



Idiopathic Interstitial Pneumonias

Serap Argun Barış, İlknur Başıyigit, and Steven D. Nathan

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1 Introduction

Idiopathic interstitial pneumonias (IIPs) are a heterogeneous group of interstitial diseases that include more than 200 acute or chronic diseases with varying degrees of inflammation or fibrosis [1]. The American Thoracic Society (ATS)/European Respiratory Society (ERS) IIP classification was last updated in 2013. This update includes some changes to the original (2002) classification [2] with the IIPs now

S. Argun Barış (✉) · I. Başıyigit

School of Medicine, Department of Pulmonary Diseases, Kocaeli University, Kocaeli, Turkey

S. D. Nathan

Advanced Lung Disease & Lung Transplant Program, Inova Fairfax Hospital, Fairfax, VA, USA

University of Virginia, Charlottesville, VA, USA

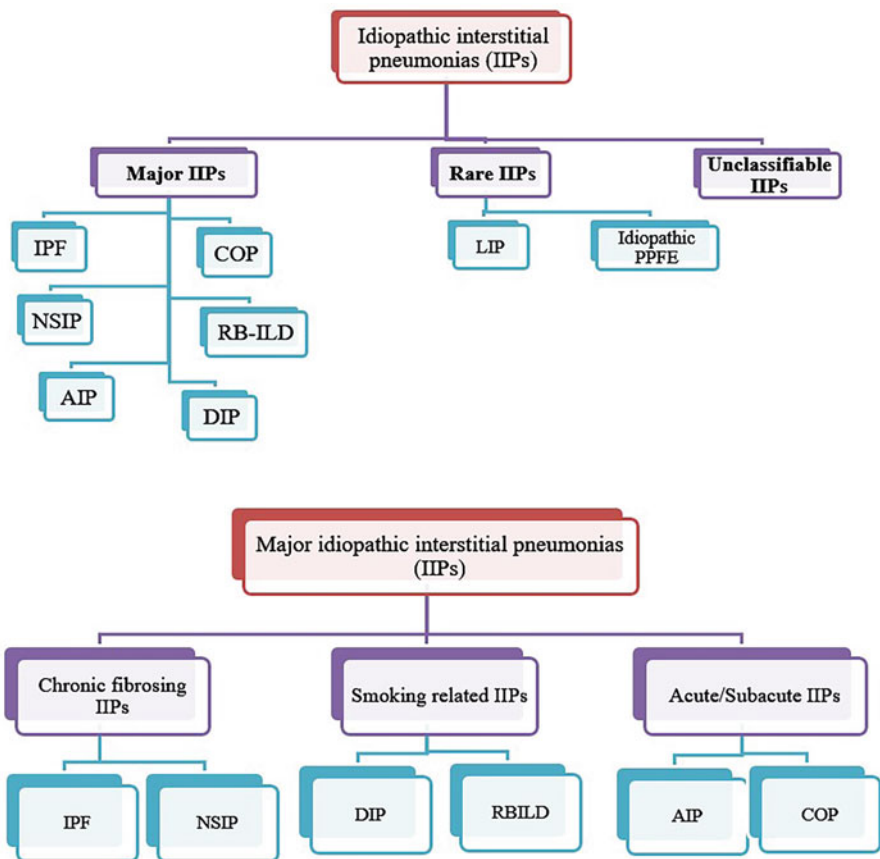


Fig. 1 Classification of IIPs

divided into four main groups: chronic fibrosing, smoking-related, acute/subacute, and rare groups, with idiopathic pleuroparenchymal fibroelastosis (PPFE) now being added to the rare IIP group (Fig. 1).

2 Major IIPs

2.1 Chronic Fibrosing IIPs

2.1.1 Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive fibrotic lung disease of unknown etiology that affects adults. It is the most common form of idiopathic interstitial pneumonia and is recognized by a radiological and/or a pathological usual interstitial pneumonia (UIP) pattern in a patient without any disorder that may cause

this pattern [3, 4]. Recognition of IPF is especially essential since it has a shorter survival time than other interstitial pneumonias and is even lower than some malignancies. However, it is now possible to reduce lung function decline and increase survival rates with the implementation of novel antifibrotics [5–7].

Epidemiology

IPF is more common in men, its frequency increases with age, and it can be seen worldwide with variable frequency rates between the races [8]. The age-adjusted incidence rate is higher in men than women, with the highest incidence between the ages of 70 and 79 [9]. IPF is a deadly disease with a reported median survival of 3–5 years. The clinical course of IPF is unpredictable although older age, male sex, and severe functional impairment are associated with a worse prognosis [3, 10].

The diagnostic criteria for IPF have changed over the years. The most similar definition of the current diagnostic criteria was reported in the American Thoracic Society (ATS)/European Respiratory Society (ERS) Guideline in 2000 [11]. The age and sex-adjusted incidence and prevalence of IPF were found as 8.8 and 27.9 per 100,000 in a population-based study in Minnesota, USA, from 1997 to 2005 when IPF was defined as UIP on a lung biopsy material or definite UIP pattern on high-resolution chest tomography (HRCT) [9]. Recent epidemiological studies based on these diagnostic criteria reported that the incidence of IPF was 0.6–17 cases per 100,000 person-years, and prevalence was 0.7–63 cases per 100,000 people [4, 12]. However, the prevalence of IPF in a population older than 65 years was found as 495 per 100,000 people in 2011, which is higher than previous reports, suggesting that the frequency of IPF may be steadily rising as the elderly population increases worldwide [10].

In Turkey, the incidence of IPF was found to be 5 per 100,000 in a study conducted between the years of 2007–2009, and IPF was the second most common disorder among diffuse parenchymal lung diseases after sarcoidosis [13].

Risk Factors

IPF is a disease with unknown origin. However, several risk factors for the development of IPF include genetic factors, demographic factors (age and male sex), smoking, occupational and environmental exposures, and comorbidities (such as gastroesophageal reflux disease) [3].

Gene mutations that have been identified as increasing the predisposition to IPF can be grouped into four categories:

1. Genes that can affect alveolar stability such as gene encoding surfactant protein A and C (SFTPA1, SFTPA2, SFTPC)
2. Genes related to short telomere and cell senescence such as TERC, TERT, TIN2, DKC1, RTEL1, PARN, and NAF1
3. Genes that can affect host defense such as gene encoding mucin 5B (MUC5B), gene encoding transforming growth factor-beta inhibition, and Toll-like receptor-mediated immune response (TOLLIP)

4. Genes that affect the integrity of the epithelial barrier such as gene encoding desmosomal protein (DSK)

Of these, MUC5B and TOLLIP polymorphism are the most common mutations in sporadic and familial IPF [3, 14].

The frequency of IPF increases with age, more common in patients older than 70 years of age and quite rare in a population younger than 40 [15]. Higher incidence and prevalence rates in older age and male sex have been reported in previous studies [9, 12, 16, 17]. It is suggested that 70% of IPF patients are males [14]. In the UIP Registry conducted in Turkey, the male/female ratio was 5.14, with no female patient younger than 50 years of age [15].

Current or ex-smoking history has been presented as an essential pathogenetic factor in IPF with smoking prevalence rates reported between 41% and 83% [8, 12, 14]. However, smoking is not considered an only etiological factor in the development of IPF since there are also certainly lifetime non-smokers among IPF patients [8].

Environmental and occupational exposures such as wood dust, metal dust, stone/sand/silica dust, textile dust, agriculture/farming, and livestock have been implicated in the development of IPF [3, 12, 14].

Several viruses like Epstein-Barr virus, cytomegalovirus, and herpesvirus and bacteria like *Staphylococcus* and *Streptococcus* have been shown in the lungs of inpatient with IPF suggesting that they may have a role in the development of the disease [3]. High bacterial load and altered lung microbiota have also been shown to be associated with disease progression [3, 14].

Increased frequency of gastroesophageal reflux, obstructive sleep apnea, and diabetes mellitus among IPF patients suggest their possible role in the pathogenesis of IPF. However, further studies are needed to determine whether these diseases contribute to the development of IPF or IPF causes an increase in their frequency [3, 4, 14].

To conclude, both genetic and environmental factors seem to contribute to the development of IPF, and determining these factors might help develop prevention and treatment strategies.

Pathogenesis

The development of IPF simply may be explained as abnormal damage/repair mechanism in the lungs. Repetitive epithelial injury in genetically susceptible patients leads to premature cell aging, production of profibrotic mediators, activation of mesenchymal cells, and eventually progressive scarring of the lungs [3, 4]. It is accepted that the pathogenesis is similar in all patients, regardless of their etiological factors [3].

In the predisposition stage of pathogenesis, genetic predisposition, cell senescence related to shortened telomeres, and environmental exposures lead to alveolar epithelial cell dysfunction. Whether this stage causes clinically significant fibrosis depends on the duration and severity of the exposure. Dysfunctional epithelial cells activate the profibrotic signaling pathways that lead to the secretion of profibrotic

mediators such as transforming growth factor-beta (TGF- β), platelet-derived growth factor (PDGF), and Wnt proteins in the initiation stage of the disease pathogenesis. These profibrotic mediators cause epithelial to mesenchymal transition (EMT), recruitment of fibrocytes, and fibroblast activation. The last stage is the progression stage, which includes the abnormal release of matrix proteins via mesenchymal cells. The extracellular matrix remodeling leads to apoptosis resistance, increased stiffness of matrix, abnormal deposition of type I and type III collagen, periostin, and fibrillin-2. The remodeled matrix and epigenetic changes may result in the progression of fibrosis through further stimulation of fibroblasts [18].

It is now acknowledged that inflammation is not the critical feature in IPF [19]. The observation of an increased risk of hospitalization and death in the treatment group compared in the PANTHER-IPF of prednisone, azathioprine, and N-acetyl cysteine suggested the potential harm of anti-inflammatory and immunosuppressive therapy in patients with IPF [20]. However, it cannot be ruled out that a low level of inflammation exists in the early phase of wound healing, contributing to pathogenesis of IPF [21]. Furthermore, T-lymphocyte-mediated profibrotic mediators and B-lymphocyte-mediated autoantibodies against alveolar epithelial cells have been reported in several studies [19].

Medical History and Clinical Findings

The most common symptoms in IPF are chronic progressive dyspnea and dry cough, which are not specific for IPF. Physicians mostly consider the diagnosis of chronic obstructive pulmonary disease (COPD) and/or heart failure in adults who admit to these symptoms, which leads to misdiagnosis resulting in misguided therapy for lengthy periods [4]. Therefore, exertional dyspnea and chronic dry cough in adult patients should raise the suspicion for IPF [3]. It should also be kept in mind that the clinical probability of IPF increases in males, advanced age (over 60 years), and smoking history [22]. IPF is quite rare in patients younger than 50 years of age. Younger patients with ILD are more likely to have an underlying connective tissue disease that may not be clinically manifest at diagnosis or conceivably could also have familial IPF [23].

Extrapulmonary symptoms are not common in IPF and, if present, should suggest other diagnoses such as an underlying connective tissue disease [15]. Also, a detailed environmental exposure history and medical history of the patient is necessary to exclude other fibrotic lung diseases like chronic hypersensitivity pneumonitis, drug-induced lung disease, and connective tissue disease [24].

Bibasilar inspiratory crackles (Velcro rales) are the most specific physical sign on auscultation of the chest at the patient's initial presentation [3]. Digital clubbing may be found in some patients with IPF and has a reported frequency of between 30% and 60% in the literature [25]. Examination of the skin and musculoskeletal system is also essential to rule out an underlying connective tissue disease [24].

To conclude, adult patients older than 60 years of age with the symptoms of exertional dyspnea with or without a dry cough, bibasilar inspiratory rales (Velcro), with or without clubbing should raise the clinical suspicion for IPF [23].

Diagnostic Procedures

A complete blood count, erythrocyte sedimentation rate, C-reactive protein levels (CRP), renal, and hepatic function tests are generally performed in patients with suspected IPF [15]. Serological tests are also recommended to exclude an underlying connective tissue disease. This evaluation should include a rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti-CCP), antinuclear antibody (ANA), and a myositis panel [15, 23]. Detailed serological tests can be ordered according to clinical symptoms and findings on a case-by-case basis. It should be kept in mind that autoantibody positivity may be found in 22% of patients with IPF and 21% of the healthy population [26].

Biomarkers for screening, diagnosis, differential diagnosis, prognosis, and response to treatment in IPF have been investigated; however, nonspecific marker has been widely accepted in routine clinical practice yet [27–32]. A multi-biomarker panel is required rather than a single biomarker to provide disease-related information that would affect the clinical approach. The most investigated biomarkers in large cohorts are matrix metalloproteinase 7 (MMP7) and MUC5B [19].

HRCT is especially vital as a definite and probable UIP pattern allows the confident diagnosis of IPF in the appropriate clinical setting without the need for a surgical lung biopsy [22]. The diagnostic algorithm in the recent ATS/ERS guideline for the diagnosis of IPF is based on HRCT findings; therefore, HRCT should be performed in all patients with the suspicion of IPF [23]. A typical UIP pattern on HRCT includes subpleural and basal predominant reticulation and honeycombing with or without peripheral traction bronchiectasis (Table 1, Fig. 2). HRCT findings such as nodules and cysts, consolidation, mosaic attenuation, extensive ground-glass opacities, upper-lobe predominance, and bronchovascular distribution are atypical findings for IPF and are suggestive of other interstitial lung diseases (ILD) [4].

Bronchoalveolar lavage (BAL) has a limited role in diagnosing IPF; however, it may help distinguish IPF from other interstitial lung diseases such as sarcoidosis, eosinophilic pneumonia, hypersensitivity pneumonitis, infection, and malignancy [15, 23]. The eosinophil and lymphocyte percentages in BAL fluid may be increased in patients with IPF compared to a healthy population. However, marked elevation of lymphocyte (>40%) and eosinophilic percentages (>10%) suggest HP and eosinophilic pneumonia, respectively [23, 33]. In the recent ATS/ERS guideline, BAL analysis is not recommended in patients with a UIP pattern on HRCT and is only a conditional recommendation for patients with suspected IPF with HRCT patterns other than UIP [23].

When clinical and radiological findings are not sufficient for a confident diagnosis, lung biopsy can be considered [4]. Video-assisted thoracoscopic surgery is preferred over open lung biopsy because of its low complication rate. For surgical biopsy to be diagnostic, biopsy samples should not be taken from advanced fibrosis areas, and it should be obtained from multiple lobes [4]. The diagnostic value of less-invasive biopsy methods such as transbronchial lung biopsy (TBLB) and bronchoscopic lung cryobiopsy (BLC) has been investigated in previous studies [34–36]. Despite having low complication rates, sensitivity for TBLB was found to be low due to the small sample size [37]. Since it is possible to take larger samples with

Table 1 Diagnostic categories according to HRCT findings [23]

UIP	Probable UIP	Indeterminate for UIP	Alternative diagnosis
Subpleural and basal predominant; distribution is often heterogeneous ^a Honeycombing with or without peripheral traction bronchiectasis or bronchiolectasis ^b	Subpleural and basal predominant; distribution is often heterogeneous ^a Reticular pattern with peripheral traction bronchiectasis or bronchiolectasis May have mild GGO	Subpleural and basal predominant Subtle reticulation; may have mild GGO or distortion (early UIP pattern) CT features and/or distribution of lung fibrosis that do not suggest any specific etiology (truly indeterminate)	Findings suggestive of another diagnosis, including the following: • CT features: - Cysts - Mosaic attenuation - Predominant GGO - Profuse micronodules - Centrilobular nodules - Nodules - Consolidation • Predominant distribution: - Peribronchovascular - Perilymphatic - Upper or mid-lung • Other findings: - Pleural plaques - Dilated esophagus - Distal clavicular erosions - Extensive lymph node enlargements - Pleural effusions, pleural thickening

CT computed tomography, GGO ground-glass opacities, UIP usual interstitial pneumonia

^aVariants of distribution; occasionally diffuse, may be asymmetrical

^bSuperimposed CT features; mild GGO, reticular pattern, pulmonary ossification

BLC, aUIP pattern can be more reliably ascertained than with TBLB; however, higher complication rates have been reported, and this procedure still requires standardization [34, 36]. In the recent ATS/ERS guideline, TBLB and BLC are not recommended in patients with a UIP pattern on HRCT, while there is no specific recommendation for or against these forms of biopsy in patients with HRCT patterns other than UIP [23].

The pathological feature of IPF is defined as a UIP pattern characterized by geographical and temporal heterogeneous involvement of the lungs (Fig. 3). In a

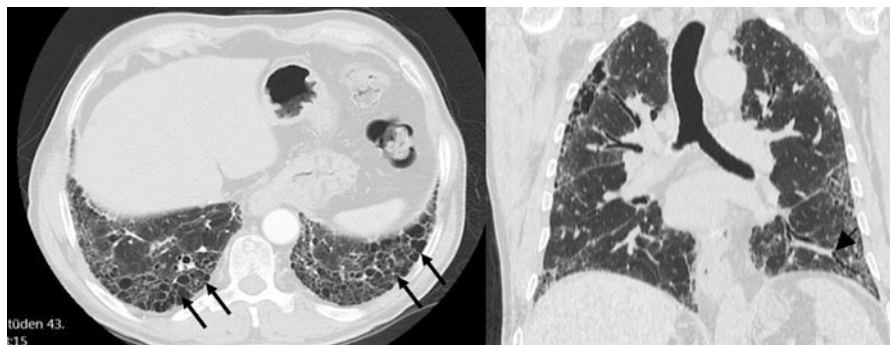


Fig. 2 Usual interstitial pneumonia pattern illustrating bilateral subpleural honeycombing (arrows) and peripheral traction bronchiectasis (arrow head)

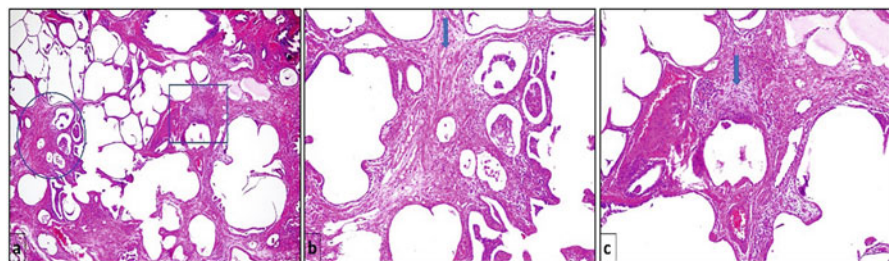


Fig. 3 (a) Patchy parenchymal fibrosis and temporal heterogeneity – old and new lesions as well as normal alveolar spaces are seen together in a lung specimen (H&E x100). (b) Interstitial inflammation and fibrotic foci (area marked with arrow) between alveoli (one large magnification of the round area in picture a) (H&E x200). (c) Young connective tissue in alveolar septa (area marked with an arrow) (one large magnification of the rectangular area in image a) (H&E x200)

UIP pattern, areas of marked fibrosis with or without honeycombing and fibroblastic foci indicating active fibrosis are seen concurrently [16].

Diagnosis

IPF has been defined as a chronic fibrotic interstitial pneumonia with a UIP pattern in the 2000 ATS/ERS guidelines, with updates in 2011 and most recently in 2018 [11, 23, 38]. According to the current diagnostic criteria, IPF is defined by a UIP pattern on high-resolution chest tomography without a known cause, or UIP on lung biopsy material; obtaining a lung biopsy is recommended conditionally when clinical and radiological findings are unclear [23]. Both radiological and pathological findings are divided into four diagnostic criteria as “UIP,” “Probable UIP,” “Indeterminate for UIP,” and “Alternative diagnosis” (Tables 1 and 2).

However, neither radiological nor histopathological UIP patterns are specific for IPF, and these can be seen in other fibrotic lung diseases such as hypersensitivity pneumonitis, collagen tissue disease, and drug-induced lung disease [4]. Therefore, the definite diagnosis of IPF requires exclusion of other fibrotic idiopathic interstitial

Table 2 Diagnostic categories according to histopathological patterns [23]

UIP	Probable UIP	Indeterminate for UIP	Alternative diagnosis
Dense fibrosis with architectural distortion (destructive scarring and/or honeycombing) Predominant subpleural and/or paraseptal distribution of fibrosis Patchy involvement of lung parenchyma by fibrosis Fibroblastic foci Absence of features to suggest an alternative diagnosis	Some histologic features from column 1 are present but to an extent that precludes a definite diagnosis of UIP/IPF AND Absence of features to suggest an alternative diagnosis OR Honeycombing only	Fibrosis with or without architectural distortion, with features favoring either a pattern other than UIP or features favoring UIP secondary to another cause ^a Some histologic features from column 1, but with other features suggesting an alternative diagnosis ^b	Features of other histologic patterns of IIPs (e.g., absent of fibroblast foci or loose fibrosis) in all biopsies Histologic findings indicative of other diseases (hypersensitivity pneumonitis, Langerhans cell histiocytosis, sarcoidosis, lymphangioleiomyomatosis)

IIP idiopathic interstitial pneumonia, *IPF* idiopathic pulmonary fibrosis, *UIP* usual interstitial pneumonia

^aGranulomas, hyaline membranes, airway-centered changes, areas of interstitial inflammation without fibrosis, marked chronic fibrous pleuritis, organizing pneumonia

^bCellular inflammatory infiltrates away from areas of honeycombing, prominent lymphoid hyperplasia including secondary germinal centers and distinctly bronchiolocentric distribution that could include extensive peribronchiolar metaplasia

pneumonias (IIP) and lung fibrosis related to environmental and/or occupational exposure, systemic disease, or drugs and frequently is best attained through a multidisciplinary approach including clinicians, radiologists, and pathologists (Fig. 4) [39].

The confident diagnosis of IPF can be made in patients with clinical features suggestive of IPF (age over 60 years, male sex, smoking history, clubbing, bibasilar Velcro rales) and a UIP pattern HRCT without known cause [22, 23]. Surgical lung biopsy is not mandatory in patients with clinical features highly suggestive of IPF and a probable UIP pattern on HRCT. A multidisciplinary approach in such patients can provide a confident diagnosis of IPF without the need for a lung biopsy [4, 22, 40].

Biopsy should be considered if clinical features are not highly suggestive of IPF, and/or HRCT findings are reported as indeterminate for UIP. However, lung biopsy carries a small risk of mortality as well as the potential for severe complications such as exacerbation of IPF. The risk of complications is higher in older patients with comorbidities and severe physiological impairment; thus patient selection is key in optimizing the risk/benefit ratio [3].

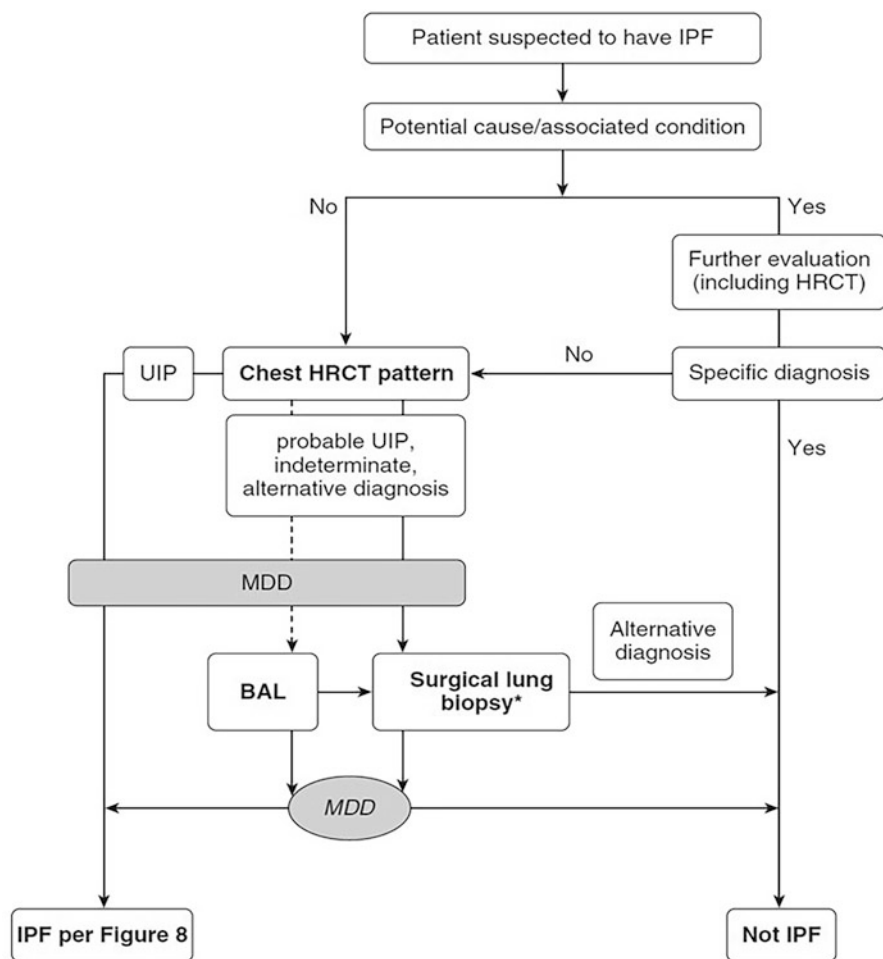


Fig. 4 Diagnostic algorithm for idiopathic pulmonary fibrosis [23]

The ATS/ERS guideline for the diagnosis of IPF recommends a diagnostic approach based on HRCT and biopsy findings shown in Fig. 5 [23]. Since the UIP pattern can be seen in other fibrotic lung diseases, all patients diagnosed as IPF should be regularly reevaluated about the diagnosis' reliability. Of note, it is a minority of patients in whom a biopsy is deemed necessary; a diagnosis of IPF can be made based on individual patient's pretest likelihood for IPF combined with their HRCT pattern.

Management

IPF is a heterogeneous disease. Its clinical course is unpredictable on an individual basis. Some patients may be stable over the years; others progress slowly, while others may deteriorate rapidly [41]. Therapeutic options in IPF are limited, and

IPF suspected		Histopathology pattern			
		UIP	Probable UIP	Indeterminate for UIP	Alternative diagnosis
HRCT pattern	UIP	IPF	IPF	IPF	Non-IPF
	Probable UIP	IPF	IPF	IPF (Likely)*	Non-IPF
	Indeterminate for UIP	IPF	IPF (Likely)*	Indeterminate for IPF**	Non-IPF
	Alternative diagnosis	IPF (Likely)* / non-IPF	Non-IPF	Non-IPF	Non-IPF

Fig. 5 Diagnosis of IPF diagnosis based on HRCT and biopsy findings [23]

management should be aimed to improve symptoms and quality of life, prevent lung function decline, and decrease mortality rates [3]. In addition to pharmacological treatment, nonpharmacological management strategies should be considered in all patients, and treatment of comorbidities should also be included in the management plan [15].

Nonpharmacological Treatment

Long-term oxygen treatment is recommended for patients with resting hypoxemia based on the 2011 American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association (ATS/ERS/JRS/ALAT) guidelines for the diagnosis and management of IPF [36]. Ambulatory oxygen therapy in patients with exertional desaturation has been investigated and reported to increase exercise capacity and reduce dyspnea scores [42, 43].

Mechanical ventilation is recommended for a minority of patients based on low-quality evidence [38]. A retrospective analysis of mechanically ventilated IPF patients between the years of 2006–2012 in the United States reported an in-hospital mortality of approximately 50% [44]. Noninvasive mechanical ventilation might have lower mortality rates and can be considered in patients with acute exacerbations of their IPF [3].

Pulmonary rehabilitation is associated with improved exercise capacity and quality of life in patients with IPF [45]. Pulmonary rehabilitation received a weak

recommendation in the 2011 ATS/ERS/JRS/ALAT IPF guidelines for most patients with IPF [38].

Lung transplantation should be considered in all patients with moderate to severe IPF since the disease is progressive and pharmacologically incurable [3]. Median survival among IPF patients was reported to be 4.5 years after transplantation, which is lower than other diseases [46]. There is no precise data about transplantation timing, but early referral should be encouraged since the evaluation may require weeks to months, and disease progression may occur during this time [3, 4, 38].

Besides these approaches, smoking cessation, vaccination against influenza and pneumococcal pneumonia, nutrition support, and education about the disease should be included in the patient's management plan [4].

Pharmacological Treatment

Antifibrotic Treatment

The most significant improvement in IPF treatment in recent years has been the introducing of two antifibrotic agents to clinical practice. Although it is still an incurable disease, pirfenidone and nintedanib help reduce disease progression, decrease lung function, and improve survival [47]. These two antifibrotics are recommended as a conditional recommendation in the 2015 ATS/ERS/JRS/ALAT IPF guidelines [48].

Pirfenidone

Pirfenidone has antifibrotic and anti-inflammatory effects; however, its exact action mechanism is not fully understood [1]. It was approved in the USA in 2014 based on the placebo-controlled Phase III CAPACITY and ASCEND trials, which showed that pirfenidone was associated with an approximately 50% reduction in FVC decline, sustenance of exercise tolerance, and improved progression-free survival in patients with IPF [7, 49]. Pirfenidone is administered orally with a maximal dose of 801 mg three times a day (2403 mg/day) [49].

Patients with severe functional impairment defined as a FVC <50% and/or a DLCO <30% were not included in the clinical trials, and therefore, the results from the pivotal pirfenidone studies may not be generalized to patients with severe IPF [48]. However, some preliminary studies have reported similar efficacy of pirfenidone in severe IPF without additional safety concerns [50].

FVC decline is considered the best follow-up test to predict disease progression and evaluate antifibrotic treatment efficacy in clinical practice. However, it is not clear whether to stop the antifibrotic treatment in patients who experienced a FVC decline of more than 10% during follow-up. Furthermore, a recent analysis of the CAPACITY and ASCEND data revealed that continued treatment with pirfenidone in patients with a decline in FVC of 10% or more was associated with a lower risk of subsequent FVC decline and death compared to placebo [51].

The most common adverse events reported with pirfenidone are nausea, fatigue, dizziness, anorexia, dyspepsia, elevation of liver enzymes, photosensitivity, and

rash. Side effects can be easily managed by slower titrations, taking doses with meals, temporary dose reductions, prescribing other medications such as anti-emetics and anti-acids, and avoiding sun exposure [52]. Recent long-term follow-up study has shown the same adverse effect profile as observed in phase III trials with pirfenidone with no additional safety signals noted. The median on-treatment survival after the first pirfenidone dose has been reported as 77.2 months in one study [53]. Additionally, it has been shown that pirfenidone is associated with a 2.47-year increase in life expectancy than best supportive care in patients with IPF [54].

Nintedanib

Nintedanib is a tyrosine kinase inhibitor that acts on growth factors including vascular endothelial growth factor, fibroblast growth factor, and platelet-derived growth factor [4]. It is approved based on the two INPULSIS trials, which were randomized controlled phase III studies which showed that nintedanib was associated with an approximately 50% reduction in FVC decline as well as a reduction in acute exacerbation of IPF [6]. Nintedanib is administered orally with a dose of 150 mg twice daily (300 mg/day).

As with pirfenidone, several analyses have been conducted with nintedanib addressing controversial IPF treatment issues [55–57]. In a study evaluating data from the INPULSIS and INSTAGE studies, nintedanib has been shown to have similar effects on FVC decline regardless of disease severity with no additional safety or tolerability signals noted [55]. Similarly, data from INPULSIS-ON which was an open-label extension study of the INPULSIS trials was evaluated to compare patients with a baseline FVC >50% to those with a FVC ≤ 50% [56]. Both groups had similar FVC decline at week 48 suggesting similar efficacy of nintedanib in patients with advanced IPF. Data from nintedanib trials have demonstrated that although FVC decline was associated with mortality, it was not associated with further decline and may not reflect the treatment response [57].

The most common adverse events reported with nintedanib are diarrhea, nausea, decreased appetite, abdominal pain, and liver enzyme elevations. The most frequent adverse event associated with nintedanib use is diarrhea; however, it rarely results in permanent discontinuation of treatment. Side effects can be easily managed by taking doses with meals, temporary dose reductions to 100 mg twice daily, and prescribing antidiarrheal agents [55, 58]. Nintedanib is also associated with an increased risk of bleeding and atherosclerotic events; therefore, it should be used with caution in patients on full dose of anticoagulation and severe cardiovascular risk factors [4]. As with pirfenidone, long-term use of nintedanib is effective for slowing disease progression with similar safety profiles observed in the phase III trials without additional safety concerns and has also been reported to increase life expectancy in patients with IPF [58, 59].

Initiation and Monitoring of Antifibrotic Treatment

There is no head-to-head comparison between two drugs, and both have similar effects on FVC decline; therefore, neither can be preferred over the other [3]. An open-label study investigating the combination of two drugs demonstrated that

Table 3 Comparison of pirfenidone and nintedanib

	Pirfenidone	Nintedanib
Mechanism of action	Unknown	Tyrosine kinase inhibition
Evidence for efficacy	CAPACITY and ASCEND trials	INPULSIS trials
Efficacy	Reducing FVC decline by 50% compared to placebo	Reducing FVC decline by 50% compared to placebo
Daily dose	801 mg three times a day (267 mg or 801 mg tablets)	150 mg twice a day
Side effects	Nausea, anorexia, dyspepsia, photosensitivity and rash	Diarrhea, nausea, decreased appetite, abdominal pain
Management of side effects	Slowing dose titration, dose taken with meal, use of anti-emetics, sun avoidance	Use of antidiarrheal agents, temporary dose reduction
Cautions	Drug interaction (fluvoxamine, ciprofloxacin, omeprazole)	Full dose anticoagulant, bleeding, and arterial thrombosis risk

combination was safe and tolerable except for an increase in gastrointestinal side effects in the combination group [60]. There are no large, controlled studies of combination therapy, so this is not recommended in the current guidelines. A comparison between pirfenidone and nintedanib is provided in Table 3 [4].

Disease progression is unpredictable and variable in patients with IPF; however, eventually all patients experience a decline in lung function [61]. Real-life observational studies revealed that clinicians prefer to wait before antifibrotics initiation, especially in patients with preserved lung function [62]. However, clinical trials on pirfenidone and nintedanib comparing patients with more preserved and less preserved lung function showed similar lung function decline in all patients irrespective of their baseline FVC levels and similar effects of the antifibrotic drugs in both groups [63, 64]. Therefore, it is suggested that treatment be initiated as soon as the diagnosis is made because of the unpredictable and progressive nature of IPF [65]. The role of antifibrotic treatment in advanced IPF remains controversial; although both drugs have been shown to have favorable effects in advanced disease, the decision to initiate antifibrotic therapy in severe IPF should be made on an individual basis. Additionally, the use of antifibrotics in severe IPF is not covered by health insurance in Turkey [15].

There is no treatment duration for antifibrotic drugs [65]. Side effects of both drugs are manageable as aforementioned and rarely cause treatment cessation. However, the best method for assessment of treatment response is not clear yet. Studies with pirfenidone and nintedanib showed continued treatment benefit in patients with declines in lung function; this suggests that FVC decline may not necessarily be a rationale for treatment cessation [51, 57]. Further studies are needed to evaluate the effects of continuing the same antifibrotic, switching to the other drug

or combination therapy in patients with declines in lung function while on antifibrotic treatment [65].

Both antifibrotics are associated with elevated liver enzymes; therefore, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and bilirubin should be measured before the initiation of treatment and monthly for 3–6 months and every 3 months thereafter. Treatment should be discontinued in the presence of clinical evidence of hepatic dysfunction, specifically elevations in bilirubin levels or AST/ALT levels of more than 5 times the upper limit of normal with or without clinical findings [4].

Antacid Therapy

Antacid treatment was afforded a conditional recommendation in the 2015 ATS/ERS/JRS/ALAT IPF guidelines [48]. Since proton pump inhibitors have been shown to increase the risk of respiratory infection in patients with IPF, clinical decision regarding the use of antacid therapy in IPF patients without clinical evidence of gastroesophageal reflux disease should be made with caution [3].

Follow-Up and Prognosis

Patients with IPF should be regularly followed-up, ideally in expert centers. There are many dimensions to their care including monitoring for disease progression, management of comorbidities, evaluation for treatment options, side effect mitigation, palliative and end-of-life care, and the need for transplantation. However, there is no consensus on how to monitor these patients, and most of the recommendations are based on expert opinion [66]. It is suggested that clinical evaluation, pulmonary function tests, 6-min walking distance (6MWD), basic laboratory tests including liver function tests, and evaluation of treatment side effects should be performed at each visit [15]. It has been demonstrated that measurements such as dyspnea scores, 6MWD, and decline in FVC can predict risk of mortality and hospitalization [67]. A clinical prediction model called GAP which includes gender (G), age (A), and physiology (P) variables (FVC, DLCO) has been shown to predict mortality in patients with IPF [68].

IPF has a poor prognosis with a median survival of 27–56 months depending on disease severity. Most the studies evaluating mortality in IPF patients were prior to the advent of antifibrotic therapy. There is data from multiple studies, including registry reports, attesting to antifibrotic therapy being associated with improved survival. Lung transplantation is recommended as one of the most definitive management options in patients with IPF; however, it is only the minority of IPF patients who are candidates for this. In one study, only 16% of patients underwent lung transplantation from an interstitial lung disease center between the years of 2000 and 2009 [69].

There are still unmet needs in treatment and follow-up of IPF regarding treatment response criteria, measurements predicting disease progression, and mortality risk. Future studies are needed to evaluate the best clinical monitoring methods implemented in routine clinical practice.

Comorbidities

There is an increased prevalence of comorbid conditions in patients with IPF compared to the general population (Table 4). Recognition and treatment of comorbidities has been shown to improve quality of life and survival in IPF patients [70].

Pulmonary hypertension (PH) is an important comorbid condition associated with poor prognosis and mortality in patients with IPF. The prevalence of PH in IPF varies from 3% to 86% depending on the severity of IPF and the method used for PH diagnosis [70]. It is more common in advanced IPF and associated with a decrease in survival. Severe dyspnea, a markedly reduced DLCO, an enlarged pulmonary artery segment on CT of the chest, low 6MWD, excess desaturation, and need for supplemental oxygen should raise the suspicion for underlying PH in patients with IPF [71, 72]. Optimal treatment of PH in patients with IPF is still unknown. Both riociguat and ambrisentan are contraindicated, and PAH-targeted therapy is not recommended for IPF-PH in current guidelines. However, a recent study of inhaled treprostinil in patients with a variety of ILD, including IPF, did show benefit based on the primary endpoint of 6MWD with multiple secondary endpoints also being met. This study (INCREASE study) has been the largest study to date in patients with ILD-PH [48, 72].

Nearly 30% of patients with IPF have concomitant emphysema. Combined pulmonary fibrosis emphysema (CPFE) is mostly seen in male patients with a heavy smoking history and is frequently accompanied by exercise-induced desaturation. Patients with CPFE have relatively normal FVC levels and total lung capacities because of the counterbalancing effects of restrictive and obstructive processes [73]. Both lung cancer and pulmonary hypertension prevalence are higher in CPFE than patients with IPF, and both are associated with poor survival [71]. There is no clinical trial investigating the effects of antifibrotics on CPFE; however, data for pirfenidone and nintedanib suggest similar beneficial effects irrespective of concomitant emphysema in patients with IPF [74, 75].

Table 4 Comorbidities in idiopathic pulmonary fibrosis

Pulmonary	Combined pulmonary fibrosis and emphysema Lung cancer Obstructive sleep apnea syndrome Pulmonary embolism
Cardiovascular	Coronary artery disease Pulmonary hypertension Congestive heart failure Arrhythmias (atrial fibrillation, etc.)
Gastrointestinal	Gastroesophageal reflux disease (GERD) Hiatal hernia
Endocrine and metabolic	Hypothyroidism Diabetes mellitus
Mental health	Depression Anxiety

Patients with IPF have a five- to sevenfold increase in the prevalence of lung cancer compared to general population. The most frequent histopathological subtype is squamous cell carcinoma followed by adenocarcinoma. Treatment of lung cancer is also controversial since surgery, chemotherapy, and radiotherapy have been reported to be associated with acute exacerbations of the underlying IPF [70, 73].

Gastroesophageal reflux disease (GERD) is thought to possibly play a role in IPF pathogenesis. Not all IPF patients with GERD have symptoms, thus performing diagnostic methods such as 24-h pH monitoring and esophageal manometry should be decided individually. Lifestyle changes known to reduce reflux is recommended for all IPF patients with or without symptoms; however, antacid therapy should be individualized and is more appropriate for symptomatic patients since proton pump inhibitors have been shown to increase the risk of respiratory infections [70].

Acute Exacerbation of IPF

Definition and Diagnostic Criteria

Acute exacerbations of IPF (AE-IPF) are defined by subacute worsening dyspnea that is typically accompanied by ground-glass infiltrates and worsened pulmonary function in patients with IPF [76]. The incidence of AE-IPF is reported at between 4% and 20% per year and is more frequent in patients with severe IPF. The median survival of patients after an acute exacerbation is generally less than 3 months [77].

The first consensus report proposing a definition and diagnostic criteria for AE-IPF was published by the Idiopathic Pulmonary Fibrosis Clinical Research Network (IPFnet) group in 2007 [78]. In this report, AE-IPF was defined as acute and clinically significant deterioration in patients with IPF without any underlying cause. The diagnostic criteria included the presence of IPF, new or worsening dyspnea within 30 days, newly developed bilateral ground-glass opacities with or without consolidation added on the background of a UIP pattern, the absence of infection, and exclusion of other disease that may cause deterioration such as pulmonary embolism, cardiac edema, and acute lung injury of known etiology. The panel suggested using the term “suspected acute exacerbation” in patients who do not meet all of the above five criteria [78]. Over the years since the publication of these diagnostic criteria, it has been found difficult to exclude alternative etiologies, particularly infections, and thus confirm suspected acute exacerbations. Furthermore, studies have demonstrated that acute deterioration of IPF with known etiologies such as infection or aspiration has a similar prognosis to idiopathic ones [76, 77]. Based on these findings, the definition and diagnostic criteria of AE-IPF were revised in 2016 (Table 5). In this report, the term “idiopathic” was removed from the definition, and both idiopathic and triggered exacerbations were included in the definition of AE-IPF with the statement “deterioration not fully explained by cardiac failure or fluid overload” added to the diagnostic criteria [79].

Table 5 Revised definition and diagnostic criteria of acute exacerbation of IPF [79]

Revised definition
An acute, clinically significant, respiratory deterioration characterized by evidence of new widespread alveolar abnormalities
Revised diagnostic criteria
• Previous or concurrent diagnosis of idiopathic pulmonary fibrosis
• Acute worsening or development of dyspnea typically of less than 1 month duration
• Computed tomography with new bilateral ground-glass opacity and/or consolidation superimposed on a background pattern consistent with usual interstitial pneumonia pattern
• Deterioration not fully explained by cardiac failure or fluid overload

Risk Factors

Risk factors for AE-IPF have been reported as a low FVC percent predicted, low DLCO percent predicted, a low 6MWD, pulmonary hypertension, low oxygen levels, younger age, high body mass index, and comorbid coronary artery disease. There are also potential triggers reported for AE-IPFs such as air pollution, bronchoscopic procedures, surgery, mechanical ventilation, radiotherapy, and certain medication, especially chemotherapy and biological agents [76].

Management

AE-IPF has a poor prognosis with a short-term mortality of approximately 50% and high risk of mortality persisting over the next year after discharge from the hospital [76]. Therefore, prevention and management of AE-IPF is especially important; however, unfortunately as yet there is no proven therapy. Accordingly, the clinical approach varies worldwide regarding antifibrotics for prevention, immunosuppressant use for treatment, and invasive mechanical ventilation for supportive care in AE-IPF [80]. Despite only having a weak level of evidence in the 2011 ATS guideline, corticosteroids are the most common therapy in patients with AE-IPF worldwide [38, 80].

Antifibrotic treatment has been shown to reduce acute exacerbations in previous studies. Clinical trials of nintedanib have demonstrated a reduction in frequency of AE-IPFs [81]. Although AE-IPF was not a prespecified endpoint in the pivotal pirfenidone clinical trials, there is data attesting to pirfenidone reducing AE-IPF in earlier Japanese studies [82]. The perioperative use of pirfenidone has also been shown to reduce the acute exacerbation risk [83]. More data is needed in order to clarify the effects of antifibrotic treatment in the prevention of AE-IPF.

Supportive care particularly supplemental oxygen therapy should be administered in hospitalized patients with AE-IPF. The IPF treatment guideline from 2011 recommended avoiding mechanical ventilation in these patients because of the high in-hospital mortality rates [38]. However, if patients are lung transplant candidates, especially if they are already listed, then mechanical ventilation and ECMO (if available) might be valuable adjuncts as a bridge to transplantation.

Potential therapies for AE-IPF have mostly been evaluated in small uncontrolled studies. These agents included corticosteroids (as monotherapy or as combination

with an immunomodulator agent), polymyxin-B immobilized fiber column hemoperfusion, cyclophosphamide, rituximab, cyclosporine, tacrolimus, and thrombomodulin. However, none of these therapies have proven efficacy, and there is an ongoing lack of randomized controlled studies evaluating any treatments for AE-IPF.

2.1.2 Idiopathic Nonspecific Interstitial Pneumonia (NSIP)

Clinical Presentation

The mean age of patients with NSIP, which occurs at a younger age than IPF, is 40–50 years. It is more common in young people and women who do not smoke. Clinical findings are dyspnea and dry cough, which are also seen in IPF, and therefore, these findings are not specific to NSIP. The incidence of clubbing in NSIP has been reported at between 10–35% [84]. Auscultation reveals basilar or widespread crackles [11].

Although lung function tests yield results similar to IPF, physiological abnormalities are milder. More than 90% of the patients have a restrictive respiratory function pattern and a decrease in DLCO. Rarely, a mild obstructive pattern can be seen. Hypoxemia develops during exercise in more than two-thirds of patients [11].

Cellular analysis of BAL fluid is not diagnostic alone, but can contribute to diagnosing interstitial lung diseases when evaluated together with clinical and radiological findings. While neutrophil dominance is observed in UIP in BAL fluid, there is a lymphocytic predominance in NSIP with 50% of patients having an increase in lymphocyte percentages [84]. Indeed, the presence of a BAL lymphocytosis, together with other findings such as HRCT and pulmonary function test results, may further reinforce the suspicion for NSIP [11].

Radiology

The characteristic HRCT findings of NSIP are symmetric, bilateral ground-glass opacities (GGO) with a basal predominance and subpleural sparing (Fig. 6a). Subpleural sparing has been reported in approximately 40% of the cases [84]. Over time, chronic NSIP can change into a fibrotic form. The ground-glass opacities can decrease and be replaced by reticulations [84]. Reticular opacities with traction bronchiectasis or bronchiolectasis can be seen in approximately 75% of cases with NSIP (Fig. 6b) [2]. However, the presence of honeycombing, a specific finding for UIP, is rare in NSIP [84].

Histopathology

There are two subtypes of NSIP, the cellular and fibrosing forms. The determination of histopathological pattern is important since this helps to determine the treatment approach and to predict the prognosis in NSIP patients [85]. There is mild to moderate interstitial inflammation (Fig. 7) in the cellular form, type II pneumocyte hyperplasia, and thickening of alveolar septa by lymphocytes and plasma cells. In addition to interstitial inflammation and thickening of alveolar septa by collagen accumulation, there is an interstitial fibrosis in fibrosing NSIP [11]. In NSIP,

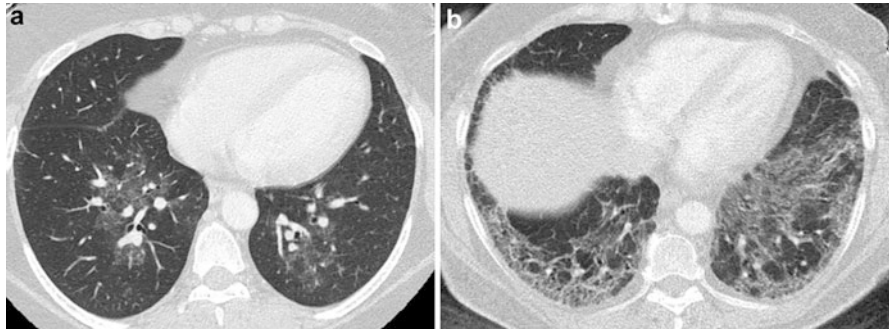


Fig. 6 (a) Central and peribronchovascular distributed GGOs in the lower lobes of the lung in cellular NSIP. (b) Fibrotic changes, traction bronchiectasis, subpleural reticulations, and interstitial septal thickening bilaterally in the lung parenchyma, more prominent in the periphery and lower zones in a patient diagnosed histopathologically with fibrotic NSIP

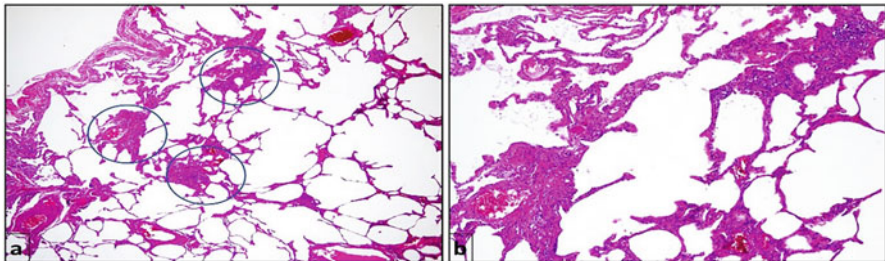


Fig. 7 NSIP case with nonspecific lymphocytic inflammation as foci in septae and perivascular areas in the lung, as well as normal alveolar structures (a: x40 H&E, b: x100 H&E)

temporal and spatial homogeneity is observed in contrast to the expected temporal heterogeneity in UIP [11, 84]. Also, the presence of dense fibrosis, honeycombing, or fibroblastic foci is not expected in NSIP [11].

Diagnosis and Differential Diagnosis

NSIP can be seen as idiopathic or secondary to conditions such as collagen vascular diseases, hypersensitivity pneumonia, drug-induced pneumonitis, resolving diffuse alveolar damage, familial pulmonary fibrosis, and immune deficiency including HIV infection [11]. Collagen vascular diseases are the most common underlying etiology; therefore, it is important to evaluate for clinical signs and symptoms suggesting an underlying rheumatological condition. An evaluation of serum autoantibodies (such as RF, ANA, and anti-CCP) is also important in this regard in patients presenting with NSIP [86]. Also, a detailed evaluation of risk factors for hypersensitivity pneumonia and drug use can differentiate idiopathic NSIP from other secondary causes of NSIP.

One of the diseases included in the differential diagnosis of NSIP is IPF. Differentiation of NSIP from IPF is important because of the different treatment options,

clinical course, and worse prognosis of IPF [86]. Age, smoking history, and HRCT characteristics are helpful to differentiate NSIP from IPF [84].

Treatment

Corticosteroids are the first-choice treatment of NSIP, but immunosuppressive agents (including azathioprine, cyclophosphamide, cyclosporine and mycophenolate mofetil) are also used in cases either as steroid-preserving agents or when there is an inadequate response to treatment [87]. Treatment with corticosteroids and/or immunosuppressive drugs tends to improve lung function in patients with idiopathic NSIP with a better clinical response in those patients with shorter symptom duration. These findings suggest that it is beneficial to initiate treatment in the early stage of the disease in patients with idiopathic NSIP [87]. The response to corticosteroids and the prognosis are significantly better in NSIP than UIP [84]. The use of antifibrotic agents is being investigated, especially in fibrotic patients who have insufficient response despite treatment and do not have any other treatment options [88]. NSIP patients with a progressive fibrotic phenotype might be candidates for antifibrotic therapy with nintedanib [89].

Clinical Course and Prognosis

The clinical course and prognosis of NSIP is variable. While some patients show clinical improvement, in others the disease remains stable, while in others death occurs due to progressive fibrosis [2]. This variable clinical course depends on the underlying histological pattern (cellular or fibrotic) and the extent of the fibrosis [11, 90]. Cellular NSIP patients have a much better prognosis than those with fibrotic NSIP. Also, 5- and 10-year survival rates are significantly better in patients with cellular NSIP than fibrosing NSIP (100% vs 90% and 100% vs 35%, $p = 0.027$, respectively) [90].

Furthermore, NSIP has a better prognosis than IPF, with a median survival ≥ 9 years [84]. The 5-year survival rate has been reported at 82% in iNSIP, whereas in IPF the median survival is shorter than 5 years [90].

2.2 Smoking-Related IIPs

For many years, it has been known that smoking is a risk factor for COPD and lung cancer. Recently, it has been shown that smoking has a role in the development of interstitial lung diseases (ILDs). Smoking leads to the accumulation of inflammatory cells including macrophages, neutrophils, and Langerhans cells in the small airways and interstitium. Also, it induces transforming growth factor- β (TGF- β), a mediator that has a crucial role in the development of lung fibrosis [91].

Smoking-related ILDs include a heterogeneous group of diseases with different clinical and radiological features [92]. Among IIPs, respiratory bronchiolitis interstitial lung disease (RB-ILD) and desquamative interstitial pneumonitis (DIP) have smoking as a major contributor [2].

2.2.1 Respiratory Bronchiolitis Interstitial Lung Disease (RB-ILD)

Clinical Presentation

Respiratory bronchiolitis (RB) is common among current or former smokers and is usually asymptomatic. However, RB-ILD, which is considered the more severe RB form, is a rare disease and is classified among the IIPs [92]. It is usually seen between the third and sixth decades of life, and there is no gender predominance [93].

RB-ILD may be asymptomatic or present with a subacute clinic course of exercise dyspnea, wheezing, and cough that develops within weeks to months [93]. The presence of end-inspiratory crackles is the most common physical examination signs. Clubbing is rare, and RB-ILD patients with clubbing should be evaluated for a possible underlying malignancy [93].

Pulmonary function test may reveal a mixed (restrictive and obstructive) pattern with a mild to moderate decrease of DLCO. BAL findings are similar to those of healthy smokers with increased alveolar macrophages containing brown, black, or golden tobacco pigments [93].

Radiology

The main HRCT findings of RB-ILD are centrilobular nodules and ground-glass opacities [93, 94]. Air trapping, centrilobular emphysema, and/or bronchial wall thickening may also accompany these typical findings due to smoking [95].

Histopathology

Respiratory bronchiolitis (RB) is a characteristic histopathologic finding in the lungs of current or former smokers [91]. In response to smoking, there is typically mild inflammation, mild bronchiolar fibrosis, and bronchiolocentric pigmented macrophage accumulation. In RB-ILD, pigmented macrophage accumulation is prominent in centrilobular alveolar spaces [93].

Diagnosis and Differential Diagnosis

RB, DIP, and acute/subacute hypersensitivity pneumonitis are included in the differential diagnosis of RB-ILD. The presence of compatible radiological and BAL findings in a smoker strengthens the likelihood of a diagnosis of RB-ILD, and surgical lung biopsy is usually not required [93]. Alternative diagnoses should be considered in the absence of alveolar macrophages with tobacco pigments or in the presence of a BAL lymphocytosis [93]. As one of the alternative diagnoses, centrilobular nodules are seen in HP, but unlike RB-ILD, there is lymphocytosis in the BAL and smoking history is rare in patients [91].

Treatment

Since RB-ILD is a smoking-related disease, the mainstay of treatment is smoking cessation. Corticosteroids are treatment option for patients with progressive disease despite abstinence from smoking [92].

Clinical Course and Prognosis

Smoking cessation helps to improve both clinical symptoms and physiological parameters such as DLCO. Also, there is regression of ground-glass opacities and centrilobular nodules on HRCT after cessation of smoking [95]. However, the clinical course of RB-ILD is heterogeneous. While some of the patients have a good response to treatment with clinical improvement, some have limited clinical or functional response or disease progression despite smoking cessation and steroid therapy [93].

Despite the heterogeneous clinical course, RB-ILD has a very good prognosis with prolonged survival in most cases [93].

2.2.2 Desquamative Interstitial Pneumonia (DIP)

Clinical Presentation

Desquamative interstitial pneumonia is an uncommon chronic disease. Generally, it presents in the fourth–fifth decades, and there is a male predominance [96–98]. Smoking incidence is 81% among patients with DIP, while 19% are never smokers [96]. Although DIP is a smoking-related disease, it may also develop in non-smokers due to secondary causes such as environmental and occupational exposures [99, 100], collagen vascular diseases such as rheumatoid arthritis and Sjögren syndrome [101, 102], infections [103], irritants, and drugs such as nitrofurantoin [104].

Presenting symptoms are dyspnea and cough, but they are not specific to the disease. The average time between symptom onset and diagnosis is about 1 year [96]. Pulmonary function tests reveal a restrictive pattern and a decreased DLCO [97]. The cellular analysis of BAL in DIP is nonspecific although there is an increase in the cellular component (eosinophil, neutrophil, lymphocyte, and macrophage counts) of BAL fluid [98].

Radiology

Bilateral ground-glass opacities with lower lobe and peripheral predominance are characteristic radiological findings of DIP, and most of the cases (92%) have these findings (Fig. 8) [11, 96]. Ground-glass opacities are often associated with fine reticulations [96]. In progressive disease, cysts and traction bronchiectasis may accompany these radiological findings, and findings are not limited only to the subpleural area. Fibrosis can also be seen but not as commonly as in NSIP or UIP [97].

Histopathology

DIP was first described by Liebow as due to epithelial cell desquamation in the alveolar spaces; however, it is now known to be due to macrophage accumulation, not epithelial desquamation [94]. DIP is characterized by diffuse accumulation of pigmented macrophages in alveolar spaces with widening of the alveolar septa (Fig. 9). Compared to RB-ILD, in DIP macrophage accumulation in the alveolar spaces is extensive, diffuse, and uniform [97]. In addition to macrophages,

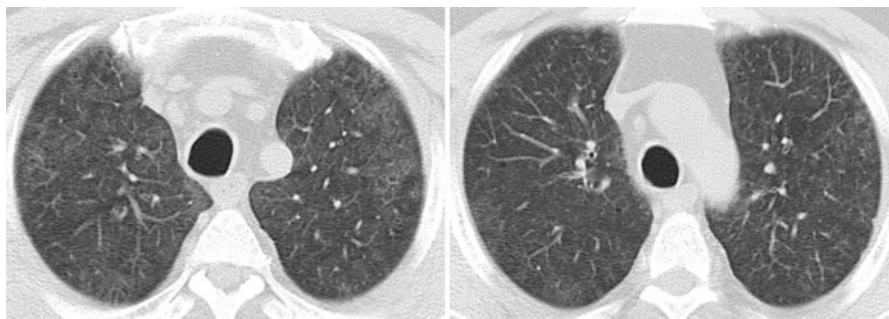


Fig. 8 Ground-glass opacities in a patient with DIP

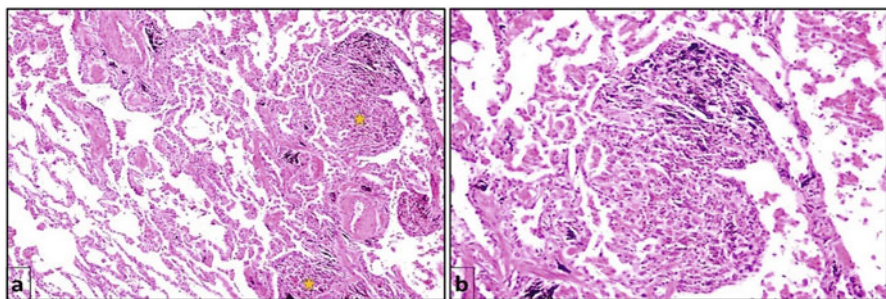


Fig. 9 Case with DIP: Accumulation of alveolar macrophages (areas marked with asterisks) in the alveoli, accompanied by anthracosis in the vessel walls and alveolar structures (a: x100 H&E, b: x200 H&E)

eosinophils and/or giant cells can be seen [96]. Septal thickening and mild to moderate fibrosis may also accompany these findings [94].

Diagnosis and Differential Diagnosis

RB-ILD, NSIP, and UIP are the main diseases in the differential diagnosis of DIP. RB-ILD, a smoking-related disease, is the disease most confused with DIP. Some authors suggest that DIP can be considered the late phase of RB-ILD, since both diseases have similarities including symptoms, smoking history, ground-glass opacities on HRCT, and an accumulation of pigmented macrophages on histopathological evaluation. In contrast to the bronchiolocentric nature of RB-ILD, DIP is distinguished from RB-ILD by its propensity to manifest as a diffuse homogeneous pneumonitis [97]. The comparison of demographic, clinical, and radiological characteristics of RB-ILD and DIP is shown at Table 6.

It is important to differentiate DIP from UIP, since DIP has a good response to steroid treatment and has a much better prognosis than UIP [98]. Unlike UIP, interstitial involvement is not subpleural, and temporal heterogeneity is not observed. The honeycombing pattern that typically accompanies UIP is very rarely present on HRCT in patients with DIP [97].

Table 6 Comparison of demographic, clinical, and radiological characteristics of smoking-related IIPs

	RB-ILD	DIP
Gender predominance	No predominance	Male predominance
Age	3rd–6th decades	4th–5th decades
Symptoms	Exertional dyspnea, cough	Exertional dyspnea, cough
Etiological factors	Smoking	Smoking Environmental exposure Occupational exposure Collagen tissue diseases Infections Irritants Drug toxicity
HRCT characteristics	Ground-glass opacities Centrilobular nodules Bronchial wall thickening Upper lobe predominance Bronchiolocentric distribution	Bilateral ground-glass opacities Reticulations Lower lobe peripherally predominance Diffuse distribution
PFT	Mixed respiratory pattern (often obstructive pattern) Decreased DLCO	Restrictive pattern Decreased DLCO
Treatment	Smoking cessation Avoiding second-hand smoke Corticosteroid	Smoking cessation Avoiding second-hand smoke Avoiding environmental & occupational exposure Corticosteroid Immunosuppressive agents Macrolide Lung transplantation
Clinical course & prognosis	Good prognosis Prolonged survival	Good response to initial treatment Good prognosis (Improvement or stabilization) 18% relapse after cessation of treatment

It is not reliable to diagnose DIP based on clinical and radiological features alone. The existence of clinical and radiological similarities between NSIP and DIP underscores the necessity of surgical lung biopsy for a definitive diagnosis. Alternatively, transbronchial biopsies can be performed as a less invasive diagnostic procedure in DIP. However, the yield of transbronchial biopsy appears limited, despite the widespread distribution of DIP in the lungs [96].

Treatment

Smoking cessation and avoiding secondhand smoke exposure after the diagnosis of DIP are the cornerstones of therapy [94, 97]. Avoiding irritants and dust exposure for those in whom the underlying cause is not smoking is also important in treating and preventing disease progression [94, 97]. Corticosteroid treatment is recommended to

patients with moderate or severe disease and who have progressive disease despite smoking cessation [98].

Other rarely used treatment options are immunosuppressive agents including azathioprine or cyclophosphamide, macrolides for their immunomodulatory effect, ribavirin, and chloroquine. These drugs can be used alone in patients unresponsive to steroid therapy or as steroid sparing agents in patients with a partial response. Lung transplantation is also an option in patients who have progressed despite all treatment options [96].

Clinical Course and Prognosis

Smoking cessation and avoiding tobacco exposure are important since smoking is a risk factor for relapse and a poor prognosis [97]. Most of the patients (92%) with DIP are treated with corticosteroids, and initial response to therapy is generally good, with improvement or stabilization most often seen. Progression to severe fibrosis is rare [91]. However, recurrences may occur after the cessation of treatment in 18% of cases [96].

Generally, most of the patients with DIP have a good prognosis, especially if smoking is stopped in the early stages of the disease [94, 96, 98]. Results from recent studies reveal an overall survival approaching 90% at 10 years [94].

2.3 Acute/Subacute IIPs

2.3.1 Acute Interstitial Pneumonia

Acute interstitial pneumonia, first described by Hamman and Rich, also known as the Hamman-Rich Syndrome, is a rapidly progressing idiopathic lung disease that causes respiratory failure and ARDS [105].

Clinical Presentation

Most of the patients are between 50 and 55 years of age, and the frequency of disease is similar in women and men. There is no association between smoking history and AIP [105]. Acute onset of symptoms including progressive dyspnea, cough, fever, and respiratory distress is characteristic for AIP. Before the onset of respiratory symptoms, patients have flu-like symptoms such as fever, weakness, myalgia, and arthralgia suggestive of infection. Physical examination reveals dyspnea, tachypnea, and bilateral diffuse crackles on auscultation of the lungs. There is severe hypoxemia on arterial blood gas analysis, and mechanical ventilation is required in most patients [105].

Radiology

HRCT reveals bilateral patchy airspace opacifications with sparing of the costophrenic angles. Findings suggestive of heart failure such as increased cardiothoracic ratio, septal thickening, and pleural effusion are absent or very rare. In the early exudative phase of AIP, there are bilateral, patchy ground-glass opacities. However, in the late phase referred to as the “organizing stage” of AIP, distortion

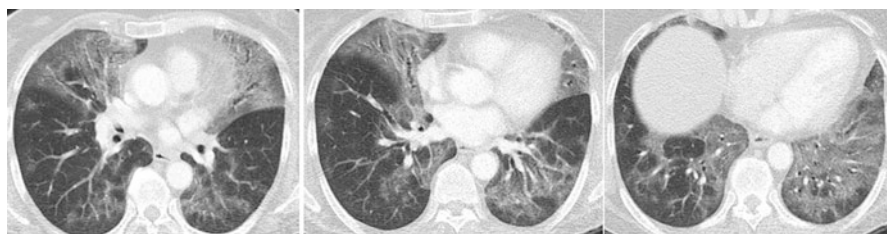


Fig. 10 Widespread patchy ground-glass opacities in AIP

of the bronchovascular bundles and traction bronchiectasis is prominent, while consolidation may also be seen (Fig. 10) [11].

Histopathology

Diffuse alveolar damage (DAD) is the characteristic histopathological change in AIP. In the early phase of the disease (within a week), there is an accumulation of exudative edema in alveolar spaces and the interstitium, while fibroblast proliferation and type 2 cell hyperplasia in the late phase are observed [105]. There is a diffuse distribution of disease with hyaline membranes often seen. Alveolar septal thickening related to organizing fibrosis may also be seen in the organizing phase [11].

Diagnosis and Differential Diagnosis

AIP is an idiopathic disease of unknown etiology [105]. The acute onset of respiratory symptoms with severe hypoxemia, bilateral lung infiltrates on radiographics, and histologically evident diffuse alveolar damage, with the absence of an identifiable etiology or coexisting disease, are the main diagnostic criteria for AIP [106].

It is important to exclude alternative diagnoses lead to acute interstitial pneumonia. Alternative diagnoses include acute exacerbation of underlying ILD, congestive heart failure, infections (especially viral infection and most recently COVID-19), diffuse alveolar hemorrhage, drug- or radiation-induced pneumonitis, and other interstitial pneumonias such as COP, acute eosinophilic pneumonia, and hypersensitivity pneumonitis [105, 107].

Approximately 50% of the cases in which clinicians encounter an acute and progressive ILD have been shown; there may be a viral pneumonia as the etiology [107]. Thus, infections and especially viral pneumonia are the first conditions that should be excluded; therefore, markers of infection as well as microbiological and serological testing should always be considered [106]. Serum BNP levels and echocardiography for excluding congestive heart failure, follow-up hemoglobin and hematocrit levels for diffuse alveolar hemorrhage, serum autoantibodies for collagen vascular disease, and detailed history for coexisting diseases and drug use are also recommended in the work-up of AIP [106].

Treatment

There is no effective and specific treatment for AIP, and therefore, the mainstay of disease management is supportive care. Mechanical ventilation is often required due to the refractory hypoxemia that typically remains uncorrected by supplemental oxygen alone. Mechanical ventilation strategies in AIP are similar to ARDS and focus on lower tidal volume ventilation and lung protective ventilation strategies [105, 108].

Treatment with corticosteroids has no clear benefit in patients with AIP, but is invariably used. Extracorporeal membrane oxygenation (ECMO) and lung transplantation may be considered for select patients who progress despite supportive care and mechanical ventilation [109].

Clinical Course and Prognosis

Patients should be followed and monitored closely due to the propensity for rapid progression to respiratory failure [105]. AIP has a poor prognosis with mortality rate that is extremely high (>50%) [106].

2.3.2 Cryptogenic Organizing Pneumonia (COP)

Organizing pneumonia is a disease characterized by deposition of fibroblastic tissue in alveolar spaces as a nonspecific response to lung injury [11]. There is confusion regarding organizing pneumonia (OP) which historically has been called bronchiolitis obliterans organizing pneumonia (BOOP). However, since OP and bronchiolitis obliterans are different clinical entities and bronchiolitis obliterans is a bronchiolar disease, this nomenclature is no longer used [110].

Organizing pneumonia may be idiopathic or may develop due to secondary causes such as infection, rheumatological diseases, autoimmune diseases, inhalation injury, drug toxicity, transplantation, and radiotherapy [111] (Table 7). The idiopathic form is named cryptogenic OP (COP) and is included in the acute-subacute group of IIPs. Most of the patients diagnosed with OP pathologically are secondary OP (86.9%), and COP constitutes only 13.9% of the cases [112].

Clinical Presentation

The frequency of COP is similar between women and men and is common in non-smokers [11]. COP is usually seen between the ages of 50–60 [110]. It is a subacute disease typically presenting within 3 months with symptoms of cough and dyspnea [112]. Constitutional symptoms such as loss of weight, sweats, intermittent fever, and myalgia are common. Presenting symptoms and radiological findings can often be confused with infection. Most patients report after clinical symptoms and radiological findings do not improve despite the implementation of one or more courses of antibiotics [11, 112]. On physical examination, there is local or widespread inspiratory crackles on auscultation of lungs. Clubbing is typically absent [11].

Laboratory findings may include neutrophilia and an increased CRP and sedimentation levels suggestive of an inflammatory process or infection [11]. There is typically a mild to moderate restrictive ventilatory pattern and reduced diffusion

Table 7 Etiological causes of COP (Table is adopted by Bacque et al. [111])

Etiology of organizing pneumonia		
Idiopathic OP	Cryptogenic OP [111]	
Secondary etiologic factors	Infection	Bacteria, virus, fungi [113] parasite
	Drugs	Nitrofurantoin, amiodarone, etc.
	Cocaine inhalation	
	Toxic gas inhalation	
	Aspirations of gastric contents	Gastroesophageal reflux disease
	Rheumatological diseases [114]	
	Transplantation	Hematopoietic stem cell or solid organ transplantation
	Radiotherapy [115]	
OP associated other lung pathologies [111]	Vasculitis (granulomatosis with polyangiitis) Tumors (lymphoma, lung cancer) Pulmonary infarct Hypersensitivity pneumonitis Eosinophilic pneumonia Interstitial lung diseases UIP, NSIP, AIP	

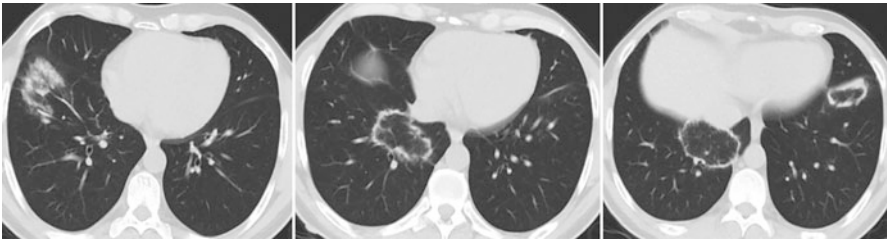


Fig. 11 The reverse halo sign (atoll sign) in a patient with COP

capacity on pulmonary function testing [110]. Bronchoalveolar lavage is not specific to COP, but often there is an increase in lymphocytes [111].

Radiology

Characteristic findings of OP on HCRT are focal or multifocal migratory consolidations with peripheral and lower lobe predominance. Nearly 60% of the cases have these classical radiologic findings [110]. There may also be unusual radiological findings including upper lung zone involvement, a crazy-paving pattern characterized by patchy GGO with interlobular septal thickening, and a nodular pattern in COP [110]. The reverse halo sign (atoll sign), an area of ground-glass opacity surrounded by a crescent of parenchymal consolidation, may also be seen in one fifth of patients with COP (Fig. 11) [11, 116]. Linear and band-like opacities characterized by thick radial bands of consolidation or subpleural curvilinear bands parallel to the pleural may be suggestive of OP [116].

Histopathology

The main histopathological finding in OP is filling of the alveolar spaces with fibroblastic tissue in response to lung injury. Mild interstitial chronic inflammation may also be present [11].

Diagnosis and Differential Diagnosis

The diagnosis of COP frequently depends on a multidisciplinary (clinical, radiological, and pathological) evaluation [110]. To assess whether OP is cryptogenic, it is necessary to exclude secondary causes associated with OP [116]. Therefore, patients should be evaluated in detail with a thorough history and examination to rule out possible precipitating causes including an underlying infection or autoimmune disease, drug use, including cocaine, or a possible toxic inhalation [111].

Some radiological findings of COP are not specific to the disease. The reverse halo sign, which was thought to be pathognomonic for COP in the past, is not a specific finding for COP. It can be seen in various other diseases such as infection, lymphomatoid granulomatosis, granulomatosis polyangiitis, lipid pneumonia, sarcoidosis, and radiation [110].

Focal cryptogenic organizing pneumonia (FOP) is a clinicopathological entity associated with nonspecific symptoms and focal radiological findings suggestive for lung malignancy or pneumonia [112, 117].

Treatment

Corticosteroid therapy is often used to treat COP [112].

Clinical Course and Prognosis

There is a rapid and good clinical and radiological response to corticosteroid therapy in the majority of cases. The 5-year survival has been reported as 98% [112]. However, relapse is common (66%) when the dose is reduced or after discontinuation of therapy [111, 112]. HRCT changes, including bilateral shadow pattern and traction bronchiectasis, as well as a partial response to steroid therapy, may be predictive factors for COP relapse [118].

In a minority of patients, there is progression and lung fibrosis (similar to NSIP radiologically and histopathologically) despite steroid therapy. International multidisciplinary classification of the IIPs mentioned “a fibrosing variant of OP (AFOP)” in 2013 for patients with this pattern of mixed fibrosis and organizing pneumonia [2]. Patients with FOP may have a rapid and fulminant course [119]. Therefore, the early diagnosis of AFOP is very important in terms of predicting the clinical course [119]. Progression to lung fibrosis is associated with poor clinical outcomes including respiratory failure and death [110, 111].

3 Rare IIPs

3.1 Lymphocytic Interstitial Pneumonia (LIP)

LIP is a rare and benign disease on the spectrum of lymphoproliferative diseases [120, 121]. It is generally associated with secondary causes such as collagen vascular diseases (Sjögren syndrome and systemic lupus erythematosus), infections (human immunodeficiency virus-HIV or Epstein Barr virus – EBV), and autoimmune diseases such as Hashimoto thyroiditis, dysgammaglobulinemia and amyloidosis [120, 122, 123]. Sjögren syndrome (42%) and HIV (17%) are the most common conditions associated with LIP [123]. However, idiopathic LIP is very rare, and it is very important to evaluate the patient for secondary causes and underlying diseases during the work-up of LIP [121].

3.1.1 Clinical Presentation

LIP has a wide age range between 40 and 70 years with a female predominance [121, 123]. LIP can be detected incidentally or may present with a subacute or chronic course [121]. Generally, the insidious onset of exertional dyspnea and a non-productive cough are the main symptoms of the disease. Some cases have constitutional symptoms such as fever, loss of weight, and night sweats [123].

Pulmonary function tests reveal a restrictive pattern with a decreased diffusion capacity. Lymphocytosis with normal CD4/CD8 can be seen in the cellular analysis of bronchoalveolar lavage, but this finding is not specific for LIP. Bronchoalveolar lavage can also be used for excluding underlying infections [121].

3.1.2 Radiology

LIP's characteristic HRCT finding is multiple thin-walled air cysts diffusely and randomly distributed in the lungs (Fig. 12) [123, 124]. Most cases of LIP (80%) have

Fig. 12 Multiple randomly distributed thin-walled air cysts in LIP



these cysts which range in size from 1 to 30 mm in diameter. Ground-glass opacities, centrilobular, and subpleural nodules may also be seen in LIP [121].

3.1.3 Histopathology

The main histopathological findings of LIP are dense lymphocytic infiltrates in the interstitium and enlargement of interlobular and alveolar septae [121].

3.1.4 Diagnosis and Differential Diagnosis

LIP is frequently associated with secondary causes, while the idiopathic form is extremely rare. Therefore, all patients diagnosed with LIP should be evaluated for underlying autoimmune diseases, infections, and immunodeficiency conditions [121].

Since LIP's main radiological finding is airway cysts, lymphangioleiomyomatosis, Langerhans cell histiocytosis, and other cystic diseases are included in the differential diagnosis [124]. Lymphocytic infiltrative diseases such as cellular NSIP, DIP, and hypersensitivity pneumonitis may also be alternative diagnoses [121].

Other lymphoproliferative diseases are also included in the differential diagnoses of LIP since it is a disease on the spectrum of lymphoproliferative disorders. There is the risk for transformation of LIP to lymphoma [121]. In the presence of extra-pulmonary findings such as peripheral lymphadenopathy, hepatomegaly, or splenomegaly in a patient diagnosed with LIP, further investigation for lymphoma should therefore be performed [121].

3.1.5 Treatment

Since LIP is most frequently diagnosed as secondary to an underlying condition, treatment should be directed to control the underlying disease. Corticosteroids are the main treatment option; however, immunosuppressive drugs can be used in patient nonrespondent to steroid therapy [121]. Also, anti-retroviral treatment has a beneficial effect in the management of patients with HIV-related LIP [120].

3.1.6 Clinical Course and Prognosis

The clinical course of LIP is variable and depends on the underlying disease. Some patients may have an asymptomatic course, while others remain stable. Rarely, patients present with acute and severe clinical symptoms. Complications such as infection, fibrosis, or transformation to lymphoma may also occur [121].

Response to steroid therapy is generally good in LIP. In 50–60% of patients, there is improvement or stabilization with steroid therapy [121, 123]. The prognosis of LIP is also dependent on the underlying disease. The 5-year mortality in LIP has been reported at between 33% and 50% [121].

3.2 Idiopathic Pleuroparenchymal Fibroelastosis (iPPFE)

Pleuroparenchymal fibroelastosis (PPFE) is a rare IIP characterized by pleural and lung parenchymal fibrosis and predominantly upper lobe involvement [125]. PPFE

can be idiopathic or associated with certain clinical conditions such as rheumatological diseases [126], lung and hematological stem cell transplantation [127], occupational exposure, and amiodarone toxicity [128]. It can also be seen in IPF and has been reported as occurring in 6.3% of IPF patients [129].

Most of the cases of PPFE are idiopathic, and this form is categorized as a rare IIP in the current classification of IIPs [11].

3.2.1 Clinical Presentation

iPPFE, which is frequently seen in adults, has a wide age range with a mean age in the sixth decade. There are actually two peaks, in the third and sixth decades. The gender distribution is equal while a smoking history is uncommon [130]. Progressive exertional dyspnea, cough, pleuritic pain, and weight loss are the main symptoms [130, 131]. Uni- or bilateral pneumothoraces have been reported in 1/3 of the patients. On physical examination, bibasilar crackles are rare. However, crackles can be heard in iPPFE patients with UIP-like changes in the lower lobes of the lung. Clubbing is also rare in patients with iPPFE. Patients often appear slender with a reduced ratio of the anteroposterior to the transverse diameter [130]. Pulmonary function test reveals a restrictive pattern and an associated decreased diffusion capacity [130].

3.2.2 Radiology

Bilateral irregular pleural thickening, dense reticular fibrosis of the parenchyma, a sharp demarcation line between normal and abnormal tissue, distortion of lung architecture with hilar retraction, and upper lobe predominance are the main characteristics of iPPFE [130]. Septal thickening, cysts, and multiple bullae may also be present. Beside this, about half of the patients show other interstitial patterns (especially UIP) in the lower lobes [129].

3.2.3 Histopathology

Fibrous thickening of the visceral pleura and, dense, homogeneous intra-alveolar fibrosis with septal elastosis, sharply separated from the normal lung parenchyma, are histological characteristics of PPFE [130].

3.2.4 Diagnosis and Differential Diagnosis

Assessment of radiological and histopathological features is both important in the diagnosis of iPPFE. The gold standard diagnostic tool is surgical lung biopsy [130, 132]. However, the disease's progressive course, propensity for respiratory failure, increased risk of pneumothorax, and the lack of effective treatment provide a rationale that surgical biopsy might not be mandated in all patients [130]. Recently, it is suggested that bronchoscopy with either transbronchial biopsy or cryobiopsy can be employed as a less invasive diagnostic procedure [125, 132].

3.2.5 Treatment

iPPFE is a progressive disease leading to respiratory failure with no proven or effective treatment as yet. Lung transplantation is the only therapeutic option for patients with advanced disease [132].

3.2.6 Clinical Course and Prognosis

Clinical outcomes vary depending on whether the disease is idiopathic or related to secondary causes. A rapid progressive course is observed especially in iPPFE [130]. Progressive respiratory failure (73.8%) is the most common cause of the death in iPPFE, followed by acute exacerbation (14.3%) [133]. Compared with IPF, the frequency of exacerbations is similar, but the propensity for respiratory failure appears higher, with survival rates that are worse. One study noted a 5-year survival of patients with iPPFE at 38.5% versus those with IPF at 63.5% ($p < 0.0001$) [133].

Male gender, % FVC, and GAP index are all poor prognostic factors for survival [133, 134].

4 Unclassifiable IIPs

The differential diagnoses of ILD are difficult due to similar clinical, radiological, and histopathological features between the various entities. Therefore, frequently a detailed evaluation by a multidisciplinary team (MDT) is required. However, despite a multidisciplinary evaluation, some patients cannot be classified into a specific subgroup and they are referred to as “unclassifiable ILD” [135]. Nonspecific or conflicting clinical, radiological, or histopathological findings (18%), the patient’s unwillingness (8%) or unsuitability for the surgical diagnostic procedure due to high surgical risk (52%), or insufficient/nondiagnostic histopathological samples (8%) are the most common scenarios resulting in patients being categorized as having unclassifiable ILD [136]. Unclassifiable ILD represents approximately 10% of all ILDs and has a heterogeneous clinical course [136].

4.1 Clinical Presentation

Unclassifiable ILD includes various undiagnosed fibrotic ILDs, and therefore, patients have similar clinical characteristics with IPF and other non-IPF ILDs. Patients tend not to have any features of an underlying autoimmune disease. Typically, much like other ILDs, the disease presents with subacute onset of dyspnea with or without a dry cough. Auscultation of the chest typically reveals bilateral crackles. In previous cohort studies of unclassifiable ILD, the mean age was 59–68 years, with approximately half the patients being male and 64% of patients having a smoking history [136, 137].

Pulmonary function tests are also similar to other fibrotic ILDs with a mild restrictive physiology and a moderately reduced DLCO [137].

4.2 Radiology

One study described HRCT findings of unclassifiable ILD to include 17% of patients with a usual interstitial pneumonia (UIP) pattern, 50% with a possible UIP pattern, and 33% with a pattern that is inconsistent with UIP [136].

4.3 Diagnosis and Differential Diagnosis

Unclassifiable ILDs describe a heterogeneous group that includes patients who cannot be placed in one of the other ILD groups, despite a multidisciplinary evaluation [135]. Therefore, diagnosis of these patients depends on exclusion of IPF and other non-IPF ILDs.

“Interstitial pneumonia with autoimmune features (IPAF)” is a subcategory of unclassifiable IIPs. IPAF patients demonstrate some clinical, serological, or morphological features of an underlying connective tissue diseases (CTD), but they do not meet the diagnostic criteria for a specific CTD [135]. The diagnostic definition of IPAF is shown in Table 8 [138].

4.4 Treatment

The therapeutic strategy for unclassifiable IIPs depends on the disease behavior [135]. Nonpharmacological supportive treatments such as smoking cessation, vaccinations, supplemental oxygen, and pulmonary rehabilitation are recommended [137]. In terms of pharmacological treatment, corticosteroids are frequently employed as first-line therapy, but not all patients respond to steroid therapy. Immunosuppressive therapy such as cyclophosphamide is an alternative treatment option in progressive and steroid refractory patients. Lung transplantation should be considered in patients with severe or rapidly progressive unclassifiable ILDs [137].

4.5 Clinical Course and Prognosis

The most important prognostic factors in unclassifiable ILD are baseline lung function, decline in lung function, and smoking history [135]. Patients with unclassifiable ILDs have an intermediate prognosis between IPF and NSIP [136–139]. They have better survival rates than IPF and similar survival rates compared to non-IPF ILDs [136]. The mean survival duration is 7.0 years for unclassifiable ILDs [139].

Patients with acute exacerbation of unclassifiable IIP are older and include more women and never smokers than those with acute exacerbations of IPF. However, acute exacerbations have a poor prognosis similar to that of IPF-AEs [140].

Table 8 Diagnostic definition of IPAF

• Presence of an interstitial pneumonia (by HRCT or surgical lung biopsy) • Exclusion of alternative etiologies • Does not meet criteria of a defined connective tissue disease • At least one feature from at least two of these domains		
A. Clinical domain	B. Serologic domain	C. Morphologic domain
- Distal digital fissuring (mechanic hands) - Distal digital tip ulceration - Inflammatory arthritis or polyarticular morning joint stiffness > 60 min - Palmar telangiectasia - Raynaud's phenomenon - Unexplained digital edema - Unexplained fixed rash on the digital extensor surfaces (Gottron's sign)	- ANA $\geq$ 1: 320 titer, diffuse, speckled, homogeneous patterns or (a) ANA nucleolar pattern (any titer) or (b) ANA centromere pattern (any titer) - Rheumatoid factor $\geq$ 2$\times$ upper limit of normal - Anti-CCP - Anti-dsDNA - Anti-Ro (SS-A) - Anti-La (SS-B) - Anti-ribonucleoprotein - Anti-Smith - Anti-topoisomerase (Scl-70) - Anti-tRNA synthetase (e.g., Jo-1, PL-7, PL-12; others are EJ, OJ, KS, Zo, tRS) - Anti-PM-Scl - Anti-MDA-5	- Suggestive radiology patterns by HRCT: (a) NSIP (b) OP (c) NSIP with OP overlap (d) LIP - Histopathology patterns or features by surgical lung biopsy: (a) NSIP (b) OP (c) NSIP with OP overlap (d) LIP (e) Interstitial lymphoid aggregates with germinal centers (f) Diffuse lymphoplasmacytic infiltration (with or without lymphoid follicles) - Multicompartment involvement (in addition to interstitial pneumonia): - Unexplained; (a) Pleural effusion or thickening (b) Pericardial effusion or thickening (c) Intrinsic airways disease (d) Pulmonary vasculopathy

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