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EDITORIAL ARTICLE

IDIOPATHIC PULMONARY FIBROSIS

By
Roland M. du Bois
Brompton hospital. UK
Email: duboisr@njc.org

BACKGROUND

There has been considerable confusion over the nomenclature of the idiopathic interstitial pneumonias. Some of this confusion has been resolved by the publication of the clinical-radiological-histopathological classification by the American Thoracic and European Respiratory Societies in 2002 Table 1. This classification is by no means the final word on the subject but does provide some order. Of the different and distinct disease entities defined, the most important clinical decision that needs to be made is whether the patient has idiopathic pulmonary fibrosis (IPF). This diagnosis carries the prediction of a 2-3 year mean survival in marked contrast to the other diseases included in this new classification where survival is better and response to treatment generally more likely. Because the outcome in IPF is so much worse and because this has an obvious impact on the patient's management, it is the need to confirm or refute this diagnosis that drives the diagnostic algorithm in the idiopathic fibrosing lung diseases. The criteria used to define IPF are shown in Table 2 for patients either with or without a surgical lung biopsy.

HISTOPATHOLOGY

Usual interstitial pneumonia is the histopathological pattern of idiopathic pulmonary fibrosis. Although this pattern is seen in a variety of clinical contexts that are not IPF, including rheumatological disease or drug exposure, when it occurs in the idiopathic setting the diagnosis is IPF. The hallmark features of usual interstitial pneumonia are (Fig. 1):

- Patchy distribution with late-stage pathology adjacent to normal lung, in a pattern described as "temporally heterogeneous".
- Inflammation is generally not prominent.
- Fibroblastic foci – accumulations of myofibroblasts – are prominent.
- Honeycombing is often prominent.

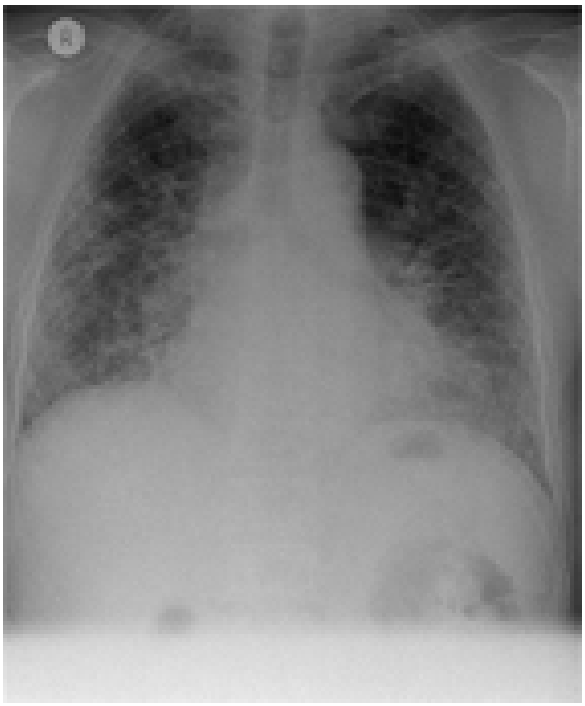


Fig 1. Plain chest radiograph of a patient with Idiopathic Pulmonary Fibrosis: note the basal predominance of reticular change obscuring the diaphragms and both heart borders.

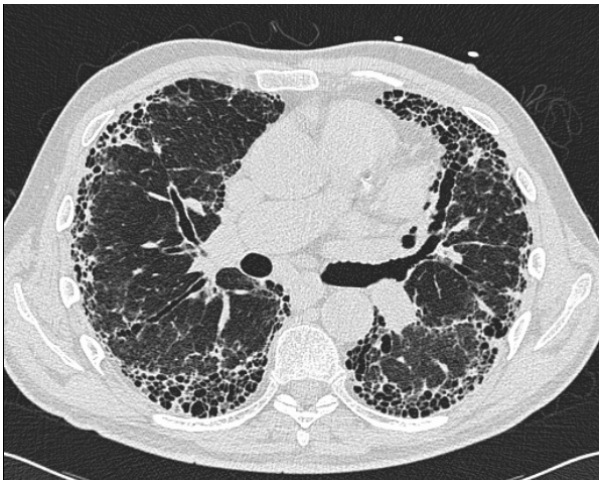
CLINICAL FEATURES

A history of progressive breathlessness on exertion in the absence of wheeze is typical. A dry cough may be present but sputum production is unusual until the later stages of the disease. Constitutional symptoms such as weight loss and lethargy are recognized.

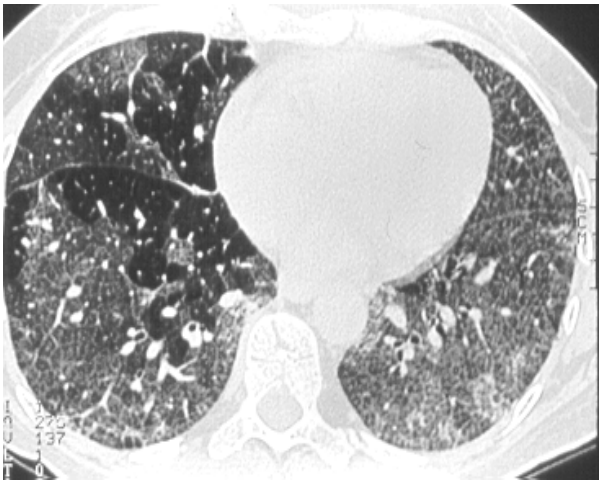
Digital clubbing is present in approximately the majority of patients. On auscultation, fine crackles are heard at the lung bases. Examination may also reveal non-pulmonary features that would suggest alternative, systemic diseases, such as arthropathy, vasculitis, skin disorders and peripheral lymphadenopathy.

INVESTIGATIONS

Chest radiography: Plain chest radiography shows small lung fields and reticulonodular shadowing particularly at the periphery of the lung and at the bases, obscuring the right and left heart borders and making the diaphragmatic surfaces irregular (Fig 2). In more advanced cases, all lung zones are involved at which point evidence of honeycomb shadowing may be present. Lymphadenopathy is rarely observed with chest radiography and the presence of pleural disease should suggest an alternative diagnosis.



A. Idiopathic Pulmonary Fibrosis. Note peripheral rim of reticular change with honeycombing. No nodules and no ground glass change.

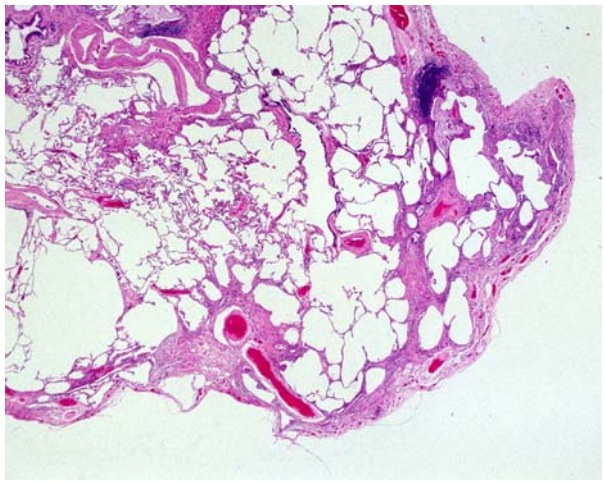


B. Desquamative Interstitial Pneumonia. Note widespread, clearly demarcated ground glass attenuation consistent with alveolar filling with alveolar macrophages.

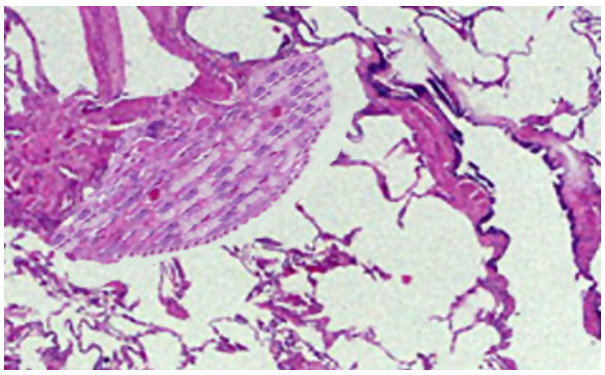
Fig 2. Computed tomography of two patients with Idiopathic Interstitial Pneumonia.

Computed tomography: Computed tomography is

diagnostic if the pattern of abnormality is classic. These classical features include peripheral basal reticular change with honeycombing. Disease is less severe in the upper zones and tends to be more prominent anteriorly in these upper areas. Nodules and ground glass changes are either absent or, in the case of ground glass change, minimal. (Fig. 3). Pleural disease is not present. In contrast to the observation on plain chest radiography, mediastinal lymphadenopathy is commonly seen.



3a. Note the patchy change with honeycombing adjacent to normal lung in a peripheral distribution.



3b. Inset shows a typical fibroblastic focus (arrowhead) from the biopsy in Figure 3 A (arrow)

Fig 3. Histopathology of a surgical biopsy from a patient with Idiopathic Pulmonary Fibrosis.

LUNG FUNCTION TESTS

IPF is characterised by a restrictive ventilatory defect . Carbon monoxide transfer factor (DLCO, a measure of diffusion capacity) is reduced and may be the only abnormality in early disease. In the majority of patients the gas transfer measurement adjusted for alveolar volume (KCO) is normal or only slightly reduced unless there is significant co-existing emphysema, in which situation lung volumes will be well-preserved in the face of a disproportionately depressed gas transfer measurement in both DLCO and KCO. Gas transfer is reduced by both the emphysematous and the fibrosing processes whereas lung volumes will tend to be increased by emphysema but reduced by fibrosis and these two opposing influences result in relatively normal-sized lungs radiographically and physiologically.

Typical blood gas measurements will reveal a reduced Pa02 value with a normal or low PaCO2 measurement. The low Pa02 is largely attributable to ventilation/perfusion mismatching. On exercise, hypoxaemia is exacerbated and a widening of the alveolar-arterial (A-a) gradient is observed during exercise. Infrequently, these abnormalities on exercise testing are the only physiological abnormalities but usually by the time the patient seeks advice there is already some abnormality in the gas transfer measurement at rest.

Lung function measurements (to include gas transfer) should be made sequentially to assess the progression of the disease process. Spirometry alone or, worse, peak flow measurements, are inadequate. It is sensible to plot out serial lung function studies in order to visualise more gradual change that may be missed if results are compared only with the previous set of measurements.

BLOOD TESTS

Blood tests are of little value in the diagnosis of idiopathic pulmonary fibrosis. Rheumatoid factor or anti-nuclear antibody may be present in abnormal titres in approximately 45% of patients.

The titres of autoantibodies do not approach those seen in the rheumatological diseases.

BRONCHOALVEOLAR LAVAGE

Bronchoalveolar lavage is valuable in excluding infection and as confirmation that the histopathology pattern is likely to be the usual interstitial pneumonia pattern in patients who cannot or will not tolerate surgical biopsy. In a typical patient with idiopathic pulmonary fibrosis, bronchoalveolar lavage would produce an increase in total cell returns of 3-6 fold (up to 6x105/ml of fluid return) and of these up to 20% may be neutrophils or eosinophils. An excess of lymphocytes suggests an alternative diagnosis such as granulomatous diseases or drug-induced causes of lung disease.

LUNG BIOPSY

Surgical lung biopsy, either through mini thoracotomy or video assisted thoracoscopic biopsy is required to confirm a diagnosis of IPF. At least two sites should be biopsied to ensure representative sampling. It is good practise to select sites from a viewing of the CT scan with the surgeon. Transbronchial biopsy cannot be used for diagnosis of idiopathic pulmonary fibrosis and is only helpful in excluding other diseases such as granulomatous disease because transbronchial samples are too small to allow an appreciation of the morphological pattern to be obtained.

TREATMENT

Historically, treatment approaches have been anti-inflammatory with a combination of corticosteroids and immunosuppression being favoured first line treatment. However, there were no placebo controlled trials that supported this approach. Over recent years there have been several publications of prospective randomised double blind studies. While none of these have been fully placebo controlled they do provide important conclusions. All of these studies have emerged from a shift in concept of the paradigm of disease from it being a fibrotic response to an inflammatory insult to the concept that the disease is predominantly fibroproliferative resulting from epithelial cell/fibroblast interactions and resulting from repeated epithelial cell injury.

N-acetylcysteine: Of the studies performed to date N acetyl cysteine appears to have provide the most promising outcome. An imbalance between oxidants and antioxidants has been proposed as an important component of the pathogenesis of IPF, with resultant oxidative stress and epithelial cell injury. In the 'Ifigenia' study, patients receiving NAC added to prednisolone and azathioprine exhibited a relative difference in rate of decline of VC (by 9%), and DLCO (by 24%) compared with those receiving placebo together with prednisolone and azathioprine. There are no data on NAC used alone.

Interferon-γ: IFN-γ is an endogenous cytokine that has diverse properties including anti-fibrotic, anti-infective, anti - proliferative and immunomodulatory effects. Raghu et al reported the results of a double blind placebo controlled multinational randomised controlled trial of IFN-γ given three times a week. Three hundred and thirty patients with a history of disease progression during the previous year and a lack of response to corticosteroid were randomised to subcutaneous IFN-γ or placebo, and subjects were permitted to continue prednisolone at a dose of 15mg or less. The trial was negative with no improvement of progression free survival (primary end point). In a secondary analysis it was seen that less severely affected individuals appeared to have a survival advantage if active drug was being taken. This formed the basis of the design of a large second study in which patients with less severe disease were recruited. This was also negative. It should be concluded therefore that interferon gamma cannot be recommended for the treatment of IPF.

Pirfenidone: A Japanese multi-centre double blind placebo controlled randomised controlled has been reported. This study showed a lesser rate of decline e in lung function in the active group compared to placebo. A second study has been

completed in Japan and the results are awaited. Two other multinational studies are almost completed. The results of these studies will be important but until they are published, pirfenidone cannot be recommended for IPF.

Bosentan: Bosentan is a non-selective endothelin receptor antagonist currently approved for use in pulmonary arterial hypertension. An international randomised double blind placebo controlled prospective study is now in press. The results were negative for the primary end point, six minute walk distance. In a secondary analysis, individuals with less honeycombing on CT who required a surgical biopsy to confirm diagnosis, appeared to have a survival advantage if receiving active drug. These indices have formed the basis of inclusion criteria for a second multinational study of this drug. It cannot be recommended at this time.

CURRENT RECOMMENDATIONS

A suggested treatment plan is to initiate treatment at diagnosis in almost all patients unless disease is really mild when it might be acceptable to observe change if that is what the patient desires. In general this disease progresses so it is only in exceptional circumstances that an observational policy can be justified. Suggested first line therapy includes low-dose corticosteroid (prednisolone 10mg daily or 20mg on alternate days) and azathioprine (initially 50mg daily and subsequently increased after four weeks to 2.5mg/kg/day (max 200mg) if well tolerated and there is no evidence of bone marrow suppression or hepatotoxicity on weekly blood tests), together with NAC.

In more severe disease, the use of nocturnal and portable supplemental oxygen should be considered in order to reduce right heart strain and increase exercise capacity. If symptomatic and lung function decline are documented despite standard therapy, patients should be assessed for lung transplantation. Worsening of status requires screening for co-morbid conditions such as heart failure, infection and thromboembolic disease. Patients should be referred for transplant assessment when the gas transfer drops below 35% predicted; late referral has been identified as a major determinant of death because of the time it takes between assessment and successful transplantation. The age limit imposed by some transplantation centres needs to be taken into account when planning management

ACUTE EXACERBATIONS OR ACCELERATED DISEASE

Sudden deterioration can occur. Supervening infection, heart failure and thromboembolism must be excluded. If more rapid disease progression is believed to be the reason for the clinical deterioration, intravenous corticosteroids (a suggested dose of around 1G methylprednisolone/day for three days) together with intravenous cyclophosphamide (600 mg/m2 as a single dose, repeated at roughly 2 week intervals if blood counts are satisfactory) should be considered.

PALLIATIVE CARE

When all treatment options have failed, and as the disease progresses to a more terminal phase, palliative care should be considered. Small dosages of opiates have been shown to suppress the sensation of extreme breathlessness that occurs as the lungs become much less compliant.

This chronic often relentlessly progressive disease has a disabling affect on the patient and the close family. It is advisable that full medical and non-medical healthcare professionals' support is made a part of the management plan. Medical social workers, physiotherapists, occupational therapists and rehabilitation programmes for patients form an important part of supportive management.

A SUGGESTED MONITORING PLAN

It is important to acknowledge that preventing symptomatic and physiological worsening needs to be considered as treatment success in this disease. In this context, it can take at least 3-6

months and sometimes longer for the effect of immunosuppression to be seen. Provide there is no physiological deterioration, therefore, immunosuppressants should not be discontinued for at least six months, provided there are no adverse effects. Lung function tests should be repeated at 3 monthly intervals during the first year and less frequently thereafter provided response is satisfactory. If evidence of disease stability or improvement is seen, treatment should be continued until the disease has stabilised for a total of one year. A tapering of corticosteroids and then immunosuppression with a view to complete withdrawal should be suggested at this point. If function deteriorates, alternative drug therapies need to be tried. Decisions should always be made in conjunction with the patient's input and wishes.

PROGNOSIS

Recent studies comparing survival of incident cases as opposed to prevalent cases and more rigid definition of idiopathic pulmonary fibrosis as outlined above have shown the median prognosis is less than 3 years and the 10 year survival 5-10%.Rate of change of lung function over six or 12 months has been shown to be a good index of prognosis in three separate studies.

COMMON QUESTIONS

What is the cause?

Patients often expect clinicians to be able to identify a cause that results in a cure and they need to be told that this will not happen. Numerous factors but especially cigarette smoking have been associated with an increased risk of disease.

Should all patients undergo surgical biopsy?

If there is any doubt about diagnosis after full clinical and computed tomography assessment, with bronchoalveolar lavage, then surgical biopsy is needed to confirm the diagnosis. This is primarily to rule in or out IPF as this disease has a much more aggressive course and the knowledge that this is the diagnosis has profound effects on patient management, particularly and advice about outcome. These decisions must always be individualised and need to be made in the context of other potentially complicating, co-morbid conditions and whether there is a likelihood of an increased complication rate. Chronological age should not be a factor but clearly biological age is.

When should treatment be started?

Immediately in almost all cases.

When should treatment be stopped?

If therapy is not changing disease course it should be stopped. After one year's disease stability, consideration should be given to tapering drug dosage with a view to stopping completely. It is suggested that prednisolone should be the drug that is tapered first to around 5 mg per day and the immunosuppression.

SUMMARY

In summary, the 2002 re-classification of the idiopathic interstitial pneumonias has allowed us to get a clearer picture of those patterns of disease that carry a better prognosis. Importantly, it emphasises the need to undertake all investigations to confirm or refute a diagnosis of IPF that carries a risk of death that matches that of most malignancies. New treatment approaches are being tested but there is no "wonder drug". It needs to be recognised that stabilising disease course should be regarded as success in this predominantly fibrotic disease. New drugs are needed.

Table 1. Correlates of histopathological pattern and clinico-radiological-pathological diagnosis. Note that the histopathogical name is identical to the name applied after clinical/radiological/histopathological consensus in some cases. This can be confusing.

Histopathological pattern	Clinical/radiological/histopathogical diagnosis
usual interstitial pneumonia	idiopathic pulmonary fibrosis
non specific interstitial pneumonia	non specific interstitial pneumonia
organising pneumonia	cryptogenic organising pneumonia
diffuse alveolar damage	acute interstitial pneumonia
desquamative interstitial pneumonia	desquamative interstitial pneumonia
respiratory bronchiolitis	respiratory bronchiolitis interstitial lung disease
lymphoid interstitial pneumonia	lymphoid interstitial pneumonia

Table 2. Requirements for a diagnosis of Idiopathic Pulmonary Fibrosis.

In the presence of a surgical lung biopsy showing the usual interstitial pneumonia pattern of histopathology:

1. Exclusion of other known causes of interstitial lung disease such as drug toxicities, environmental exposures, and collagen vascular diseases.
2. Abnormal pulmonary function studies that include evidence of restriction (reduced VC often with an increased FEV1/FVC ratio) and/or impaired gas exchange [increased AaPO2 (alveolar–arterial pressure difference for O2) with rest or exercise or decreased DLCO (diffusing capacity of the lung for CO)].
3. Abnormalities (described below) on conventional chest radiographs or high-resolution computed tomography (HRCT) scans.

In the absence of a surgical lung biopsy showing the usual interstitial pneumonia pattern of histopathology:
Major Criteria (all should be present):

1. Exclusion of other known causes of ILD, such as certain drug toxicities, environmental exposures, and connective tissue diseases.
2. Abnormal pulmonary function studies that include evidence of restriction (reduced VC often with an increased FEV1/FVC ratio) and impaired gas exchange [increased AaPO2 with rest or exercise or decreased DLCO].
3. Bibasilar reticular abnormalities with minimal ground glass opacities on HRCT scans.
4. Transbronchial lung biopsy or bronchoalveolar lavage (BAL) showing no features to support an alternative diagnosis.

Minor Criteria (3 of 4 should be present):

1. Age >50 yr.
2. Insidious onset of otherwise unexplained dyspnea on exertion.
3. Duration of illness > 3 mo.
4. Bibasilar, inspiratory crackles (dry or "Velcro" type in quality).

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