

Diffuse Parenchymal Lung Disease: A Practical Approach

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Abstract

Diffuse parenchymal lung disease is a term we have given to a heterogeneous group of clinical entities that share the following features: dyspnea, hypoxemia, restrictive ventilatory defect, and the presence of bilateral diffuse pulmonary infiltrates on the chest roentgenograms. This review article provides some clinical hints to help in the diagnostic approach to these various conditions, using common clinical tools: medical history, physical examination, chest x-ray, pulmonary function tests, and bronchoalveolar lavage.

INTRODUCTION

Interstitial lung disease (ILD) is a term given to a heterogeneous group of clinical entities^{1,2} that share the following features: dyspnea as the main symptom; hypoxemia; restrictive ventilatory defect pattern in pulmonary function tests; and the presence of reticular, nodular, reticulonodular, or ground glass-appearing infiltrates on chest roentgenograms. However, "interstitial lung disease" is a misnomer, because this condition affects not only the interstitium but also the alveolar space and sometimes the airways. We consequently think that the term diffuse parenchymal lung disease (DPLD) is more appropriate.

CLASSIFICATION

If we were to attempt to establish a complete differential diagnosis list and to enumerate all the causes of DPLD, we could easily come up with more than a hundred potential etiologies.³ It is therefore advisable to classify the causes into certain general groups, as follows: DPLD from infectious causes (e.g., *Pneumocystis carinii* pneumonia [PCP], cytomegaloviral pneumonia, and miliary tuberculosis); bacterial infections tend not to cause DPLD. Dust-related disease, involving either inorganic dust (e.g., asbestosis and silicosis) or organic dust (e.g., hypersensitivity pneumonitis [HSP; also known as extrinsic allergic alveolitis]). Collagen vascular diseases (CVD) with or without vasculitis. Drug-induced lung disease, either idiosyncratic (e.g., after administration of phenytoin, penicillin, or nitrofurantoin) or following a more predictable and dose-related pattern (e.g., after administration of

bleomycin, interleukin-2, amiodarone, busulfan, or methotrexate).^{4,5} Neoplastic disease with a lymphangitic spread pattern or bronchoalveolar cell carcinoma. Granulomatous disease, either infectious or noninfectious (e.g., sarcoidosis, berylliosis [which mimics sarcoidosis], HSP, histoplasmosis, and tuberculosis. Idiopathic pulmonary fibrosis (IPF) (sometimes called cryptogenic fibrosing alveolitis).⁶ Hereditary disorders (e.g., cystic fibrosis, tuberous sclerosis, alveolar microlithiasis, and bronchiectasis [dyskinetic cilia syndromes]). Miscellaneous diseases (e.g., eosinophilic granuloma [EG], lymphangioleiomyomatosis [LAM], pulmonary alveolar proteinosis, and eosinophilic lung disorders).

CLINICAL APPROACH

The first steps in the work-up of a patient with DPLD are to take a thorough medical history and to perform a thorough physical examination, including pulmonary function tests, occupational history, and to review the previous radiological examinations.

The medical, occupational, and hobby histories will establish the chronicity of the disease and any family history of lung disease or collagen vascular disorder⁷ and may lead to consideration of such hereditary conditions as cystic fibrosis, tuberous sclerosis, or even familial IPF. An acute clinical situation will make us consider pulmonary edema (congestive heart failure [CHF] or adult respiratory distress syndrome) or diffuse alveolar hemorrhage. Any underlying disease with potential involvement of the lungs will induce us to see the chest x-rays from a different perspective, e.g., CHF (pulmonary edema with not-so-evident enlargement of

the cardiac silhouette), emphysema (which may appear similar to DPLD on x-rays because of crowding of the vessels displaced by overinflated areas), and rheumatological conditions. Any history of cancer, radiation therapy and even the outline of the radiation portal are to be elucidated in an attempt to establish any relationship with the new radiological abnormalities. Consideration of a history of cigarette smoking is also important, since a cause-and-effect relationship has been hypothesized between smoking and some DPLDs such as EG, Goodpasture's syndrome, respiratory bronchiolitis, pulmonary alveolar proteinosis, and amiodarone-induced lung toxicity. A complete list of all drugs taken must be compiled, including not only regular medications but also drugs taken occasionally or recreational drugs.

Although symptoms of DPLD vary widely, the most common presentation is dyspnea. Cough and wheezing suggest such bronchocentric diseases as sarcoidosis, HSP, and LAM. Hemoptysis raises the possibility of vasculitis, necrosis and diffuse alveolar hemorrhage. Chest pain is highly suggestive of sarcoidosis or CVD; if its onset does not coincide with the development of pneumothorax, probably as a result of granulomatous and vasculitic inflammation. Occasionally a characteristic external appearance suggests the diagnosis, as is the case for patients with tuberous sclerosis and neurofibromatosis.

Some signs, such as clubbing and crackles, are often features of advanced disease. Clubbing is seen most frequently in patients with advanced IPF and asbestosis but is also seen in patients with cystic fibrosis, bronchiectasis, or lung cancer; clubbing is almost never seen in patients with emphysema or sarcoidosis. Crackles are rarely heard in patients with bronchocentric diseases such as sarcoidosis or EG, but they are frequently detected in patients with IPF. The clinical search must consider signs of CHF in order to rule it out as a cause of the interstitial changes.

Most of the DPLDs have an indolent course, but if the patient experiences an acute presentation we should consider an infectious process, PCP, HSP, drug-induced pneumonitis, bronchiolitis obliterans organizing pneumonia (BOOP),⁸ CHF, diffuse alveolar hemorrhage, or acute eosinophilic pneumonia. It is also imperative to know the patient's immunological status and risk of acquiring certain infectious and noninfectious diseases. For example, the presence of neutropenia may lead us to think of disseminated aspergillosis or gram-negative septicemia/pneumonia; a B-cell immunodeficiency may indicate overwhelming infection

by encapsulated organisms or viruses; a T-cell immunodeficiency (e.g. in fludarabine-treated patients or patients with acquired immunodeficiency syndrome) may indicate PCP, Mycobacteriosis, or cytomegaloviral pneumonia.

Furthermore, for patients who have received a transplant, either solid organ or bone marrow transplantation, the physician must consider the phases after transplantation (early or late) and the presence or absence of graft-versus-host disease.

PULMONARY FUNCTION TESTS

Most of the DPLDs disclose a restrictive ventilatory pattern, low lung volumes, and reduced diffusing lung capacity in the pulmonary function tests (PFTs). However, some DPLDs may show obstructive patterns due to the bronchocentric nature of involvement; examples are sarcoidosis, EG, chronic HSP, some presentations of rheumatoid arthritis, LAM, tuberous sclerosis, silicosis, allergic bronchopulmonary aspergillosis, cystic fibrosis, and bronchiectasis.

CHEST RADIOLOGY

Another important initial step in the diagnostic approach is to review the entire series of chest x-rays to establish the degree of disease activity.

Both the distribution of the radiographical findings and the radiographical pattern are relevant in patients with DPLD. Diseases such as silicosis, EG, sarcoidosis (stages III and IV), HSP, mycobacterial infection, ankylosing spondylitis, and PCP in patients who have received aerosolized pentamidine prophylactically have a predilection for the upper lobes, whereas conditions such as asbestosis, desquamative interstitial pneumonitis (DIP), lymphocytic interstitial pneumonitis, connective tissue disorders, and BOOP have preference for the lower lobes.

The radiographic pattern also has discriminating power. An alveolar pattern is most frequently seen in pulmonary alveolar proteinosis, bronchoalveolar cell carcinoma, or HSP. Reticular pattern is most common in lymphangitic spread, asbestosis, or scleroderma. A miliary pattern is seen in patients with tuberculosis, histoplasmosis, or varicella pneumonia. Hilar involvement is most commonly seen in patients with sarcoidosis, berylliosis, lymphoproliferative diseases, or CVD; hilar involvement is also occasionally seen in infectious processes but almost never seen in HSP. Kerley-B lines may be seen in patients with lymphatic

congestion of CHF, lymphangitic carcinomatosis, LAM, lymphoma, and post radiation lymphangiectasis. A honeycomb pattern (coarse reticulation with cystic lesions) usually indicates advanced disease and is most commonly seen in patients with IPF, rheumatoid arthritis, scleroderma, or asbestosis. Finally a ground-glass appearance, although not specific for any particular disease, usually indicates a sign of active inflammation.

Additionally, the presence of mediastinal/hilar lymphadenopathy is suggestive of sarcoidosis (including berylliosis), lymphoma, tuberculosis, metastatic carcinoma, the endemic fungal diseases, or leprosy. Finally, when patients have paucity of symptoms and obvious radiographical abnormalities (clinico-radiological dissociation), the clinician may suspect sarcoidosis, EG, or silicosis.

BRONCHOSCOPY FINDINGS

In recent years, the routine use of fiberoptic bronchoscopy has proven useful in the diagnosis of infectious processes causing DPLD; however, the sensitivity and specificity of this method for other forms of DPLD are low. The bronchoalveolar lavage fluid normally contains 95-98% macrophages and very few neutrophils, lymphocytes, or eosinophils. The predominance of certain subgroups of cells in patients with DPLD might be helpful in the differential diagnosis. Neutrophils are often predominant in smokers and in patients with IPF, HSP, or CVD. Lymphocytic predominance is seen mainly in patients with sarcoidosis or HSP. Eosinophils predominate in patients with chronic eosinophilic pneumonia, Loeffler's syndrome, or Churg-Strauss angiitis.

On the other hand, bronchoalveolar lavage (BAL) may yield a specific diagnosis in DPLD, patients with certain findings such as asbestos bodies (which indicate asbestosis), silica-filled macrophages (silicosis), periodic acid-Schiff (PAS)-stained lipoproteinaceous material (pulmonary alveolar proteinosis), or the so-called X bodies (EG).

Transbronchial lung biopsy is often diagnostic in cases of sarcoidosis, lymphangitic carcinomatosis, bronchoalveolar cell carcinoma, eosinophilic pneumonia, pulmonary alveolar proteinosis, and is occasionally helpful in cases of eosinophilic granuloma, HSP, BOOP, lymphocytic interstitial pneumonitis, and amyloidosis. However, when bronchoscopy fails to yield a definitive diagnosis and the risk of empirical therapy is not acceptable, as in a patient with a reasonable surgical risk, we should proceed to open lung biopsy or video-assisted thoracoscopy.

In summary, these are some clues to be used in the taking of the history, physical exam, PFTs, radiological, and bronchoscopical approach; but they have to be added to our daily common sense just like in everything else in clinical medicine.

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