Surfactant Protein C Deficiency in a Puerto Rican Adolescent With a Rare SFTPC Genetic Variant

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Abstract

Surfactant protein C (SP-C) is a hydrophobic lipoprotein necessary for lowering alveolar surface tension and lung defense mechanisms. Defects in its function due to genetic mutations in the SFTPC gene have been increasingly identified in patients presenting with childhood interstitial lung disease. SP-C mutations are inherited in an autosomal dominant pattern with reduced penetration and variable expressivity, although de novo mutations have also been documented. In this article, we present the case of an oxygen-dependent 13-year-old male with interstitial lung disease and severe pulmonary hypertension. Genetic analysis and lung biopsy confirmed the diagnosis of SP-C deficiency with the rare heterozygous mutation IVS4+2. To our knowledge, this is the first documented case of SP-C deficiency in the Puerto Rican population and the second worldwide with the IVS4+2 genetic mutation.

Categories: Pediatrics, Pulmonology
Keywords: surfactant protein c, sftpc mutations, childhood interstitial lung disease, rare lung disease, digital clubbing

Introduction

Pulmonary surfactant is a lipoprotein exclusively produced and secreted by type II alveolar cells and is necessary for lowering alveolar surface tension and providing innate defense mechanisms against inhaled pathogens such as respiratory syncytial virus (RSV) [1,2]. To date, four distinct surfactant proteins (SP-A, SP-B, SP-C, and SP-D) have been identified [3]. The human SFTPC gene encodes for a large (21 kD) precursor SP-C (proSP-C) that requires processing into mature SP-C (3.7 kD) [4]. It has been proposed that mutations in the SFTPC gene lead to misfolding of the large proSP-C with subsequent accumulation in type II alveolar cells. This activates a pro-inflammatory cascade that triggers cellular death and recruitment of T-cells, along with fibroblasts, eventually leading to the development of childhood interstitial lung disease (chILD) [5]. These malfunctions or deficiencies in SP-C have been increasingly identified in previously unknown causes of chILD due to advancements in diagnostic technologies including genetic testing and histopathological analysis of lung tissue [6-12]. These mutations were first described by Nogee et al. [5] as having an autosomal dominant mode of inheritance with variable expressivity and penetration. However, de novo mutations are also commonly reported [10-12].

Clinical manifestations of SP-C deficiency are highly variable and may present with a range of nonspecific symptoms such as dyspnea, dry cough, exercise intolerance, and recurrent respiratory infections [13]. In more severe cases, children may develop acute respiratory distress triggered by respiratory viruses [13,14]. Symptoms usually spare the neonatal period and begin to manifest later in infancy [5]. As these patients grow older, other signs such as tachypnea, digital clubbing, hypoxia, resting or exercise-induced cyanosis, and failure to thrive may develop [11,13].

Clinical cases and evidence-based treatment options of SP-C deficiency due to SFTPC mutations are scant in the medical literature, especially in the Hispanic population. In this article, we report a case of chILD secondary to SP-C deficiency in a 13-year-old Puerto Rican male with a rare SFTPC genetic variant and discuss our treatment approach and multidisciplinary management strategies.

Case Presentation

A 13-year-old adolescent male presented with a history of progressive dyspnea on exertion, recurrent wheezing, bronchiolitis, pneumonia, and chronic respiratory failure since infancy. He was born at term (38 weeks, 6 days) via vaginal delivery and had no neonatal respiratory distress or complications. Family history was significant for asthma in his brother and one uncle. His mother had no significant past medical history and his father had expired six years prior due to a traumatic accident with no apparent medical history. Beginning at six months of age, the patient started to develop respiratory symptoms and had amassed 29 hospitalizations for respiratory distress, with eight of them requiring Pediatric Intensive Care...
Unit (PICU) admissions and two endotracheal intubations. Two weeks prior to our initial encounter, the patient was admitted to the PICU for four days due to an acute episode of shortness of breath and associated chest pain with hypoxemia. On initial presentation to our clinic, the patient required 24-hour oxygen supplementation via nasal cannula at 2 L per minute (LPM). Pulse oximetry was 92-95% with a nasal cannula on rest and decreased to 80-85% on room air with physical activity. Physical examination demonstrated a chronically ill-appearing 13-year-old boy with a heart rate of 114 beats per minute, respiratory rate of 25 breaths per minute, oxygen saturation of 92% at 2 LPM, body mass index of 18.16 (45th percentile), generalized digital clubbing of both upper and lower extremities (Figure 1), and lungs clear to auscultation bilaterally.

![Generalized digital clubbing](image)

**FIGURE 1: Generalized digital clubbing.**
Symmetric abnormal nail angulation of the hands (A) and toes (B) at 12 years of age.

A complete pulmonary function test (PFT) was performed following the American Thoracic Society guidelines [15]. Forced vital capacity (FVC) was 58% predicted, forced expired volume in one second (FEV1) was 58% predicted, FEV1/FVC ratio was 100%, and DLCOcor was 32% predicted, consistent with a restrictive airflow pattern. A flexible fiberoptic bronchoscopy with bronchoalveolar lavage was performed which was remarkable for bronchial cells with reactive and inflammatory features as well as reactive macrophages, activated histiocytes, polymorphonuclear infiltrates with degenerative changes, fibrin, and amorphous material. The patient underwent a left lung wedge biopsy which showed bronchiectasis and cystic changes of airspace consistent with chILD. Periodic acid Schiff stain was negative. The immunology workup showed appropriate levels of immunoglobulins and normal CH50. Sweat test for cystic fibrosis and alpha-1-antitrypsin levels were within normal ranges. Cardiac echocardiography (ECHO) suggested evidence of pulmonary arterial hypertension (PAH) with right ventricle and pulmonary artery dilatation secondary to chronic lung disease. The maximal tricuspid regurgitation velocity on ECHO was 3.17 m/s (normal <2.5 m/s). Cardiac catheterization confirmed the diagnosis of severe PAH revealing baseline pulmonary arterial pressure of 64/34 mmHg with 10.2 WU m² and a positive acute vasoreactivity testing with nitric oxide (NO) to 45/20 mmHg and 5.4 WU m².

The earliest radiological imaging of the patient was a high-resolution computed tomography (HRCT) of the lungs performed at 14 months of age which was remarkable for evidence of marked, patchy ground-glass opacities (Figure 2, Panels C, D). When the patient was three years old, a follow-up HRCT demonstrated the development of a myriad of pulmonary cystic lesions. A subsequent scan performed when the patient was six years old continued to demonstrate diffuse pulmonary cysts of varying sizes, but with decreased attenuation of ground-glass opacities (Figure 2, Panel E). Simple chest X-rays showed bilateral and diffuse interstitial changes (Figure 2, Panels A, B).
The patient underwent genetic testing using a diagnostic genetic panel which was sequenced for 111 genes, including ABCA3, CSF2RA, CSF2RB, FOXF1, NKX2-1, SFTPB, and SFTPC. Genetic results were remarkable for one likely pathogenic variant in the SFTPC gene, IVS4+2, which is associated with autosomal dominant SP-C deficiency. All these findings were consistent with a diagnosis of SFTPC-related disorder.

Baseline dual-energy X-ray absorptiometry scan and ophthalmologic evaluation were obtained before treatment was initiated. The medication regimen included hydroxychloroquine 10 mg/kg/day at start dose for three months and 5 mg/kg/day as maintenance and azithromycin 500 mg three times a week as anti-inflammatory therapy. Verapamil 120 mg daily, sildenafil 20 mg three times a day, and bosentan 62.5 mg twice daily were added for pulmonary hypertension management. The patient was also started on serial intravenous pulses of methylprednisolone at 1 g/day for three doses on a monthly basis. Following three months of therapy, the patient tolerated breathing on room air and reserved his nasal cannula use for more demanding physical activities. Furthermore, the predicted DLCO increased to 38%. His most recent HRCT showed no progression of his pulmonary lung disease with persistent diffuse lung cysts (Figure 2, Panel F).

**Discussion**

Surfactant proteins play a coordinating role in the synthesis, secretion, film formation, and recycling of phospholipids. SP-C has been postulated to modulate membrane-associated viral sensors such as toll-like receptor 3 [14]. Diseases that affect the production of these lipoproteins result in the development of chILD [13]. Previous studies have demonstrated that mutations that affect SP-B are incompatible with life if not corrected with bilateral lung transplantation [9,16]. However, given the normal pulmonary function of neonates and infants with SFTPC mutations, it is presumed that surfactant function remains stable until challenged by overwhelming inflammatory responses from common viral infections such as RSV [9,14]. This has been demonstrated with genetically modified SP-C null mice that exhibit decreased clearance of RSV with an associated prolonged inflammatory response. With the high prevalence and high reinfection rate of RSV, SP-C-deficient children suffer from increased and recurrent lung injury [14]. Furthermore, misfolded proSP-C accumulates in type II alveolar cells, leading to inflammation and cellular death. Destruction of type II alveolar cells prevents their normal function of replenishing type I alveolar cells after cellular injury. Ultimately, this leads to the development of pulmonary fibrosis, as seen in our case [1].

The phenotype of SFTPC-mutated patients is highly variable and depends little on the type of mutation, localization in the gene, or the age of onset. Even when different patients inherit the most prevalent SFTPC mutation, p.I73T (c.218T>C), the disease manifestation can vary from death in infancy to an asymptomatic carrier state [3,8]. This suggests that clinical presentation is likely multifactorial. As such, it is difficult to compare SFTPC-mutated patients based on their genetic sequence alone [11].
To our knowledge, our case comprises the second known documented case of the IVS4+2 genetic variant. This mutation causes a sequence change (c.435+2T>C) on the SFTPC gene that induces an altered splice site that leads to a shortened protein product. IVS4+2 was discovered by van Moorsel et al. [10] in a 30-year-old Dutch patient with a personal history of ILD and a family history of pulmonary fibrosis. With reverse transcription-polymerase chain reaction (PCR) of the patient’s lung sample, they were able to demonstrate a truncated 200 bp product compared to the expected wild-type PCR product of 311 bp. Sequencing of the IVS4+2 PCR product revealed a lack of exon 4 of SFTPC. It cannot be established if the mutation in our patient was sporadic or part of a familial pulmonary fibrosis pattern because there is missing history and genetic sample from his father. The patient’s mother, however, tested negative for the presence of any SFTPC mutation.

Treatment of SP-C deficiency is derived from the overall management of chILD [16]. The therapeutic approach is mostly supportive therapy with empiric pharmacological treatment with corticosteroids, hydroxychloroquine, and azithromycin. Corticosteroids such as methylprednisolone pulse or oral prednisone are the mainstay treatments in chILD with inflammatory lung damage [13,16]. Hydroxychloroquine has been used successfully in several cases of SFTPC mutations. It is postulated to interfere and decrease the accumulation of aberrant proSP-C on type II alveolar cells [11,12,17]. In extreme cases, lung transplantation has been implemented, although this practice is more common in SP-B deficient patients [9,11,16]. No clinical studies on pharmacological treatment have been conducted specifically with SP-C deficient patients. Other strategies, such as surfactant replacement, only seem to provide transient relief and provide no long-lasting benefits [18]. Our patient also had evidence of severe PAH, which is not often detailed in case studies of SP-C deficiency. This was first seen on ECHO and later confirmed during cardiac catheterization. Verapamil, sildenafil, and bosentan were added to his medication regimen to control PAH as per the established guidelines [19].

Kroner et al. [11] reported that outcomes for treated SFTPC-mutated patients tend to be halting of disease progression, with significant improvement only seen in a minority of cases. Our patient continued this disease-halting trend given that complete PFTs following treatment managed to slightly increase DLCOcor parameters and there was no significant change on HRCT. This suggests the need for swift recognition of this disease to prevent irreversible lung damage. Given the high variability in clinical presentation, lack of standardization of treatment, wide side effect profile of medications, and multiple comorbidities associated with SP-C deficiency, a multidisciplinary approach that includes a variety of subspecialties should be established to manage clinically complex pediatric patients with rare pulmonary diseases (Table 1).
| Subspeciality | Screening | Evaluation |
|-------------|-----------|------------|
| Cardiology  | Evaluate for the presence of congenital heart malformations or pulmonary arterial hypertension. Detection of prolonged QTc interval in view of long-term use of medications that affect QTc | 2D echocardiography with tissue Doppler and color flow to evaluate heart function and detection of right heart strain. ECG prior to long-term use of hydroxychloroquine and azithromycin combination due to QTc prolongation and torsade de pointes. Cardiac catheterization for documentation of pulmonary arterial pressures, if clinically indicated |
| Endocrinology | Monitoring for the development of Cushing’s syndrome/adrenal suppression secondary to exogenous corticosteroid use and appropriate withdrawal from chronic steroid therapy. Provide recommendations about stress doses prior to surgeries or invasive procedures | Morning cortisol, serum ACTH, and glucose levels |
| Genetics     | Diagnostic genetic testing for SFTPC gene mutations and genetic counseling about family planning. Rule out other genetic child/L disorders as part of the differential diagnosis | Referral to a genetic counselor for diagnostic discussion and prognostic and family planning |
| Nutrition    | Monitor for height/weight to achieve a goal at the 50th percentile for age | Weight loss management strategies. Caloric intake adjustments to meet specific nutritional daily requirements |
| Ophthalmology | Screening for cataracts and glaucoma as a side effect of chronic steroid and hydroxychloroquine use | Ophthalmologic examination at baseline, followed by annually |
| Primary care | Detection of anemia, leukopenia, thrombocytopenia, or G6PD deficiency in view of chronic treatment with hydroxychloroquine. Screening for systemic hypertension | Baseline lab work (CBC, LFTs) prior to initiating hydroxychloroquine, baseline DEXA scan prior to corticosteroid therapy due to risk of osteopenia. Monitor blood pressure levels. Follow immunization schedule, including influenza, pneumococcal polysaccharide vaccine (PPSV23), and SARS-CoV-2 vaccine as per the American Academy of Pediatrics guidelines |
| Pulmonology  | Screening for baseline and exertional hypoxemia, exercise intolerance, and evaluation airflow limitations. Documentation of abnormal pulmonary sounds on examination, and presence of clubbing. Assessment for lung transplantation, if needed | Baseline radiographic imaging of the chest X-ray or high-resolution computed tomography of the lungs. Record the percentage of oxygen saturation during every visit at rest and with activity. Serial spirometry every 3 months and complete pulmonary function test with DLCO every 6-12 months. Six-minute walk test to monitor for exertional hypoxemia |
| Sleep medicine | Screening of pediatric sleep disorders and nocturnal hypoxemia or hypoventilation | May consider diagnostic polysomnography with end-tidal CO₂ and/or CPAP titration studies if evidence of obstructive sleep apnea is present. Management of sleep-related disorders |

**TABLE 1: Suggested multidisciplinary approach to manage SP-C deficiency in pediatrics.**

ECG: electrocardiogram; ACTH: adrenocorticotropic hormone; chILD: childhood interstitial lung disease; CBC: complete blood count; LFT: lung function test; DEXA: dual-energy X-ray absorptiometry; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

Ground-glass opacities either alone or mixed with small, diffuse lung cysts have been reported as the most frequent findings seen on HRCT of SFTPC-mutated patients [20]. Furthermore, it has been reported that, although nonspecific to SP-C deficiency, ground-glass opacities tend to decrease with age while lung cysts generally increase. Ground-glass opacities can be appreciated as early as nine months of age on all reported SFTPC-mutated cases [11,20]. Our patient presented with the same progression as evident by extensive ground-glass lesions seen on HRCT at 14 months of age (Figures 2C, 2D), and presented with a myriad of pulmonary cysts but scarcely appreciated ground-glass lesions on follow-up imaging at 6 and 13 years of age (Figures 2E, 2F). Mechri et al. [20] established a correlation between radiologic findings of HRCT with histopathology of lung biopsy. Ground-glass opacities on HRCT correlated with diffuse alveolar septal thickening, type II pneumocyte hyperplasia, and intra-alveolar accumulation of macrophages, while lung cysts correlated with dilation of the respiratory bronchiolue and alveolar ducts. Our patient’s biopsy results were consistent with these findings.
SFTPC mutations and SP-C deficiency had not been previously documented in the Puerto Rican population. With better screening tools, previously unknown etiologies of ILD may become apparent. This grants the patient a more specific prognosis and disease-oriented management strategies [16]. Additionally, there is overall scarce data available for SP-C deficiency. Therefore, further identification and classification of SFTPC mutations are crucial to gain a better understanding of the disease, especially in pediatrics.

Conclusions
We present the first known documented pediatric case of chILD due to SP-C deficiency in a Puerto Rican patient. Moreover, this is the second known case of the IVS4+2 genetic variant, and the first case described in a pediatric patient. Due to its variable phenotypic presentation, early screening with genetic testing for surfactant protein disorders, including SFTPC mutations, in patients presenting with ILD of unknown etiology should be considered.

Additional Information
Disclosures
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