Child interstitial lung disease in an infant with surfactant protein C dysfunction due to c.202G>T Variant (p.V68F)

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PEDIATRIC PULMONARY DISEASE

Child Interstitial Lung Disease in an Infant with Surfactant Protein C Dysfunction due to c.202G>T Variant (p.V68F)

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Abstract

For newborns suspected having childhood interstitial lung disease (ChILD), the sequencing of genes encoding surfactant proteins is recommended. However, it is still difficult to interpret the clinical significance of those variants found. We report a full-term born female infant who presented with respiratory distress and failure to thrive at 2 months of age and both imaging and lung biopsy were consistent with ChILD. Her genetic test was initially reported as a variant of unknown significance in surfactant protein C (c.202G > T, p.V68F), which was modified later as likely pathogenic after reviewing a report of the same variant as causing ChILD. The infant was placed on noninvasive ventilation and treated with IV Methylprednisolone, Hydroxychloroquine, and Azithromycin but did not show significant clinical and radiological improvement underwent tracheostomy and is awaiting lung transplantation at 8 months of age. The challenges interpreting the genetic results are discussed.

Keywords Interstitial lung disease · Surfactant protein C · *SFTPC* · Respiratory failure · Infant

Introduction

Childhood interstitial lung disease (ChILD) is a rare and heterogeneous condition. Its prevalence is estimated to be between 1.3 and 3.6 cases per million [1]. ChILD presenting in infancy differs from interstitial lung disease (ILD) observed in older children and adults in terms of pathophysiology, diagnosis, management, and outcome. The American Thoracic Society (ATS) guidelines define ChILD syndrome as a diffuse lung disease (DLD) in an infant (< 2 years old) with exclusion of the common primary causes of DLD and at least three of the following four criteria: (1). Respiratory symptoms (cough, rapid/difficult breathing, or exercise intolerance), (2). Respiratory signs (tachypnea, adventitious sounds, retractions, clubbing, failure to thrive, or respiratory failure), (3). Hypoxemia, and (4). Diffuse abnormalities on imaging [2].

For newborns suspected of having ChILD, or when severe disease is present, or when a family history of ILD exists, the ATS guidelines strongly recommend analysis for sequence variants in genes encoding surfactant proteins: surfactant protein B (*SFTPB*), surfactant protein C (*SFTPC*), and adenosine triphosphate-binding cassette family member 3 (*ABCA3*) [2]. However, the interpretation of such results can be challenging due to sparse information of the clinical significance of variants discovered. In this report we discuss a female infant who presented with failure to thrive and respiratory distress, the evaluation for ChILD which revealed a sequence variant in *SFTPC*, and the rationale for concluding that the variant was the cause of her disease.

Case Report

A 2-month-old African American female presented with coughing, sneezing, and respiratory distress after feeding. Her birth history was notable for full-term birth, dysmorphic

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facies, and a negative cardiac evaluation. She had poor weight gain since birth (admission weight 3.8 kg, 1.7th%). Her oxygen saturation was noted to be 91–93% with cough and tachypnea when she was seen in her primary care physician's office for 2-month-old health care maintenance visit and she was referred to the emergency department (ED). Covid/flu/RSV test was negative, but she had desaturations to 85% so was started on nasal cannula (NC) at 1 LPM and chest X-ray (CXR) showed bilateral perihilar opacities and pulmonary hyperinflation which was felt consistent with bronchiolitis and she was admitted (Fig. 1A).

She was initially started on low flow nasal cannula but subsequently escalated to noninvasive ventilation (NIV) with maximum setting 14/7 cm H_2O, 30% FiO2 due to worsening tachypnea and hypoxemia. Her newborn screening was normal and chromosomal microarray was negative (normal female). Her chest CT scan (Fig. 1B) showed patchy ground glass parenchymal haziness seen throughout both lungs and bilateral hyperinflation consistent with ILD. Lymphocyte subsets total counts, cystic fibrosis panel, carnitine levels, and thyroid function were all normal. Echocardiogram showed normal cardiac and valve function.

Results from a surfactant dysfunction panel (Ambry Genetics) demonstrated that she was heterozygous for variants of unknown significance in *ABCA3* (c.446C > T, p.A149V) and in *SFTPC* (c.202G > T, p.V68F). The classification of the *SFTPC* variant was subsequently modified as likely pathogenic after reviewing a report of this variant as causing ILD, consistent with a diagnosis of *SFTPC*-related surfactant dysfunction [3].

Left open lung biopsy of the lingular segment (Fig. 2) was done which showed light microscopic features typical of surfactant dysfunction: type 2 pneumocyte hyperplasia, interstitial widening, intraalveolar foamy macrophages, and extracellular proteinaceous material. Electron microscopic images showed reactive type 2 pneumocytes with lamellar bodies without diagnostic abnormality. Tissue microbiology was negative. Endoscopy by pulmonary, ENT, and GI was performed with findings of laryngomalacia, but no tracheoesophageal fistula. There were no significant histopathologic findings on esophagogastroduodenoscopy. An expanded Neonatal Respiratory Distress Gene Panel of 111 genes (Invitae, surfactant-like disorders), including *CSF2RA/B*, *FOXF1*, *NKX2.1*, *SLC7A7*, *FLNA*, and *ITGA3*, was sent with variants of uncertain significance for *ABCA3*, *AGTR1*, *BBS10*, *RTEL1*, and *SFTPC* (all heterozygous). The variants in *ABCA3* and *SFTPC* were the same as detected by Ambry. Targeted sequencing for the *SFTPC* variant found in the child was negative for the variant in both parents.

She was started on Chlorothiazide 20 mg/kg/day to avoid fluid overload and received the first course of IV Methylprednisolone 10 mg/kg/dose for 3 days. A repeat chest CT 17 days after the first course of steroid pulse showed diffuse ground glass opacification and hyperinflation which were not substantially changed from the initial CT (Fig. 1C). She had another course of IV Methylprednisolone at the same dose for 3 days after 1 month later and also was started on Hydroxychloroquine 5 mg/kg/dose, daily and Azithromycin 10 mg/kg/dose, Mon/Wed/Fri. She remained on the same Bi-level pressure of NIV, still having same degree of increased work of breathing and there was no significant or consistent increase in her weight.

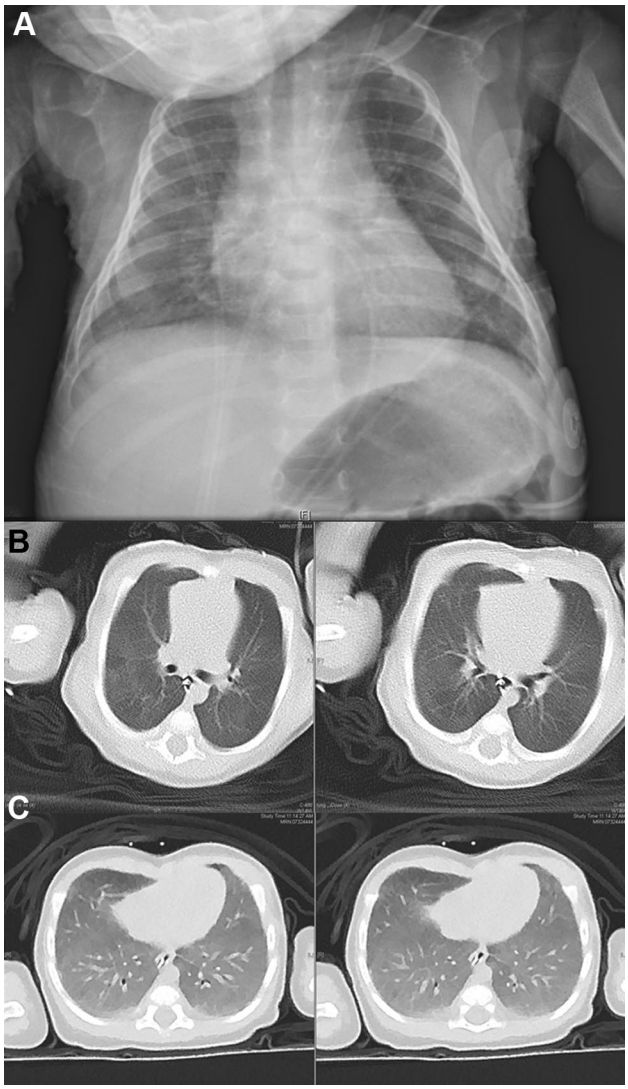

Fig. 1 **A** Initial chest X-ray on arrival to the emergency department: bilateral perihilar opacities and pulmonary hyperinflation which may be seen with bronchiolitis. **B** Initial chest CT scan: patchy ill-defined parenchymal haziness seen throughout both lungs consistent with interstitial lung disease. There is bilateral hyperinflation. No adenopathy or pleural effusion. No cystic changes or areas of bronchiectasis. **C** Repeated chest CT scan: evidence of interstitial lung disease status post-open lung biopsy. Diffuse ground glass opacification and hyperinflation are not substantially changed from prior CT chest. Mild-dependent bibasilar subsegmental atelectasis

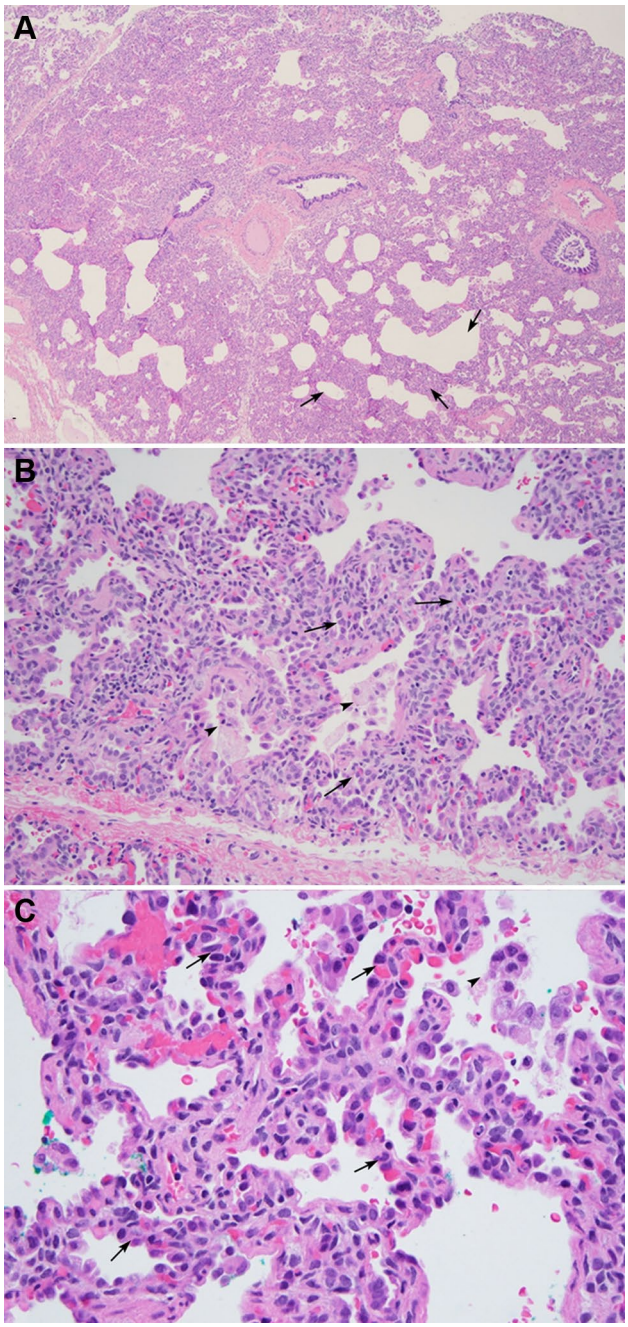

Fig. 2 Lung biopsy. **A** Low power: abnormal parenchymal appearance and note altered alveolar and interstitial architecture with varying sizes (arrow). **B** Higher power view of the alveolar walls: widened with increased interstitial cellularity (arrow). Small pale clusters of alveolar macrophages seen within the alveolar spaces (arrowhead). **C** Highest power magnification: thick alveolar walls with prominent lining pneumocytes (arrow). Some but not a significant inflammatory presence. Note, alveolar macrophages in the alveolar spaces (arrowhead)

There was also concern for possible cow milk protein allergy with consideration of Heiner Syndrome (ILD and failure to thrive). Fecal occult blood test, stool A1AT, and stool elastase were normal. She was transitioned to a fully hydrolyzed formula but due to frequent emesis she needed transpyloric feedings and total parenteral nutrition. She was continued on Omeprazole 5 mg daily for presumed gastroesophageal reflux. However, we were not able to assess for reflux by upper GI series due to her significant respiratory distress requiring NIV. She remained on NIV and was transferred to Children's hospital of Philadelphia for lung transplant evaluation at the age of 4 months.

Discussion

Childhood ILD includes a large and heterogeneous group of diseases and while very rare, causes serious morbidity and mortality [4]. Diagnosis in infants can be established according to the ATS guideline [2] and diagnostic tools include imaging, lung function tests, bronchoalveolar lavage, genetic testing, and lung biopsy. Genetic causes resulting from pathogenic DNA sequence variants in multiple gene, including *SFTPC*, *SFTPB*, *ABCA3*, GM-CSF receptors α and β (*CSF2RA/B*), Forkhead Box F1 (*FOXF1*), and thyroid transcription factor-1 (*NKX2.1*/TTF1), have been identified. Genetic testing can at times help avoid more invasive testing, such as lung biopsy. Autosomal recessive pathogenic sequence variants in *SFTPB* are associated with fatal respiratory distress in the neonatal period. Pathogenic sequence variants in *SFTPC* are associated with a highly variable age at presentation and natural history and cause ILD in older infants, children, and adults [5]. The familial cases of lung disease due to *SFTPC* variants are generally inherited as an autosomal dominant with variable penetrance, but de novo variants may cause sporadic diseases [6].

The most commonly identified pathogenic *SFTPC* variant is c.218 T > (p.I73T) [7]. Numerous other pathogenic *SFTPC* variants have been reported in different populations [8] and premature babies with severe respiratory distress [9]. Our patient was born at term and presented within the first 2 months of life with respiratory failure and failure to thrive. She met criteria for ChILD syndrome according to ATS guideline [2] and a diagnosis of surfactant protein C dysfunction was suspected with genetic testing and lung biopsy was consistent with ILD due to surfactant dysfunction. The c.202G > T variant is located in coding exon 3 of *SFTPC* with the valine in codon 68 replaced by phenylalanine. This variant has been previously reported as causing ILD in a Japanese infant [3]. The child presented in infancy and had a lung biopsy interpreted as consistent with desquamative interstitial pneumonitis (DIP) but no other clinical findings or follow-up were reported. However, a full-term female infant with neonatal respiratory distress and ChILD who had a novel sequence variant in the same *SFTPC* codon (c.203 T > A,

p.Val68Asp) has been reported [10] and a mutation in the same codon previously associated with disease supports that the variant which our patient has is pathogenic.

SFTPC c.202G > T variant is located in the first base of exon 3 and the change from a G to a T could potentially disrupt splicing. *SFTPC* sequence variants in the last codon of exon 4, one synonymous and one resulting in a conservative amino acid substitution, have been demonstrated to affect normal splicing and thus cause lung disease. [11, 12] We cannot exclude that the c.202G > T variant causes disease by disrupting splicing as frozen lung tissue from which to prepare mRNA was not available.

Our subject also has a variant of unknown significance in *ABCA3* (c.446C > T, p.A149V). A previous study reported that *ABCA3* variants may act as a modifier gene for disease severity in patients with a *SFTPC* variants [7, 13]. It is unclear whether the *ABCA3* variant which this patient has is affecting the clinical phenotype or not. This patient was not found to have any abnormal variants for other genes, such as *CSF2RA/B*, *FOXF1*, or *NKX2.1/TTF1*.

The mainstay of the treatment for childhood ILD is supportive care, systemic steroid, Hydroxychloroquine, and immunosuppressive agents [4]. There have been no controlled trials and decision is usually made by case by case on clinical experience. Our patient received a steroid pulse for 3 days, but repeated CT scan did not show any substantial change or improvement. She received one additional course of steroid pulse one month later but remained on the same pressures of NIV with no significant clinical improvement in terms of increased work of breathing and poor weight gain. She was also initiated on Hydroxychloroquine and Azithromycin empirically and then transferred for lung transplant evaluation. She was unable to be ventilated via noninvasive means and underwent tracheotomy placement for chronic mechanical ventilation. Ultimately, she was deemed to be a candidate and at the time of this publication at 8-months of age, she is awaiting bilateral sequential lung transplantation.

SP-B deficiency is the most common indication for lung transplant in infants younger than 1 year [14] and there are prior reports of pediatric patient with pathogenic *SFTPC* variants who were successfully treated with lung transplant. [10, 15, 16] For infants and children who had lung transplant for genetic disorders of surfactant metabolism, the survival rate at 1- and 5-year post-transplant were 82%/56% and 100%/79% in infants and children, respectively, as per a study in 2018 [17]. In summary, we report a case of an African American female infant with ILD which was likely caused by a pathogenic *SFTPC* variant, p.V68F (c.202G > T). This variant is considered to be pathogenic for the following reasons. Her lung histopathology and clinical presentation were consistent with ILD and another variant in same codon associated with disease has been previously reported and apparently occurred de novo in the family, while being absent in large population databases.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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