Histologic Features and Decreased Lung FOXF1 Gene Expression in Severe Bronchopulmonary Dysplasia without a Genetic Diagnosis of Alveolar Capillary Dysplasia

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Introduction

Severe bronchopulmonary dysplasia (sBPD) after preterm birth is associated with high late mortality and pulmonary hypertension (PH). Impaired alveolar and vascular growth with hypertensive remodeling are hallmarks of sBPD, which are features that overlap with the lethal developmental disorders, alveolar capillary dysplasia with misalignment of pulmonary veins (ACDMPV) that has been linked to loss of *FOXF1* expression. As with sBPD, ACDMPV is causes severe respiratory failure and PH, and causes death despite aggressive cardiopulmonary therapies. Past studies of ACDMPV have shown that the "MPV" are prominent bronchial veins that reflect recruitment of intrapulmonary bronchopulmonary anastomoses (IBA), which connect the pulmonary vasculature with bronchial vessels. The presence of prominent IBAs have also been identified in fatal sBPD, but the potential role of impaired FOXF1 signaling in sBPD is unknown.

Case presentation

This 530-gm female newborn was delivered to a G_1P_0 female by an emergency cesarean-section due to eclampsia at 25 weeks' gestation. Her early course was characterized by profound hypoxemic respiratory failure with supra-systemic PH requiring invasive ventilation and PH-targeted therapies. Despite aggressive treatment, her course worsened, the family elected to redirect care and the infant died at 10 months. Clinical exome sequencing (ES) was performed before death that was negative for *FOXF1* or related *TMEM100* abnormalities. Autopsy showed histopathologic features consistent with both ACDMPV or sBPD (Figure 1). Transcript levels of *FOXF1* and *TMEM100* was determined by real time-qPCR and compared to those of controls and previously diagnosed ACDMPV infants. *FOXF1* and *TMEM100* expression were dramatically reduced in the lungs of the proband, resembling levels in patients with genetic *FOXF1* deficiency due to pathogenic CNV deletion. (Figure 2)

Results

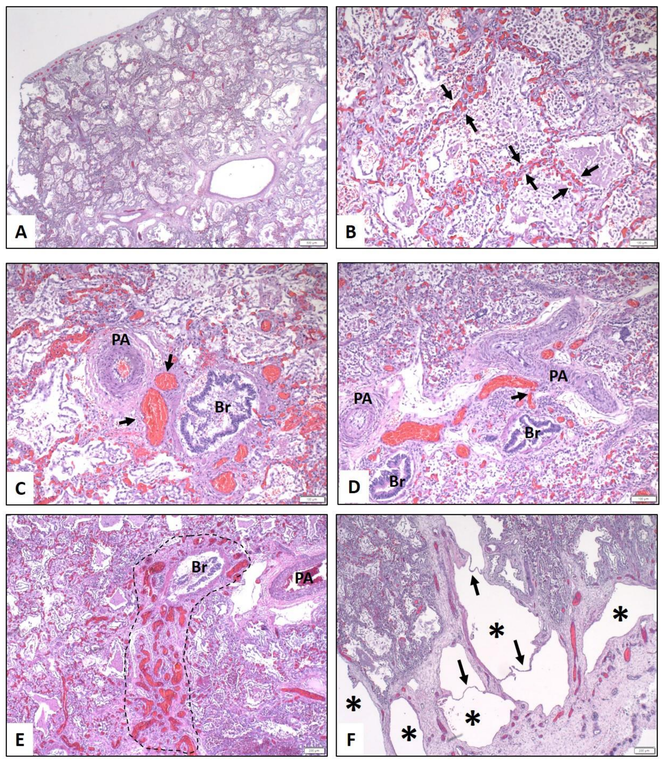

Figure 1. Lung histopathology. A: Low power view shows underdeveloped lung parenchyma with many enlarged and simplified alveoli and thick interstitium. B: Dilated alveoli are associated with double capillary layers (arrows). C: Markedly dilated and congested thin wall vessels are present within the bronchoarterial bundles (Br: bronchiole, PA: pulmonary arteries resembling those of misaligned pulmonary veins seen in alveolar capillary dysplasia (arrows). D: Pulmonary vessels connect with the bronchial microvessel consistent with bronchopulmonary shunt vessel (arrow). E. Markedly dilated peribronchial microvessel resembling those of type 1 plexiform lesion *(ref: Westoo et al, Am J Physiol Lung Cell Mol Physiol. 2021*). E: Extensive lymphangiectasia (asterixis) with visible lymphatic valves (arrows).

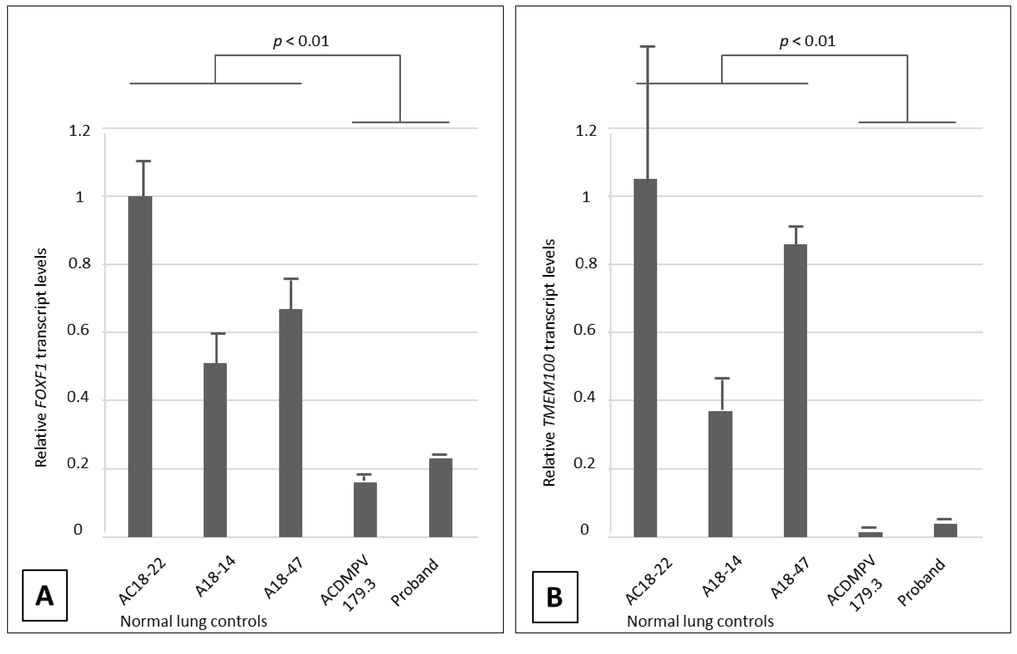

Figure 2. A decrease in the expression of *FOXF1* (A) and *TMEM* (B) in the proband similar to that observed in ACDMPV patients due to *FOXF1* haploinsufficiency (One-way ANOVA with Tukey Test: $p < 0.01$) ACDMPV 179.3: paternal deletion of the *FOXF1* enhancer. Error bars represent standard deviation.

Discussion

This case of an extremely preterm infant who died with sBPD and refractory PH had striking histologic features compatible with the diagnosis of sBPD or ACDMPV but had negative genetic findings for *FOXF1*. These findings suggest that impaired *FOXF1* signaling in sBPD may contribute to the severity of disease in the absence of a genetic diagnosis of ACDMPV.

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