1 Diffuse Parenchymal Lung Disease: A Clinical Overview

Venerino Poletti

1.1 Introduction

Diffuse parenchymal lung disease (DPLD) is a generic term for a large group of disorders. A definition based on precise criteria to identify these disorders is not yet universally accepted. A "morphologic definition" includes in this group all the disorders that are characterized by a pathologic accumulation/infiltration of extracellular substances, fluids, or cells in the structures of the secondary pulmonary lobule [1]. Secondary pulmonary lobule is an anatomic and functional unit supplied by a cluster of three to five terminal bronchioles, and it is usually separated from other secondary pulmonary lobules by connective tissue septa. It is irregularly polyhedral in shape and approximately 1–2.5 on each side [2]. This accumulation/infiltration is, by definition, not limited to one single lobe. This definition is quite inclusive because almost all lung disorders may present with this morphologic background. However in this huge group are included systemic disorders in which the lung is one of the main organs involved, idiopathic diseases limited to the lungs, and diffuse parenchymal disorders of known cause or well-known pathogenesis (Table 1.1). The clinical profiles with which these diseases manifest are variegated from very acute onset with respiratory failure needing invasive respiratory supports to mild chronic symptoms lasting for more than 6 months (dry cough, dyspnea on effort) (Table 1.2). Diagnosis is a complex process beset with pitfalls—often representing the balancing of different uncertainties—that starts having in mind a model based on pathophysiologic elements and other scientific knowledges. Thereafter it requires acquisition of data deriving from a comprehensive clinical history, a careful physical examination, as well as clues provided by laboratory and pulmonary function tests. Imaging, mainly high-resolution CT has a pivotal role in the detection of these disorders and in the diagnostic workup providing information robust enough to draw up a differential diagnosis list and sometimes identifying pathognomonic features. More invasive procedures are deemed necessary only when these steps are inconclusive or do not allow a confident clinical-radiological hypothesis.

1.2 Pathophysiology of DPLD

Due to the variety of entities included under the DPLD umbrella term, it is virtually impossible to have a common pathogenetic scheme. The structures injured are heterogeneous including bronchioles (terminal and respiratory), alveolar septa,

V. Poletti (✉)
Department of Diseases of the Thorax, Ospedale Morgagni-Pierantoni, Forlì, Italy

Department of Respiratory Diseases and Allergy, Aarhus University Hospital, Aarhus, Denmark

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Table 1.1 Classification of diffuse parenchymal lung disorders

Systemic disorders	Unknown cause	Known cause/pathogenesis
Sarcoidosis	IPF	Drugs/radiation
		Infections
CVDs	NSIP	Organic exposure (*hypersensitivity pneumonitis*)
Neoplastic (*metastases, lymphoproliferative disorders, LAM, LCH, myeloid disorders*)	COP	Inorganic exposure (*silicosis, asbestosis*)
Immunodeficiencies	AIP	Smoking related (*RB-ILD, DIP, SRIF*)
Telomeropathies (*Dyskeratosis congenita*, ...)	LIP	Pulmonary alveolar proteinosis
Inborn errors of metabolism (*Niemann-Pick, Gaucher, Hermansky-Pudlak, Fabry, Mucopolysaccharidoses*)	PPFE	Pulmonary alveolar microlithiasis
Neurofibromatosis	Chronic eosinophilic pneumonia	Mutations in genes coding for surfactant proteins or in ABCA3 transporter gene
Tuberous sclerosis		
Hypereosinophilic syndrome	Acute eosinophilic pneumonia	
IgG4-related disease		
Infections		

CVD collagen vascular disease, *LAM* lymphangioleiomyomatosis, *LCH* Langerhans cell histiocytosis, *IPF* idiopathic pulmonary fibrosis, *NSIP* nonspecific interstitial pneumonia, *COP* cryptogenic organizing pneumonia, *AIP* acute interstitial pneumonia, *LIP* lymphocytic interstitial pneumonia, *PPFE* pleuroparenchymal fibroelastosis, *RB* respiratory bronchiolitis, *DIP* desquamative interstitial pneumonia, *SRIF* smoking-related interstitial fibrosis, *ABCA3* ATP-binding cassette subfamily A member 3

Table 1.2 Time course of disease onset

Acute (in days to few weeks)	Subacute (<3 months)	Chronic (>3 months)
AIP	HP	IPF
		Smoking-related ILDs
		HP
AEP	COP	LCH
DAH/capillaritis	NSIP	LAM
Drug-induced ILDs	Drug-induced ILDs	Drug-induced ILDs
Antisynthetase syndrome	Sarcoidosis	Sarcoidosis
AFOP		Chronic eosinophilic pneumonia
Infections	Infections	Infections
Acute exacerbation of IPF		

AIP acute interstitial pneumonia, *AEP* acute eosinophilic pneumonia, *DAH* diffuse alveolar hemorrhage, *AFOP* acute fibrinous organizing pneumonia, *IPF* idiopathic pulmonary fibrosis, *HP* hypersensitivity pneumonitis, *COP* cryptogenic organizing pneumonia, *NSIP* nonspecific interstitial pneumonia, *LCH* Langerhans cell histiocytosis, *LAM* lymphangioleiomyomatosis

interlobular septa, small pulmonary and bronchiolar arteries, capillaries and veins, and lymphatics. These structures have also a different embryogenic origin and different regenerative machineries. The pathogenetic events in DPLD may be divided into five patterns. The neoplastic and infectious processes have pathogenetic events that are in common with all the other organs or systems. However in the lungs some events taking place in the alveolar spaces (production of degradating enzymes in lymphangioleiomyomatosis) may lead to characteristic cystic changes. Recently lymphangioleiomyomatosis has been reclassified as a low-grade sarcoma (belonging to the so-called PEComas) and Langerhans cell histiocytosis and Erdheim-Chester disease as inflammatory myeloid neoplasms with specific drug-targetable mutations along the RAS-RAF mitogen-activated protein kinase (MEK) and extracellular signal-regulated kinase (ERK) signaling cascade [3–5].

The other three pathophysiologic patterns left are granulomatous inflammation/fibrosis, inflammation/fibrosis, and, finally, alveolar stem cell

senescence-bronchiolar dysplastic proliferation/fibrosis. Genetic predispositions have been clearly documented in some disorders and are suspected to have a role in the large majority of the others.

Granulomatous inflammation/fibrosis is usually the morphologic background of sarcoidosis, hypersensitivity pneumonitis, and berylliosis. The inflammatory process is, at least in the florid phases, driven by Th1 cells (with release of interferon-gamma, IL-2, and IL-12) and macrophages. Granuloma formation is the key marker of these disorders [6]. When the disorders evolve to fibrosis, a switch to a Th2-like response seems to represent an important pathogenetic step. B-cell dysregulation and B-T cell interconnections may also have a role in granulomatous disorders as suggested by the association between granulomatous-lymphocytic interstitial lung disease (GLILD) and common variable immunodeficiency or 22q11.2 deletion syndrome [7] .

In nongranulomatous inflammatory/fibrotic DPLDs, the exact composition of inflammation and the distribution of inflammatory cells in the secondary pulmonary lobule vary depending on the individual disorders. Neutrophils are predominant in vasculitis, lymphocytes in nonspecific interstitial pneumonia (NSIP), eosinophils in chronic eosinophilic pneumonia, and macrophages in smoking-related diseases. Typical giant cells are a hallmark of hard metal lung disease. Necrosis (ischemic or apoptotic) is usually observed when the inflammatory cells are predominantly neutrophils. In the majority of these disorders, autoimmunity has a significant role. Accumulation of type I collagen and fibroblasts/myofibroblasts represents a progression toward the irreversible stage. These complex events are driven by activation of a variety of pathways that are very similar regardless the cause or the clinical settings in which these disorders appear [8].

The prototype of alveolar stem cell senescence-bronchiolar dysplastic proliferation/fibrosis is idiopathic pulmonary fibrosis (IPF). The pathogenetic mechanisms leading to lung parenchymal derangement typically observed in this disorder are only partly elucidated. The cross talk between different cell components is provided by an extremely complex exchange of molecular signals, depending on a discrete number of pathways, signaling molecules, receptors, and transcription factors, including among others TGF-beta, Wnt, Notch, BMP, SOX2, and Hedgehog signaling pathways that are also involved in lung development and cancer. Their aberrant expression has been proposed as relevant in the pathogenesis of IPF [9, 10]. In this pathogenic scheme, alveolar stem cell failure is the crucial event. When precursor cell exhaustion is reached for the concurrent action of intrinsic defects (genetic predisposition such as TERT/TERC mutations, mutations of genes coding for surfactant proteins, etc.) and extrinsic agents (smoke, air pollution), the damage caused to alveolar epithelial cells by endoplasmic reticulum and oxidative stress at sites of maximal mechanical stress in lower lobes cannot be properly repaired. Frustrated attempts of epithelial regeneration trigger an exaggerated activation of proliferative and/or antiapoptotic signals. Senescent aspects and oncogene-induced senescence features have been identified in this context. In IPF senescent alveolar stem cells behave as robust secretors that interfere [“senescence-associated secretory phenotype” (SASP) or “senescence-messaging secretome” (SMS)] with the correct tissue renewal. When this wave of damage reach the bronchiolar epithelial basal cells, these cells start to proliferate, and bronchiolar proliferative lesions (these lesions are unproperly called “honeycomb changes”) represent the irreversible phase in IPF remodeling as also suggested by the recent demonstration of abnormal production of mucins in bronchiolar cysts. There are evidences that a common polymorphism in the promoter of MUC5B gene is a predisposing factor for IPF development [11–13].

1.3 Clinical History

Patients should be divided in different subsets mainly considering two elements: how the disease manifests (Table 1.2) and if accompanying

signs/symptoms are limited to the respiratory system or are also systemic and/or extrathoracic. Patients with acute lung injury (having usually as histological background diffuse alveolar damage without or with eosinophils, capillaritis, and alveolar hemorrhage or organizing pneumonia with accumulation of fibrin) tend to seek medical attention for rapidly progressive dyspnea. In this group the more characteristic disorders are acute eosinophilic pneumonia (AEP), rapidly progressive cryptogenic organizing pneumonia (COP), acute interstitial pneumonia, subacute hypersensitivity pneumonitis (HP) and a not yet clear entity or group of entities called acute fibrinous and organizing pneumonia (AFOP), and collagen vascular disorders (mainly antisynthetase syndrome and systemic lupus erythematosus) or ANCA-associated vasculitis. Rarely idiopathic pulmonary fibrosis may manifest with acute respiratory failure being acute exacerbation the first clinical overt event. The prototype of chronic DPLD is IPF, manifesting with long-lasting dry cough and exertional dyspnea. Fever, asthenia, and weight loss are frequently present when a diffuse parenchymal lung disease has an acute/subacute presentation or when it has a manifestation of a systemic disorder. Extrathoracic manifestations may draw attention addressing toward a diagnosis of a systemic disorder: skin and/or articular lesions or alterations in other organs in collagen vascular diseases; vasculitis, oculocutaneous albinism, and colitis in Hermansky-Pudlak disease; dyskeratosis, early hair graying, in telomeropathies; and fibrofolliculomas in Birt-Hogg-Dubè syndrome. Some forms present with short and episodic events (mainly dyspnea or dry cough with or without fever). In this group HP and COP are most frequently represented. The age is an important diagnostic clue. Sarcoidosis, lymphangioleiomyomatosis (LAM), and hereditary forms such as Hermansky-Pudlak syndrome, telomeropathies, and Langerhans cell histiocytosis (LCH) present usually in the first 40–50 years of age. IPF is a disorder of elderly (mean age at diagnosis 64). Some disorders are strictly related to gender. LAM is almost always limited to women. Also lung injury associated to collagen vascular diseases is, except rheumatoid arthritis, more frequently observed in females. Pneumoconioses is, because of professional exposure, more frequently observed in males. Familial history is fundamental to identify subjects affected by neurofibromatosis and tuberous sclerosis. Early gray hair, the presence of cryptogenic liver cirrhosis, or myelodysplastic syndrome in the family suggest a diagnosis of telomeropathy. Hermansky-Pudlak, Gaucher and Niemann-Pick diseases have an autosomal recessive pattern of inheritance. Finally smoking habit (IPF is mainly observed in smokers or former smokers, and other disorders—LGH, pulmonary alveolar proteinosis, lung hemorrhage due to Goodpasture syndrome and the so-called smoking-related DPLDs—are almost always detected in current or former smokers), professional exposure, assumption of licit and illicit drugs [cocaine is the cause of a variety of lung injuries; a long list of drugs have been associated to a variety of diffuse lung injury patterns (www.pneumotox.com)], and the immunologic status [common variable immunodeficiency, HIV infection) should be elicited from all patients with known or suspected DPLD.

1.4 Physical Examination

Teleinspiratory, bibasilar, and dry crackles are typically auscultated in patients with IPF or fibrosing interstitial pneumonias and very rarely in granulomatous disorders. Scattered late inspiratory high-pitched rhonchi, called squeaks, are heard in patients with bronchiolitis. Hemoptysis may be observed in patients with vasculitis but also in sarcoidosis (mainly when it is associated to lung aspergillomas). Digital clubbing is a marker of fibrotic DPLD and may precede the appearance of the lung disease for years. Extrathoracic signs are present in patients with collagen vascular disease, and some of them are quite specific [Gottron nodules, mechanic's hands and heliotrope rash in dermatomyositis, cutaneous and oral ulcerations, panniculitis and alopecia in anti-melanoma differentiation-associated gene 5 (MDA5) dermatomyositis]. Tattoo or scar

granulomatous reaction is a specific sign of sarcoidosis. Pneumothorax may be a manifestation of LAM or LCG.

1.5 Laboratory Testing

Some laboratory tests are quite specific enabling a definite diagnosis. Identification of obligatory pathogens on body fluids (*Mycobacterium tuberculosis*), autoantibodies against GM-CSF in autoimmune alveolar proteinosis, D-VEGF in lymphangioleiomyomatosis, and blood or bronchoalveolar lavage (BAL) beryllium lymphocyte proliferation test (BeLPT) is used to confirm the beryllium as cause of DPLD. Other tests may strongly support the diagnosis already hypothesized on the basis of clinical and radiological features: autoantibodies seen in association with antisynthetase syndrome (anti-Jo-1, anti-PL-7, anti-PL-12, anti-EJ, anti-OJ, etc.), anti-MDA5 antibodies, ANCA autoantibodies, serum monoclonal heavy chains, or Bence Jones proteins in urine. However the presence of autoantibodies does not automatically address to a diagnosis of an "autoimmune" disorder as autoantibodies may merely be considered an epiphenomenon of senescence. Finally some laboratory findings may simply represent a clue to hypothesize specific disorders. Precipitins indicate specific exposures; a huge increase of LDH is typically present when intravascular lymphoma is the cause of the interstitial infiltrates. Eosinophils in peripheral blood are significantly increased in chronic eosinophilic pneumonia or in hypereosinophilic syndrome. Lymphopenia is a marker of advanced HIV infection, but it may be observed also in cases of lymphomatoid granulomatosis. Decreased levels of immunoglobulins suggest a diagnosis of common variable immunodeficiency. Hemophagocytic syndrome (fever, hepatosplenomegaly, blood cytopenia, increased liver enzymes, hypofibrinogenemia, high triglyceride levels, and hemophagocytic features in the bone marrow) may be associated to NK nasal type lymphoma appearing first in the lungs.

In well-known genetic disorders manifesting with lung infiltrates, specific mutations are already clearly identified (i.e., Birt-Hogg-Dubè syndrome, Hermansky-Pudlak syndrome, neurofibromatosis, tuberous sclerosis, etc.). Furthermore genetic tests are increasingly becoming an important piece of information for identification of some forms of familial or sporadic DPLD. Telomere-related mutations account for up to 10% of sporadic IPF, 25% of familial IPF, and 10% of connective tissue disease-associated interstitial lung disease. Furthermore, single-nucleotide polymorphisms (SNPs) in TERT, TERC, OBFC1, and RTEL1, as well as short telomere length, have been associated with several DPLDs. Additionally, it was found that also SNPs in telomere-related genes are risk factors for the development of pulmonary disease. Mutations in gene coding for surfactant proteins A1, A2, and C and for ABCA3 are associated to peculiar forms of interstitial lung disease. The MUC5B promoter variant rs35705950 accounts for a substantial risk of developing IPF.

1.6 Pulmonary Function Tests

Most forms of diffuse parenchymal lung disease produce a restrictive defect with reduced total lung capacity, functional residual capacity, and residual volume. A minority of disorders are associated to an obstructive defect (lymphangioleiomyomatosis, bronchiolitis, rarely in sarcoidosis, and hypersensitivity pneumonitis). Pulmonary function studies have been proved to have prognostic value in patients with IPF. The resting arterial blood gases may be normal, but hypoxemia is detected in the majority of cases even during the first visit. Usually hypocapnia precedes the appearance of hypoxemia at rest. A 6-min walking test or, more precisely, a cardiopulmonary test may reveal the disease in the early stage.

1.7 Chest Imaging

The radiograph in patients with suspected DPLD has substantial limitations due to the intrinsic defects of the technique. However a correct diagnostic hypothesis (based on the distribution of

the shadows and the prevalence of nodules, lines, or honeycombing) may be done in around 30% of cases. High-resolution CT scan is superior to the plain chest X-ray for higher definition of the images (elementary lesions) and the capacity to identify the distribution of the lesions in the structures of the secondary pulmonary lobules. The combination of these elements defines different reproducible patterns [14, 15]:

1. Septal pattern (linear pattern with preserved architecture)
2. Fibrotic pattern (linear pattern with distorted architecture)
3. Nodular pattern
4. Alveolar pattern
5. Tree in bud pattern
6. Cystic pattern
7. Dark lung pattern

A *septal* pattern is present when a network of white lines representing thickened perilobular septa is appreciable. Thickening of the sleeves wrapping the bronchovascular bundles may be identifiable as well. The white lines or the thickened sleeves around bronchovascular bundles may be regular, smooth, or irregular, and beaded, but the intralobular architecture is preserved. Hilar and mediastinal lymph node enlargement is frequently observed as an ancillary finding. An important diagnostic clue is represented by the preferential distribution of the lesions. This pattern may be observed in a variety of disorders: pulmonary edema due to heart failure, veno-occlusive disease, carcinomatous lymphangitis, sarcoidosis, lymphoproliferative disorders, Erdheim-Chester disease, and amyloidosis.

Fibrotic pattern is defined by the loss of volume, presence of irregular linear opacities in the intralobular zones, traction bronchiectasis and bronchiolectasis, and honeycomb changes. At the pulmonary interface, a pleural line with shaggy margins and connections with parenchymal irregular lines (the so-called interface sign) may be evident. When the honeycomb changes are predominant in the subpleural zones and mainly in the lower lobes, the descriptive term usual interstitial pneumonia (UIP) pattern is used. This pattern is observed mainly in IPF, collagen vascular disorders with lung involvement, idiopathic fibrosing nonspecific interstitial pneumonia (NSIP), chronic hypersensitivity pneumonitis, asbestosis, and chronic drug-induced lung disease. A subset of fibrotic pattern (called also "tug-of-war" pattern) is defined by the presence of irregular linear opacities stretching between the mediastinum and the thoracic boundaries, bridging over variably involved bronchi, fissures, and more generally anatomic structures and even pathologic elements found on their way. This pattern may be found in chronic sarcoidosis, berylliosis, and pleuroparenchymal fibroelastosis.

The *nodular* pattern is defined by the presence of multiple roundish opacities ranging from 2 to 10 mm. These nodules may be solid or may have a ground-glass density; they may be distributed along the lymphatic routes, in a random way, or may be centrilobular. Disorders that may have this pattern are subacute hypersensitivity pneumonitis, respiratory bronchiolitis, follicular bronchiolitis, Langerhans cell histiocytosis, sarcoidosis, silicosis, miliary tuberculosis, viral or fungal infections, and hematogenous metastases. Mainly infections, Langerhans cell histiocytosis and metastases may present cavitation (so-called "cheerios in the lung" pattern).

The *alveolar* pattern is characterized by an increase in pulmonary attenuation that obscures the vessels and the airway walls (alveolar consolidation). The bronchial lumen may remain visible inside the consolidation (air bronchogram). When the increase of lung attenuation does not cancel the vascular margins, the term ground-glass attenuation is used. Subsets included in this group are the so-called "crazy paving pattern" (a smooth, regular network of white lines superimposed on a background of ground-glass attenuation), the halo sign (a central area of consolidation surrounded by a halo of ground-glass attenuation), the reverse halo sign (a ring or crescent of dense consolidation that surrounds a core of ground-glass attenuation), and the perilobular pattern (poorly defined band-like opacities with an arcade-like or polygonal appearance with a pleural base). In this group are included all the disorders characterized by filling of distal

airways by cells, exudates, or proteins or, more rarely, diseases with a significant thickening of alveolar septa. The list is quite long: infectious pneumonia, organizing pneumonia (cryptogenic or secondary), alveolar proteinosis, lymphomas, mucinous adenocarcinoma, alveolar hemorrhage, pneumocystosis, acute and chronic eosinophilic pneumonia, acute interstitial pneumonia, acute respiratory distress syndrome, desquamative interstitial pneumonia, lipoid pneumonia, and nonspecific interstitial pneumonia.

The *tree in bud* pattern is characterized by centrilobular dense branching linear structures originating from a single stalk and often ending in a nodular form (thus resembling a budding tree). This pattern is typical of cellular bronchiolitis (the most frequent being infectious bronchiolitis). Rarely a similar pattern may be due to thrombotic neoplastic microangiopathy.

Cystic pattern is present when multiple roundish, well-defined air-containing spaces are variably scattered throughout the lung parenchyma. Distribution of the cysts, their shape, association with nodules, or content (usually it is air but in infections mainly they may contain fluid) are useful information for discriminating between different disorders. Disorders that typically have this pattern are Langerhans cell histiocytosis, lymphangioleiomyomatosis, Birt-Hogg-Dubè syndrome, cystic metastases, lymphocytic interstitial pneumonia (LIP), and pneumocystosis. Rarely hypersensitivity pneumonitis and bronchiolitis (constrictive or proliferative) may appear with cysts in the lung.

When variable portions of lung parenchyma present a reduced attenuation to the X-rays, the descriptive term *dark lung* is used. When patchy the aspect is called mosaic perfusion. This aspect is due to lower perfusion, and lower perfusion recognizes two causes: vascular obstruction or bronchiolar obstruction. In patients with "dark lung" secondary to bronchiolar disease, hyperlucent areas of lobule size are common, usually with well-defined margins. When the disorder is characterized by vascular obstruction, the areas of low attenuation are often larger and poorly defined. The differentiation between vascular versus bronchiolar origin of the decreased attenuation may be done also using the dynamic CT (CT expiratory scan compared to inspiratory CT scan). In the dark lung of vascular origin, a homogenous increase in density occurs everywhere. On the other hand, when the dark lung is due to constrictive bronchiolitis, the contrast increases (expiratory air trapping). The list of diseases presenting with dark lung includes chronic thromboembolism, primary pulmonary hypertension, constrictive bronchiolitis, and diffuse idiopathic pulmonary neuroendocrine cell hyperplasia. In the last disorder small, well-defined, randomly distributed nodules may also be identified. These nodules represent histologically tumorlets or even small carcinoids.

A significant number of diseases may manifest with combined patterns, or they may present different patterns during the course. The so-called *headcheese* pattern is characterized by areas of mosaic oligemia along with ground-glass attenuation or alveolar consolidation. It may be mainly observed in subacute hypersensitivity pneumonitis or *mycoplasma pneumoniae* pneumonia. Acute exacerbation of IPF presents with areas of ground-glass attenuation or even alveolar consolidation superimposed on a fibrotic pattern. Langerhans cell histiocytosis has a nodular pattern in the active phase and appears cystic or even with features of "dark" lung in the fibrotic stage.

1.8 The Invasive Diagnostic Procedures

Bronchoalveolar lavage (BAL) is a safe procedure that may even been carried out in ventilated patients [16]. The fluid recovered by the maneuver may be subjected to a variety of investigations: microbiological tests, cytological analysis and cell count, flow cytometry analysis, and assessment of various biochemical mediators. In the daily clinical practice, microbiological tests, cytological analysis, cell count, and flow cytometry are routinely done. BAL may be diagnostic in a minority of cases when specific "signatures" may be recognized: alveolar

proteinosis, Langerhans cell histiocytosis (when >3.5% of macrophages express CD1a protein or Langerhin), epithelial neoplasms, low-grade B-cell lymphomas, infections (pneumocystosis, etc.), atypical type II pneumocytes in diffuse alveolar damage, hemosiderin laden macrophages in alveolar hemorrhage, macro-vacuolated, oil red positive histiocytes in lipoid pneumonia, and asbestos bodies in exposed subjects. Cytological and immunophenotypical profiles may represent a clue for the final diagnosis: lymphocytosis in granulomatous disorders, in drug-induced lung disorders, or in viral infections, mixed pattern (increase of lymphocytes and, in a lesser degree, of eosinophils and neutrophils associated to scattered mast cells) in organizing pneumonia, eosinophilia in chronic and acute eosinophilic pneumonia or in desquamative interstitial pneumonitis, neutrophilia (+/− scattered eosinophils) in fibrosing processes or in bacterial infections, foamy macrophages in amiodarone lung-induced injury or in Niemann-Pick disease, and "wrinkled paper" macrophages in Gaucher disease.

Bronchial biopsy may be diagnostic in carcinomatous lymphangitis, sarcoidosis, and even in low-grade B-cell lymphomas.

Transbronchial lung biopsy with flexible forceps is also a safe procedure (the more frequent complication being pneumothorax, observed in around 5% of cases; the most life-threatening complication being bleeding observed in less than 1% of cases). With this approach the sampling is mainly in the centrilobular parenchyma. However samples so obtained are tiny and usually with crush artifacts. Therefore it is diagnostic mainly in sarcoidosis, carcinomatous lymphangitis, organizing pneumonia, chronic eosinophilic pneumonia, diffuse alveolar damage, subacute hypersensitivity pneumonitis, low-grade B-cell lymphomas. Very rarely the morphological pattern UIP (with patchy fibrosis and fibroblastic foci with or without honeycomb changes) may be identified in these smaller samples. However recently it has been suggested that with the use of a genomic-based machine trained to identify a specific molecular signature identified from RNA sequencing on tiny transbronchial lung biopsy samples, the sensitivity of the procedure increases significantly. In this study the classifier identified UIP pattern in TBLB with an 88% specificity and 70% sensitivity. Considering all the DPLDs as a group, transbronchial lung biopsy appears to have a diagnostic yield varying from 30 to 70%, being it higher in disorders with simple morphology and in those located mainly in the centrilobular zones.

Surgical lung biopsy and nowadays video-assisted thoracoscopy was and is considered the gold standard for obtaining decent lung tissue samples to reach a specific morphological diagnosis. This approach is suggested when a morphological diagnosis of interstitial pneumonia (UIIP, NSIP, DIP, etc.) need to be validated, or when HRCT scan documents scattered nodules in the subpleural zones. However complications related to this approach are no longer negligible. Mortality is around 2% in 1 month, and it increases significantly when there is a clinical suspicion of IPF or collagen vascular disease, in elderly (patients >67 years) or with a reduced lung function (DLCO <45% of the predicted value). Mortality rate is significantly higher (around 16%) for not elective admissions, i.e., when the procedure is carried out in patients with rapidly decline of lung function. Morbidities are represented by subcutaneous emphysema, prolonged air leakage, empyema, chronic thoracic pain, and wound paraesthesia. These complications seem to be significantly reduced when a uniportal tubeless video-assisted thoracoscopy is applied. The limitation of this approach is, however, that areas easy to sample are mainly located on the lingula, the middle lobe, or on the anterior basal segment of the lower lobes.

Transbronchial cryobiopsy is a recently developed technique to obtain larger portions of lung tissue in an attempt to improve the yield of diagnostic tissue in lieu of an open surgical lung biopsy [17–19]. The main histologic benefits of cryobiopsy compared to transbronchial lung biopsy are the capacity to obtain larger and well-preserved samples. Complex morphological patterns such as usual interstitial pneumonia (UIP) may be recognizable.

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