Case report

Recurrence 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 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 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
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, FEV₁ was 65% predicted, the FEV₁/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
| Mutation            | Age of onset | Severity                                                                 | Response to treatment                                      | Reference          |
|---------------------|--------------|---------------------------------------------------------------------------|------------------------------------------------------------|--------------------|
| IVS4DS, G-A, +1     | Mother diagnosed at 1 year | Respiratory insufficiency                                                  | Treated with glucocorticoids until 15 yo                   | Nogee et al. [27]  |
| p.ILE8PHE c.112 A > T | Son diagnosed in infancy | Recurrent pneumothorax, repetitive cough, hypoxia, failure to thrive, and gastro-esophageal reflux | Died after childbirth                                       |                    |
| p.VAL39LEU c.115 G > T | 11 years old | Cough, shortness of breath on minimal exertion at 11 yo                  | Treated for 38 months - asymptomatic                       | Avital et al. [6]  |
| VAL39ALA c.16 T > C | 4 months | Virus infection at onset                                                  | NA                                                        |                    |
| GLY66LYS 1509 G-A   | 13 days |ILD                                                                        | NA                                                        | Stevens et al. [28]|
| ILE73THR c.218 T > C | 5.9 months (average for 10 patients) not neonatal 1 month - 2.5 years | Variable (asymptomatic to fatal)                                    | Treated for 7 months - restarted at 19 yo for 6 years Patient treated at 16 months for 7 months, restarted 6 weeks later for 7 months - cough in adolescence and adulthood, SOB during exercise: Patient treated at 5.5 years (asymptomatic at 2.5) for 16 months with good response - asymptomatic | Avital et al. [6]  |
| – c.325-1 G > A     | Birth | Viral infection at onset                                                  | NA                                                        | Guillot et al. [28]|
| p.TYR113HIS c.337 T > T/C | 7 days | Cough, tachypnea and exhibited failure to thrive                          | Slight improvement on antibiotics and nasal oxygen         | Da Hong et al. [30]|
| ALA116ASP           | 5 months |                                                                             | Good response to hydroxychloroquine                        | Rosen and Waltz [31]|
| p.HIS142fs c.424delC | Birth | Viral infection at onset                                                  | NA                                                        | Guillot et al. [28]|
| GLN145HIS c.435 G > C | 1 month |                                                                             | NA                                                        | Guillot et al. [28]|
| ARG167HIS c.435 G > A | 9 months | Respiratory insufficiency                                                 | NA                                                        | Thomas et al. [31]|
| LEU188GLN           | Variable |                                                                             | Offline therapeutic broncho-alveolar lavages               |                    |
| LEU188PRO c.563 T > C | 2 months | Bootstrap failure, decannulated from chronic ventilation at 5 years       | NA                                                        |                    |
| LEU188GLN c.563 T > A | 1 day | Respiratory failure, decannulated from chronic ventilation at 5 years     | Clearance, steroids, azathioprine                          |                    |
| CYS189TRP c.566 G > A | Birth | No viral infection in n = 2, others unknown                               | Variable: severe in first months of life and asymptomatic in adults |                    |
| p.CYS189TRP c.567 C > G | 4 months | Tachypnea in infancy                                                   | Steroids, azithromycin, hydroxychloroquine 8 months to 3 years on home ventilation |                    |
| LEU194PRO S81T-C    | 2 months (virus infection at onset) and adult                             | Infant with ILD – Adults with pulmonary fibrosis               | NA                                                        | Guillot et al. [28]|

**Table 1**

Mutations previously observed in SFTPC and associated clinical phenotype.
3. Discussion

SP-C deficiency is a rare lung disease with highly variable age of onset, severity and natural history (Table 1). It is associated with acute respiratory failure and interstitial lung disease [7] and has been described in neonates with severe, fatal disease as well as in adults who remain asymptomatic for years [8–12]. The variability is likely due to the type of mutation, age, modifier genes, and treatment [13]. Our patient represents one of the few cases of SP-C deficiency with long-term outcome after initial hydroxychloroquine and steroid treatment for infantile DLD. Patients with SFTPC mutations and DLD respond to hydroxychloroquine, generally with elimination of pulmonary symptoms and without limitations in daily life [4,5]. Treatment has been stopped after variable periods of time (a few months [14] to seven years [8]) and restarted in cases of pulmonary exacerbations [6].

The exact mechanism of action of hydroxychloroquine has not been fully elucidated [15]. When the SP-C gene is mutated, the precursor of surfactant protein C (proSP-C) is misfolded and accumulates within the ER and Golgi apparatus of AEC2s, leading to cellular injury and apoptosis [6]. It has been suggested that the lung disease is not only due to the lack of normal SP-C but also to the expression of abnormal proSP-C [15]. Chloroquine and hydroxychloroquine may affect lysosomal activities to decrease vesicle fusion, decrease exocytosis, and decrease digestive efficiency of phagolysosomes [17–19], interfering with abnormal proSP-C accumulation [8] and its intracellular post-translational processing [15].

SFTP-C-positive AEC2s are long-term tissue stem cells that can self-renew and differentiate into AEC1s for over a year to replenish alveolar epithelium [20]. In SP-C deficient patients, symptom recurrence has been associated with viral infection or lung injury: diffuse lung injury triggers the destruction of AEC1s and stimulates the proliferation of AEC2s to restore the alveolar epithelium. However, it is plausible that apoptosis of AEC2s [6] and inhibition of AEC2 proliferation in patients with an SFTPC mutation leads to pulmonary fibrosis [22]. In SP-C deficient mice (Sftpc−/−) in a 129S6 background, which develop spontaneous interstitial lung disease with age [23], intra trabecular Pseudomonas aeruginosa leads to an exaggerated inflammatory response and bacterial load resulting in decreased survival [23]. Additionally, Sftpc−/− mice have an increased and persistent inflammation, and pulmonary fibrosis in response to LPS and bleomycin induced lung injury, respectively [24,25]. Whereas, restoration of SP-C in a Sftpc−/− compound transgenic mouse protected the mice against respiratory syncytial virus induced inflammation and improved viral clearance [26]. These findings suggest that in addition to SP-C being important in maintaining the bio-physical properties of surfactant, it plays an important role in limiting pulmonary inflammatory responses to injury.

4. Conclusion

The use of hydroxychloroquine in our patient for two years early in life might have inhibited the accumulation of misfolded proSP-C and AEC2 damage in infancy, enabling normal lung growth and maturation. Recurrence and worsening of the symptoms 24 years after hydroxychloroquine discontinuation may be related to progressive accumulation of proSP-C in AEC2 over the intervening 24 years after an infection exacerbated lung injury by impairing AEC2 proliferation and differentiation.

Successful reports of treatment of children with SFTPC mutations with hydroxychloroquine demonstrates the clinical utility of genetic testing for children with DLD.

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