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RESEARCH ARTICLE

An overview of Interstitial Lung Disease for the Pulmonary medicine resident

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ABSTRACT

With the rapid developments in the field of interstitial lung diseases or diffuse parenchymal lung diseases as it is now called, this review provides an overview of ILDs and explains the gamut of knowledge needed to understand the disease, starting from the anatomy of the interstitium to the causes of interstitial involvement in various diseases and the clinicoradiological patterns of involvement in various interstitial lung diseases. The review is in the format of questions and answers to make it easier for the resident to comprehend.

Introduction

Interstitial lung disease (ILD) has fascinated pulmonologists in the past two decades and there has been a boom of information and knowledge with newer researches and developments in this field. This review discussed in a simple question and answer format, is a bird's eye view on ILDs for the residents to approach the disease with greater confidence. What the pulmonary interstitium means, how it is affected in the process, the various causes of interstitial diseases and the clinicoradiological presentations of various ILDs are herewith discussed.

What is Interstitial Lung Disease?

ILD is a heterogenous collection of lung disorders that are grouped together because they share clinical, radiological and pathological features. They are also referred to as diffuse parenchymal lung disease (DPLD) since interstitium is not the only lung compartment to be affected. The process can also involve cellular and biochemical components of the alveolar wall, the alveolar space, the terminal bronchioles and the small vessels. For example, organising pneumonia and pulmonary alveolar proteinosis are alveolar filling processes, whereas bronchiolitis obliterans and chronic hypersensitivity pneumonitis may center on the airway. [1,2]

What is the Pulmonary Interstitium and how is it involved in ILD?

The lung interstitium is the space between the air sacs and the small blood vessels that surround the air sacs. It contains connective tissue. When we breathe, oxygen from the air passes through our air sacs and lung interstitium and into our blood. At the same time, Carbon dioxide moves from our blood through the lung interstitium and into our air sacs. If we have an ILD, our lung interstitium becomes thick and stiff. This makes it harder for oxygen to move out of the lungs and into the bloodstream and for carbon dioxide to move out of the bloodstream and into the lungs.

How are ILDs classified?

The Current classification of ILD is based on ATS consensus classification of 2018 (1), which is based on radiographic, histopathological and clinical characteristics. Exposure/causation history and clinical features including specific patient characteristics help to classify the disease. Radiographic featuressuch as basilar traction bronchiectasis, honeycombing, ground glass opacities and pathological patterns like acute or granulomatous inflammation, fibrosis and collagen deposition help to classify ILDs.

How do you Classify Based on the Exposure?

Based on the exposure, ILDs are classified as aetiology known and aetiology unknown. [1,2]

ILDs with unknown aetiology include the various idiopathic interstitial pneumonias and the rare forms of ILDs like Lymphangiomyomatosis (LAM) & the various vasculitis. Idiopathic interstitial pneumonias are further classified into Idiopathic pulmonary fibrosis (IPF) and non IPF (which includes NSIP, COP, LIP, AIP), a classification which helps for prognostication and management.

ILDs with known etiology include the various occupational ILDs caused by inorganic exposure such as silicosis, asbestosis, Hypersensitivity pneumonitis caused by organic exposure. Smoking associated ILDs such as DIP, RBILD, LCH, ILDs due to drugs, connective tissue diseases and granulomatous ILDs like sarcoidosis.

What is the Importance of duration of illness in Clinical History of ILDs?

The duration of illness prior to diagnosis gives a clue to the diagnosis of ILDs. Acute ILDs of less than 3 weeks include acute interstitital pneumonitis, esonophilic pneumonitis and BOOP. Subacute ILDs presenting with symptoms lasting 3 to 12 weeks include Sarcoidosis, Drug induced ILDs, alveolar haemorrhage syndromes and CTD- ILDs. Chronic ILDs with symptoms lasting more than 12 weeks include IPF, Sarcoidosis and Pulmonary Histiocytosis X.

What is the Importance of Patient demographics in clinical history of ILD?

Various ILDs present in different age groups and gender. While IPF is predominantly a disease of old age, CTDILDs, Sarcoidosis, LAM and Hereditary ILDs present in a younger age group. Certain ILDS like CTDILD and LAM are more common in women while IPF and LCH are more common in men.

What are the ILDs which present with Respiratory symptoms?

IPF usually presents with progressive dyspnoea and cough. Airway centric ILDs like Hypersensitivity pneumonitis, Esonophilic pneumonitis and Sarcoidosis present with wheezing. Substernal chest pain can be a presentation of Sarcoidosis, while pleuritic chest pain can occur due to serositis in CTD ILD or due to pneumothorax in LAM or LCH. Hemoptyis may a presenting feature of diffuse alveolar haemorrhage.

What are the ILDs which present with systemic symptoms or signs?

Crackles on auscultation may be a feature of any ILD. Inspiratory squeaks may be heard in HP and

pleural rub in CTD ILD. A loud P2 on cardiac auscultation may herald the onset of secondary pulmonary Hypertension.

Peripheral lymphadenopathy and hepatosplenomegaly can be seen in sarcoidosis. Systemic features of CTD ILD include subcutaneous nodules, muscle weakness, erythema nodosum, joint arthritis, heliotrophe rash, malar rash, features of scleroderma and Raynaud's phenomenon. Neurological symptoms like facial palsy may be seen in Sarcoidosis and the vasculitis. Eye signs like Uveitis may be seen in Sarcoidosis and the vasculitis.

What are the clues to diagnosis which can be obtained from past medical history?
A prior diagnosis of Connective tissue disease gives a clue to underlying CTDILD. Past history of HIV may point towards a diagnosis of LIP. Prior liver disease may be a clue to Sarcoidosis or primary biliary cirrhosis and renal disorder may suggest underlying vasculitis or CTD.

How is occupational History important?
Occupational ILDs can occur following exposure to organic or inorganic pollutants. ILDs following inorganic exposure include Silicosis, Asbestosis, Beryllosis and coal workers pneumoconiosis. Silicosis caused by exposure to crystalline silica can be seen in occupations like stone cutting, mining, sand blasting and stone countertop production, Electricians, plumbers, ship builders exposed to asbestos may develop asbestosis. Metal workers may develop berylliosis and coal workers coal worker's pneumoconiosis.

ILDs following organic exposure include Bird breeder's lung which develops due to exposure to bird droppings or feathers, Farmer's lung due to Thermophilic bacteria, Hot tub hypersensitivity pneumonitis seen following exposure to mycobacteria and ILDs seen in office workers following exposure to fungi or molds in humidification systems. [2]

What is the importance of Environmental, Medication and Family History in ILD?
Environmental factors like exposure to pet animals and birds may be associated with Hypersensitivity pneumonitis. Hobbies like playing wind instruments contaminated with fungi and bacteria could lead to hypersensitivity pneumonitis. Several medications like antibiotics such as Nitrofurantoin, antiarrhytmics like Amiodarone, Chemotherapy agents and immunotherapy have been associated with ILDs. Familial ILDs include inborn errors of metabolism like Niemann Picks and Gauchers and rare disorders like Hermansky Pudlak and Neurofibromatosis.

What is the Utility of Imaging in Diagnosis of ILD?
An abnormal chest radiograph is often the first indication of an underlying ILD. The pattern and distribution
of abnormalities gives a clue to the diagnosis. Too many lines are called reticular opacities and too many dots mean nodular opacities, reticulonodular being a combination of the two.HRCT is more sensitive and is the gold standard in the diagnosis of ILD.

HRCT Interpretation

What is secondary pulmonary lobule and why is it important in HRCT interpretations in ILD? [3,4]
The secondary lobule is the basic anatomic unit of pulmonary structure and function. It is the smallest unit of lung surrounded by a connective tissue septa. The type of involvement of the secondary lobule is the basis of interpretation of ILDs.

The secondary lobe measures about 1 to 2 cms and has about 5 to 15 pulmonary acini that contain the alveoli for gas exchange, the secondary lobule is supplied by a small bronchiole (terminal bronchiole) in the centre, that is parallel to the centrilobular artery. Pulmonary veins and lymphatics run in the periphery of the lobule within the interlobular septa. Under normal conditions only a few of these very thin septa will be seen.

There are two lymphatic systems: a central network, that runs along the broncho vascular bundle towards the center of the lobule and a peripheral network, that is located within the interlobular septa and along the pleural linings.

Centrilobular area is the central part of the secondary lobule. It is usually the site of diseases, that enter the lung through the airways (i.e. hypersensitivity pneumonitis, respiratory bronchiolitis, centrilobular emphysema). Perilymphatic areas is the peripheral part of the secondary lobule. It is usually the site of diseases, that are located in the lymphatics of the interlobular septa (i.e. sarcoid, lymphangitic carcinomatosis, pulmonary edema).

What are the basic steps in interpretation of HRCT pertaining to ILD?
A systematic approach to interpretation of HRCT involves the following questions:

- What is the dominant HR-pattern: Reticular or nodular high attenuation (ground-glass, consolidation)
- low attenuation (emphysema, cystic)

- Where is it located within the secondary lobule (centrilobular, peri lymphatic or random)
- Is there an upper versus lower zone or a central versus peripheral predominance
- Are there other associated findings (pleural fluid, lymphadenopathy, traction bronchiectasis)

What are the ILDs presenting with Reticular pattern in HRCT?(4)

A. Lymphangitic carcinomatosis: irregular septal thickening, usually focal or unilateral 50% adenopathy', known carcinoma.

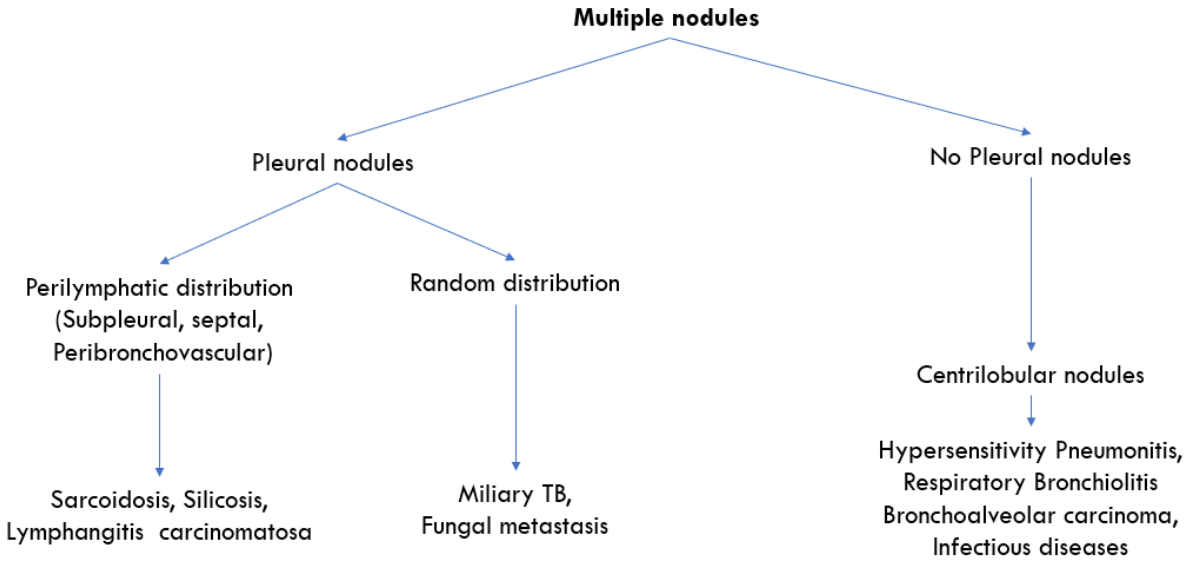
B. Cardiogenic pulmonary edema: incidental finding in HRCT, smooth septal thickening with basal predominance (Kerley B lines), ground-glass opacity with a gravitational and perihilar distribution, thickening of the peribronchovascular interstitium (peribronchial cuffing)

C. Lymphangitic carcinomatosis.

D. Lymphangitic carcinomatosis with hilar adenopathy.

E. Alveolar proteinosis: ground glass attenuation with septal thickening (crazy paving).

F. Cardiogenic pulmonary edema.



What are tree in bud nodules in HRCT and its clinical significance?

Tree in bud nodules are of significance in narrowing the differential diagnosis in centrilobular nodules. Tree-in-bud indicate the appearance of irregular and nodular branching structure, which are more easily identified in the lung periphery. They represent centrilobular bronchioles filled with mucous or pus.

Tree-in-bud almost always indicates the presence of:

- Endobronchial spread of infection (TB, MAC, any bacterial bronchopneumonia)
- Airway disease associated with infection (cystic fibrosis, bronchiectasis)
- An airway disease associated primarily with mucus impaction (allergic bronchopulmonary aspergillosis, asthma).
  - Infection: Tuberculosis, MAC (mycobacterium avium), bacterial and fungal
  - Airway disease (i.e., cystic fibrosis or bronchiectasis)
  - ABPA (Allergic bronchopulmonary aspergillosis (rare))

What is the significance of septal thickening in HRCT?

Septal thickening is due to reticular opacities caused by thickening of interstitium by fluid, fibrous tissue or cells. Septal thickening is uncommon as a predominant finding and has a narrow differential diagnosis. It can be smooth or nodular and irregular. Smooth septal thickening is commonly seen in interstitial pulmonary edema (Kerley B lines on chest film); lymphangitis carcinomatosa, lymphoma and pulmonary alveolar proteinosis while Nodular or irregular septal thickening is seen in lymphangitis carcinomatosa, lymphoma, sarcoidosis and silicosis.

What is the importance of distribution of lesions in HRCT interpretation?

Upper versus lower zone	
Upper zone	***Lower zone***
Inhalation diseases	
Sarcoidosis *Silicosis* *Coal workers pneumoconiosis* *Centrilobular emphysema* *Langerhans cell histiocytosis* *Chron hypersens pneumonitis*	*Edema* *Panlobular emphysema* *UIP in IPF* • *Collagen vascular disease* • *Asbestosis*

Central versus peripheral zone	
Central zone	***Peripheral zone***
Sarcoid	*BOOP/COP*
Bronchitis	*Chronic eosinophilic pneumonia* *Hematogenous metastases* *UIP in:* *IPF (Idip. Pulmon. fibrosis)* *Collagen-vascular diseases* *asbestosis*

What are the associated findings which may be seen in HRCT of ILDs and its clinical significance?

Pleural effusion

- Pulmonary edema
- Lymphangitic carcinoma-often unilateral
- Tuberculosis
- Lymphangiomyomatosis
- Asbestosis

Hilar/mediastinal lymphadenopathy

- Lung carcinoma
- Lymphangitic spread of carcinoma
- Progressive systemic sclerosis
- Active tuberculosis/atypical mycobacterium infection
- Sarcoidosis
- Coal workers' pneumoconiosis (rare)
- Silicosis (rare)

What are the types of increased lung attenuation seen in HRCT?

Increased lung density in HRCT is due to replacement of air in the alveoli by fluid, cells or fibrosis. If the underlying vessels are obscured it is called consolidation and if the vessels are seen it is called ground glass opacity. Dark bronchus sign is seen in GGO where the density of intrabronchial air appears darker than air in the surrounding alveoli. Air bronchogram is a sign seen in consolidation due to air left intrabronchial.

What is Ground Glass Opacity?

Ground-glass opacity (GGO) indicates filling up of alveolar space with fluid, cells or fibrosis. So ground-glass opacification may be the result of air space disease (filling of the alveoli) or interstitial lung disease (fibrosis). The location of the abnormalities in ground glass pattern can indicate the probable etiology

- Upper zone predominance: Respiratory bronchiolitis, PCP.
- Lower zone predominance: UIP, NSIP, DIP.
- Centrilobular distribution: Hypersensitivity pneumonitis, Respiratory bronchiolitis

Ground glass opacity	
Acute	Chronic
Pulmonary edema • Heart failure • ARDS	Hypersensitivity pneumonitis Organizing pneumonia (BOOP, COP) Chronic eosinophilic pneumonia
Pulmonary hemorrhage	
Pneumonia • Viral • Mycoplasma • PCP	Alveolar proteinosis Lung fibrosis • UIP • NSIP
Acute eosinophilic pneumonia	Bronchoalveolar carcinoma

What is Mosaic Attenuation?

Mosaic attenuation indicates patchy areas of black and white lungs caused by density differences between affected and non affected lung areas. The abnormality could be in the black or white lung and the key lies in distinguishing which is the abnormal area. Mosaic attenuation can be caused by infiltrative process adjacent to a normal lung, a normal lung appearing dense adjacent to areas of air trapping or due to a hyperperfused lung adjacent to areas of oligemia due to chronic thromboembolic disease. It is usually seen in Ashtma, bronhchiolitis obliterans, hypersensitivity pneumonitis and pulmonary embolism.

Which ILDs can present as Consolidation?

- Pneumonia: PCP, viral, mycoplasma, bacterial eosinophilic pneumonia, organizing pneumonia (BOOP, COP)
- Edema: Heart failure, ARDS, AIP
- Fibrosis: UPI, NSIP, radiation
- Tumor: Bronchoalveolar carcinoma, lymphoma
- Idiopathic: Sarcoid, alveolar proteinosis

What are the conditions presenting with decreased lung attenuation?

This includes abnormalities that result in decreased lung attenuation or air-filled lesions.
These include:

- Emphysema
- Lung cysts (LAM, LIP, Langerhans cell histiocytosis)
- Bronchiectasis
- Honeycombing

What is the diagnostic criteria for Idiopathic pulmonary fibrosis (IPF)?(1)

- Diagnostic criteria
  - Exclusion of other known causes of ILD
  - Presence of HRCT pattern of UIP
    -UIP pattern – subpleural and basal predominant; distribution often heterogenous
    -Honeycombing with or without traction bronchiectasis or bronchilectasis
  - Specific combinations of HRCT pattern and HPE patterns in patients subjected to lung tissue sampling

How is Non specific interstitial pneumonia (NSIP) identified in HRCT and distinguished from Usual insterstitial pneumonia (UIP)?

NSIP is temporally and spatially homogeneous, while UIP is typically heterogeneous, patchy, and irregular in size. The extent of honeycombing and traction bronchiectasis is greater in UIP than the extent of ground glass opacity or micronodules, which are more commonly associated with an NSIP pattern

What are the important Lab Tests in ILD?

- Transaminitis and Hypercalcemia in sarcoidosis
- Renal insufficiency in Pulmonary-renal syndromes and CTD
- Peripheral eosinophilia in chronic eosinophilic pneumonia, eosinophilic granulomatosis, drug reaction, and vasculitis
- Serum IgG in hypersensitivity pneumonitis
- Serological tests like ANA, Scl 70, RF, CCP, ANCA etc
- Anemia in hemolytic conditions and inflammatory bowel disease
- Elevated creatine kinase and aldolase in inflammatory myopathies
- Lab tests are also needed in determining patient's treatment options

What is the Importance of Pulmonary Function Testing?

- Assessing severity and determining progression, response to therapy and prognosis
- Tests including spirometry, lung volumes, and DLCO
- Typically, spirometry shows a restrictive pattern due to decreased lung compliance and increased lung recoil
- FVC is the commonest measure used to assess a decline in lung function
- OAD in spirometry indicates concomitant COPD, prior smoking exposure, and airway-centric ILDS like LCH, LAM or sarcoidosis
- Decreased DLCO is often the earliest physiological abnormality and can be used to assess the progression and also the development of PHT
- Measuring MIP and MEP useful in inflammatory myopathies
- Exercise testing including 6MWT and pulse oximetry with ambulation.

What is the Role of Bronchoscopy in Diagnosis?
BAL

- Cell count, differential, cytology and culture depending on clinical scenario
- Bloody in DAH
- Milky white in PAP
- Eosinophilic differential >25 % in eosinophilic pneumonia

- Lymphocytic differential >25 % in granulomatous disease

TBLB

- Especially useful in granulomatous disorders like sarcoidosis, HP, infections and malignancy
- EBUS guided aspiration of mediastinal nodes useful in sarcoidosis
- Genomic testing on TBB samples is useful in differentiating UIP from Non UIP where surgical biopsy not possible*

Transbrochial cryo biopsy

- Larger and better-preserved tissues
- Good histopathological yield and lesser mortality and acute exacerbation compared to surgical lung biopsy
- Not yet a recommended part of society guidelines and risk of mild to moderate bleeding about 20%

What is the Role of Surgical Lung Biopsy?

- Yield of TBLB is low
- Cryobiopsy needs expertise
- Surgical lung biopsy more accurate diagnosis performed as VATS
- Wedge biopsies from three separate lobes and should include areas of normal-appearing lungs
- Risks include prolonged air leaks, bleeding, infection and incisional site pain.
- Post-op complications include exacerbation of ILD, Respiratory failure, significant pulmonary hypertension, problems with clotting, and immunosuppression.
- Look for perioperative cardiac events.

What are the various approaches needed for a comprehensive cascade of care for ILD patients?

The cascade of care approach to ILDs includes removal from exposure (such as exposure to birds and pets, cleaning upholstery and environmental modifications), antifibrotic agents, supportive therapies like Oxygen supplementation, management of chronic cough, rehabilitation including smoking cessation, optimising patients activities of daily living and mobility, treatment of comorbidities and complications as they arise, palliative care and lung transplant where needed.

What is the role of antifibrotics and immunosuppressants in the management of ILDs?

Pirfenidone and Nintedanib are the two FDA-approved antifibrotics currently used in the treatment of ILDs. Pirfendone reduces fibroblast proliferation, inhibits transforming growth factor beta-stimulated collagen production, and reduces the production of fibrogenic mediators such as transforming growth factor-beta. It's approved for the treatment of IPF. Nintedanib is a tyrosine kinase inhibitor against fibroblast growth factor receptor (FGF-R), Vascular endothelial growth factor receptor (VEGF –R), and Platelet-derived growth factor receptor (PDGF-R). It is approved in the treatment of IPF, Scleroderma lung disease, and progressive fibrotic lung disease where it has been shown to reduce decline in lung function.

Some patients like scleroderma require a combination of immunosuppression with antifibrotics. Steroids are used in diseases like COP, CEP and HP. Azathioprine and Mycophenolate mofetil in CTILD and Rituximab and cyclophosphamide in scleroderma lung disease, vasculitis with alveolar haemorrhage and severe CTILD

References and further reading

1. Diagnosis of Idiopathic Pulmonary Fibrosis.An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med 2018; 198(5), e44–e68
2. Mathur A, Antin-Ozerkis DE. Interstitial Lung Disease: A Clinical Overview and General Approach. In: Grippi MA, Antin-Ozerkis DE, Dela Cruz CS, Kotloff RM, Kotton C, Pack AI. eds. *Fishman's Pulmonary Diseases and Disorders, 6e*. McGraw-Hill Education; 2023. Accessed March 09, 2024.
3. Webb WR. High-resolution CT of the lung parenchyma. *Radiol Clin North Am* 1989; 27: 1085–1097.
4. Hadda V, Shekh I, Banday IA.,Interstitial Lung Diseases. In: Wander GS (Ed). Postgraduate Medicine, Vol. 1. New Delhi: Jaypee Brothers Medical Publishers; 2022. pp. 1705-17.