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Case report

Recurrent diffuse lung disease due to surfactant protein C deficiency

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ABSTRACT

Surfactant protein C (SP-C) deficiency causes diffuse lung disease with variable prognosis and severity that usually presents in infancy. We present the case of a patient with diffuse lung disease who was successfully treated with hydroxychloroquine and steroids in infancy, who presented again as a young adult with respiratory symptoms. Exome sequencing identified a novel *de novo SFTPC* mutation (c.397A > C p.S133R). Mutated SP-C accumulates and leads to injury of alveolar type II cells, which normally replenish alveolar type I cells after injury. This may explain the symptom recurrence after lung injury in young adulthood. Although hydroxychloroquine has been hypothesized to interfere with mutated SP-C accumulation, data on long term outcome remains limited.

1. Introduction

Children's diffuse lung diseases (DLD) encompass a heterogeneous group of conditions defined by at least three of the following: 1-respiratory symptoms; 2-respiratory signs; 3- hypoxemia; and 4-diffuse abnormalities on chest imaging [1]. Some resemble adult interstitial lung diseases, but in infancy (< 2 yr old) many DLDs, such as neuroendocrine hyperplasia and pulmonary interstitial glycogenosis, are not seen in adults. The severity and prognosis of DLD in infancy varies, ranging from mild symptoms with supplemental oxygen requirement for pulmonary interstitial glycogenosis to poor outcomes with extensive fibrosis for surfactant protein B mutations [2].

Mutations in several surfactant-related genes have been increasingly recognized as causes of DLD in infants. Surfactant is composed of phospholipids and proteins secreted by alveolar type II cells (AEC2s). Surfactant protein C (SP-C) normally helps reduce surfactant tension at the air liquid interface, has anti-inflammatory properties, and signals cell differentiation [3]. Mutated SP-C accumulates and leads to injury of AEC2s, which normally replenish alveolar type I cells (AEC1s) after injury. Because of the low prevalence of DLD in infancy, evidence-based treatments are limited [4]. We report a case of DLD due to a novel *de novo* Surfactant Protein C (*SFTPC)* mutation successfully treated with hydroxychloroquine and prednisone in infancy followed by recurrence in young adulthood.

2. Case report

The full-term male patient had a neonatal period notable for a wet cough. After discontinuing breastfeeding at four months of age, he had inadequate weight-gain and his wet cough became severe, especially at night. He was tachypneic with no perceptible wheezing. At 9-months, chest-x-ray and CT were normal. At 11-months, he was admitted for respiratory distress with severe hypoxemia, cyanosis, and clubbing. A chest x-ray showed diffuse interstitial markings on both lung fields and a chest CT revealed extensive interstitial markings. The Tc-DTPA half-time clearance was 13 minutes bilaterally, indicating increased pulmonary epithelial permeability. A sweat test was normal. Lung biopsy demonstrated diffuse moderate interstitial fibrosis with eosinophilic inflammation and alveolar epithelial cell hyperplasia. Parainfluenza was recovered from the cultured lung biopsy tissue. He was diagnosed with interstitial lung disease and treated with prednisone and hydroxychloroquine. He required oxygen supplementation for three months. At 3-years, his pharmacological therapy was stopped since his symptoms had resolved, and his pulmonary function and chest X-ray had normalized. He grew and functioned normally for the next 24 years, including participating in sports and living at altitudes ranging from 6000 to 12,000 feet with no dyspnea.

At 27-years of age, he again developed a dry cough and dyspnea during strenuous activities. He reported that a leaky shower had led to water damage on his bedroom wall the year prior. Air samples from the

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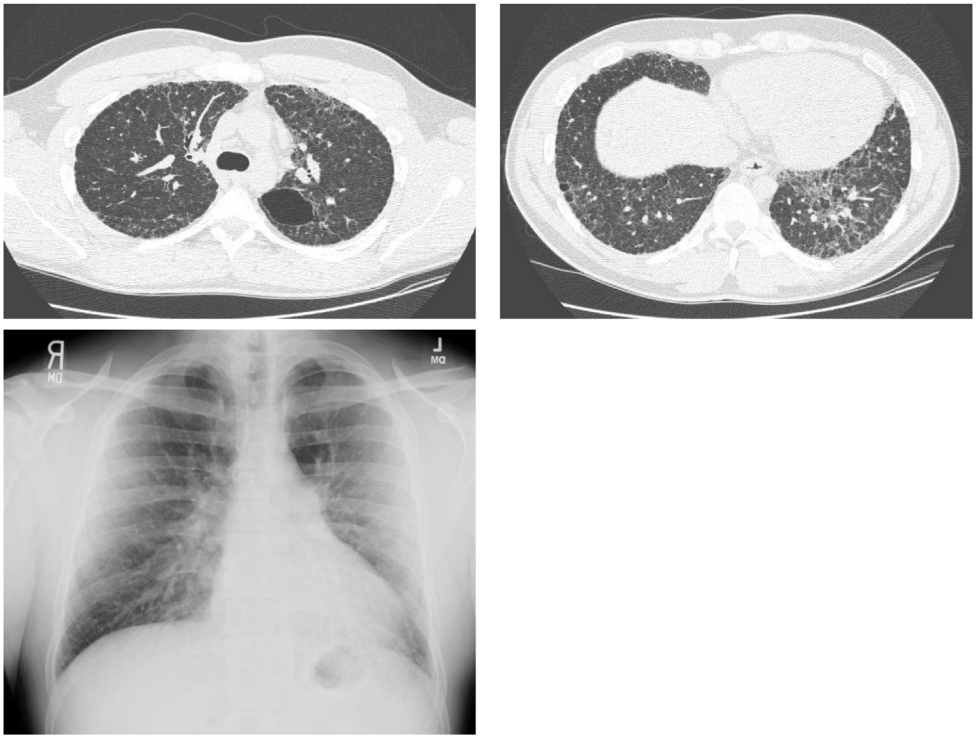

Fig. 1. Chest CT and X-rays, patient age 27 years.

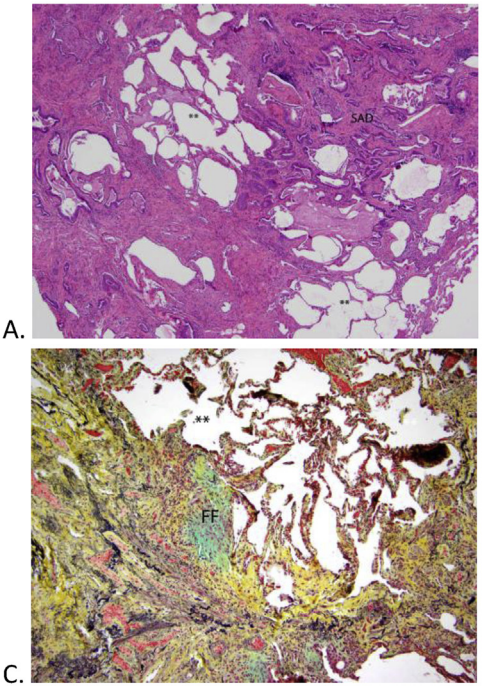

Fig. 2. A: Low magnification of the lower lobe shows temporal heterogeneity with dense pink areas representing fibrosis, intervening uninvolved areas (**) and small airways disease (SAD) (top right). B: High magnification demonstrates fibrosis (left lower) and relatively uninvolved areas (**) with fibroblastic foci (FF) separating the two. C: A high magnification on the Movat stain highlights the fibroblastic foci (FF) alongside fibrosis (yellow) and uninvolved lung (**). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

affected area of the home grew Aspergillus/Penicillum-like mold. His Aspergillus antibody and precipitin test were negative. A review of other environmental exposures and autoimmune symptoms was unrevealing. There was no known family history of lung disease. His physical examination was notable only for bilateral crackles heard posteriorly. There was no clubbing. Forced vital capacity was 68% predicted, FEV_1 was 65% predicted, the FEV_1/FVC ratio was 0.79, and the diffusing capacity was 48% predicted. A high-resolution computed tomographic scan of the chest showed diffuse interlobular septal thickening with several areas of bulla or large cysts, without bronchiectasis or significant fibrosis (Fig. 1).

A right sided thoracoscopic lung biopsy showed patchy, fibrosing and minimally cellular interstitial pneumonitis, focal pleural fibrosis and adhesions on the right upper and middle lobes. Biopsy of the right lower lobe showed fibrosing and cellular interstitial pneumonitis with extensive peribronchiolar metaplasia, pleuritis, adhesions, and extensive fatty metaplasia (Fig. 2). Some metaplasia was also present in the upper and middle lobes (data not shown).

Exome sequencing identified a heterozygous novel *de novo* c.397A > C p.S133R, likely pathogenic variant in *SFTPC*, consistent