






Use of antifibrotic drugs in familial interstitial pneumonia: analysis of one family

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TO THE EDITOR,

Familial interstitial pneumonia (FIP) is defined as the occurrence of interstitial lung disease (ILD) in two or more individuals within the same family.^(1,2) The majority of FIP kindreds present autosomal dominant inheritance with a pattern of incomplete penetrance.⁽²⁾ The prevalence of idiopathic pulmonary fibrosis (IPF) among patients with FIP is 0.5% - 20.0%; nonetheless, FIP has also been reported in fibrotic hypersensitivity pneumonitis (fHP) and connective tissue disease-associated ILD.^(2,3)

Although usual interstitial pneumonia (UIP) is the most prevalent HRCT pattern in FIP, other HRCT and histological patterns within the same family have been reported in 40% - 45% of cases.^(1,3) Interstitial lung abnormalities (ILA) have been found in asymptomatic first-degree relatives of patients with FIP, and this pattern of interstitial pneumonia has been associated with a risk of progression to ILD.⁽²⁾ The appropriate pharmacological treatment of FIP has yet to be defined.^(3,4) Here, we describe six cases of FIP within the same family and discuss treatment-related outcomes.

The present case series involved six siblings who were followed up at the Outpatient Clinic for Interstitial Pulmonary Diseases of the Federal University of Minas Gerais' Clinical Hospital, located in the city of Belo Horizonte (MG), Brazil. Data were obtained from medical records and updated through interviews with the patients using a form developed at the clinic. The HRCT scans and histological samples were classified by a radiologist and a pathologist, both with experience in ILD.⁽⁵⁾ Pulmonary function tests (PFTs) were performed in accordance with current recommendations.⁽⁶⁾ All participants gave written informed consent. This study was part of a research project approved by the Research Ethics Committee of the Federal University of Minas Gerais (CAAE no. 44843215.5.0000.5149).

Among 17 siblings from the same family, eight were diagnosed with ILD, two of whom died before the beginning of this study. The characteristics of the six remaining siblings with ILD are detailed in Table 1. In five of them, ILD was identified only after the onset of symptoms, when their lung function was already impaired.

In accordance with the current classification,⁽⁵⁾ the HRCT patterns found included "UIP" (n = 2), "probable UIP" (n = 2), "consistent with other diagnoses" (n = 1), and "indeterminate for UIP" (n = 1). One of the patients with a "probable UIP" HRCT pattern and another with "consistent with other diagnoses" underwent surgical lung

biopsy. The patient with a "probable UIP" HRCT pattern had "UIP" confirmed by histology and, therefore, presented the IPF phenotype. The patient with an HRCT pattern "consistent with other diagnoses" exhibited a histological pattern of "airway-centered interstitial fibrosis", with fHP as the phenotype. The other participant with a "probable UIP" pattern did not undergo lung biopsy because he was diagnosed after his three affected siblings, having ruled out exposure to airborne antigens and connective tissue disease-associated ILD. Thus, he was considered as having FIP with the IPF phenotype. The patient with the "indeterminate for UIP" pattern has been stable regarding clinical, functional, and tomographic findings and, therefore, was not submitted to biopsy. At diagnosis, the spirometry results showed some degree of restrictive lung disease in five of the six patients.

Of the six patients evaluated, five have been treated with antifibrotic drugs, with the exception of the patient with the "indeterminate for UIP" HRCT pattern. Among the five patients undergoing antifibrotic treatment, only one showed disease progression after 12 months. Notably, this patient had fHP and, despite antigen avoidance, progressed to death due to exacerbation. The choice of antifibrotic was based on a shared decision with each patient.⁽⁵⁾ We could infer that the use of antifibrotic drugs prevented the progression of the disease in the four other siblings.

The HRCT patterns and the final diagnoses differed among the six siblings analyzed herein, corroborating the findings described in other studies.^(4,7) Although UIP is the most commonly reported HRCT pattern in the literature, patterns consistent with other diagnoses have also been reported.^(1,7) Most of the siblings in this series had the IPF phenotype, which has been shown to be present in 20% of patients with FIP; other studies have reported even higher rates, ranging from 54.5% to 85.9%.^(1,4) In the present study, it was not possible to classify the phenotype of the sibling with an "indeterminate for UIP" HRCT pattern, perhaps because the disease was diagnosed at a very early stage. In FIP, this pattern has a prevalence of 31.4% - 55% and may be associated with the early onset of symptoms.⁽⁷⁾

Screening for FIP in individuals with ILD has recently taken on greater importance. One study showed that relatives of patients with FIP have a greater risk of developing ILD than the general population.⁽²⁾ Results from the same study, while investigating asymptomatic relatives of patients with FIP, showed that ILA were present at the initial assessment in 22.9% of the individuals;

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Table 1. Characteristics of the six siblings with familial interstitial pneumonia (FIP).

Variable	Patient					
	1	2	3	4	5	6
	Case - index					
Sex	Male	Male	Female	Male	Male	Male
Age (years)	81	79	75	69	65	60
Time from symptom onset to first consultation (months)	8	6	6	6	14	0
Diagnosis	IPF	IPF	fHP	IPF	IPF	Undetermined
Smoking	Yes	No	No	Yes	Yes	No
Exposure	None	None	Mold	None	None	None
GERD	Yes	No	Yes	No	Yes	No
Treatment	Pirfenidone	Nintedanib	Nintedanib	Nintedanib	Nintedanib	No
Exacerbation	Yes	No	Yes	No	No	No
HRCT pattern	UIP	Probable UIP	Consistent with other diagnoses	UIP	Probable UIP	Indeterminate for UIP
Histology	-	-	ACIF	-	IPF	-
mMRC score (at 1/12/24 months)	2/3/4	1/2/2	2/4/-	1/2/2	0/0/0	0/0/0
FVC, L (%)						
Baseline	3.27 (81%)	3.16 (81%)	1.35 (54%)	3.54 (80%)	2.99 (65%)	4.20 (94%)
12 months	3.24 (81%)	3.03 (78%)	1.13 (46%)	3.50 (75%)	2.83 (62%)	4.25 (97%)
24 months	3.06 (77%)	3.07 (78%)	-	3.41 (74%)	2.96 (65%)	4.10 (92%)
Death	No	No	Yes	No	No	No

IPF: idiopathic pulmonary fibrosis; fHP: fibrotic hypersensitivity pneumonitis; GERD: gastroesophageal reflux disease; UIP: usual interstitial pneumonia; ACIF: airway-centered interstitial fibrosis; mMRC: modified Medical Research Council (dyspnea scale); and FVC: forced vital capacity

among those, 63% exhibited disease progression within five years.⁽²⁾ Exposure to tobacco and mold must be identified and ceased due to correlations with disease progression.⁽²⁾ Although genetic biomarkers are known to be associated with FIP, genetic testing is currently not approved or accessible for clinical use.⁽⁴⁾ Despite the growing scientific evidence, specific guidelines for FIP screening are not yet available. One study suggested performing HRCT in patients with respiratory symptoms or abnormal clinical examination and proposed an HRCT in asymptomatic patients at age 40 or 10 years before the age of onset in the proband; according to the authors of that study, if ILD is absent, they suggest repeating the HRCT after 5 years of follow-up.⁽⁸⁾ In spite of the low sensitivity of PFTs, the authors also recommended these tests be conducted at the initial evaluation for all relatives of FIP patients, and, in the absence of ILD in the HRCT, the tests should be repeated within 5 years.⁽⁸⁾ Considering this evidence, our suggestion would be to follow up first-degree relatives of patients with FIP as described above, especially those with signs of disease progression.

Data on specific antifibrotic treatments for FIP are scarce. In one study, treatment with pirfenidone reduced disease progression in patients with short telomeres.⁽⁹⁾ Another study, although not specific for FIP, showed that nintedanib was effective in slowing the progression of non-IPF forms of ILD, such as fHP.⁽¹⁰⁾ These results suggest that antifibrotic therapy may play a role in progressive fibrotic FIP, although further studies are required.

Thus, screening for ILD in relatives of individuals with FIP is necessary for the early recognition of this entity. Antifibrotic drugs may be of benefit in the management of this disease.

AUTHOR CONTRIBUTIONS

DRE, EVM, and RAC: conception and planning of the study; data collection and tabulation; statistical analysis and table creation; drafting and revision of the manuscript; formatting of the manuscript in accordance with the JBP instructions for authors, and approval of the final version.

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