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Familial interstitial pneumonia in an adolescent boy with surfactant protein C gene (Y104H) mutation

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Abstract. Recent studies have suggested that some cases of familial interstitial pneumonia are associated with mutations in the gene encoding surfactant protein C (SFTPC). We report here a case of familial interstitial pneumonia in an adolescent boy whose paternal grandfather and father suffered from idiopathic interstitial pneumonia (IIP). The patient was asymptomatic but showed an abnormal shadow in the chest at his medical check-up. The surgical biopsy of the patient revealed non-specific interstitial pneumonia and showed pathological findings similar to those in his father's autopsy. Genomic DNA from blood leucocytes of the patient was sequenced for the Thy104His (Y104H) SFTPC mutation. Based on these results, he was diagnosed with SFTPC mutation-associated familial interstitial pneumonia. There has been no clinical, physiologic and radiologic progression for 4 years since the diagnosis. The relation between clinical manifestation and the mutation site of the patient may broaden the spectrum of SFTPC mutation-associated interstitial pneumonia. *(Sarcoidosis Vasc Diffuse Lung Dis 2013; 30: 73-77)*

Key words: final interstitial pneumonia (FIP), surfactant protein C, mutation, Y104H

Introduction

Familial interstitial pneumonia (FIP) was originally defined when two or more individuals in a single family had idiopathic interstitial pneumonia (IIP) (1). During the past decade, genetic causes of FIP have been revealed (2). Some familial cases of interstitial pneumonia have been caused by mutations in the gene encoding surfactant protein C (SFTPC) (3-5). Since Nogee et al. first described an SFTPC mutation in 2001 (3), various mutations within the SFTPC gene have been associated with pediatric and adult-onset ILD (4-10). The I73T mutation in exon 3 is the most common SFTPC mutation, and it is associated with not only progressive but also chronic pediatric interstitial lung disease (ILD) (7-9). In this report, we describe fibrosing nonspecific interstitial pneumonia (NSIP) in an adolescent boy whose grandfather and father had been clinically diagnosed with IIP. Genetic analysis was performed to investigate the relationship between mutations in SP-C genes and ILD in the younger generation. The pathological and radiological findings of the patient were compared with those of his father and discussed.

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Case Report

A 15-year-old Japanese male displayed abnormal findings in a chest-radiograph at his medical check-up. He had never smoked and had no respiratory symptoms. His medical record described bronchial asthma in his childhood. There was no history of dust exposure. His paternal grandfather and father had been diagnosed with IIP based on clinical presentation. The medical record of his paternal grandfather described idiopathic interstitial pneumonia. However, there is no information of radiological and pathological findings. His father had also displayed abnormal chest findings at a medical check-up in his late twenties. Conventional chest CT demonstrated sub-pleural honeycombing throughout the whole lung, and the distribution was more extensive in upper lung zones. Surgical lung biopsy (SLB) was performed in the 1980s. Biopsy specimens of the lung showed heterogeneous appearance. Fibroblast foci were occasionally seen, and honeycombing was distributed predominantly to paraseptal lesions. Based on these radiological and pathological findings, his father had been diagnosed with IIP in the 1980s.

While the detailed treatment of the patient's grandfather was unknown, his father had been treated with oral corticosteroid according to his medical records. Despite treatments with corticosteroid and supplemental oxygen, his condition progressively worsened, and the grandfather died of IIP complicated with lung cancer in his eighties. The patient's father died of progressive respiratory failure related to IIP in his thirties. An autopsy performed on his father revealed fibrous thickening of the alveolar walls with scattered lymphocyte and monocyte infiltration in addition to the pathological findings of the SLB.

On physical evaluation, the patient had no crackling on auscultation. There were no physical signs suggestive of collagen vascular diseases. Rheumatological, immunological, and general laboratory studies were negative. C-reactive protein was <0.1 mg/dL, rheumatoid factor and anti-nuclear antibodies were negative, and creatine kinase, lactate dehydrogenase, aldolase and angiotensin-converting enzyme (ACE) levels were normal. Sputum culture to detect bacteria, fungus and mycobacterium were negative. A chest radiograph showed bilateral small nodular shadows in the whole lung field. High-resolution computed tomography (HRCT) demonstrated bilateral ground-glass attenuation with small nodules and interlobular septa thickening throughout both lungs. Hilar or mediastinal lymphadenopathy was not seen (Figure 1). Pulmonary function testing (PFT) revealed no obstructive defect; FVC was 85% of predicted value. Diffusing capacity of carbon monoxide was 89% of predicted value. Oxygen saturation ranged from 97% to 95% with exercise while breathing room air.

Flexible bronchoscopy revealed normal airway anatomy. Bronchoalveolar lavage (BAL) revealed mild inflammatory changes, with a cell differential count of 91% macrophages, 8% lymphocytes and 1% neutrophils. Microbiological studies were negative in BAL fluid.

Video-assisted thoracoscopic surgical (VATS) lung biopsy was performed of the right upper lobe. Biopsy specimens of the lung showed patchy interstitial fibrosis around the alveoli and thickened alveolar septa with lymphocyte infiltration. Fibroblastic foci were occasionally seen (Figures 2a and b). Immunostaining for PE-10 (DAKO Japan, Kyoto) revealed hyperplasia of type II pneumocytes (Figure 2c). Those patterns were consistent with features of fibrosing non-specific interstitial pneumonia (fNSIP) and were similar to the findings in his father's autopsy. In some areas of lung specimens, bronchiolocentric lesions and giant multinucleated cells were also observed (Figure 2d).

Sequencing of the SP-C locus was performed from genomic DNA isolated from peripheral blood leucocytes obtained from the patient. Sequence reactions were performed using an ABI prism Big Dye terminator cycle sequencing ready kit (Applied Biosystems, Forster, CA, USA) as described previously (10). Genetic analysis revealed a heterozygous (T to H transition at amino acid position 104 in exon 3), Y104H SFTPC mutation. Therefore, we diagnosed the condition as familial interstitial pneumonia associated with SFTPC mutation. No SFTPC mutation was detected in blood leucocytes from the patient's mother or older sister.

Over the 4 years since presentation, the patient has shown no clinical, physiologic, or radiographic progression. No empiric therapies have been introduced.

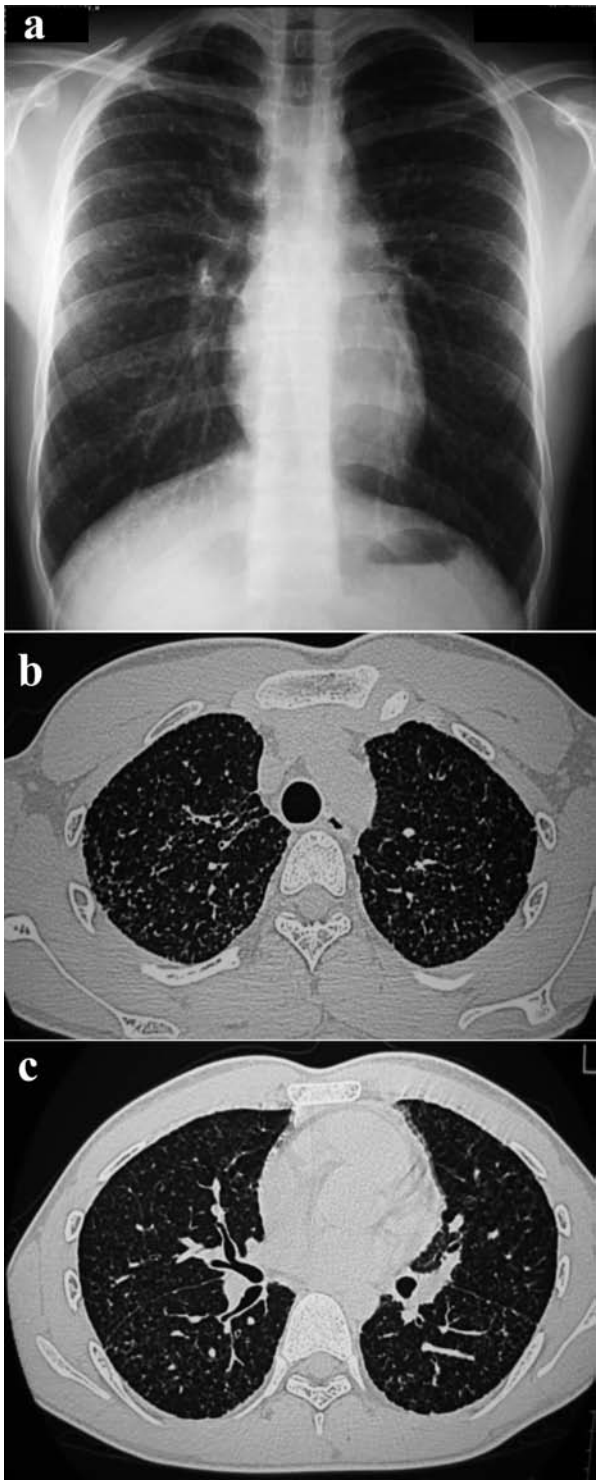

Fig. 1. (a) Chest radiology at the age of 15 years showing small nodular shadows in the whole lung field. b and c, High-resolution CT demonstrates bilateral ground-glass attenuation with small nodules and interlobular septal thickening throughout both lungs; upper (b) and lower (c) lobes

Discussion

This is the first case report of familial interstitial pneumonia in an adolescent associated with an Y104H SFTPC mutation. The patient displayed an abnormal chest shadow at the age of 15 without showing any symptoms. His grandfather and father were both diagnosed with IIP and died in their eighties and thirties, respectively. Pathological findings of the surgical biopsies were consistent with fNSIP and were similar to those found at his father's autopsy. Katzenstein and Fiorelli proposed the concept of NSIP in 1994 (11), and the definition of IIPs became more restrictive in the ATS/ERS consensus statement of 2002 (12). His father was diagnosed with IIP based on radiological and pathological findings in the 1980s. The findings of his SLB and autopsy were re-examined and re-diagnosed as fNSIP according to the present criteria.

Genetic analysis revealed a mutation of T to H transition at amino acid position 104 in exon 3. Therefore, we concluded that our patient was an adolescent case of familial interstitial pneumonia associated with an Y104H SFTPC mutation.

Nogee et al. reported an SFTPC mutation associated with NSIP in an infant who had an onset of respiratory symptoms at 6 weeks of age and whose mother had been diagnosed with desquamative interstitial pneumonia at the age of 1 year. More than 40 distinct mutations in the SFTPC gene have been identified in ILD. In regard to exon 3, missense mutations such as I73T, G100V, Y104H, and P115L as well as a 9-bp deletion mutation have been reported (7). A heterozygous substitution of A for G was identified at the first base in intron 4 in the SP-C gene of the patient (3). Hamvas et al. reported on a 14 month-old infant with progressive, severe ILD who successfully underwent lung transplantation. Sequence analysis showed a 9-bp deletion in one allele in exon 3 of the SP-C gene (6). The I73T mutation, a change of isoleucine to threonine at amino acid position 73 in exon 3, is the most common SFTPC mutation, and it is associated with severe and chronic ILD (7-9). The natural history of ILD associated with SFTPC mutations is poorly understood, with unpredictable short- and long-term outcome. In addition, mechanisms by which SFTPC mutations could contribute to the pathophysiology of interstitial pneumonia are still unclear (13). Aber-

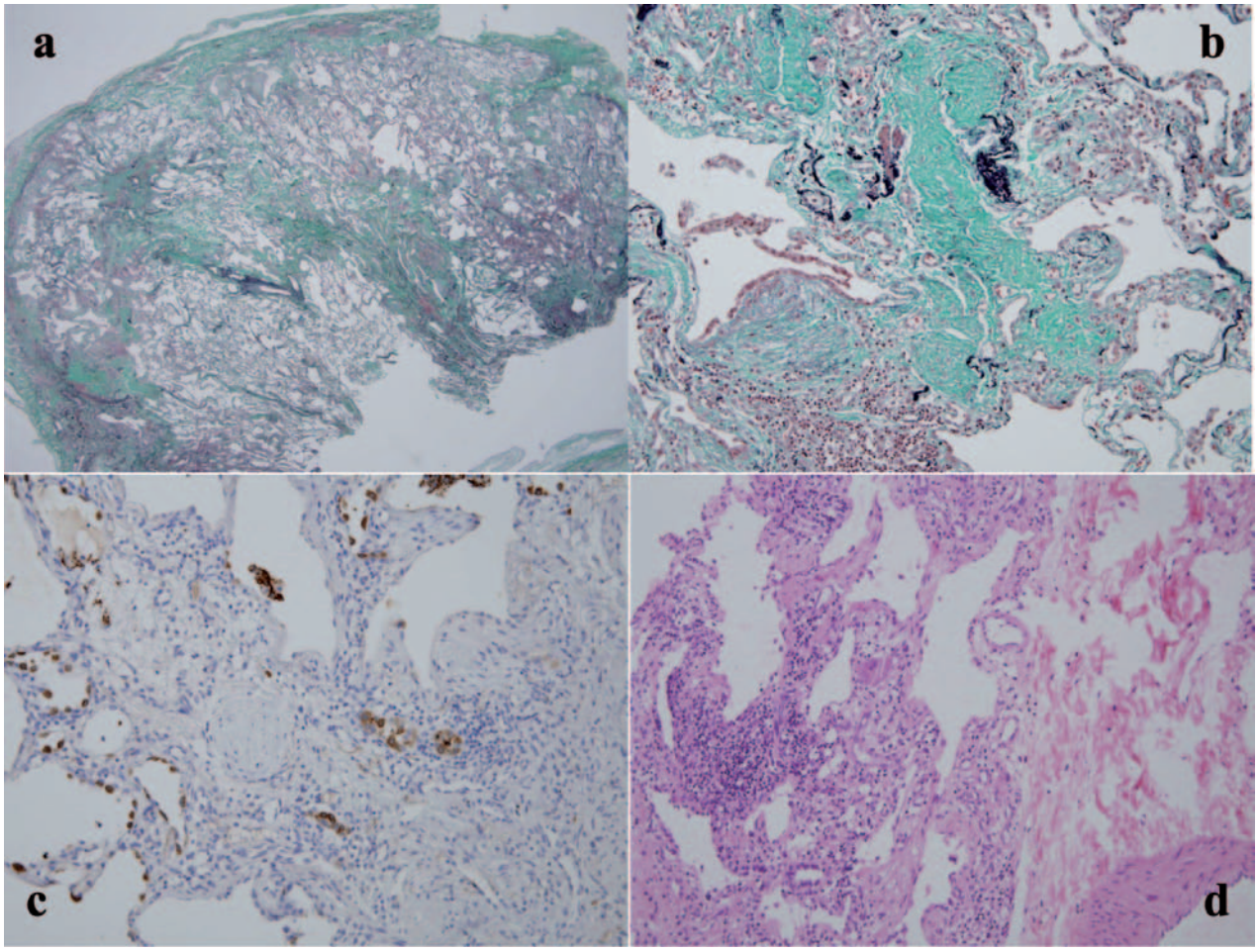

Fig. 2. (a) Low magnification of biopsied samples from the right upper lobe showing multiple patchy interstitial fibrosis (Elastica Masson Goldner; EMG staining). (b) Interstitial fibrosis around the alveoli and thickened alveolar septa with lymphocyte infiltration (EMG staining). Fibroblastic foci were occasionally seen. (c) Immunostaining for PE-10 revealed hyperplasia of type II pneumocytes. (d) Bronchiolocentric lesions and giant multinucleated cells were also observed (Hematoxylin and Eosin staining).

rant intracellular processing of pro-SP-C and then misfolding of SP-C could cause type II alveolar epithelial cell injury and apoptosis, followed by inflammation (14, 15). Mutations in the ATP-binding cassette A3 (ABCA3) have been associated with fatal respiratory failure in neonates without deficiency in SP-B and SP-C (16). A recent report suggested association of mutations in both SFTPC and ATP-binding cassette A3 (ABCA3) with adult-onset ILD (17).

There are few reports of ILD associated with the Y104H SFTPC mutation. It is unknown whether the Y104H SFTPC mutation affects SP-C function and then causes interstitial lung disease. However, accumulation of mutant pro SP-C peptide is expected to result in ILD in Y104H missense SFTPC mutation, as well as in the other SFTPC mutations in exon 3.

The radiological features in this case were not always similar to those of his father. In his father's chest CT sub-pleural honeycombing was identified throughout the whole lung, and the distribution was more extensive in upper lung zones (10). Chest HRCT in the present case displayed less honeycombing and less lower lung zone distribution, which is consistent with radiological features in FIP cases (18).

The presence of bronchiolocentric lesions and giant multinucleated cells in some areas of the lung specimen may possibly suggest chronic hypersensi-

tivity pneumonitis. The pathologic heterogeneity observed in this family was consistent with previous reports on different histopathologic subtypes in families with SFTPC-related ILD (3, 4).

Although the onset of ILD in the patient has been earlier than those of his grandfather and father, the patient has shown no clinical, physiologic or radiographic progression for four years since the diagnosis. Careful clinical observation is needed in order to characterize the natural course of the disease associated with Y104H SFTPC mutations. Future studies will be also required to elucidate whether different mutations within SFTPC affect the clinical manifestations of ILD differently. This case may broaden the spectrum of ILD associated with SFTPC mutations in younger adults.

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