INTERSTITIAL LUNG DISEASE

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Definition: Interstitial lung disease (ILD) refers to a broad range of conditions that have common clinical, physiological, and radiological features. ILD is not one disease, but several diseases that do not necessarily share a common histopathological or pathophysiological basis. By strict definition, ILD involves abnormalities of the interstitium, the potential space between the epithelial and capillary endothelium basement membranes within the alveolus. However, many of the conditions that have been traditionally included under the heading of ILD actually involve other anatomic structures within the lung. For this reason, the more general term "diffuse parenchymal lung disease" (DLPD) is now considered to be preferable, unless the nature of the disease is defined anatomically. However, the term ILD remains in common clinical usage.

Epidemiology: There are limited data that detail the incidence or prevalence of various ILD's. By rough estimate some of the more common ILD's (such as idiopathic pulmonary fibrosis (IPF), sarcoidosis, or occupational lung disease) together affect about 40 individuals per 100,000 population per year. These numbers indicate that ILD isn't common, but about 81,000 individuals are affected by IPF alone in the United States. Although various ILD's can affect individuals of any age, most occur in adults. Some, such as IPF are uncommon under the age of 50 years, and demonstrate increased incidence with each subsequent decade. Other ILD's, such as sarcoidosis and rheumatologic-associated ILD, tend to affect younger adults. The age distribution and male:female ratio vary greatly for specific ILD's. The prognosis, choice of therapy, and natural history differ greatly depending on the specific ILD, so establishing the exact cause of ILD is critical.

Causes of ILD: There are many causes of ILD. ILD can occur acutely and can be self-limiting, for example after exposure to a drug or toxin. Most of the clinically relevant ILD's are chronic, and develop over a prolonged time. A careful history and systematic evaluation is required to help characterize the cause of an ILD. ILD (DPLD) can be divided into the following categories: ILD due to systemic disease, ILD due to environmental exposure, ILD due to toxic or medicinal exposure, and idiopathic causes. There are also a number of unclassified disorders that fall under the heading of ILD. An ILD can affect the lung only, or be part of a systemic process. A multi-disciplinary approach is often needed to correctly identify the nature of an ILD, and to attempt to determine its cause.

Clinical Presentation of ILD: There are two clinical hallmarks of ILD in early stages of disease: persistent cough that is usually non-productive, and dyspnea with exertion. It is often difficult to elicit a history of exertional dyspnea because many of the ILD's present insidiously and develop slowly, so the affected individual has time to adapt to a slowed life-style, or assumes that deconditioning and advancing age are responsible for their symptoms.

The history must also detail possible exposures to occupational or environmental causes of ILD (such as inorganic dusts or organic compounds), medications and illicit drugs, or respiratory infections. A detailed family history is also needed, as some of the ILD's (e.g., familial IPF) are known to be inheritable. Many of the defined ILD's are idiopathic. It is important to recognize that many of the same histopathologic entities that are associated with ILD can be seen when the cause is unknown (i.e., idiopathic), are due to environmental exposures, or are part of a broader systemic process (e.g., rheumatologic disease). Practically speaking, a lung biopsy that demonstrates findings that are compatible with an ILD cannot be diagnostic in the absence of a carefully obtained history and detailed physical and clinical exam.

Physical Findings: The two most frequent physical findings in individuals who have ILD are tachypnea and inspiratory crackles that are heard best in the postero-basilar chest. The tachypnea can be observed at rest; often the individual is unaware of the relative rapidity or shallowness of their breathing pattern. Crackles on exam are always an abnormal finding, but are not specific for ILD: pulmonary edema, pneumonia, and scarring can cause similar findings, as examples. Digital clubbing can be seen in some cases of idiopathic ILD (e.g., idiopathic pulmonary fibrosis). Cyanosis, low lung volumes, and tachycardia are usually associated with more advanced disease. It is important to observe whether there are signs of systemic disease (e.g., rheumatologic disease) that can cause ILD, or other confounding conditions (e.g., signs of pulmonary hypertension or heart failure).

Physiologic Findings: Oxygen desaturation with exercise is an early abnormality found in most ILD's. This can be observed during the clinical exam by measuring pulse oxymetry at rest and following ambulation or stair climbing. Desaturation in excess of 2-3% is considered to be abnormal. The degree of exertional desaturation often correlates with poorer prognosis. Desaturation at rest is most often a late finding of ILD. Desaturation is due largely to abnormal V/Q matching, but decreased transit time in the alveolar-capillary bed and shunting via aberrant arterio-venous connections have also been implicated.

Most ILD's result in a loss of lung compliance and decreased lung volumes. On spirometry, this is manifest as a low FVC with a preserved FEV1/FVC ratio (actually, the FEV1/FVC ratio often rises as the disease progresses), and preserved flow rates. Similarly, the lung volumes (e.g., TLC, FRC, RV) decrease. Spirometry and lung volumes often worsen as various ILD's progress,

but these measures alone may misrepresent the degree of impairment, prognosis, progression of disease, or response to therapy. The diffusion capacity (DlCO) is usually low, and frequently is the first pulmonary function test to become abnormal in the course of an ILD. For this reason, DlCO together with measures of oxygen saturation with exercise are useful screens when ILD is suspected clinically. Neither a low DlCO or desaturation with exercise is unique to ILD, but both are abnormal findings that warrant further evaluation.

The work of breathing is higher for individuals who have ILD, a consequence of low lung compliance and relatively high dead space ventilation. Disproportionately high work of breathing for a given effort contributes to the sense of dyspnea, which itself can be debilitating. High work of breathing can be quantified by cardiopulmonary exercise testing, including measures such as an elevated ratio of ventilation to CO2 production (VE/Vco2).

Various physiologic abnormalities in ILD contribute to low exercise capacity and endurance. Standard measures of these parameters can be used to help quantify the severity and progression of ILD, including the distance walked in six minutes, the maximal oxygen uptake and work output during graded exercise (cardiopulmonary exercise testing), and the maximum voluntary ventilation (MVV). Pulmonary rehabilitation including endurance training can help improve exercise capacity in individuals who have ILD despite worsening of lung mechanics.

Laboratory Testing: There are no laboratory tests that specifically diagnose or define the progression of ILD's. However, many ancillary tests can help determine whether there is an alternative explanation of a suspected ILD, or whether the ILD is due to a systemic process or exposure. Routine hematologic and serum chemistry testing, rheumatologic serologies (e.g. rheumatoid factor, anti-nuclear antibodies) and measures of systemic inflammation can be helpful.

Chest Radiology: Plain chest x-rays characteristically reveal a pattern of bilateral linear ("interstitial") infiltrates that affect the bases more than the apices. It is important to recognize the plain chest x-ray is frequently normal even when the individual has marked symptoms. Also, some of the ILD's can affect the apices more than the bases, or instead can be diffuse in distribution. Nodular opacities or areas of consolidation can be seen in addition to, or instead of linear infiltrates.

The high-resolution chest CT scan (HRCT) is generally more useful to help diagnose and monitor ILD's than plain chest x-rays. The HRCT can reveal subtle abnormalities long before the plain chest x-ray reveals any abnormalities, and the patterns of infiltration seen on HRCT (but not on plain x-ray) can sometimes be specific enough to be diagnostic of a specific ILD in the absence of a lung biopsy. ILD can be of appreciable severity in the absence of any radiologic abnormality, so negative radiology does not exclude a diagnosis of ILD.

Lung Biopsy: In general, histopathologic examination is needed to diagnose ILD definitively. Three approaches to lung biopsy are usually appropriate for the diagnosis of ILD: Percutaneous core biopsy, transbronchial biopsy via a bronchoscope, or wedge biopsy obtained via a surgical approach. Percutaneous and bronchoscopic biopsies offer the advantage of being less invasive, but are limited technically be the size of the biopsy. Biopsies obtained by these techniques lack geographic representation of the ILD histopathology, so these techniques are only useful to help diagnose some of the ILD's which tend to be more uniform in distribution, or which occur in a peri-bronchial distribution (e.g., sarcoidosis). In general, the ILD's require larger pieces of tissue that has been obtained from different areas of the lung for diagnosis (i.e., areas that are both more and less involved grossly and radiologically), so the surgical approach is preferred. The latter is achieved by video-assisted surgical techniques (("VATS") to minimize surgical morbidity.

Bronchoalveolar lavage (BAL) has been studied extensively as a means to diagnose and monitor the course or response to therapy of various ILD's. This technique samples the alveolar space by infusing and then recovering sterile saline from a sub-segment of lung. The type and distribution of various inflammatory cells and various chemical constituents of the alveolar space can be determined in this way. BAL analysis of ILD relies on the assumption that abnormalities within the alveolar space accurately reflect abnormalities within the interstitium. In many cases, this assumption is not justified. In general, this technique remains experimental, and has not obviated the need to obtain a lung biopsy. BAL is useful to help exclude alternative diagnoses, however, particularly infection.

Histopathology: Several patterns of histopathology can be observed in ILD. Some of these involve cellular inflammation (e.g., infiltration by lymphocyte and monocyte lineage cells, plasma cells, neutrophils, or eosinophils), but in others there is a paucity of observable inflammation. The inflammation can be prominent within the interstitium, but may involve the alveolar space ("alveolitis") or blood vessels ("vasculitis") more prominently. Matrix deposition and collagen fibrosis are often found, particularly as the ILD progresses. The abnormalities can be found uniformly within the lung, in a central or peripheral distribution, or be airway centric. Often, the abnormalities are patchy in distribution, and different aspects of the histopathologic process can be observed in different areas of the lung. In short, there is no unifying histopathological definition of ILD. A lung biopsy is needed to discern the exact nature of the ILD in most cases. It is important to recognize that a histologic pattern alone does not define an ILD: diagnosis requires the combination of history, physical findings, physiological measurements, radiology, and laboratory testing together with the histopathology to establish a diagnosis.

Management of ILD: Management depends on the exact diagnosis of ILD. Some of the ILD's respond well to conventional immunosuppressive or anti-inflammatory therapy, such as corticosteroids, cyclophosphamide, or azothioprine. In general, conditions that involve cellular infiltration of the interstitium by lymphoid or monocyte-lineage cells (e.g., cellular NSIP), or that involve granulomatous inflammation (e.g., sarcoidosis), are more likely to respond to this approach to therapy. There is no available therapy for most ILD's; ILD's that have a paucity of inflammatory cells, or a predominance of fibrosis (such as IPF) are less likely to respond to anti-inflammatory or immunosuppressive therapy. There is a concerted effort to define alternative approaches to treat ILD's in the latter category, as these conditions often have a poor prognosis with no available specific therapy, and constitute the majority of cases. Approaches based on altering signaling pathways (e.g., interruption of endothelin or TNF-directed pathways, or augmentation of interferon gamma-1b pathways) are currently being tested in clinical trials. Non-specific modes of therapy, such as oxygen supplementation, exercise programs, and aggressive treatment of superimposed respiratory infections can be helpful in optimizing function and prolonging life in individuals who have ILD. Lung transplantation is often the only available long-term option for many who have ILD, provided they are in an appropriate age group (generally, less than 65 years) and lack other co-morbid disease that could limit success after transplant (e.g., heart or kidney failure).

Examples of ILD: Idiopathic pulmonary fibrosis (IPF) is one of the most common ILD's. It affects about 81,000 individuals in the U.S., most of whom are over fifty years of age. The disease begins insidiously, and can develop slowly over several years. The disease can progress quickly, but it is unclear whether an accelerated course is due to the disease itself, or to superimposed processes such as infection. The prognosis of IPF is poor: the expected five-year survival is under three years from the time of diagnosis, suggesting that the prognosis of IPF is worse than most common malignancies or heart failure. These data are somewhat misleading, however, as most patients seem to seek medical attention late in the course of their disease. Surprisingly, recent data suggests that the risk of acute decompensations and death is similar among symptomatic individuals whether their disease is "early" or "late" by spirometric criteria. This suggests that therapy that can prevent or successfully treat "acute exacerbations" may improve survival for those with IPF.

The histopathology of IPF is usual interstitial pneumonia, which itself is characterized by its patchy, sub-pleural distribution, and the absence of active inflammatory infiltration. Instead, rather bland interstitial thickening and fibrosis is observed. Recent evidence indicates that the myofibroblast is central to the pathogenesis of IPF. Myofibroblast activation and proliferation occurs in response to an injury, presumably at the alveolar-capillary membrane in the case of IPF. Instead of healing by repair, myofibroblast proliferation and subsequent matrix and collagen deposition (fibrosis) proceeds unchecked. Data obtained

from micro-dissection of “fibroblastic foci” from biopsy specimens obtained from individuals with IPF, and subsequent gene-chip array analysis, coupled with in vitro analysis of cells obtained by BAL, have led to the identification of new targets for therapy of IPF. Traditional methods of therapy using immunosuppressive and anti-inflammatory agents have been unsuccessful in IPF, an observation supported by the refractory nature of myofibroblasts to these agents in vitro. Animal models of IPF (and most other ILD’s) are very limited in applicability, so most knowledge concerning the natural history of IPF and therapeutic strategies comes from clinical trials and observation.

Non-specific interstitial pneumonitis (NSIP) is very similar to IPF on clinical grounds, and most often a surgical biopsy is needed to distinguish NSIP from IPF. In contrast to IPF, the lungs are more uniformly affected in NSIP, and cellular inflammation can be observed (cellular NSIP). NSIP is more likely to be associated with an underlying systemic disease than usual interstitial pneumonia (but it can be idiopathic), tends to occur in younger patients, and portends a better response to conventional immunosuppressive therapy and a better prognosis overall than IPF.

Chronic hypersensitivity pneumonia (CHP) is another condition that can mimic IPF. Again, a surgical lung biopsy if frequently needed to distinguish CHP from IPF. As the name implies, CHP is thought to arise from chronic exposure to an environmental agent (frequently, exposure to certain fungi or birds in the parrot family are etiologic), although the inciting agent is frequently not identified. None-the-less, the first line of therapy of CHP is removal of the offending agent, if possible. CHP seems to be the result of granulomatous inflammation, so therapy using corticosteroids is frequently helpful.

Sarcoidosis is an example of a disease that is included under the heading of an ILD, although it affects the lung primarily in a peri-bronchial distribution. Sarcoidosis can affect individuals in any age group, but characteristically it affects young adults. Sarcoidosis is a systemic disease of unknown cause, with the lung and thoracic lymph glands as a particularly common target for characteristic granulomatous inflammation. Many individuals with sarcoidosis are asymptomatic, and are discovered incidentally, usually after having a routinely obtained chest x-ray. Even among those who are symptomatic, sarcoidosis tends to be a self-limited disease that does not require specific therapy. For those who require therapy (there are several clinical guidelines to help make this decision), sarcoidosis usually responds to therapy using systemic corticosteroids. In contrast to most other ILD’s, pulmonary sarcoidosis can most often be diagnosed by bronchoscopic biopsy.

Approach to the patient with possible ILD: From the foregoing, it is clear that evaluation of ILD requires a step-wise, systematic process. ILD should be suspected whenever there is unexplained dyspnea, prolonged cough, or radiologic abnormalities, or when there are abnormal physical findings such as

crackles on chest auscultation. A multi-disciplinary team approach is most useful in helping to establish the diagnosis of an ILD, and to plan management of the individual who has ILD.

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