






Holt-Oram Syndrome with Pulmonary Involvement—A Valuable Algorithm to Follow

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Abstract

Holt-Oram syndrome comprises a rare spectrum of congenital cardiovascular and appendicular skeletal anomalies. However, only a few cases have reported lung involvement in Holt-Oram syndrome. We reported the rare case of a 1-year-old male child patient who presented with upper limb abnormalities and respiratory distress and was diagnosed with pulmonary agenesis and pulmonary arterial hypertension secondary to an atrial septal defect.

Keywords

- ▶ lung agenesis
- ▶ Holt-Oram syndrome
- ▶ posterior lung herniation
- ▶ horseshoe lung
- ▶ cardiac limb syndrome

Introduction

Holt-Oram syndrome (HOS) comprises a rare spectrum of congenital cardiovascular and preaxial skeletal anomalies with a prevalence of 1 in 100,000 live births.¹ HOS has an autosomal dominant inheritance with variable expression.² However, lung involvement in HOS was only reported in a few cases with severe respiratory distress.^{2–5} Various lung anomalies have been reported along with HOS.^{2–4} We suggest an algorithm for classifying lung abnormalities in cases of HOS.

Clinical Presentation

A 1-year-old male child patient presented with dyspnea and suboptimal weight gain in the last 3 months. There were no episodes of cyanosis or recurrent respiratory tract infections associated with dyspnea.

He was first in birth order from a nonconsanguineous marriage and had a preterm vaginal delivery at 34 weeks. He weighed 2.3 kg at birth and was identified with right upper limb abnormalities and respiratory distress soon after. He received standard neonatal care and was discharged at 4 weeks of age on improvement. On examination, his right thumb was absent with deformation of the forearm, which was confirmed by an upper limb X-ray (▶ **Fig. 1A, B**). His oxygen saturation at room air was 99%.

The chest X-ray showed a dextroposed heart and a significant deviation of the trachea with mild hyperinflation of the left lung (▶ **Fig. 1C**). The aerated area of the right hemithorax showed a straight border on the medial side and a convex border on the lateral side, classical of posterior lung herniation.⁶ Additional vertebral anomalies were identified by computed tomography (CT) (▶ **Fig. 1D**). Echocardiography revealed a large atrial septal defect (ASD) of the ostium secundum with a 1.5:1 shunt and moderate pulmonary hypertension.

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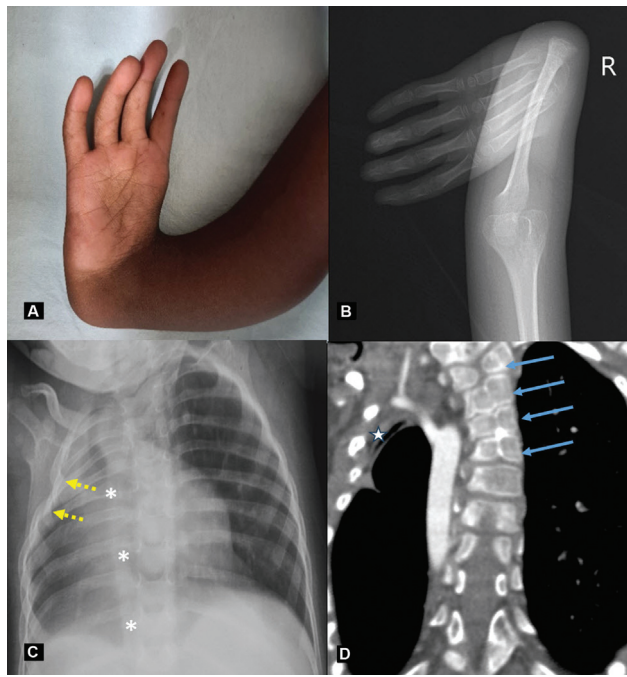


Fig. 1 (A) Clinical photograph of right hand showing absent thumb and inward curvature of the forearm and (B) X-ray of right forearm showing absent radius and thumb. (C) Chest X-ray in posteroanterior (PA) shows volume loss and rib crowding (yellow dotted arrows) in right hemithorax with right-sided mediastinal shift and convex outer contour of lung suggesting hyperinflation. Medial border of lung on the right side is straight along the descending thoracic aorta (*). A significant deviation of the trachea to the right by the aortic arch is also noted. (D) Butterfly vertebrae are noted between D1 and D4 levels (blue arrows) in coronal computed tomography (CT) section.

Cardiac CT showed the absence of the right mainstem bronchus, right pulmonary artery, and right pulmonary veins (→**Fig. 2A**), suggestive of right lung agenesis. Dextroposition of the heart, large ASD, and dilatation of the right atrium and ventricle were the significant cardiac abnormalities identified (→**Fig. 2B**). Normal arrangement of visceral organs was noted in inferior sections of cardiac CT (→**Fig. 2C**). The lung parenchyma occupying the right hemithorax was hyperinflated and received its pulmonary artery supply and pulmonary venous drainage from the left side, suggesting a posterior herniation of the left lung (→**Fig. 2D, E**). There was marked deviation of the trachea and esophagus to right and anteriorly and the descending thoracic aorta (DTA) to the right of midline, with the medial segment of the left lower lobe herniating between the esophagus and DTA and reaching the lateral border of the right hemithorax (→**Fig. 2D–F**).

The patient underwent a surgical ASD closure, and follow-up echocardiography at 3 and 6 months showed reduced

severity of pulmonary artery hypertension and improved symptoms. Weight gain of the child was 40% over the next 6 months.

Discussion

HOS is an important cardiac-limb syndrome with classic involvement of the preaxial skeleton of the upper extremity and involvement of the cardiac septum or conduction bundles.⁷ The *TBX5* gene, located on chromosome 12q24.1, is considered a plausible triggering event in multiorgan involvement but occurs with variable penetrance, resulting in many dominant carriers not being identified.⁸ The cooccurrence of various other mutations also leads to several additional clinical features unrelated to HOS diagnosis.⁷

Lung involvement in HOS has been described only in a few cases. Kullmann et al described pulmonary involvement in an infant with HOS for the first time.⁵ The first case of right lung agenesis associated with HOS was reported in 2007 by Tseng et al, but a CT image has not been published.² There is a reduction in fibroblast growth factor (*FGF10*) expression in *TBX5* mutation, resulting in failure of mesenchymal induction of epithelial branching and the absence of a right lung bud.⁸ In 2015, a case of HOS with left lung hypoplasia and right-sided horseshoe lung was reported, although *TBX5* genetic mutation was not identified.⁴ Notably, the right lung was more involved in HOS.⁴ Genetic testing could not be done on our patient.

A method for distinguishing horseshoe lung from posterior lung herniation was described by Kim et al, where the location of the herniated lung anterior to the esophagus and aorta was common in horseshoe lung while a location in between the esophagus and aorta was noted in posterior lung herniation.⁶ Another difference is that the horseshoe lung develops in contralateral lung hypoplasia, whereas posterior lung herniation is noted in contralateral lung agenesis. This is probably the first posterior lung herniation ever reported, along with right lung agenesis in a patient with clinical HOS.⁶ Below is the algorithm for distinguishing the spectrum of right lung hypoplasia in HOS (→**Fig. 3**). Differentiating between lung hypoplasia and lung agenesis was necessary for planning the appropriate anesthesia strategy during endotracheal intubation during and after surgery.

Conclusion

Pulmonary anomalies in HOS are infrequent and its identification mandates an algorithmic approach to predict accurate diagnosis.

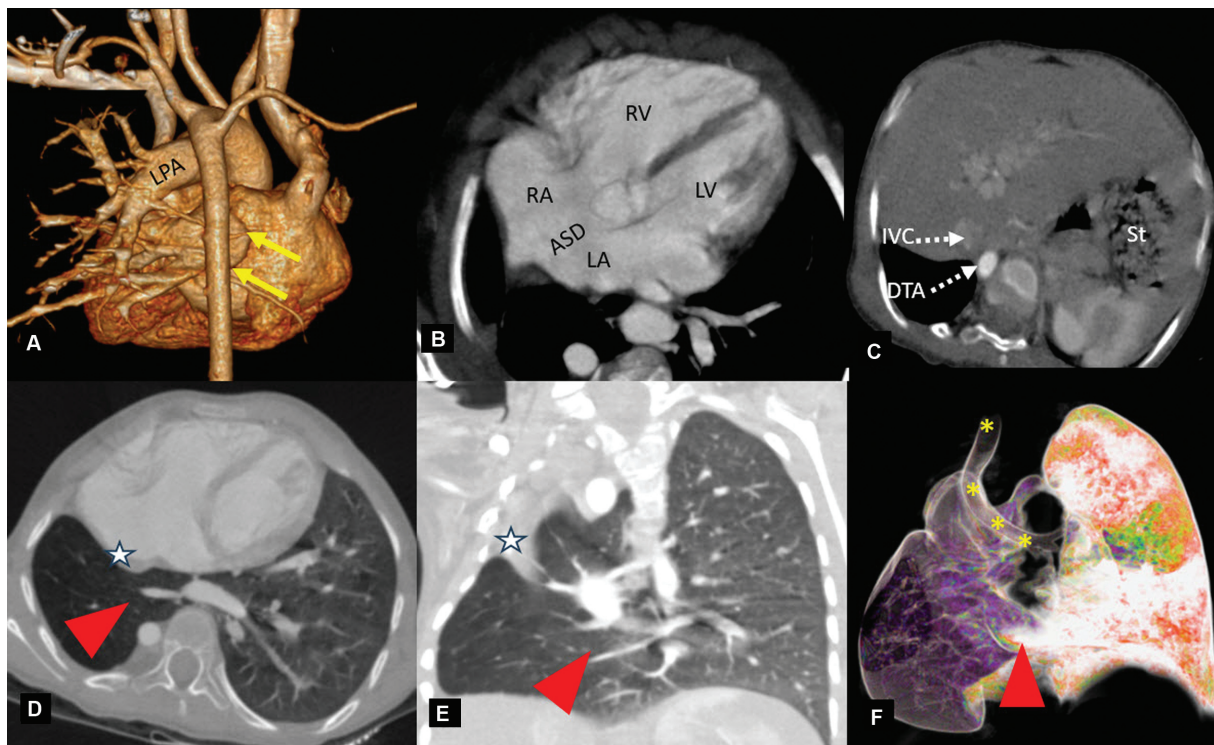


Fig. 2 (A) Three-dimensional volume rendering technique (3D VRT) image of the heart and great vessels from the posterior shows absent pulmonary venous drainage on the right side (yellow arrows) and a small lower lobe vein from the right joining the left lower pulmonary vein. The absence of the right pulmonary artery branch from the main pulmonary artery (MPA) is also noted. (B) Four-chamber view of ventricles shows a large atrial septal defect (ASD) and dilation of the right atrium and ventricle. (C) The axial section of the abdomen in cardiac computed tomography (CT) shows a normal visceral arrangement with the liver on the right and gastric bubble on the left side. (D) Axial, (E) oblique coronal, and (F) 3D VRT images from the minimum intensity projections of lung fields show herniation (red arrowhead) of the medial and lower part of the left lung to right hemithorax posterior to the heart in between anterior esophagus (denoted by ☆) and posterior descending thoracic aorta (DTA). The herniated lung is more hypodense compared with left-sided lung lobes. Right ward displacement of trachea along with the absence of right bronchus is noted in (F), denoted by *.

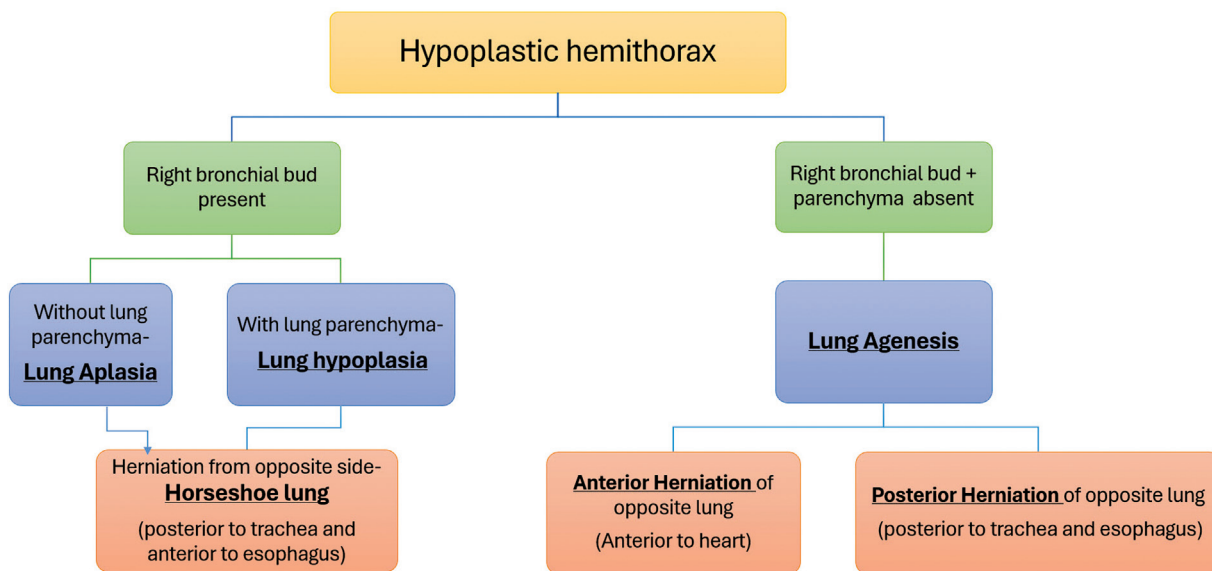


Fig. 3 Algorithm for diagnosing various pulmonary pathologies in hypoplastic right hemithorax in Holt-Oram syndrome covering the different variations.

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None.

Conflict of Interest

None declared.

References

- 1 Elek C, Vitéz M, Czeizel E. Holt-Oram syndrome [in Hungarian]. *Orv Hetil* 1991;132(02):73–74, 77–78
- 2 Tseng Y-R, Su Y-N, Lu FL, et al. Holt-Oram syndrome with right lung agenesis caused by a de novo mutation in the TBX5 gene. *Am J Med Genet A* 2007;143A(09):1012–1014
- 3 Smets K, Mortier G, Zecic A. Perinatal/neonatal case presentation: unexpected severe respiratory insufficiency in a newborn with Holt-Oram syndrome. *J Perinatol* 2005;25(11):745–746
- 4 Qin X, Wei W, Fangqi G. Horseshoe lung associated with Holt-Oram syndrome. *Iran J Pediatr* 2015;25(02):e251
- 5 Kullmann F, Koch R, Feichtinger W, Giesen H, Schmid M, Grimm T. Holt-Oram syndrome in combination with reciprocal translocation, lung hypoplasia and cardiomyopathy [in German]. *Klin Padiatr* 1993;205(03):185–189
- 6 Kim JY, Kim WS, Lee KS, et al. Posterior lung herniation in pulmonary agenesis and aplasia: chest radiograph and cross-sectional imaging correlation. *Korean J Radiol* 2021;22(10):1690–1696
- 7 Al-Qattan MM, Abou Al-Shaar H. Molecular basis of the clinical features of Holt-Oram syndrome resulting from missense and extended protein mutations of the TBX5 gene as well as TBX5 intragenic duplications. *Gene* 2015;560(02):129–136
- 8 Cebra-Thomas JA, Bromer J, Gardner R, Lam GK, Sheipe H, Gilbert SF. T-box gene products are required for mesenchymal induction of epithelial branching in the embryonic mouse lung. *Dev Dyn* 2003;226(01):82–90