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Case Report

Clinical features and genetic characterization of familial pulmonary fibrosis in a Chinese family

Zhang-Rong Chen, Jing-Min Deng, Zhi-Yi He, Xuan Wei, Chen Gong, Si-Qiao Liang, Xiao-Ning Zhong, Jian-Quan Zhang, Jing Bai, Mei-Hua Li

Department of Respiratory Medicine, First Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi, China

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Abstract: Familial pulmonary fibrosis (FPF) is defined as idiopathic pulmonary fibrosis occurring in at least two members of a family. Studies showed that genetic factors and environmental common play an important role in the pathogenesis of FPF. We present the clinical data of a Chinese family with FPF. Based on the clinical and radiological features, the proband was diagnosed with idiopathic pulmonary fibrosis at the age of 44 years. Her family history showed that two deceased relatives died of idiopathic pulmonary fibrosis, and four members may die from this disease. Furthermore, the genomic DNA of the proband was sequenced and showed mutations in telomerase reverse transcriptase gene, surfactant pulmonary-associated protein B, and surfactant pulmonary-associated protein A.

Keywords: Familial, idiopathic pulmonary fibrosis, gene

Introduction

Idiopathic pulmonary fibrosis (IPF) is a specific form of chronic, progressive, interstitial lung disease of unknown etiology with usual interstitial pneumonia (UIP) appearing in histological evidence or high-resolution computed tomography (HRCT) scan findings [1]. Familial pulmonary fibrosis (FPF) is defined as IPF occurring in two or more members of a family [2, 3]. The exact prevalence of FPF is unknown. Studies in the United Kingdom and Finland suggested a prevalence of 1.34 FPF cases per 10^6 in the UK population and 5.9/million for FPF in Finland [4, 5]. FPF cases are reported worldwide; however, limited information is available among Chinese patients with FPF. Studies reported four Chinese families with FPF. In the present study, we describe a Chinese family with FPF, and the proband was diagnosed because of dyspnea on exertion, radiographic abnormalities, pathological features, family history, and genetic abnormalities.

Case report

A non-smoking female from Guangxi Province, China, complained of mild dyspnea on exertion at the age of 44 years (in year 2008) and then visited our outpatient clinic. The patient was diagnosed with IPF and recommended for further treatment, which she refused because of the mild symptoms. Four years later, she was admitted to our hospital because of exacerbation of dyspnea after a cold.

She was a housewife who denied any pulmonary disease during childhood and had no history exposure to industrial materials and chemical and environmental fibrogentic agents.

Based on the physical examination, she was not clubbed or cyanosed. Only end-inspiratory crackles over the lower zone of the lungs were noted on auscultation. Pulmonary function revealed normal ventilatory function, except for a mild reduction in diffusing capacity for carbon monoxide (DLCO). HRCT scan demonstrated patchy reticular opacities and diffuse honeycombing that involved mainly the subpleural and basal segments of the lower lobes (**Figure 1A-D**).

Laboratory investigations revealed normal erythrocyte sedimentation, serological studies for collagen vascular disease and other routine laboratory tests.

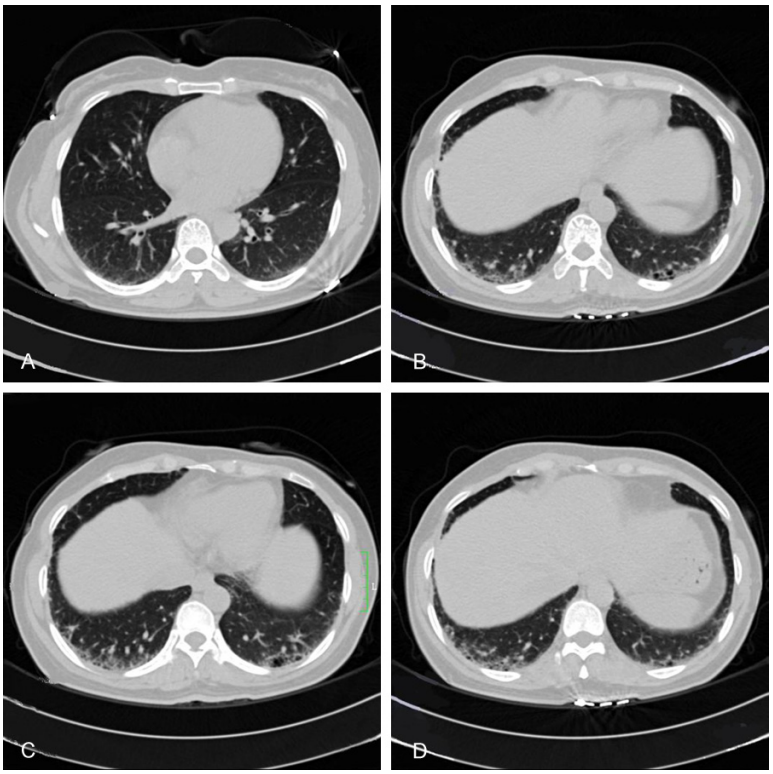

Figure 1. A-D. HRCT scans revealed patchy, reticular opacities and diffuse honeycombing involving mainly the subpleural and basal segments of the lower lobes.

Family history: The patient's mother and brother were diagnosed with IPF in their local tertiary hospitals. The patient's grandmother, aunt, and two uncles were unconfirmed affected patients with IPF. The age at death of four members in this family was lower than 60 years. The detailed clinical features and a genealogical tree of this family are presented in **Table 1** and **Figure 2**, respectively.

Pathological findings

A video-assisted thoracoscopic surgical lung biopsy was performed on the visceral pleura of the dorsal and posterior basal segments of the right lower lobe. Pathology (hematoxylin and eosin stain (**Figure 3A**), reticular fiber stain (**Figure 3B**), and Masson stain (**Figure 3C**)) showed an association between fibrotic (reticular fibrotic and collagen fibrotic) thickening and type 1 pneumocyte hyperplasia of the alveolar septa without inflammatory cells. No exudates were found in the alveolar lumen. The proliferation of fibrous tissue predominantly affected the peripheral subpleural, and it was associated with the hyperplasia of mesothelial cells and infiltration of some inflammatory cells.

Gene sequencing data: The genomic DNA of the proband was sequenced for the gene encoding surfactant pulmonary-associated protein A (SFTPA), surfactant pulmonary-associated protein B (SFTPB), surfactant pulmonary-associated protein C (SFTPC), ELMO domain-containing protein 2 (ELMOD2), and telomerase genes (telomerase reverse transcriptase gene (hTERT) and telomerase RNA component gene (hTR)), which were reported in patients with FPF. Heterozygous mutations of A for G were found at position 71 in exon 9 of hTERT (**Figure 4A**), those of C for T were found at position 50 in exon 5 of SFTPA1 (**Figure 4B**), and those of A for C were found at position 49 in exon 3 of SFTPA2 (**Figure 4C**). The homozygous mutations of A for C were found at position 37 in exon 2 of SFTPB (**Figure 4D**) in the proband. Genetic analysis of SFTPC, hTR, and ELMOD2 genes from the DNA of the proband was also performed, and no mutations were identified. (The genome sequences and primer pairs were synthesized by Huijing Biotech, Wuhan, China).

A diagnosis of FPF was established based on her clinical presentation, laboratory investigations, pulmonary function abnormalities, radiographic abnormalities, histological examination of lung biopsy, family history, and genetic abnormalities. She never received any therapy until the current admission; during which levofloxacin combined with cefoxitin therapy was prescribed. She felt better when she was discharged from hospital than when she was hospitalized. One year later, her clinical symptoms did not progress even without taking prednisone and other drugs. According to the recent follow up, she is still alive.

Discussion

FPF is defined as IPF occurring in two or more members of a family [2, 3]. In our case, three members were diagnosed with IPF and satisfied the criteria for FPF. The average onset age

Table 1. The detailed clinical features of a family with FPF

Member	Sex	Age O	Exertional dyspnoea	Cough	Em	Diagnosed IPF	CT	Pathology	Age D
I1	Female	*	*	*	-	*	*	*	63
II2	Female	40	+	-	-	+	+	+	57
II3	Male	20	+	-	-	*	*	*	<60
II4	Male	20+	+	-	-	*	*	*	<60
II5	Female	*	+	*	-	*	*	*	<60
III2	Female	44	+	-	-	+	+	+	#
III3	Male	*	-	*	-	*	*	*	*
III4	Male	<37	*	*	-	+	+	*	<39
III5	Female	*	-	+	-	-	-	*	*
III6	Male	*	+	+	-	*	*	*	*
III7	Male	*	-	+	-	*	*	*	*
IV1	Male	-	-	-	-	-	-	-	#
IV2	Female	-	-	-	-	-	-	-	#

Note: (*) unknowing; (+) yes; (-) no; (#) Still alive; (Age O) Age of onset (year); (Em) Extrapulmonary manifestation, such as Haematological, Mucocutaneous, Liver involvement, and so on; (Pathology) the appearance of UIP; (Age D) Age at death (year).

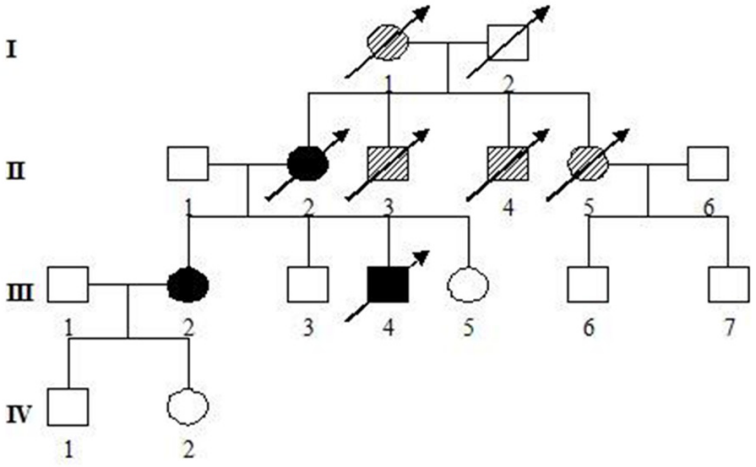

Figure 2. (Pedigree chart of a family with FPF): Black and unfiled shapes represent affected and unaffected individuals, respectively. Squares represent males and circles represent females, respectively. The black arrow denotes deceased individuals, and the shapes with hash marks indicate unconfirmed affected individuals. III2 is the proband.

for this family was approximately 40 years. Lee et al. [3] reported that patients with FPF do not show any notable differences in clinical, radiological, or pathological features compared with patients with sporadic IPF. However, some clinical features of the proband were atypical for sporadic IPF. For instance, she experienced mild dyspnea on exertion and was diagnosed with IPF at the age of 44 years. By contrast, sporadic IPF usually presents between 50 and 70 years old. In addition, the proband is female with a 4-year history of mild disease and slow progression of clinical symptoms. Once IPF is diagnosed, the mean survival time is about 2-3 years [1]. These findings led us to further investigate FPF.

Upon further examination, our patient exhibited bibasilar end-inspiratory crackles on auscultation but no digital clubbing and cyanosis. Pulmonary function revealed that the patient demonstrated normal ventilatory function, except for a mild reduction in DLCO, which was almost similar to a previous case report [6]. In such cases, we also define the abnormal lung function as a limitation of ventilation and diffusion dysfunction [7].

HRCT is an essential component of the diagnostic pathway in IPF. UIP is characterized by HRCT based on the presence of reticular opacities, ground glass opacities, and honeycombing that mainly involve the subpleural and basal locations of the lung and are often associated with traction bronchiectasis [1]. An article about the HRCT findings in FPF did not reveal

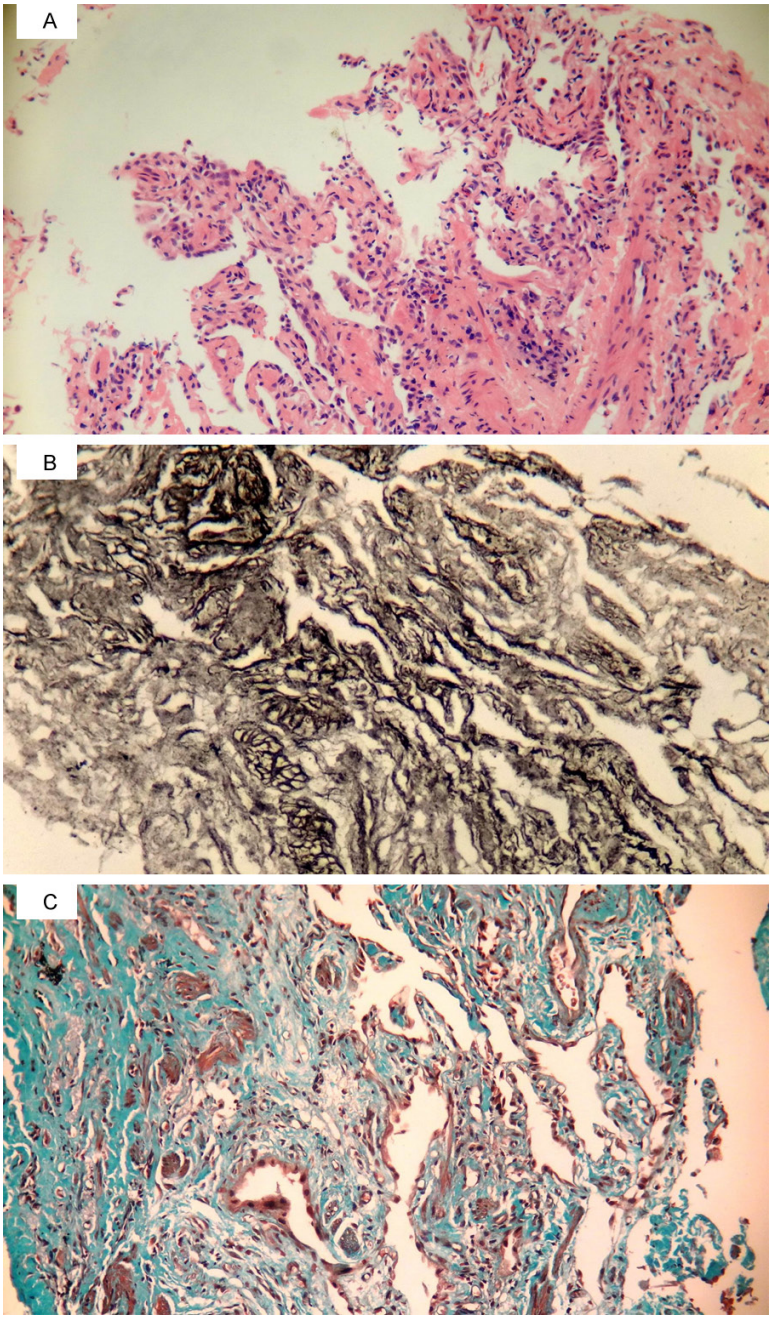

Figure 3. A. Association of fibrotic thickening and type 1 pneumocyte hyperplasia of the alveolar septa without inflammatory cells. No exudates were found in the alveolar lumen. (Hematoxylin and eosin stain) at ×200 magnification. B. Association of reticular fibrotic thickening of alveolar septa (reticular fiber stain) at ×200 magnification (black filaments indicate the reticular fibrotic). C. Association of collagen fibrotic thickening of alveolar septa. (Masson stain) at ×200 magnification (blue filaments indicate the collagen fibrotic).

any noticeable difference compared with sporadic IPF [3]. Another article showed that the HRCT findings revealed a lower prevalence of honeycombing and predominant lower lung zone distribution in FPF than in non-familial IPF [8]. In our case family, the HRCT scans of three members showed UIP, which was critical for establishing a definite diagnosis.

UIP is the histopathological pattern that identifies patients with IPF. The histological hallmark and chief diagnostic criterion is a heterogeneous appearance at low magnification with alternating areas of normal lung, interstitial inflammation, fibrosis, and honeycomb change [9]. The pathological features of patients with FPF are similar to those of patients with non-familial IPF [3]. The proband and her mother complained of mild dyspnea on exertion, which is atypical with sporadic IPF. Therefor, for further diagnosis they underwent surgical lung biopsy. The pathological findings revealed a classic UIP pattern, which led to a diagnosis of IPF. If the HRCT specifically recognizes a histopathological UIP pattern, an open or thoracoscopic lung biopsy is unnecessary [1].

Genetic influences, including the existence of familial clusters and some genes mutations, are involved in the pathogenesis of IPF. Although the mode of genetic transmission of FPF is unclear, FPF possibly follows an autosomal dominant inheritance pattern [2, 3]. Recent studies revealed that the pathogenesis of FPF is due to mutations in the gene encoding SFTPA [10], SFTPB, SFTPC [11, 12], hTERT, hTR [13, 14], and ELMOD2 [15]. In our case family, the genomic DNA of the proband was sequenced and showed mutations in hTERT, SFTPB, SF-

Figure 4. A. A for G heterozygous mutations in exon 9 of hTERT (red arrow indicates the position of the mutation). B. C for T heterozygous mutations in exon 5 of SFTPA1 (red arrow indicates the position of the mutation). C. A for C heterozygous mutations in exon 3 of SFTPA2 (red arrow indicates the position of the mutation). D. A for C homozygous mutations in exon 2 of SFTPB (red arrow indicates the position of the mutation).

TPA1, and SFTPA2. However, no specific mutations in SFTPC or ELMOD2 genes were identified.

Based on the genetic characteristics of the patients with FPF in our case family and some candidate genes for FPF worldwide, FPF is a polygenetic and multi-site mutation disease. This characteristic may also be the reason for the occurrence of IPF in numerous individuals from the same family.

IPF is a chronic, progressive, diffuse parenchymal lung disease of unknown origin, with a mortality rate exceeding that of many cancer types. Lung transplantation is an effective treatment for prolonged survival and must be considered in young patients [1]. Nintedanib and pirfenidone recently showed efficacy in slowing the functional decline in IPF; thus, these agents were recommended for patients with IPF [16]. However, the treatment for FPF is seldom studied, and most of the studies were case reports. A study was conducted [6] on three affected patients of a FPF family treated with prednisone, but their symptoms did not improve. In this work, the patient exhibited mild exertional dyspnea. Without the treatment of prednisone and immunosuppressants, the symptoms did not change; this finding differed from the results in the literature. An article described [6] 12 members with IPF in a large family with FPF; the onset age was low in this family, and 11 documented affected family members died from this disease at an average age of 37 years (range: 25-50 years). Considering that FPF is clinically rare, early detection and intervention are important. No specific treatment is developed for FPF associated with gene mutations, and no guidelines have been created for this topic. Thus, further studies are warranted for the treatment of FPF.

Disclosure of conflict of interest

None.

Address correspondence to: Jing-Min Deng, Department of Respiratory Medicine, First Affiliated Hospital of Guangxi Medical University, 6 Shuang Yong Road, Nanning 530021, Guangxi, China. Tel: +86 771-5356782; Fax: +86 771-5356782; E-mail: ldyyy666@163.com

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