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Fibrosing Interstitial Lung Diseases: Characteristics of Patients Attended at a Brazilian Public University Hospital

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Abstract: ***Background and objectives: Define the epidemiological profile, radiological and or histological characteristics of patients with fibrosinginterstitial lung diseases (FILDs), in addition to determining diagnostic methods, lung functional capacity and treatments performed for these patients. Materials and methods: Retrospective cross-sectional observational study carried out with patients with FILDs in the pulmonology outpatient clinic of the Hospital UniversitárioCajuru (HUC) at the Pontifícia Universidade Católica do Paraná (PUC-PR) in Brazil, between January 2017 and December 2017. Data from medical records of 53 patients with interstitial lung diseases (ILDs) including physical examination findings, tomographic patterns; presence or absence of transbronchial biopsy and cellularity of bronchoalveolar lavage if performed. All information wasreviewed and inserted into an Excel spreadsheet. Data analysis was carried out using the SPSS v.22.0 computer program. The results were expressed as means, medians, minimum values and standard deviations or as frequencies and percentages. Inferential analysis was carried out using statistical tests relevant to the study, such as Chi Square, Fischer's exact Test and Student's T Test. The comparative analysis between radiologists in terms of tomographic criteria was performed using the Kappa coefficient of agreement. Results: Of the 53 patients initially selected, 43 met all inclusion criteria. Of these patients, there was a slight predominance of female patients (53%) and a mean age of 62.2 years. Of the clinical characteristics evaluated, 49% had exposure (mold or birds). Most patients did not undergo surgical lung biopsy (82%) and only 32% underwent transbronchial biopsy (TBB). Bronchoalveolar lavage (BAL) was performed in 60% of cases. Of the patients who underwent BAL (25 of 43), 20 of them had a predominance of lymphocytes in the cell differential. Regarding the treatment of these patients, 17 (40%) received treatment with corticosteroids, 9 (21%) with immunosuppressants. Of the 43 patients evaluated, 23 (53%) did not have a definitive diagnosis or were still under etiological investigation and, therefore, did not receive any treatment. Regarding the degree of agreement between radiologists, it was observed that there was very good agreement in the presence of the ground glass finding (71% of cases) k=0.83 (95% CI 0.61-1.0) and the presence of Velcrocrackles was significantly correlated with the drop in FVC, with FVC of 50% (average) in relation to predicted. Conclusions: The FILDs affects elderly patients more, with a slightly higher prevalence among women. A relevant number of patients (49%) were exposed to mold and bird feathers, which suggests a greater number of possible diagnoses of hypersensitivity pneumonitis (HP).Although much has been learned about FILDs in recent decades, more research in this area is needed. It is clear that MDD (multidisciplinary discussion) improves the possibilities of diagnostic accuracy, and that functional tests more accurately predict the severity and speed of progression of ILDs.***

Keywords: interstitial, radiologic, histologic, fibrosis, pneumonitis

1. Introduction

Interstitial lung diseases (ILDs) constitute a heterogeneous group of disorders with inflammatory and interstitial lesions, fibrosing or not, of different etiologies, clinical presentations and radiological patterns, but with different histological patterns, therapeutic response, and natural history (1, 2, 3, 4). They are characterized by cell proliferation, inflammation, fibrosis, or a combination of these findings within the alveolar wall.

Pulmonary fibrosis was initially described by VON BÜHL in 1872 (1). The first generally accepted classification of idiopathic interstitial pneumonitis was introduced by LIEBOW in 1975 (1). The first multidisciplinary international consensus classification of common interstitial pneumonitis was developed in 2002 by the ATS/ERS (American Thoracic Society and European Respiratory Society) (8) by a group of clinical pulmonologists, pathologists and radiologists, with the aim of standardizing this classification and achieve broad acceptance among participating areas, subsequently updated in 2013 (9).

ILDs occur throughout the world and their prevalence, although little known, is due to the impossibility of using older statistics due to changes in histological classification; appears to be rare but increasing due to increasing numbers of hospital admissions and deaths. According to American data, the prevalence of idiopathic pulmonary fibrosis in the general population in the USA was estimated at between 10 and 60 cases per 100,000 inhabitants (6,9). They appear in people over 50 years of age and, for some reason, more in men and tend to increase with age, with the average survival

rate (before the era of antifibrotics) being only 3 years from the moment of diagnosis (6.9).

Among ILD, there is a group characterized by presenting an interstitial lesion with a fibrosing predominance, thus certain fibrosing interstitial lung diseases (FILDs). Among the FILDs, the most common are chronic hypersensitivity pneumonitis (HP) due to exposure to mold or birds),pulmonary sarcoidosis, secondary to autoimmune diseases (most commonly systemic sclerosis, rheumatoid arthritis and systemic lupus erythematosus) or, if the cause is not found, idiopathic pulmonary fibrosis (IPF) (6,7,8,9).

Its classification, diagnostic difficulty and high mortality emphasizes the need for correlation between histopathological findings, clinical and radiological data to reach a diagnosis, highlights the poor prognosis of idiopathic pulmonary fibrosis in particular and shows us that, even after multidisciplinary evaluations, there is disagreement among experienced lung pathologists regarding the exact classification of FILDs, which poses a problem regarding treatment in particular (5,11).

2. Methodology

This study is characterized by the Retrospective Cross-Sectional Observational design.

The sample was made up of patients being monitored for FILDs at the Pulmonology outpatient clinic of the Hospital Universitário Cajuru (HUC) in Curitiba-PR from January 2017 to December 2017.

Data from the medical records of 53 patients with FILDs treated at the HUC outpatientclinic in 2017 were reviewed. Data such as name, age, date of birth, sex, oxygen saturation at rest, presence of Velcro crackles, digital clubbing, wheezing or croaking and presence of comorbidities. Radiological, histological and functional data were also evaluated, such as forced vital capacity (FVC), forced expiratory flow in one second (FEV1), and ratio (FEV1/FVC). In our service we do not have plethysmography to measure lung volumes. In addition, tomographic characteristics such as the presence of honeycombing, ground glass, reticulation and the presence or absence of surgical or transbronchial biopsy (BTB) were evaluated, in addition to bronchoalveolar lavage (BAL). Finally, the determination of the final diagnosis and actions taken.

Data were collected and stored in a Microsoft Excel spreadsheet. Data analysis was carried out using the SPSS v.22.0 computer program. The results were expressed as means, medians, minimum values, maximum values and standard deviations (quantitative variables) or as frequencies and percentages (qualitative variables). Inferential analysis was carried out using statistical tests relevant to the study (example: Chi Square, Fisher's Exact Test, Student's T Test) and p values lower than 0.05 were considered significant. The comparative analysis between radiologists in terms of tomographic criteria (presence or absence of tomographic findings of ground glass, traction bronchiectasis, honeycombing, emphysema, consolidation and nodules or micronodules) was performed using the Kappa coefficient of agreement, where: $k > 0$ .80 is very good; 0.61 to 0.80 is good; 0.41 to 0.60 is moderate; 0.21 to 0.40 is weak and finally $K < 0.21$ is poor agreement.

3. Results

Of the 53 patients initially selected, 43 met all inclusion criteria. Of these patients, there was a slight predominance of female patients (53%) and a mean age of 62.2 years (Table 1). Of the clinical characteristics evaluated, 49% had exposure (mold or birds). Of the patients who underwent spirometry, the mean FVC was 59% (SD +/- 21) of predicted and the mean FEV1/FVC ratio was 0.8, which demonstrates the predominance of non-specific pulmonary pattern (NSP). However, due to the average reduction in FVC being less than 60% and being associated with the presence of Velcrocrackles and signs of fibrosis on HRCT, it can be deduced that most of the pulmonary patterns were truly restrictive in nature. Most patients did not undergo surgical lung biopsy (82%) and only 32% underwent BTB. BAL was performed in 60% of cases. Of the patients who underwent BAL (25 of 43), 20 of them had a predominance of lymphocytes in the cell differential (average26± 24). Regarding the treatment of these patients, 17 (42%) received treatment with corticosteroids, 9 (23%) with immunosuppressants. Of the 43 patients evaluated, 23 (53%) did not have a definitive diagnosis or were still under etiological investigation and, therefore, did not receive any treatment.

Of the 43 patients evaluated in the present study, we concluded that the majority of them (25.5%) remained with an inconclusive diagnosis,as Nonspecific interstitial pneumonia (NSIP) until the end of the study; another 13.9% were diagnosed with ILD secondary to systemic sclerosis (SSc-ILD); 11.6% with fibrosing HP; 6.9% secondary to drugs, as Drug induced interstitial lung disease (DILD); 4.6% with Sarcoidosis and finally; IPF, Eosinophilic Pneumonia (EP), ILD secondary to polymyositis (PM-ILD), combined pulmonary fibrosis and emphysema (CPFE), desquamative pneumonia (DP) and cryptogenic organizing pneumonia (COP), individually accounted for 2.3% of cases.

Table 1: Clinical, functional characteristics, procedures and treatment

	N = 43			
Sex (Male/Female)	**M 20 / F 23**			
Age (years), SD	**62.2 (25 - 87)**			
Clinical features	**Yes**	**No**	**Unknown**	**To be clarified**
Crackles	31% (13)	69% (33)	-	-
Exposure	49% (21)	23% (10)	28% (16)	-
Digital clubbing	16% (8)	30% (15)	54% (24)	-

Croaking	12% (7)	88% (40)	-	-
Collagenosis	14% (6)	79% (37)	-	7% (4)
Functional Features	**Liters**	**%**	**SD**	
FVC (%)	2.2	59%	+/- 21	
FEV1 (%)	1.8	60%	+/- 20	
FEV1/FVC	0.8	104%	+/- 15	
Procedure	**Yes**		**No**	
OSB	18% (7)		82% (34)	
BAL	60% (26)		40% (17)	
BTB	32% (13)		68% (29)	
Treatment	**Yes**		**No**	
Corticosteroid	42% (17)		58% (23)	
Immunosuppressant	23% (9)		77% (31)	
Corticosteroid and immunosuppressant	7% (3)		93% (40)	
Neither	53% (23)		47% (20)	

Definition of abbreviations: FVC = forced vital capacity. FEV1 = forced expiratory flow in one second. OSB = open surgical biopsy. SD = standard description. BAL= bronchoalveolar lavage. BTB = transbronchial biopsy. *Exposure: mold and birds.

Furthermore, it was observed that the presence of Velcro crackles significantly correlated with the drop in FVC, with FVC of 50% (average) in relation to predicted (Table 2). As expected, a significant correlation was observed between the presence of ground glass and reduced FVC (54% on average) in relation to the predicted value, denoting the presence of fibrosis. Furthermore, a correlation was observed between findings of traction bronchiectasis and reduction in FVC (p=0.001). As for the variables honeycombing, emphysema and consolidation, there was no correlation with a reduction in FVC. It should be noted here that all tomographic findings described and associated in this evaluation were considered by only one elected reference radiologist.

Table 2: Association between clinical and tomographic variables and lung function

Tomographics variable	FVC (l) (SD)	FVC (%) (SD)	FEV1/FVC (l) (SD)
Velcro crackles	1.8 (+/- 0.6)	50% (+/- 13%)	0.9 (+/- 0.1)
	p: 0.09	p: 0.04	p: 0.01
Ground glass	2.0 (+/- 0.7)	54% (+/- 16%)	0.9 (+/- 0.1)
	p: 0.04	p: 0.02	p: 0.12
Traction bronchiectasis	1.9 (+/- 0.6)	50% (+/- 14%)	0.8 (+/- 0.1)
	p: 0.01	p: 0.001	p: 0.26
Honeycombing	2.1 (+/- 0.9)	53% (+/- 18%)	0.8 (+/- 0.1)
	p: 0.44	p: 0.19	p: 0.88
Emphysema	2.3 (+/- 1.0)	59% (+/- 19%)	0.8 (+/- 0.1)
	p: 0.76	p: 0.93	p: 0.60
Consolidation	1.5 (+/- 0.3)	45% (+/- 11%)	0.9 (+/- 0.005)
	p: 0.03	p: 0.07	p: 0.51

Definitions and interpretation: SD = standard deviation.
Significant P = $p < 0.05$

Regarding the degree of agreement between radiologists, it was observed that there was very good agreement in the presence of the ground glass finding (71% of cases) K=0.83 (95% CI 0.61-1.0). In the findings of traction bronchiectasis and honeycombing, a good relationship of agreement in presence is observed, K=0.78 (CI 0.55 – 1.0) and K=0.79 (CI 0.57 – 1.0), respectively. For the findings of emphysema, consolidation, nodules/micronodules, the total agreement was moderate, K=0.52 (CI 0.09 – 0.96); K=0.52 (0.09 – 0.96) and K=0.54 (CI 0.11 – 0.96) respectively (Table 3).

When the predominance of ground glass and reticulated glass on computed tomography of the thorax (CT) was quantified, there was 50% agreement between radiologists for the predominance of reticulated in relation to ground glass on chest tomography (R>GG), with 4 cases (13%) discordant overall. There was 33% agreement regarding the predominance of GG, and only 4% agreement regarding the absence of predominance between reticulation and ground glass (R = GG). The total agreement for all relationships was 87%, with K considered good, 0.75 (CI 0.44- 1.0) (Table 4).

Table 3: Agreement Assessment between two Radiologists: Kappa agreement coefficients (K).

Tomographic variables	Agreement in presence	Agreement in absence	Agreement	K	CI 95%
Ground glass	71%	23%	94%	0.83	0.61 - 1.0
Traction bronchiectasis	61%	29%	90%	0.78	0.55 - 1.0
Honeycomb	32%	58%	90%	0.79	0.57 - 1.0
Emphysema	16%	74%	90%	0.52	0.09 - 0.96
Consolidation	10%	77%	87%	0.52	0.09 - 0.96
Nodules / Micronodules	10%	77%	87%	0.54	0.11 - 0.96

Legend: K (coefficient of agreement). CI 95% (95% confident interval).
K > 0.80 = very good. 0.61 a 0.80 = good. 0.41 a 0.60 = moderate. 0.21 a 0.40 = weak. < 0.21 = poor.

Table 4: Coefficients of agreement referring to the predominance of ground glass and reticulation

Relation of predominant	Agreement	Disagreement	K	CI
R >GG	50%	13% (4)	0.75	0.44 - 1.0
R < GG	33%			
R = GG	4%			
Full agreement	**87%**			

Legend: R = reticulated. GG = Ground glass. K = kappa. CI = (95% confident interval)

The percentage of cases in which there was agreement between radiologists regarding the predominance of lesions on tomography were also analyzed. The following are described: basal predominance, upper thirds, central, peripheral and diffuse axial. The number of concordant cases in total was 20 (64.5%) of the tomography scans analyzed. There were 11 discordant cases (35.5%). Agreement kappa was not calculated in these criteria, given that there were more than 3 items. When applying the tomographic criteria established by ATS/ERS 2022, both radiologists agreed in 17% of cases regarding the tomographic classification of Usual interstitial pneumonia (UIP) (Table 5).

Table 5: Tomographic classification: 2017 Fleischner Society criteria and agreement between radiologists

Fleishner Society Criteria	UIP	Probable UIP	Indeterminate for UIP	Incompatible	Agreement	K	CI
	17%	-	7%	48%	72%	53%	0.30 - 0.76

Legend: UIP = usual interstitial pneumonia. K = coefficient of agreement. CI = (95% confident interval)

There were no cases classified as probable UIP. In 7% of cases, there were agreement for the indeterminate UIP classification and to a greater extent, there was agreement in 48% of cases for the classification of incompatibility with UIP, with total agreement in the classification in 72% of cases, with a moderate K of 0.53 (CI 0.30 – 0.76).

2. Discussion

In this study, we observed that FILDs affects elderly patients more, with an average age of 62.2 years, with a slightly greater prevalence among women, accounting for 23 of the 43 cases. Furthermore, it was observed that a relevant number of patients (49%) were exposed to mold and bird feathers, considered positive in this study, which suggests a greater number of possible diagnoses of hypersensitivity pneumonitis (HP).

Chronic HP is a FILD that results from a long period of exposure to a certain antigen, in a genetically predisposed individual, which can cause an exaggerated immune response in the small airways and lung parenchyma (13,14).

Among the main causative antigens are: fungi, bacteria, protozoa, proteins present in feathers; and some low molecular weight compounds (13, 15).

In contrast to IPF, there are no defined criteria or accepted consensus for the definitive diagnosis of HP. However, several studies have proposed diagnostic criteria mainly to standardize the inclusion of these patients in clinical studies (13, 14, 28, 29). Therefore, there is enormous variation between diagnostic centers and multidisciplinary clinical, radiological and pathological evaluation teams (14).

Regarding the procedures, 60% of patients underwent BAL, with subsequent cellularity assessment, where a predominance of lymphocytes was seen in 20 (60%) of the 25 patients who underwent the procedure, which once again strongly suggests possible diagnoses of HP for the majority of cases analyzed and interpreted as inconclusive (NSIP), which accounted for 25.58% of all cases.

According to Keith et al, BAL analysis can direct the diagnosis of a pulmonary infection, as well as provide differential cell counts that can help in the diagnosis and management of various lung diseases. However, BAL analysis should always be interpreted in a clinical and radiological context, along with other pertinent tests.

BAL obtained from a healthy, never-smoking individual should contain, on average, a majority of alveolar macrophages (80 to 90%), some lymphocytes (5 to 15%), and very few neutrophils (≤3%) or eosinophils (<1%) (19).

BAL is considered a highly sensitive method for detecting inflammation in a patient with suspected HP. An increase in total cell count with a significant increase in T lymphocytes, generally above 50%, characterizes HP (15).

According to Raghu et al and Morisset et al, the general predominance of lymphocytes in the BAL increases the probability of HP, since more than 80% of patients with chronic HP have more than 20% of lymphocytes in the lavage. The dramatic alveolitis found in this pathology often increases lymphocytes to 50% or more, however, these values are much more prominent in acute HP (14, 16).

According to the literature, an increase in lymphocytes > 40% was the only scenario where experts considered it sufficient to establish the diagnosis of chronic HP, without the need for a lung biopsy (14).

We know that many of the cases submitted to biopsy, whether surgical or transbronchial, were also not capable of definitive diagnosis, given the great difficulty of histopathological analysis due to the lack of specialist professionals in this area. Even though there were more pathologists specializing in the lung, as previously reported, there is a great deal of disagreement among experienced pathologists regarding the exact classification of DPIF in the literature (5,11). Furthermore, many patients do not wish or are not clinically capable of undergoing surgical lung biopsy. Therefore, these patients end up being classified as unclassifiable interstitial lung disease (NSIP) (30).

Regarding tomographic findings, a significant correlation was observed between the presence of ground glass, Velcro crackles and a drop in FVC, which demonstrates the real relationship between the worsening of lung function and the

progression of the disease, andconsequently, an increase in clinical and radiological findings suggestive of the evolution of pulmonary fibrosis.

Idiopathic fibrosing interstitial pneumonias comprise usual interstitial pneumonitis (UIP), which defines the histopathological pattern observed in IPF, and non-specific interstitial pneumonitis (NSIP).The tomographic features seen on high resolution computerized tomography (HRCT) are reticular changes and honeycombing, seen predominantly in the basal and subpleural regions of the lungs. Honeycombing is considered the strongest predictor of UIP and the extent of fibrosis on HRCT is an important prognostic indicator in pulmonary fibrosis. When ground-glass attenuations are seen in IPF, they will commonly progress to fibrosis and honeycombing. Therefore, images are extremely important to detect complications of pulmonary fibrosis, suchas accelerated progression, lung cancer and secondary infections (20).

It is also known that the understanding of tomographic findings is still being improved and the guidelines are constantly changing and being updated. CT findings of NSIP, UIP, organizing pneumonia (OP) and desquamative interstitial pneumonia (DIP) often overlap, making biopsy necessary in some cases. Furthermore, there are numerous other idiopathic interstitial pneumonias that present fibrosis, such as acute interstitial pneumonitis (AIP), lymphoid interstitial pneumonia (LIP), pneumonias secondary to connective tissue diseases (CTD-ILD), and finally chronic HP, which, as previously mentioned,can be difficult to distinguish between IPF (14, 20, 21).

Identifying the UIP pattern may be more challenging in patients with associated fibrosis and emphysema, a disease combination seen in more than a third of patients with interstitial pulmonary fibrosis. In a study of 40 patients with pulmonary fibrosis and emphysema, the radiological diagnosis was correct in only 30 of 68 cases (44%). Therefore, it is important for the radiologist to describe the extent and severity of coexisting emphysema to assess the patient's management and prognosis (21).

According to Lynch et al (20), when a group of radiologists and a separate group of physicians evaluated HRCT, the positive predictive value of a diagnosis of UIP in each group was 85 and 87%, respectively. When radiologists felt confident about their tomographic diagnoses (approx. 60% of the cases they evaluated), the positive predictive value increased to 96%. Subpleural honeycombing and septal thickening were the tomographic findings most predictive of IPF, and patients who had these examination findings had worse survival.

In patients with NSIP with concordant assessments, a better prognosis was demonstrated than in patients with UIP and concordant assessments. Patients with discordant assessments (CT scan consistent with NSIP and biopsy demonstrating UIP) exhibited intermediate survival, which was better than patients with concordant UIP but worse than those with concordant NSIP. Above all, this study emphasizes the importance of identifying the UIP patterns with concordant tomographic and histological findings. This group would be less likely to benefit from treatment and, therefore, would have a worse prognosis (22).

Regarding agreement coefficients, our radiologists achieved good or very good values for the general agreement between the tomographic characteristics evaluated. The total agreement kappa between the reticulated and ground glass predominance (87%) demonstrates good agreement between the two experts.

According to Munson et al (27), the authors found that the integration between the tomographic findings changed the primary diagnosis in 51% of the cases and increased the total agreement between 6 pulmonologists despite the most probable diagnosis with the kappa coefficients increasing from 0.47 before the HRCT to 0.72 after. They also found that tomographic characteristics changed the decision of whether or not to indicate biopsy in 29% of cases. There is also some evidence that the integration between tomographic findings not only changed the physician's differential diagnosis, but also improved the diagnostic accuracy of the clinical assessment.

Another study showed that interobserver agreement regarding the presence of the main findings had a kappa of 0.45 for honeycombing, 0.74 for cysts, 0.63 for broncho vascular thickening and 0.56 for ground-glass opacities (23). Agreement for the craniocaudal distribution of the main findings had a kappa of 0.48 for honeycombing, 0.52 for broncho vascular thickening and 0.32 for ground-glass opacities. The predominant findings of honeycombing and broncho vascular thickening were associated with more than 90% accuracy in relation to the first diagnostic hypothesis of diffuse lung disease. Accuracy increased when ground-glass opacities were combined with honeycombing or lower lobe distribution (23). In a third study, interobserver agreement was moderate to very good (kappa coefficient 0.49 to 0.7) for reliable tomographic diagnosis in a wide variety of interstitial lung diseases. Although a reliable diagnosis and an accurate diagnosis cannot be confused, several studies have reported that a reliable tomographic diagnosis is generally correct (24).

Finally, according to a study of agreement between pulmonologists, the results showed that academic status, participation in multidisciplinary discussions (MDD) and level of experience of specialist doctors are independently associated with better prognostic discrimination between idiopathic pulmonary fibrosis and interstitial lung diseases (25). In particular, using mortality to validate the accuracy of IPF diagnosis, they showed that the accuracy of IPF diagnosis made by university hospital practitioners with more than 20 years of experience is equivalent to diagnoses made by international IPF experts (25).

3. Conclusion

Although much has been learned about interstitial fibrosing diseases in recent decades, more research in this area is needed. Diagnosis has been late, treatment is still quite limited, and lung transplantation remains the best option. It is clear that MDD improves the possibilities of diagnostic

accuracy, and that functional tests more accurately predict the severity and speed of progression of ILD.

The identification of clinical, radiological and molecular predictors will be crucial in these diseases and, therefore, it is essential that radiologists, pathologists and pulmonologists work together to establish these diagnoses and consequently increase the survival of these patients.

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