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Broadening the TBX4/TBX2 Phenotypic Spectrum: Surviving Neonatal ECMO and Reverse Potts Shunt for Suprasystemic Pulmonary Hypertension

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Abstract

Mutations in TBX4 and TBX2 cause a spectrum of developmental lung disease with clinical phenotypes ranging from hypoxemia to pulmonary arterial hypertension (PAH) with lethal neonatal respiratory failure. We report a female neonate with a 2.1 Mbp 17q23 deletion (encompassing TBX4/2) presenting with severe PAH necessitating extracorporeal membrane oxygenation (ECMO) at birth who was successfully decannulated and managed with invasive ventilation. A functional reverse Potts shunt, created via transcatheter patent ductus arteriosus (PDA) stenting, preserved right ventricular function and maintained lung transplant eligibility despite multiple pulmonary hypertensive crises. She underwent successful lung transplantation at 20 months of age. This case highlights that severe initial presentations of TBX4/2 mutations requiring ECMO at birth—a clinical scenario associated with high mortality —can be successfully bridged to lung transplantation, and supports PDA stenting as a feasible bridge strategy in neonates with genetic PAH, reinforcing 2025 American Thoracic Society recommendations.

Keywords: Pulmonary arterial hypertension; Developmental Lung Disease; Pulmonary-Systemic Shunt; Reverse Potts shunt; TBX2; TBX4

Introduction

TBX4 and TBX2 are cell signaling genes that play a critical role in embryologic development of the lung and skeletal system [1]. Notably, published reports of neonates with TBX4/2 deletions range in clinical severity, but cases requiring early ECMO have resulted in mortality [2-4]. We present a newborn with a 2.1 Mbp deletion encompassing TBX4/2 presenting with severe pulmonary arterial hypertension necessitating ECMO, in whom creation of a functional reverse Potts shunt by PDA stenting provided a bridge to lung transplantation.

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Case Presentation

A female neonate was born 2520 g (4.7th percentile) at 37 weeks. Poor APGARs and persistent hypoxemia prompted intubation with surfactant administration escalating to High Frequency Jet Ventilation and veno-arterial ECMO on Day of Life (DOL) 1. Echocardiogram demonstrated small patent foramen ovale (left to right shunt) and severe PAH with complete right to left shunting across the PDA with no forward flow to the pulmonary arteries. Physical exam revealed arachnodactyly without other dysmorphisms; a subsequent skeletal survey was normal. Patient tolerated weaning of ECMO with the addition of inhaled nitric oxide (iNO) prompting initiation of sildenafil. Lung biopsy was obtained, demonstrating alveolar simplification and patchy pulmonary interstitial glycogenosis, with some clinical improvement after high dose steroids. Whole exome gene sequencing revealed heterozygous 2.1 Mb deletion from chromosome 17q23.1q23.2, including TBX4 and TBX2.

Improvement on PAH therapies led to ECMO decannulation on DOL 23. First cardiac catheterization occurred on DOL 77 on bosentan and sildenafil only. Hemodynamics confirmed severe PAH with mPA pressure of 62 mmHg, wedge pressure of 9 mHg, PVR of 8.6 WUxm2, and QpQs 0.83:1. On 100% FiO2 and iNO 40 ppm, hemodynamics improved with mPA pressure of 30 mmHg, wedge pressure of 11 mmHg, PVR 2.85 WUxm2, and QpQs 1.38:1. During this catheterization and ventilator manipulation she had an acute PAH crisis (mPA pressure 122mmHg). She was started on treprostinil and weaned off iNO. Subsequent echocardiograms revealed volatile hemodynamics with predominantly right-to-left shunting across a now small PDA despite maximal pharmacologic therapy. Acute decompensation on DOL 135 involved profound hypoxemia and a PAH crisis, necessitating re-intubation and eventual tracheostomy.

A functional reverse Potts shunt was created via PDA stenting with a 4x16 mm Formula 418 stent (Cook Medical, USA) to palliatively decompress the RV while maintaining transplant eligibility. Post-stenting hemodynamic improvement allowed discontinuation of iNO and treprostinil. Over the subsequent 14 months before transplantation, the patient experienced multiple PAH crises—two requiring chest compressions, epinephrine, and iloprost—yet echocardiograms consistently demonstrated preserved RV function.

She underwent bilateral lung transplant at 20 months of age (ABO compatible, DSA negative, CMV D+/R−). Immediate post-operative period complicated by severe adenovirus infection treated with cidofovir from which she recovered and was discharged home. At 7 months post-transplant, she remains without chronic lung allograft dysfunction and successfully decannulated. She is off oxygen and exhibits global developmental delays.

Discussion

We report an infant with copy number variation at the 17q23.2 locus resulting in deletion encompassing TBX4/2 who presented with PAH necessitating ECMO who was able to decannulate and palliate to lung transplant. Obtaining a lung biopsy on ECMO, despite risks, was critical to rule out lethal developmental disorders like acinar dysplasia, which aided both family counseling and clinical decision-making prior to whole exome return. This case highlights the broad phenotypic spectrum associated with TBX4/TBX2 mutations, confirming that heterozygous deletions with severe presentation are not inherently lethal as previous reports might suggest [2-4]. Phenotypic outcomes are likely modulated by complex genetic factors, including non-coding variants on the opposite allele [5-7].

American Thoracic Society (ATS) guidelines suggest pulmonary-systemic (reverse Potts) shunts for suprasystemic PAH refractory to medical therapy, though evidence remains largely observational [8]. Unlike atrial septostomy, advantages of reverse Potts shunts include maintaining cerebral and myocardial oxygenation, reducing paradoxical emboli risk, and relieving RV pressure while increasing cardiac output at the cost of distal systemic desaturation. Transcatheter PDA stenting is less invasive, with lower complication rate, than surgical reverse Pott's procedure for patients with suitable anatomy [9]. Beyond acute decompression, Kerstein et al. found that PDA stenting produced sustained reductions in RV strain after six months, suggesting potential for long-term functional adaptation and remodeling [10]. Together, these findings support PDA stenting as a technically feasible intervention, capable of providing durable physiologic improvement. This case supports PDA stenting as a feasible bridge to lung transplant in neonates with genetic lung disease and suprasystemic PAH, adding to the limited evidence base supporting the 2025 ATS recommendations.

Abbreviations: PAH: Pulmonary arterial hypertension; PDA: Patent ductus arteriosus; RV: Right ventricular; ECMO: Extracorporeal membrane oxygenation; DOL: Day of Life; PFO: Patent foramen ovale; iNO: Inhaled nitric oxide; PA: Pulmonary artery; PVR: Pulmonary vascular resistance; QpQs: Pulmonary-to-systemic blood flow ratio; ATS: American Thoracic Society.

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