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# INSTERSTITIAL LUNG DISEASE: CLINICAL EVALUATION AND WAYS TO DIAGNOSIS

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The diffuse parenchymal lung diseases (DPLD), often collectively referred to as the "interstitial lung diseases" (ILD) encompass approximately 150 entities in which the lung is altered by combination of interstitial and/or granulomatous inflammation and usually — fibrosis. Most of these diseases affect not only the interstitium of the lung (structure situated in between the alveoli) but also alveolar space, walls of bronchioles, blood and lymphatic vessels and pleura.

This heterogenous group of disorders is classified together because of similar clinical, radiologic, physiologic and pathologic manifestations. The common features of ILD include relatively subacute to chronic course (usually longer than 6 months), progressive dyspnea on exertion, bilateral interstitial-alveolar infiltrates, restrictive pulmonary dysfunction, diminished diffusing capacity for carbon monoxide, exercise-induced hypoxemia, hypocarbia in the initial stages, and nonspecific histological findings (varying degrees of inflammation, fibrosis and remodeling).

Infections, cardiac failure and malignant diseases are usually not included in this group, although they should be included in the differential diagnosis.

Few data are available on the epidemiology of ILD in general population. In USA task force study in 1972 revealed that diffuse lung diseases constituted 15% of all problems encountered by practicing pulmonary physicians.

In a population-based study in New Mexico in the period 1988–1990 prevalence of ILD was estimated as 81/100 000 males and 67/100 000 females and incidence of ILD was estimated as 32/ 100 000/per year in males and of 26/100 000/per year in females (table 1).

ILD include disorders of known cause (e.g. drug, radiation therapy, environmental exposures and connective tissue diseases), but in majority — the cause is unknown. Among them sarcoidosis represents granulomatous diseases but other e.g. lymphangioleiomyomatosis or pulmonary Langerhans cell granulomatosis — represent specific forms of interstitial diseases. The most common and important group of ILD is idiopathic interstitial pneumonia (IIP).

Recently ILD are classified broadly into 7 main groups (table 2)

It seems likely that these diseases are underdiagnosed in life and misclassified at death.

There are number reasons why the management of diffuse lung disease is inconsistent: 1) however the clinical symptoms, radiologic lesions and functional disturbances are very similar, but individual disease has specific pathogenesis, natural history and likely responsiveness to treatment, 2) many physicians equate all diffuse lung disease as having the same prognosis as most lethal diffuse lung disease-fibrosing alveolitis, 3) only small numbers of patients are seen in any one unit.

To often diseases are diagnosed on the basis of "clinical features". These features normally include a chest radiograph but it is not good enough in supporting diagnosis of a number of ILD.

**The purpose of this paper** is to show how improvements might be made in diagnosis approach to interstitial lung diseases.

**The role of selective investigations**

The clinical assessment of a patient with ILD includes history and physical examination, chest-imaging studies, lung function tests, selected blood tests including autoantibodies (antinuclear-ANA and antineutrophil cytoplasmic-ANCA), precipitins, angiotensin converting enzyme. An initial phase of investigation ought to be followed by more specific examinations including high resolution computed tomography (HRCT) examination, bronchoalveolar lavage (BAL) and histological examination of lung biopsy specimen.

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**History**

Although the rate of symptomatic progression and physiologic deterioration for individual patient with ILD is variable, it generally runs a chronic course that ranges from 6 months up to 10 or more years, depending on the specific etiology. Chronic presentation (months to years) is typical in idiopathic pulmonary fibrosis, chronic hypersensitivity pneumonitis, chronic occupational diseases (e.g. asbestosis); pulmonary Langerhans cell granulomatosis, ILD associated with connective tissue diseases. Subacute (weeks to months) presentations include cryptogenic organizing pneumonia, subacute hypersensitivity pneumonitis, drug- induced ILD.

Age and gender are sometimes useful in general evaluation of ILD. Between 20 and 40 years sarcoidosis, Langerhans cell granulomatosis, connective tissue — associated ILD, pulmonary vasculitis, LAM, the inherited ILD and alveolar microlithiasis are more likely to occur. Above the age of 50 years, idiopathic pulmonary fibrosis could be suspected.

Smoking history is very important. In Langerhans cell granulomatosis >90% of patients are active smokers at the time of diagnosis and LCG is unlikely in the absence of smoking history. Respiratory bronchiolitis associated with ILD is another ILD in which almost all affected individuals are smokers. Goodpasture's syndrome is observed in 100% of smokers in comparison with only 20% of affected nonsmokers. Patients exposed to asbestos who smoke will develop asbestosis more often than nonsmokers.

**Respiratory symptoms and signs**

The most recognizable presentation of ILD is symptomatic patient with abnormal chest radiogram. Progressive dyspnea, initially with exercise and then at rest is most common complaint, but cough and fatigue may be also prominent. Although cough is nonspecific, it can be initial manifestation of ILD. Hemoptysis may suggest diffuse alveolar haemorrhage. About 10% of patients have dyspnea with normal chest radiograph. In this situation HRCT, extensive lung physiologic testing, investigation of gas exchange with exercise often help to make diagnosis or lead to lung biopsy. Alternatively, patients with ILD may be asymptomatic and have abnormal chest radiograph, which should not be ignored because most of forms of ILD progress and cause symptomatic and functional impairment. Even with normal spirometry and lung volumes, measurement of rest and exercise gas exchange reveals physiologic abnormalities in asymptomatic patients with abnormal chest radiograph. Early identification of ILD makes possibilities to therapeutic intervention.

Extra pulmonary symptoms can help in diagnosis. History of dyspepsia and gastroesophageal reflux disease may suggest idiopathic pulmonary fibrosis or scleroderma-related ILD. Overt aspiration or dysphagia suggests aspiration pneumonia, scleroderma or mixed connective tissue disease. Frank inflammatory arthritis suggests connective tissue disease or sarcoidosis, dry eyes and dry mouth (sicca syndrome) is usually associated with Sjoegren syndrome or other CTD. Neurologic symptoms (cranial nerve involvement) suggest the sarcoidosis or vasculitis, whereas polyuria and polydypsia of diabetes insipidus suggest sarcoidosis or Langerhans cell granulomatosis (table 3).

**Physical examination**

The characteristic physical sign of ILD is bibasilar inspiratory crackles, but it is not consistent finding. For example, in sarcoidosis, hypersensitivity pneumonitis, silicosis, Langerhans cell granulomatosis coracles are less frequently in comparison with IPF, connective tissue diseases or asbestosis. Clubbing is characteristic in IPF, and rare — in sarcoidosis.

**The chest radiograph** remains the most practical first step for the detection, verification and classification of ILD. The clinician should make every effort to obtain previous chest radiograph for review. This may allow ascertaining the onset, chronicity, rate

*Table 1*

**Prevalence and incidence of interstitial lung diseases, (Demedts)**

| Diagnosis | Prevalence | Per 105 | Incidence | Per 105 per year |
|---|---|---|---|---|
| | Male | Female | Male | Female |
| Total interstitial lung disease | 80,9 | 67,2 | 31,5 | 26,1 |
| Idiopathic pulmonary fibrosis | 20,2 | 13,2 | 10,7 | 7,4 |
| Post inflammatory pulmonary fibrosis | 10,1 | 14,3 | 3,9 | 4,1 |
| Sarcoidosis | 8,3 | 8,8 | 0,9 | 3,6 |
| Connective tissue diseases | 7,1 | 11,6 | 2,1 | 3 |
| Drugs and radiation | 1,2 | 2,2 | 1,8 | 1,1 |
| Occupational/ environmental | 20,8 | 0,6 | 6,2 | 0,8 |

*Table 2*

**Clinical classification of the interstitial lung diseases**

| |
|---|
| 1. Drug-induced lung diseases |
| 2. Environmental and occupational exposures |
| a) Pneumoconiosis |
| b) Hypersensitivity pneumonitis (HP) |
| 3. Connective tissue diseases (CTD) |
| 4. Primary diseases — unique entities |
| a) Sarcoidosis |
| b) Langerhans cell granulomatosis (LCG)-histiocytosis X |
| c) Lymphangioleiomyomatosis — LAM |
| d) Diffuse alveolar hemorrhage (DAH) |
| e) Eosinophilic pneumonia — EP |
| f) Pulmonary alveolar proteinosis |
| g) Alveolar microlithiasis |
| h) Amyloidosis |
| 5.Inherited diseases |
| 6. Idiopathic interstitial pneumonias |
| a) Idiopathic pulmonary fibrosis-IPF |
| b) Nonspecific interstitial pneumoni — NSIP |
| c) Acute interstitial pneumonia — AIP |
| d) Respiratory bronchiolitis- interstitial lung disease-RB-ILD |
| e) Desquamtive interstitial pneumonia — DIP |
| f) Lymphomatoid interstitial pneumonia —LIP |
| g) Cryptogenic organizing pneumonia — COP |

of progression, or stability of the disease. The use of high **resolution computed tomography (HRCT)** over the past 10 years has revolutionized the approach to ILD. Recently it should be considered as a standard procedure.

The abnormalities seen on chest X-ray and CT-scan in ILD range from a "ground glass" appearance to end-stage honeycombing and include changes described as acinar, reticular, micronodular and reticulonodular. Unfortunately none of these patterns is specific for any particular type of ILD. The distribution of chest-X-ray infiltrates may be of some value in predicting disease etiology: bilateral hilar and paratracheal lymphadenopathy may suggest sarcoidosis or berylliosis, while coexistent pleural plaques or calcifications may indicate asbestos-related pleuropulmonary disease. The pattern of abnormality may be characteristic in several diseases and is virtually pathognomic in most cases of idiopathic pulmonary fibrosis (table 4).

In another disease HRCT is useful in selecting the site for lung biopsy.

**Bronchoalveolar lavage (BAL)** is used to estimate cells and non-cellular material from the lower respiratory tract in ILD. BAL is

*Table 3*

**Systemic signs accompanying ILD**

| Sign/symptom | Disease |
|---|---|
| Systemic hypertension | CTD, Goodpasture S., Wegener G., MPA |
| Erythema nodosum | Sarcoidosis, Behcet S. (BS), CTD |
| Maculopapular rash/cutaneous vasculitis | CTD, WG, drug induced (DI), MPA. |
| Teleangiectasia | Scleroderma |
| Raynaud's phenomena | CTD, idiopathic pulmonary fibrosis (IPF) |
| Subcutaneous nodules | rheumatoid arthritis, neurofibromatosis, sarcoid. |
| Keratoconjunctivitis sicca | Sjoegren syndrom, CTD. |
| Uveitis | Sarc., BS, |
| Lymphadenopathy | Sarc., HP, Churg-Strauss S (Ch-SS). |
| Pericarditis | CTD, Radiotherapy, Ch-SS |
| Hepatosplenomegaly | Sarc., CTD, LIP |
| Diabetes insipidus | Sarc., Langerhans cell granulomatosis |
| Neurologic abnormalities | Sarc., NF, CTD, WG, Ch-SS |
| Arthritis | Sarc., CTD, WG, IPF |

MPA — microscopic polyangiitis, CTD — connective tissue disease, HP — hypersensitivity pneumonitis.

*Table 4*

**Diseases, in which HRCT shows characteristic patterns**

| |
|---|
| 1. Idiopathic pulmonary fibrosis |
| 2. Langerhans cell granulomatosis |
| 3. Lymphangioleiomyomatosis |
| 4. Sarcoidosis |
| 5. Hypersensitivity pneumonitis |
| 6. Pulmonary proteinosis |
| 7. Microlithiasis |
| 8. Asbestosis |

*Table 5*

**Diagnostic value of BAL in ILD**

| |
|---|
| 1. Opportunistic infection: Pneumocystis carini, fungi, and tuberculosis |
| 2. Alveolar haemorrhage: hemosiderin-laden macrophages |
| 3. Pulmonary alveolar proteinosis: milky effluent, PAS-positive noncellular substance, foamy macrophages |
| 4. Eosinophilic pneumonias-eosinophilia > 25% |
| 5. Asbestosis: asbestos bodies |
| 6. Lipid aspiration: cytoplasmic lipid vacuoles within alveolar macrophages |
| 7. Microlithiasis: calcic bodies |

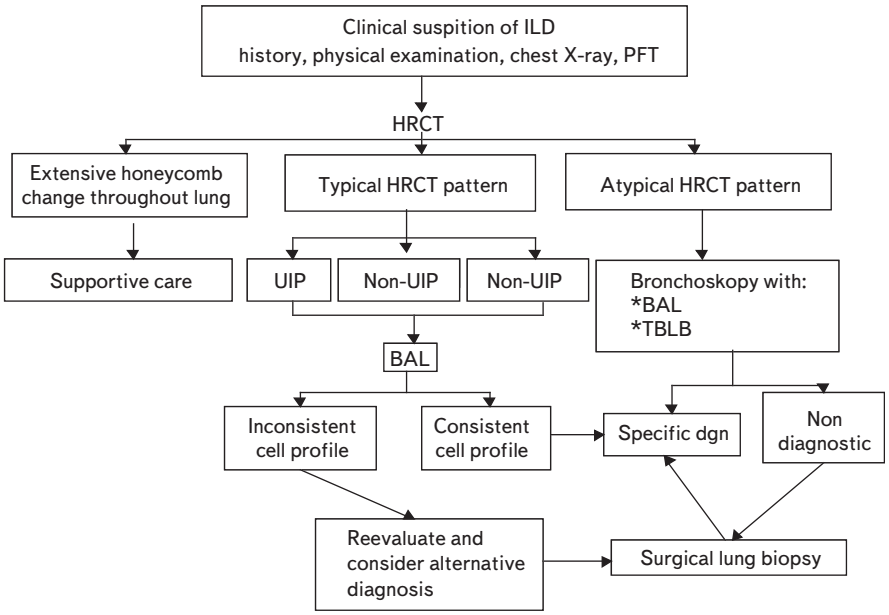


*Fig. 1. Algorithm of diagnostic strategy in ILD according to Meyer*

useful particulary to rule out infections as a cause of diffuse infiltrates. Although it is infrequently diagnostic by itself (table 5), when combined with clinical data and radiographic imaging, BAL cell patterns can be useful in reaching a likely diagnosis without performing lung biopsy.

Generally diagnosis of interstitial lung disease should be confirmed by biopsy if HRCT is not diagnostic and unless the patient's general condition precludes the procedure — e.g. severe respiratory failure or uncontrolled heart failure. In patients in whom tomographic appearances may be pathognomic decision to perform lung biopsy depends on assessment of individual cases. A patient over 65 or with poor lung function, especially with hypoxia at rest is at high risk from any operation. It is often argued that treatment will be the same with or without confirmation of the diagnosis by biopsy. It is true if empirical treatment always produce an improvement, but during recurrence of disease the next step in management is more difficult. It is important to perform a biopsy before treatment started. **Transbronchial lung biopsy** will often confirm diagnosis in several diseases and in other ILD **open lung biopsy /or videothoracoscopy** is necessary (table 6).

The physician who evaluates ILD has to amass specific knowledge that relates to a large number of potential diagnoses. A clear diagnosis confirmed by biopsy allows clinicians and patients to discuss fully the implications of the disease, to develop a clear plan of treatment and weigh up the advantages and disadvantages of treatment. Morbidity and mortality from open biopsy are low.

*Table 6*

**Choice of biopsy procedure**

| Transbronchial | Open or videothoracoscopic biopsy |
|---|---|
| 1. Sarcoidosis | 1. Langerhans cell granulomatosis |
| 2. Berylosis | 2. Lymphangioleiomyomatosis |
| 3. Eosinophilic pneumonias | 3. Idiopathic interstitial pneumonia |
| 4. Organizing pneumonia | 4. Wegener's granulomatosis |
| 5. Alveolar proteinosis | |

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