ORIGINAL ARTICLE

Familial pulmonary fibrosis: a heterogeneous spectrum of presentations

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ABSTRACT

Objective: To describe the clinical, functional, and radiological features of index cases of familial pulmonary fibrosis (FPF) in Brazil. **Methods:** We evaluated 35 patients with FPF - of whom 18 (51.4%) were women - with a median age of 66.0 years (range, 35.5-89.3 years). All of the patients completed a standardized questionnaire, as well as undergoing pulmonary function tests and HRCT of the chest. In 6 cases, lung tissue samples were obtained: from surgical biopsies in 5 cases; and from an autopsy in 1 case. **Results:** A history of smoking and a history of exposure to birds or mold were reported in 45.7% and 80.0% of the cases, respectively. Cough and marked dyspnea were reported by 62.8% and 48.6% of the patients, respectively. Fine crackles were detected in 91.4% of the patients. In 4 patients, the findings were suspicious for telomere disease. The median FVC and DLCO, as percentages of the predicted values, were 64.9% (range, 48.8-105.7%) and 38.9% (range, 16.0-60.0%), respectively. Nine patients had reduced DLCO despite having normal spirometry results. Regarding HRCT, patterns typical of usual interstitial pneumonia were found in 6 patients (17.1%). In 25 cases (71.5%), the HRCT features were consistent with a diagnosis other than idiopathic pulmonary fibrosis. In 11 cases (31.4%), the radiological patterns were uncharacteristic of interstitial lung disease. Of the six lung tissue samples analyzed, four showed interstitial pneumonia with bronchiolocentric accentuation, and, on the basis of the clinical and radiological data, the corresponding patients were diagnosed with hypersensitivity pneumonitis. **Conclusions:** Patients with FPF can present with a wide variety of clinical features. Most HRCT scans of these patients exhibit patterns not typical of usual interstitial pneumonia. The family history of fibrotic lung diseases should be investigated in all patients under suspicion, regardless of their age.

Keywords: Idiopathic pulmonary fibrosis; Respiratory function tests; Tomography, X-ray computed.

INTRODUCTION

Familial pulmonary fibrosis (FPF) occurs when at least two members of the same biological family are affected by a fibrosing interstitial lung disease (ILD).[1] Although some studies have used more stringent criteria for FPF, including the presence of at least two cases of fibrosing ILD in individuals related within three degrees, the aforementioned definition is widely accepted.[2,3] It should be noted that the affected family members do not necessarily have to have the same ILD.[1,2]

FPF has classically been described as rare. According to an official American Thoracic Society (ATS)/European Respiratory Society (ERS)/Japanese Respiratory Society (JRS)/*Asociación Latinoamericana de Tórax* (ALAT, Latin American Thoracic Association) statement, familial forms of idiopathic pulmonary fibrosis (IPF) account for less than 5% of all IPF cases.[4] However, in a study in which relatives of individuals diagnosed with IPF were screened for fibrosing ILD by trained health professionals, the prevalence of familial disease was found to be as high as 20%.[5] Therefore, FPF might be much more common than previously thought, its prevalence varying according to the screening methods used.

There has been increasing interest in FPF in recent years because genetic mechanisms involved in familial forms of fibrosing ILD might also be involved in the pathogenesis of sporadic forms of fibrosing ILD, particularly IPF. One such genetic mechanism is the rs35705950 polymorphism in the promoter of the *MUC5B* gene; when it involves two alleles, it increases the risk of FPF and sporadic IPF by more than 20-fold.[6] Mutations in telomere-related

genes have also been associated with sporadic and familial forms of fibrosing ILD.[7,8]

Although it is important to investigate the genetic aspects of FPF, it is equally important to investigate clinical, radiological, and pathological features of the disease because of the large diversity of phenotypes in patients with FPF.[1-3] To the best of our knowledge, there have been no studies of FPF in the Brazilian population. In view of this, the objective of the present study was to describe the clinical, functional, and radiological features of index cases of FPF in Brazil. A secondary objective was to present and discuss histological findings in patients undergoing lung biopsy.

METHODS

Patients

The present study was a case series involving index cases of FPF. Active case finding was conducted from March of 2014 to November of 2017 at the University of São Paulo at Ribeirão Preto School of Medicine *Hospital das Clínicas*, located in the city of Ribeirão Preto, Brazil. The inclusion criteria were as follows: being over 18 years of age, having been diagnosed with fibrosing ILD, and having at least one member of the same biological family affected by fibrosing ILD. Only patients whose chest X-rays/HRCT scans and those of at least one affected relative were available for analysis by our research group were included in the study. All participants gave written informed consent, and the study protocol was approved by the local research ethics committee (Protocol no. 883,203).

Clinical and laboratory evaluation

A standardized form was used in order to record clinical information on all identified index cases. The following data were collected: demographic data; age at onset of symptoms; age at diagnosis of fibrosing ILD; degree of relatedness to the closest affected relative; environmental exposure history; manifestations consistent with collagen vascular disorders; upper gastrointestinal symptoms; degree of dyspnea, as assessed by the modified Medical Research Council scale[9]; severity of cough; presence of expectoration, wheezing, fine crackles, and digital clubbing; resting SpO_2; and room-air SpO_2.

Participants underwent spirometry with ATS-approved spirometers, lung capacities, lung volumes, and DLCO being measured in accordance with the Brazilian Thoracic Association guidelines for pulmonary function testing.[10] Normal lung function values were calculated on the basis of reference equations for the Brazilian population.[11-13]

Chest HRCT scans were performed on multidetector scanners, volumetric images being acquired during inhalation and exhalation without iodinated contrast medium.

All HRCT scans were blindly reviewed by two thoracic radiologists, who categorized the findings into four patterns, in accordance with criteria proposed by the Fleischner Society[14]: (i) typical usual interstitial pneumonia (UIP); (ii) probable UIP; (iii) indeterminate UIP; and (iv) findings consistent with a diagnosis other than IPF. In the case of HRCT findings consistent with a diagnosis other than IPF, an attempt was made to identify a specific pattern of ILD, such as nonspecific interstitial pneumonia (NSIP), hypersensitivity pneumonitis (HP), and organizing pneumonia (OP).[15,16] In cases in which it was impossible to establish a definitive diagnosis, the findings were classified as constituting an uncharacteristic pattern. Disagreements were resolved by consensus.

All available pathological data were reviewed by the same pathologist (specializing in pulmonary pathology), in accordance with histomorphological criteria established by the ATS/ERS and the Pulmonary Pathology Society.[15,17]

The results are presented as category frequencies and, given the nature of the distribution of most of the data, as medians and ranges.

RESULTS

The case series comprised 35 patients, whose clinical characteristics are presented in Table 1. There was a slight predominance of women (51.4%) in the study. The median age at screening was 66.0 years (range, 35.5-89.3 years). The median age at onset of symptoms was 63.2 years (range, 34.0-84.0 years). The median age at diagnosis of lung disease was 64.0 years (range, 35.3-85.0 years). Evidence of fibrosing ILD affecting at least one family member was obtained by reviewing HRCT scans in 22 cases (62.9%); by reviewing HRCT scans and pathological data in 3 cases (8.6%); and by reviewing conventional chest X-rays in 10 (28.6%). More detailed information on the available data regarding affected family members can be found in the online supplement of the JBP (Chart S1, available at http://www.jornaldepneumologia. com.br/detalhe_anexo.asp?id=64).

A history of smoking was reported by 45.7% of the study participants, and other relevant environmental exposures were reported by 80.0%. A history of exposure to birds was reported by 57.1%. Cough was reported by 62.8%, and grade 2, 3, or 4 dyspnea (as assessed by the modified Medical Research Council scale) was reported by 48.6%. Wheezing and expectoration were uncommon findings. Fine crackles were found in 91.4%, whereas digital clubbing was found in only 20.0%. Manifestations consistent with collagen vascular disorders were reported by or found in none of the study participants. The median room-air SpO_2 was 96% (range, 70-98%). An SpO_2 of ≤ 90% was found in 6 patients.

In 4 patients (11.4%), the clinical findings were suspicious for telomere disease: myelodysplastic syndrome, in 2, and chronic liver disease, in 2 (1 with liver cirrhosis only and 1 with liver cirrhosis and a history of hair graying before the age of 25 years).

Table 1. Clinical characteristics of 35 index cases of familial pulmonary fibrosis.

Characteristic	n (%)
Sex	
Male	17 (48.6)
Female	18 (51.4)
Age at screening, years	
≤ 30	0 (0.0)
30-39	2 (5.7)
40-49	2 (5.7)
50-59	5 (14.3)
60-69	12 (34.3)
70-79	10 (28.6)
≥ 80	4 (11.4)
Age at symptom onset, years	
≤ 30	0 (0.0)
30-39	2 (5.7)
40-49	3 (8.6)
50-59	9 (25.7)
60-69	14 (40.0)
70-79	5 (14.3)
≥ 80	2 (5.7)
Age at diagnosis, years	
≤ 30	0 (0.0)
30-39	3 (8.6)
40-49	2 (5.7)
50-59	6 (17.8)
60-69	14 (40)
70-79	8 (22.9)
≥ 80	2 (5.7)
Degree of relatedness to closest affected relative	
First degree	34 (97.1)
Second degree	1 (2.9)
Smoking status	2 (5.7)
Current smoker	14 (40.0)
Former smoker	19 (54.3)
Never smoker	
Current or past environmental exposures	
No exposure	7 (20.0)
Mold	8 (22.9)
Birds	20 (57.1)
Cough	
No cough or mild cough	13 (37.2)
Daily, mild cough	16 (45.7)
Daily, severe cough	6 (17.1)
Degree of dyspnea, mMRC scale	
0	6 (17.1)
1	12 (34.3)
2	6 (17.1)
3	4 (11.5)
4	7 (20.0)
Expectoration	
Absent	23 (65.7)
Present	12 (34.3)
Bloody sputum	2 (5.7)

mMRC: modified Medical Research Council.

Table 1. Continued...

Characteristic	n (%)
Wheezing	
Absent	23 (65.8)
During airway infections	10 (28.6)
Common but mild	2 (5.7)
Digital clubbing	
Absent	28 (80.0)
Present	7 (20.0)
Fine crackles	
Absent	3 (8.6)
Present	32 (91.4)
SpO_2, %	
≥ 96	20 (57.1)
91-95	9 (25.7)
86-90	1 (2.9)
81-85	3 (8.6)
≤ 80	2 (5.7)

mMRC: modified Medical Research Council.

Median percent predicted TLC, FVC, FEV_1, FEV_1/FVC, and DLCO were 68.0% (range, 41.3-102.4%), 64.9% (range, 48.8-105.7%), 69.3% (range, 49.1-117.9%), 108.5% (range, 84.0-124.0%), and 38.9% (range, 16.7-60.0%), respectively (Table 2). Supranormal expiratory airflow, defined as an FEV_1/FVC ratio > 105% of predicted, was found in 77.1% of the study participants. Of the 35 study participants, 22 (62.8%) had restrictive lung disease; 7 (20.0%) had normal lung function; 5 (14.3%) had indeterminate lung disease; and 1 (2.9%) had mild obstructive lung disease. DLCO was found to be reduced in all of the patients in whom it was measured (n = 30).

HRCT findings consistent with typical UIP and indeterminate UIP were found in 6 patients (17.1%) and 4 patients (11.4%), respectively. HRCT findings were consistent with a diagnosis other than IPF in most of the patients (n = 25; 71.4%). Of those 25 patients, 11 (31.4%) had HRCT findings that were uncharacteristic of ILD; that is, they were inconsistent with previously described radiological features of ILD. Of the remaining 14 patients, 9 (25.7%) had HRCT findings that were consistent with NSIP, 3 (8.6%) had HRCT findings that were consistent with OP, and 2 (5.7%) had HRCT findings that were consistent with chronic HP (Table 3 and Figure 1).

Lung tissue samples were obtained from 6 patients for pathological examination. Of those 6 samples, 1 was obtained from autopsy and 5 were obtained from surgical biopsies. Of those 6 patients, 1 had HRCT findings that were initially suggestive of NSIP. However, the patient subsequently presented with extensive areas of ground-glass opacities and consolidations. Pathological examination of the autopsy tissue revealed diffuse alveolar damage and OP at different stages of organization. In another patient, HRCT findings were consistent with indeterminate UIP, and surgical biopsy showed unclassifiable cellular

and fibrosing interstitial pneumonitis with multiple lymphoid aggregates (Figure 2A). The patient had no clinical manifestations suggestive of collagen vascular disorders, and autoantibody testing was negative. In the 4 remaining patients, HRCT findings were suggestive of NSIP (in 2) and chronic HP (in 2). Histological examination showed interstitial pneumonitis with bronchiolocentric accentuation in all 4, patchy areas of OP being observed in 3 (Figure 2B). Although none had any relevant gastrointestinal symptoms, all 4 reported exposure to birds and were therefore diagnosed with HP after a multidisciplinary discussion.

DISCUSSION

Ours is the first study to describe the clinical features of index cases of FPF in Brazil. It is of note that FPF has a wide variety of clinical and radiological manifestations.

Although the onset of the clinical manifestations of FPF occurred between the ages of 50 and 69 years in 65.7% of the patients in the present study, the onset of symptoms can be as early as age 34 years and as late as age 84 years. Of the 35 FPF patients in the present study, 14.3% were diagnosed before the age of 50 years and 5.7% were diagnosed after the age of 80 years. The presence of fibrosing ILD in a patient younger than 50 years of age is suggestive of familial disease.[1,5] However, this is not usually the case for older individuals, particularly those older than 80 years of age. Therefore, the results of the present study indicate that there is a need for careful screening of family members for other ILDs, independently of patient age at symptom onset or diagnosis.

In the present study, 97.1% of the participants had at least one first-degree relative (father, mother, or brother) who also had a fibrosing ILD. A maternal uncle was the closest affected relative in only one

Table 2. Lung function parameters in 35 index cases of familial pulmonary fibrosis.[a]

Parameter	n (%)
TLC[b]	
≥ 80	12 (38.7)
70-79	3 (9.7)
60-69	6 (19.4)
50-59	6 (19.4)
40-49	4 (12.9)
≤ 39	0 (0.0)
FVC	
≥ 80	8 (22.9)
70-79	6 (17.1)
60-69	8 (22.9)
50-59	11 (31.4)
40-49	2 (5.7)
≤ 39	0 (0,0)
FEV$_1$	
≥ 80	11 (31.4)
70-79	6 (17.1)
60-69	13 (37.1)
50-59	4 (11.4)
40-49	1 (2.9)
≤ 39	0 (0.0)
FEV$_1$/FVC	
≥ 110	16 (45.7)
100-109	14 (40.0)
90-99	4 (11.4)
80-89	1 (2.9)
≤ 79	0 (0.0)
DLCO[c]	
≥ 60	0 (0.0)
50-59	8 (26.7)
40-49	5 (16.7)
30-39	10 (33.3)
20-29	4 (13.35)
≤ 19	3 (10.0)

[a]All results are expressed as percentages of the predicted values. [b]Data available for 31 patients. [c]Data available for 30 patients.

case. This underscores the relevance of the results of the present study.

Of the 35 study participants, 45.7% reported being smokers or former smokers, and 80.0% reported exposure to mold or birds. It is widely accepted that FPF cannot be attributed to genetic factors alone; rather, it is caused by an interaction between genetic factors and harmful environmental exposures resulting in an additional intracellular and interstitial microenvironment that modulates molecular pathways dependent on single nucleotide polymorphisms, alternative splicing, small RNAs, enzymatic activity, and epigenetic mechanisms promoting a favorable

environment for fibrosis onset. [18-20] In other words, individuals are born with a predisposition to FPF and may or may not develop the disease depending on environmental exposures. Our findings corroborate this hypothesis. In addition, the prevalence of risk factors for HP in patients in Brazil was found to be extremely high. This might be due to the fact that the study sample consisted almost exclusively of patients living in the countryside of the state of São Paulo, Brazil (91.4%). In FPF patients living in larger urban areas, exposure to birds and other animals might be less common.

As expected in ILD patients, dyspnea and dry cough were the most common clinical complaints, in 82.9% and 61.8% of the patients, respectively.[21] In addition, auscultation revealed fine crackles in 91.4%, a finding that shows the importance of screening for fine crackles in patients suspected of having fibrosing ILD.[22,23]

In 4 of our patients, FPF was clinically attributed to telomere disease on the basis of the combined presence of hematological abnormalities, chronic liver disease, and premature graying of hair.[24,25] Although the aforementioned findings are not specific for telomere disease, they should be screened for in patients and their relatives because they are an indication for the use of molecular biology testing to measure telomere length in peripheral blood and for specific gene sequencing in younger generations.[26]

With regard to pulmonary function tests, most of the patients in the present study had results that were consistent with restrictive lung disease, a finding that was expected in view of the nature of the lung diseases under study. The only patient who was found to have (mild) obstructive lung disease had a smoking history of 50 pack-years. It is of note that DLCO was substantially reduced in all of the patients in whom it was measured, a finding that underscores the high diagnostic sensitivity of DLCO measurement in patients with fibrosing ILD.[27] The fact that 9 patients had reduced DLCO despite having normal spirometry results is further evidence of the importance of DLCO measurement in patients with FPF.

In the present study, only 6 patients (17.1%) had HRCT findings consistent with typical UIP. The vast majority of patients (n = 25; 71.4%) had CT findings that were consistent with a diagnosis other than IPF. Of those 25 patients, only 14 (40.0%) had specific CT findings. Therefore, a large number of patients (n = 11; 31.4%) had CT findings that were uncharacteristic of ILD.

Although at least one study has shown a high frequency of CT findings consistent with UIP in patients with FPF,[2] the results of the present study are similar to those of a study involving a large number of FPF patients (n = 289), 160 (55%) of whom had CT findings consistent with unclassifiable ILD.[28] In that study, those who had CT findings consistent with definite or probable ILD were diagnosed with UIP (22%), NSIP (12%), HP (6%), or OP (2%).[28] The

Table 3. CT patterns in 35 index cases of familial pulmonary fibrosis.

CT pattern	n	%
Typical UIP	6	17.1
Probable UIP	0	0.0
Indeterminate UIP	4	11.4
Consistent with a diagnosis other than IPF	25	71.4
Inconsistent with fibrosing ILD	11	31.4
Consistent with NSIP	9	25.7
Consistent with organizing pneumonia	3	8.6
Consistent with hypersensitivity pneumonia	2	5.7

UIP: usual interstitial pneumonia; IPF: idiopathic pulmonary fibrosis; ILD: interstitial lung disease; and NSIP: nonspecific interstitial pneumonia.
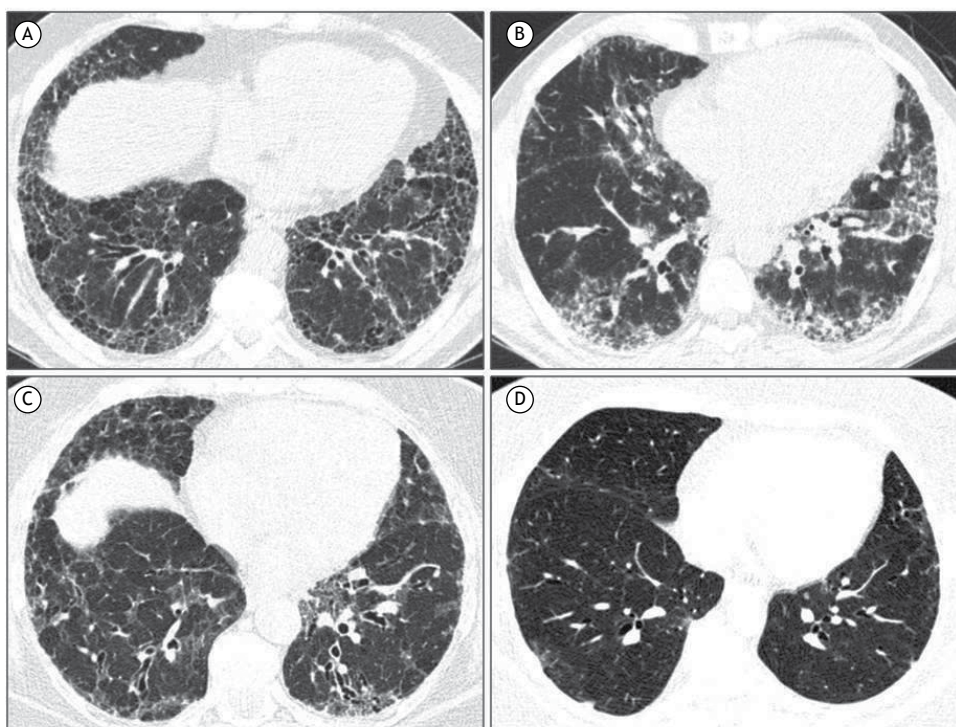

Figure 1. Axial HRCT scans (lung window) of patients with familial pulmonary fibrosis. In A, CT findings consistent with typical usual interstitial pneumonia. In B, CT findings consistent with a diagnosis other than idiopathic pulmonary fibrosis, i.e., consistent with nonspecific interstitial pneumonia. In C, CT findings consistent with a diagnosis other than idiopathic pulmonary fibrosis, i.e., consistent with chronic hypersensitivity pneumonia. In D, CT findings consistent with indeterminate usual interstitial pneumonia.

study in question was conducted by renowned experts and appears to have involved a thorough review of previously published data. Therefore, our results are consistent with previous evidence suggesting that a typical UIP pattern is found in only a minority of patients with FPF. Unlike what was observed in the aforementioned study,[28] UIP was less common than NSIP in the present study, a finding that might be due to local characteristics. Nevertheless, the present study reinforces the notion that CT findings consistent with unclassifiable ILD are the most common.

It can be argued that CT findings consistent with unclassifiable ILD indicate incipient disease that will later progress and result in findings that are more specific; in particular, findings that are consistent with UIP. Well-designed longitudinal studies are needed in order to confirm this possibility. However, in the present study, even elderly patients had findings that were uncharacteristic of ILD. In a study reviewing CT scans of 26 FPF patients on two occasions, separated by a median of 1,049 days, a typical UIP pattern was observed only in those patients in whom initial CT findings were consistent with possible UIP.[29] Therefore, although CT findings of unclassifiable ILD in patients with FPF have yet to be fully understood, it appears that they do not necessarily correspond to an early stage of UIP.

Lung tissue samples were available for review in only 6 cases, having been obtained from surgical
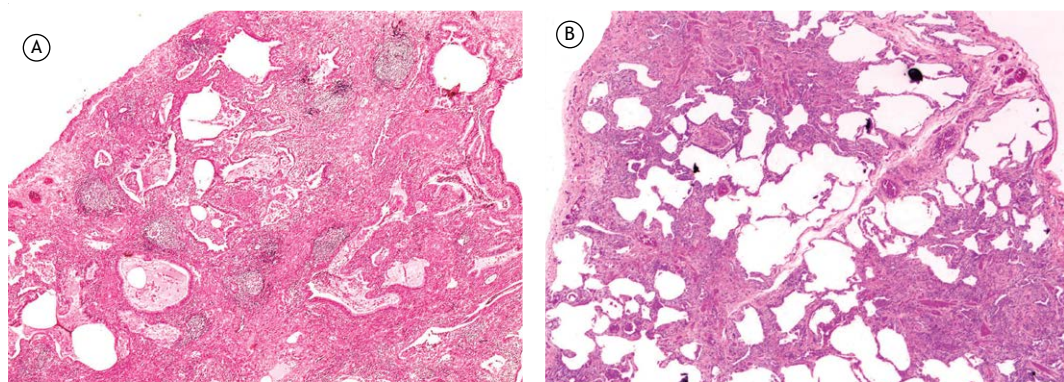
Figure 2. Representative histopathological findings of familial interstitial lung disease. In A, findings consistent with unclassifiable ILD. Note diffuse fibroplastic architectural distortion with cyst formation and lymphoid aggregates. In B, findings consistent with interstitial pneumonia with bronchiolocentric accentuation. Note the predominance of fibroplastic peribronchiolar involvement and delta-shaped subpleural extension associated with organizing pneumonia. Note also that the interlobular septum and the remaining pleura have a normal appearance (H&E; magnification, ×5 for both).

biopsies in 5 and from an autopsy in 1. Pathological examination of the autopsy tissue revealed diffuse alveolar damage and areas of OP at different stages of organization, findings that indicate terminal events related to a fatal acute exacerbation, a systemic infection, or prolonged mechanical ventilation.[30] The five lung tissue samples obtained from elective surgical biopsies provided information that was more relevant. Those samples were obtained in an unsystematic way, the decision to request a biopsy having been made by the attending physicians on the basis of their own health care practices.

The fact that 1 patient was diagnosed with unclassifiable cellular and fibrosing interstitial pneumonitis is not surprising, given that 43.3% of biopsy samples from FPF patients in a previous study were diagnosed as such.[31] In that study,[31] a definite UIP pattern was identified in only 40% of cases. According to the authors,[31] although most biopsy samples from patients with FPF exhibit individual histopathological features that are commonly associated with UIP, current diagnostic criteria for UIP are not met in most cases.

Of the six lung tissue samples analyzed in the present study, four showed interstitial pneumonitis with bronchiolocentric accentuation. Of those four samples, three also showed areas of OP. Of the patients who reported exposure to birds, 2 reported current exposure to birds, 1 reported current exposure to birds and goose feathers (in a pillow), and 1 reported past exposure to birds. CT findings were consistent with HP in 2 and with NSIP in 2. Findings of interstitial pneumonitis with bronchiolocentric accentuation can be challenging to interpret.[32,33] After a multidisciplinary discussion, 3 patients were diagnosed with HP, whereas 1 was diagnosed with probable HP because of a history of occupational exposure to substances involved in the tire vulcanization process.

It is difficult to establish a diagnosis of HP in a family setting because it can be argued that HP in this context is due to simultaneous exposure to antigens in individuals living in the same environment. However, even in this context, only a few will develop HP. Therefore, if two or more family members develop HP when exposed to the same environmental conditions, it can be assumed that they share a genetic predisposition to the disease. A review of the available information on the relatives of the 4 patients who had interstitial pneumonitis with bronchiolocentric accentuation did not suggest simultaneous cases of HP. In addition, lung tissue samples were obtained from only 5 of the 29 patients without a typical UIP pattern, either because of the presence of significant comorbidities or because the patients declined to undergo biopsy. Therefore (and given the high prevalence of HP in Brazil), the prevalence of HP was likely underestimated in the present study.

The present study has several limitations, one of which is the fact that we did not collect information on the characteristics of relatives of the index cases. Although an effort was made to investigate as many (symptomatic or asymptomatic) family members as possible, few families were properly investigated, the vast majority of which had insufficient data for analysis. However, the fact that the study was limited to index cases ensured the homogeneity of the inclusion criteria. Another limitation is that interstitial pneumonia with autoimmune features might have gone undiagnosed in some cases because no autoantibody testing was performed in several patients. Likewise, because upper gastrointestinal endoscopy and esophageal pH monitoring were not routinely performed, it was impossible to identify cases in which gastroesophageal reflux might have contributed to the pathogenesis of the disease. A final limitation is the absence of genetic study results, which were still pending at this writing.

The phenotypic heterogeneity of FPF in the present study could be due to the various molecular genomic and epigenetic mechanisms involved in the pathogenesis of the disease. However, this does not seem to be the case, because previous studies have

shown that a single genetic disorder can have different presentations, and vice versa.[1,7,34] In view of this and of the findings of the present study, we propose that term FPF be replaced with the term familial ILD, which more accurately reflects the complexity of the disease.

In conclusion, pulmonologists should be aware of the various clinical presentations of familial ILD. It appears that clinicians tend to associate familial ILD with IPF. This has implications, including therapeutic implications. Even in a family setting, the initial treatment of HP should consist of removal of exposure and the use of corticosteroids rather than antifibrotic agents, which should be reserved for patients with HRCT or biopsy findings consistent with UIP. In the near future, therapeutic decisions for patients with familial ILD will ideally be based on an appropriate characterization of individual integrated molecular patterns.[35]

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