ABSTRACT

Idiopathic pulmonary fibrosis is a relentlessly progressive interstitial lung disease characterized pathologically by fibroblastic proliferation and progressive lung scarring and clinically by progressive dyspnoea and restrictive lung disease. The cause remains undetermined. The condition appears to evolve from a cryptic alveolar injury. The condition is established by exclusion of other known causes of interstitial lung diseases. The amount of fibrosis is determined by HRCT. Corticosteroids are used to suppress inflammation thus preventing progression of fibrosis. Immunosuppressive agents and supplements of oxygen are useful in the management.

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a relentlessly progressive interstitial lung disease (ILD) characterized pathologically by fibroblast proliferation, extracellular matrix deposition and progressive lung scarring.

The term interstitium is a misnomer as it refers specifically to a potential space between the alveolar epithelial and capillary endothelial basement membranes. The interstitial space contains the elements of connective tissue consisting of collagen and elastic fibres embedded in proteoglycan ground substance. It is predominantly made up of type I and type II collagen. Collagen forms 60-65% of pulmonary interstitium. It also contains fibroblasts, lymphocytes, dendritic cells and mononuclear cells that are undergoing maturation into macrophages. In addition there are non-collagenous proteins, fibronectin and laminin (1). These spaces are continuous with perivascular and peribronchial interstitial spaces. Though alveolar wall forms the major structure of the pulmonary interstitium, the fibrotic process is not confined to the wall, but brings about extensive alterations in the discrete architecture of the alveolar unit.

DEFINITION

Hamman and Rich identified diffuse idiopathic fibrotic lung diseases as diffuse interstitial pulmonary fibrosis in 1944 (2). Scadding referred the condition as diffuse fibrosing alveolitis in 1964, to encompass the features of both interstitial and intra-alveolar changes in the interstitial lung diseases (3). Since the cause was unknown it was considered cryptogenic (4). Liebow and Carrington in 1969 gave description of five histopathologic subgroups of chronic idiopathic interstitial pneumonias (IIP), based on specific histologic criteria and the above condition was classified as undifferentiated or usual interstitial pneumonia (UIP) (5).

The American Thoracic Society-European Respiratory Society (ATS-ERS) has defined IPF as a clinical condition characterized by progressive dyspnoea and chronic cough, restrictive lung disease and the histologic pattern of UIP (6).

AETIOLOGY

The disease in IPF is limited to the lung and the insult that produces interstitial lung disease (ILD) is undetermined, hence cryptogenic (cryptogenic fibrosing alveolitis). There is no known aetologic stimulus that initiates this condition. Many factors are likely to play in a susceptible host and cause damage of the alveolar epithelial cells and trigger the development of the disease. Thus the condition appears to evolve from a cryptic alveolar injury. Epithelial damage induces a fibrotic process. IPF used to be established by excluding other conditions leading to diffuse interstitial pulmonary fibrosis. But now is recognized by `what it is rather than by what it is not’. The condition may be familial affecting two or more members of the same family. Though there are many initiating factors or causes of IPF, the terminal stages are characterized by fibroblast proliferation and accumulation of connective tissue replacing normal functioning parenchyma.

PATHOLOGY

Idiopathic pulmonary fibrosis exhibits histologic features of usual interstitial pneumonia (UIP). The disease process is patchy predominantly affecting the basilar and peripheral regions in the subpleural and paraseptal areas. The effect of the injury appears to be felt in the distal portions of the lobules and acini that later extend upwards centripetally into the lung parenchyma (7). There is a temporal heterogeneity in the lung injury characterized by alternating areas of normal lung parenchyma and interstitial mononuclear infiltrates, septal fibroblastic foci (fibroblasts or fibroblast-like cells clustered together and relatively well-demarcated from surrounding cells) and honeycomb lung. Occurrence of ‘honeycomb lung’ (small cystic spaces lined by

PS Shankar, Gulbarga

metaplastic bronchial epithelium) is the end-stage of the damage and scarring. These changes imply that the interstitial injuries have occurred at different period of time and are at different stages of healing. Pleura is not affected.

The histological changes are akin to that seen in collagen vascular diseases, drug-induced interstitial diseases, chronic hypersensitivity pneumonitis or asbestosis.

**PATHOGENESIS**

It was believed for many years that a generalized inflammation played a dominant role in the initiation of widespread parenchymal pulmonary fibrosis following a lung injury. This was based on observation that bronchoalveolar lavage (BAL) fluid from patients with IPF demonstrated an increased number of inflammatory cells, such as neutrophils and eosinophils. As the inflammatory response led to progressive fibrosis, the treatment was directed to control the inflammatory process with the hope that fibrosis could be limited and/or prevented. UIP is a distinct pathophysiologic entity characterized by minimal inflammation and chronic fibroproliferation caused by abnormal parenchymal healing (8).

There appears to be 2 different pathologic routes for development of pulmonary fibrosis. An inflammatory pathway explains the pathology of most interstitial lung diseases which do not include IPF (8). Initially there is an inflammatory response in disease of known (hypersensitivity pneumonitis, drug-induced fibrosis; or unknown (sarcoidosis, desquamative interstitial pneumonia) aetiology, to be followed by fibrosis. An epithelial pathway is followed in the development of IPF. The condition is associated with scanty inflammation initially. It demonstrates fibrosis and scarring, and alternate zones of normal lung. Though there is inflammatory response, it does not appear to precede or play a dominant role in the pathogenesis. Pulmonary fibrosis results from epithelial injury in the absence of preceding inflammation (9).

Now there is a paradigm shift in the earlier view and airway inflammation is the result rather a cause of fibrosis. This has been based on the following observations (10).

1. **Hyperplastic alveolar type II cells:** There is injury to alveolar type II cells and epithelial cell apoptosis in early stages (11). There is disruption of the integrity of the subepithelial basement membrane. It leads to exposure of the underlying basement membrane to oxidative injury. There is loss of basement membrane integrity signaling epithelial cell regeneration. There is hyperplasia of alveolar type II cells, which is promoted by a number of growth factors that accumulate in the region following epithelial cell injury. Tumor necrosis factor-alpha appears to promote apoptosis in the alveolar epithelial cells (12).

2. **Angiogenesis:** Alveolar epithelial cells are the principal source of cytokines and growth factors involved in fibroblast migration and proliferation. There is an increased angiogenic activity in the lung due to an imbalance between pro-angiogenic (interleukin (IL)-8) and angiostatic (C V C, IP-10) chemokines (13). The latter is induced by interferon (IFN)-gamma. IFN-gamma plays a key role in regulation of fibroblast activation. It is able to suppress fibroblast proliferation and collagen deposition. An increased angiogenesis is seen in early stages of the disease and the level of IL-8 which is derived from pulmonary fibroblasts is increased. There is a deficiency of angiostatic factor, IP-10 in the lung tissue. IFN-gamma is a major inducer of IP-10. Angiogenesis appears to recede with advancing disease.

3. **Abnormal matrix turnover:** There is an imbalance between the production and destruction of extracellular matrix (10). A markedly increased production of extracellular matrix including collagen, tenasin and proteoglycans is noted. Transforming growth factor (TGF)-beta promotes matrix production. Alveolar epithelial cells are main sites of synthesis of TGF-beta. TNG-alpha and platelet derived growth factor (DGF) responsible for pulmonary fibrosis.

4. **Cytokine imbalance:** An imbalance in cytokines appears to be present in IPF. There is an increased production of TH2 cytokines (IL-4, IL-5 and IL-13) in the lung tissue compared to TH1 cytokines (14). IL-13 appears to increase the fibrotic process directly by stimulating fibroblasts and through a cytokine network that involves the expression of TGF-beta.

5. **Growth factor production:** There is an increased production of a number of growth factors that influence fibroblasts and myofibroblasts facilitating fibrosis. TGF-beta is the most important mediator of lung fibrosis (15). Activins are members of the TGF-beta family. They enhance proliferation and differentiation of fibroblasts implicated in the occurrence of pulmonary fibrosis.

6. **Altered fibroblast properties:** Fibroblasts exhibit different growth rates in the region of new and old fibrosis unlike normal fibroblasts (16).

7. **Myofibroblasts recruitment:** There is a greater accumulation of myofibroblasts promoting lung fibrosis. These mesenchymal cells may participate in remodeling and destruction of the lung parenchyma through different mechanisms. Myofibroblasts take a crucial role in the progression of fibrosis. Myofibroblast differentiation occurs through combinatorial signals involving transforming growth factor (TGF)-beta and integrin signaling. Myofibroblast differentiation is regulated by a dual-specificity protein and lipid phosphatase, phosphatase and tensin homolog deleted in chromosome 10 (PTEN).

There is a diminished PTEN expression in fibroblasts isolated from lungs of patients with IPF (17). Inhibition of PTEN in vivo promotes fibrosis and PTEN inhibits myofibroblast differentiation (18). PTEN is a central negative regulator of
myofibroblast differentiation. There is an inverse correlation between PTEN and alpha-smooth muscle actin (BMA) expression in fibroblastic foci of lung tissue from patients with IPF. Inhibition of PTEN augments alpha-SMA expression both in fibroblasts in vitro and in pulmonary fibrosis in vivo.

8. Oxidative stress: Normal lung homeostasis is dependent on a balance between intracellular and extracellular oxidants and anti-oxidants. An imbalance of oxidant (elevated levels of myeloperoxidase and eosinophil cationic proteins, reactive oxygen species, and reactive nitrogen species) and anti-oxidants (decreased levels of glutathion, superoxide dismutase) in the lower respiratory tract has a critical role in the pathogenesis of IPF. Cellular oxidative stress may have a critical role in the gene expression of a variety of profibrotic factors (19).

CLINICAL FEATURES

History: A detailed history of occupational exposure in inorganic dusts (silica, asbestos, coal dust) of inhalation and subsequent sensitization to organic dusts containing spores from thermophilic fungi (Farmer’s lung), bacterial enzymes, thermotolerant bacteria, avail proteins and animal dander to gases (high concentration of oxygen, chlorine and oxides of nitrogen) and fumes (oxides of cadmium, zinc, copper, nickel and brass) in the work place and in the home has to be reviewed. Often there is a long latent period between an occupational exposure and the onset of clinical manifestations.

A history of medication especially immuno-suppressive and cytotoxic agents, ionizing radiation and of collagen vascular diseases must be taken. In IPF no inhalant aetiology can be found by careful and detailed environmental and occupational history.

Clinical presentation: The clinical presentation of interstitial pulmonary fibrosis has an insidious onset. It is noted in the fourth and fifth decades of life, men and women are equally affected.

The manifestations are limited to the lungs. Initially dyspnoea is noted only on exertion. It takes a long time to make the individual severely disabled. At that stage the breathlessness is severe leading to profound disturbances in the pulmonary function. There is tachypnoea. The increased resistance to the distension of the lung leads to an increased respiratory effort. The lowered arterial oxygen tension accelerates the ventilatory drive. There are easily fatigued and there is loss of weight. There may be a dry irritating, non-productive cough. The patient is able to speak only in phrases of a few words, and exhibits an anxious appearance. Digital clubbing is often noted in patients with IPF. Clinically the expansion of the chest is restricted. There may be an impaired percussion note over the bases. On auscultation, there are bibasilar crackles. The crackles are numerous, and harsh (Velcro), and occur in increasing number towards the end of inspiration without any change in the breath sounds (20). They persist after cough. They are characteristically audible over the lobes posteriorly. They may disappear on lying over the face or on bending forwards. They appear to be due to the decreased lung volume and closure of small airways on expiration, which on reopening during inspiration induce pressure changes within the airways. Such crackles are never heard in obstructive or granulomatous (sarcoïdosis, extrinsic allergic alveolitis, silicosis) lung diseases. The onset of pulmonary artery hypertension and cor pulmonale is associated with a loud, pulmonary component of second heart sound, right-sided parasternal lift and S3 gallop, peripheral oedema and cyanosis.

INVESTIGATIONS

Imaging study: Chest radiograph: The chest radiograph shows diminished lung volumes. There are symmetric, bibasilar and peripheral reticulations (21). A patchy pattern of honeycomb changes that is more prominent in the bases of the lungs, traction bronchiectasis and the absence of prominent ground glass opacity are noted (22) (Fig 1). Pleural involvement is unusual and the costophrenic angles are spared. Patchy consolidation may superimpose when the condition gets deteriorated (23). Computerized tomography reveals (CT) reveals pulmonary fibrosis with little active inflammation. The periphery and bases are predominantly involved exhibiting honeycomb cysts, distorted

Fig. 1: Chest radiograph showing bibasal reticulations, honecomb changes and traction bronchiectasis.

Fig. 2: HRCT showing honeycombing and intralobular reticulation.
interlobar reticulations and traction bronchiectasis (24).

High resolution CT (HRCT) scanning: The interstitial fibre network of the lung is thickened by fibrous tissue and it gives rise to an increase in the reticular lung opacities on HRCT. Interlobular septa of 0.1 mm thickness are better developed in the periphery of the lung and are better visualized by HRCT. IPF has peripheral, subpleural, basal predominance with reticular opacities and traction bronchiectasis/bronchiolectasis. IPF is more likely to show honeycombing, traction bronchiectasis and bronchiolectasis and lower lobe volume loss (Fig. 2). HRCT is useful as an integral part of the evaluation of patients with suspected IPF (25).

Physiologic testing: The physiologic alterations in interstitial pulmonary fibrosis are restrictive. The lungs become small, stiff and noncompliant. The tidal volume is low. The minute ventilation is great at rest and on exercise. The vital capacity (VC) is reduced. The total lung capacity (TLC) is reduced more than residual volume (RV) resulting in an increase in the ratio of RV to TLC. There is no airflow obstruction unless there is history of cigarette smoking. The ratio of the forced expiratory volume in one second (FEV1) to forced vital capacity (FVC) usually remains normal. There is reduction in carbon monoxide diffusing capacity due to destruction of the effective gas exchanging areas.

Patients with exertional breathlessness demonstrate exercise-induced hypoxaemia and widened alveolar-arterial pressure difference for oxygen (A-a) O2. Hypoxaemia is an early manifestation of the disease. There is respiratory alkalosis. With advanced disease there is resting arterial hypoxaemia. Carbon dioxide retention is noted only in terminal stages of disease. The blood gas abnormalities are essentially due to ventilation-perfusion inequality following disruption of gas-exchanging units (25). A diffusion defect may develop during exercise. The pulmonary function abnormalities do not correlate well with the degree of fibrosis. Diffusion capacity of carbon monoxide is highly correlated with HRCT findings (26).

Pulmonary function tests have a limited role in predicting prognosis and responsiveness to treatment. However, serial measurements are necessary in an individual patient to determine disease progression or response to treatment (27).

Bronchoalveolar lavage: the analysis of the cellular constituents of bronchoalveolar lavage fluid obtained through the wedged flexible fiberoptic bronchoscope reveals an increase of inflammatory cells predominantly neutrophils and/or eosinophils in IPF (28).

Lung biopsy: The pathologic diagnosis is established by an open lung biopsy through limited thoracotomy with subperioisteal rib resection. Since the pathologic changes are patchy, an open lung biopsy has to be carried out through a small incision at the edge of grossly abnormal areas of the lung, which should include more than one lobe of the lung. Biopsy must be deep, extending well into the subpleural lung parenchyma (29). Video-assisted thoracoscopic surgery is utilized in the recent years for surgical lung biopsy. There is correlation between the pathologic fibrosis and HRCT fibrosis; hence HRCT is used in the assessment of patients with IPF. However HRCT has not replaced the need for histologic confirmation in most patients (29).

DIAGNOSIS

Interstitial lung disease leading to pulmonary fibrosis may be classified into two groups: those secondary to some aetiologic conditions (asbestosis, silicosis, hypersensitivity pneumonitis, drug-induced lung diseases, infection) and those of unknown cause (sarcoidosis, fibrosing alveolitis). When no aetiology is found, the condition becomes cryptogenic or of undetermined cause or idiopathic.

The ATS/ERS consensus statement has included major and minor criteria for the clinical diagnosis of IPF (6).

Major criteria

- exclusion of other known causes of ILD such as certain drug toxicities, environmental exposure, and connective tissue diseases
- abnormal pulmonary function studies that include evidence of restriction (reduced VC, often with an increased FEV1/FVC ratio) and impaired gas exchange (increased P(A-a)O2, decreased PaO2 with rest or exercise or decreased DLCO.
- bibasilar abnormalities with minimal ground glass opacities on HRCT scan
- Transbronchial lung biopsy or BAL showing no features to support an alternative diagnosis

Minor criteria

- age > 50 years
- insidious onset of otherwise unexplained dyspnoea on exertion
- duration of illness >3 months
- bibasilar inspiratory crackles

In the immuno-competent adult the presence of all of the major diagnostic criteria as well as at least three of the four minor criteria increases the likelihood of a correct clinical diagnosis of IPF.

PROGNOSIS

IPF pursues a variable clinical course. Though majority of patients with mild-to-moderate IPF may remain stable for prolonged period of time, some may exhibit a rapid decline in their clinical course (30). These patients demonstrate features of diffuse alveolar damage on the background of UIP (31). IPF is a relentlessly progressive condition and the median survival of patients with the disease is about three years after diagnosis or five years after the onset of symptoms (32). Spontaneous remission does not occur and treatment is not effective in most cases. However there is variability of the natural history of the disease and some individuals survive for many years.
The factors causing rapid progression and shortened survival are: age older than 50 years, male sex, tobacco smoking, severe dyspnoea, and poor pulmonary function abnormalities at the time of presentation, hypoxaemia at rest and with exertion, extensive radiologic abnormalities, honeycomb changes on HRCT scan, increased number of neutrophils or eosinophils in BAL fluid, extensive fibrosis on histologic study, decreased surfactant protein (SP)-A content and SP-A/ phospholipids ratio, and absence of response to therapy. Periodic HRCT scanning of the chest helps to determine the severity of ground glass infiltrates and fibrosis.

The total amount of fibrosis determined by HRCT is an important prognostic factor. The biopsy gives a small specimen and it many not convey accurate information about the total amount of fibrosis. In order to quantitatively assess the morphologic features on CT of the entire lung, CT morphometry (CTM) technique is under evaluation (32). CTM is done be segmenting the lung parenchyma from the chest wall and central vessels for each slice. The volume of the slice is determined by totaling the volume of three dimensional pixels (voxels) in the slice. The density of the lung tissue in the voxel is estimated by addition of 1024 to the Hounsefield units of each voxel and then dividing the sum by 1024. Lung weight equals the product of mean lung density, which is lung tissue in the voxel is estimated by addition of 1024 to the Hounsefield units of each voxel and then dividing the sum by 1024. Lung weight equals the product of mean lung density, which is determined from the densities of all voxels (33). The lung volume is the sum of all voxels and is expressed as ml gas per gram of lung tissue.

**COMPLICATIONS**

The complications are right heart failure, pulmonary infections and carcinoma of the lung. The lung that has become rigid from scarring and has undergone honeycomb changes offers an important background for atypical epithelial cell proliferation leading to malignancy. Nearly 10 per cent of elderly male smokers with IPF may develop lung cancer with histologic type of squamous cell carcinoma. It may present as a peripheral pulmonary nodule or mass. Repeated examination of sputum for malignant cells and demonstration of fresh radiologic shadows in the background of the fibrotic pattern helps in the diagnosis of the condition (34).

**MANAGEMENT**

A composite clinical, roentgenographic and physiologic (CRP) score developed by Watters et al helps in determining the severity of the underlying radiologic process, rate of progression of the disease and therapeutic benefit (35). The score is based on relative points given to eight variables including the degree of dyspnoea, extent, severity and profusion of parenchymal interstitial infiltrates and presence of honeycombing and evidence of pulmonary hypertension on chest roentgenogram, changes in physiologic parameters such as FVC, FEV1, diffusion, resting alveolar-arterial oxygen gradient, and oxygen desaturation with exercise. The scoring system helps in predicting the survival of the patient with IPF.

Since HRCT scans were not available earlier, the surgical biopsies were utilized in the scoring system. It included four features such as fibrosis, interstitial cellularity, alveolar space cellularity and granulation, and young connective tissue.

CRP scoring system was revised as abbreviated CRP score in 2001 which does not include estimation of oxygen tension at maximal exercise as it was not possible to perform such a test on subjects with advanced disease (36). This modification possesses relatively high predictive value on survival of patients. Inclusion of HRCT into the scoring system has added to its utility. Since survival is related to HRCT fibrosis score, the total amount of fibrosis plays a major role in determining the prognosis.

Wells and coworkers have developed a composite physiologic index (CPI) based on physiologic results obtained from pulmonary function tests (FVC, FEV1 and diffusing capacity). It takes into consideration of coexisting emphysema. The index is promising as it can stage the severity of disease and predict outcome (39).

**Corticosteroids:** Corticosteroids are the main form of therapy in the management of interstitial pulmonary fibrosis (40). They are used based on the concept that suppression of inflammation prevents progression of fibrosis. It helps in suppression of cough. The response to corticosteroids alone is unpredictable and rarely it is effective. Prednisolone is to be administered in a dosage of 1 mg/kg body weight daily as a single oral dose in the morning for the first 3 months followed by a tapering dose of 0.5 mg/kg body weight for up to 18 months. The response has to be assessed by clinical, physiologic and radiographic examination. If the assessment shows improvement corticosteroid therapy may be tapered to a maintenance level of 10 to 20 mg per day. Corticosteroids are discontinued if there is no response.

**Immunosuppressive therapy:** Non-steroidal immunosuppressive agents should be considered in those who fail to show response or do not tolerate corticosteroids therapy. Cyclophosphamide or azathioprine, 1-2 mg/kg body weight per day given orally as a single daily dose alone or in combination with prednisolone 0.25 mg/kg body weight orally per day may be administered for 3 months. Cyclophosphamide therapy often has to be discontinued because of neutropaenia, thrombocytopenia or haemorrhagic cystitis. Azathioprine therapy is associated with leukopaenia, anaemia, thrombocytopenia, nausea and vomiting. Immunosuppressive therapy is continued if there is an objective improvement. There is no good evidence to support the routine use of any specific therapy in the management of IPF.

**Advanced disease:** Supplemental oxygen therapy helps in improving exercise tolerance in advanced disease. Young patients without other significant diseases with progressive severe disease unresponsive to treatment may be considered for unilateral lung transplantation (39).

**New therapy:** The new insights into pathogenesis of the condition have given new therapeutic approach with the following
agents; antioxidant therapy with N-acetyl cysteine, anti-TNF-alpha, interferon-gamma 1 beta and TGF-beta antagonist (imatinib mesylate). These therapeutic agents instead of targeting the inflammatory response are directed at regulation of fibroblast functions. IFN-gamma 1 beta has been tried on advanced IPF. But it has not been proved effective in patients with severely impaired lung function and reduced diffusion capacity (40). However a subgroup analysis has suggested its effect on early disease. Acetylcysteine, a precursor of the major antioxidant glutathione, at a dose of 600 mg three times daily added to prednisone and azathioprine improves vital capacity and DLCO better than standard therapy alone (41). Pirfenidone may improve lung function and decreases the number of episodes of acute exacerbations (42). Strategies designed to enhance PTEN expression or activity within in cells can inhibit further fibroblast proliferation and collagen secretion (18). Prostaglandin E2 inhibits fibroblast migration by augmenting PTEN activity (43).

CONCLUSION

Injury to the alveolar-capillary wall leads to loss of integrity of basement membrane. There is failure of re-epithelialization and re-endothelialization, loss of alveoli and fibrosis. There is improper repair and fibrosis. IFP develops in the absence of preceding inflammation. TGF-beta plays an important role in dys-regulated repair and fibrosis. The search for new therapeutic strategies is concerned on the aberrant pathways leading to fibrosis.

REFERENCES

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