

## THE ROLE OF TRANSBRONCHIAL LUNG BIOPSY FOR THE DIAGNOSIS OF DIFFUSE DRUG-INDUCED LUNG DISEASE: A CASE SERIES OF 44 PATIENTS

M. Romagnoli<sup>1</sup>, C. Bigliuzzi<sup>1</sup>, G. Casoni<sup>1</sup>, M. Chilosi<sup>2</sup>, A. Carloni<sup>3</sup>, A. Dubini<sup>4</sup>, Ch. Gurioli<sup>1</sup>, S. Tomassetti<sup>1</sup>, C. Gurioli<sup>1</sup>, V. Poletti<sup>1</sup>

<sup>1</sup>Interventional Pulmonology, Department of Thoracic Diseases, Forlì, Italy, <sup>2</sup>Institute of Pathology, University of Verona, Italy, <sup>3</sup>Institute of Radiology, Terni, Italy, <sup>4</sup>Institute of Pathology, Forlì, Italy

**ABSTRACT.** At present, no studies have evaluated the role of bronchoscopic transbronchial lung biopsy (TBLB) in the diagnosis of diffuse drug-induced lung disease (DILD), and there is no consensus for a definite diagnostic workup approach for this rare clinical entity. The aim of the present study was to evaluate the clinical usefulness of TBLB in diffuse DILD. This study was a retrospective analysis of patients with diffuse DILD, who underwent bronchoscopy. The role of TBLB was assessed to determine whether the histological results are useful for the final diagnosis. Over a 5-yr period, 44 patients underwent bronchoscopy, and all had a bronchoalveolar lavage (BAL). Thirty-three of the 44 patients underwent TBLB (75%), and the results of TBLB were diagnostically helpful in 25 (75.7%) of the procedures. No histopathologic abnormality was identified in 6 (18%) of the 33 patients. In 2 patients (6%) the obtained samples were not adequate, since no lung parenchyma was obtained. No severe complications related to bronchoscopic procedures occurred. In conclusion, TBLB is a safe procedure, and is diagnostically helpful in the majority of cases of patients with diffuse DILD. Histological data obtained by TBLB further corroborate clinical, laboratory, radiologic and BAL results for a definitive diagnosis of diffuse DILD. (*Sarcoidosis Vasc Diffuse Lung Dis* 2008; 25: 36-45)

**KEY WORDS:** Bronchoscopy, bronchoalveolar lavage (BAL), high-resolution computed tomography (HRCT), interstitial lung disease, pathology.

### INTRODUCTION

Diffuse drug-induced lung disease (DILD) is an increasingly observed cause of a potentially fatal acute or invalidating pulmonary chronic disease. At present, more than 350 drugs, including cytotoxic

and non-cytotoxic drugs, are known to cause lung injury (1-5).

Clinical and radiographic features of diffuse DILD are often difficult to distinguish from other causes of diffuse lung disease (e.g. infections, lung involvement of an underlying malignancy, pulmonary edema, etc.), and there are no signs, symptoms, laboratory or radiologic data that could be considered as pathognomonic.

The diagnosis is often complex and is mainly made by meticulous exclusion of all other possible causes. It involves four elements: 1) clinical suspicion, including a history of drug exposure, 2) chest high resolution computed tomography (HRCT)

Received: 20 July 2008

Accepted after Revision: 01 September 2008

Correspondence: Venerino Poletti, MD

Interventional Pulmonology,

Department of Thoracic Diseases,

Pierantoni-Morgagni Hospital, Via C. Forlanini, 34,  
47100 Forlì, Italy.

Tel. +39 0543 735042, Fax: +39 0543 735039.

E-mail: v.poletti@ausl.fo.it

findings (6-8), 3) exclusion of other causes of diffuse lung disease, with a compatible pathologic pattern, 4) the prevalence of reported cases with the suspected drug (1, 9-11).

Although BAL is helpful for the exclusion of other diseases, such as malignancies with pulmonary metastases and infections (12-14), its diagnostic yield is limited.

The need for histological documentation in the diagnostic workup of patients with suspicion of diffuse DILD is still controversial, especially because of the potential side effects of the procedures. Although a formal evaluation of the risk-benefit is not available, lung histology might be required in patients with suspicion of DILD. Limited information on diffuse DILD and histological features obtained by transbronchial lung biopsy is available (15-17), and some reports also advocate more invasive procedures, such as surgical lung biopsy (13, 18-19).

Although lung histology is not specific for drug toxicity and correlation with clinical, laboratory, and radiological data still is required, it can be a powerful tool in the evaluation of suspected drug-induced pulmonary disease by helping to exclude other underlying pathology, including infection, and documenting the pattern of lung injury. The latter information is helpful in making the diagnosis of drug toxicity as well as guiding the optimal management of patients.

At present, there is no consensus for a definite diagnostic workup approach in patients with a suspicion of diffuse DILD, and no data are available on the role of TBLB in the diagnosis and management of this complex disease. The purpose of the present analysis was to determine whether histological information obtained by TBLB is helpful for the diagnosis and management of patients with diffuse DILD.

## METHODS

### *Study subjects*

The study was a retrospective analysis of patients hospitalized in the Unit of Interventional Pulmonology, Forlì, Italy, between January 1<sup>st</sup>, 2003 and March 1<sup>st</sup>, 2008. Subjects were identified through the Hospital medical records database (specific section referring to our Unit) by searching for the term

“drug-induced lung disease”. This database records each observed patient, and one of the obligatory fields is the term “diagnosis”, giving the opportunity to select the term “suspicion” or “definitive diagnosis”. We selected for the study only patients with a “definitive diagnosis” of “drug induced lung disease”. Medical records were reviewed for history, laboratory, functional (pulmonary function and blood gas analysis) and chest HRCT findings. All patients authorised their records to be reviewed.

## PROCEDURES

BAL and TBLB were carried out using rigid bronchoscopy under general anesthesia. General anesthesia was induced using propofol (1-2 mg/kg). Assisted spontaneous ventilation was applied. Topical anesthesia was administered with lidocaine 2% before intubation. After anesthesia induction, the patients were intubated with a rigid bronchoscope (Storz; Tutlingen, Germany). Anesthesia was maintained with intravenous propofol (4 to 6 mg/kg/h) according to the hemodynamic parameters of the patients. All TBLBs were performed under fluoroscopic guidance, using flexible forceps (Model K 022V-120, Diflex, Germany) with cup sizes, 3 x 2 x 0.9 mm. For each patient a number of at least 6 transbronchial biopsies were obtained. To minimize major complications in case of haemorrhage, a non inflated Fogarty balloon and a rigid aspirator (diameter 4 mm) were placed in the lobar bronchus, before performing TBLB in the more involved lobe, as shown by HRCT scan.

Diagnostic criteria for diffuse DILD included at least 3 of the following criteria: 1) presence of respiratory symptoms and signs, with or without fever, in patients exposed to drugs potentially causing lung disease (1); 2) chest X-ray and HRCT evidence of diffuse lung disease (involvement of more than one lobe); 3) BAL and histopathologic features on TBLB specimens compatible with the clinical hypothesis; 4) no other identifiable cause for diffuse parenchymal lung disease (e.g. heart failure, pulmonary infections, lung malignancies, graft *versus* host disease, etc.).

BAL was performed by instillation of six 25 mL aliquots of sterile saline solution warmed at 37° (0.9% NaCl solution); fluid was aspirated immediately af-

ter each aliquot was instilled and collected in a sterile container. After recovery, BAL fluid was filtered through a monolayer of surgical gauze to remove mucus and centrifugated at 34xg for 7 min. Cytospin preparations were stained by both the Diff Quick and Papanicolau methods. Quantitative BAL cultures for common bacteria, culture for acid fast bacilli and fungi, as well as viral cultures and/or immunofluorescence tests for viruses (*cytomegalovirus*, *adenovirus*, *herpes simplex viruses*, *syncytial respiratory virus*, *influenzae and parainfluenza viruses*) and *Legionella* were performed. In all cases the specimens were stained by Haematoxylin & Eosin, Grocott-Gomori methenamine silver stain, PAS, Ziehl Neelsen; and by immunohistochemical methods using monoclonal antibodies against *Pneumocystis J.*, *Cytomegalovirus*, and *Herpes Simplex virus*. BAL was considered to be "compatible" with DILD when it excluded opportunistic infections and/or malignancies, and showed a lymphocyte or neutrophilic predominance (12,13).

According to *Mayers and El-Zammar* (20), the following histopathologic patterns were considered consistent with drug-induced lung disease: cellular interstitial pneumonitis [(CIP) interstitial infiltration of mononuclear cells with maintenance of alveolar architecture] (Fig. 1a); hypersensitivity pneumonitis [(HP) granulomas +/- cellular interstitial pneumonitis +/-organizing pneumonia +/-foamy alveolar macrophages] (Fig. 1b); organizing pneumonia [(OP) intra-alveolar buds of granulation tissue +/-interstitial inflammation] (Fig. 1c); diffuse alveolar damage [(DAD)] (Fig. 1d); alveolar hemorrhage [(AH) intra-alveolar accumulation of haemosiderin laden macrophages +/- intra-alveolar bleeding] (Fig. 1e); eosinophilic pneumonia [(EP)] (Fig. 1f).

As previously reported (21-22), TBLB was considered clinically useful if: a) it resulted in a histopathological pattern consistent with the clinical-radiological diagnosis of diffuse DILD, or b) other pathological processes were excluded on the basis of the biopsy finding and/or the clinical information, or c) the clinical management changed and a specific therapeutic decision was then made. TBLB was considered unhelpful when the procedure failed to obtain lung tissue, or failed to obtain a characteristic histopathologic pattern (normal tissue).

Complications related to bronchoscopic procedures were routinely recorded in an electronic pa-

tient management system, and could then be retrospectively identified through the database records. They were reviewed for evidence of: endobronchial haemorrhage, iatrogenic pneumothorax, severe respiratory failure (oxygen saturation < 85% and/or need of assisted ventilation), and cardiac arrhythmias, or cardiac arrest during or immediately after the bronchoscopic procedures.

## RESULTS

A total of 50 medical records of patients with "drug-induced lung disease" were reviewed. Six patients were excluded, since their final diagnosis was lipoidic pneumonia induced by inhalation of medications containing oils. Thus, forty-four patients with diffuse DILD were included in the study.

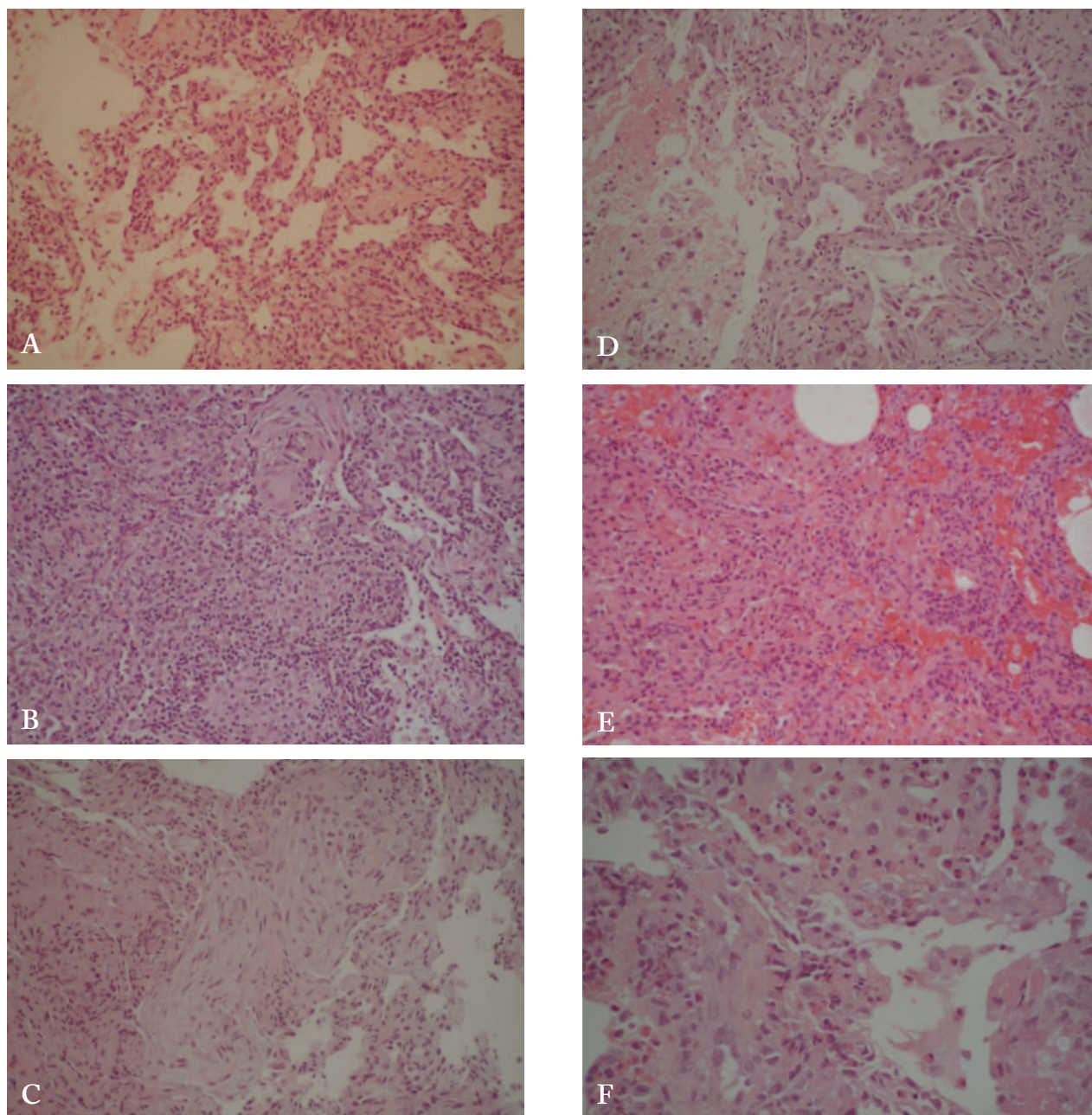
Demographic, clinical, functional, radiographic and histopathologic characteristics of the patients are shown in table 1 and in table 2. The clinical profile at onset (Tab. 1) appeared to be non specific, with dyspnoea, cough and fever being the most frequent symptoms. Respiratory failure was present in 11 patients of the total 44 (25 per cent of cases). Laboratory tests showed, in the majority of cases, a normal WBC count, whereas CRP, ERS and LDH values were usually increased. In four of the 13 patients presenting with fever, an elevated WBC count and increased values of CRP, ERS and LDH were detected.

Pulmonary function test (Tab. 1) was performed in 36 of the 44 patients. In eight patients (patients n. 1, 2, 4, 6, 11, 24, 26 and patient n. 44) functional parameters were not recorded because of the presence, of severe dyspnea and/or severe acute respiratory failure (blood gas analysis findings, data not shown).

All patients underwent bronchoscopy with BAL, and 33 underwent also TBLB. The average number of biopsy samples taken per patient was  $6.27 \pm 0.67$  (SD), (range 5-8). In four cases TBLB were judged as contraindicated due to severe respiratory failure (patients N. 6, 11, 24 and 26, data also available from Table 2). In the remaining 7 cases, patients did not undergo TBLB because of advanced concurrent malignancy in one case (Patient N.7), withholding of consent in another one (Patient N. 36), and because of unknown reasons in 5 cases (data not available from database).

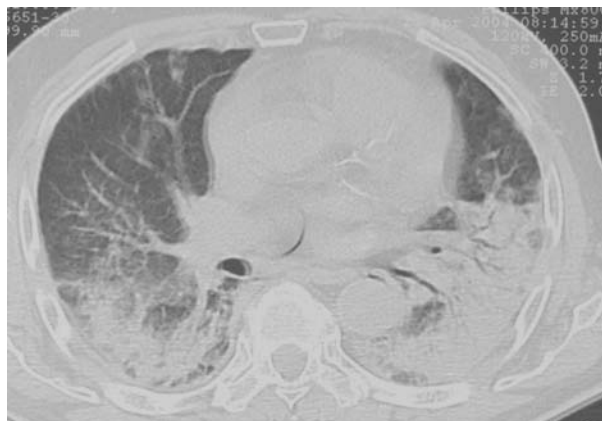
As reported in Table 3, TBLB provided *adequate* (presence of alveolar parenchyma) and *diagnostic* (presence of a characteristic abnormal histopatho-

logic pattern) samples in 25 patients of the total 33 (76%). In 6 patients (18%) the specimens were adequate, but not diagnostic (two of them underwent



**Fig. 1.** Histological patterns obtained by transbronchial biopsy: a) Cellular Interstitial Pneumonitis (CIP): mild interstitial chronic infiltrate causing thickening of the alveolar walls (Patient n. 20); b) Hypersensitivity Pneumonitis (HP): peribronchiolar chronic inflammatory infiltrate, poorly formed granulomas, and intraluminal budding fibrosis (Patient n. 8); c) Organizing Pneumonia (OP): intra-alveolar buds of organizing connective tissue (Patient n. 41); d) Diffuse Alveolar Damage (DAD): alveolar fibrin, hyperplastic type 2 pneumocyte, and thickened alveolar walls (Patient n. 2); e) Alveolar Hemorrhage (AH): intra-alveolar accumulation of red blood cells, with fibrin and haemosiderin laden macrophages (Patient n. 19); f) Eosinophilic Pneumonia (EP) showing alveolar spaces filled with a fibrinous exudate, and numerous eosinophils (Patient n. 42). All transbronchial biopsy specimens stained with H&E.

VATS lung biopsy). In 2 patients (6% of the total 33) TBLB specimens were not helpful, since they did not contain alveolar tissue adequate. These patients did not give consent for more invasive procedures. In



**Fig. 2.** HRCT scan showing areas of ground glass attenuation and alveolar consolidation, mainly involving the lower lobes (Patient n. 17).

**Table 1.** Clinical, functional and HRCT characteristics of patients.

<b>N° of patients</b>	44 (27 M; 17 F)
<b>Mean age yrs (± SD)</b>	55.8±16.6
<b>Smoke history pack/years (± SD)</b>	6.5±2.2
	21 non-smokers, 21 ex and 2 current smokers
<b>Symptoms and signs N. (%):</b>	
- Dyspnoea	36 (81)
- Cough	24 (54.5)
- Fever	13 (29.5)
- Respiratory failure at onset	11 (25)
<b>Laboratory (± SD):</b>	
- WBC (x10 <sup>3</sup> /mL)	4.27 ± 2.4
- CRP (mg/dL)	8.21 ± 2.4
- ERS (mm/h)	54 ± 38.8
- LDH (U/L)	481 ± 211
<b>FEV1% pred. (± SD)</b>	90±24
<b>DLCO% pred. (± SD)</b>	63.6±19.2
<b>PaO<sub>2</sub> mmHg (± SD)</b>	61.5±15.6
<b>Mortality n. (%)</b>	5 (11.3)
<b>Chest HRCT patterns n. (%):</b>	
- Bilateral ground-glass opacity	33 (75)
- Bilateral alveolar consolidation	27 (61.3)
- Bilateral intralobular reticular pattern	9 (20.4)
- Bilateral nodules	6 (13.6)
- Mediastinal lymph nodes	6 (13.6)
- Bilateral pleural effusion	6 (13.6)

two cases an open lung biopsy (VATS) was performed: surgical lung biopsy was diagnostically helpful (OP and CIP pattern, respectively), in spite of TBLB specimens demonstrating normal lung parenchyma (case n. 12 and case n. 23).

All BAL samples (cytological features, microbiologic analyses) were negative for infections (in two cases *Enterobacter cloacea* and *Pseudomonas aeruginosa* were cultured but with CFU <10<sup>4</sup>/ml; therefore these bacteria were considered to be colonizers), and did not reveal any malignancies. Cytological characteristics of BAL findings were not specific, as neutrophilia (neutrophils >4% of total cells) was found in 24 patients and lymphocytosis (lymphocytes >15% of total cells) was found in 20 patients. Reactive type II pneumocytes (typically clusters of large vacuolated cells with a low nuclear to cytoplasmic ratio and peripheral nuclei) were observed in all the five patients who died, and were absent in BAL fluid of the remaining 39 patients. The presence of these cells in BAL was significantly associated with death (Fisher's exact test, p<0.0001).

No major nor minor complications related to bronchoscopic procedures were identified.

Patients were treated by high doses of systemic corticosteroids and withdrawal of suspected drugs.

## DISCUSSION

This is the first study assessing and showing the importance of the role of bronchoscopic TBLB for the diagnosis of diffuse DILD. Thus, in the 76% of cases TBLB samples were considered *adequate* and *diagnostic*, helpful in excluding other etiologic causes of diffuse lung injury, and in confirming the diagnosis of diffuse DILD. There are no guidelines nor consensus statements for a definite diagnostic workup in DILD, and this is likely related to the fact that DILD is a rare disease entity. In fact, our series of 44 patients is the largest one ever reported. The need for histological documentation in the diagnostic workup of patients with suspicion of DILD is still controversial. Some reports underline the role of BAL (12, 13) and limited information is available on histological features obtained by TBLB (15-17), or by the more invasive surgical lung biopsy (13, 18-19).

Although lung histology is not pathognomonic for drug toxicity, the addition of histological data

**Table 2.** Clinical and pathological characteristics of patients.

Pt No.	Age (yrs)	Sex	Baseline disease	Therapy used	Bone marrow transplant (before diagnosis)	Duration of respiratory symptoms (days)	Symptoms and signs	Chest HRCT pattern	Pathological findings at TBLB
1 (†)	67	M	CLL	Fludarabine	No	12	Dyspnea, fever, ARF, ARDS	G+C+M+P	Not adequate
2 (†)	76	F	NHD	Cyclophosphamide Vincristine Bleomycin VP16	No	20	Dyspnea, fever, ARF, ARDS	G+M+P	DAD
3	40	M	HD	Doxorubicin, Bleomycin, Vinblastine Dacarbazine	No	3	Dyspnea, fever, cough, ARF	G	Not adequate
4	74	M	NHD	Vincristine Procarbazine	No	7	Dyspnea, cough, ARF	I+G+M	CIP
5	40	M	NHD	MTX Adriamycin Cyclophosphamide Vincristine Bleomycin Rituximab	No	15	Fever	C	TBLB not done
6 (†)	53	M	NHD	MTX Adriamycin Cyclophosphamide Vincristine Bleomycin Rituximab	No	7	Dyspnea, cough, ARF, ARDS	P+C+G	TBLB not done
7	34	F	NHD	MTX Adriamycin Cyclophosphamide Vincristine Bleomycin	No	3	Dyspnea, fever, cough	C+G+M+I	TBLB not done
8	47	M	MM	Cytarabine, Daunorubicin, Etoposide	No	60	Cough	C	HP
9	29	F	HD	Doxorubicin, Bleomycin, Vinblastine Dacarbazine	No	37	Cough, haemoptysis	C	OP
10	63	F	ALM	Oncocarbide Daunorubicin, Aracytin	No	40	Cough	C	OP
11 (†)	64	M	NHD	Cyclophosphamide	No	3	Dyspnea, ARF, ARDS	C + G	TBLB not done
12	58	M	NHD	Bleomycin	No	20	Dyspnea	N	At TBLB: normal parenchyma At surg. biopsy: OP
13	23	M	NHD	MTX Adriamycin Cyclophosphamide Vincristine Bleomycin	Yes	80	Dyspnea, Fever, cough	C + G + N	OP
14	58	F	MM	Cyclophosphamide, Methotrexate	Yes	60	Dyspnea, cough	C + G	Normal parenchyma

15	69	M	Colon carcinoma	5 Fluoro-uracile oxaliplatinum	No	180	Cough	C + G	OP
16	72	F	Breast carcinoma	Cyclophosphamide, Adriamycin, Docetaxel	No	10	Cough	C + G + P + M	CIP
17	23	M	HD	Doxorubicin, Bleomycin, Vinblastine Dacarbazine	No	30	Dyspnea, cough	C + G	TBLB not done
18	64	M	ALM	Busulfan, melfalan	No	30	Dyspnea	C + G	DAD
19	59	M	ALM	Cytarabine, VP16, Fludarabine	No	3	Dyspnea, fever	G	AH
20	61	F	HD	Doxorubicin, Bleomycin, Vinblastine Dacarbazine	No	20	Dyspnea, cough	G + I	CIP
21	43	M	ALL	Etoposide, Cytarabine, Busulfan, Cyclophosphamide	Yes	60	Dyspnea Fever, cough	G	DAD
22	63	F	Endometrial carcinoma	Paclitaxel + RT	No	15	Dyspnea	C + G	TBLB not done
23	70	M	NHD	Cyclophosphamide, Doxorubicin, Vincristine	No	60	Dyspnea	G + N	AT TBLB: normal parenchyma At surg. biopsy: CIP
24	76	M	NHD	Cyclophosphamide	No	7	Dyspnea, ARF	C	TBLB not done
25	68	F	HD	Doxorubicin, Bleomycin, Vinblastine Dacarbazine	No	25	Dyspnea, cough	G + I	DAD
26	64	M	NHD	Rituximab Cyclophosphamide, Doxorubicin, Vincristine + RT	No	2	Dyspnea, ARF	C	TBLB not done
27	28	F	HD	Doxorubicin, Bleomycin, Vinblastine Dacarbazine	No	10	Dyspnea, cough	G + C + M	Normal parenchyma
28	20	M	Ewing Sarcoma	Adriamicin Cyclophosphamide Vincristine VP16 Busulfan/Melfalan RT	No	30	Dyspnea, fever	G + C	DAD
29	65	F	Endometrial carcinoma	Paclitaxel + RT	No	20	Dyspnea	G + C	CIP
30	70	M	Colorectal carcinoma	5 fluorouracil	No	30	Cough	C + N	OP
31	50	M	HD	Doxorubicin, Bleomycin, Vinblastine Dacarbazine	No	15	Dyspnea, cough	G + C	Normal
32	54	F	Breast + colon carcinoma	Oxaliplatinum	No	7	Cough	G + C	DAD

33	70	F	Systemic hypertension	Valsartan	-	20	Dyspnea	I + G	CIP
34	41	M	Main depression	Venlafaxine	-	15	Dyspnea, fever, cough	G + N	CIP
35	66	M	Psoriatic arthritis	MTX	-	15	Dyspnea, cough, weight loss	G + I	CIP
36	55	F	Main depression	Venlafaxine	-	12	Dyspnea, fever, cough	G	TBLB not done
37	33	F	RA	MTX	-	20	Dyspnea,	C	TBLB not done
38	75	F	Wegener vasculitis	Cyclophosphamide	-	120	Dyspnea, cough	G + I	TBLB not done
39	40	M	Schizophrenia	Clozapine	-	60	Dyspnea, cough	C + P	Normal parenchyma
40	70	M	RA	MTX	-	20	Dyspnea	C + I	DAD
41	70	M	RA	MTX	-	180	Dyspnea	N + G	OP
42	44	F	Acne	Minocycline	-	2	Dyspnea, ARF	G	EP
43	65	M	Main depression	Amitriptyline; sertraline; merpraline; lorazepam; perfenazine	-	12	Dyspnea, Fever, ARF	G + C	OP
44(+)	84	M	Atrial fibrillation	Amiodarone	-	15	Dyspnea, Fever, ARF	G + I + P	DAD

(+): deceased.

CLL: chronic lymphatic leukaemia; NHD: non-Hodgkin disease; HD: Hodgkin disease; ALM: acute myeloid leukaemia; MM: Multiple Myeloma; ALL: acute lymphatic leukaemia. RA: rheumatoid arthritis.

Cyclophosphamide, Doxorubicin, and Vincristine are also known as CHOP. Doxorubicin, Bleomycin, Vinblastine and Dacarbazine are also known as ABVD. Cytarabine is also known as Ara-C.

Bleomycin, Methotrexate (MTX), and Cyclophosphamide are drugs more probably involved when used in combination.

RT: radiotherapy.

G: Ground-glass opacity; C: Alveolar consolidation; M: Mediastinal lymph nodes; P: Pleural effusion; I: Intralobular reticular pattern; N: nodule.

ARDS: adult respiratory distress syndrome; ARF: acute respiratory failure.

CIP: cellular interstitial pneumonia; DAD: diffuse alveolar damage; AH: alveolar haemorrhage; HP: hypersensitivity pneumonia; OP: organizing pneumonia; EP: eosinophilic pneumonia.

**Table 3.** Data on adequacy of TBLB samples.

Total N° of diffuse DILD observed	44
N° of patients who underwent bronchoscopy	44 (100%)
N° of patients who underwent BAL	44 (100%)
N° of patients who underwent TBLB	33 (75%)
N° of patients with adequate and diagnostic TBLB	25 (75.7%)
N° of patients with adequate TBLB	31 (93.9%)
N° of patients without histopathologic abnormality	6 (18%)
N° of patients without adequate TBLB	2 (6%)
N° of severe complications related to the procedures	None
N° of patients without TBLB *	11 (25%)
N° of surgical lung biopsy (VATS) §	2 (4.5%)

\* Severe baseline ARF = 4, advanced concurrent malignancy = 1, with-holding of consent = 1, unknown reasons = 5.

§ 1. Nodules in NHD treated by bleomycin (Patient n. 12): At TBLB: normal alveoli; At VATS biopsy: OP.

2. NHD treated by CHOP regimen (Patient n. 23): At TBLB: normal alveoli; At VATS biopsy: cellular CIP.

consistent with diffuse DILD together to the clinical, laboratory, HRTC scan and BAL cytological and microbiological features can be essential to exclude other diseases.

The clinical presentation of this patient series was clearly heterogeneous, confirming previous data (1). Thus, the presentation may be acute, sub-acute or chronic, with the same drug possibly leading to either acute or subacute/chronic interstitial lung disease. In the 25% of cases, patients presented with respiratory failure, demonstrating the frequent clinical severity of this disease. In the 30% of cases, patients presented with fever and elevated inflammatory signs, indicating that drug-induced toxicity may mimic pneumonia in a significant number of patients. Smoking habits did not seem to influence the prevalence of DILD in this casistic. However, the



data are not sufficient to support a lack of effect of smoking upon DILD prevalence.

Similar to the clinical presentation, also chest high resolution CT scan patterns are of limited value in the diagnosis of diffuse DILD, since a wide variety of unspecific radiological patterns have been described in this clinical entity. As expected, all the patients of this case series presented with a diffuse bilateral pulmonary pattern. Thus, in the majority of previously reported cases, drug-induced lung disease presents with a bilateral pulmonary involvement (1, 6). HRCT manifestations of diffuse DILD may imitate other pulmonary entities, e.g. infections and cancer (1, 6-8). In the present series, ground glass opacities and alveolar consolidations were observed in the majority of cases, regardless of the involved drugs, confirming - as previously highlighted - that chest HRCT is of limited value in determining the histological pattern and the prognosis of the disease (7). Malignant lymphomas, lymphocytic B cell leukaemia and myeloid leukaemia may spread into the lung along the lymphatic system, appearing as ground-glass attenuation, centrilobular nodules, and thickening of bronchovascular bundles (22). Such diagnoses need to be excluded by the assessment of transbronchial lung biopsies. Also in some of the cases of this series, chest HRCT features, for example, raised the suspicion of diffuse bilateral malignancies, either primary lung cancer (i.e. bronchiolo-alveolar carcinoma and mucosa-associated lymphoid tissue (MALT) lymphomas), or lung metastatic involvement.

Although BAL is advocated for the diagnosis of diffuse DILD (12-13), the evidence for this recommendation appears to be weak. BAL might help to exclude infectious diseases (24-25), but the cellular pattern is unspecific, not diagnostic *per se*, and histology is still needed.

In this retrospective analysis, the presence of reactive type II pneumocytes in BAL fluid was significantly associated with death. This finding is in accordance with a previous report in which these cells were found to be associated with conditions of acute lung injury (26), but needs to be further assessed in prospective studies.

Transbronchial lung biopsy has been reported to be helpful in several variants of diffuse interstitial lung diseases (21-22). However, no data exist on the role of TBLB for the diagnosis of diffuse DILD, which often represents a clinical challenge, and some

reports still advocate the need for surgical biopsy (13). In this series, histopathologic patterns consistent with drug induced lung toxicity were identified in 75.7% of cases by TBLB, which is very similar to the finding by *Ensminger and Prakash* (21), and only in a minority of cases there was the clinical need for further (surgical) lung biopsy.

Although TBLB has been performed also in patients with acute respiratory distress syndrome (ARDS) and under mechanical ventilation without severe complications (27), in the present study TBLB was not performed in four patients, because of the presence of severe acute respiratory failure and unstable general conditions.

One criticism of this study might be the heterogeneity of the patients, in terms of different underlying diseases, and in terms of different drug treatments potentially implicated in lung toxicity. However, drug-induced lung toxicity does represent *per se* a heterogeneous clinical entity, involving numerous drugs, acting by different and sometimes overlapping mechanisms of action, and presenting with a wide spectrum of clinical, radiological and pathological manifestations. These aspects do represent the crucial problem for the (differential) diagnosis of this specific pulmonary entity.

Another limitation of this study is its retrospective nature, but given the low prevalence of diffuse DILD, prospective trials for this disease entity with sufficient patient number are highly unlikely ever to be realized. Furthermore, the selection bias concerning patients not undergoing TBLB is limited, suggesting the usefulness of a unit protocol to always perform TBLB when practicable. Finally, and similar to previous report on TBLB in diffuse interstitial lung disease (21), the definition of "clinical usefulness" of histology is somewhat arbitrary. For the purpose of this report, therefore, "clinical usefulness" is defined in a pragmatic sense as any information that contributes to the definite diagnosis of DILD. We did not analyze it in details since the main issue of the paper was to define the role of TBLB in the diagnosis of drug-induced lung disease. However, since in this case series no "clinically false positive cases" eventually diagnosed as non-DILD were included, a prospective study on suspect DILD cases shall be conducted to confirm the clinical utility of the procedure.

In conclusion, TBLB seems to be a useful and safe procedure allowing to obtain histological pul-

monary specimens helpful in excluding other etiologic causes of diffuse lung injury, and in confirming the diagnosis of diffuse DILD. The findings from this study suggest that the best standard workup approach in the diagnosis and clinical care of diffuse DILD could include a bronchoscopy with transbronchial biopsies, without the need for more invasive procedures.

### Acknowledgment

The Authors gratefully acknowledge Prof. Klaus F. Rabe, MD, PhD, for his helpful assistance in editing the manuscript.

### REFERENCES

1. Drug Induced Lung Diseases. [www.pneumotox.com](http://www.pneumotox.com)
2. Camus, P., P. Bonniaud, A. Fanton, C. Camus, N. Baudaun, and P. Foucher. Drug-induced and iatrogenic infiltrative lung disease. *Clin Chest Med* 2004. 25(3):479-519.
3. Camus, P., A. Fanton, P. Bonniaud, C. Camus, and P. Foucher. Interstitial lung disease induced by drugs and radiation. *Respiration* 2004. 71(4):301-26.
4. Foucher, P., M. Biour, J. P. Blayac, P. Godard, C. Sgro, M. Kuhn, J. M. Vergnon, D. Vervloet, P. Pfitzenmeyer, M. Ollagnier, C. Mayaud, and P. Camus. Drugs that may injure the respiratory system. *Eur Respir J* 1997;10(2):265-79.
5. Lock, B. J., M. Eggert, and J. A. Cooper, Jr. Infiltrative lung disease due to noncytotoxic agents. *Clin Chest Med* 2004. 25(1):47-52.
6. Akira, M., H. Ishikawa, and S. Yamamoto. Drug-induced pneumonitis: thin-section CT findings in 60 patients. *Radiology* 2002. 224(3):852-60.
7. Cleverley, J. R., N. J. Screaton, M. P. Hiorns, J. D. Flint, and N. L. Muller. Drug-induced lung disease: high-resolution CT and histological findings. *Clin Radiol* 2002. 57(4):292-9.
8. Ellis, S. J., J. R. Cleverley, and N. L. Muller. Drug-induced lung disease: high-resolution CT findings. *AJR Am J Roentgenol* 2000;175(4):1019-24.
9. Muller, N. L., D. A. White, H. Jiang, and A. Gemma. Diagnosis and management of drug-associated interstitial lung disease. *Br J Cancer* 2004. 91 Suppl 2:S24-30.
10. Ozkan, M., R. A. Dweik, and M. Ahmad. Drug-induced lung disease. *Cleve Clin J Med* 2001;68(9):782-5, 789-95.
11. Flieder, D. B., and W. D. Travis. Pathologic characteristics of drug-induced lung disease. *Clin Chest Med* 2004;25(1):37-45.
12. Costabel, U., E. Uzaslan, and J. Guzman. Bronchoalveolar lavage in drug-induced lung disease. *Clin Chest Med* 2004. 25(1):25-35.
13. Camus, P., and U. Costabel. Drug-induced respiratory disease in patients with hematological diseases. *Semin Respir Crit Care Med* 2005. 26(5):458-81.
14. Poletti V, Poletti G, Murer B, Saragoni L, Chilosi M. Bronchoalveolar lavage in malignancy. *Semin Respir Crit Care Med* 2007, 28(5):534-545.
15. Cho I, Mori S, Imamura F, Kiyofuji C, Sugimoto M. Methotrexate pneumonia lacking dyspnea and radiographic interstitial patterns during treatment for early rheumatoid arthritis: bronchoalveolar lavage and transbronchial lung biopsy in a differential diagnosis. *Mod Rheumatol*. 2007;17(3):256-261. Epub 2007 Jun 20.
16. Roberts RJ, Wells AC, Unitt E, Griffiths M, Tasker AD, Allison ME, Bradley JA, Watson CJ. Sirolimus-induced pneumonitis following liver transplantation. *Liver Transpl*. 2007;13(6):853-6.
17. Howard L, Gopalan D, Griffiths M, Mahadeva R. Sirolimus-induced pulmonary hypersensitivity associated with a CD4 T-cell infiltrate. *Chest*. 2006;129(6):1718-21.
18. Kalambokis G, Stefanou D, Arkoumani E, Tsianos E. Bronchiolitis obliterans organizing pneumonia following cHDorambucil treatment for chronic lymphocytic leukemia. *Eur J Haematol*. 2004;73(2):139-42.
19. Flieder DB, Travis WD. Pathologic characteristics of drug-induced lung disease. *Clin Chest Med*. 2004;25(1):37-45.
20. Myers JL and El-Zammar O. Pathology of Drug-induced lung disease. In: *Surgical Pathology of Non-Neoplastic Lung Disease*. Saunders Elsevier. Eds: ALA Katzenstein. 2006, Fourth Edition, Philadelphia. Chapter 4: 85-125.
21. Ensminger SA, Prakash UB. Is bronchoscopic lung biopsy helpful in the management of patients with diffuse lung disease? *Eur Respir J*. 2006;28(6):1081-4. Epub 2006 Aug 9.
22. Leslie KO, Gruden JF, Parish JM, Scholand MB. Transbronchial biopsy interpretation in the patient with diffuse parenchymal lung disease. *Arch Pathol Lab Med*. 2007;131(3):407-23.
23. Okada F, Ando Y, Kondo Y, Matsumoto S, Maeda T, Mori H. Thoracic CT findings of adult T-cell leukemia or lymphoma. *Am J Roentgenol*. 2004;182(3):761-7.
24. Vélez L, Correa LT, Maya MA, Mejía P, Ortega J, Bedoya V, Ortega H. Diagnostic accuracy of bronchoalveolar lavage samples in immunosuppressed patients with suspected pneumonia: analysis of a protocol. *Respir Med*. 2007;101(10):2160-7. Epub 2007 Jul 12.
25. Davis KA, Eckert MJ, Reed RL 2nd, Esposito TJ, Santaniello JM, Poulakidas S, Luchette FA. Ventilator-associated pneumonia in injured patients: do you trust your Gram's stain? *J Trauma*. 2005;58(3):462-467.
26. Linssen KC, Jacobs JA, Poletti VE, van Mook W, Cornelissen EI, Drent M. Reactive type II pneumocytes in bronchoalveolar lavage fluid. *Acta Cytol*. 2004 Jul-Aug;48(4):497-504.
27. Agarwal R, Gupta D, Aggarwal AN, Behera D, Jindal SK. Experience with ARDS caused by tuberculosis in a respiratory intensive care unit. *Intensive Care Med*. 2005;31(9):1284-7. Epub 2005 Jul 9.