lungs. Note the absence of lobation from the otherwise normal appearing right lung.

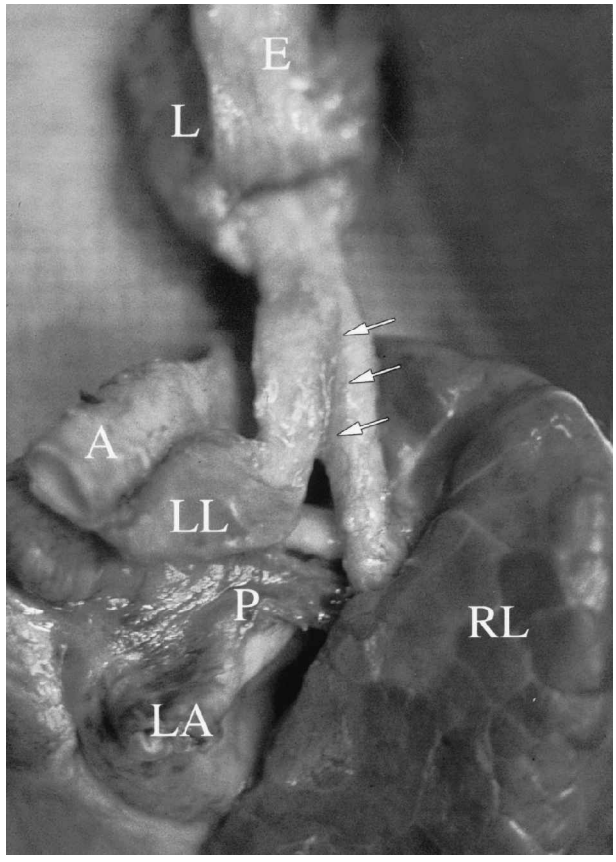


FIG. 2

Close-up view of Figure one demonstrating the left tracheal segment leading to a severely hypoplastic left lung, and the right tracheal segment leading to a fully-formed right lung. Note the absence of a carina, and the fibrous adhesions (arrows) between the two tracheal segments hinting at an incomplete duplication. A hypoplastic left pulmonary artery was discovered (hidden by the left lung), however no left pulmonary veins were identified. E oesophagus, L larynx, A aorta, P right pulmonary vessels, LL and RL left, and right lungs.

The tracheal cartilages (Figure 3) display evidence of a variable zipper-like midline division, suggesting incomplete (abortive) tracheal duplication. Figure 3 shows that, except for a normal appearing cricoid cartilage, none of the tracheal cartilages formed a complete 'C'.

A 1 cm renal abscess and a focus of bronchopneumonia was found, that had contributed to his demise. The remainder of the gross pathologic examination was unremarkable.

## Methods

After fixation, the technique for the dissection-clearing-staining of the post-mortem laryngotracheal tree was a slight modification of the method described by Landing and Wells,[1] with 70 per cent ethanol at an alcohol pH of 2–2.5 used for differentiation. The cartilage is stained with toluidine blue, and the soft tissue is cleared by Wintergreen oil (oil of Gaultheria or methyl salicylate).

## Discussion

Embryologically, the respiratory system normally forms as a midline, ventral diverticulum, that itself arises from the proximal foregut at 26 days gestation. Within 10 days, the laryngotracheal grooves appear laterally and deepen to form the tracheoesophageal septum. This process has long been thought to proceed in a cephalad direction, eventually separating the respiratory primordium from the oesophagus. Recent experiments suggest that, rather than cellular proliferation, pre-programmed cell death in the area designated as the tracheoesophageal septum is responsible for separation. Stable landmarks in the area indicate that no migration of the position occurs. Meanwhile, the respiratory diverticulum bifurcates to form the lung buds and a cartilaginous framework forms from surrounding mesenchymal tissue.

The laryngotracheobronchopulmonary anomalies that may arise from abnormalities of development forms a continuum, the most severe of which is agenesis of the trachea, an anomaly that is considered to be incompatible with life.[2,3] Animal experiments have shown that lung development depends on two primary factors: 1), the presence of a sufficient quantity of fluid in the lungs; and 2), the presence of adequate foetal breathing movements. Because fluid is breathed into the developing lungs via an obligatory oesophageal-bronchial fistula, pulmonary agenesis/aplasia is not a necessary consequence of tracheal agenesis. Rather, pulmonary agenesis implies an intrinsic failure of the lung primordia to develop properly. In contrast, pulmonary hypoplasia, a reduced number of pulmonary segments or terminal air sacs, usually represents a response to insufficient quantity of fluid in the lungs and, to restriction of the foetal breathing movements. The most common cause of pulmonary hypoplasia in humans is congenital diaphragmatic hernia.[4]

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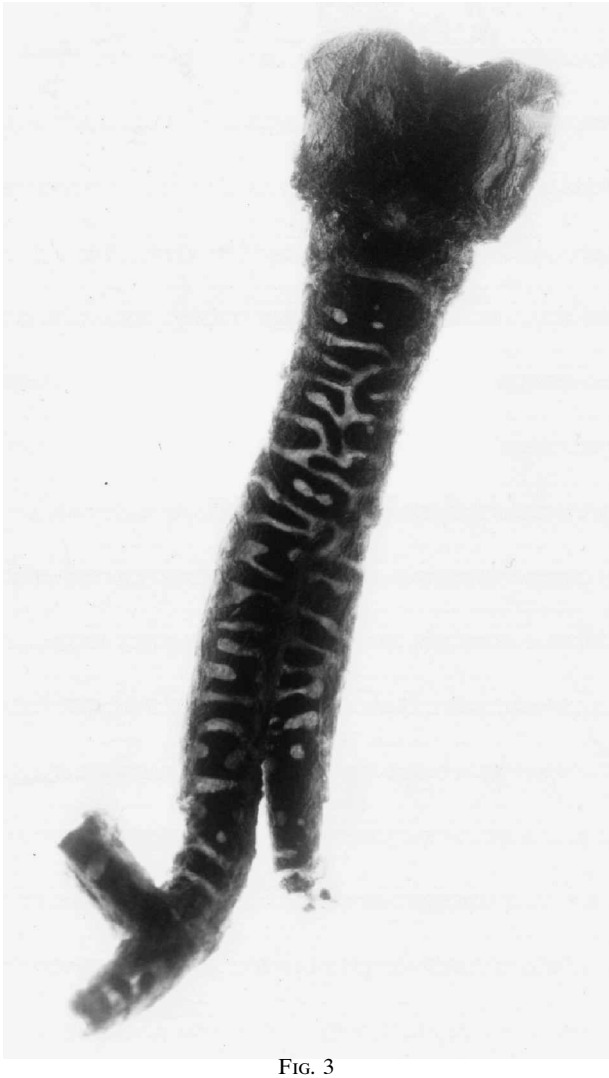

FIG. 3

Fixed-dissected-cleared laryngotracheal specimen stained for cartilage (black). Note the zipper-like appearance of the common tracheal segment, and absence of a carina. The cricoid cartilage appears normal. The left tracheal segment ends in a fibrocartilaginous hypoplastic segment without discernable primary bronchi. The right primary and secondary bronchial cartilaginous framework is unilaterally normal in size, number and configuration.

Oligohydramnios (Potter's syndrome) and anomalies of the great vessels (Scimitar syndrome) are also well-recognized aetiological factors. Pulmonary hypoplasia in the absence of volume loss in the pleural cavity is unusual. In the present case, the left lung hypoplasia may have resulted from the limitation of fluid flowing through the hypoplastic left tracheal segment during fetal breathing.

The association of foregut duplications with other multi-organ congenital malformations has been a topic of interest. The high incidence of associated anomalies has led some authors to suggest that foregut duplications may be one of the components of the VACTERL association (an expansion of the VACTER syndrome). This includes vertebral anomalies, anal atresia, cardiac anomalies, tracheoesophageal fistula and/or oesophageal atresia, renal malformations, and limb deformities. It can be seen that the main structures involved in the VACTERL association make their appearance from four to seven weeks (during the same period as the respiratory tree), these developmental errors seeming to arise before, or during, the second half of the embryonic period proper.[5] A

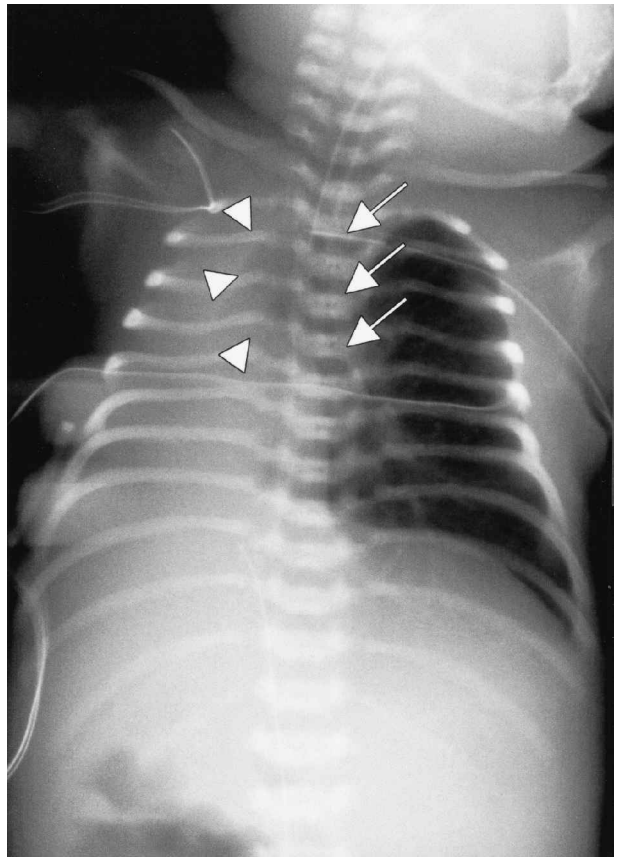

FIG. 4

Chest radiograph taken upon arrival at our institution. The tip of a 3.5 mm endotracheal tube (uppermost arrow) is visible at the T2 vertebral level. This would correspond to well within the right tracheal segment (selective right sided-intubation). The remainder of the right tracheal segment air column is well delineated (lower arrows). The hypoplastic left lung shadow is also seen (arrowheads). Note there is no corresponding left tracheal segment air column.

common pathogenesis for foregut duplications and anomalies of the VACTERL association have been made in animal models,[6] and maybe related to a shared ischaemic event experienced by these various primordia which have close anatomical proximity during that period. True bronchopulmonary foregut tubular duplications are exceedingly rare.

The cartilaginous support of the respiratory tree is mesenchymal in origin. Term neonates have a mean of 17 tracheal rings. Growth in the length of the trachea occurs secondarily to an increase in both the size and number of tracheal cartilaginous rings. A short trachea[7] is a consequence of a reduction in the number of rings to fewer than 15, resulting in transposition of the carina from its normal thoracic position, to a high thoracic, or even cervical one (T3 vertebral level or higher). A short trachea can be associated with DiGeorge syndrome (deletion 22q11), skeletal dysplasia, brevicollis, and myelomeningocele.[8] Clinically, patients with a short trachea exhibit a greater risk of bronchial intubation and its associated complications. Air bronchograms may be utilized to delineate tracheobronchial anatomy non-invasively prior to intubation in selected high risk patients. A post-intubation chest X-ray may also be utilized to delineate the right and left mainstem air columns in most cases. Normally, the right main stem bronchus is shorter and wider than the left, having three to five cartilaginous rings.

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The left, typically has nine.[1] Accidental bronchial intubation occurs more frequently on the right owing to this differential anatomy. Normally, a 3.5 mm endotracheal tube can be used to selectively intubate the right mainstem bronchus in a term newborn, permitting ventilation of the right lung. Impaction of the endotracheal tip's bevel at a high tracheal bifurcation with severe unilateral pulmonary hypoplasia may result in an unusual cause of 'frozen chest'. Poor chest movement may be the only clinical sign of a high tracheal bifurcation, despite apparently adequate ETT position by chest X-ray. In the case presented, postmortem examination determined that the tracheal bifurcation was high, and a 3.5 mm ETT could not be passed via either the right or left tracheal segments. The bevel of the ETT was located at the high bifurcation, and oriented so that the air entry to the right segment and lung were not optimized, accounting for the poor chest movement observed. Although a patent left tracheal segment was present at pathologic examination, a corresponding air column was not demonstrated on chest X-ray (Figure 4), a clinical point that may aid future physicians.

While cartilaginous respiratory tract anomalies similar to those reported here have been described in a patient while Ellis-van Crevald syndrome,[1] the present case lacks the short limbs, short ribs, polydactyly, and heart defect that characterize this condition. Inglis *et al*.[9] reported an interesting anomaly of the trachea, that of vertically-fused cartilages. In the four cases presented, however, three were associated with craniosynostosis, and the fourth with Goldenhar's syndrome. The lack of a similar phenotype, and the gross pathologic differences support the distinction of the process presented here.

The clinician should be cognizant of the more common tracheal anomalies. Tracheal bronchus, an aberrant bronchus that typically arises above the carina on the right side (in the absence of other respiratory tract abnormalities) is the result of an additional tracheal outgrowth early in embryonic life.[10] It is a pre-eparterial bronchus characteristically supplying the apical segment of the right upper lobe.[1] Incidence ranges from one to five per cent, and it is usually an incidental finding at bronchoscopy, or during accidental selective intubation. No specific therapy is indicated, unless it represents the underlying aetiology for chronic pulmonary disease.

Interestingly, infants with lung hypoplasia secondary to congenital diaphragmatic hernia seem to have higher rates of mortality and acute respiratory distress than those with isolated lung agenesis.[11] In pulmonary hypoplasia a mainstem bronchial remnant is present to communicate with an abnormally developed tracheal bifurcation. The size, shape and location of the mainstem bronchus on the affected side is expected to be distorted, however, the cartilaginous support is usually normal. Mediastinal shift, tracheal kinking, and retained secretions may result in acute distress and demise. Surgical intervention is usually indicated to correct the underlying diaphragmatic hernia. Pneumonectomy is not generally necessary in the neonatal period. In pulmonary agenesis the ipsilateral mainstem bronchus is absent, and the trachea continues directly to the mainstem bronchus of the normally developed side. Overall, persistent pulmonary hypertension is the most common cause of morbidity and mortality in neonates with congenital malformations of the lung,[12] as it was in the case presented. Primarily a clinical entity, haemodynamic findings on ultrasonography are consistent with the diagnosis, as would be their disappearance with appropriate management. Histopathologic signs of persistent pulmonary hypertension are rarely encountered. The infant presented here was at high risk for persistent pulmonary hypertension owing to the severe left pulmonary hypoplasia. Generally, this is a major cause of potentially reversible cardiorespiratory compromise. Contemporary management includes the avoidance of hypoxaemia, acidosis, agitation and hypotension. The widespread use of nitric oxide and high frequency ventilation have made it possible to stabilize many infants without ECMO. The role of ECMO in medical management of persistent pulmonary hypertension is still evolving, however, its use in the setting of pulmonary hypoplasia secondary to congenital diaphragmatic hernia has been accepted by many institutions.[13]

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