Etiological Profile of an Interstitial Lung Disease Cohort in a Pulmonology Department of Algeria

A Kheliouen¹*, L Baough¹, B Mansouri², K Bendissari³ and N Zidouni¹

¹*MATIBEN Pulmonary Diseases Clinic, Algiers, Algeria*

²*Medical Imaging Service, Algiers, Algeria*

³*Pathological Anatomy Service, Algiers, Algeria*

*Corresponding Author: A Kheliouen, MATIBEN Pulmonary Diseases Clinic, Algiers, Algeria.

Abstract

The etiological diagnosis of interstitial lung disease is often difficult requiring multidisciplinary confrontations.

Material and Methods: Prospective monocentric study, collecting interstitial lung diseases from several provinces of Algeria.

Aim of the Study: To describe the etiological profile of these interstitial lung diseases.

Complementary Exams Performed: Inflammatory assessment, ACE, immunological assessment, high resolution thoracic computed tomography, spirometry, bronchial fibroscopy, bronchoalveolar lavage, broncho pulmonary biopsies, extra thoracic biopsies.

Results: 110 cases of interstitial lung diseases were notified, representing a morbidity burden about 3.29% of cases. Sex ratio F/M: 2.14/1 (SD, p < 10-6). Average age: 50 years. 76, 36% of non-smokers. Occupational exposure found in 8.2% of cases, bird exposure in 6.3% of cases.

Diagnosis Retained: Sarcoidosis (n = 37), ILD- connective tissue diseases (n = 29), idiopathic non-specific interstitial pneumonia (n = 15), hypersensitivity pneumonitis (n = 7), idiopathic pulmonary fibrosis (n = 6), respiratory bronchiolitis-ILD (n = 5), pneumoconiosis (n = 5), iatrogenic pneumonia (n = 3), Langerhans histiocytosis (n = 2), primary hemosiderosis (n = 1).

Comments: This study showed that mediastino-pulmonary sarcoidosis ranks first, followed by diffuse infiltrative pneumonia associated with connective tissue diseases. Idiopathic non-specific interstitial pneumonia, hypersensitivity pneumonitis and idiopathic pulmonary fibrosis are less common. Accurate and early diagnosis is required before succeeding to respiratory disability and requires the use of multidisciplinary confrontations between pulmonologists, radiologists and pathologists.

Keywords: *ILD; Sarcoidosis; HRTCT; ILD-Connective Tissue Diseases; IPF; Multidisciplinary Confrontations*

Introduction

Interstitial lung diseases (ILD) are a heterogeneous group of several diseases which constitute an exponential burden in most countries of the world. In Algeria these diseases constitute an increasing part of the pathology currently observed. This situation is explained by the persistence of communicable respiratory diseases and the emergence of chronic respiratory diseases [1].

The etiological diagnosis of ILD is often difficult, requiring the use of multidisciplinary confrontations between pulmonologists, radiologists and pathologists.

Material and Methods

This study is a prospective observational descriptive study, collecting patients with ILD in a pulmonology department of Algiers.

The selection criteria were as follows: Patients over the age of 18 years with unexplained respiratory symptoms and diffuse parenchymal abnormalities consistent on high resolution thoracic computed tomography (HRCT) of the chest were included.

All patients with interstitial syndrome caused by cardiac, infectious or tumor origin were excluded.

The recruitment of patients was carried out from January 1, 2005 to December 31, 2008.

For all patients admitted to the study, in addition to the clinical examination and the high resolution thoracic computed tomography, additional examinations were carried out such as an inflammatory assessment, an immunological evaluation, a respiratory functional exploration, a bronchoalveolar lavage (BAL), bronchial biopsies, skin biopsies, accessory salivary gland biopsy, hepatic biopsy in case of hepatomegaly, peripheral lymph node biopsy. In the absence of contraindication, a lung biopsy was discussed. The unavailability of certain biological and functional exams decrease the ability to obtain an accurate diagnosis. Among these constraints, the measurement of the DLCO which could not be carried out by the non-availability of the CO and the avian serology which was not made for technical reasons.

Statistical analysis

Data entry was performed on the EPI-DATA version 3.2 software. Statistical data control and analysis was carried out on the EPI-INFO6 version 6.04dfr software. The qualitative variables were expressed as numbers and %; Quantitative variables in the form of means (m) ± 95% confidence intervals (CI). The degree of significance retained ά equal to 5.

Ethics: All patients admitted to study completed an informed consent form.

Results

110 cases of ILD were collected during this period of the study. According to the gender, women were more numerous, 68.2% of cases versus 31.8% for men (DS, $p < 10^{-6}$). The sex ratio was 0.47. The average age in this study, was 50 years old. It was 50.21 years for women and 51.74 years for men, with a non-significant difference ($p = 0.5$). 23.6% of patients had a history of smoking and 13.64% of cases smoked more than 20 P/A. Occupational exposure was found for 8.1% of patients, represented mainly by massive inhalation of silica dust (3.6%). In 0.9% of the cases, it was asbestos, copper or isocyanates. The characteristics of these ILD are summarized in table 1.

Charactéristics	Résults
Average age (years)	50
Gender M %	31,8
Active smoking %	23,6
Avian exposer %	6,3
Occupational exposure %	8,2
Long-term drug intake %	0,9
Family ILD %	1,8
ILD revealing connectivity	12,7

Table 1: *Characteristics of ILD.*

Exposure to avian allergens was found in 6.3% of patients. PID was indicative of connective tissue disease in 12.7% of cases. Long-term use of Haloperidol in one case was the only probable etiology.

Respiratory clinical signs

The comparison of respiratory clinical signs shows that dyspnea was the most common with 80.9% of cases versus dry cough with 57.3% of cases ($p < 10^{-3}$).

The distribution of dyspnea according to the mMRC, shows that dyspnea stage 1 was the most common with 66.3% of cases followed by dyspnea stage 2 with 30.3% of cases and finally stage 3 with 3.4% (DS, P < 10-6). The analysis of the delay between the onset of symptoms and the first specialized consultation shows that 64.4% of patients consulted during the first year. Patients consulting at least 2 years after onset of symptoms accounted for 20.9% of cases (SD, p < 10-6). The average delay was 19.73 months [95% CI, 15.31-24, 15] The main respiratory signs are summarized in table 2.

Respiratory signs (RS)	N (%)
Dyspnea	89 (80,9)
Dry cough	63 (57,3)
Average delay of onset of RS (months)	19,73

Table 2: *Respiratory signs.*

Extra respiratory signs

The most common pathologies associated with extra-respiratory manifestations were sarcoidosis, rheumatoid arthritis and systemic scleroderma. 2 cases of sarcoidosis had uveitis and in 2 other cases, an hepatosplenomegaly (HPSM) was diagnosed. Gastro oesophageal reflux disease (GERD) was found in one idiopathic pulmonary fibrosis (IPF) case and one case of idiopathic non-specific interstitial pneumonia (INSIP). Pulmonary hypertension (PHT) was found in 2 cases of systemic Scleroderma (Ss) and one case of systemic lupus erythematosus (SLE). See table 3.

Extra respiratory signs	N (%)
Arthralgia	18 (16,3)
Raynaud's phenomenon	10 (9)
Dry syndrome	7 (6,3)
Nodes	5 (4,5)
Uvéitis	2 (1,8)
HPSM	2 (1,8)
GERD	2 (1,8)
P H T	3 (2,7)

Table 3: *Extra respiratory signs.*

Imaging characteristics on HR CT

The high-resolution computed tomography (HRCT) of the chest contributed to the diagnosis of the majority of ILD cases admitted, according to characteristic patterns in table 4.

Imaging characteristics (HRCT)	ILD diagnosis (N)
Basilar-predominant ground-glass opacities with or without subpleural sparing; reticular abnormality (infrequent), and no Honeycombing (NSIP)	CTD-ILD (28) INSIP (15) Drug-induced ILD (1) Isocyanates-ILD (2)
Upper lung predominant perilymphatic distribution of nodules with or without mediastinal or hilar lymphadenopathy	Sarcoïdosis (37)
Upper lobe predominant ground-glass opacities, poorly defined centrilobular nodules; mosaic attenuation, air trapping	HSP (7)
Subpleural and basilar predominant, reticular abnormality, honeycombing (UIP)	IPF (6)
Upper lobe predominant dense micronodules with current or past work occupation	Silicosis (4) Asbestosis (1)
Diffuse bronchial thickening with micronodules	RB-ILD (5)
Thin-walled cysts, thick-walled cycts with nodules	LH (2)
Ground glace isolated	PH (1)
Thickening of interlobar septa	Indétermined (1)

Table 4: *Imaging characteristics on HR CT.*

Definition of abbreviations: CTD: Connective Tissue Disease; HSP: Hypersensitivity Pneumonitis; HRCT: High-Resolution Computed Tomography; ILD: Interstitial Lung Disease; INSIP: Idiopathic Nonspecific Interstitial Pneumonia; NSIP: Nonspecific Interstitial Pneumonia; UIP: Usual Interstitial Pneumonia; LH: Langerhans Histiocytosis; RB-ILD: Respiratory Bronchiolitis-Associated ILD; PH: Primary Hemosiderosis

In figure 1 representative high-resolution computed tomography (HRCT) images of chest from patients with interstitial lung disease (ILD) enrolled.
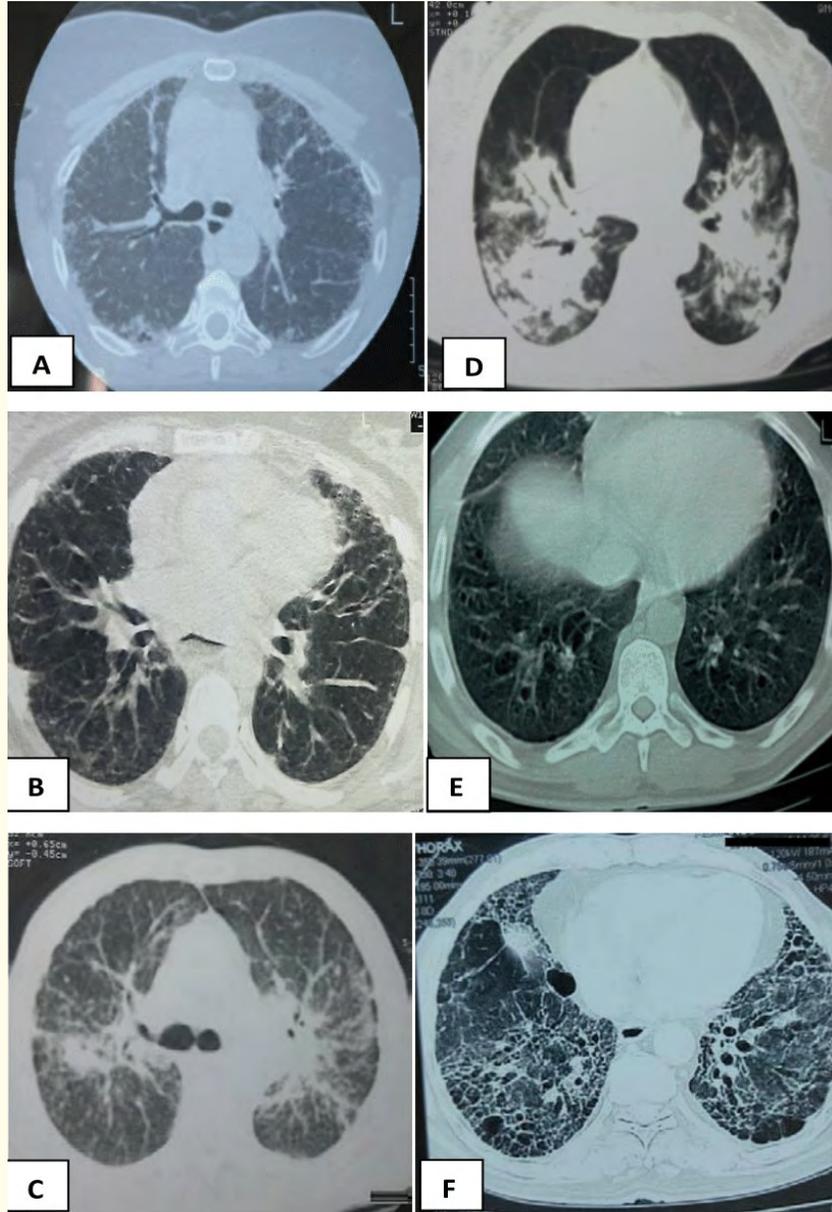

Figure 1: *HRCT images of ILD.*
A: Idiopathic non-specific interstitial pneumonia (no symptoms of CTD, negative CTD serologies). B: NSIP revelating a systemic scleroderma with oesophageal deforma-tion. C: Sarcoidosis stage III. D: Sarcoidosis stage IV. E: Langerhans Histiocytosis. F: UIP with no history of environmental exposure known, no signs of CTD and negative CTD serology (IPF).

Pulmonary function tests

Overall, ventilatory function was normal in 32.7% of the cases mainly in sarcoidosis and INSIP. A restrictive syndrome was found in 49.1% of the cases represented by the IPF, the ILD associated with systemic scleroderma. A mixed syndrome mainly restrictive was observed in 6.3% of cases (pneumoconiosis). Blood gasometry was normal in 63.6% of cases. The average values of the spirometry parameters are summarized in table 5.

PFT	Results
FVC %	75±18
FEV 1 %	79± 5
Pao$_2$ mmHg	69± 12
Sao2%	80± 7

Table 5: Pulmonary function tests (PFT).

Abbreviations: FVC: Forced Vital Capacity % of Predicted Value; FEV1: Forced Expiratory Volume Second % of Predicted Value; Pao$_2$: Partial Pressure of Oxygen; Sao$_2$: Oxyhemoglobin Saturation

BAL cytology

The cytological study of bronchoalveolar lavage (BAL) showed lymphocytic alveolitis in 31% of cases, mainly in sarcoidosis, HSP and INSIP, polynuclear neutrophil alveolitis in cases of IPF, systemic scleroderma or HSP at fibrosis stage (Table 6) and in a case of alveolar haemorrhage, the BAL showed brownish intra-macrophage pigments related to hemosiderosis (Figure 2).

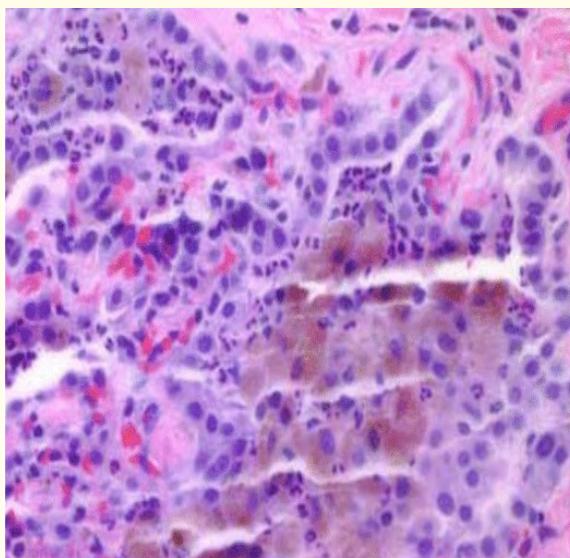| BAL cytology %	Results
Macrophage	5,5
Lymphocyte	31
Polynuclear neutrophil	29
Multicellular	20
Uninterprétable	14 ,5

Table 6: BAL cytology.

Figure 2: Collection of BAL fluid of hemosiderosis.

Results of histological samples

Distal bronchial biopsy confirmed 6 cases of sarcoidosis and 1 case of usual interstitial pneumonia(UIP) with no history of environmental exposure or symptoms of CTD and negative CTD serologies from a 64 old –men corresponding to idiopathic pulmonary fibrosis. The bronchial biopsy confirmed 8 cases of sarcoidosis.

Two liver biopsies were made for two cases, concluding to tuberculoid granuloma. One had a mediastino-pulmonary involvement with hepatosplenomegaly, the second had mediastino-pulmonary involvement with hepatosplenomegaly and peripheral lymph node. Only 5 patients underwent a surgical lung biopsy. It allowed the diagnosis of asbestosis for one case, NSIP in 2 patients and the diagnosis of the first case of Langerhans Histiocytosis in the study. The results of the histological samples are summarized in figure 3.
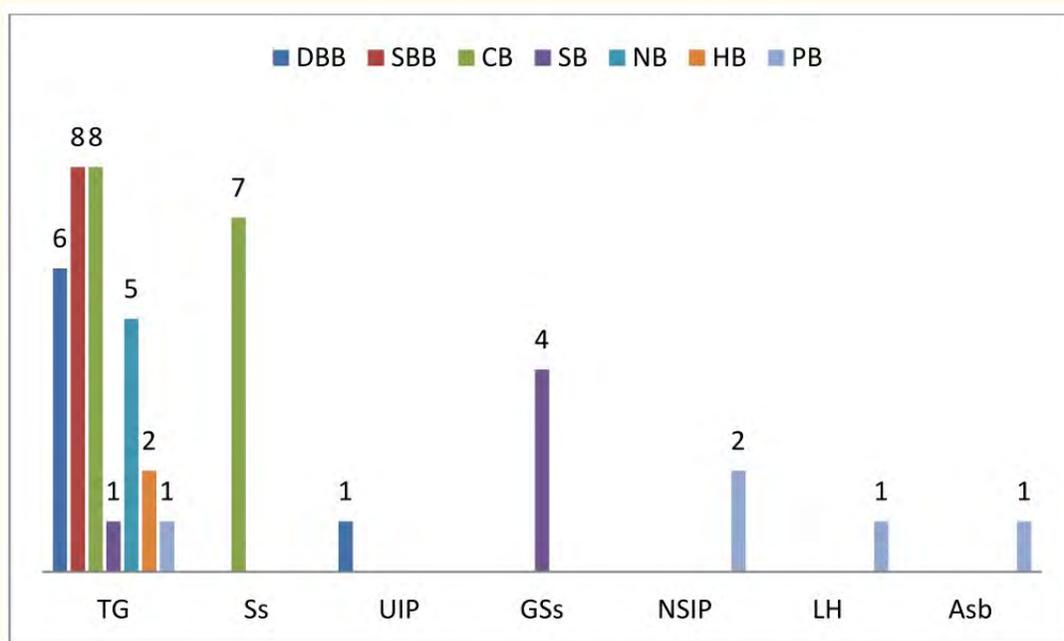

***Figure 3:** Results of histological samples.*
Abbreviation: DBB: Distal Bronchial Biopsy; SBB: Staged Bronchial Biopsy; CB: Cutaneous Biopsy; SB: Salivary Biopsy; NB: Node Biopsy; HB: Hepatic Biopsy; PB: Pulmonary Biopsy; TG: Tuberculoid Granuloma; Ss: Systemic Scleroderma; UIP: Usual Interstitial Pneumonia; GS s: Gougerot Sjogren Syndrome; Asb: Asbestosis; L H: Langerhans Histiocytosis

Diagnostic approach

The etiological diagnosis of these ILD was based on the TDMHR associated with anamnestic, clinical, biological and cyto-histological data. In this study in order of frequency, sarcoidosis was ranked in 1st position with 37 cases followed by ILD associated with connectivitis (ILD-CTD =28 cases) represented by rheumatoid arthritis (R A = 9), systemic scleroderma (Ss = 8), mixed connective tissue disease (MCTD = 4), Sjogren's syndrome (GSs = 4), systemic lupus erythematosus (SLE = 3) in third place, idiopathic non-specific interstitial lung disease (INSIP) in 15 cases, followed by hypersensitivity pneumonitis (HSP) in 7 cases and IPF in 6 cases. The distribution of diagnoses according to the observed frequency is summarized in table 7 and figure 4.

ILD diagnosis	Proven		No proven		Total	
	N	%	N	%	N	%
Sarcoïdoses	22	59,4	15	40,5	37	33,6
Mixed connective (MCTD)	4	100			4	
Systémic scleroderma (Ss)	8	100			8	
Rhumatoid arthritis (RA)	6	66,6	3	33,3	9	
Ssystémic lupus erythematosus (SLE)	2	66,6	1	33,3	3	25,4
Gougerot Sjogren syndrome (GSs)	4	100			4	
Hypersensitivity pneumonitis (HSP)	0		7	100	7	6,3
Iatrogenic pneumonitis (IP)	0		3	100	3	2,7
Silicosis	0		4	100	4	3,6
Asbestosis	1	100			1	0,9
Idiopathic pulmonary fibrosis (IPF)	1	16,6	5	83,3	6	5,4
Respiratory bronchiolitis-ILD	0		5	100	5	4,5
Langerhans Histiocytosis (LH)	1	50	1	50	2	1,8
INSIP	1	6,6	14	93,3	15	13,6
Primary hemosiderosis	0		1	100	1	0,9
Indetermined	0		1	0,9	1	0,9
Total	51	46,3	59	53,6	110	100

Table 7: *ILD diagnosis.*

Figure 4: *ILD diagnosis.*

Correlation between TDMHR, spirometry and BAL cytology

A close correlation was found between the importance of honeycombing, the severity of respiratory failure, and neutrophil polymorphonuclear alveolitis. Restrictive ventilatory syndrome was much more disturbed in diffuse honeycombing images with 88.2% of cases and resting hypoxemia mainly concerned this diffuse honeycomb with 76.4% of cases. Polymorphonuclear alveolitis with or without eosinophilic polynuclear cells was found in 97.05% of cases of diffuse honeycombing. In case of localized honeycombing, blood gasometry was normal in 88.8% of cases and Lymphocyte alveolitis was found in 38.8% of cases.

Discussion

The comparability of this population recruited in this study with other studies in similar conditions is summarized in table 8.

Author	Type of study Duration (months)	Study population (N)	Average age	Sexe ratio F/M	Smoking %	Professional exposure %	Avian exposure %
Coultas DB [2] New Mexico 1994	Prospective Multicentric (24)	202	69	1/1,10	ND	14	1,5
Thomeers M [3] Belgium 2001	Prospective Multicentric (48)	365	52	1/1,29	ND	0	12,9
Schweisfurth H [4] Germany 2003	Rétrospective Multicentric (60)	1142	51,1	1/1,01	ND	ND	13,2
Xaubet A [5] Spain 2004	Prospective Multicentric (12)	511	61	1/1,2	ND	ND	6,6
Tinelli C [6] Italy 2005	Prospective Multicentric (30)	1382		1/1,5	47	ND	3,6
Karakatsani A [7] Greece 2009	Prospective Multicentric (12)	967	58	1,2/1	ND	2	2,7
Christopher JR [8] USA 2011	Prospective Monocentric (24)	52	64	1/1,27	60	0	13
Study presented Algéria 2013	Prospective Monocentric (58)	110	50	2,14/1	23,6	8,1	6,3

Table 8: *Characteristics of the population studed and comparability of ILD.*

In the current study, sarcoidosis is the most common disease, similar to the Greek and Italian studies [6,7] followed by ILD associated with connective tissue diseases. Idiopathic pulmonary fibrosis (IPF) is ranked in 5th position.

The distribution by sex shows that the sex ratio: woman/man in the presented study is 2.14/1: two women for one man (DS, p < 10-6).

According to data from the literature, the sex ratio of ILD varies between 1/1.5 in the Tinelli C series [6] and 1, 2/1 in the Karakatsani A series [7].

In the Coultas and karakatsani studies [2,7] study, the average age of patients with ILD is relatively advanced between 51 and 69 years. The age of the patients in the study presented is similar to Schweifurt H and Thomeers [3,4] studies.

Occupational exposure to pneumoconiosis was found in 5 cases (8.1%) in the study presented, mainly in mountainous areas. Few data are available on pneumoconiosis. Their occurrence depends on the natural resources of the countries and their exploitation. In Greece, they represent 2% of ILD [7] and in New Mexico, they reach 14% of these lung diseases in the Coultas DB study [2]. In this area where mining is important, massive exposure to silica is prevalent. Occupational exposure to isocyanates causes 2 cases (1.8%) of ILD. Several authors [9-11] report cases of HSP caused by subacute or chronic exposure to isocyanates in painters and polyurethane plant workers. In contrast, Reyes U., et al. [12] report in their study 18.7% of cases of NSIP secondary to iso cyanate inhalation. The cases in the study presented are similar to the cases reported by Reye U. Occupational exposure to copper represents 0.9% of the cases of the study presented, revealed by an aspect of NSIP.

Copper-induced ILD are reported by Dagli CE. and collaborators [13] in boilermakers in Turkey. The aspect of NSIP is found in 29, 4% of the cases in these series.

The avian exposure responsible for HSP is found in 7 patients (6.3%) of the study presented. It is due to the breeding of birds. It is found in 1.5% of cases in the Coultas series [2] and in 12.9% of cases in the Thomeers M. study [3]. The series presented finds more cases than Coultas study and nearly half of the Belgian and German [4,9] studies.

ILD associated- connective tissue disease

In the study presented, connective tissue disease was revealed in several cases by diffuse interstitial lung disease despite the rarity of this form in some connective tissue, HSP and diseases [14,15]. This difference of data in other studies, is due to the presence of multiple co morbidities which delayed the diagnosis of these ILD.

Dyspnea is the predominant symptom in ILD. Dry cough is seen much more frequently in sarcoidosis cryptogenic organized lung disease [16,17].

Dyspnea and cough are the main symptoms of respiratory manifestations of connective tissue disease [18]. Dry cough is the main symptom in respiratory involvement of Sjogren's syndrome [19]. In the Wesolowski series [20], dyspnea is present in 96.5% of cases and cough in 84.2% of cases. In the present study, hemoptysis is reported in only one case of ILD, related to primary hemosiderosis after exclusion of hemosiderosis secondary to endocardic disease. Gastroesophageal reflux disease (GERD) is incriminated in the pathogenesis of pulmonary fibrosis and ILD associated with systemic scleroderma. Savarino reports this morbid condition [21]. Tobin [22] reports 25% of cases of GERD. In the presented study, the GERD rate was 1.8% and in patients with idiopathic pulmonary fibrosis, GERD was found in only 16.6% of cases. This low rate is due to the inclusion of only GERD confirmed cases, while some studies have included even cases of IPF whose questionnaire reported the presence of symptoms suggestive of GERD.

Drug toxicity may cause PID [23]. It manifests itself as a HSP, a NSIP or an UIP. In the study presented, long-term use of Haloperidol was the etiology retained. This haloperidol-ILD is described [24-26].

The concept of familial fibrosis is reported and some members of the same family present other types of ILD [27]. This heterogenicity is found in the study presented: one patient has a NSIP and his brother has an IPF.

The extra-respiratory locations, were common in sarcoidosis [28] and connective tissue diseases [29] and facilitates the diagnosis of these ILD. In the study presented, 21 cases (56.7%) of sarcoidosis had extra-respiratory locations: two cases of uveitis, cutaneous involvement in 8 cases, lymph node location in 5 cases, hepatosplenomegaly in 5. The extra pulmonary locations of sarcoidosis are revealing or occur during follow-up [28,30]. They are seen in 20 to 60% of cases of endothoracic sarcoidosis with extra respiratory locations.

HRCT of the chest is a major help in the diagnosis of ILD [31] and IPF [9,32]. It has been performed at different stages of the disease. In the presented study, a confrontation between pulmonologists, radiologists and pathologists, allowed the increasing accuracy of the diagnosis and restricted the indications of the surgical lung biopsy in 5% of the cases. This has been reported in several studies [31,33,34].

The study of the respiratory function in the presented study shows normal spirometric indices in more than half of the cases of sarcoidosis and NSIP, whereas the restrictive syndrome is frequently described in the IPF and the chronic HSP [34], with impaired diffusion [35,36].

The lymphocyte alveolitis predominates in sarcoidosis and HSP whereas neutrophil or multicellular alveolitis is seen mainly in the IPF, the chronic HSP and the ILD - scleroderma [37]. The results found in our study are comparable to the results of the literature.

Functional radiological correlations and cytological BAL

In the study presented, a close correlation is found between the main tomodensitometric images, the respiratory functional parameters and the cytology of BAL. Restrictive ventilatory syndrome is more disturbed in diffuse honeycomb images with resting hypoxemia. Polynuclear neutrophil alveolitis is found in more than 2/3 of cases of diffuse honeycombing. This correlation has been reported by Colin [38] and Best [39].

Conclusion

Interstitial lung diseases are an important cause of morbidity and mortality. Their evolution is variable determined by the underlying cause. Idiopathic pulmonary fibrosis is the most severe ILD with a poor prognosis. Mediastino-pulmonary sarcoidosis has a better prognosis. An accurate and early diagnosis is required before leading to respiratory disability. The diagnostic contribution of the HR CT is considerable. The respiratory functional exploration has a prognostic value. The multidisciplinary discussion improves the quality of diagnosis of ILD and avoids the need for surgical lung biopsy.

Declaration of Interest

Absence of interest links.

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Volume 7 Issue 7 July 2018