

“Unboxing” the pulmonary effects of *TBX4* germline mutation, an autopsy case study

Beth Doughty¹, A. Levin², J. Bodmer^{1,2}, C. Westoo³, O. Van Der Have³, K. Lundmark³, S.H. Abman², Csaba Galambos^{1,2}



¹Department of Pathology and Laboratory Medicine, The University of Colorado Anschutz Medical Campus, Aurora, CO, USA
²Pathology and Laboratory Services, Children’s Hospital Colorado, Aurora, CO, USA
³Department of Experimental Medical Science, Lund University, Lund, Sweden

Contact: Beth Doughty at elizabeth.doughty@cuanschutz.edu
 The authors attest that there are no conflicts of interest in this research presented for 2022 Spring SPP

Introduction

An association between pediatric onset of pulmonary arterial hypertension (PAH) and genetic variations coding for the T-box transcription factor 4 gene (*TBX4*) are increasingly recognized. *Tbx4* protein is expressed in developing lung tissue mesenchyme, contributes to airway branching, and is involved with hind-limb formation. Recent studies show bimodal distribution of the *TBX4*-related PAH: patients with severe to lethal PAH in the neonatal period, and chronic lung remodeling with PAH later in life.

Objective

We report an autopsy case of a 24-year-old male with unremarkable perinatal, childhood, and family cardiopulmonary history who developed PAH at age 12 years. At age 20, molecular analysis revealed a germline heterozygous missense variant of *TBX4*. Despite maximized PAH therapy, his cardiovascular function continued to decline and he passed away. We aim to define the progressive pulmonary histopathologic features of childhood-onset PAH in the setting of *TBX4* heterozygous germline mutation.

Methods

At autopsy, the large pulmonary vessels were injected with contrasting ink. Twelve tissue blocks of lung parenchyma were formalin-fixed and embedded in paraffin for histologic evaluation. Routine hematoxylin and eosin (H&E) stain were performed; select blocks were chosen for serial sectioning, trichrome special staining, and immunohistochemical studies for pan-cytokeratin, smooth muscle actin, and endothelial cells (CD31).



Figure 1: *Left* – Incomplete horizontal fissure of the right lung; *Middle* – Dense heterogeneous parenchyma and infarct cavities; *Right* – Intravascular dye injection highlighting atypical pleural vascular patterns

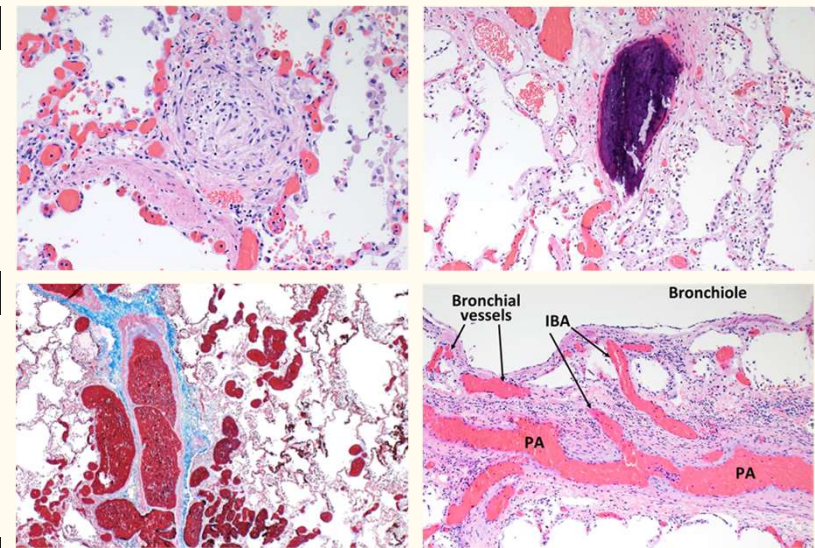


Figure 2: *Upper left* – Pulmonary artery lumen obliteration and wall muscularization (H&E, 200x); *Upper right* - Ectopic bone formation and stromal vessel dilation with congestion (H&E, 100x); *Lower left* - Plexiform lesion of a pulmonary artery, note the glomus-like capillary proliferation (Trichrome, 40x); *Lower right* - Intrapulmonary bronchopulmonary anastomoses (IBA) allow blood flow between bronchial vessels and pulmonary artery (PA) branches creating right to left shunt and contributing to hypoxia (H&E, 100x)

Results

Autopsy (Figure 1):

- Heavy lungs and an incomplete horizontal fissure of the right lung
- Peripheral cyanosis
- Anasarca, cardiomegaly, and massive hemopericardium

Histologic evidence of maldevelopment and remodeling (Figures 2-3):

- Alveolar growth abnormality and bronchialization
- Abnormal growth of interstitial mesenchymal elements and fibrosis
- Striking pulmonary vascular disease with moderate hypertensive arterial remodeling with multiple plexiform lesions
- Thrombotic arteriopathy with infarcts
- Lymphatic vessel muscularization
- Vessel hyalinization
- Recruitment of intrapulmonary bronchopulmonary anastomoses (IBA)

Conclusions

This unique case of germline *TBX4* variant highlights strikingly complex pulmonary histopathology leading to lethal cardiopulmonary failure. Over time and under the influence of abnormal *Tbx4* signaling, all compartments of the lung continue to remodel, resulting in worsening PAH, impaired airway and distal airspace structure, and hypoxemia, which cause end stage lung disease and death. **Studies focusing on signaling pathways downstream to *Tbx4* are needed to intervene pulmonary remodeling and attenuate progressive PAH.**

References

- Galambos C, Mullen MP, Shieh JT, et al. *Eur Respir J* 2019; 54:1801965.
- Haarman MG, Kerstiens-Frederikse WS, Berger RMF. *Curr Opin Pulm Med* 2020; 26: 277-284.



Figure 3: *Left* – Evidence of intrapulmonary bronchopulmonary anastomoses (IBA) (H&E with contrasting intravascular ink, 20x); *Middle* - Stromal vessel proliferation (CD31, 100x); *Right* - Diffuse lymphatic and patchy pleural muscularization (SMA, 40x)