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An approach to interstitial lung disease in India

JN Pande

Senior Consultant in Medicine
Sitaram Bhartia Institute of Science and Research, New Delhi

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ABSTRACT

Interstitial lung diseases are common and have varied etiology, clinical presentation, clinical course and outcome. They pose a diagnostic challenge to physicians and pulmonologists. Patients present with dry cough, exertional dyspnoea, interstitial lesions on X-ray of the chest and restrictive ventilatory defect on spirometry. A sharp decline in oxygen saturation with exercise is characteristic. Careful evaluation of the history of the patient and physical examination help in narrowing down diagnostic probabilities. HRCT of the chest has emerged as an important tool in the evaluation of these disorders. Idiopathic Interstitial Pneumonias (IIP) are a group of conditions which are classified into several types based on pathological features. Bronchoscopic procedures are helpful in diagnosis of certain disorders but are of limited value in classification of IIP which requires surgical biopsy. Usual Interstitial Pneumonia (UIP), also referred to as Idiopathic Pulmonary Fibrosis, has a progressive course and an unfavourable outcome. Certain new drugs have recently become available for treatment of UIP. Our approach towards diagnosis and management of interstitial lung diseases based on personal experience over the past three decades is reported here.

Key words : Usual interstitial pneumonia – sarcoidosis – pneumoconiosis – bronchoscopy – lung biopsy

Correspondence : Dr. J.N Pande, Senior Consultant in Medicine, Sitaram Bhartia Institute of Science and Research, B 16, Qutab Institutional Area, New Delhi 110016.
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INTRODUCTION

Interstitial lung diseases (ILD) have numerous causes, varied clinical presentation and non-specific radiological findings which make definitive diagnosis a challenging task. Idiopathic interstitial pneumonia (IIP) constitute a bulk of ILDs referred to pulmonologists for diagnosis and management. Idiopathic Pulmonary Fibrosis (IPF), also referred to as Usual Interstitial Pneumonia (UIP) is the most common form of IIP and is associated with a poor prognosis. Lung biopsy is often recommended for definitive diagnosis of ILDs and IIPs. Even experienced lung pathologists are sometimes unable to make a definitive diagnosis, particularly on tiny trans-bronchial lung biopsy (TBLB) specimens. Adequate lung biopsy specimen requires an open surgical biopsy which is often a formidable task in these patients who may have severely compromised pulmonary reserve even at the time of first presentation. A coordinated approach with chest physician, radiologist, microbiologist and pathologist is required for best results. Therapeutic trial with treatment directed at the most likely diagnosis is sometimes justified.

Clinical Features:

The spectrum of disorders which may present with features of ILD is very large. Careful clinical, radiological, functional and laboratory evaluation is often helpful in narrowing down the diagnostic probabilities. ILD presents with a clinical triad of dry cough with exertional dysnpoea, reticulo-nodular opacities on X-ray of the chest, and restrictive ventilatory and diffusion defects with sharp fall in oxygen saturation on exercise. Presentation may be acute, sub-acute or insidious **(Table 1)**.

Table 1 : Common ILDs according to onset of clinical presentation

Acute	Sub-acute	Insidious
Infections (TB, viral, fungus, mycoplasma, PCP)	Hypersensitivity pneumonitis	Pneumoconiosis
Intrapulmonary haemorrhage (Goodpastures, SLE, WG, Idiopathic pulmonary hemosiderosis, bleeding diathesis)	Tropical pulmonary eosinophilia	Idiopathic interstitial pneumonias
Pulmonary congestion, LVF	Infections: TB, fungus	Collagen vascular disease (PSS, RA, overlap syndrome)
Acute injury related to drugs, fumes, radiation	Sarcoidosis	Chronic eosinophilic pneumonia

Acute idiopathic interstitial pneumonia	Drug, radiation induced, oxygen toxicity	Sarcoidosis
	Cryptogenic organizing pneumonia	Langerhans cell histiocytosis
	Non-specific interstitial pneumonitis	
	Collagen vascular disease	
	Carcinomatosis lymphangitis	

Detailed clinical history is of utmost importance and cannot be superceded by expensive and invasive investigations. Of particular note are attention to occupational and environmental exposures, drug intake, constitutional symptoms, extra-thoracic manifestations, associated co-morbidities (diabetes mellitus, heart failure, HIV infection, malignancy) and rate of progression of disease.

Tables 2 and **3** list important clinical features which are helpful in differential diagnosis of ILDs.

Table 2 : Clinical characteristics helpful in differential diagnosis

- **Age:** Sarcoidosis, RA, SLE, PSS, Sjogren's syndrome common in young, IIPs (particularly UIP) in the older age groups
- **Gender:** CVDs, Lofgren's syndrome in women
- **Tobacco smoking:** DIP, respiratory bronchiolitis associated IIP
- **Occupational exposure:** Hypersensitivity pneumonitis, pneumoconiosis
- **Onset of symptoms:** Acute, subacute or chronic
- **Drug intake:** cytotoxics, amiodarone, NFT
- **Family history:** sarcoidosis, UIP
- **Febrile illness:** infections, SLE, vasculitis, sarcoidosis, TPE
- **Hemoptysis:** vasculitis (WG), pulmonary haemorrhage, hemosiderosis, Goodpasture's
- **Athralgia/arthritis:** sarcoidosis (ankle arthritis), RA (hands)
- **Skin lesions:** Sarcoid lesions, EN, vasculitic ulcer, subungual infarct, heliotrope, PSS, rheumatoid nodule, butterfly rash
- **Eye involvement:** Uveitis, conjunctivitis, scleritis, xerophthalmia in sarcoidosis, CVD, WG, Sjogren's
- **Peripheral lymphadenopathy:** TB, sarcoid, fungal infection, HIV
- **Digital clubbing:** UIP
- **Raynaud's phenomenon:** PSS

Table 3 : Clinical features helpful in differential diagnosis

- Dyspnea aggravated by exercise, rapid shallow breathing, labored respiration, fall in SpO_2 with exercise are characteristic of most forms of ILDs
- Bibasilar fine inspiratory crepitations (velcro) and digital clubbing are characteristic of UIP.
- Few symptoms (dyspnea and cough) and crepitations despite significant radiological abnormalities favor sarcoidosis
- Few crepitations despite dyspnea and radiological findings seen in PSS, pneumoconiosis

Sarcoidosis :

It is an important cause of interstitial lung disease when it progresses to stage II or beyond. Sometimes stage I disease, characterized by large bihilar and right paratracheal lymphadenopathy, remains unrecognized because of paucity of symptoms at that stage and patients present after the development of respiratory symptoms and interstitial pulmonary infiltrates. A routine enquiry regarding the availability of any old x-rays of the chest is sometimes rewarding as it may show characteristic radiological abnormalities which had been missed earlier.

Sarcoidosis is a multi-system disorder (1) with involvement of cervical lymph nodes, salivary and lacrimal glands, eyes, brain, heart, skin, joints, erythema nodosum, Bell's palsy, hypercalcemia, hepatosplenomegaly, and constitutional symptoms such as fever in some of the patients. There are widespread non-caseating granulomas in one or more of these organs whose biopsy would help in confirming the diagnosis. Intrathoracic disease is present in almost all at various stages of disease. Tuberculin skin test is negative and serum angiotensin converting enzyme is raised in a majority of patients with active disease. We have reported observations on various aspects of sarcoidosis several years ago when this disease was considered relatively uncommon in India (2-6).

In stage II and III disease, the magnitude of pulmonary parenchymal involvement on X-ray of the chest is out of proportion to the clinical symptoms, particularly shortness of breath, adventitious sounds in the chest, pulmonary dysfunction, and lung shrinkage. Extensive pulmonary fibrosis with marked disability and severe hypoxemia is a late development after several years or decades of disease.

At the stage of mediastinal lymphadenopathy and mild pulmonary infiltration (Stage I or early stage II disease), the differential diagnosis is mainly tuberculosis. Fiberoptic

procedures including transbronchial needle aspiration from the lymph node are often undertaken, but they are unhelpful in differentiating between the two conditions as AFB stains and culture are rarely positive.

Progression to stage III is associated with regression of characteristic hilar and mediastinal lymphadenopathy and increase in pulmonary parenchymal lesions. On HRCT of the chest the lung lesions are characterized by pulmonary reticulo-nodular lesions with peri-bronchovascular configuration which is distinct from sub-pleural interstitial septal thickening seen in UIP or NSIP.

Oral steroids are the mainstay of treatment for patients with stage II or III disease. Treatment should be initiated only when the patient is sufficiently symptomatic, as there is no evidence to suggest that the long term outcome is influenced by early treatment. Patients requiring prolonged steroid or other immunosuppressant therapy should be carefully assessed for the need of prophylactic anti-tuberculosis drugs to prevent reactivation of latent tuberculosis, particularly when the probability of tuberculosis can not be ruled out.

Overall, the diagnosis of sarcoidosis is much simpler, and the prognosis much better, compared to IIPs: UIP or NSIP.

Hypersensitivity Pneumonitis :

Numerous environmental and occupational exposures may lead to hypersensitivity pneumonitis (7). High level of clinical suspicion, detailed history of environmental exposures, predominant involvement of upper and mid-zones, demonstration of precipitins against common offending antigens, mild peripheral blood eosinophilia and favourable response to oral steroids characterize this disorder. Farmer's lung and exposure to pigeons are the most frequent disorders in India, but remain largely undiagnosed because of the lack of facilities for serological diagnosis.

Pneumoconiosis :

Several forms of pneumoconiosis are associated with interstitial lung disease with variable degree of fibrosis. Incidence of silicosis has gone down in the recent years with greater awareness of this dreadful disease and stricter enforcement of industrial hygiene at work place in the organized sector. Occasional patients with silicosis are still encountered amongst those exposed to dust in stone-crushing industry. Diagnosis is straightforward once the occupational history is obtained, but the disease has also been noted in those living or working in the vicinity of the stone crushers. Relentless progression of disability and destructive and sometimes conglomerate fibrosis with few auscultatory findings on examination of the chest are characteristic of this disorder. Presence of lymphocytosis in the boncho-alveolar lavage fluid, and a favourable response to oral steroid

therapy were reported by us many years ago (8,9). Silicosis however is a fatal disease and almost all patients seen by us died within a decade.

Asbestosis and coal-workers' pneumoconiosis are other forms of pneumoconoses seen in India. Their incidence is declining rapidly with strict enforcement of health safety measures in the mining industry.

Interstitial lung disease secondary to collagen vascular diseases :

Progressive systemic sclerosis is invariably associated with interstitial pulmonary fibrosis of variable degree. Disease is slowly progressive with respiratory failure and pulmonary hypertension as the cause of death in most patients. Diagnosis is literally written on the face, but some patients may have only Raynaud's phenomenon and minimal skin changes at the time of presentation with pulmonary symptoms. Basal inspiratory crackles are usually present at the time of presentation. We reported beneficial effect of oral steroids many years ago, and pulse therapy with steroids and cyclophosphamide has also been practiced. Recent observations, however, negate the benefit from these forms of treatment and the condition continues to progress despite currently available therapies.

Rheumatoid arthritis is the most common rheumatological disorder which is occasionally associated with pulmonary manifestations. Interstitial pulmonary fibrosis is one form of lung involvement, besides rheumatoid nodules and pleural effusion. The diagnosis is relatively simple but the joint symptoms in sarcoidosis may be confused with rheumatoid arthritis in early stages.

Multi-system involvement with distinctive extra-pulmonary features in **systemic lupus erythematosus, dermatomyositis, Wegener's granulomatosis** (10), **Churg-Strauss Syndrome and systemic vasculitides** can usually be recognized on the basis of clinical features and appropriate serological tests.

Infections with an ILD Radiological appearance :

Several infections caused by bacteria, fungi and parasites look like ILD on an X-ray of the chest. This is an important consideration in India where infectious diseases continue to be rampant and are important diagnostic considerations globally. The list of agents responsible for ILD like appearance radiologically is very large. Most of these conditions are acute or sub-acute and illness is febrile. Examples include interstitial pneumonia caused by atypical pathogens and viruses, Pneumocystis, mycobacteria (11) and fungi. Bronchoscopic procedures are helpful in establishing the microbiological diagnosis in some of these patients whereas serological investigations are helpful in others.

Tropical pulmonary eosinophilia is common in certain parts of the country and the diagnosis is established by

presence of intense eosinophilia and response to diethyl carbamazine.

A **miscellaneous group of conditions** may produce a picture of ILD. Various conditions include lymphatic obstruction in carcinomatosis lymphangitis, radiation fibrosis, drug induced pneumopathies, Langerhans histiocytosis, oxygen toxicity, sequel of acute respiratory distress syndrome, intra-pulmonary haemorrhage (Goodpasture's syndrome, other causes), pulmonary hemosiderosis (idiopathic or secondary to chronic pulmonary congestion in mitral stenosis) and pulmonary alveolar microlithiasis. Pulmonary congestion due to left ventricular dysfunction has sometimes been mistaken for ILD; ground-glass appearance on HRCT has sometimes added to this confusion. Each one of these disorders has its own clinical spectrum and familiarity with all of them is necessary to arrive at a definitive diagnosis.

Idiopathic Interstitial Pneumonias (IIPs) :

Exclusion of all of the above groups of conditions by appropriate clinical history, physical examination, radiological and laboratory investigations including organ biopsies leaves behind a group of conditions included under the broad heading of IIPs. These include Usual Interstitial Pneumonia also known as Idiopathic Pulmonary fibrosis, Nonspecific Interstitial Pneumonia (NSIP), Acute Interstitial Pneumonia (formerly termed Hamman-Rich syndrome), Lymphoid Interstitial Pneumonia (LIP), Desquamative Interstitial Pneumonia (DIP), Cryptogenic Interstitial Pneumonia (COP) or Respiratory Bronchiolitis associated pneumonia. UIP and NSIP account for majority of patients, other conditions are rare. Excellent reviews, consensus statements and management guidelines have been published in the past 5 years (12-25). Areas of uncertainty have been identified as also the areas for future research. We reported our observations on idiopathic pulmonary fibrosis in India several years ago (26,27). Considered an uncommon disorder and often misdiagnosed 25 years ago, IPF today accounts for almost 20% of the outpatients seen by me at a private hospital. This of course may reflect a large referral bias.

UIP which accounts for more than half of IIPs continues to have a dismal prognosis with a median life expectancy of 3-5 years. NSIP continues to be poorly defined and has a better prognosis with favourable response to oral steroids.

Radiological features on plain X-ray of the chest are shown in **Table 4.** X-ray of the chest is the usual initial investigation which raises the suspicion of interstitial lung disease. It also shows the type, extent, severity and distribution of the lung lesions. Presence of lung shrinkage, if present, can also be noted. The type of lung lesions, their distribution, presence of associated mediastinal lymphadenopathy, pleural involvement, honeycombing, ground glass appearance, cardiomegaly, pulmonary venous

Table 4 : Radiological findings on plain radiograph of chest

- Reticular, reticulonodular lesions, often more prominent at the bases
- Micronodular lesions, miliary shadows
- Diffuse alveolar damage, ground glass
- Lung shrinkage
- Honeycombing, cystic lesions, cavitations
- Hilar, mediastinal lymphadenopathy
- Pleural reaction, pneumothorax, calcification

hypertension, and several other features provide important clues regarding the likely diagnosis.

HRCT of thorax has emerged as one of the most important investigations in the evaluation of patients with ILD. Careful evaluation of distribution interstitial septal thickening noting its distribution (patchy or diffuse, symmetrical or asymmetrical, basal or upper zone predominance, subpleural or interlobar, interlobular or peribroncho-vascular predominance), presence honeycombing, traction bronchiectasis, air-trapping, and ground-glass appearance, mediastinal lymphadenopathy, and pleural involvement are extremely helpful in differentiating usual interstitial pneumonia (UIP or idiopathic pulmonary fibrosis) from non-specific interstitial pneumonia (NSIP), desquamative interstitial pneumonia (DIP), cryptogenic organizing pneumonia, hypersensitivity pneumonitis, and sarcoidosis. A typical UIP pattern on HRCT with typical bibasilar velcro crepitations and digital clubbing virtually confirms the diagnosis of UIP and obviates the need of open surgical biopsy of the lung. CT chest is diagnostic in Langerhans histiocytosis and miliary tuberculosis. Presence of necrotic and conglomerate mediastinal lymphadenopathy is helpful in differentiating tuberculosis from sarcoidosis.

Bronchoscopic procedures are useful in some patients when sarcoidosis, intra-pulmonary haemorrhage, DIP or infectious disorders (e.g., tuberculosis, fungal infections, Pneumocystis etc) are being considered. Bronchoscopic procedures include bronchial biopsy, transbronchial lung biopsy, trans-tracheal/bronchial needle aspiration and bronchoalveolar lavage fluid analysis. We have reported our observations of broncho-alveolar lavage in a variety of patients with interstitial lung diseases including sarcoidosis, miliary tuberculosis, silicosis, tropical pulmonary eosinophilia and several others (28-30). However, undertaking bronchoscopic procedures in patients with HRCT findings suggestive of UIP or NSIP is non-contributory and unrewarding.

Immunological investigations are helpful in the diagnosis of ILD secondary to collagen vascular diseases in patients with joint and skin involvement. Presence of anti-neutrophilic cytoplasmic antibodies (ANCA) in patients with lung nodules would confirm the diagnosis of Wegener's granulomatosis without a lung biopsy. Presence of antinuclear antibodies or rheumatoid factor in high titers would suggest appropriate diagnosis; low titers are not uncommon in UIP and NSIP. Biopsy/FNAC of easily accessible organs such as skin, subcutaneous nodules, parotid, and palpable peripheral lymph nodes are highly rewarding in patients with such lesions.

UIP is a dreaded disease which is relentlessly progressive and ends fatally within 3-4 years after diagnosis. It does not respond to steroids except for providing temporary relief during acute exacerbations. It can mostly be diagnosed from clinical features and HRCT findings, but an open lung biopsy (transthoracic route using VATS) may be required for patients with overlapping features. American Thoracic Society has proposed certain criteria for the diagnosis of UIP which may be adequate for diagnosis in the absence of lung biopsy **(Table 5)**.

Table 5 : ATS/ERS criteria for diagnosis of idiopathic pulmonary fibrosis in absence of surgical lung biopsy

Major Criteria:

1. Exclusion of other known causes of ILDs such as certain drug toxicities, connective tissue diseases, environmental exposures
2. Abnormal lung functions with restrictive ventilatory defect, impaired gas exchange with hypoxemia worsened by exercise and impairment of pulmonary diffusing capacity
3. Bibasilar reticular opacities with minimal ground glass changes on HRCT
4. Transbronchial lung biopsy or BAL showing no features to support an alternative diagnosis

Minor Criteria:

1. Age >50 years
2. Insidious onset
3. Duration of illness more than 3 months
4. Bibasilar Velcro crepitations

NSIP appears to be related to some kind of poorly defined immunological disorder at the present time. It responds to oral steroids and has a much better prognosis. DIP occurs mainly in elderly smokers, responds well to steroids after smoking cessation, and has good prognosis. COP also is steroid responsive, but the final prognosis depends on its cause. Sarcoidosis is eminently responsive to steroids. Use of steroids in patients with tuberculosis or other infections may be disastrous. Prolonged use of steroids, without using chemoprophylaxis in patients with latent tuberculosis (tuberculin or interferon gamma release assay positive) may also spell trouble. There are no clear guidelines on this issue in our country, and clinical judgement is required for risk/ benefit analysis.

Major clinical features of IIPs have been summarized in **Tables 6-12**

Table 6 : Idiopathic pulmonary fibrosis (Usual interstitial pneumonia)

- Most common and dreaded form of IIP
- More common in older subjects, males
- Basal predominant reticular lesions, patchy and asymmetrical, lung shrinkage
- Subpleural interstitial septal thickening, honeycombing, bronchiolectasis, traction bronchiectasis, architectural distortion, rare focal ground-glass. (UIP appearance)
- 50-80% mortality in 5 years; more lethal and disabling than many cancers

Table 7 : Non-specific interstitial pneumonia

- Subacute to chronic; 25% of IIP
- Ground-glass and reticular opacities on X-ray chest. CT shows peripheral distribution, sub-pleural location, basal predominance, symmetrical interstitial septal thickening, ground-glass appearance, honeycombing unusual
- Cellular and non-cellular NSIP pathology
- Overlap with UIP appearance common
- Responds to corticosteroids; <10% mortality in 5 years

Table 8 : Cryptogenic organizing pneumonia

- 10% of IIP
- Patchy bilateral consolidation on X-ray chest
- CT: peripheral/peribronchial distribution of patchy consolidation and/or nodules
- Differential diagnosis includes infections, sarcoidosis, vasculitis, bronchoalveolar carcinoma, NSIP
- Steroid responsive; death rare

Table 9 : Acute interstitial pneumonia

- Rare disorder (? Same as Hamman-Rich)
- Characterized by diffuse alveolar damage pathologically
- Progressive diffuse ground-glass density or consolidation on X-ray chest and CT
- Differential diagnosis: Pneumonia, pulmonary edema
- Steroids may be tried
- 60% mortality in <6 months

Table 10 : Desquamative interstitial pneumonia

- Subacute/chronic disorder in smokers, accounting for 15% of IIP
- Ground-glass attenuation on X-ray chest and CT: lower zone and peripheral predominance, reticular lines
- Differential diagnosis: PCP, sarcoidosis, hypersensitivity pneumonitis, RB-ILD
- Smoking cessation and steroids are curative; 5% mortality in 5 years

Table 11 : Respiratory bronchiolitis associated interstitial pneumonia

- Subacute/chronic disorder in smokers
- X-ray chest and CT show bronchial wall thickening, centrilobular nodules, patchy ground-glass opacities
- Differential Diagnosis: DIP, NSIP, HSP
- Smoking cessation and steroids highly effective, mortality 5% in 5 years

Table 12 : Lymphoid interstitial pneumonitis

- Rare disorder, females predominate
- Diffuse reticular opacities and nodules on x-ray chest
- CT: centrilobular nodules, ground-glass, septal and bronchovascular thickening, thin walled cysts
- Differential diagnosis: Sarcoidosis, lymphangitis carcinomatosis, Langerhans cell histiocytosis
- Steroid responsive

Definitive treatment for UIP is lung transplantation. This is currently not available in our country for lack of brain-dead organ donors. Not advising this option for patients in the US may land physicians in legal trouble. Not advising open lung biopsy in suspected UIP may also spell the same. The experience of Indians going to the US for lung transplantation has been pathetic.

Is there any hope for patients with UIP beyond symptomatic treatment, family and physician support, BiPAP or CPAP, continuous oxygen therapy, antibiotics when indicated, and occasional use of steroids during acute exacerbations? N-acetyl cysteine was reported to retard the progression of disease three years ago. The drug has no major side-effects and may be used for all patients with UIP (31). The use of azathioprine, a cytotoxic drug,is no longer justifiable in view of the recent reports. The use of Pirfenidone (pirfinex) has been shown to be beneficial in retarding the progression of disease in a meta-analysis of four published RCTs. (32,33,34*). It appears to be a logical choice in our present state of ignorance about this disease. It is being extensively used in patients with UIP in India. It became available in India ahead of its approval by the FDA for use in the US. Although there are no published reports, both physicians and the patients appear satisfied with the outcome. The risk of development of skin cancers appears less likely in Indians who have lower incidence of cancers caused by exposure to UV radiations. Acute exacerbations of UIP respond to short courses of steroids.

Palliative care is as important in the management of patients with advanced pulmonary fibrosis and respiratory failure as in cancer management. The expected natural history of disease along with likely complications needs discussion with the family members and the patient. End of life issues also need to be discussed. 'Non-abandonment' of the patient who becomes terminally ill is important. Advance directives from the patient and the family members regarding the use of ventilator support in the intensive care unit would help physicians make informed choices.

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