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DIFFUSE PARENCHYMAL LUNG DISEASE

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Summary

Diffuse parenchymal lung disease (DPLD) is a group of diseases that have the common characteristic of involving the pulmonary parenchyma diffusely. The pulmonary parenchyma consists of all structures distal to the terminal bronchiole. DPLD are numerous, there are some 150 different entities that qualify for the group. Most of these diseases are diagnosed according to common algorithm, but the etiology, prognosis and therapy are quite different. Lung transplantation is the ultimate therapeutic option for some of these diseases, most frequently it is the idiopathic pulmonary fibrosis (IPF).

Keywords: diffuse parenchymal lung disease; lung transplantation; idiopathic pulmonary fibrosis.

INTRODUCTION

Diffuse parenchymal lung disease (DPLD) comprises a number of clinical disorders [1] that affect the alveoli, alveolar septa, respiratory bronchioli, blood vessels, lymph vessels, i.e. the pulmonary parenchyma. These disorders are caused by numerous known agents, may be idiopathic, granulomatous or rare (*Table 1*).

The known causes are diverse inorganic agents leading to pneumoconioses (asbestos, silica, etc.), organic, causing hypersensitivity pneumonitis (farmer's lung, bird fancier's lung, etc.), drugs, irradiation, toxic gases and fumes, bacteria, fungi, viruses, protozoa, and parasitic infections or infestations. When treating a patient with DPLD the clinician must carry out a detailed occupational and environmental history [2] because organic dusts are an increasing cause of occupational exposure and respiratory disease, pneumoconiosis still accounts for a significant proportion of ILDs, new sources of exposure and newly identified agents are emerging and finally more knowledge regarding the toxicological effects of nanoparticles is funda-

mental. The exposure to illicit drugs and personal habits should be considered. The results of recognition of the offending agent result in its avoidance and prevention. For a DPLD to be considered idiopathic all the possible etiologic factors, including environmental or occupational, have to be excluded.

Table 1. Classification of Diffuse Parenchymal Lung Disease (DPLD)

DPLD OF KNOWN CAUSE
• Anorganic particles -pneumoconiosis • Organic particles –hypersensitivity pneumonitis • Gases. • Fumes • Drugs. • Irradiation • Microbes
IDIOPATHIC INTERSTITIAL PNEUMONIAS
• Idiopathic pulmonary fibrosis (IPF), • Non-specific interstitial pneumonia (NSIP), • Organizing pneumonia (OP), • Acute interstitial pneumonia (AIP), • Desquamative interstitial pneumonia (DIP) • Respiratory bronchiolitis-interstitial lung disease (RB-ILD), • Lymphoid interstitial pneumonia (LIP) • Pleuropulmonary fibroelastosis (PPFE)
GRANULOMATOSIS
• Sarcoidosis • Granulomatosis with polyangitis (Wegener's granulomatosis,) • Churg-Strauss Syndrome • Necrotizing sarcoid granuloma • Lymphomatoid granulomatosis • Bronchocentric granulomatosis • Langerhans cell histiocytosis (LCH) • Erdheim-Chester disease
RARE DPLD
• Alveolar proteinosis • Alveolar mikrolithiasis • Amyloidosis • Eosinophilic pneumonia • Lymphangioleiomyomatos(LAM) • Idiopathic pulmonary hemosiderosis • Pulmonary manifestation of connective tissue diseases

Idiopathic interstitial pneumonias according to new classification [3] (*Table 2*) comprise of several entities, among them there is a new entity called pleuropulmonary fibroelastosis. Also, of great help to the practicing physicians is the inclusion of a category of unclassifiable group of DPLD. The everyday life experience resulted in this change, because almost 30% of these diseases even after the most complete and thorough examination, stay unclassifiable.

The third group consists of diseases that histologically show the pattern of *granuloma*, like sarcoidosis.

And finally, the fourth group consists of diverse, mostly *rare diseases* among them diffuse connective tissue diseases (systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, ankylosing spondylitis, mixed connective tissue), lymphangioleiomyomatosis, alveolar proteinosis and alveolar microlythiasis. Some of these diseases are benign and self-limiting; others are chronic, progressive, irreversible, and fatal. The lung manifestation may be the one manifestation of a systemic process. Or it may be the only organ affected. All DPLDs, however, have certain common clinical, imaging, and physiologic features that should be recognized.

Table 2. Revised ATS/ERS classification of idiopathic interstitial pneumonias (IIPs)[3]

MAJOR IIPs
• Idiopathic pulmonary fibrosis
• Idiopathic non-specific interstitial pneumonia
• Respiratory bronchiolitis–interstitial lung disease
• Desquamative interstitial pneumonia
• Cryptogenic organizing pneumonia
• Acute interstitial pneumonia
RARE IIPs
• Idiopathic lymphoid interstitial pneumonia
• Idiopathic pleuroparenchymal fibroelastosis
UNCLASSIFIABLE IIPs*

*__Causes of unclassifiable idiopathic interstitial pneumonia include__ (1) inadequate clinical, radiologic, or pathologic data and (2) major discordance between clinical, radiologic, and pathologic findings that may occur in the following situations:(a) previous therapy resulting in substantial alteration of radiologic or histologic findings (e.g., biopsy of desquamative interstitial pneumonia after steroid therapy, which shows only residual nonspecific interstitial pneumonia [153]);(b) new entity, or unusual variant of recognized entity, not adequately characterized by the current American Thoracic Society/European Respiratory Society classification(e.g., variant of organizing pneumonia with supervening fibrosis) (79); and(c) multiple high-resolution computed tomography and/or pathologic patterns that may be encountered in patients with idiopathic interstitial pneumonia.

COMMON CLINICAL FEATURES

A thorough occupational, history of recent or past exposure to inorganic or mineral particles, or to organic dusts and animal antigens (pets) should be identified. Drugs and chemicals known to cause ILD, history of pulmonary infections (particularly HIV), immune disorders, and collagen vascular disorders should be inquired. A smoking history, the country of origin and recent travel history are often critical for establishing the diagnosis.

Dyspnea is the most frequent symptom of DPLD. At first, dyspnea is evident on exercise; later it progresses to breathlessness at rest. The duration of progressive dyspnea usually ranged from months to years. Dyspnea is commonly associated with dry cough, particularly on exertion, and fatigue is frequently present. Fever, chills, and weight loss are the main symptoms in interstitial pulmonary infections but may also occur in collagen vascular disorders.

In 10% to 15% of the patients who have DPLD, tachypnea is present. Auscultation of the lungs reveals end-inspiratory bibasilar "Velcro®-like" crackles. Wheezing is present in 20% of the patients with hypersensitivity pneumonitis as well as the squawk, the ominous auscultatory sign, typical for advanced HP. Digital clubbing is common in idiopathic pulmonary fibrosis (IPF) and asbestosis.

The most helpful *diagnostic procedures* are radiographic imaging, chest X- ray and high resolution computed tomography (HRCT), bronchoscopy with bronchoalveolar lavage and transbronchial lung biopsy, lung function tests and finally the open lung biopsy.

Chest roentgenogram is abnormal in more than 90% of the patients who have DPLD.

High-resolution computed tomography (HRCT) [4] is superior to conventional radiography in delineating the presence and extent of parenchymal involvement in DPLD. HRCT is also useful in characterization of the pattern of the disease, narrowing the differential diagnosis, as a guide to the site of biopsy and as an aid in the follow up of the patients.

As a result of inflammation and fibrosis of the alveolar and the vicinal structures, the lung become stiff and have low lung compliance. Lung volumes are reduced, diffusing capacity is impaired, and alveolar-to-arterial oxygen difference is widened either at rest or exercise or both. The large airway function usually remains normal, but the small airway dysfunction is often present. Airway obstruction is prominent in some interstitial lung disorders. The exercise testing in everyday management of DPLD is very useful.

Laboratory and immunologic tests are of limited value in establishing the cause of ILD.

L*ung biopsy* should be performed in diffuse parenchymal lung disease. One should attempt to obtain a lung biopsy early in the course of the disease, particularly in a young and middle-aged patient. Transbronchial biopsy is useful in the diagnosis of sarcoidosis, alveolar proteinosis, miliary tuberculosis, and *Pneumocystis* pneumonia. The procedure has limitations because the amount of tissue obtained is often insufficient for extensive diagnostic studies. Surgical open lung biopsy is being replaced by video assisted thoracoscopic (VAT) lung biopsy. The diagnostic accuracy of thoracoscopic lung biopsy is equivalent to open lung biopsy. Furthermore, peri-operative morbidity, length of hospital stay, and duration of chest pain are significantly lower in patients who undergo thoracoscopic lung biopsy. Recently, it has been reported that the awake VATS lung biopsy is easily feasible by regional anesthesia and resulted in low morbidity, excellent diagnostic yield, short hospital stay, and low cost [5].

Bronchoalveolar lavage (BAL) [6] has expanded our understanding of the pathogenesis of many interstitial lung diseases. The minimally invasive bronchoalveolar lavage (BAL) procedure is an important diagnostic instrument that can facilitate the diagnosis of various diffuse parenchymal lung diseases (DPLD). BAL fluid white blood cell profiles are analyzed, malignant cells looked for, and in certain circumstances particular stains are performed to detect yet other cell types. Additionally, BAL can play a very important role in the diagnosis of respiratory tract infections. All these analyses are usually readily performed in a moderately equipped cytological laboratory.

In the *differential diagnosis* of diffuse parenchymal lung disorders, sarcoidosis, pulmonary affection of connective tissue diseases, idiopathic pulmonary fibrosis, and organizing pneumonia are the most common and are responsible for about two thirds of all cases [7].

MANAGEMENT

The management of diffuse parenchymal lung disease depends upon the precise diagnosis, and disease extent, activity and severity. Exclusion of exposition, etiologic therapy with antibiotics, antifungal agents or antituberculosis drugs, immunosuppressants (corticosteroids, azathioprine, cyclophosphamide, methotrexate, leflunomide), biologicals and immunomodulators (imfliximab, interferons, rituximab, nintedanib), antifibrotics (pirfenidon, thalidomide, penicilamin) are all the agent of choice in specific circumstances. Symptomatic therapy (oxygen, antitusics) is used in advanced cases.

Pulmonary rehabilitation is also important. The aim of pulmonary rehabilitation is not only to improve daily functioning but also to help people with DPLD live full, satisfying lives. To that end, pulmonary rehabilitation programs focus on physical exercise, to improve the endurance, breathing techniques that improve lung efficiency, emotional support and nutritional counseling

Lung transplantation (LTx) offers a survival benefit in carefully selected patients with DPLD. Indications for lung transplant referral among fibrotic lung disease [8] are histologic or radiographic evidence of usual interstitial lung disease (UIP) or nonspecific interstitial pneumonia (NSIP), FVC<60% predicted, diffusion capacity <39% of predicted (UIP) or <35% of predicted (NSIP), drop in FVC by ≥10% or diffusion capacity by ≥15% over 6-month period, drop in SaO2 on pulse oxymetrya by <88% on 6-minute walk test, high-resolution CT imaging with honeycombing (fibrous score>2), and pulmonary hypertension.

DPLD most frequently subjected to lung transplantation are the diseases [9] with UIP like HRCT/PHD pattern (~ 80 % of all LTx for DPLD) like idiopathic pulmonary fibrosis (IPF), chronic hypersensitivity pneumonits (HP), connective tissue disease (CTD) and miscellanea („lung fibroses", unclassifiable DPLD, etc.). Diseases with NSIP like HRCT/PHD pattern (~ 4 % 0f all LTx), sarcoidosis (~2.5 of all LTx) and rare disease: Langerhans cell histiocytosis (LCH), microlithiasis, lymohangioleiomyomatosis (LAM), pulmonary alveolar proteinosis (PAP) and others, are less frequent thus less frequently subjected to LTx.

Idiopathic pulmonary fibrosis comprises some 23% of all the indications for lung transplantation, raising its proportion in that respect in recent years.

IDOPATHIC PULMONARY FIBROSIS

Idiopathic pulmonary fibrosis (IPF) is archetypal example of «lung fibrosis». It is the most frequent of all "fibroses".

IPF is defined as a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause, occurring primarily in older adults, limited to the lungs, and associated with the histopathologic and/or radiologic pattern of usual interstitial pneumonia (UIP) [10].

The diagnosis of IPF requires: a. Exclusion of other known causes of interstitial lung disease (ILD) (e.g., domestic and occupational environmental exposures, connective tissue disease, and drug toxicity). b. The presence of a UIP pattern on high-resolution computed tomography (HRCT) in patients not subjected to surgical lung biopsy. c. Specific combinations of HRCT and surgical lung biopsy pattern in

patients subjected to surgical lung biopsy. The major and minor criteria proposed in the 2000 ATS/ERS Consensus Statement have been eliminated.

The prevalence of IPF in Europe is 2-23/100.000, Croatia 8/100.00, and in patients above 75 years 177/100.000. The mean length of survival after diagnosis is 3.2–5 years.

Although the disease is idiopathic, many causes or facilitating circumstances are under investigation. Exposure to an inciting agent (smoke, environmental pollutants, environmental dust, viral infections, gastroesophageal reflux disease, chronic aspiration), genetic mutations (surfactant protein C, gene encoding mucin 5B (MUC5B), mutant telomerase known to be associated with familial idiopathic pulmonary fibrosis and telomere shortening which also occurs with aging and can also be acquired are in the focus of extensive research. This telomere shortening could promote the loss of alveolar epithelial cells, resulting in aberrant epithelial cell repair, and therefore should be considered as another potential contributor to the pathogenesis of idiopathic pulmonary fibrosis. Today the aging lung is in the focus of several investigations, not only regarding the pathogenesis of IPF, but also lung cancer and COPD [11].

Clinical presentation most often consists of slowly progressive breathlessness, tightness of the chest and dry cough, which does not respond to antitussive agents. The symptoms are usually present for more than 6 months before presentation. Physical examination reveals bilateral, bibasilar, end-inspiratory fine crackles on auscultation ("Velcro®-like" crackles) and digital clubbing .

The diagnostic approach includes performance of radiological imaging techniques, the plain radiograph of the chest and particularly the high resolution computed tomography (HRCT), assessment of pulmonary function and laboratory tests, and open lung biopsy in those who do not fulfill the diagnostic criteria.

Pulmonary function tests typically reveal restrictive ventilatory changes (reduced vital capacity [VC], and total lung capacity [TLC]) at some point in the course of the disease. The DLco is reduced and may precede the reduction of lung volumes. The respiratory arterial blood gases may be normal, or they may reveal mild hypoxemia. With cardiopulmonary exercise testing early abnormalities of gas exchange could be detected. Pulmonary hypertension rarely occurs at rest, but it is common during exercise.

The plain radiograph is the screening test to detect the presence of IPF, although it may be normal in about 10% of the patients. *HRCT technique* has changed the diagnostic procedure in these patients as it allows earlier diagnosis and helps to narrow the differential diagnosis. The characteristic HRCT in IPF is the summoned feature of different patterns that together make the usual interstitial pneumonia (UIP) ima-

ge ; the honeycombing, reticulation, traction bronchiectasis, architectural distortion and volume loss with no other specific patterns (granuloma, ground-glass, cysts, etc.), (*Figure 1*), which are inconsistent with UIP pattern [12].

Transbronchial lung biopsy is not helpful in making the diagnosis of IPF, but it can help to exclude some other entities that are considered in differential diagnosis.

Open lung biopsy, or video assisted thoracoscopic (VAT) lung biopsy are performed in the minority of patients. The usual interstitial pneumonia (UIP) is the pathological abnormality essential to the diagnosis of IPF; it refers to a morphologic entity defined by a combination of [1] patchy interstitial fibrosis with alternating areas of normal lung, [2] temporal heterogeneity of fibrosis characterized by scattered fibroblastic foci in the background of dense acellular collagen, and [3] architectural alteration due to chronic scarring or honeycomb change.

It is evident that some *therapies* are effective in the treatment of IPF. Pirfenidone (Esbrie) [13] and Nintedanib (Ofev) [14] show statistically significant improvement in clinical trials, patients taking either drug experienced significantly reduced declines in forced vital capacity compared with patients who received placebo [15].

Future trials are therefore unlikely to use placebo as a control group for ethical reasons. Future clinical assessment will probably include add-on trials in which a new drug is combined with an intervention with established efficacy; this development is in turn likely to herald the use of combination regimens in clinical practice [16].

The combination of inhalation NAC and pirefenidon showed that the progression-free survival PFS) in IPF was longer in the NAC plus pirfenidone group than in the pifenidone group [17].

GER medications due to high prevalence of gastroesophageal reflux (GER) showed that the use was associated with a longer survival time, additionally, patients taking GER medications had a lower fibrosis score on HRCT.

Other recommendations are to quit smoking, oxygen therapy to maintain a saturation of at least 90% at rest, with sleep, and with exertion, and vaccination against influenza and pneumococcal infection should be encouraged in all patients with idiopathic pulmonary fibrosis.

If all the earlier mentioned interventions fail, the patient deteriorates, and if the patient accomplishes the indications for lung transplantation he will be referred to the procedure.

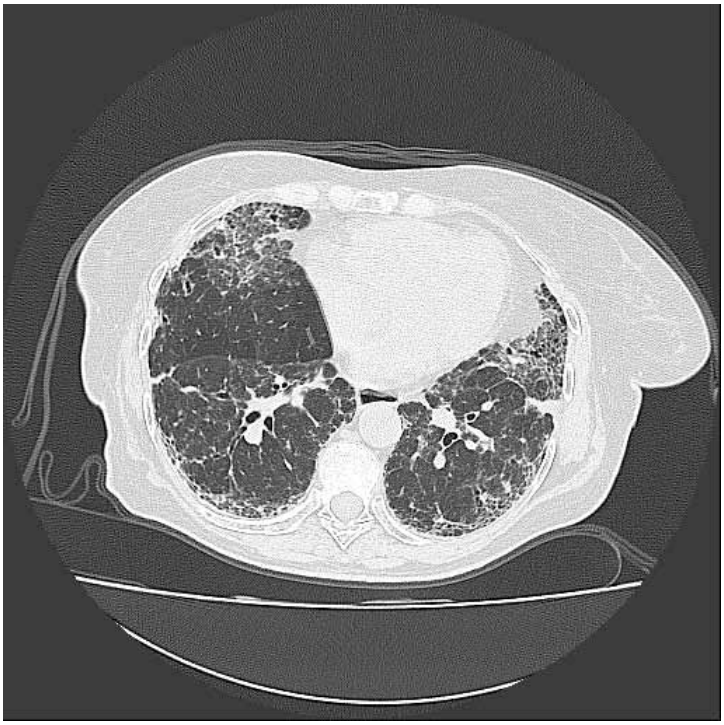

Figure 1. Typical high resolution computed tomography (HRCT) scan in idiopathic pulmonary fibrosis (IPF)

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Sažetak

Difuzne bolesti plućnog parenhima

Difuzne bolesti plućnog parenhima su grupa bolesti kojima je zajednička osobina da difuzno zahvaćaju plućni parenhim. Plućni se parenhim sastoji od svih struktura koje se prostiru distalno od terminalnih bronhiola. Ove su bolesti brojne, pa tako čak oko 150 različitih entiteta zadovoljava kriterije uključivanja u ovu skupinu bolesti. Dijagnoza većine ovih bolesti postavlja se prema zajedničkom dijagnostičkom algoritmu, ali su etiologija, prognoza i terapija vrlo različite. Transplantacija pluća krajnja je terapijska opcija za neke od ovih bolesti, a najčešće se zahvat se vrši u bolesnika s idiopatskom plućnom fibrozom.

***Ključne riječi**:* difuzne bolesti plućnog parenhima; transplantacija pluća; idiopatska plućna fibroza.

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