Case Series

Familial interstitial pulmonary fibrosis in two different families in India: A case series

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ABSTRACT

Introduction: Idiopathic pulmonary fibrosis (IPF), a chronic progressive interstitial lung disease (ILD), Occasionally, IPF occurs in families. Familial interstitial lung disease has been reported worldwide, limited information is available on the disease among Indian patients. **Case Presentation:** A 59-year-old woman presented with a 2-year history of progressive dyspnoea. Based on clinical and radiological features, our patient was diagnosed with idiopathic pulmonary fibrosis. Several family members of her first and second generations had died from respiratory failure. Her sister also diagnosed as IPF based on typical High resolution computed tomography (HRCT) finding though she was asymptomatic and came for screening. In addition, another male patient also had similar history and diagnosed as familial IPF based on HRCT and genetic testing in spite of significant occupational exposure. Genetic study revealed SFTPA1 gene was associated with susceptibility to idiopathic pulmonary fibrosis. **Conclusion:** Our report illustrates that asymptomatic screening of family member can uncover such a serious disease in patients with familial interstitial fibrosis. Otherwise, clinical, radiological, and histological features are indistinguishable from those of sporadic cases. Furthermore, our work highlights the importance of compiling a thorough family history in individuals presenting with cough and dyspnoea, particularly in younger patients identified with idiopathic pulmonary fibrosis.

KEY WORDS: Familial interstitial pulmonary fibrosis, high-resolution computed tomography, screening

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INTRODUCTION

Idiopathic pulmonary fibrosis (IPF), a chronic progressive idiopathic interstitial pneumonia (IIP), occasionally, IPF occurs in families. IPF is largely unresponsive to medical treatment and is associated with an estimated survival of 20%–50% at 5 years.[1-4] Although no true epidemiological study on the prevalence of interstitial lung diseases (ILDs) and its different subgroups from India is available; according to the studies available proportion of IPF may vary between approximately 30% and 45% in India.[5] IPF seems to have presented a decade earlier in our country compared to the West. Both the burden of tuberculosis and its role as a "mimicker" of diffuse parenchymal lung disease (DPLD) caused a significant delay in the diagnosis of IPF in our country.[6] Classically, there are diffuse peripheral and basilar-predominant reticular interstitial changes with usual interstitial pneumonitis (UIP) on histopathology.[7]

Familial IIP is defined as when IIP in two or more members of the same family. To date, approximately 150 such families have been reported worldwide.[8,9] In

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1966, Adelman *et al*. reported a large family in which six members were affected with IPF that proved fatal at a young age (35–50 years).[10] Here, we are describing two different families with familial IPF.

FAMILY 1

Case 1

A 59-year-old nonsmoking female from Mizoram, a retired school teacher presented in March 2009 with a history of progressive grade 2 dyspnea as per modified medical research scale (mMRC) and dry cough for 2 years. Several members of her first and second generations had died from respiratory failure presumably related to underlying ILD as shown in Figure 1.

On examination, she had clubbing and bilateral end-inspiratory crackles over infrascapular area. Her routine hematological investigations were within normal limits. A blood test was negative for rheumatoid factor (RF), antinuclear antibody (ANA), and other serological tests for collagen vascular disease. X-ray chest showed bilateral reticular pattern. Pulmonary function test showed severe restrictive defect with decreased diffusion capacity for carbon monoxide (DLCO) and 6 min walk test showed significant exercise desaturation [Table 1].

High-resolution computed tomography (HRCT) [Figure 2] showed irregular reticular lines, and architectural distortion in the form of traction bronchiolectasis and honeycombing, with basal and subpleural predominance consistent of definite UIP pattern. The patient had been labeled with IPF, based on a typical HRCT scan, and since that time she was being initiated on treatment with oral prednisolone, azathioprine, and N-acetyl cysteine based on triple drug therapy recommendations in the year 2009 and advised regular follow-up.

Her condition remained essentially unchanged till October 2012 when she presented with symptomatic worsening. Radiology and pulmonary function tests confirmed disease worsening. She was commenced on treatment with pirfenidone and other drugs were stopped. She has tolerated pirfenidone well, and she is on regular follow-up.

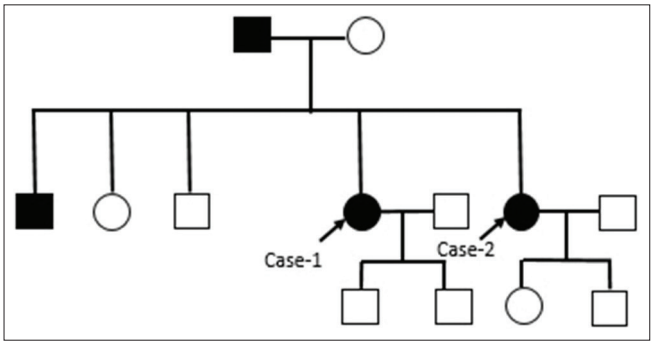

Figure 1: Pedigree of family 1 evaluated for FIPF with four affected members. Dark shading indicates the affected family members

Case 2

A 59-year-old female non-smoker, clerk in government office, twin sister of case 1, is asymptomatic but presented to us for screening to rule out ILD, because of the strong family history. On examination, she did not have finger clubbing. Bibasilar end-inspiratory crackles were present on auscultation. Blood investigation was normal including RF and ANA. Chest X-ray showed bilateral reticular pattern with normal lung volume. Pulmonary function studies showed mild restriction with normal DLCO. Six-minute walk test revealed no critical desaturation. Pulmonary function test and 6-minute walk test data as shown in Table 1.

An HRCT revealed irregular reticular lines, ground glass opacity, and architectural distortion in the form of traction bronchiolectasis and fine honeycombing, with basal and subpleural predominance suggestive of definite UIP pattern [Figure 3]. Since asymptomatic and repeat pulmonary function test showed no worsening, she was advised regular follow-up.

FAMILY 2

Case 3

A 45-year-old nonsmoker male without any known comorbidity presented to us in September 2014 with a dry cough and progressive dyspnea (Grade 3 mMRC). He did not have a history suggestive of connective tissue disorder. He works as a senior technician in steel plant and has exposure to fumes. Family history revealed that his father apparently had a similar illness at the age of

Table 1: Pulmonary function studies and 6MWD data

Variable	Case 1	Case 2	Case 3
FVC (% predicted)	(1.52l) 56.3%	(1.73l) 69.0%	(1.18l) 34.7%
FEV_1 (% predicted)	(1.39l) 64.5%	(1.44l) 74.0%	(1.02l) 34.7%
TLC (% predicted)	(2.18l) 52.5%	(2.71l) 67.7%	(1.86l) 36.8%
DLCO (% predicted)	(3.37l) 58.6%	(5.85l) 115.1%	-
PaO_2, mmHg	40	40	42
$PaCO_2$, mmHg	70	82	72
SaO_2 at rest, %	95	96	94
Distance, m	385	413	424
Initial SPO_2, %	96	97	93
Lowest SPO_2, %	86	94	77
Initial Borg Score	0	0	0
Final Borg Score	5	0	3

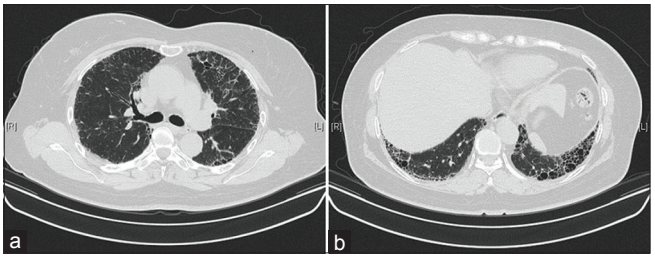

Figure 2: Case 1 - (a) High-resolution computed tomography scan obtained at the upper lobe shows reticular opacities and honeycombing. (b) High-resolution computed tomography scan from the basal parts of the lungs showing reticulations and traction bronchiectasis

38 years who was also working in the steel plant. Father succumbed to illness at the age of 40 years. However, two of his sisters also had progressive dyspnea of 2 and 3 years of duration respectively which did not improve with treatment and they succumbed to the disease at 37 and 47 years of age due to respiratory failure [Figure 4]. The sibs had no exposure to metal dust or had stigmata of any autoimmune disease.

On examination, he had clubbing and bibasilar inspiratory crackles. The routine hematological investigation was normal including RF and ANA. Pulmonary function studies and 6-minute walk test revealed severe restrictive defect with decreased DLCO and marked oxygen desaturation to 77% during the 6-min walk test [Table 1].

HRCT chest showed irregular reticular lines, ground glass opacity, and architectural distortion in the form of traction bronchiolectasis and honeycombing, with basal and subpleural predominance suggestive of UIP pattern [Figure 5]. He was evaluated elsewhere and was diagnosed to have ILD on the basis of HRCT chest and was started on treatment with steroids and pirfenidone. He did not have any improvement with above treatment. He is on long-term oxygen therapy and pulmonary rehabilitation since last 1 year with progressive worsening of his illness.

Since there was a strong autosomal dominant history of the illness, provisional diagnosis of familial pulmonary fibrosis was made, and genetic analysis of the proband was considered. Proband's DNA was extracted from peripheral blood. Targeted exome sequencing analysis was performed using Trusight One sequencing panel from Illumina on MiSeq platform. Variant call format file so generated was imported into Variant Studio software, and variant analysis (annotation, filtering, and classification) was performed. The variants were filtered based on the quality scores, mode of inheritance, and genes of interest. We found a novel heterozygous variant which was mapping to two distinct genes (paralogues) on chromosome 10, namely SFTPA1, and SFTPA2 due to significant degrees (95%) of sequence homology. After sanger sequencing using separate sets of primers, we could validate that the variation was indeed coming from SFTPA1 gene. This gene has been previously associated with susceptibility to IPF (MIM ID: 178,500).[11] The heterozygous variant c.605T >C (Genomic coordinate hg 19 build: Chr10:81373682, transcript: ENST00000419470) leads to change in amino acid at position p.V202A. This variant is previously unreported as disease causing, however, extensive in silico analysis determined it to be deleterious. In addition, the variant is in C-type lectin fold domain conserved across primate species. Considering the above evidence, it can be concluded that the variant may be disease causing and hence confirming the clinical diagnosis.

DISCUSSION

IPF is a nonmalignant disease, yet it carries a prognosis akin to, or even worse than, many cancers. In IPF, there

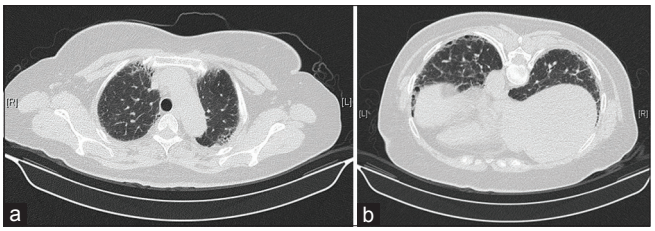

Figure 3: Case 2 - (a) High-resolution computed tomography scan obtained at the upper lobe shows reticular opacities and honeycombing. (b) High-resolution computed tomography scan prone cuts from the basal parts of the lungs showing reticular and nodular densities, and traction bronchiectasis

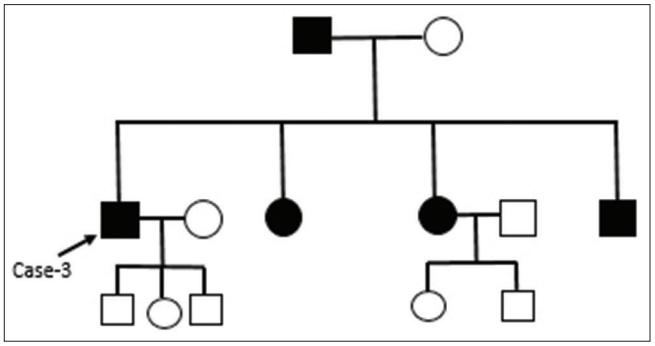

Figure 4: Pedigree of family 2 evaluated for FIPF with five affected members. Dark shading indicates the affected family members

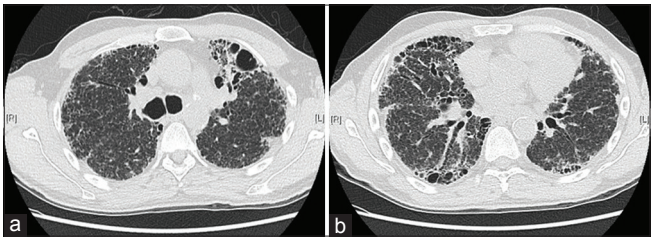

Figure 5: Case 3 - (a) High-resolution computed tomography scan obtained at the upper lobe shows reticular opacities, ground-glass attenuation and honeycombing. (b) High-resolution computed tomography scan from the basal parts of the lungs showing ground-glass attenuation, reticular and nodular densities, and traction bronchiectasis

is an imbalance between the profibrotic mediators that promote extracellular expansion, fibroblast recruitment, proliferation and differentiation, and antifibrotic mediators that drive the process of tissue remodeling.[12] Several strands of evidence point to repetitive alveolar epithelial injury as an important driver for the development of this imbalance.

The condition of Fédération internationale des professeurs de français (FIPF) was first described in 1907 by Sandoz.[13] Another report[14] described IPF in identical twin sisters, and since then 15 definite cases and 3 other probable cases of pulmonary fibrosis have been diagnosed in the same family.[15] In 2000, Marshall *et al*.[16] published the first large collection of IPF kindreds, and estimated that 0.5%–2.2% of IPF cases are familial. In 2005, Steele *et al*.[9] published

an even larger number of kindreds with familial IPF, the largest of which demonstrated autosomal dominant inheritance with reduced penetrance. Multiple studies have been performed to investigate genetic associations with common single-nucleotide polymorphisms.[17] The most significant result has been found for a variant located within the cluster of mucin genes on chromosome 11, which is present in approximately 35% of subjects with familial or sporadic IPF and 9% of controls.[18]

The clinical presentation, radiologic and pathologic features, and survival of FIPF patients are essentially similar to those of nonfamilial IPF patients.[8] FIPF has also been suggested to occur at a younger age than IPF in nonfamilial cases.[19] Nishiyama *et al*.[20] described HRCT findings in nine patients with biopsy-proven familial IPF, and found a resemblance between familial IPF and nonfamilial IPF, except that the prevalence of honeycombing (33%) and lower lung zone distribution (67%) was lower in familial IPF patients compared to those with nonfamilial IPF. Rosas *et al*. evaluated family members of patients affected by familial IPF to identify asymptomatic subjects with ILD.[21] The cited authors found that 22% of asymptomatic subjects showed radiographic evidence of ILD when screened by HRCT. Similarly, in our second case, we found HRCT finding of UIP though the patient was asymptomatic. Transbronchial lung biopsy is a safe investigation with high diagnostic yield and should be performed in patients with DPLD after excluding characteristic "IPF pattern" on HRCT thorax.[22] The diagnosis of IPF is based on characteristic HRCT finding in our patient hence we did not performed lung biopsy. Bronchoalveolar lavage (BAL) may act as an important test along with the clinical and HRCT findings for a proper diagnosis in some ILDs including IPF, whereas in others, HRCT was found to be more successful in predicting the diagnosis. BAL assists in predicting the acute/chronic nature of the disease and gives a hint on the superadded infection status that would help in proper management. Thus, in addition to routine clinical evaluation and HRCT, BAL should be employed more routinely in the evaluation of patients with ILD including IPF.[23]

Four surfactant proteins (SPs) have been identified and are divided into two groups: The hydrophilic proteins SP-A and SP-D and the hydrophobic proteins SP-B and SP-C. SP-A, SP-B, and SP-D are synthesized by both alveolar cells and nonciliated bronchiolar cells of the lung, whereas SP-C is produced only by alveolar type II cells. SPC plays a critical role in reducing surface tension in the alveoli, whereas SP-C absence or mutation in SFTPC mutant patients causes mechanical injury to the respiratory epithelium leading to respiratory failure and severe ILD.[24] Selman *et al*. evaluated genetic polymorphic variants of the SPs SP-A1, SP-A2, SP-B, SP-C, and SP-D in a group of patients with IPF.[25] The SP-A1_6A4 allele was noted to be associated with nonsmoker IPF, whereas the SP-B B1580_C allele was more associated with smoker IPF patients compared to control subjects.

Even though FIPF is relatively uncommon, such cases indicate that genetic factors can regulate the responses to lung injury and repair leading to the development of fibrosis. In addition, a number of classic genetic syndromes, including neurofibromatosis and Hermanksy-Pudlak syndrome, demonstrate ILD with deposition of extracellular matrix as part of their clinical spectrums, although the patterns of lung fibrosis in those disorders are clinically distinct from those in IPF.

Genetic testing for FIPF has not yet been established. Nonetheless, the prudent clinical screening of unaffected family members, the avoidance of injurious inhalational agents (e.g., tobacco smoke), and periodic monitoring would appear to be justified, and will further define the incidence of FIPF.

CONCLUSION

Characteristically, patients with familial IPF present at a younger age and screening of family members shows evidence of early interstitial changes in asymptomatic subjects. Thus, examination of family members with IIP provides an opportunity to uncover the pathogenesis of IPF at early stages when therapy might be effective.

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Conflicts of interest
There are no conflicts of interest.

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