REVIEW ARTICLE

Approach to Diffuse Parenchymal Lung Disease (Interstitial Lung Disease) for the Hospitalist

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Abstract: Diffuse parenchymal lung diseases (DPLD, historically known as interstitial lung diseases) are a heterogeneous group of diseases that are uncommon and grouped together for their similarity in one or more clinical, radiological, and pathological findings. There is no universally acceptable classification system yet for such a varied group of diseases and hence impossible to have one unified diagnostic pathway. Diagnostic work up requires that the clinician have an initial list of differential diagnoses based on a thorough history and clinical evaluation. For acutely progressive diseases such as diffuse alveolar hemorrhage, urgent evaluation is necessary so that appropriate therapy can be quickly instituted; whereas, for the chronic progressive diseases like idiopathic interstitial pneumonia most of the evaluation can be done in the ambulatory setting. The decision for bronchoscopy and surgical lung biopsy should be individualized by incorporating informed decision making due to large variations in practice patterns among clinicians. Below is a brief summary of the most likely diseases to be encountered in hospital medicine practice.

Keywords: Interstitial lung diseases, pulmonary fibrosis, eosinophilic pneumonia, sarcoidosis.

INTRODUCTION

Interstitial lung diseases (ILD) are a heterogeneous group of pulmonary diseases initially thought to involve only the pulmonary interstitium and this has not always proven to be the case (1). Hence, they are now grouped under the name of diffuse parenchymal lung diseases (DPLD). The typical clinical presentation will involve a patient with cough and/or dyspnea, who on exam may demonstrate crackles and their pulmonary function test (PFT) will suggest a restrictive pattern or less commonly an obstructive or a mixed defect. A computed tomography (CT) of the chest will typically have a pattern suggestive of any of the DPLD's. Final diagnosis often requires a multi-disciplinary approach involving inputs from pulmonary, radiology and pathology subspecialties. For the hospitalist, DPLDs can present with various combinations of cough, dyspnea and/or hemoptysis with or without hypoxia. Rarely, incidental lung findings on CT of the abdomen and/or neck done for other reasons are encountered and following a further focused review of history, may unmask a diagnosis of DPLD. Not all of such cases will require a complete work up during hospitalization. Most of them can be followed up as outpatient with pulmonary clinics for further work up. In this manuscript

we intend to provide an overview of evaluation of DPLDs followed by a brief discussion of some specific DPLDs which are more likely to be seen in an inpatient setting. This article is not meant to be a detailed discussion of individual DPLDs.

Classification: There is no widely accepted classification for DPLDs and the true incidence or prevalence are also not known because most of these disorders are uncommon (2). A broad classification of the DPLD's are listed below (Table 1).

Table 1. Classification of diffuse parenchymal lung diseases

Idiopathic Interstitial Pneumonia:	Idiopathic Pulmonary Fibrosis (IPF)
	Idiopathic Nonspecific Interstitial Pneumonia (NSIP)
	Cryptogenic Organizing Pneumonia (COP)
	Lymphocytic Interstitial Pneumonia (LIP)
Smoking associated:	Respiratory Bronchiolitis Interstitial Lung Disease (RBILD)
	Desquamative Interstitial Pneumonia (DIP)
	Pulmonary Langerhans Cells Histiocytosis (PLCH)
Cystic Lung Diseases:	Lymphangioleiomyomatosis (LAM)
	Pulmonary Langerhans Cell Histiocytosis (PLCH)
ANCA associated Vasculitis:	Granulomatosis with Polyangiitis (GPA, formerly Wegner's granulomatosis)
	Microscopic Polyangiitis (MPA)
	Eosinophilic Granulomatosis with Polyangiitis (EGPA, formerly Churg Strauss syndrome)
Granulomatous Lung Diseases:	Sarcoidosis
	Hypersensitivity Pneumonitis
Drug Induced Lung Diseases:	Amiodarone, Methotrexate, Nitrofurantoin, Bleomycin etc.
Connective Tissue associated:	Systemic Lupus Erythematosus (SLE)
	Rheumatoid Arthritis
	Scleroderma
	Sjogren's Syndrome
	Polymyositis/Dermatomyositis
Occupational Lung Disease:	Coal, Silica, Asbestos, etc.

CLINICAL EVALUATION

Clinical History: From the above table it is evident that a good history is essential to narrow down the differential diagnoses. The first step is to know host immune status, because in immune-compromised hosts, the predominant causes for DPLDs are infectious in nature including *Pneumocystis jiroveci,* histoplasmosis, etc. The next focus on history should be analysis of the mode of onset of cough and/or dyspnea. Most of the DPLDs present with a sub-acute onset of these symptoms. Few of these diseases can present acutely over days to weeks, e.g. diffuse alveolar hemorrhage (DAH) from vasculitides or an acute pneumonitis from nitrofurantoin. Rarely Polymyositis/ Dermatomyositis (PM/DM) can present with an accelerated decline in lung function. It is important to remember that the absence of hemoptysis is not a good marker to rule out vasculitides, because alveolar hemorrhage can occur without overt hemoptysis. Acute exacerbation of idiopathic pulmonary fibrosis (IPF) and acute interstitial pneumonia (AIP) can also present with acute hypoxia and the degree of hypoxia is much more severe with AIP requiring admission to the intensive care unit for acute respiratory failure. Cryptogenic organizing pneumonia is often misdiagnosed as pneumonia and patients often provide a past history of being treated for recurrent pneumonia. Idiopathic chronic eosinophilic pneumonia (ICEP) can present as asthma with recurrent exacerbations needing frequent steroid bursts to control symptoms. Likewise, the smoking related diseases (RB-ILD, DIP, PLCH) are almost never seen in non-smokers.

Past medical and Medication history: A thorough medication history is vital and even though numerous drugs are thought to cause lung diseases, it is worthwhile asking about the most commonly used drugs like amiodarone, nitrofurantoin and chemotherapeutic drugs. www.Pneumotox.com is a good resource. Likewise, a history of a connective tissue disorder or prior radiation for head and neck cancer, breast cancer or lymphoma would also suggest radiation fibrosis of the lung. A history of amyotrophic lateral sclerosis or other neuro-muscular conditions causing respiratory failure should prompt chronic aspiration to be considered in the differential diagnoses.

Occupational history: A complete list of the patient's occupational exposures over the past several years is important, and in most instances, patients are aware (exposure to beryllium, working in mines, etc.) Having pet birds at home or even at their workplace is important for hypersensitivity pneumonitis.

Physical exam: Exam should focus on clinical features of specific causes, such as features of Raynaud's, skin changes suggestive of scleroderma, Gottron papules and mechanic's hands of polymyositis/dermatomyositis, erythema nodosum and parotid enlargement of sarcoidosis.

Blood Tests: On a complete blood count, eosinophilia is commonly seen with ICEP and EGPA unless the patient recently received systemic steroids. Presence of renal dysfunction on a BMP or presence of microscopic hematuria on a urinalysis could suggest a pulmonary-renal syndrome such as granulomatosis polyangiitis (GPA) (formerly Wegner's granulomatosis) or Goodpasture syndrome. Brain natriuretic peptide levels help in screening for congestive heart failure (CHF) as this can be the cause of dyspnea and bilateral pulmonary infiltrates and is also more prevalent than DPLDs. Molecular tests such as a pulmonary pathogen polymerase chain reaction (PCR) panel would help to

identify common respiratory viruses and mycoplasma. Finally, evaluation is incomplete without serologic testing for connective tissue diseases-based DPLD, by obtaining a complete anti-nuclear antibody (ANA) panel, rheumatoid factor (RF) or anti-cyclic citrullinated peptide (anti-CCP) antibodies, anti-neutrophil cytoplasmic antibodies (ANCA) directed against myeloperoxidase (MPO) and proteinase-3 (PR3), and anti-glomerular membrane (anti-GBM) antibodies for Goodpasture syndrome.

Imaging studies: A thin slice CT of the chest (slice thickness between 0.625mm and 1.5mm) (18) is usually the imaging of choice when a DPLD is suspected (3). Intravenous contrast is not routinely needed unless diseases with mediastinal involvement are suspected, e.g. sarcoidosis. Most hospitals in the US now employ multi-slice helical/spiral CT scanners and store the images for a variable time and it is possible to request radiology to reconstruct them to 1mm slices for further evaluation for DPLD if not done initially (4). Routine inspiratory/expiratory images and or prone/supine images are not needed in all cases. Some DPLDs have very characteristic CT patterns and can be diagnostic, e.g. cystic lung diseases. On CT, lymphangioleiomyomatosis and pulmonary Langerhans cell histiocytosis (PLCH) have a classic usual interstitial pneumonia (UIP) pattern showing a combination of bilateral subpleural honeycombing in an apico-basal gradient with traction bronchiectasis and minimal or absent ground-glass pattern.

Role of bronchoscopy: The role of bronchoscopy is often subjective. Bronchoscopy could help in excluding infections such as mycobacterial and fungal diseases. Bronchoalveolar lavage (BAL) fluid cell counts can aid in the diagnosis of idiopathic acute and chronic eosinophilic pneumonias (5). For example, BAL eosinophil count of >25% is diagnostic of either AEP or CEP. Bronchoscopic mediastinal lymph node sampling can be confirmatory for sarcoidosis. Similarly, a transbronchial lung biopsy could be diagnostic in hypersensitivity pneumonitis and sarcoidosis. Excluding a few DPLDs like sarcoidosis and hypersensitivity pneumonitis (HP), bronchoscopy with biopsies are often inconclusive to diagnose vasculitis or to differentiate idiopathic interstitial pneumonias because the biopsies sampled are not large enough compared to a surgical lung biopsy.

Surgical lung biopsy: There are no evidence-based guidelines for the indications or timing of surgical lung biopsy (6). It is often performed when vasculitis is suspected based on clinical, radiological or serological findings or in those with a rapidly declining clinical course. It is prudent to be mindful that a biopsy report will reflect the histological pattern of ongoing pathology but not a clinical diagnosis. Surgical lung biopsy also carries the risk of causing an acute exacerbation of the existing disease, and it is done under general anesthesia with procedure-related mortality ranging from 1-7% for elective and 16% for non-elective cases (7).

SPECIFIC INTERSTITIAL LUNG DISEASES

Pulmonary Sarcoidosis: Sarcoidosis is a multi-system granulomatous disease of unknown etiology and the lung is the most common organ affected (8). Pulmonary sarcoidosis is a diagnosis of exclusion. Males are usually 30-50 years of age and females 50-60 (8). Sarcoidosis initially presents with a cough or less often with dyspnea on exertion, and chest x-ray may show mediastinal and or hilar lymph node enlargement. Hypercalcemia and/or elevated

serum Angiotensin Converting Enzyme (ACE) levels may be present and both of them are non-specific findings. Usually diagnosis can be obtained by fine needle aspiration (FNA) of the involved lymph node via endo-bronchial ultrasound guided biopsy or a trans-bronchial biopsy. Cytology for malignancy and cultures for mycobacteria and fungi should be sent in order to exclude these diseases. Pulmonary sarcoidosis is usually steroid responsive but not all require treatment as many of them have asymptomatic, non-progressive, or self-limited disease.

Idiopathic Pulmonary Fibrosis (IPF): IPF is the most well-defined of the idiopathic interstitial pneumonias (IIP) as well as the most common (9). It is usually a disease which occurs in the fifth to seventh decades of life however it can rarely occur in much younger age as well. About two thirds of patients are current or past smokers. IPF is a diagnosis of exclusion and the corresponding radiological findings and pathology is described as Usual Interstitial Pneumonia (UIP) (10). IPF is diagnosed after a "UIP pattern" is noted on CT or on a surgical biopsy specimen and no other etiology is found on clinical and laboratory evaluation. Connective tissue diseases, asbestosis and chronic hypersensitivity pneumonitis are some diseases which can cause a UIP pattern on CT and pathology. Patients present with chronic cough and/or dyspnea on exertion. Occasionally, patients are found to have CT abnormalities while evaluating a non-resolving chronic cough. Bibasilar crackles are often heard on auscultation but may be absent in early stage fibrosis. HRCT scans may be diagnostic and this obviates the need for a surgical lung biopsy if it satisfies certain criteria released by Fleischner Society in 2018 (14). If the CT features are not consistent with a UIP pattern then surgical lung biopsy may be warranted. Treatment consists of supplemental oxygen if hypoxic. Anti-fibrotic agents are now available which could potentially slow the rate of decline in lung function (11,12). Definitive long-term therapy is lung transplantation.

Organizing Pneumonia: Organizing pneumonia is classified under IIP but the radiological and pathological patterns of organizing pneumonia can be caused by a multitude of etiologies including post-infectious, connective tissue disease-related, or medication-induced among others. If an etiology is not evident then it is labelled as Cryptogenic Organizing Pneumonia (COP), which was historically known as idiopathic bronchiolitis obliterans organizing pneumonia (BOOP). Usual onset is during the fourth and fifth decades of life with an equal incidence among males and females (18). At the onset, it mimics a flu-like illness and often mistaken for a pneumonia and treated as such. It is not uncommon for it to present as recurrent pneumonia or non-resolving pneumonia. Routine labs may only show a mild leukocytosis. Chest imaging studies often show bilateral consolidations with varying degree of ground-glass infiltrates. Rarely it may present as a solitary dense consolidation mimicking a lung mass. Response to steroid therapy is consistently good and relapses can occur following weaning or cessation of steroids. Prognosis is usually good.

Non-Specific Interstitial Pneumonia (NSIP): NSIP is a pathological diagnosis when lung biopsy does not show features consistent with other Idiopathic Interstitial Pneumonias. Up to a fifth of patients diagnosed with NSIP have an occult autoimmune disease or eventually develop one (13). Symptoms are usually cough and dyspnea for a few months and patients are more likely to present as outpatients. Hospitalizations are often the result of an

acute exacerbation or if they develop pneumonia or heart failure superimposed on their NSIP. Imaging shows predominant bilateral ground-glass infiltrates with or without fibrosis. Honey combing is rare and minimal if present. Most of them respond to variable extent to systemic steroids.

Interstitial Pneumonia with Autoimmune features (IPAF): It has been well recognized that idiopathic interstitial pneumonia could be the first and/or the only presenting feature of an underlying connective tissue disease. In 2015, the American Thoracic Society and the European Respiratory Society published criteria for diagnosing this condition (15). IPAF includes patients with features of an ILD along with some combination of clinical and/or serological features insufficient to completely satisfy a diagnostic criterion for a connective tissue disease. Whenever one of the IIPs is suspected based on radiological features and an autoimmune serology is positive, a surgical lung biopsy may not be needed for confirmation if both are compatible (e.g. serology suggestive of SLE and CT showed features of organizing pneumonia).

Idiopathic Chronic Eosinophilic Pneumonia (ICEP): ICEP is classified as an eosinophilic lung disease and is usually a disease of middle age. It is twice more common in females than males (15). Up to two thirds of patients have asthma and are non-smokers (16). The classic radiologic picture is bilateral peripheral subpleural infiltrates (described as "photographic negative of pulmonary edema"), but this finding is not universal. Blood eosinophilia is almost always present unless recently or currently treated with steroids. If bronchoscopy is performed, BAL often shows eosinophils >25% (not always needed for a diagnosis if systemic eosinophilia is present). Treatment consists of long-term systemic steroids requiring tapering over several weeks. Recurrence rate is common when steroids are discontinued (17).

Hypersensitivity Pneumonitis: HP is a disease which occurs in susceptible individuals exposed to either organic or inorganic dusts over time (20). Factors which make these individuals susceptible are yet to be elucidated. Thin slice CT shows features suggestive of HP including centri-lobular nodules, ground-glass pattern, air trapping, and in some cases varying degree of fibrosis, especially in chronic HP. Serological testing can be done though a positive test only indicates an exposure to the antigen and is not in itself indicative of underlying disease. Surgical lung biopsy or in some cases trans-bronchial biopsy will show poorly formed granulomas in a background of lymphocytic infiltrate. None of these features are diagnostic on their own. Treatment consists of avoidance of the trigger and systemic steroids if symptomatic.

Notes

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