Interstitial Lung Disease (ILD) is a condition in which the interstitium becomes inflamed. After the inflammation occurs, the scarring (fibrosis) develops. Even among the many types of the disease, ILD’s progression can vary from person to person, and people respond differently to therapy. This is why it is important to have the specific diagnosis made along with the staging of the disease (how much of the affected tissue is involved and how much is scarred).

CFA is a progressive fibrosing inflammatory disease of lungs of unknown etiology. It is the end result of multiplicity of pathological processes, from infection to autoimmune diseases.

The term “Pulmonary fibrosis” describes a clinical endpoint of many pathological processes and the adjective, idiopathic or cryptogenic is applied.

Hamman-Rich syndrome were the first to describe this condition which was slow gradually progressive, with dyspnoea, following a fulminant course and leading to death with cor-pulmonale or respiratory failure.

The most common symptoms are shortness of breath with exercise and a non-productive cough. Some patients may also have fever, weight loss, fatigue, muscle and joint pain, and abnormal chest sounds, depending upon the cause. Rounding of the fingers (clubbing) is common in one form of ILD. Heart involvement is generally seen only in advanced cases.

Clinical Classification of Interstitial Lung Disease

Connective Tissue Diseases

Scleroderma
Polymyositis - dermatomyositis
Systemic Lupus Erythematosus

Rheumatoid arthritis
Mixed connective tissue disease
Ankylosing spondylitis
Treatment or Drug-induced
Antibiotics (furantoin, sulfasalazine)
Antiarrhythmics (amiodarone, tocainide, propranolol)
Anti-inflammatory agents (gold, penicillamine)
Anticonvulsants (phenytoin)
Chemotherapy agents (mitomycin C, bleomycin, busulfan, cyclophosphamide, Azathioprine, BCNU, methotrexate)
Therapeutic radiation
Oxygen
Cocaine

Primary Diseases
Sarcoidosis
Eosinophilic granuloma
Amyloidosis
Lymphangitic carcinoma
Bronchoalveolar carcinoma
Pulmonary lymphoma
Adult Respiratory Distress Syndrome

Acquired immunodeficiency syndrome (AIDS)
Bone marrow transplantation
Postinfectious
Respiratory bronchiolitis
Eosinophilic pneumonia
Diffuse alveolar hemorrhage syndrome

Occupational and Environmental
Inorganic dusts
Asbestosis
Silicosis
Coal worker’s pneumoconiosis
Talc pneumoconiosis
Organic dusts
Bird breeder’s lung
Farmer’s lung

Idiopathic Pulmonary Fibrosis (IPF)
Acute interstitial pneumonia (AIP)
Usual interstitial pneumonia (UIP)
Sporadic form
Familial form (Familial pulmonary fibrosis (FPF))
Desquamative interstitial pneumonia (DIP)/ Respiratory bronchiolitis interstitial lung disease (RBILD)
Nonspecific interstitial pneumonia (NSIP)

Epidemiology
The median age of diagnosis is seventh decade. Increased reports of death due to ILD in developed as well as developing countries. M>F. Data collected from death certificates (1981-90) from people who died of CFA, it was concluded that there was very little evidence of any contribution from environmental factors.

Pathogenesis
The pathogenesis is not completely understood. It is a combination of type III (immune complex) and type IV (cell mediated) reactions. Aberrant defensive reaction at alveolar level caused by unknown agent triggers lymphocyte/cytokine mediated in ammatory reaction. Toxic O2 metabolites and proteases damage pneumocytes and intersitium. monocytes/macrophages move in and release growth
factors leading to fibrosis, vascular and smooth muscle proliferation. The initial inflammatory reaction leads to healing by inappropriate alveolar wall fibrosis and destruction of normal alveolar wall of type I and endothelial cell, with proliferation of type II cell. Lung damaged by collagen scarring. Why this process of destruction continues? Because the trigger is in situ, so it continues to damage alveolar wall. “HONEYCOMB LUNG” - end stage scarred, retracted, shrunken, lung - dilated air spaces from destroyed lung alternate with fibrous scars - pleura is “hobnailed” (bumpy) due to interstitial retraction.

Clinical Features
Most commonly presents in older patients, with progressive dyspnoea on exertion (90%), non productive cough (75%), 5% of the patients are discovered at a asymptomatic stage by incidental chest film or doctor hearing crepitations. Systemic symptoms such as fever, weight loss, myalgia, arthralgia may be the mode of presentation which shows the slow, progressive and chronic nature of the disease. Finger clubbing 50% of the patients, auscultation of the chest reveals bilateral gravity dependant inspiratory crepitations. With further progression and pulmonary hypertension cyanosis become evident. In some patients sign of connective tissue disorder like rheumatoid arthritis, SLE, Scleroderma may coexist. HPOA and pneumothorax, may occasionally be seen. The course of the disease is variable, it may range from an acute, rapidly progressive condition that may progressive to death within month to very slowly progressive one, even apparently arrested pulmonary fibrosis. But in general the younger the patient, the more acute the history, the more likely the response to treatment.

Radiology
In the early stage the Chest X-ray (CXR) may be normal inspite of dyspnoea, initial CXR resembles bilateral pneumonia with extensive patchy shadows, more in the lower zones, mottling - ground glass appearance (2 mm diameter) shadows, which may increases to 3 mm in size and take the shape of honey combing of lung, emphysematous bullae, fibrosis may occur with shrinkage of lung, elevation of diaphragm and cor-pulmonale.

Computer Tomography
HRCT, three types of shadows may be recognized, early active in ammatory disease is characterised by ground glass appearance, with hazy appearance of normal lung parenchyma, but preservation of vascular of vascular shadows. As fibrous tissue is laid down the appearance of a thickened interlobular and interlobar septa, giving a reticular pattern. The shadows are predominantly in the lower zones and subpleural initially and later it becomes generalized. Finally mature fibrosis with bronchial ectasia and destruction of lung architecture is represented by thickwalled cystic changes 5-10mm in diameter, so called “honey combing”

Pulmonary Function Test
In earlier stage the lung volumes may normal, but as disease progresses all compartments of the lung decreases with relatively greater reduction in vital capacity. The single breath diffusion capacity for CO is reduced early and PaO₂ may be normal at rest, but falls during exercise when the alveolar arterial PaO₂ is increased. Hyperemia is associated V:P mismatch. Lung compliance is reduced with greater transpulmonary pulmonary pressure changes and consequent increase in work of breathing. The T.V. is reduced in proportion to reduction in Vital Capacity and increased ventilation during exercise is achieved by increase in respiratory rate.

Bronchial Alveolar Lavage
BAL uid shows excess of neutrophils and eosinophils. BAL is more informative in a prognostic sense, in that high proportion of neutrophils (74%) over eosinophils (73%) are indicative of poor response to
steroids. Relative lymphocytosis (>11%) may also be an indication of active alveolar infiltration and a better response to steroids.

Treatment
The goals of treatment are:
Early identification and aggressive treatment to lessen inflammation and prevent further lung damage.
Remove the source of the problem, if known.

Lessen Complications
Because therapy will not reverse scarring which has already taken place, it is extremely important to diagnose and treat the disease as early as possible. If an occupational or environmental exposure has been identified, removal from the source of the problem is essential. Patients who respond well to therapy generally report fewer symptoms, show chest x-ray improvement, decreased shortness of breath with exercise and stable breathing tests.

Oral prednisone or methylprednisone is frequently the first medication used. For a small percentage of patients steroids will help decrease inflammation and cause a dramatic improvement.

However, some patients experience only partial improvement with steroids. The response to treatment is related to the type of ILD and the amount of inflammation present. Follow up chest x-ray, exercise tests, and pulmonary function tests will help evaluate if disease has stabilized or improved. Improvement may not be seen for 6-12 weeks. Cyclophosphamide may be used if steroid therapy has failed to be effective or if corticosteroid treatment is not possible. Response to therapy may be slow and require up to 6 months or longer. In some cases, a combination of prednisone and cytoxan is used with good results. Some of the side effects associated with cyclophosphamide are: gastrointestinal irritation, bladder in ammation, bone marrow suppression, infection, irregular menstruation, and blood disorders.

Azathioprine is used if there are problems tolerating the side effects of the above medications. The side effects may include fever, skin rash, gastrointestinal irritation, and blood disorders.

Oxygen therapy is required for some patients with ILD. Due to their decreased lung function, their blood oxygen level is inadequate. Some may need oxygen therapy all of the time while others may need it only during sleep and exercise. A pulmonary rehabilitation program is often recommended to help an ILD patient achieve his/her highest possible functioning capacity. This program includes education, exercise conditioning, breathing retraining, energy saving techniques, respiratory therapy, nutritional counseling, and psychosocial support. Lung transplant is becoming a viable option for some patients with advanced stage ILD.

Although current therapy for IPF has been less than successful, molecular biologic approaches have provided substantial insight into the pathogenesis of IPF. As a result, a wide range of potential mediators of inflammation and fibrosis—including pro-inflammatory and regulatory cytokines, adhesion molecules, angiogenesis factors, growth factors, and fibrogenic factors have been identified, and some of these are now the focus of clinical research. Potential targets for therapeutic intervention include the initial injurious agent in IPF. Unfortunately, this agent has not yet been identified. Pro-inflammatory cytokines that are released early in the disease process and initiate a cascade of other pathogenetic mechanisms represent a second potential target. These include cytokines that affect the balance between pro-inflammatory factors and anti-inflammatory factors. Finally, those growth factors that participate in the final common pathway leading to fibrosis represent a logical target.

ILD Program Clinical Research Studies
Current Trials for the efficacy and safety of newer therapies in IPF are being undertaken like:
- Etanercept (Embrel),
- Bosentan (Tracleer),
- FG-3019 (Recombinant human monoclonal antibody to Connective Tissue Growth Factor,
- Interferon-gamma l-b(rIFN-g lb).

Suggested Further Reading

2. Erofton and Doudlas’s Respiratory Diseases. 5th Edition.
3. Fishman’s Pulmonary diseases and Disorders by A.P. Fishman.