CASE REPORT

Holt-Oram Syndrome and Pulmonary Artery Sling with Tracheal Stenosis: A Case Report of a Rare Combination of Two Rare Diseases

Pailin Ratanawatkul, MD[1], Wipa Reechaipichitkul, MD[1], Worawat Chumpangern, MD[1], Itthiphat Arunsurat, MD[1], Burabha Pussadhamma, MD[2]

[1] Division of Pulmonary and Critical Care Medicine, Department of Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand

[2] Division of Cardiology, Department of Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand

Background: Holt-Oram syndrome is a rare genetic disorder characterized by abnormalities in the upper extremities and commonly associated with heart problems. Pulmonary arterial sling is a congenital disorder in which the left pulmonary artery originates from the right pulmonary artery, encircling the trachea or esophagus. The authors report a unique case involving the rare combination of these two distinct diseases.

Case Report: A 21-year-old female presented with fever, wheezing, and respiratory failure. Physical examination revealed central rhonchi, a loud P2, systolic ejection murmur, and radial polydactyly on both hands. The electrocardiogram displayed sinus tachycardia and a notch in the QRS complex in all inferior leads, consistent with the Crochetage sign, suggesting an atrial septal defect (ASD). After intubation, elevated peak airway pressure was detected. Bronchoscopy identified circumferential narrowing of the trachea. CT chest revealed a pulmonary arterial sling wrapping around the trachea. Echocardiography confirmed the presence of ASD and pulmonary hypertension.

Conclusion: This case represents the co-occurrence of Holt-Oram syndrome, a heart-hand syndrome, with a pulmonary arterial sling. Pulmonary infection in this case exacerbated pulmonary hypertension, resulting in increased constriction of the sling and compromised airway function.

Keywords: Holt-Oram syndrome; Pulmonary arterial sling; Tracheal stenosis; Heart-hand syndrome; Atrial septal defect

Received 1 April 2024| Revised 28 May 2024| Accepted 4 June 2024

J Med Assoc Thai 2024;107(Suppl. 1):S157-60

Website: http://www.jmatonline.com

Holt-Oram syndrome is a rare autosomal dominant genetic disorder characterized by upper extremity bone abnormalities and heart problems, collectively known as heart-hand syndromes(1). Pulmonary artery sling (PAS) is a rare congenital cardiovascular disease in which one main pulmonary artery arises from the contralateral main pulmonary artery, encircling the trachea or esophagus. If the ring surrounds the trachea, it can cause tracheal stenosis (TS) and compromised respiratory function(2). Such patients may present with central wheezing, especially during forceful expiratory maneuvers, leading to misdiagnosis as asthma. Our case report presents the uncommon coexistence of these two rare diseases.

Correspondence to:

Ratanawatkul P.

Division of Pulmonary and Critical Care Medicine, Department of Medicine, Faculty of Medicine, Khon Kaen University, 123 Moo 16, Mittraphap Road, Nai-Muang, Muang, Khon Kaen 40002, Thailand.

Phone: +66-62-1496551

Email: pailin@kku.ac.th

How to cite this article:

Ratanawatkul P, Reechaipichitkul W, Chumpangern W, Arunsurat I, Pussadhamma B. Holt-Oram Syndrome and Pulmonary Artery Sling with Tracheal Stenosis: A Case Report of a Rare Combination of Two Rare Diseases. J Med Assoc Thai 2024;107(Suppl.1):S157-60

DOI: 10.35755/jmedassocthai.2024.S01.S157-S160

Case Report

A 21-year-old female presented with fever, shortness of breath, and wheezing for three days. She arrived at our hospital with acute respiratory failure and hypotension. She had been diagnosed with asthma and received treatment for ten years due to a history of wheezing and exertional dyspnea. Initial vital signs revealed a blood pressure of 49/22 mmHg, heart rate of 149 bpm, respiratory rate of 30/min, and SpO_2 (room air) of 80%. Physical examination showed poor air entry in both lungs with inspiratory and expiratory rhonchi at the sub-sternal area. The patient exhibited grunting and air grasping. Cardiac examination revealed right ventricular heaving, loud P2, and a systolic ejection murmur grade II at the left upper parasternal border. Radial polydactyly was observed in both upper extremities (Figure 1A). Chest X-ray displayed bilateral alveolar infiltrations. Immediate endotracheal intubation and assisted ventilation were performed. High peak airway pressure was detected, with respiratory system compliance at 15 ml/cmH_2O and airway

resistance at 55 $cmH_2O/L/sec$. Fiberoptic bronchoscopy revealed circumferential tracheal narrowing (Figure 1B). Computed tomography (CT) of the chest confirmed the presence of a pulmonary artery sling, formed by the left pulmonary artery arising from the right main pulmonary artery, causing long-segment circumferential tracheal narrowing (Figure 1C). Enlargement of the pulmonary trunk, hypertrophy of the right ventricle, and right atrium were also noted. Electrocardiogram (ECG) demonstrated notching on the QRS complex in all inferior leads, consistent with the Crochetage sign (Figure 2), a specific indicator of atrial septal defect (ASD). Echocardiography revealed a secundum ASD size 2.3 centimeters (Figure 3) and pulmonary hypertension. Right heart catheterization displayed a mean pulmonary arterial pressure (mPAP) of 45 mmHg, pulmonary vascular resistance (PVR) of 5.7 wood units, pulmonary capillary wedge pressure (PCWP) of 17 mmHg, and the ratio between pulmonary and systemic flow (Qp/Qs) of 2.18, indicating a left-to-right shunt. Antibiotic, diuretic, inotrope, vasopressor, and a pulmonary vasodilator were administered, resulting in clinical improvement and a decrease in airway resistance. A cardiothoracic surgeon was consulted for definitive surgical management; however, the patient passed away before the scheduled surgery due to septic shock.

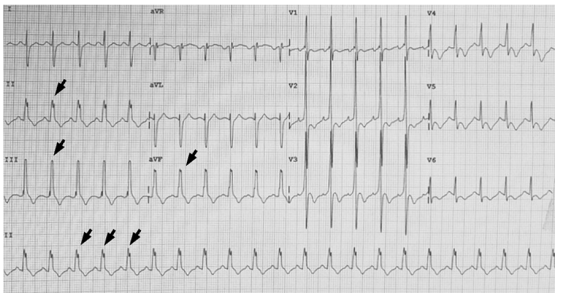

Figure 2. Electrocardiogram demonstrated "Crochetage sign" or notching R wave on inferior limb leads.

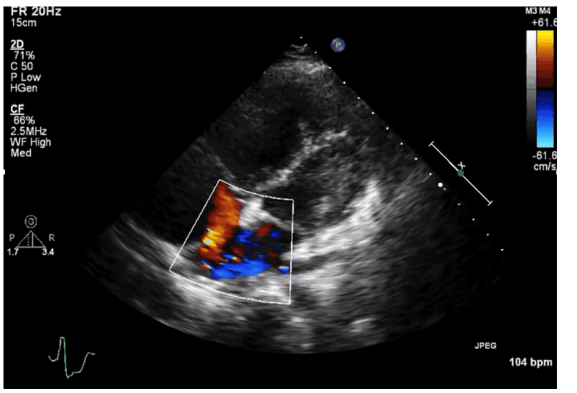

Figure 3. Color doppler echocardiography demonstrated secondum atrial septum defect.

Discussion and Conclusions

Tracheal stenosis (TS) can develop due to various causes, including 1) intraluminal injury such as post-extubation or injuries from tracheostomy; 2) external compression from a tumor, lymph node, adjacent vascular, or other nearby structure; 3) inflammation such as relapsing polychondritis, tracheal papillomatosis, sarcoidosis, amyloidosis, or granulomatosis with polyangiitis; 4) post-radiation; 5) infection such as invasive pulmonary aspergillosis or post-endobronchial tuberculosis, etc.; and 6) congenital structural malformation[3,4]. Patients with TS typically present with symptoms such as cough, shortness of breath, especially during exertion, stridor, central monotonic wheezing that is refractory to bronchodilators, cyanosis, dysphagia, or recurrent pneumonia. TS patients are occasionally misdiagnosed as having asthma. Treatment modalities for TS vary based on the underlying cause such as anti-microbial for infection, anti-inflammatory for autoimmune disease or chemotherapy for cancer compression, and may include tracheal surgical reconstruction, laser therapy, bronchoscopic balloon dilatation, and tracheal stenting[4]. In our case, TS was caused by external compression from PAS, worsened by deteriorating pulmonary hypertension resulting from hypoxic pulmonary vasoconstriction induced by pneumonia.

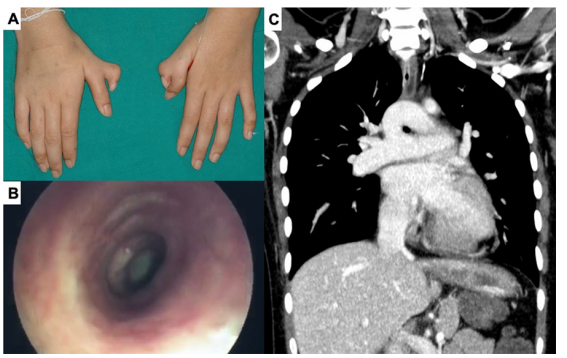

Figure 1. A) Radial polydactyly on both upper extremities, B) Circumferential tracheal stenosis from bronchoscope view, C) Pulmonary arterial sling (PAS) from CT pulmonary angiogram.

PAS accounts for 20 to 60% of congenital TS cases[2,5]. PAS is characterized by the aberrant origin of one main pulmonary artery from the contralateral main pulmonary artery, with the common type being a left pulmonary artery arising from the superior and posterior aspect of the right main pulmonary artery. Complete ring formation is observed in up to 80% of cases of PAS[6]. Symptom severity tends to escalate when the ring is completely formed. Coexisting intracardiac anomalies are found in approximately 30% of PAS cases[6]. In our case, a secundum

ASD was identified through observations of a heart murmur and electrocardiogram (ECG) finding of the Crochetage sign. This Crochetage sign, characterized by notching in the R wave of inferior leads resembling a crochet needle, is highly specific to secundum ASD[7]. Other reported cardiac conditions associated with PAS include patent ductus arteriosus (PDA), ventricular septal defect (VSD), left subclavian vena cava (LSVC), tetralogy of Fallot (TOF), hypoplastic lung, absent lung, and bridging bronchus. Additionally, radial polydactyly observed in both hands of our patient contributed to the diagnosis of "Holt-Oram syndrome".

Holt-Oram syndrome (Mandelian Inheritance in Man (MIM) No. 142900), first described by Holt and Oram in 1960, is a complex congenital syndrome and a prototype of heart-hand syndromes[1]. The genetic abnormality is located on the long arm of chromosome 12 (12q2)[8]. Mutations in the TBX5 gene are the underlying culprit and can be identified in up to 74% of cases[9]. The TBX5 gene is expressed in the embryonic heart and forelimbs, governing the transcription of downstream genes. Consequently, mutations in this gene lead to anomalies in both hand and heart development[10]. Differential diagnoses of Holt-Oram syndrome include heart-hand syndrome type II (Tobatznik's syndrome) and heart-hand syndrome type III (MIM No. 140450); however, atrial septal defects are usually absent in the latter two conditions[11]. Holt-Oram syndrome is transmitted as an autosomal dominant trait with high penetrance; however, 85% of cases arise from new mutations[8]. Limb malformations may range from mild thumb abnormalities to the complete absence of the arm or even additional phocomelia. Abnormalities can be present on either the unilateral or bilateral sides, with a predilection for the left rather than the right side and typically sparing the lower limbs[10,12]. Commonly affected areas include the radial, carpal, and thenar regions[8]. Approximately 50% of individuals with Holt-Oram syndrome manifest cardiac malformations. Commonly observed cardiac abnormalities were atrial and ventricular septal defects. Additionally, cardiac conduction abnormalities, such as sinus bradycardia and varying degrees of atrioventricular block, are also frequently found[12]. The prevalence of Holt-Oram syndrome has been estimated at 0.95 per 100,000 total births[8]. Prenatal genetic diagnosis is recommended for pregnant individuals with a family history of Holt-Oram syndrome. Treatment is directed at managing associated cardiac conditions.

Conclusion

The present case report highlights the rare coexistence of Holt-Oram syndrome and pulmonary artery sling, contributing to tracheal stenosis exacerbated by worsening pulmonary hypertension. This complex clinical presentation emphasizes the importance of a thorough diagnostic approach and multidisciplinary management in cases involving rare and concomitant congenital disorders.

What is already known on this topic?

Holt-Oram syndrome is a genetic disorder characterized by anomalies in the upper extremity bones and concomitant heart disorders. Another congenital disorder, pulmonary arterial sling, manifests as the left pulmonary artery originating from the right pulmonary artery, forming a loop around the trachea or esophagus.

What this study adds?

We unveiled a rare case where Holt-Oram syndrome and pulmonary arterial sling are both present. The presence of an infection induced hypoxic pulmonary vasoconstriction, intensifying pulmonary hypertension and accentuating tracheal stenosis associated with pulmonary arterial sling.

Conflicts of interest

The authors declare no conflict of interest.

References

1. Holt M, Oram S. Familial heart disease with skeletal malformations. Br Heart J 1960;22:236-42.
2. Landing BH, Dixon LG. Congenital malformations and genetic disorders of the respiratory tract (larynx, trachea, bronchi, and lungs). Am Rev Respir Dis 1979;120:151-85.
3. Al-Qadi MO, Artenstein AW, Braman SS. The "forgotten zone": acquired disorders of the trachea in adults. Respir Med 2013;107:1301-13.
4. Bacon JL, Patterson CM, Madden BP. Indications and interventional options for non-resectable tracheal stenosis. J Thorac Dis 2014;6:258-70.
5. Tanh NTV, Thach PN, Phong LS, Ngoc LTD, Nguyen PT, Van Anh Dung H, et al. Tracheal reconstruction surgery for congenital tracheal stenosis. Pediatr Surg Int 2023;39:123.
6. Backer CL, Russell HM, Kaushal S, Rastatter JC, Rigsby CK, Holinger LD. Pulmonary artery sling: current results with cardiopulmonary bypass. J Thorac Cardiovasc Surg 2012;143:144-51.
7. Heller J, Hagège AA, Besse B, Desnos M, Marie FN, Guerot C. "Crochetage" (notch) on R wave in inferior limb leads: a new independent electrocardiographic sign of atrial septal defect. J Am Coll Cardiol 1996;27:877-82.
8. Basson CT, Cowley GS, Solomon SD, Weissman B, Poznanski AK, Traill TA, et al. The clinical and genetic spectrum of the Holt-Oram syndrome (heart-hand syndrome). N Engl J Med 1994;330:885-91.
9. Cross SJ, Ching YH, Li QY, Armstrong-Buisseret L, Spranger S, Lyonnet S, et al. The mutation spectrum in Holt-Oram syndrome. J Med Genet 2000;37:785-7.

10. Caglayan AO, Koklu E, Saatci C, Gunes T, Ozkul Y, Narin N, et al. Holt-Oram syndrome in two generations with translocation t(9;15)(p12;q11.2). Ann Saudi Med 2008;28:209-12.
11. Basson CT, Solomon SD, Weissman B, MacRae CA, Poznanski AK, Prieto F, et al. Genetic heterogeneity of heart-hand syndromes. Circulation 1995;91:1326-9.
12. Böhm M. Holt-Oram syndrome. Circulation 1998;98:2636-7.