INTERSTITIAL LUNG DISEASES

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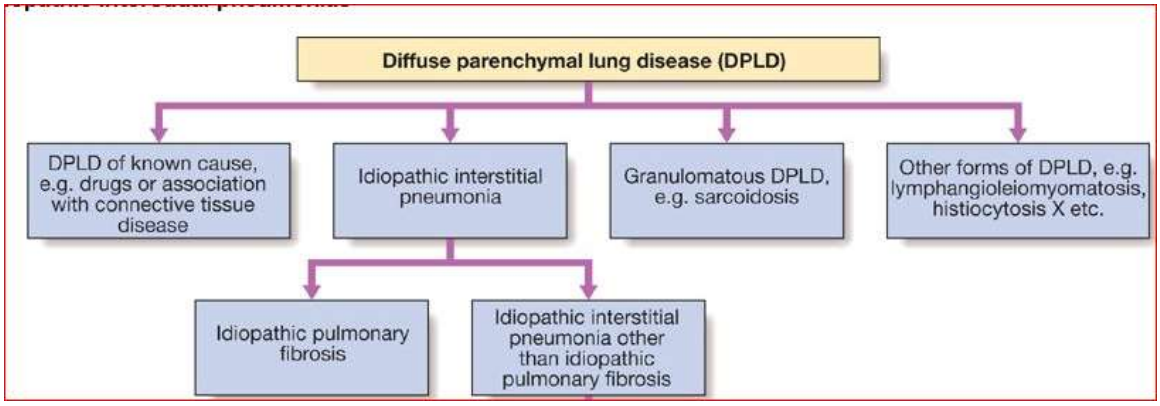
The diffuse parenchymal lung diseases (DPLDs) or ILDs are a heterogeneous group of conditions with varying prognoses and clinical behaviors affecting the pulmonary interstitium and/or alveolar lumen. inflammation of alveolar walls with fluid in alveolar air spaces leading to progressive bilateral destruction of the lung parenchyma.

The natural history of these may differ widely, but they share similar symptoms, physical signs, pulmonary function abnormalities and radiological changes. Interstitial lung disease (ILD) refers to a broad category of lung diseases rather than a specific disease entity.



Idiopathic Pulmonary Fibrosis: Cryptogenic Fibrosing Alveolitis

This relatively rare disorder, chronic lung disease characterized by a progressive and irreversible decline in lung function. Symptoms typically include gradual onset of shortness of breath and a dry cough. Other change (clubbing fingers).

The cause is unknown. Risk factors include a strong association with cigarette smoking, certain viral infections, and a family history of the condition. The underlying mechanism involves scarring of the lungs.

It is a fatal lung disease characterised by an unpredictable decline of lung function due to lung fibrosis, Progressive decline in lung function restricts routine physical activity Prognosis is extremely poor .Median survival 2–5 years.

IPF: Presentation:

Approximately 5% of patients are asymptomatic at diagnosis – routine chest radiograph/lung biopsy , In these group however, symptoms developed approximately 2.5 years after the recognition of the radiographic abnormality.

Gradual onset, often greater than 6 months, of dyspnea – exertional, progressive and/or a nonproductive cough Systemic symptoms (uncommon) : Weight loss , Low-grade fevers , Fatigue ,Arthralgias and Myalgias.

Complications may include pulmonary hypertension, heart failure, pneumonia, or pulmonary embolism.

It is important to obtain a complete history, including :medication history amiodarone, bleomycin, nitrofurantoin. Social history , occupational history , exposure history , review of systems to exclude other causes of interstitial lung disease.

On examination:

Clubbing fingers occurs in two-thirds of cases, Fine Crackles (most patients) end-inspiratory crackles are heard on auscultation at lung lower zone which is early Sign, Cyanosis, respiratory failure then Pulmonary Hypertension (Loud P2) , Cor Pulmonale, loud P2 , fixed split S2, – pan systolic murmur of tricuspid regurgitation , legs edema, right ventricular heave , elevation of the jugular venous pressure (JVP). A features of right side heart failure .

Investigations:

Diagnosis requires ruling out other potential causes. It may be supported by a CT scan or lung biopsy which show **Usual Interstitial Pneumonia** (UIP).

Non-specific findings include hypergammaglobulinaemia, positive rheumatoid factor or antinuclear factor ,anti-cyclic citrullinated peptide 2 (anti-CCP2), Presence of high titers may suggest the presence of a connective-tissue disease.

CRP, ESR – may be elevated and an elevated LDH which may reflect active pneumonitis .

Exercise-induced arterial hypoxaemia: 6-Minute walk testing (6MWT) a marker of functional exercise capacity that is being used in the clinical assessment of patients with idiopathic pulmonary fibrosis.

Chest X-ray : lower zone bi-basal reticular and reticulonodular opacities. A 'honeycomb' appearance may be seen in advanced disease but is non-specific .

High resolution CT Scan(HRCT) :a patchy, peripheral, subpleural and basal reticular pattern with subpleural cysts (honeycombing) and/or traction bronchiectasis.

A Lung biopsy is not usually required in those with typical clinical features and HRCT appearances, particularly if other known causes of interstitial lung disease have been excluded, but should be considered in cases of diagnostic uncertainty or with atypical features.

a surgical lung biopsy is required for definitive diagnosis. surgical lung biopsy specimen are obtained through either an open lung biopsy or video-assisted thoracoscopic surgery.

The histopathological lesion associated with idiopathic pulmonary fibrosis shows a focus of fibroblastic proliferation with an area of fibrosis chronic inflammatory cell infiltrate within areas of interstitial collagen deposition fibroblasts and myofibroblasts arranged in a linear fashion.

Pulmonary function Testing –(Restrictive Pattern): Pulmonary function testing Findings are nonspecific and should be used in conjunction with clinical, radiologic, and pathologic information to ensure an accurate diagnosis and for prognosis .

- **Spirometry**
  - **FVC, FEV1:---------Decreased**
  - **FEV1/FVC: -------- Normal or increased**
  - **DLCO----------Decreased**

    Lung Volumes
  - **TLC, RV: ---------Decreased**

Patients who have >10% decline in FVC (percent predicted) over 6 months, decline in DLCO greater than 15% over 1 year have a 2.4-fold increased risk of death.

ECG shows p. pulmonale reflect the pulmonary HTN and Transthoracic Echocardiography to assess right side heart failure.

Management:

- **Prednisolone** therapy (0.5 mg/kg) combined with **azathioprine** (2-3 mg/kg) for patients who are highly symptomatic or have rapidly progressive disease, have a predominantly 'ground glass' appearance on CT or a sustained fall of > 15% in their FVC or gas transfer over a 3-6-month period.
- **Pirfenidone**: Antifibrotic agents a novel compound with combined anti-inflammatory, antioxidant, with antifibrotic effects.
- **Nintedanib** a tyrosine kinase inhibitor
- **Etanercept** (anti TNF-alpha) endothelin receptor antagonists .
- **warfarin, N-acetylcysteine, IFN-γ1b, Sidenafil ,bosentan** is being explored but cannot be recommended outside clinical trials at present.
- **Oxygen** may be provided for palliation of breathlessness .Long term Oxygen therapy when SpO2<88% or PaO2< 55mmHg .
- **Opiates** may be required for relief of severe dyspnoea.
- **Vaccination** against influenza and pneumoccocal infections
- **Lung transplantation:** definitive treatment any patient diagnosed with IPF or probable IPF should be referred for lung transplantation evaluation, regardless of the vital capacity

Prognosis:

- the rate of disease progression varies considerably from death within a few months to survival with minimal symptoms for many years.
- Serial lung function testing may provide useful prognostic information, with relative preservation of lung function suggesting longer survival
- Desaturation on exercise heralding a poorer prognosis.
- The finding of high numbers of fibroblastic foci on biopsy suggests a more rapid deterioration.
- IPF is associated with an increased risk of carcinoma of the lung.

Sarcoidosis:

Sarcoidosis is a multisystem granulomatous disorder commonly affecting young adults and usually presenting with bilateral hilar lymphadenopathy, pulmonary infiltration and skin or eye lesions. unknown etiology characterized by the presence of non-caseating granulomas.
Sarcoidosis often follows a benign course without symptoms or long-term consequences, and it can spontaneously remit.
Arabs and Chinese are rarely affected ,while in USA sarcoidosis is the most common form of ILDs . Sarcoidosis occurs less frequently in smokers.

Clinical features:

Pulmonary disease may also present in a more insidious manner with cough, exertional breathlessness and radiographic infiltrates,chest auscultation is unremarkable. Fibrosis occurs in around 20% of cases of pulmonary sarcoidosis and may cause a silent loss of lung function .
Pleural disease is uncommon and finger clubbing is not a feature.
Complications such as bronchiectasis, aspergilloma, pneumothorax, pulmonary hypertension and cor pulmonale have been reported but are rare.

Löfgren's syndrome-an acute illness of sarcoidosis , characterised by erythema nodosum, peripheral arthropathy, uveitis, bilateral hilar lymphadenopathy (BHL), lethargy and occasionally fever-is often seen in young adults.
Alternatively, BHL may be detected in an otherwise asymptomatic individual undergoing a chest X-ray for other purposes.

Asymptomatic: abnormal routine chest X-ray (~30%) or abnormal liver function tests
Respiratory and constitutional symptoms (20-30%)
Erythema nodosum and arthralgia (20-30%)
Ocular symptoms (5-10%)
Skin sarcoid (including lupus pernio) (5%)
Superficial lymphadenopathy (5%)
Other (1%), e.g. hypercalcaemia, diabetes insipidus, cranial nerve palsies, cardiac arrhythmias, nephrocalcinosis
Lupus pernio: is a chronic raised indurated (hardened) lesion of the skin, often purplish in color. It is seen on the nose, ears, cheeks, lips, and forehead. It is pathognomonic of sarcoidosis.

Investigations and Staging of Pulmonary Sarcoidosis:

Chest radiography has been used to stage sarcoid
Stage I: BHL (usually symmetrical); paratracheal nodes often enlarged: Often asymptomatic, but may be associated with erythema nodosum and arthralgia. The majority of cases resolve spontaneously within 1 year .
Stage II: BHL and parenchymal infiltrates :Patients may present with breathlessness or cough. The majority of cases resolve spontaneously.
Stage III: parenchymal infiltrates without BHL :Disease less likely to resolve spontaneously
Stage IV: pulmonary fibrosis: Can cause progression to ventilatory failure, pulmonary hypertension and cor pulmonale .

Lymphopenia is characteristic and **liver function tests** may be mildly deranged .
Hypercalcaemia may be present (reflecting increased formation of calcitriol-1,25-dihydroxyvitamin D3-by alveolar macrophages), particularly if the patient has been exposed to strong sunlight .

Hypercalciuria may also be seen and may lead to nephrocalcinosis .
Serum angiotensin-converting enzyme (ACE) is a non-specific marker of disease activity and can assist in monitoring the clinical course.

Pulmonary function testing may show a restrictive defect accompanied by impaired gas exchange.
Exercise tests may reveal oxygen desaturation .
Transbronchial (and bronchial) biopsies show non-caseating granulomas .and the mucosa may have a 'cobblestone' appearance at bronchoscopy .
The Broncho alveolar lavage (BAL) fluid typically contains an increased CD4:CD8 T-cell ratio.
HRCT appearances include reticulonodular opacities that follow a perilymphatic distribution centred on bronchovascular bundles.

The occurrence of **erythema nodosum** with BHL on chest X-ray is often sufficient for a confident diagnosis, without recourse to a tissue biopsy. Similarly, a typical presentation with classical HRCT features may also be accepted. However, in other instances the diagnosis should be confirmed by histological examination of the involved organ. The presence of anergy : a lack of reaction (e.g. to tuberculin skin tests) may support the diagnosis.

Management:

Patients who present with acute illness and erythema nodosum should receive NSAIDs and, if symptoms are severe, a short course of corticosteroids.

The majority of patients spontaneous remission and so if there is no evidence of organ damage, systemic corticosteroid therapy can be withheld for 6 months. However, prednisolone (at a starting dose of 20-40 mg/day) should be commenced immediately in the presence of hypercalcaemia, pulmonary impairment, renal impairment and uveitis.

Topical steroids may be useful in cases of mild uveitis, and inhaled corticosteroids have been used to shorten the duration of systemic corticosteroid use in asymptomatic parenchymal sarcoid.

Patients should be warned that strong sunlight may precipitate hypercalcaemia and endanger renal function.

In patients with severe disease methotrexate (10-20 mg/week), azathioprine (50-150 mg/day) and specific TNF-α inhibitors have been effective.

Chloroquine, hydroxychloroquine and low-dose thalidomide may be useful in cutaneous sarcoid with limited pulmonary involvement.

Selected patients may be referred for consideration of single lung transplantation. The overall mortality is low (1-5%) and usually reflects cardiac involvement or pulmonary fibrosis.

Poor prognosis:

Age > 40 years ،

Afro-Caribbean ethnicity،

Persistent symptoms for more than 6 months ،

Involvement of more than three organs ،

Lupus pernio

Stage III/IV chest X-ray.