Evaluation of the use of transbronchial biopsy in patients with clinical suspicion of interstitial lung disease*

Avaliação da utilização de biópsia transbrônquica em pacientes com suspeita clínica de doença pulmonar intersticial

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Abstract

Objective: To study the clinical, radiological, and histopathological patterns of transbronchial biopsy (TBB) used in order to confirm the diagnosis in patients with clinical suspicion of interstitial lung disease (ILD) treated at a tertiary-care university hospital. **Methods:** We reviewed the medical records, radiology reports, and reports of transbronchial biopsies from all patients with suspected ILD who underwent TBB between January of 1999 and December of 2006 at the *Hospital das Clínicas de Botucatu*, located in the city of Botucatu, Brazil. **Results:** The study included 56 patients. Of those, 11 (19.6%) had a definitive diagnosis of idiopathic pulmonary fibrosis (IPF), the rate of which was significantly higher in the patients in which ILD was a possible diagnosis in comparison with those in which ILD was the prime suspect (p = 0.011), demonstrating the contribution of TBB to the diagnostic confirmation of these diseases. The histopathological examination of the biopsies revealed that 27.3% of the patients with IPF showed a pattern of organizing pneumonia, which suggests greater disease severity. The most common histological pattern was the indeterminate pattern, reflecting the peripheral characteristic of IPF. However, the fibrosis pattern showed high specificity and high negative predictive value. For CT scan patterns suggestive of IPF, the ROC curve showed that the best relationship between sensitivity and specificity occurred when five radiological alterations were present. Honeycombing was found to be strongly suggestive of IPF (p = 0.01). **Conclusions:** For ILDs, chest CT should always be performed, and TBB should be used in specific situations, according to the suspicion and distribution of lesions.

Keywords: Lung diseases, interstitial; Diagnosis, differential; Bronchoscopy.

Resumo

Objetivo: Estudar os padrões clínicos, radiológicos e histopatológicos da biópsia transbrônquica (BTB) utilizados para a confirmação diagnóstica em pacientes com suspeita clinica de doença pulmonar intersticial (DPI) atendidos em um hospital universitário de nível terciário. **Métodos:** Os prontuários, laudos radiológicos e de biópsias transbrônquicas de todos os pacientes com suspeita de DPI submetidos a BTB entre janeiro de 1999 e dezembro de 2006 no Hospital das Clínicas de Botucatu, localizado na cidade de Botucatu (SP), foram revisados. **Resultados:** Foram incluídos no estudo 56 pacientes. Desses, 11 (19,6%) apresentaram o diagnóstico definitivo de fibrose pulmonar idiopática (FPI), que foi significativamente maior nos casos nos quais DPI era uma possibilidade diagnóstica em comparação com aqueles nos quais DPI era a principal suspeita (p = 0,011), demonstrando a contribuição da BTB para a definição diagnóstica dessas doenças. O exame histopatológico dessas biópsias revelou que 27,3% dos pacientes com FPI apresentavam o padrão de pneumonia organizante, o que pode sugerir doença mais avançada. O padrão histológico indeterminado foi o mais frequente, refletindo a característica periférica da FPI. Entretanto, o padrão fibrose apresentou alta especificidade e alto valor preditivo negativo. Para os padrões sugestivos de FPI em TC, a curva ROC indicou que a melhor relação entre sensibilidade e especificidade ocorreu com a presença de cinco alterações radiológicas, sendo o aspecto de favo de mel fortemente sugestivo de FPI (p = 0,01). **Conclusões:** Nas DPIs, a TC de tórax deve ser sempre realizada e a BTB usada em situações individualizadas, conforme a suspeita e distribuição das lesões.

Descritores: Doenças pulmonares intersticiais; Diagnóstico diferencial; Broncoscopia.

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Introduction

Interstitial lung diseases (ILDs) constitute a heterogeneous group of diseases with similar clinical, radiological, and pulmonary function profiles. The principal pathological change in ILD is the involvement of the interstitial alveolar structures. However, this does not necessarily indicate that the pathophysiological mechanisms of ILDs are understood, since ILDs can also affect the small airways and pulmonary blood vessels.[1]

The ILD group comprises over 150 diseases.[2] Among those, idiopathic pulmonary fibrosis (IPF) is noteworthy due to its frequency and associated mortality, the present study being therefore based on analyses of IPF, as well as on those of sarcoidosis.[2-4] The diagnostic approach to ILDs is complex, and CT evaluation of patients is indispensable.[5] The histopathological evaluation of samples obtained by transbronchial biopsy (TBB) can be used in patients suspected of having diseases such as sarcoidosis and hypersensitivity pneumonitis. Although the rates of morbidity and mortality are higher for surgical biopsy than for TBB, the former is the method of choice for histopathological analysis.[6,7] Therefore, although surgical biopsy is the gold standard for the diagnosis of ILDs, it is performed in only 12% of cases, whereas TBB is performed in 28% of cases.[8]

Nearly all of the studies comparing the diagnostic power of ancillary tests (CT and TBB) in the identification of ILD were performed at large referral centers for ILDs and might not reflect the diagnostic reality of other hospitals, especially that of those in developing countries.[8] In cases of clinical and radiological suspicion of ILD encountered at such facilities, the diagnostic procedure is based on CT and TBB,[9,10] surgical biopsy being only occasionally employed. The principal advantage of TBB is the possibility of ruling out a series of differential diagnoses, such as infectious diseases,[11] with lower rates of morbidity and mortality than those associated with surgical biopsy.[12]

Meticulous and integrated analysis of ancillary tests, such as TBB and CT, therefore plays an important role in the diagnosis of ILDs. The objective of the present study was to analyze the clinical, radiological, and histopathological patterns of TBB and determine their diagnostic accuracy in patients with clinical suspicion of ILD treated at a tertiary-care university hospital.

Methods

We conducted a retrospective study of patients treated at the ILD outpatient clinic of the *Faculdade de Medicina de Botucatu da Universidade Estadual Paulista* (FMB-UNESP, São Paulo State University Botucatu School of Medicine) *Hospital das Clínicas*, located in the city of Botucatu, Brazil. The patients had undergone bronchoscopy for TBB between January of 1999 and December of 2006. The patients included in the study were those in whom there was a high level of clinical suspicion regarding ILD or there was a working diagnosis of ILD. All of the patients with gaps in their clinical history or an incomplete physical examination were excluded, as were those who had not undergone CT evaluation. Clinical suspicion of ILD was defined as the presence of dyspnea or dry cough accompanied by radiological findings of nodules or reticular pattern for at least three months. The final diagnosis was established by correlating the clinical, radiological, and histological criteria, in accordance with the 2002 American Thoracic Society/European Respiratory Society consensus.[1] The present study was approved by the Research Ethics Committee of the FMB-UNESP.

All of the patients underwent bronchoscopy[13] with a flexible bronchoscope (model 1T10; Olympus Corp., Tokyo, Japan). The bronchoscope was directed toward the middle lobe/lingula or the most affected site. In general, at least three samples were obtained.

The TBB samples were processed and submitted to histopathological, bacteriological, and cellular analysis in the Pathology Departments of the FMB-UNESP *Hospital das Clínicas* and of the University of São Paulo School of Medicine *Hospital das Clínicas*, the latter located in the city of São Paulo, Brazil.

We reviewed the medical records of the patients and tabulated the demographic data (gender and age), as well as the data related to clinical symptoms (dyspnea, cough, chest pain, hemoptysis, wheezing, joint pain, weight loss, and fever) and smoking history. We also investigated the presence of comorbidities that were possibly related to interstitial pulmonary involvement, including tuberculosis, heart failure/other heart diseases, systemic arterial hypertension, COPD, collagen diseases (rheumatoid arthritis, systemic lupus erythematosus, and scleroderma),

diabetes mellitus, gastroesophageal reflux, schistosomiasis, renal diseases, hematologic diseases, neoplasia, and AIDS.

The radiology reports, which had been analyzed by two radiologists and attached to the medical records, were reviewed for nodules, ground-glass opacities, reticular pattern, traction bronchiectasis/bronchiolectasis, honeycombing, vascular changes, right ventricular changes, air trapping, cysts, and parenchymal alterations (peribronchial, diffuse, or subpleural).[14]

The TBB samples were fixed in 10% buffered formalin and embedded in paraffin. The samples were cut into serial sections of 5 µm, which were deparaffinized and processed for histology in accordance with laboratory protocol. For histological evaluation, the following staining methods were used: H&E staining; Ziehl-Neelsen staining (for mycobacteria); periodic acid-Schiff staining and the Grocott-Gomori methenamine-silver stain technique (for fungi, *Pneumocystis* sp., and *Nocardia* sp.); and Gram staining (for bacteria).

The biopsies were considered representative when the histological section was composed of at least one bronchovascular axis in continuity with interstitial septa, alveolar spaces, and peripheral interstitium. The lung parenchyma was histologically divided into four compartments of reference: interstitium (septal, peripheral, and axial); airways (respiratory and terminal bronchioles); vessels (arteries, veins, and lymphatic vessels); and alveoli/alveolar ducts. The histological changes in the four anatomical compartments were evaluated by the temporal evolution of acute changes (necrosis, degeneration, edema, hemorrhage, congestion, thrombosis, fibrin deposition, hyaline membrane formation, and the appearance of polymorphonuclear cells) and chronic changes (hyperplasia and neoplasia, as well as the presence of mononuclear cells, granulation tissue, granuloma, and proliferation of fiber cells). On the basis of those criteria, seven histological patterns were identified:

- Granuloma, characterized by a focus of epithelioid cells surrounded by lymphocytes and, occasionally, Langhans/foreign body giant cells or caseous necrosis
- Organizing pneumonia, characterized by fibroblast proliferation in an edematous stroma, forming intraluminal plugs in alveolar ducts and alveoli
- Fibrosis with a diffuse radial pattern, characterized by proliferation of fibroblasts and small vessels in alveolar septa and around the bronchovascular axis with secondary invasion of the alveolar septa
- Respiratory bronchiolitis, characterized by macrophage accumulation in the bronchiolar and alveolar lumens
- Normal pattern—lung tissue adjacent to the lesion (periphery of the lesion)
- Others, characterized by other processes, including vasculitides and lymphatic dissemination of carcinoma
- Indeterminate pattern, characterized by histopathological features that are distinct from those of the abovementioned patterns

For samples that presented more than one histopathological pattern, the predominant pathological pattern was adopted. The slides were reviewed by three pathologists, all of whom were blinded to the clinical diagnoses.

The frequencies of the histological, radiological, and clinical variables were compared by chi-square test or two-tailed Fisher's exact test, as appropriate. The level of significance was set at $p < 0.05$. We calculated, as appropriate, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy, and likelihood ratio of the diagnostic tests, adopting the prevalence of IPF in our hospital during the study period as the prevalence of IPF for analysis. In addition, we constructed a ROC curve based on the number of radiological changes suggestive of ILD. The data were analyzed with the Statistical Package for the Social Sciences, version 15.0 (SPSS Inc., Chicago, IL, USA).

Results

Between January of 1999 and December of 2006, 86 patients underwent TBB. Of those, 56 (65.1%) met the criteria for inclusion in the present study, and 11 (19.6%) had a final diagnosis of IPF. Of the 56 patients, 25 (45%) were female and 31 (55%) were male, the median age being 56 years (range: 15-80 years). In addition, 11 (19.6%) were younger than 40 years of age. Of those, 5 (45.4%) were initially suspected of having sarcoidosis. Among those with a final diagnosis of IPF, the median

age was also 56 years (range: 36-80 years), and only 1 patient was younger than 40 years of age. That patient was clinically suspected of having ILD. The most common symptoms were dyspnea (70%), dry cough (59%), and weight loss (36%). A total of 26 patients (46%) were smokers. The principal comorbidities were hypertension (36%), COPD (25%), and diabetes mellitus (20%). Autoimmune diseases, such as systemic lupus erythematosus, rheumatoid arthritis, and scleroderma, were diagnosed in 14% of the patients. There were significant differences between patients with a final diagnosis of IPF and those with other diagnoses in terms of the frequency of dyspnea (91% vs. 64%; p = 0.08), chest pain (54% vs. 24%; p = 0.06), and productive cough (45% vs. 20%; p = 0.09); however, there were no significant differences between the two groups of patients in terms of the comorbidities (Table 1). The principal clinical hypothesis was specific ILD, which was the clinical hypothesis in 36 (64.3%) of the patients. Of those 36 patients, only 3 were diagnosed with IPF (p = 0.011; Table 2).

The most common radiological findings were alteration of the peribronchial parenchyma, in 69.9% of the patients; nodules, in 64.3%; and diffuse parenchymal alteration, in 55.4%. In patients with a final diagnosis of IPF, the most common radiological findings were parenchymal

Table 1 - Frequency of the epidemiological data, clinical data, and comorbidities in patients with a diagnosis of idiopathic pulmonary fibrosis and in those with other diagnoses.[a]

Parameter	Non-IPF	IPF	p
	n = 45	n = 11	
Epidemiological data			
Age, years[b]	56 (15-80)	56 (36-80)	
Males/Females[c]	25/20 (55/45)	6/5 (54/46)	0.60
Smokers	19 (42)	7 (64)	0.20
Clinical data			
Dyspnea	29 (64)	10 (91)	0.08
Dry cough	28 (62)	5 (45)	0.24
Productive cough	9 (20)	5 (45)	0.09
Hemoptysis	2 (4)	0 (0)	0.64
Chest pain	11 (24)	6 (54)	0.06
Wheezing	12 (26)	2 (18)	0.44
Joint pain	6 (13)	2 (18)	0.49
Weight loss	14 (31)	6 (54)	0.13
Fever	6 (13)	2 (18)	0.49
Comorbidities			
Tuberculosis	1 (2)	0 (0)	0.80
Heart failure	1 (2)	2 (18)	0.09
Arterial hypertension	17 (37)	3 (27)	0.39
Scleroderma	2 (4)	1 (9)	0.48
Heart disease	5 (11)	1 (9)	0.66
Asthma	2 (4)	0 (0)	0.64
COPD	12 (26)	2 (18)	0.44
Rheumatoid arthritis	2 (4)	1 (9)	0.35
Lupus	2 (4)	1 (9)	0.48
Diabetes mellitus	8 (17)	3 (27)	0.36
Gastroesophageal reflux	5 (11)	1 (9)	0.66
Peptic ulcer	2 (4)	1 (9)	0.48
Schistosomiasis	1 (2)	0 (0)	0.80
Renal diseases	1 (2)	1 (9)	0.35
Hematologic diseases	1 (2)	0 (0)	0.80

IPF: idiopathic pulmonary fibrosis. [a]Values expressed as n (%), except where otherwise noted. [b]Values expressed as median (range). [c]Values expressed as n/n (%/%).

Table 2 - Frequency of patients with clinical suspicion or possible differential diagnosis of interstitial lung disease vs. final diagnosis of idiopathic pulmonary fibrosis.

Type	Final diagnosis of IPF		Total
	Absent	Present	
Differential diagnosis	12 (21.4)	8 (14.3)	20 (35.7)
Clinical suspicion	33 (58.9)	3 (5.4)	36 (64.3)
Total	45 (80.4)	11 (19.6)*	56 (100)

IPF: idiopathic pulmonary fibrosis. [a]Values expressed as n (%). *p = 0.011 (Fisher's exact test).

distortion (peribronchial), in 81.8%; diffuse parenchymal alteration, in 63.6%; and traction bronchiectasis, in 54.5% (Table 3). Nodules contributed significantly to the exclusion of the diagnosis of IPF (p = 0.03), whereas honeycombing and traction bronchiectasis aided in confirming the diagnosis of IPF (p = 0.01 and p = 0.043, respectively).

The most common histopathological finding was fibrosis with a diffuse radial pattern (in 32.2%), followed by the indeterminate pattern (in 17.8%), respiratory bronchiolitis (in 14.3%), granuloma (in 12.5%), organizing pneumonia (in 10.7%), the normal pattern (in 7.2%), and other patterns (in 5.3%). Among the patients with a diagnosis of IPF, the indeterminate pattern and the organizing pneumonia pattern were the most common (in 45.4% and 27.3%, respectively). The patterns of granuloma, fibrosis, and others were observed in 9.1% each. There were no cases of respiratory bronchiolitis. The indeterminate pattern was significantly more common among patients with IPF (p = 0.018). Evaluating the IPF patients in comparison with the remaining patients, the fibrotic pattern was less common and the organizing pneumonia pattern was more common.

Of the 56 patients in the sample, 8 (14.3%) had also undergone surgical biopsy for diagnostic investigation. Of those 8 patients, 6 were older than 40 years of age, and 4 had a final diagnosis of IPF. Of those, only 1 was clinically suspected of having a specific ILD (sarcoidosis). The remaining 4 patients had final diagnoses of sarcoidosis (2 patients), ILD (1 patient), and hypersensitivity pneumonia (1 patient). Initially, however, 3 of those patients were suspected of having sarcoidosis.

The radiological and pathological patterns were evaluated in terms of their sensitivity, specificity, PPV, NPV, accuracy, and likelihood ratio. Few radiological findings suggestive of ILD actually indicated the presence of an interstitial disease, as evidenced by the high sensitivity. However, a greater number of changes translated to greater chances of

Table 3 - Frequency of radiological changes in patients with a diagnosis of idiopathic pulmonary fibrosis and in those with other diagnoses.[a]

Radiological changes	Non-IPF	IPF	p
	n = 45	n = 11	
Reticular pattern	5 (11)	3 (27)	0.18
Honeycombing	4 (8)	5 (45)	0.01
Parenchymal alterations			
Subpleural	9 (20)	4 (36)	0.22
Peribronchial	30 (66)	9 (81)	0.27
Diffuse	24 (53)	7 (63)	0.39
Ground-glass opacities	12 (26)	3 (27)	0.61
Nodule	32 (71)	4 (36)	0.03
Air trapping	1 (2)	0 (0)	0.80
Cyst	2 (4)	1 (9)	0.48
Traction bronchiectasis/bronchiolectasis	10 (22)	6 (54)	0.04
Vascular changes	8 (17)	3 (27)	0.36
Right ventricular changes	4 (8)	1 (9)	0.68

IPF: idiopathic pulmonary fibrosis. [a]Values expressed as n (%).

a diagnosis of IPF, as demonstrated by the increase in specificity (Table 4). The PPV, NPV, accuracy, and likelihood ratio also increased with the number of changes. However, the best relationship between sensitivity and specificity occurred when five radiological changes were present, as shown by the ROC curve (Figure 1). Regarding the histological patterns, fibrosis with a diffuse radial pattern showed high specificity and NPV for IPF. However, a diagnosis of IPF cannot be confirmed by a finding of fibrosis (Table 4).

The study of the diagnostic tests for sarcoidosis revealed that a radiological finding of nodules had high sensitivity (85.7%) and NPV (90%) but low specificity (42.8%). In contrast, the histological pattern of granuloma had low sensitivity (42.8%) and high specificity (97.6%).

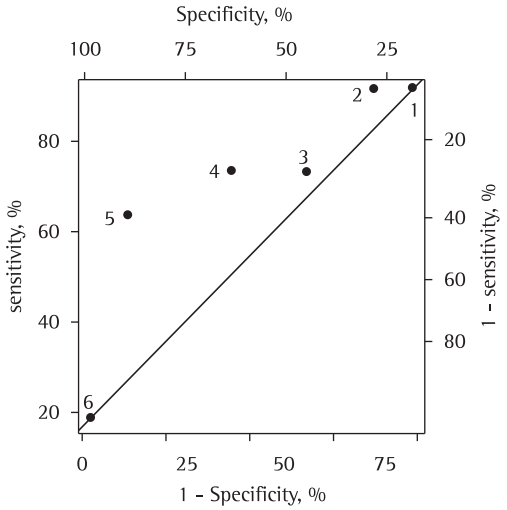

Figure 1 - ROC curve showing the relationship between sensitivity and specificity according to the number of radiological changes (from 1 to 6) detected by CT in the diagnosis of idiopathic pulmonary fibrosis.

Discussion

In the present study, the patients suspected of having ILD presented with a highly prevalent clinical and epidemiological profile, meaning that age, gender, prevalence of dyspnea, and prevalence of chest pain were similar to those reported in studies conducted at other referral centers.[15] The same was observed for the patients with IPF.[16,17]

Clinical suspicion of ILD is fundamental due to the wide variety of differential diagnoses with similar clinical profiles. Our results show that the frequency of IPF cases was greater when IPF was only a possible diagnosis and lower when ILD was the prime suspect (p = 0.011). This underscores the need for ancillary tests in order to establish a definitive diagnosis.

In the present study, honeycombing was the least common radiological finding (14%). However, the presence of honeycombing was highly suggestive of IPF (p = 0.01). Although nodules are extremely common in ILDs, they are uncommon in IPF. Nodules are most common in sarcoidosis, showing high sensitivity (86%). In the absence of this lesion, the possibility of sarcoidosis is more remote (NPV = 90%). The presence of at least six radiological changes had a PPV of 67% for IPF, a value very similar to that found in another study (71%).[18] The PPV increased as the number of changes increased. However, the ROC curve showed that the best

Table 4 - Correlation of radiological and histological changes with the diagnosis of idiopathic pulmonary fibrosis.

Type	Sensitivity, %	Specificity, %	PPV, %	NPV, %	Accuracy, %	LR
Radiological changes, n						
≥ 1	90.9	2.2	18.5	50.0	19.6	0.5
≥ 2	90.9	13.3	20.4	85.7	28.6	0.6
≥ 3	72.7	33.3	21.0	83.3	41	0.8
≥ 4	72.7	55.5	28.6	89.3	58.9	0.5
≥ 5	63.0	86.7	53.8	90.7	82.1	0.4
≥ 6	18.1	97.7	66.7	83.0	82.1	0.8
Histological changes						
Radial fibrosis	9.0	86.6	14.2	79.6	71.4	1.0
Diffuse fibrosis	9.0	71.1	7.1	76.1	58.9	1.3

PPV: positive predictive value; NPV: negative predictive value; and LR: likelihood ratio.

relationship between sensitivity and specificity occurred when five changes were present. This difference shows the need for qualifying such changes. Although the number of radiological changes is important, the patterns observed must be those that the literature associates with high specificity for IPF, such as honeycombing.[18-20]

The predominant histopathological pattern in IPF was the indeterminate pattern. This is due to the peripheral characteristic of IPF[21,22] and rules out other differential diagnoses. Therefore, the indeterminate pattern was associated with consistent clinical and radiological findings, which aided in establishing a final diagnosis of IPF.[22,23] We find it curious that 27.3% of the patients presented with a pattern of organizing pneumonia, which can be suggestive of greater disease severity.[24] There is currently no treatment that can change the prognosis and complications of this type of profile.[9,16] In general, fibrosis was the most common finding, similarly to what has been reported in other studies.[25] Fibrosis with a radial pattern showed high specificity and high NPV and might have resulted from the extension of peripheral fibrosis. Although the granulomatous pattern was a common TBB finding, it was shown to be far more specific for sarcoidosis, having high PPV and NPV, in agreement with the findings of a previous study.[26] Therefore, in order to increase the diagnostic yield, it is fundamental that specialists in ILDs evaluate the clinical, radiological, and histopathological aspects in conjunction.[27]

The patients with ILD investigated in the present study had the same clinical, radiological, and pathological profiles as those of patients treated at other referral centers. For patients with clinical suspicion of ILD and for those in whom ILD is only a possible differential diagnosis, CT is an indispensable ancillary test. In some cases, the use of CT in combination with clinical and functional evaluation is sufficient to establish a diagnosis. The histopathological analysis complements the diagnostic rationale; however, the use of histopathological analysis and the type of biopsy employed (TBB or surgical biopsy) should be considered on a case-by-case basis.

The study of the accuracy of ancillary tests, such as CT and TBB, in diagnosing ILDs at the FMB-UNESP *Hospital das Clínicas* revealed values that were very similar to those found at large referral centers and should be used in all hospitals at which the required equipment is available and there are qualified, multidisciplinary medical teams working in concert to treat patients with ILDs.

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