

Idiopathic Pulmonary Fibrosis – Diagnosis and Treatment

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Abstract

Idiopathic pulmonary fibrosis (IPF) is a chronic progressive irreversible fibrotic lung disease of unknown cause. It occurs in older patients and is limited to the lungs. The prognosis is dismal with a median survival of 3-5 years after diagnosis. The diagnosis is based on a definite pattern of usual interstitial pneumonia on high resolution computed tomography or specific combinations of radiological and histopathological patterns. Early diagnosis and referral is recommended as anti-fibrotic treatment with pirfenidone or nintedanib that can slow down progression has become available. All patients should be evaluated for lung transplantation.

Keywords: IPF; Idiopathic pulmonary fibrosis; Nintedanib; Pirfenidone; Diagnosis

Introduction

Idiopathic pulmonary fibrosis (IPF) is a progressive irreversible fibrotic lung disease of unknown cause. The prognosis is dismal with a median survival of 3-5 years, worse than most cancers. The disease is localized solely in the lungs, occurs only in adults and is associated with a radiological and/or pathological pattern called usual interstitial pneumonia (UIP). The diagnosis demands the exclusion of other types of interstitial pneumonias, the exclusion of any known cause of fibrosis such as occupational or environmental diseases, medication or connective tissue diseases [1]. New anti-fibrotic treatment can inhibit the development of IPF and prolong survival; early and correct diagnosis is thus paramount.

Classification

In recent years, new international definitions, classifications, guidelines and treatment possibilities have developed in interstitial lung disease (ILD) and specifically in IPF. The term ILD covers more than 200 distinct entities. The first pathologic classification was described in the 1960ies, and in the following 20-30 years no clear distinction was made between the inflammatory and fibrotic ILDs which led to an exaggerated optimism of the effect of steroid treatment. In the 1990ies, it was discovered that not all ILDs were steroid sensitive; this led to a new pathological classification and new guidelines in 2000 and 2002 in which the distinction between the different types of ILD were specified for the first time [2,3].

The first guideline specifically for IPF was published in 2011 and provided a new definition of the disease based on the exclusion of all known causes for ILD and the identification of specific combinations of radiological and histological patterns of UIP [1]. Thus, a surgical lung biopsy was no longer necessary for making a confident diagnosis in patients with a definite UIP pattern on a high resolution computed tomography (HRCT). In 2013, the most recent multidisciplinary classification of ILD was published in which, for the first time, it was acknowledged that not all patients can be sub-typed and the term “unclassifiable ILD” was introduced (Figure 1) [4]. Nevertheless, idiopathic pulmonary fibrosis remains the most common of the idiopathic interstitial pneumonias.

Epidemiology

Studies on the prevalence and incidence of IPF are sparse and the results depend on the research method used (questionnaire, national registries, health care databases etc.) and on the definition of IPF. A new Danish retrospective study found a prevalence of IPF of 1.3 cases/

100,000 inhabitants [5]. The prevalence in other studies varies between 0.5-27.9/100,000 and the incidence between 0.22-8.8/100,000 [6].

The incidence of IPF seems to have increased in recent years, probably due to improved and faster diagnostic procedures. Most general practitioners perform a spirometry and can distinguish between obstructive or restrictive functional impairment; moreover, access to CT/HRCT examinations has become easier and faster. Furthermore, the demographic development points towards an ageing population [7].

Symptoms

IPF is rarely diagnosed before the age of fifty and incidence increases with age and the mean age at diagnosis is 67 years. Approximately 75% of the patients are males and 2/3 are smokers or former smokers [1,5].

Typical symptoms of IPF are progressive dry cough and dyspnea, typically deteriorating over months. Some patients have symptoms for many years before they contact a physician or are referred for investigations. In the beginning, symptoms are normally experienced in relation to exercise, but later even the slightest movement can result in severe dyspnea, cough and desaturation. Weight loss is not typical, but may be seen in the terminal phase of the disease when the respiratory work load increases. In these cases, cancer should always be excluded. Some patients have recurrent “airway infections” prior to diagnosis often characterized by increased dyspnea, cough and phlegm, and crackles at lung auscultation, but without fever or significantly raised C-reactive protein. Antibiotic therapy rarely improves symptoms and should probably be interpreted as minor acute exacerbations of IPF [8].

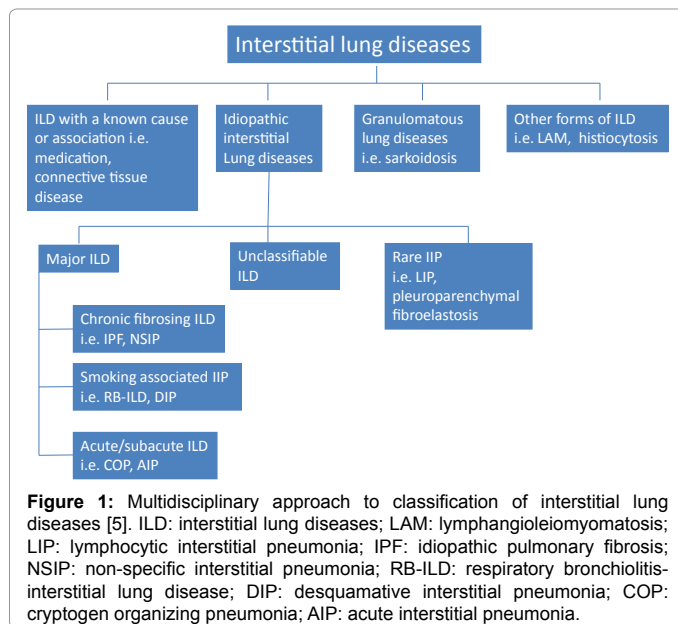
When pulmonary function becomes severely reduced, chronic respiratory insufficiency usually develops with cyanosis, in the beginning at exercise, but later also at rest. Pulmonary hypertension may cause peripheral edemas, increased dyspnea, need of oxygen and decreasing diffusion capacity, which is a relatively common complication to severe IPF and a serious prognostic sign [1].

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The clinical findings are often subtle or non-existing in the beginning of the disease, but may include basal velcro crackles and clubbing (Figure 2) [9]. These findings may precede the respiratory symptoms for several months. It is important to search for extrapulmonary manifestations of connective tissue disease, as this would exclude IPF but instead classify the lung disease as related to the rheumatologic disease. The differential diagnosis is important since prognosis and treatment of ILD related to connective tissue diseases are different from that of IPF.

Early Diagnosis

Early diagnosis of IPF has become highly relevant after the introduction of anti-fibrotic therapy in IPF. Medication inhibits disease progression, but do not improve the disease and therefore early diagnosis, referral and treatment is important.

Reduced ventilatory capacity in a patient with a dry cough and exertional dyspnea should lead to referral on suspicion of ILD. In some IPF patients, spirometry may be in the normal range even though the diffusion capacity is reduced. Decline in oxygen saturation of more than 4% at exercise is an easy marker of a reduced diffusion capacity.

The detection of drumstick fingers and/or hour glass nails read clubbing (Figure 2) and especially velcro crackles should lead to immediate referral to a pulmonary specialist. Radiographic signs of lung fibrosis should raise the suspicion of interstitial lung disease and prompt referral for further investigations. Due to the low incidence of IPF, screening programmes using CT or HRCT do not seem cost effective.

Diagnosis

IPF is seen only in adults and is limited to the lungs. The diagnosis requires a specific combination of a radiological and/or a histopathological UIP pattern, and other interstitial lung diseases, environmental and occupational reasons must be excluded [1]. The diagnosis demands highly specialized knowledge of IPF and other interstitial lung diseases.

HRCT patterns are divided into definite UIP, possible UIP and non-UIP patterns depending on the presence and localization of

honey combing, reticulation and traction bronchiectasis as well as the exclusion of other specified findings (nodules, air trapping, cysts, ground glass opacities etc.) (Figure 3) [1]. Diagnosis of a definite or possible UIP pattern can be difficult and even among experienced radiologists with a special interest in ILD, inter-individual variation is large with kappa-values of 0.4-0.58 [10]. The histopathological patterns are divided into definite UIP, possible UIP, probable UIP and non UIP patterns, and the inter-individual variation between pathologists is also high [1].

Different combinations of these patterns determine a diagnosis of definite, possible or not IPF (Figure 4). If the HRCT shows a definite UIP pattern in the correct clinical setting, a surgical lung biopsy is not needed. On the other hand, if the HRCT shows a possible UIP pattern, a biopsy is per definition required to make a confident diagnosis [1].

The most common differential diagnosis is chronic hypersensitivity pneumonitis and fibrotic non-specific interstitial pneumonitis (NSIP).

International guidelines recommend that the diagnosis is based on a multidisciplinary approach with the participation of pulmonologists, radiologists and pathologists [1].

Investigations

A detailed history with the specific aim of identifying or excluding any specific cause of ILD is paramount for the diagnosis. It is important to obtain a systematic occupational history, to identify extrapulmonary manifestations of connective tissue diseases, housing, pets and other animals, pharmacological treatment, previous chemotherapy, radiation therapy etc.

X-ray of thorax is typically the first radiological investigation performed but is only a rough screening method. Bilateral basal fibrosis is a classic sign, but the identification of specific patterns such as UIP requires a HRCT. In some interstitial lung diseases, i.e. sub-acute hypersensitivity pneumonitis, the X-ray of thorax may be normal in spite of severely reduced diffusion capacity and widespread ground glass opacities on HRCT.

HRCT is the most important investigation and if performed optimally, it provides a detailed picture of the lung parenchyma. The performance and description of HRCTs requires a specialized radiologist.

Pulmonary function test shows restriction by measuring the dynamic volumes (forced expiratory volume in 1 second (FEV1),

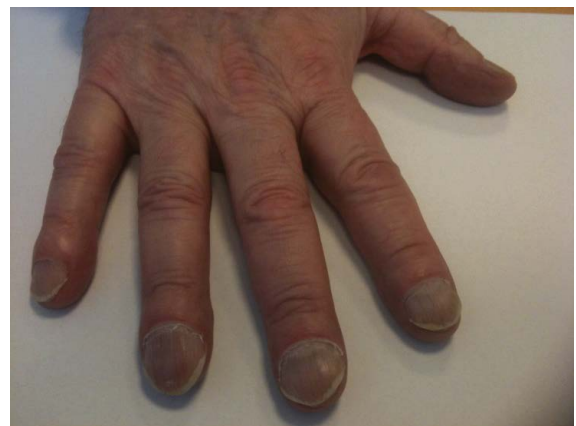


Figure 2: Clubbing is seen in approximately 50% of patients with IPF.

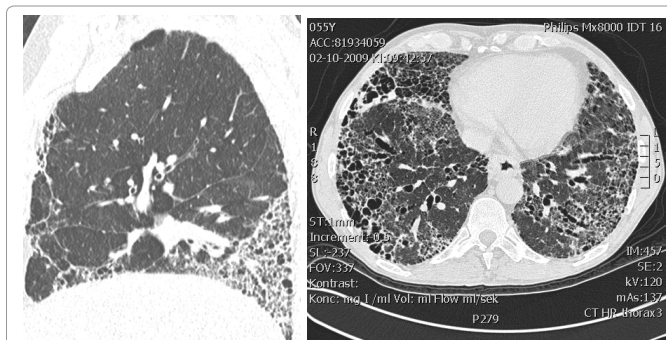


Figure 3: UIP pattern with honeycombing, reticulation and traction bronchiectasis.

		Histopatologi				
		UIP	Sandsynlig UIP	Mulig UIP	Uklassificerbar fibrose	Ikke-UIP
HRCT	UIP	IPF	IPF	IPF	IPF	ikke IPF
	Sandsynlig UIP	IPF	IPF	Sandsynlig IPF	Sandsynlig IPF	ikke IPF
	Not UIP	Mulig IPF	ikke IPF	ikke IPF	ikke IPF	ikke IPF

Figure 4: Specific combinations of HRCT and histopathology in IPF [5]. A diagnosis of IPF demands certain combinations of HRCT and histopathology. A definite UIP pattern on HRCT is consistent with IPF, no matter what the histopathology shows, and therefore a surgical lung biopsy is not needed.

forced vital capacity (FVC), FEV1/FVC, the static lung volumes (total lung capacity (TLC), residual volume (RV)) and the diffusion capacity. The dynamic lung volumes are typically normal or equally reduced with a normal or high FEV1/FVC ratio. The static lung volumes and the diffusion capacity are all typically reduced.

A standard 6-minute walk test is performed according to the ATS guidelines [11] with the registration of the walking distance in 6 minutes, and the saturation before and after. The 6-minute walk test is a very sensitive marker for a reduced diffusion capacity, demonstrated by desaturation of more than 4%. It has to be kept in mind that desaturation is not specific for ILD. Patients with i.e. pneumonia or congestive heart failure can also show a reduced walking distance and pathological desaturation. Reduced walking distance and desaturation in IPF is a severe prognostic sign.

There are no specific serologic assays or blood tests in the diagnostics of IPF. Typically, routine blood tests include hematology, liver enzymes and renal parameters. Antibodies such as anti-CCP, IgM-RF, ANA, ACE and ANCA are used as a screening tool for connective tissue disease.

The presence of pulmonary hypertension increases the risk of bleeding complications to a lung biopsy and it is also a severe prognostic sign. Therefore, an echocardiography is a part of most IPF diagnostic investigations.

Bronchoscopy with bronchoalveolar lavage (BAL, instillation of minor amounts of sodium chloride and examination of the aspirate) is a part of the diagnostic procedure in many centers. The ATS/ERS statement has a weak recommendation against the performance of BAL but does not distinguish between patients with a definite or possible UIP

pattern. The investigations seem justified in patients without a definite UIP pattern. The aspirate is examined for microbes and malignant cells, and often, a cytological differential count of the inflammatory cells is performed. In patients with IPF, neutrophil inflammation is typical, while other inflammatory patterns are seen in other types of ILD such as eosinophils > 25% in eosinophilic pneumonia.

Transbronchial biopsies (TBB) can be performed if the HRCT shows diffuse inflammatory changes but is seldom helpful in fibrotic diseases such as IPF. New techniques such as cryobiopsies have been developed and seem to give larger biopsies with less crush artifacts and have the potential to identify a UIP pattern.

A surgical lung biopsy is most often performed by video-assisted thoracoscopic surgery (VATS) and has fewer complications than a thorcotomy. VATS is associated with risk of infection, bleeding, persisting air leakage, and neuralgic pain. The procedure-related mortality is 2-7% and is primarily caused by acute exacerbations in IPF. The mortality risk is increased in patients older than 65 years, in patients with a diffusion capacity below 40% of predicted, severe co-morbidities and in patients on supplementary oxygen or assisted ventilation. Therefore, patients referred for VATS should be carefully selected and also carefully informed of the aim and risks.

Treatment

During the last 10-15 years, an increasing number of randomised, placebo-controlled trials in IPF have been published, culminating in 2014 with the publication of three studies of which two were positive and showed a reduced disease progression of IPF [12,13].

Historically, the treatment of IPF has been immunosuppression with high-dose corticosteroids, azathioprin and cyclophosphamide. Before year 2000, a number of smaller, less well-designed studies found a beneficial effect of immunosuppressive treatment probably due to the study population not only being IPF but also patients with inflammatory ILD. In recent years, it has been realized that high-dose corticosteroids have no impact on the disease course of IPF but instead imply a high risk of side effects. The Panther study was a placebo-controlled study comparing the triple combination of N-acetylcysteine (NAC), azathioprin and corticosteroids to mono-therapy with NAC and placebo [14]. The study showed that triple therapy resulted in more hospital admissions, more side effects and a decreased survival. Furthermore, mono-therapy with NAC did not influence the level of decline in FVC.

Pirfenidone is a new anti-fibrotic drug that has just been approved by the Food and Drug Administration (FDA). Pirfenidone has been approved in Japan for several years and in Europe since 2011. Pirfenidone inhibits several growth factors such as TGF- β and TNF- α inhibitors and inhibits the formation of collagen. Pirfenidone has been studied in several trials of which CAPACITY and ASCEND are the most recent. These trials have promoted the approval of the drug in USA and Europe [13,15]. In the ASCEND study, 555 patients were randomized to pirfenidone 2403 mg daily or placebo. The primary endpoint was the change in FVC or death. There was a relative reduction of 47.9% in the proportion of patients who had an absolute decline of 10 percentage points or more in the percentage of the predicted FVC or who died in the pirfenidone group as compared to placebo. A pooled analysis of ASCEND and CAPACITY showed a significantly increased survival in the pirfenidone treated group. In Europe, pirfenidone is indicated for patients with mild to moderate IPF with a FVC > 50% and a diffusion capacity > 30%. Patients with severe IPF were not included in the trials, but in USA, FDA has approved pirfenidone for all patients. Pirfenidone

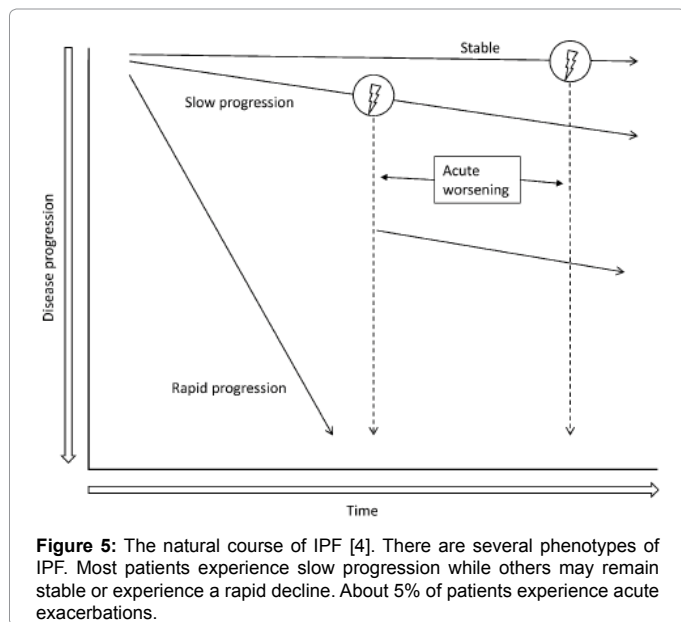


Figure 5: The natural course of IPF [4]. There are several phenotypes of IPF. Most patients experience slow progression while others may remain stable or experience a rapid decline. About 5% of patients experience acute exacerbations.

side effects include nausea, reduced appetite, anorexia, reflux and weight loss, photosensitivity and hepatitis but rarely led to treatment discontinuation.

The INPULSUS trial was a 52 week, randomized double-blind trial that evaluated the efficacy and safety of the tyrosine kinase inhibitor Nintedanib (Orfev®). The primary end point was the annual rate of decline in FVC. A total of 1066 patients were randomized to Nintedanib 150 mg twice daily or placebo. The adjusted annual rate of change in FVC was -114.7 ml with Nintedanib versus -239.9 ml with placebo in INPULSIS-1 and -113.6 ml with nintedanib versus -207.3 ml with placebo in INPULSIS-2. The treatment effect is comparable to pirfenidone although the patients included were not completely comparable. So far, no studies have compared the two drugs. Nintedanib side effects were primarily diarrhoea (62%), but the drop-out rate in the study was acceptable at 5%. Nintedanib has been approved by the FDA and awaits approval in Europe in the spring of 2015.

Supplementary oxygen is indicated when hypoxemia is present at rest or when exertional desaturation is demonstrated. Cough can be treated with codeine or low dose corticosteroids. A single study has shown a beneficial effect of thalidomide on invalidating cough [16]. In case of severe dyspnea, morphine treatment can be attempted. Many patients benefit from referral to palliative care programmes.

Lung transplantation should always be considered in IPF. The median survival after lung transplantation in IPF is 4.7 years [17].

Comorbidities

Most IPF patients have one or more co-morbidities. Arterial hypertension, ischemic heart disease, gastro-oesophageal reflux, pulmonary hypertension, depression, emphysema and cancer are among the most commonly reported co-morbidities. Although no evidence exists, IPF experts recommend screening, diagnosis and treatment of co-morbidities and believe that treatment improves the prognosis [18].

Prognosis

The prognosis of IPF is dismal with a median survival of 3-5 years, but there are phenotypes with different survival. Some patients remain

stable for several years, some progress slowly, others experience a rapid decline over a few months. About 5% of the patients develop acute exacerbations (Figure 5) [1]. Acute exacerbations in IPF are associated with a very high mortality of 90-95% [1].

Severely reduced pulmonary function, hypoxemia, severe dyspnea, and severe fibrosis on HRCT at the time of diagnosis are all signs of a dismal prognosis. More than 10% reduction in FVC over six months, progressive reduction of diffusion capacity and increasing dyspnea are also poor prognostic signs [1].

No tests or biomarkers have been able to identify the phenotype of the individual patient. The GAP-index combines gender, age and physiology and divides the patients into three groups with a 3-year survival of 16%, 42% and 77%, respectively [19].

Conclusion

IPF is an irreversible, progressive fibrotic lung disease with a median survival of 3-5 years. The diagnosis should be made using a multidisciplinary approach with evaluation of the environmental and occupational exposure, pharmacologic treatment, co-morbidities, history, HRCT, cytology and histopathology, if available. Diagnosis and treatment is a specialist task. Treatment includes anti-fibrotic treatment with the potential of slowing disease progression and prolonging survival. Other important components in the care of patients with IPF include supplementary oxygen, transplantation evaluation, and palliation such as rehabilitation, counseling and end-of-life decisions. Referral for specialist evaluation is necessary when velcro crackles, clubbing, restrictive pulmonary function or radiological signs of fibrosis are observed, as early identification of IPF is paramount for the timely initiation of anti-fibrotic treatment.

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