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Surfactant protein C dysfunction with new clinical insights for diffuse alveolar hemorrhage and autoimmunity

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ABSTRACT

Importance: Surfactant protein C (SP-C) dysfunction is a rare disease associated with interstitial lung disease. Early therapies may improve outcomes but the diagnosis is often delayed owing to variability of manifestations.

Objective: To investigate the manifestations and outcomes of SP-C dysfunction.

Methods: We retrospectively analyzed the records of five pediatric patients who were diagnosed with SP-C dysfunction between February 2014 and April 2017 at Beijing Children's Hospital.

Results: The five patients included two boys and three girls with a median age at diagnosis of 1.3 years. All patients presented with interstitial lung disease and had a heterozygous *SFTPC* mutation, including an I73T mutation in three patients, a V39L mutation in one patient, and a Y104H mutation in one patient. In addition to common respiratory manifestations, hemoptysis and anemia were observed in one patient with the I73T mutation. Elevated levels of autoantibodies and a large number of hemosiderin-laden macrophages in bronchoalveolar lavage fluid were found in two patients with the I73T mutation, suggesting the presence of diffuse alveolar hemorrage and autoimmunity. Chest high-resolution computed tomography features included ground-glass opacities, reticular opacities, cysts, and pleural thickening. Transbronchial lung biopsy was performed in one patient with the I73T mutation, which revealed the presence of some hemosiderin-laden macrophages in alveolar spaces. All patients received treatment with corticosteroids; two received combined treatment with hydroxychloroquine. During follow-up, the two patients who received hydroxychloroquine showed improved symptoms; of the remaining three patients, two died after their families refused further treatment, while the final patient was lost to follow-up.

Interpretation: This is the first report to describe a new phenotype of diffuse alveolar hemorrhage with autoimmunity in patients with I73T *SFTPC* mutation. Treatment with hydroxychloroquine should be considered for patients with SP-C dysfunction.

KEYWORDS

Autoimmunity, Diffuse alveolar hemorrhage, Interstitial lung disease, Rheumatoid arthritis, Surfactant protein C

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INTRODUCTION

Surfactant protein C (SP-C) dysfunction is a rare autosomal dominant disease caused by a mutation in the *SFTPC* gene. It is reportedly associated with progressive respiratory insufficiency and interstitial lung disease (ILD) with variations in the age of onset, severity, and clinical manifestations.[1-13] The pathophysiology of the disorder is presumed to involve aberrant surfactant protein processing and epithelial type II cells injury.[2] In this study, we assessed five pediatric patients with pathogenic heterozygous *SFTPC* mutations associated with ILD, and report new clinical aspects of diffuse alveolar hemorrhage (DAH) with autoimmunity in two pediatric patients with the I73T *SFTPC* mutation.

METHODS

We retrospectively analyzed five pediatric patients who were diagnosed with SP-C dysfunction between February 2014 and April 2017 in the Second Department of Respiratory Medicine at Beijing Children's Hospital. All diagnoses were made by genetic testing using a broad next generation sequencing panel that include more than 4000 known genetic diseases, then confirmed by Sanger sequencing. Data collected in this study included age, sex, clinical manifestations, chest high-resolution computed tomography (HRCT) features, autoantibody tests results, pathology findings, coagulation function test results, bronchoalveolar lavage fluid (BALF) results, echocardiography results, 24-hour esophageal pH monitoring results, upper gastrointestinal contrast findings, lung biopsy results, genetic data, treatment, and prognosis.

RESULTS

Demographic features

The five pediatric patients included two boys and three girls. The median age at diagnosis was 1.3 years (0.4–9 years).

Clinical manifestations

Clinical symptoms of the five patients included cough (five patients), clubbing figure (four patients), tachypnea (four patients), exercise intolerance (three patients), failure to thrive (four patients), hypoxemia (three patients), dyspnea (two patients), retractions (two patients), crackles (two patients), and wheezing (one patient). In addition, one patient presented with hemoptysis and anemia (Table 1).

Laboratory tests and other investigations

Autoantibody tests were performed in all five patients. Elevated levels of autoantibodies were found in two patients with the I73T *SFTPC* mutation: elevated levels of rheumatoid factors (RFs) in Patient 1; elevated levels of antinuclear antibodies (ANA), RF and anti-cyclic citrullinated peptide (CCP) in Patient 2 (Table 1). In all patients, pathology findings were negative for *Pneumocystis jiroveci*, cytomegalovirus, Epstein–Barr virus, mycoplasma, and tuberculosis. Coagulation function was normal in all patients. Bronchoscopy was performed in four of the five patients (Patients 1, 2, 4 and 5); large numbers of hemosiderin-laden macrophages were found in the BALF of Patients 1 and 2, which suggested the presence of DAH. Elevated levels of lymphocytes were found in the BALF of Patients 1 and 4. Periodic acid-Schiff (PAS) staining of the BALF were negative in all four patients tested. Twenty-four-hour esophageal pH monitoring or upper gastrointestinal contrast procedures were performed in four patients (Patients 1, 2, 3, and 4) and gastroesophageal reflux was found in Patients 2 and 3. All five patients underwent echocardiography, which did not demonstrate ventricular dysfunction or pulmonary hypertension (Table 1).

Chest HRCT features and pathological findings

All five patients had diffuse infiltrates on chest HRCT, indicative of ILD (Figure 1). Ground-glass opacities were the most common features present in all five patients. Cystic lesions were present in two patients, reticular opacities were present in two patients, and pleural thickening was present in one patient. Enhanced CT pulmonary angiography was performed in Patients 1 and 2 who had DAH without findings of pulmonary vascular malformation. A transbronchial lung biopsy was performed in Patient 2, which revealed a thickened alveolar septum with mild infiltration of lymphocytes and the presence of some hemosiderin-laden macrophages in alveolar spaces (Figure 2).

Genetic tests

Next generation sequencing and Sanger sequencing assays showed that all five patients were heterozygous for mutations in the *SFTPC* gene, including c.218T>C, p.I73T in three patients (Patients 1, 2 and 3); c.115G>T, p.V39L in Patient 4; and c.310T>C, p.Y104H in Patient 5. The mutation in Patient 2 was inherited from her father, who had ILD and rheumatoid arthritis (RA) with positive autoantibodies. The mutation in Patient 5 was inherited from her asymptomatic father. In contrast, the mutations in Patients 1, 3, and 4 were *de novo*. Some identified variants in other genes were shown in Table S1.

Treatment and prognosis

All five patients were treated with corticosteroids. In addition, Patient 1 received combined treatment with hydroxychloroquine with a daily dosage of 6 mg/kg. Patient 2 received combined treatment with cyclophosphamide in the first year, followed by treatment with hydroxychloroquine at 6 mg/kg daily. Patients 3 and 5 received combined treatment with intravenous immunoglobulin.

During follow-up, Patient 1 showed improved respiratory symptoms based on chest HRCT at 2.3 years after initial

TABLE 1 Clinical manifestations, laboratory investigations, genetic data, treatment and prognosis of patients with surfactant protein C dysfunction

Variables	Patient 1	Patient 2	Father of Patient 2	Patient 3	Patient 4	Patient 5
Age at diagnosis (years)	1.3	3	31	0.4	9	0.5
Age of onset (years)	0.8	2	NA	0.3	6.5	0.1
Sex	Male	Female	Male	Male	Female	Female
Clinical manifestations						
Cough	+	+	−	+	+	+
Tachypnea	+	+	−	−	+	+
Dyspnea	−	+	−	−	−	+
Hypoxemia	+	+	−	−	−	+
Exercise intolerance	+	+	+	−	+	−
Retractions	−	+	−	−	−	+
Wheezing	−	−	−	−	−	+
Crackles	+	−	−	+	−	−
Digital clubbing	+	+	+	+	+	−
Hemoptysis	−	+	−	−	−	−
Anemia	−	+	−	−	−	−
Failure to thrive	+	+	−	+	−	+
Arthritis	−	−	+	−	−	−
GER	−	+	NA	+	−	NA
Laboratory data						
ANA	Normal–Normal*	Elevated (titer 1:640–titer 1:160*)	Elevated (titer 1:640)	Normal	Normal	Normal
Ds-DNA	Normal–Normal*	Normal–Normal*	Normal	Normal	Normal	Normal
RF (IU/mL)	Elevated (85.4)–Normal*	Elevated (726.0–113.0*)	Elevated (134.0)	NA	Normal	Normal
CCP (RU/mL)	Normal–Normal*	Elevated (54.0–41.3*)	Elevated (37.6)	NA	Normal	Normal
ANCA	Normal–Normal*	Normal–Normal*	Normal	Normal	Normal	Normal
BALF tests	A large number of hemosiderin-laden macrophages with elevated lymphocytes; PAS stain (−)	A large number of hemosiderin-laden macrophages; PAS stain (−)	NA	NA	Elevated lymphocytes, neutrophil granulocytes and eosinophilic granulocytes; PAS stain (−)	Normal cytology index; PAS stain (−)
Genetic data	*SFTPC* c.218T>C p.I73T	*SFTPC* c.218T>C p.I73T	*SFTPC* c.218T>C p.I73T	*SFTPC* c.218T>C p.I73T	*SFTPC* c.115G>T p.V39L	*SFTPC* c.310T>C p.Y104H
Phenotype	ILD, DAH	ILD, DAH	ILD, RA	ILD	ILD	ILD
Treatment	Corticosteroids; Hydroxychloroquine	Corticosteroids; Cyclophosphamide; Hydroxychloroquine	NA	Corticosteroids; IVIG	Corticosteroid	Corticosteroids; IVIG
Status at last following up	Alive, with improved symptoms and HRCT	Alive, with improved symptoms and HRCT	NA	Died	Lost to follow-up	Died
Age at last following up or died (years)	3.3	6.5	NA	0.6	NA	0.6

*Results of repeated laboratory tests at final follow-up; +, positive; −, negative; NA, not available; GER, gastroesophageal reflux; ANA, antinuclear antibodies; RF, rheumatoid factors; CCP, anti-cyclic citrullinated peptide; ANCA, anti-neutrophil cytoplasmic antibodies; BALF, bronchoalveolar lavage fluid; PAS, periodic acid-Schiff; ILD, interstitial lung disease; DAH, diffuse alveolar hemorrhage; RA, rheumatoid arthritis; IVIG, intravenous immunoglobulin; HRCT, high-resolution computed tomography; *SFTPC*, surfactant protein C.

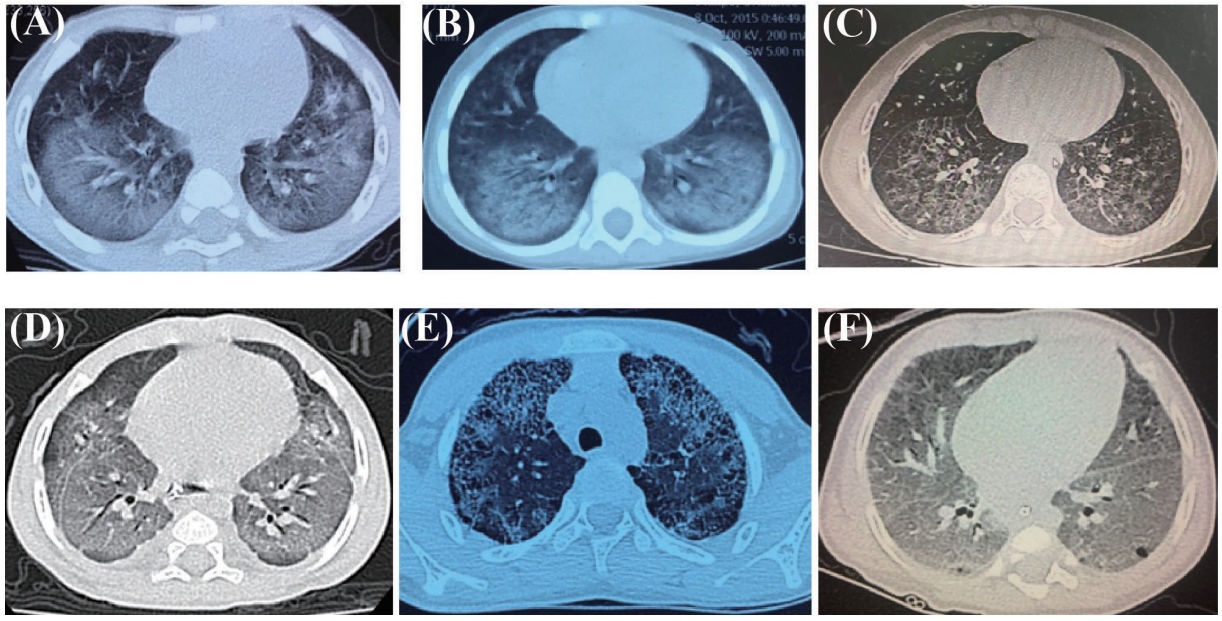

FIGURE 1 Chest high-resolution computed tomography (HRCT) of patients with surfactant protein C dysfunction. (A) HRCT of Patient 1 before treatment shows bilateral diffuse ground-glass opacities. (B) HRCT of Patient 2 before treatment shows bilateral diffuse ground-glass opacities. (C) HRCT of Patient 2 three years later after the treatment of prednisone and hydroxychloroquine shows bilateral reticular opacities and improvement of ground-glass opacities. (D) HRCT of Patient 3 before treatment shows bilateral diffuse ground-glass opacities. (E) HRCT of Patient 4 before treatment shows bilateral diffuse cysts and reticular opacities. (F) HRCT of Patient 5 before treatment shows bilateral diffuse ground-glass opacities with cysts.

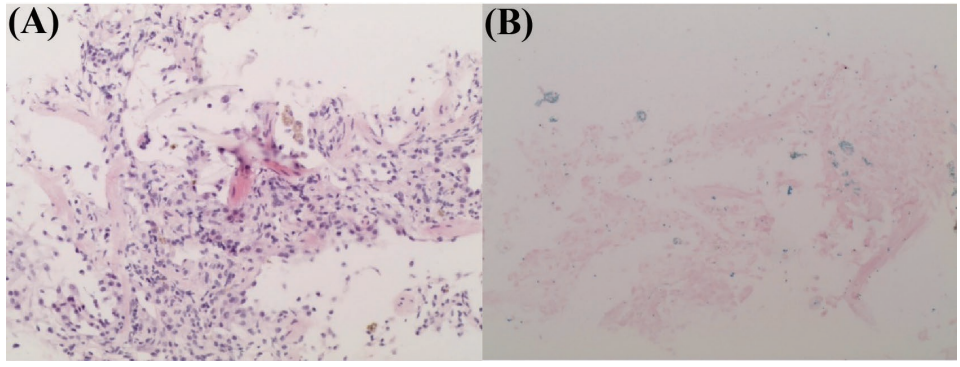

FIGURE 2 Lung pathological findings of one patient with surfactant protein C dysfunction. (A) Transbronchial lung biopsy (Hematoxylin-eosin stain; magnification ×20) of Patient 2 reveals thickened alveolar septum with mild infiltration of lymphocytes. (B) Transbronchial lung biopsy (Iron stain; magnification ×20) of Patient 2 reveals some hemosiderin-laden macrophages in alveolar spaces (staining blue).

treatment. Patient 2 also showed improved respiratory symptoms, and the results of pulmonary ventilation function tests performed at 6.5 years of age were normal. Chest HRCT at 3.5 years after the initial treatment of Patient 2 showed improvement in ground-glass opacities, whereas it showed progression of cysts and reticular opacities (Figure 1C). The families of Patients 3 and 5 declined further treatment and both patients subsequently died of respiratory failure. Patient 4 was lost to follow-up (Table 1).

DISCUSSION

Here, we described five pediatric patients with SP-C dysfunction caused by three *SFTPC* mutations, including I73T, V39L and Y104H. Since the initial identification of *SFTPC* mutations in 2001,[1] several mutations have been reported in patients with ILD.[1-13] The I73T mutation is the most common *SFTPC* mutation.[1,3-5,9,10] The V39L *SFTPC* mutation has also been identified in many patients, including five Chinese patients.[9,10] There have been a few reports of ILD associated with the Y104H *SFTPC* mutation[3]; notably, an adolescent boy with a family history of ILD was reported to have a Y104H mutation.[11] The presence of a Y104H mutation in one patient in our study further evidence that this mutation is pathogenic.

SP-C dysfunction is associated with a variety of

ILD phenotypes, including respiratory distress syndrome in neonates, pulmonary alveolar proteinosis, histopathological pattern of nonspecific interstitial pneumonia, desquamative interstitial pneumonia, and usual interstitial pneumonia.[10,12-15] The severity of SP-C dysfunction ranges from mild or no respiratory symptoms to fatal respiratory failure. To the best of our knowledge, this is the first report of SP-C dysfunction associated with the DAH phenotype in two patients. Patient 2 had symptoms of hemoptysis and anemia, diffuse ground-glass opacities in HRCT, a large number of hemosiderin-laden macrophages in BALF, and hemosiderin-laden macrophages in alveolar spaces (identified via lung biopsy). Patient 1 also had diffuse ground-glass opacities in HRCT, a large number of hemosiderin-laden macrophages in BALF, but no symptoms of hemoptysis or anemia. DAH may be easily missed diagnosed in patients without symptoms of hemoptysis or anemia; therefore, bronchoscopy with BALF analysis may be necessary in patients with SP-C dysfunction. The cause of DAH in our patients was unknown. Infectious diseases, such as pulmonary tuberculosis and fungal infection, as well as pulmonary vascular malformation and coagulation disorders, were ruled out by the normal pathogenic detection results and normal findings in enhanced CT pulmonary angiography and coagulation function tests. Furthermore, both patients with DAH had elevated levels of autoantibodies, which suggests an underlying autoimmune process may play a role in the DAH.

Two of the patients in this study had elevated levels of autoantibodies; however, neither had developed any symptoms of arthritis or rashes at the time of the study, nor did they meet the established criteria for RA or other connective tissue disease (CTD). Nevertheless, the findings suggested that these patients might develop RA or CTD in later life. Notably, the father of Patient 2 (with the same I73T *SFTPC* mutation as the patient) developed RA at 31 years of age, several years after the onset of ILD. Therefore, these pediatric patients may be in a pre-RA or pre-CTD state, and should be closely monitored. It is uncertain whether the I73T *SFTPC* mutation is responsible for the presence of autoimmunity in these patients. It is possible that another pathogenic gene mutation coexists, such as the *COPA* gene mutation, which can cause COPA syndrome (characterized by DAH, ILD, and arthritis),[16] or the *TMEM173* gene mutation, which can cause STING-associated vasculopathy with onset in infancy (SAVI) (characterized by ILD, rashes, and elevated levels of autoantibodies).[17] Although both of these genes were included in the broad next generation sequencing panel, no known pathogenic mutations were found. In a previous study, the coexistence of RA and SP-C dysfunction was observed in one adult with the same I73T *SFTPC* mutation and RA-ILD.[18] In our study, Patients 1 and 2 had I73T *SFTPC* mutations and elevated levels of autoantibodies, and the father of Patient 2 had an I73T *SFTPC* mutation and RA; these findings imply that SP-C dysfunction is potentially associated with an underlying autoimmune process that may progress into RA or another type of CTD. *SFTPC* mutations have been reported to contribute to ILD pathogenesis via endoplasmic reticulum stress in alveolar epithelial type II cells,[15,19] as well as regulation of inflammation.[20] The presence of coexisting SP-C dysfunction and RA or pre-RA in patients in the present study highlights the possibility for a new pathogenic mechanism involving *SFTPC* mutations in autoimmune disease. Furthermore, ILD is a common complication of RA, and may rarely present as an initial manifestation.[21-23] DAH has also been reported in patients with RA[24,25]; thus, SP-C dysfunction may be misdiagnosed in these patients. We propose that SP-C dysfunction, as well as COPA syndrome and SAVI should be considered as possible differential diagnoses in patients with RA or other CTD-associated ILD and/or DAH; moreover, genetic tests should be considered, especially in patients who present with ILD and/or DAH as an initial or primary manifestation.

Hydroxychloroquine has previously been reported as an effective treatment for ILD associated with SP-C dysfunction.[10,26-28] The presumed mechanism of activity of hydroxychloroquine includes its anti-inflammatory properties and possible inhibition of the intracellular processing of SP-C precursors.[26,29] In our study, two pediatric patients received treatment with hydroxychloroquine as a component of therapy; both responded well with improved respiratory symptoms. Follow-up HRCT in Patient 2 showed improvement in ground-glass opacities, but progression of cysts and reticular opacities, suggesting that the ILD was partially controlled. In addition, hydroxychloroquine demonstrated a therapeutic effect on the autoimmune process in Patient 1, who had undetectable levels of RF after treatment, and in Patient 2, who showed reduced levels of RF and CCP autoantibodies.

Here, we have reported a new phenotype of DAH with autoimmunity in pediatric patients with the I73T *SFTPC* mutation, which highlights the possibility of an association between the *SFTPC* mutation and autoimmunity. Treatment with hydroxychloroquine should be considered for pediatric patients with SF-C dysfunction.

CONFLICT OF INTEREST

The authors have indicated no conflicts of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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