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ORIGINAL RESEARCH

Radiological and histological characteristics of patients with interstitial lung disease undergoing lung biopsy in a reference institution from eastern Colombia

Características radiológicas e histológicas de pacientes con enfermedad pulmonar intersticial llevados a biopsia pulmonar en una institución del oriente colombiano

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Abstract

Introduction: Interstitial lung disease (ILD) diagnosis requires a multidisciplinary approach and, in some cases, lung biopsy.
Objective: To describe the sociodemographic and clinical characteristics, as well as the radiological and histological findings, of patients with ILD who required lung biopsy after a multidisciplinary board (pneumology, radiology, and pathology) of a reference center for respiratory diseases in Bucaramanga, Colombia, failed to reach the ILD diagnosis.
Materials and methods: Cross-sectional study. The medical records of 56 patients treated at the Instituto Neumológico del Oriente who underwent lung biopsy between 2015 and 2019 were reviewed. Measures of central tendency and dispersion were calculated for demographic and clinical variables, respectively, to characterize them. A bivariate analysis was performed using Fisher's exact test to determine whether there were differences in the distribution of the sociodemographic and clinical variables according to the radiological patterns and the final histological diagnosis.
Results: Participants' median age was 67 years (IQR: 59-72) and 55.35% were men. 43 patients had a radiological pattern inconsistent with usual interstitial pneumonia (UIP); 4 had a pattern consistent with possible UIP; and 9 had a pattern consistent with UIP. The most common histologic diagnoses were hypersensitivity pneumonitis (HP) (32.14%), nonspecific interstitial pneumonia (NSIP) (17.86%), and UIP (19.64%).
Conclusion: In the study population, the primary reason for performing a lung biopsy was the presence of a radiologic pattern inconsistent with UIP, with HP being the predominant histopathological diagnosis. This is the first study to characterize patients with ILD who underwent lung biopsy in eastern Colombia, making a significant contribution to our understanding of the disease's epidemiology in the country.

Resumen

Introducción. El diagnóstico de la enfermedad pulmonar intersticial (EPI) requiere un enfoque multidisciplinar y, en ocasiones, de una biopsia pulmonar.
Objetivo. Describir las características sociodemográficas y clínicas, y los hallazgos radiológicos e histológicos de pacientes con EPI que requirieron biopsia pulmonar luego de no lograrse un diagnóstico de esta enfermedad por la junta médica multidisciplinar (neumología, radiología y patología) de un centro de referencia en enfermedades respiratorias de Bucaramanga, Colombia.
Materiales y métodos. Estudio transversal. Se revisaron las historias clínicas de 56 pacientes atendidos en el Instituto Neumológico del Oriente y que fueron remitidos a biopsia pulmonar entre 2015 y 2019. Se analizaron variables demográficas y clínicas, calculando medidas de tendencia central y de dispersión para su respectiva caracterización. Se realizó un análisis bivariado mediante test exacto de Fisher para determinar si existían diferencias en la distribución de las variables sociodemográficas y clínicas de acuerdo con los patrones radiológicos y el diagnóstico histológico definitivo.
Resultados. La mediana de edad fue 67 años (RIC: 59-72), 55.35% fueron hombres. 43 pacientes presentaron patrón radiológico inconsistente con neumonía intersticial usual (NIU); 4, patrón de posible NIU y, 9, patrón de NIU. Los diagnósticos histológicos más frecuentes fueron neumonitis por hipersensibilidad (NH) (32.14%), neumonía intersticial no específica (17.86%) y NIU (19.64%).
Conclusión. La principal razón para realizar biopsia pulmonar en la población de estudio fue la presencia de un patrón radiológico inconsistente con NIU, siendo la NH el principal diagnóstico histopatológico. Este es el primer trabajo que caracteriza a pacientes con EPI del oriente colombiano llevados a biopsia pulmonar, lo que representa un importante aporte al conocimiento de la epidemiología de esta enfermedad en Colombia.

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Introduction

Interstitial lung disease (ILD) comprises a group of lung disorders that share radiological and clinical characteristics but are pathophysiologically distinct.[1] The frequency of this disease varies depending on the population studied and the criteria used to define it, as its classification has been updated multiple times over the last few years.[2]

The etiology of ILD is very diverse, with more than 150 known causes; however, a clear causative agent can be identified in only about 35% of patients, which may include environmental/occupational factors, use of medications, collagen diseases, radiation, and infections.[3,4] In 2002, the classification of this group of diseases was modified and standardized following the consensus developed by the American Thoracic Society (ATS) and the European Respiratory Society (ERS)[5]. ILD was classified as of known cause (medication, inhaled organic antigens, collagen diseases, among others) and of unknown cause; the latter category included idiopathic interstitial pneumonia, granulomatous diseases, and other forms of ILD such as lymphangioleiomyomatosis and Langerhans cell histiocytosis. The most significant modification to this classification was the separation of idiopathic pulmonary fibrosis (IPF) from other idiopathic interstitial pneumonias that may have an underlying cause.[5-8]

The diagnostic process for ILD is complex because it requires a multidisciplinary approach that incorporates concepts from pneumology, radiology, pathology, and, if possible, rheumatology in order to integrate clinical and radiological data[9]; pulmonary function tests and immunological evaluation results; and, in some cases, anatomopathological data.[5] This clinical approach aims to determine the etiology of the disease, which, of course, excludes the diagnosis of idiopathic disease.

To make an accurate diagnosis of ILD, special consideration must be given to the patient's occupational history, exposure to the environment, and medications taken.

The prognosis for this group of diseases varies according to the type of disease of each patient and the time of diagnosis.[10] Thus, several risk factors associated with mortality from ILD have been described, such as male sex, advanced age, and difficulties in obtaining specialized assessment and treatment in a timely manner.[11]

In approximately half of patients, adequate clinical and radiological evaluation is sufficient to diagnose ILD; however, for the remaining idiopathic diseases that comprise ILD, this approach is insufficient, and a surgical lung biopsy is required to confirm the diagnosis.[12]

Given this scenario, the aim of this study is to describe sociodemographic and clinical characteristics, as well as the radiological and histopathological findings, of patients diagnosed with ILD who underwent lung biopsy between 2015 and 2019 after failing to obtain a definitive diagnosis of the disease after being assessed by a multidisciplinary medical board (pneumology, radiology, and pathology) at a respiratory disease referral center in Bucaramanga, Colombia.

Materials and methods

Type of study and study population and sample

Cross-sectional study. All medical records of patients with ILD evaluated in the outpatient consultation service at the Instituto Neumológico del Oriente de Bucaramanga between 2015 and 2019 that contained the International Classification of Diseases (ICD-10) codes for interstitial pulmonary disease (J849) and idiopathic pulmonary fibrosis (J84.112) were included consecutively (N=246). From these records, patients who were referred for lung

biopsy after the institution's multidisciplinary group failed to reach a diagnosis through case analysis were selected; thus, the final sample consisted of 56 patients.

It should be noted that, for case analyzes, the institution's multidisciplinary board used the ATS and ERS guidelines[5,13] for the diagnosis and classification of ILD, as well as the international consensus for IPF diagnosis.[14]

Procedures

The demographic variables (age, sex, and occupation) and clinical variables (environmental exposure, associated diseases, concomitant medication, lung function test results, radiological patterns, and histological diagnosis) for each patient were collected through a review of the institution's medical records database. This process was performed jointly by a pulmonologist and a general practitioner.

Statistical analysis

Categorical variables (sex, occupation, associated diseases, environmental exposure, concomitant medication intake, radiological patterns, histological diagnosis, and pulmonary function) were expressed as absolute and relative frequencies. Age, on the other hand, is a continuous variable with a non-normal distribution when analyzed graphically using the histogram or numerically using the Shapiro–Wilk test, so it was reported in terms of median and interquartile range.

Additionally, a bivariate analysis was performed using Fisher's exact test to determine whether there were statistically significant differences in the distribution of sociodemographic and clinical variables according to radiological patterns and definitive histological diagnosis. The level of significance was set at $p<0.05$.

Ethical considerations

The study took into account the ethical principles for medical research involving human subjects established by the Declaration of Helsinki[15] and the standards for health research of Resolution 8430 of 1993 of the Colombian Ministry of Health.[16] Although informed consent was not required for this study due to its nature, the Ethics Committee of the Instituto Neumológico del Oriente approved the study in accordance with Minutes No. 131 of April 16, 2020.

Results

Of the 56 patients who underwent lung biopsy, 55.35% were men; the median age was 67 years (IQR: 59-72). With regard to occupation, housewife was the most common occupation in the general population, followed by technicians (administrative assistants, dental laboratory assistants, food processors, and automotive technician), and professionals (nurses, engineers, teachers, graphic designers, and lawyers) (Figure 1). On the other hand, when stratifying occupations by sex, housewife (52%) was the most common among women, and agriculture (12.90%) and construction (12.90%) among men.

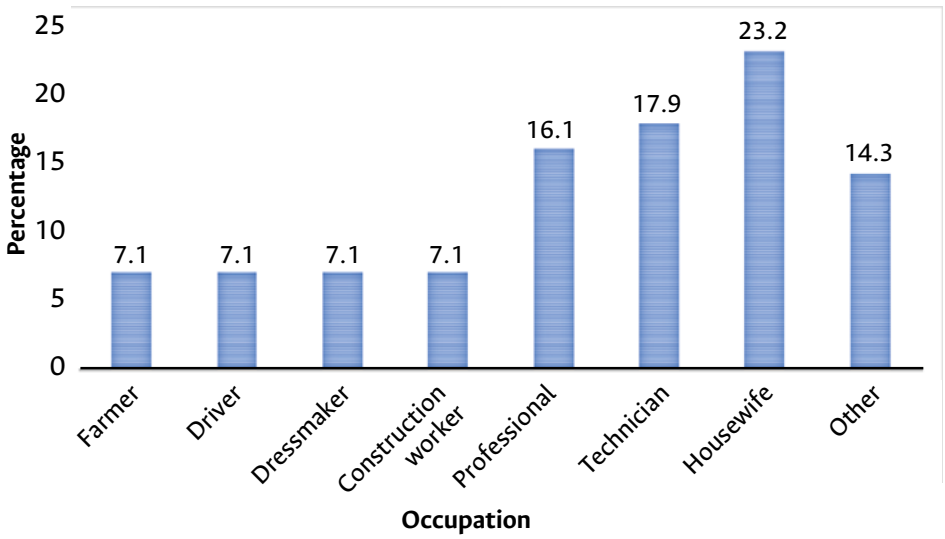

Figure 1. Occupation analysis of the study population.
Professional: nurses, engineers, teachers, graphic designers, and lawyers.
Technicians: administrative assistants, dental laboratory assistants, food processors, and automotive technician.
Other: military, pipeline foremen, mattress manufacturing workers, artisans, quarry workers, guards, freight workers.
Source: Own elaboration.

75.0% of the sample had comorbidities, the most frequent being hypertension (32.14%), hypothyroidism (16.07%), and hypercholesterolemia (12.5%). In addition, 10 patients presented with rheumatological diseases: 4 with Sjögren's syndrome, 3 with rheumatoid arthritis, 2 with systemic lupus erythematosus, and 1 with microscopic polyangiitis.

One or more medications were used by 66.07% of patients, including levothyroxine, atorvastatin, calcium, losartan, and amlodipine; 10.71% were being treated with prednisolone.

Regarding the radiological patterns analyzed by the multidisciplinary board, it was found that 43 patients had a pattern inconsistent with usual interstitial pneumonia (UIP), of which 18 had a histopathological diagnosis of hypersensitivity pneumonitis (HP); 8 had non-specific interstitial pneumonia (NSIP); and 9 had organizing pneumonia. In addition, 2 of the patients had sarcoidosis, 2 had respiratory bronchiolitis, and the remaining 4 had alveolar proteinosis, amyloidosis with respiratory bronchiolitis, UIP, and granulomas with non-caseous necrosis. 9 patients were diagnosed with UIP using tomography, but at the discretion of their treating pulmonologist, a biopsy was performed to confirm the radiological diagnosis. Finally, the radiology service suspected UIP in 4 patients, of which 2 were diagnosed with NSIP confirmed by histopathology, 1 with follicular bronchiolitis, and 1 with UIP (Table 1).

The mean age of patients with HP was 64.8 years and the reported occupational exposures were acrylics (n=1), fuel fumes (n=1), wood (n=1), textiles (n=1), food chemicals (n=1), and air conditioning (n=1); silica was found to be the only exposure in 2 patients, and 4 had a history of exposure to birds. There were no measurements of serum immunoglobulin G antibody against HP-associated antigens in any of these patients.

Following HP, the most common histological diagnosis was NSIP, which was found in 10 patients with an average age of 64.8 years. As significant findings in this population, it was found that 4 patients had a history of rheumatologic diseases: 1 had Sjögren's syndrome, 1 had rheumatoid arthritis, 1 had systemic lupus erythematosus, and the other had scleroderma; the remaining patients did not have comorbidities.

Table 1. Results of radiological and histological patterns in the study population.

Pattern		n	%
Radiological	Diagnosis inconsistent with UIP	43	76.79
	Definitive diagnosis of UIP	9	16.07
	Probable diagnosis of UIP	4	7.14
Histological	HP	18	32.14
	NSIP	10	17.86
	UIP	11	19.64
	Organizing pneumonia	9	16.07
	Respiratory bronchiolitis associated with ILD	3	5.36
	No UIP	2	3.57
	Sarcoidosis	2	3.57
	Alveolar proteinosis	1	1.79

UIP: usual interstitial pneumonia; HP: hypersensitivity pneumonitis; NSIP: nonspecific interstitial pneumonia; ILD: interstitial lung disease.
Source: Own elaboration.

On the other hand, of the 10 patients in the entire sample with a history of rheumatologic disease, 3 were given a radiological diagnosis of probable UIP, but it was found that 2 of them had NSIP and the other had follicular bronchiolitis. The tomographic diagnosis in the remaining 7 patients was inconsistent with UIP, histopathologically corresponding to organizing pneumonia in 2 cases, NSIP in 2 cases, HP in 2 cases, and granulomas with non-caseous necrosis in 1 case.

In the bivariate analysis, when stratified by sex, statistically significant differences were observed in the histological pattern (p=0.02), but not in the radiological pattern (p=0.08), as shown in Table 2.

Table 2. Bivariate analysis relating sex and radiological and histological patterns.

Pattern		Sex		p-value
		Female n (%)*	Male n (%)*	
Radiological	Diagnosis inconsistent with UIP (n=43)	22 (51.16)	21 (48.84)	0.08
	Definitive diagnosis of UIP (n=9)	1 (11.11)	8 (88.89)	
	Probable diagnosis of probable UIP (n=4)	2 (50.0)	2 (50.0)	
Histological	HP (n=18)	9 (50.0)	9 (50.0)	0.02
	NSIP (n=10)	7 (70.0)	3 (30.0)	
	UIP (n=11)	1 (9.0)	10 (90.9)	
	No UIP (n=2)	1 (50.0)	1 (50.0)	
	Respiratory bronchiolitis associated with ILD (n=3)	0	3 (100.0)	
	Organizing pneumonia (n=9)	5 (55.56)	4 (44.44)	
	Alveolar proteinosis (n=1)	0	1 (100.0)	
	Sarcoidosis (n=2)	2 (100.0)	0	

UIP: usual interstitial pneumonia; HP: hypersensitivity pneumonitis; NSIP: nonspecific interstitial pneumonia; ILD: interstitial lung disease.
*Percentages are calculated based on the n that each pattern had, i.e., by rows.
Source: Own elaboration.

Regarding pulmonary function, 21.42% (n=12) of the study population had normal spirometry; 26.78% (n=15) had a mild restrictive pattern; 28.57% (n=16) had a moderate restrictive pattern; 16.07% (n=9) had severe restriction; 3.57% (n=2) had very severe restriction; and another 3.57% (n=2) had an obstructive pattern. Diffusing capacity of the lungs for carbon monoxide (DLCO) test results were available in 47 patients, with a mean of 53.9% (moderate decrease).

Discussion

ILD is a group of rare lung disorders. The epidemiological data available in Colombia on this disease are limited, so its true incidence and prevalence are unknown.[17,18] Some of the reasons why this information is scarce in the country are low clinical suspicion in primary care networks and late referral to specialists. Moreover, although the ATS and the ERS consensus[5] has recommended since 2002 to evaluate patients with suspected ILD in multidisciplinary groups of specialists who provide their knowledge to reach a definitive diagnosis, there are few groups of this type in the country, and the learning curve of the existing ones depends on their formation time and the expertise of their members.[5,14,19,20] Thus, a lung biopsy is required in patients who cannot be assessed clinically and radiologically through multidisciplinary groups.[21]

In the present study, there were 9 patients who, despite having radiological findings that allowed for a definitive diagnosis of UIP, were referred for lung biopsy to confirm the diagnosis. This could be explained by the time period in which the patients were included in the study, because in some cases it coincided with the start the work activities of the multidisciplinary group, when the members did not yet have sufficient knowledge to establish a definitive diagnosis.

The most common histopathological diagnosis was HP, which was previously reported in Colombia by Dueñas *et al.,*[22] who conducted a study in 60 patients with ILD who underwent lung biopsy to determine the clinical functional and radiopathological presentation of this disease and found this diagnosis in 20% of the participants, with pigeons as the main exposure factor (n=10). In this sense, only 4 of the 56 patients analyzed in this study reported exposure to birds as a possible cause of ILD.

Furthermore, no results for serum immunoglobulin G antibody against HP-associated antigens were available as a diagnostic aid. This is partly explained by the lack of laboratories where such tests are carried out, which is the case in many regions of Colombia. In the remaining patients, some exposures previously described as causative of HP were described.[23]

It is critical to remember that the variability in HP prevalence is not only due to geographical factors, agricultural/industrial practices, host factors that predispose to illness, and the intensity of exposure to environmental factors, but also to underdiagnosis, as chronic forms of HP may be mistaken for UIP and acute forms for asthma. This also has a significant impact on treatment, as the primary intervention in cases of HP is to discontinue exposure, followed by public health measures that could be established if the epidemiology of the disease were better understood.[24]

In patients with HP, no differences by sex were found, which contrasts with the reports by Costabel *et al.*,[25] who state that although there is an almost equal sex distribution between men and women, there is some variation depending on the type of HP and exposure conditions, being chronic HP more frequent in men in some case series.

In the present study, the mean age was 63 years, which is consistent with the findings of Selam *et al.*,[24] who stated that HP is a rare disease in children, although it should be noted that some cases have been described in that population.[25] At this point, it is also worth noting that some studies indicate that mortality rates increase with age.[26-28]

In the sample analyzed here, multiple comorbidities were observed, with hypertension being the most frequent, followed by dyslipidemia, gastroesophageal reflux disease, pulmonary hypertension, and hypothyroidism. This finding is consistent with that of Wälscher *et al.*,[29] who, in a study conducted in 211 patients with HP to describe the relationship between comorbidities and survival in subjects with this disease, found that the most frequent comorbidities were hypertension (56%), gastroesophageal reflux disease (24%), diabetes (20%), and coronary heart disease (18%).

In the case of patients with a histological pattern of UIP (n=11), it was found that it was more frequent in men, that the mean age of those who presented it was 72.1 years, and that more than half of them (54.54%) had a history of smoking, all of which are characteristics commonly associated with this condition.[30-32] The most common comorbidities observed in these patients were hypertension, atrial fibrillation, coronary heart disease, sleep apnea, gastroesophageal reflux, and diabetes *mellitus*, which is also consistent with previous reports.[33,34]

With regard to patients with a histological pattern of NSIP, the female sex was the most prevalent, a finding consistent with that described by Travis *et al.*[35] and that may be explained by genetic predisposition and hormonal factors that increase women's susceptibility to develop systemic autoimmune diseases, which these authors believe are closely related to the development of this disease.

Occupation is critical when evaluating ILD because a thorough examination of the patient's exposures is required for diagnosis, as they are associated with the disease's origin and prognosis. In this regard, Lee *et al.*,[36] in a study on the prognosis of IPF based on the patient's occupation, stated that occupational exposure to dust has been identified as a risk factor for the early onset and poor prognosis of this type of fibrosis.

It is noteworthy that the present study reported only one case of a woman with HP who had a history of exposure to birds in her household, while no possible trigger was described in the other women. These findings emphasize the relevance of conducting an extensive interrogation, not only of the patients, but also of their families, in order to detect conditions within the homes that are associated with the onset of the disease, such as the presence of humidity and fungi or the use of feather blankets or pillows. In this sense, Jenkins *et al.*[37] have proposed the use of standardized questionnaires during medical assessments to allow for appropriate data collection. It should be noted that misclassifications may occur if an exhaustive search for exposures that may influence the development of ILD, especially HP, is not conducted, resulting in misdiagnosis.[38,39]

One of the limitations of this study is its retrospective nature, which restricted the comprehensive assessment of pulmonary function tests and clinical and functional follow-up in all patients, thereby preventing the establishment of prognosis for the diseases that comprise ILD and determining response to treatments. Moreover, in this study, spirometry data were available in only 62.5% of patients, DLCO testing in 78.57%, and lung volumes in 30.35%. Serum immunoglobulin G antibodies against HP-associated antigens could not be measured, which, while not specific for diagnosis, allows us to isolate the patient from exposure, being the most critical aspect of the treatment;[23] additionally, the lack of recognition of the causative agent can have a negative effect on prognosis.[40]

Another limitation of this study is that patients did not undergo fibrobronchoscopy. As a result, there were no descriptions of bronchoalveolar lavages that may contribute to the diagnosis because the presence of lymphocytes >20% has a high sensitivity if there is clinical and imaging suspicion of ILD; however, it should be noted that its specificity is low.[41]

Conclusion

The main reason for performing lung biopsy in the study population was the presence of a pattern inconsistent with UIP, with the histopathological diagnosis of HP being the most common in these patients. The present study is the first to characterize patients with ILD who have undergone lung biopsy in an eastern Colombian population, which is a significant contribution to the knowledge of the epidemiology of the disease in Colombia.

Conflicts of interest

None stated by the authors.

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