The world of rare interstitial lung diseases

Katharina Buschulte[1], Vincent Cottin[2], Marlies Wijsenbeek[3], Michael Kreuter[1] and Rémi Diesler[2]

Number 2 in the Series "The world of rare lung diseases"
Edited by Michael Kreuter, Marc Humbert, Thomas Wagner and Marlies Wijsenbeek

[1]Center for Interstitial and Rare Lung Diseases, Thoraxklinik, University of Heidelberg, German Center for Lung Research (DZL), ERN-LUNG, Heidelberg, Germany. [2]National Reference Centre for Rare Pulmonary Diseases, Louis Pradel Hospital, Hospices Civils de Lyon, UMR 754, Claude Bernard University Lyon 1, ERN-LUNG, Lyon, France. [3]Center for Interstitial Lung Diseases and Sarcoidosis, Department of Respiratory Medicine, Erasmus MC-University Medical Center, ERN-LUNG, Rotterdam, The Netherlands.

Corresponding author: Michael Kreuter (kreuter@uni-heidelberg.de)

Shareable abstract (@ERSpublications)
Many rare and ultrarare ILDs are underdiagnosed. Increasing insight into pathobiology, genetics and disease behaviour have led to better treatment options. Early consultation with or referral to expert centres (ERN-LUNG) is advised. https://bit.ly/3vwYrib

Cite this article as: Buschulte K, Cottin V, Wijsenbeek M, *et al*. The world of rare interstitial lung diseases. *Eur Respir Rev* 2023; 32: 220161 [DOI: 10.1183/16000617.0161-2022].

Copyright ©The authors 2023

This version is distributed under the terms of the Creative Commons Attribution Non-Commercial Licence 4.0. For commercial reproduction rights and permissions contact permissions@ersnet.org

This article has an editorial commentary: https://doi.org/10.1183/16000617.0006-2023

Received: 8 Sept 2022
Accepted: 21 Dec 2022

Abstract
The world of rare interstitial lung diseases (ILDs) is diverse and complex. Diagnosis and therapy usually pose challenges. This review describes a selection of rare and ultrarare ILDs including pulmonary alveolar proteinosis, pulmonary alveolar microlithiasis and pleuroparenchymal fibroelastosis. In addition, monogenic ILDs or ILDs in congenital syndromes and various multiple cystic lung diseases will be discussed. All these conditions are part of the scope of the European Reference Network on rare respiratory diseases (ERN-LUNG). Epidemiology, pathogenesis, diagnostics and treatment of each disease are presented.

Introduction: an overview of interstitial lung diseases (ILDs)
ILDs comprise over 200 different entities of known and unknown causes characterised by a large variation in clinical manifestations, radiological and pathological patterns, and outcome [1, 2]. ILDs are divided into different categories (figure S1) [3].

A selection of rare or ultrarare ILDs with a higher probability of being faced in clinical practice will be discussed in this review. Although these diseases are called "interstitial lung diseases", some of them mainly affect the alveolar space, such as in pulmonary alveolar proteinosis (PAP) and pulmonary alveolar microlithiasis (PAM), or the pleura and subpleural lung parenchyma, as in pleuroparenchymal fibroelastosis (PPFE) [4]. We also describe some ultrarare ILDs, including various congenital syndromes (*e.g.* Hermansky–Pudlak syndrome, HPS) and various multiple cystic lung diseases.

PAP
PAP, first described in 1958 [5], has an incidence of 0.5–1.5 cases per 1 million [6]. Surfactant accumulates in the alveoli due to a defective clearance by alveolar macrophages resulting in different degrees of respiratory insufficiency [7]. Three forms are known (table 1) [8, 9].

Autoimmune PAP
Epidemiology and clinical presentation
Autoimmune PAP is caused by neutralising autoantibodies against granulocyte–macrophage colony-stimulating factor (GM-CSF) [11] that prevent GM-CSF from binding to its receptor, thereby reducing macrophage stimulation and impairing surfactant clearance [12]. Most patients are between 30

TABLE 1 Overview of different forms of pulmonary alveolar proteinosis (PAP) [5, 7, 10]

Autoimmune PAP (>90%)	
GM-CSF antibodies	
Secondary PAP (5–10%)	
Toxic inhalation	Inorganic and organic dusts Vapours
Haematological disorders	Myelodysplastic syndrome Acute lymphoblastic leukaemia Acute myeloid leukaemia Chronic myeloid leukaemia Hodgkin's lymphoma *etc.*
Infections	Cytomegalovirus *Mycobacterium tuberculosis* HIV *Nocardia* *Pneumocystis jirovecii*
Other malignancies	Adenocarcinoma Glioblastoma Melanoma
Immunodeficiency	Monoclonal gammopathy Selective IgA deficiency Severe combined immunodeficiency
Others	Membranous glomerulonephritis Dermatomyositis Lung transplantation
Genetic PAP (2%)	
Mutations with involvement of surfactant production (PAP-like diseases)	*SFTPB, SFTPC*, *ABCA3*, *NKX2-1*
Mutations of GM-CSF receptor	*CSF2RA* and *CSF2RB* (α or β subunit)
Lysinuric protein intolerance	*SLC7A7*
Mutations in macrophages and degradation of surfactant	*GATA2*
Mutations in telomerase complex	*TERT*

GM-CSF: granulocyte–macrophage colony-stimulating factor.

and 50 years old when diagnosed [8]. Patients are predominantly male (2:1) and have a smoking history in 80% of cases [8].

The disease usually becomes symptomatic with exertional dyspnoea. In one third of cases, however, patients are asymptomatic [13]. Other common symptoms include cough, fatigue and weight loss [8, 13], and occasionally chest pain or haemoptysis, which is usually a sign of complications [9].

Diagnosis

As clinical examination is generally normal [9], the diagnosis is usually made on the basis of thoracic imaging and bronchoalveolar lavage (BAL) (figure 1).

In chest computed tomography (CT) a "crazy paving" pattern is often present, which consists of reticulation superimposed on ground-glass opacities with a geographic distribution. Healthy and diseased areas are located directly next to each other [14].

Body plethysmography reveals a restrictive ventilatory disorder. Typically, the transfer factor is decreased [13]. Hypoxaemia can be detected especially during exercise and in 30% of patients also at rest [8].

BAL fluid has a milky appearance. BAL cytology may show an increased proportion of lymphocytes [15, 8] and an increased total cell count [16]. The diagnosis is confirmed by the detection of periodic acid Schiff (PAS)-positive extracellular corpuscles and foamy macrophages [15].

In the vast majority of cases, the combination of typical radiology with the results of BAL are sufficient for diagnosis. Occasionally, a transbronchial biopsy might be required, while surgical lung biopsy is mostly unnecessary [5].

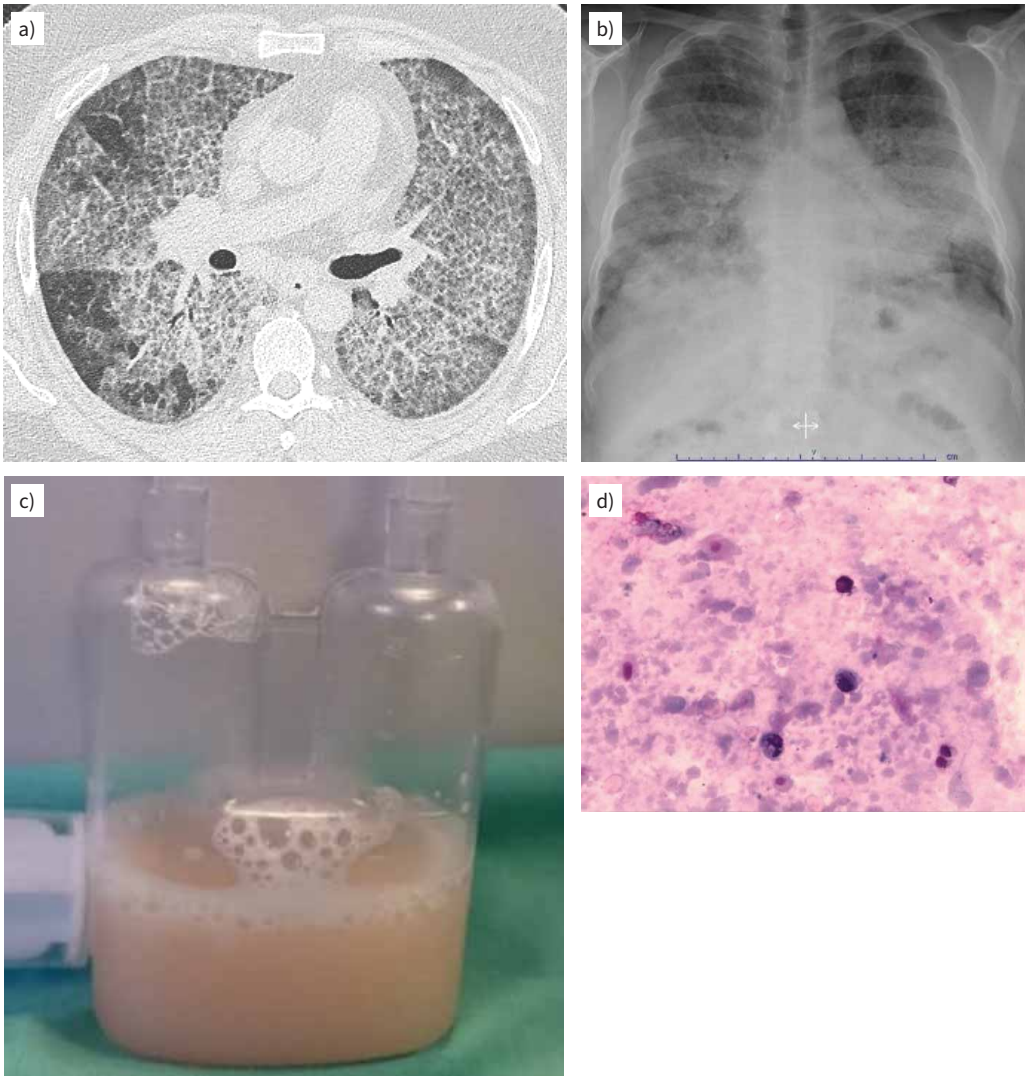


FIGURE 1 a) and b) Chest computed tomography scan and X-ray (same date) of a 37-year-old patient with a diagnosis of pulmonary alveolar proteinosis. a) "Crazy paving" pattern with geographical ground-glass opacities and thickened interlobar septa. b) Bi-pulmonary consolidations with punctum maximum in the left centre field without pleural effusion. c) and d) Bronchoalveolar lavage (BAL) from the same 37-year-old patient. c) Typical BAL with milky appearance. d) BAL cytology with foamy macrophages, cellular detritus and periodic acid Schiff-positive extracellular corpuscles.

A titre of anti-GM-CSF autoantibodies >19 $\mu g \cdot mL^{-1}$ has a sensitivity and specificity of almost 100% [17] for the diagnosis of autoimmune PAP, while a titre <10 $\mu g \cdot mL^{-1}$ is normal [5, 18].

Differential diagnoses should consider diseases that may be associated with crazy paving patterns on CT, including acute idiopathic pulmonary fibrosis (IPF) exacerbations, acute interstitial pneumonias, acute respiratory distress syndrome, pulmonary oedema, drug-induced pneumonitis and *Pneumocystis jirovecii* pneumonia [10].

Treatment

The gold standard of treatment is whole lung lavage (WLL), which removes the proteinaceous material from the alveoli, thus restoring oxygenation [19]. The prerequisites are a general anaesthesia and intubation *via* a double-lumen endotracheal tube. One lung is treated at a time with up to 40 L of warmed saline solution, while the patient is ventilated on the contralateral side. The liquid is applied until it becomes clear. During the procedure, regular bronchoscopic position checks of the tube and physiotherapeutic

measures are required [19]. However, depending on the centre, the exact practice (*e.g.* choice of the first lung to be lavaged, position and volume instilled per lung) shows a great variation [20]. The result of WLL is a significant clinical and radiological improvement [21]. A small case series showed different surfactant components accumulating in the airways after WLL, *e.g.* increased surfactant protein (SP) A until the second hour with a rapid decrease afterwards [22]. If necessary, the procedure can be repeated contralaterally [9].

Recent pilot studies have investigated the efficacy and tolerability of inhaled and subcutaneous GM-CSF substitution in autoimmune PAP [9, 23]. This was recently confirmed by two large randomised studies [23, 24]. The IMPALA-study was a double-blind, placebo-controlled study with nebulised molgramostim, a recombinant GM-CSF which met the primary end-point, change in Aa-DO2 (alveolar–arterial oxygen gradient) from baseline to 24 weeks. The secondary end-point quality of life also showed significant improvement with continuous, daily molgramostim administration. In addition, molgramostim showed a good safety profile [23]**.** In the Pulmonary Alveolar Proteinosis GM-CSF Inhalation Efficacy (PAGE) trial, also double-blind and placebo-controlled, sargramostim (recombinant human GM-CSF) treatment was associated with a significant positive change in alveolar–arterial oxygen difference P_{aO_2} (partial pressure of oxygen) [24].

The use of immunosuppressants such as corticosteroids is not recommended [25]. Plasmapheresis can decrease circulating anti-GM-CSF antibodies. However, only very few case reports exist in which the procedure was successful after a previously failed WLL [26], while in other patients this procedure was not successful [9].

In cases of failed WLL, rituximab has been studied in a few small trials [9]. It showed effectiveness in terms of arterial blood oxygenation, CT scans and pulmonary functional parameters. BAL showed lower levels of anti-GM-CSF antibodies, but this could not be confirmed in serum [27, 28]. Another real-life setting retrospective study showed contrasting results [9]. After 6 months, 0/13 patients showed improvement following treatment with rituximab [29]. Rituximab may be considered as an off-label therapy on a case-by-case basis in severe, refractory cases pending availability of inhaled recombinant GM-CSF; however, prospective clinical trial data are not yet available [5].

A case of recurrence after lung transplantation has been documented; nevertheless, lung transplantation can be cautiously considered [9]. With the idea of targeting lipid homeostasis, statin therapy could be taken into consideration; however, with effectiveness in only two patients the evidence is low [30]. In exceedingly rare cases of PAP with progressive fibrosis, antifibrotic therapy might be considered, analogous to the INBUILD-trial [31].

Secondary PAP

Haematological disorders account for the largest proportion (75%) of secondary PAP [32], especially myelodysplastic syndromes and acute myeloid leukaemia [33]. Rarely, PAP occurs in immunodeficiency (*e.g.* severe combined immunodeficiency, agammaglobulinemia and after organ transplantation) [25]. Treatment of the underlying disease is essential as a cure can be achieved by haematologic therapy, chemotherapy and bone marrow transplantation alone, especially in acute leukaemia [5, 9]. The effect of WLL does not last long in secondary PAP [9].

Inhalation noxious agents include organic and inorganic dusts such as quartz, metal or chemical substances [33]. Relevant dust exposure is also present in autoimmune PAP in up to 50% of cases [8]. Therefore, avoidance is of utmost importance.

Genetic PAP

In genetic PAP, children are most affected and the diseases are associated with a poor prognosis [7, 9]. Mutations predominantly occur in genes involved in the production of surfactant (table 1). Genetic PAP shares features with autoimmune PAP, but differs with respect to radiology and histology.

Mutations with involvement of surfactant production include *SFTPB*, *SFTPC*, *ABCA3* and *NKX2-1*. Typical findings are diffuse ground-glass opacities and lung cysts [5]. Mutations can also affect macrophages and the degradation of surfactant [5]. The diseases behave very similarly to autoimmune PAP. There are no anti-GM-CSF antibodies, but high concentrations of GM-CSF [5]. Corticosteroids are the preferred drug and can be combined with other immunomodulators. In advanced cases, lung transplantation must be considered.

Genetic defects of the GM-CSF receptor mainly affect children and result in diseases similar to autoimmune PAP. High concentrations of GM-CSF are detectable, but no antibodies against GM-CSF. WLL can be effective while GM-CSF therapy shows no effects [34].

Mutations in *SLC7A7* result in lysinuric protein intolerance, an autosomal-recessive inherited disease. Frequent manifestations are renal and pancreatic insufficiency as well as different pulmonary manifestations like PAP. Management includes WLL and nebulised GM-CSF therapy [34].

Prognosis

With regard to all forms of PAP, Bonella *et al.* [8] reported an improvement or stabilisation within 12 months with no WLL required in 43 out of 70 patients. In smokers, more WLLs are needed to achieve remission [8]. Secondary PAP is associated with higher mortality, particularly in the case of underlying haematologic diseases [32].

PAM

The first description of PAM dates back to 1918 [35]. The disease is associated with the accumulation of hydroxyapatite microliths within alveolar spaces. With about 1000 cases worldwide, PAM is among the ultrarare lung diseases [36]. It is caused by mutations in the sodium phosphate co-transporter gene *SLC34A2*, which represents a possible future target for therapies [36].

Epidemiology and clinical presentation

A review of the 1022 cases reported worldwide showed that PAM is present in all continents with a majority in Asia (56.3%) and in Europe (27.8%), and a slight predominance in men. Patients between the ages of 20 and 30 are most commonly affected. Inheritance plays a role in 32–61% of the reported cases, which is autosomal recessive [37].

A mutation in the *SLC34A2* gene, described in 2016, results in a defective sodium phosphate-IIb transporter protein and subsequently in the formation of microliths due to a reduced phosphate clearance [38]. By direct DNA sequencing, more and more gene variants are being identified [39].

Affected people are often only mildly symptomatic, with dyspnoea, dry cough, chest pain and asthenia [40]. Occasionally, the diagnosis is made incidentally [41]. In more severe cases, cyanosis and clubbing develop, and pneumothoraces may occur in rare cases [40]. Extrapulmonary manifestations includes nephrocalcinosis or nephrolithiasis, and calcifications of the lumbar sympathetic chain, pericardium, aortic and mitral valves, and testicles [42].

While first microliths most probably develop in childhood, the first symptoms occur only decades later [38]. In advanced stages, a decreased transfer factor and a restrictive pattern as well as impaired perfusion and gas exchange develop. This leads to hypoxaemia and, with further progression, pulmonary hypertension and right heart failure [40]. Progression is common, although the rate of disease progression varies considerably [37].

Diagnosis

High-resolution CT (HRCT) shows the pathognomonic sandstorm pattern with small, calcified nodules, areas of ground-glass opacities and consolidation, beginning in the lower lobes (figure S2) [43]. Additionally, calcifications are found alongside interlobular septa, bronchovascular bundles and pleura. Subpleural cysts may also occur in the lung periphery and can cause pneumothorax [44]. When typical, HRCT findings may be sufficient to establish the diagnosis, especially when a family history is present [45].

The diagnosis can be confirmed by the detection of microliths [5] of 50–1000 µm in size [46]. They can be detected in sputum, bronchial wash and BAL [5]. Also, they are detectable in biopsies, where they are PAS-positive, onion-shell-like calcium deposits in the complete alveolar space [47]. Molecular analysis is not mandatory for the diagnostic process, but may play a role once targeted treatment is available [5].

Treatment

To date, most therapeutic approaches to progressive PAM have proven unsuccessful. Attempts were made to remove the microliths by repeated WLL. However, this proved to be ineffective, as were systemic corticosteroids [48]. Sodium etidronate inhibits the formation of hydroxyapatite crystals, but mixed results were reported [49]. The only remaining option therefore is lung transplantation [37] with a favourable

long-term outcome [50]. Additionally, supportive therapy should be given, *e.g.* vaccination and oxygen therapy when needed [51].

PPFE

Introduction

PPFE [52] is a rare form of interstitial pneumonia [53, 54]. It is characterised by upper lobe and subpleural fibrosis [53], involving both the visceral pleura and the subjacent subpleural lung parenchyma, and comprising prominent elastosis of the alveolar walls and fibrous thickening of the visceral pleura [55–57].

Epidemiology

Although rare [58], PPFE is now diagnosed regularly in ILD referral centres. In retrospective studies, PPFE was the main pattern radiologically in 7.7% of idiopathic interstitial pneumonias [59], 25% of fibrotic ILDs registered for lung transplantation [60], 0.28–1.9% of lung transplant recipients [61, 62] and 7.5% of haematopoietic stem cell transplantation recipients [62].

Aetiology and disease associations

PPFE can be idiopathic or secondary to lung or liver transplantation, haematopoietic stem cell transplantation, alkylating drugs, radiation therapy, connective tissue diseases, fibrotic hypersensitivity pneumonia, IPF and other idiopathic interstitial pneumonias, environmental exposures, telomere-related gene mutations, and recurrent respiratory infections. In addition, PPFE-like features can be present in various fibrotic ILDs, including IPF [63–67], fibrotic hypersensitivity pneumonitis [55, 68], systemic sclerosis-associated ILD [69] and rheumatoid arthritis-ILD [70], and are associated with a poor outcome.

Clinical presentation and lung function

PPFE predominates in females, aged 30–60 years, with no link to cigarette smoking. Onset of disease is insidious [54, 56, 71–74], with progressive shortness of breath, dry cough, basolateral pleural chest pain, alteration of general status, weight loss and eventually cachexia [75]. Fine crackles on chest auscultation are present in ∼40% of patients, finger clubbing in 15–20% [75] and platythorax, *i.e.* anteroposterior flattening of the thorax, in ∼50% [75, 76]. Lung volumes are more severely altered than diffusion capacity for carbon monoxide [75, 76]. A pneumothorax or pneumomediastinum can be inaugural [77], be secondary to lung biopsies [57] and eventually occurs in 25–60% of patients [73, 78]. Pneumothoraces recur in more than half of patients; however, only a minority require chest drainage, which is often complicated by persistent air leak [78].

Diagnosis

Chest CT shows volume loss and dense pleural and subpleural consolidation coexisting with reticulation, architectural distortion and traction bronchiectasis, predominantly in the upper lobes [56, 77–81] (figure 2). PPFE is often more than 5 mm thick and is generally progressive [56]. A pattern of PPFE in the upper lung zones can be associated with a usual interstitial pneumonia (UIP) pattern in the lung bases [63–67].

Although the diagnosis in theory requires histopathology [82], the risk of pleural complications means that the use of video-assisted thoracoscopic lung biopsy is generally discouraged. In one small series, a majority of patients meeting radiologic criteria for PPFE were histologically confirmed as having PPFE [63]. When performed, the lung biopsy demonstrates subpleural intra-alveolar fibrosis and elastosis, pleural thickening, and prominent deposit of elastic fibre dense collagen [53, 55, 56, 75]. Forceps transbronchial biopsies, transbronchial cryobiopsy and transthoracic core lung biopsy have been successfully used to diagnose PPFE, but with an unclear benefit/risk ratio [83].

Diagnostic criteria were proposed, based on both chest CT and histopathology [56], or on chest CT features and radiologic confirmation of disease progression [75]. The latter are increasingly used to support the diagnosis of PPFE in multidisciplinary discussions.

Outcome

Retrospective series found a heterogeneous disease course, with a median survival time of 35–96 months [59, 75, 76]. The main causes of death are hypercapnic chronic respiratory failure, acute exacerbation of pulmonary fibrosis, cachexia, aspiration pneumonia and pulmonary embolism [59, 75].

Management

Experience with pulmonary rehabilitation [75] and lung transplantation [84] is still limited. Lung transplantation is the only treatment that can cure PPFE [85]. Drug therapy has not been evaluated prospectively. Patients often receive low-dose glucocorticoids; however, higher doses of corticosteroids and

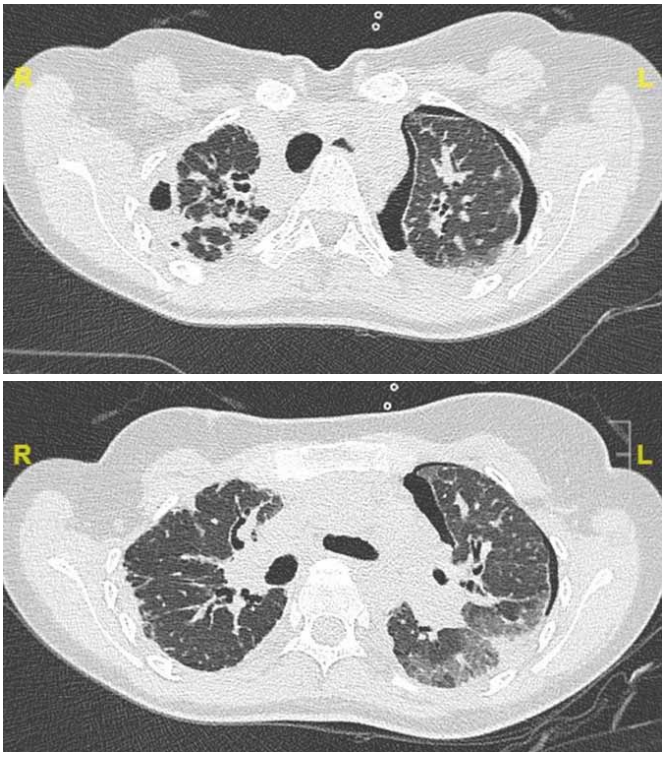


FIGURE 2 Computed tomography scan of the chest (parenchymal window) in a 23-year-old female patient with pleuroparenchymal fibroelastosis, demonstrating pleural thickening and subpleural consolidation in the upper lung zones, together with left-sided spontaneous pneumothorax.

second-line immunosuppressive therapy is discouraged due to an increased risk of infections [4]. Data regarding the antifibrotic agents nintedanib and pirfenidone are still preliminary, with conflicting results in two retrospective series for nintedanib [86, 87] and controversial results for pirfenidone [4]. However, in PPFE cases with associated fibrotic progressive ILD, the use of antifibrotics can be considered.

ILD in selected congenital syndromes

Dyskeratosis congenita and telomerase-associated pulmonary fibrosis

Introduction

Telomerase is an enzyme complex composed of the telomerase reverse transcriptase, the telomerase RNA component, dyskerin and other stabilising proteins that help maintain telomere length during mitosis [88]. Dyskeratosis congenita (DC) and telomere biology disorders (TBDs) are multisystem diseases associated with mutations in 16 telomere-related genes [89], with overlapping features including cutaneous abnormalities, premature hair greying, bone marrow failure, liver disease and pulmonary manifestations, of which pulmonary fibrosis is the most common [90].

Epidemiology and clinical presentation

The prevalence of DC is about one in a million [91]. The cumulative incidence of pulmonary fibrosis over 20 years in DC/TBD has been estimated to ∼20% [92]. Telomere-related mutations and/or shortened telomeres are found in approximately 25% of patients with familial pulmonary fibrosis [93–96]. Additionally, telomere-related mutations account for ∼10% of sporadic cases of pulmonary fibrosis [93, 97, 98] and 12% of rheumatoid arthritis-associated ILD [99]. Transmission depends on the gene involved. The shortening of telomeres beyond a critical threshold results in cell senescence or apoptosis [100], especially in tissues with high replicative rates. Additional aggression (smoking, professional exposure) is found in about 70% of patients and is likely to increase the risk of ILD [101, 102].

The clinical spectrum of DC/TBD is broad and ranges from classic dyskeratosis congenita to isolated clinical findings of TBD. The classical clinical triad of DC is lacy reticular hypopigmentation of the skin, dystrophic nails and oral leukoplakia [103]. This well-characterised phenotype mainly affects children and

is associated with pulmonary fibrosis in those surviving to the second decade of life. Telomere-related pulmonary fibrosis, however, is more frequent and affects young adults. The following personal or familial findings in a patient referred for pulmonary fibrosis work-up are suggestive of telomere biology disorder: cutaneous, hair and nails abnormalities, cirrhosis or unexplained repeated elevated liver enzymes, bone marrow failure (*e.g.* myelodysplastic syndromes- features) or milder haematological abnormalities, and head and/or neck cancer [91].

Radiological findings

A UIP pattern is seen in half of the patients. In IPF patients with telomere-related gene mutation, atypical features such as air trapping and consolidations may be present (figure 3a) [102, 104, 105]. IPF is the most common diagnosis in approximately half of patients, followed by unclassifiable fibrosis (around 20%) and chronic hypersensitivity pneumonitis (around 10%) [104, 105].

Disease course

Despite the wide range of ILD subtypes associated with telomere-related mutations, the disease course is almost always progressive and comparable to or worse than IPF, regardless of the pattern of lung disease [104]. Particular attention should be paid to extra-respiratory surveillance of these patients to detect other potential telomere-related manifestations (cytopenia, liver disease, cancers).

Diagnosis

Genetic testing is warranted in patients with familial pulmonary fibrosis or sporadic pulmonary fibrosis with familial or personal findings suggestive of TBD. Indication of lung transplantation for pulmonary fibrosis should also prompt testing for telomere-related mutations [106].

Treatment

In patients with progressive fibrotic ILD, antifibrotic therapy should be implemented. Danazol, a synthetic androgen, is currently being evaluated in short telomere-associated pulmonary fibrosis in a phase 2

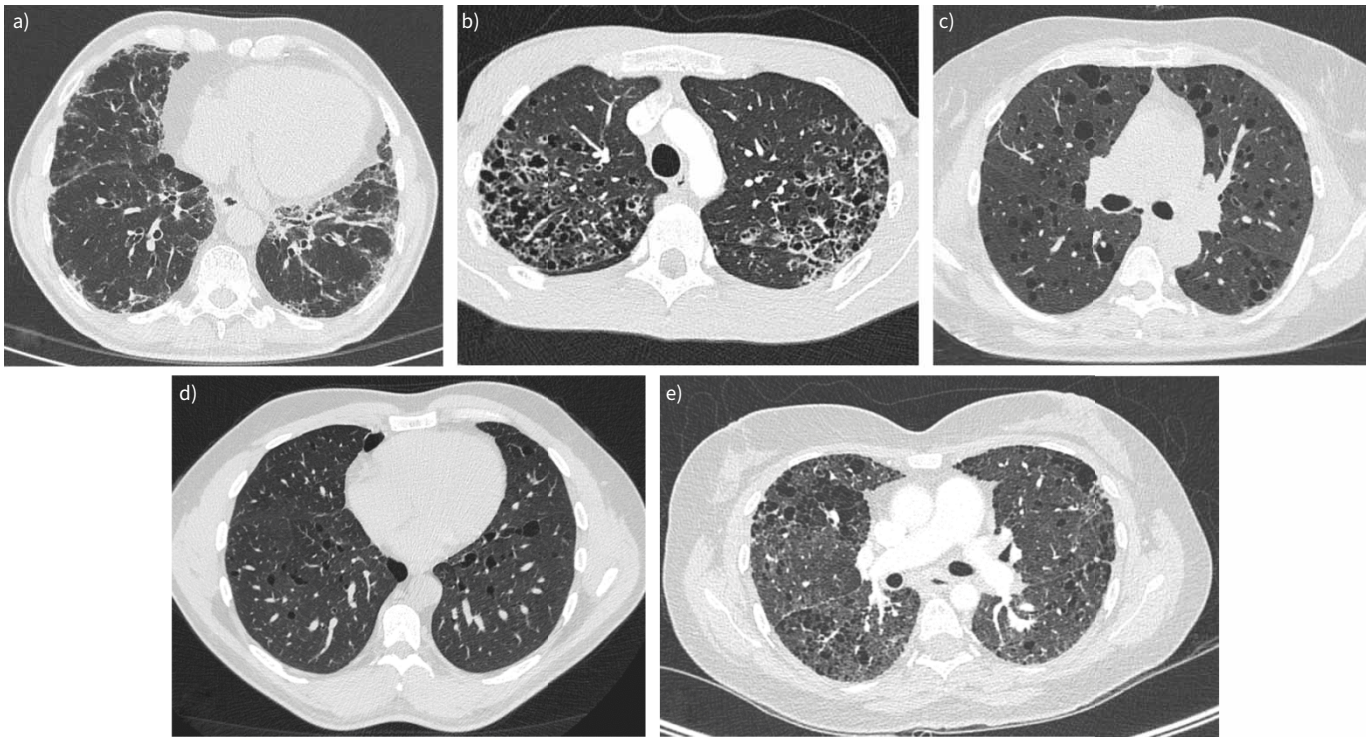


FIGURE 3 Axial high-resolution computed tomography of different interstitial lung diseases. a) Probable usual interstitial pneumonia pattern in a patient with a heterozygous *TERC* mutation. b) Bilateral irregular nodular and cystic lesions with upper lobe predominance in a patient with pulmonary Langerhans cell histiocytosis. c) Multiple bilateral centimetric thin-walled cysts in a patient with sporadic lymphangioleiomyomatosis. d) Lower lobe predominant distribution of bilateral thin-walled cysts in a patient with Birt–Hogg–Dubé syndrome. e) Unclassifiable pulmonary fibrosis with microcystic destruction in a patient with a heterozygous *SFTPC* I73T mutation.

randomised trial [107]. Patients with telomere-related gene disorders and rapidly progressive lung disease should be referred early to lung transplant centres; however, particular attention must be paid to immunosuppressant therapy with respect to bone marrow reserve. In patients with a complete DC phenotype, all reported lung transplantation cases were preceded by bone marrow transplantation [108]. Gene therapy might be a future option [109].

Surfactant-associated pulmonary fibrosis

Introduction

Surfactant-related disorders range from fatal neonatal respiratory distress syndrome to familial ILDs in children and adults. Surfactant-related genes involved in adult-onset pulmonary fibrosis code for SP-A1 and SP-A2, SP-C, ATP-binding cassette transporter A3 (ABCA3) and thyroid transcription factor NK2 homeobox 1 (NKX2-1) [110, 111]. Mutations in *SFTPA1/2* and *NKX2-1* are also associated with lung cancer [112].

Epidemiology and clinical presentation

Mutations in surfactant-related genes account for approximately 3–5% of familial pulmonary fibrosis cases [113]. Inheritance is autosomal dominant with incomplete penetrance for *SFTPC* and *SFTPA1/2* mutations and autosomal recessive for *ABCA3* mutations.

Depending on the protein domain involved, mutations in *SFTPC* promote ILD and pulmonary fibrosis by impairment of autophagy and phospholipids recycling, increased cellular sensitivity to injury or cytotoxicity resulting from aggregation of misfolded protein [114–116]. Mutations in *SFTPA1* or *SFTPA2* result in reduced protein secretion, thereby impairing normal surfactant function and disrupting the lung inflammation modulation ability of SP-A [112, 117]. *ABCA3* mutations also impair normal surfactant function by preventing the formation of lamellar bodies [118].

Phenotypic heterogeneity is considerable in surfactant-related pulmonary fibrosis, ranging from asymptomatic patients to end-stage respiratory insufficiency. Severe pulmonary hypertension may develop. Age of onset varies from infancy to late adulthood. Neonatal diagnosis is frequent in homozygous *ABCA3* mutation carriers but is uncommon in *SFTPC* and *SFTPA1/2* mutation carriers [112, 119, 120].

Radiological findings

HRCT features reflect the clinical heterogeneity, with no clear genotype–phenotype correlation. The most frequent pattern seen in *SFTPC* or *ABCA3*-related ILD is the association of diffuse ground-glass opacities with cysts and septal thickening (figure 3e), with honeycombing later in the course of the disease. Combined pulmonary fibrosis with emphysema is also described [112, 121–124].

Diagnosis

Occurrence of pulmonary fibrosis in a familial context or before 50 years old should prompt genetic testing for telomerase and surfactant-related genes [113]. The suspected mode of transmission helps to tailor genetic analysis.

Management

Disease stabilisation or improvement with methylprednisolone pulses, glucocorticoids, azithromycin or hydroxychloroquine have been reported [122, 125]. Antifibrotic drugs have not been evaluated. Lung transplantation is a reasonable option in severe cases [112, 122].

HPS

Introduction

HPS is a group of autosomal recessive disorders combining bleeding diathesis and oculocutaneous albinism, caused by mutations in 11 genes [126]. HPS can also be associated with granulomatous colitis [127] and pulmonary fibrosis, depending on the subtypes.

Epidemiology and clinical presentation

HPS worldwide prevalence is estimated at one to nine cases per million individuals, with the highest worldwide prevalence of 1:1800 in north-western Puerto Rico [128]. Only patients with HPS types 1, 2 and 4 are prone to ILD [127]. All patients with HPS type 1 will develop pulmonary fibrosis [129].

The mutations in HPS-related genes cause dysfunction in lysosome-related organelles. Putative mechanisms of fibrogenesis include lysosomal accumulation of ceroid material [130], autophagy [131], impaired surfactant trafficking and endoplasmic reticulum stress [132].

Ocular and cutaneous manifestations include variable pigmentation of hair and skin, horizontal nystagmus, and impaired visual acuity [133]. Bleeding symptoms include spontaneous bruising and prolonged minor bleedings (epistaxis, menorrhagia). ILD is often diagnosed during the third and fourth decades of life [127].

Radiologic findings

Features seen on chest CT include septal thickening, diffuse ground-glass opacities, peribronchovascular and pleural thickening. A reticular pattern with subpleural honeycombing may be present in advanced disease [127]. Ground-glass opacities might be the main radiological feature [134].

Disease course

Pulmonary fibrosis accounts for approximately 70% of HPS-related deaths [135]. The disease course is progressive with notable interindividual variability [136, 137]. Survival is approximately 2 years when predicted forced vital capacity reaches 50% [136].

Diagnosis

The diagnosis of HPS is based on the demonstration of oculocutaneous albinism in the presence of a deficit in platelet storage pool. Genetic testing is used to confirm the diagnosis and subtype [126].

Management

There are no specific therapeutic options for the treatment of HPS-associated pulmonary fibrosis. Two trials of pirfenidone in HPS patients were not conclusive [136–138]. In patients with advanced disease, lung transplantation is the only therapeutic option for eligible patients. HPS-related bleeding diathesis has been considered a contraindication for lung transplantation, but a good outcome has been reported with appropriate bleeding diathesis prophylaxis [139]. Otherwise, management is based on palliative care [140].

Other rare diffuse lung diseases of genetic origin

The genetic cause is still unknown in 60% of cases of familial pulmonary fibrosis. Several diffuse lung diseases linked with genetic defects not described in detail in this review are briefly summarised in table 2.

Multiple cystic lung diseases

Lymphangioleiomyomatosis (LAM)

LAM is a very rare multisystem disease that primarily affects women, either sporadically or in association with tuberous sclerosis complex (TSC) [147, 148]. LAM is characterised by the presence of abnormal smooth muscle-like LAM cells from an unknown source and infiltrating the tissues. Beside lung

TABLE 2 Overview over other rare diffuse lung diseases of genetic origin

Disease	Gene (protein)	Transmission	Clinical phenotype	References
STING-associated vasculopathy with onset in infancy	*TMEM173* (STING)	AD	Fibrosing ILD/emphysema, skin vascular damage, auto-inflammatory syndrome	[141]
Copa syndrome	*COPA* (coatomer protein subunit alpha)	AD	Diffuse alveolar haemorrhage, ILD, inflammatory arthritis, renal disease	[142]
Neurofibromatosis, type I	*NF1* (neurofibromin)	AD	Cutaneous abnormalities, optic gliomas, fibrosing ILD/thin-walled bullae	[143]
Hyper IgE syndrome	*STAT3*	AD	Recurrent skin and respiratory infections, interstitial pneumonia, enteropathy	[144]
Acid sphingomyelinase deficiency (Niemann–Pick, type B)	*SMPD1* (sphingomyelin phosphodiesterase 1)	AR	Hepatosplenomegaly, hypotonia, ILD, dyslipidaemia and haematological abnormalities	[145]
Gaucher disease, type I	*GBA1* (glucocerebrosidase)	AR	Bone disease, hepatosplenomegaly, cytopenia, ILD	[145]
Fabry	*GLA* (α-galactosidase A)	X-linked	Renal disease, angiokeratoma, cardiac and neuropathic involvement, ILD, obstructive lung disease	[145]
Lysinuric protein intolerance	SLC7A7	AR	Renal tubulopathy, haemophagocytic lymphohistiocytosis, pulmonary alveolar proteinosis	[146]

AD: autosomal dominant; AR: autosomal recessive; ILD: interstitial lung disease; STING: stimulator of interferon gene.

manifestations, LAM is associated with angiomyolipomas, lymphangioleiomyomas, chylous effusions [149] and, in a TSC setting, with epilepsy and cutaneous abnormalities [147].

Epidemiology and clinical presentation

Prevalence of LAM has been estimated as five cases per million women, with great variations suggesting that this number is underestimated [150]. LAM is sporadic in two-thirds of cases. In patients with TSC, prevalence of LAM increases with age, reaching 81% at the age of 40 [147].

Both TSC-LAM and sporadic LAM are caused by mutations in *TSC1* and *TSC2* [147, 151] resulting in uncontrolled cellular proliferation, expression of vascular endothelial growth factor (VEGF)-A, VEGF-C and VEGF-D, angiogenesis stimulation, immune evasion, and cell survival [149, 152].

LAM typically occurs in women of childbearing age. Respiratory symptoms are nonspecific: dyspnoea, cough, wheezing and haemoptysis. Pleural or peritoneal chylous effusions are seen in 20% and 5% of the cases, respectively [153]. Spontaneous pneumothorax is the presenting manifestation in 24–36% of patients. Around 40% of patients present renal angiomyolipomas, more frequently in TSC [153]. Pulmonary function testing often reveals airway obstruction [153, 154].

Radiological findings

On HRCT, LAM is characterised by diffuse cystic changes without predilection in distribution. Cysts are thin-walled and of intermediate size (figure 3c). Additional findings include ground-glass opacities, interlobular septa thickening, pneumothoraces and pleural effusion [155].

Disease course

Women before menopause experience a more marked lung function decline and exacerbations can occur during pregnancy or oestrogen supplementation [156], whereas the disease tends to abate after menopause. The 10- and 20-year transplantation-free survival rates are 85% and 64% respectively [157].

Diagnosis

Diagnosis is achieved in the setting of characteristic or compatible HRCT pattern with a combination of other characteristics, including angiomyolipoma, lymphangioleiomyoma, confirmed or probable TSC, or chylous effusion or a VEGF-D $\geqslant$800 pg·mL^{-1} or consistent histology [158, 159].

Management

Sirolimus, a mammalian target of rapamycin (mTOR) inhibitor, has been shown to effectively stabilise lung function and alleviate angiomyolipomas [160–162]. Everolimus, another mTOR inhibitor, seems to be similarly effective [163]. Some studies are ongoing with several drugs for treatment of LAM. Given the high rate of pneumothorax recurrence, pleurodesis should be considered after the first episode. In end-stage respiratory failure, lung transplantation is a viable option with a reported median survival of 12 years [164]. Previous pleurodesis is not contra-indicative of lung transplantation.

Birt–Hogg–Dubé syndrome (BHDS)

BHDS caused by germline mutations in *FLCN*, the folliculin gene [165], is associated with lung cysts, spontaneous pneumothoraces, renal tumours and typical skin lesions named fibrofolliculomas.

Epidemiology and clinical presentation

The prevalence of BHDS in the general population has been estimated at around two cases per million based on epidemiological data inferred from spontaneous pneumothoraces [166].

The exact mechanism of renal tumorigenesis and lung cysts formation in BHDS is unknown, but a tumour-suppressor role of folliculin is postulated through the Akt-mTOR pathway [165]. In most renal tumours from BHDS patients, additional *FLCN* mutations are found, fitting the two-hits model of oncogenesis [167].

Lung cysts are present in around 85% of patients, resulting in 30–70% of them in spontaneous pneumothoraces, which are often the presenting manifestation [168]. Most patients have normal lung function. The classical fibrofolliculomas are hair follicle tumours, presenting as white or skin-coloured papules of the face and upper torso. Lung cysts are present from the second decade of life, the majority of pneumothoraces occur between the ages of 40 and 50 years, and renal tumours are diagnosed after 40 [168].

Radiological findings

Chest CT of patients with BHDS reveals thin-walled cysts of all sizes but predominantly irregular or oval-shaped. The majority of cysts siege in the lower lobes and are often bordering the pleura (figure 3d) [165].

Disease course

In patients with a sentinel pneumothorax episode, recurrence is frequent despite pleurodesis, with the average patient experiencing approximately three pneumothoraces [168]. The lung disease appears to remain stable through the years [169].

Diagnosis

Diagnosis of BHDS is made in patients with at least five fibrofolliculomas or carrying a heterozygous pathogenic mutation in *FLCN*. The diagnosis can be made if two of the following criteria are present: multiple lung cysts compatible with BHD, renal cancer before 50 years old, multifocal or bilateral renal cancer, hybrid chromophobe-oncocytic renal cancer, or a first relative with BHDS [165].

Management

There is no specific treatment of BHDS. The management of pneumothorax is similar to other pneumothorax patients. A screening and follow-up for renal cancer is suggested [170]. Fibrofolliculomas can be treated by laser, surgery or dermal sirolimus application, but recurrence is frequent [171].

Pulmonary Langerhans cell histiocytosis (PLCH)

Langerhans cells are a subset of dendritic cells, localised in the epiderma and the mucosal epithelium (including the airways epithelium), characterised by cluster of differentiation (CD) 1a and CD207 ("Langerin") expression [172]. In PLCH, accumulation of $CD1a^+$ cells in the lungs causes inflammatory cystic-nodular pulmonary parenchyma destruction in predisposed smokers [173].

Epidemiology and clinical presentation

One survey-based study in Japan reported a prevalence of 0.27 in males and 0.07 in females per 100 000 people [174], which is probably underestimated. The strongest risk and likely causal factor is current or former tobacco smoking [173, 175].

Somatic activating mutations in genes of the mitogen-activated protein kinase pathway are found at the inception of the disease [176, 177]. The mutated $CD1a^+$ dendritic cells exhibit resistance to apoptosis and a decreased tendency to exit the lung through lymph nodes, resulting in the formation of cellular nodules and the subsequent centrilobular fibrotic lung remodelling [178]. Cigarette smoke probably acts as a "second hit".

PLCH often presents in the fourth decade of life [173]. Symptoms include cough, dyspnoea, chest pain, fever and general malaise, but up to 50% of patients are asymptomatic [174]. Approximately 20% of patients have extrapulmonary manifestations, most frequently bone and pituitary gland lesions [173, 174]. The most frequent anomaly on pulmonary function tests is reduced diffusing capacity [179].

Radiological findings

The typical aspect on HRCT consists of bronchiolocentric micronodular/nodular and cystic lesions with parenchymal destruction, of predominant upper and middle lobes distribution with typical sparing of costophrenic angles [180–182]. Depending on the stage of PLCH, the octopus sign (central scar with septal strands and associated airspace enlargement) can be identified [183]. Cysts can be of various shapes (round, bilobed, clover-leafed, irregular or "bizarre") (figure 3b).

Disease course

Most of the cases experience regression with smoking discontinuation but in around 20–30% of the cases the disease progresses to end-stage lung disease [184]. Between 12–32% of patients will present pneumothorax in their lifetime [185]. A prospective series followed newly diagnosed patients with PLCH for 2 years and found that 38% presented lung function decline, with predictors of deterioration being smoking status and baseline P_{aO_2} [175]. 10-year survival has been estimated at 93% [179].

Diagnosis

A definite diagnosis requires confirmation either by BAL or sometimes histology, but a high-confidence diagnosis can often be made with a combination of a typical HRCT pattern and suggestive history, especially in smokers [186].

Treatment

Smoking cessation alone can be sufficient to obtain stabilisation or regression of PLCH [187], but tobacco and marijuana weaning are sometimes temporary and are insufficient in approximately one-third of cases. Pharmacological treatment with cladribine has been shown to be effective [188] and BRAF kinase/MEK inhibition represents promising leads in case for specific mutations [189]. In advanced cases, lung transplantation is effective, but recurrence can occur [190].

Conclusion

Many rare and ultrarare ILDs are likely underdiagnosed. Increasing insights into their pathobiology, genetics and disease behaviour have led to the development of better treatment options, with very effective targeted therapies for some of the diseases, whilst in others transplant or palliative care may be the only remaining option. To diagnose, optimally treat and support patients with rare ILDs as well as advance the field, early consultation with or referral to expert centres is advised. The organisation of these expert centres for rare ILDs within the European Reference Network on rare respiratory diseases (ERN-LUNG) further stimulates clinical and research collaboration to advance the care for patients with rare ILDs across Europe.

Provenance: Commissioned article, peer reviewed.

Previous articles in this series: No. 1: Simonneau G, Fadel E, Vonk Noordegraaf A, *et al.* Highlights from the International Chronic Thromboembolic Pulmonary Hypertension Congress 2021. *Eur Respir Rev* 2023; 32: 220132.

Conflict of interest: K. Buschulte has received payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from BI. V. Cottin has received an unrestricted grant to his institution from Boehringer Ingelheim; consulting fees from Boehringer Ingelheim, Roche, Shionogi, RedX, Pure Tech, Celgene/BMS, AstraZeneca, CSL Behring, Sanofi, United Therapeutics/Ferrer and Pliant; fees for lectures from Boehringer Ingelheim and Roche; support for attending meetings from Boehringer Ingelheim and Roche; reports participation on a Data Safety Monitoring board for Galapagos and Galecto; and participated in an Adjudication committee for Fibrogen. M. Wijsenbeek has received payment for a DSMB from savarapharma. M. Kreuter has received grants or contracts, consulting fees and payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from BI and Roche; and has leadership or fiduciary roles at ERS, EU IPFF and DGP. R. Diesler has received support for attending meetings and/or travel from Laidet Medical/Asdia and Vitalaire; and has other financial or non-financial interests (conference organisation) with Laidet Medical/Asdia, Vitalaire, ALLP, Agiradom and Lowenstein.

References

1 Wijsenbeek M, Cottin V. Spectrum of fibrotic lung diseases. *N Engl J Med* 2020; 383: 958–968.
2 Wijsenbeek M, Suzuki A, Maher TM. Interstitial lung diseases. *Lancet* 2022; 400: 769–786.
3 Kreuter M, Ladner UM, Heussel CP, *et al.* The diagnosis and treatment of pulmonary fibrosis. *Dtsch Arztebl Int* 2021; 118: 152–162.
4 Chua F, Desai SR, Wells AU, *et al.* Pleuroparenchymal fibroelastosis. a review of clinical, radiological, and pathological characteristics. *Ann Am Thorac Soc* 2019; 16: 1351–1359.
5 Cottin V, Cordier JF, Richeldi L. Orphan Lung Diseases. London, Springer, 2015.
6 Goldstein LS, Kavuru MS, Stoller JK, *et al.* Pulmonary alveolar proteinosis: clinical features and outcomes. *Chest* 1998; 114: 1357–1362.
7 Hadchouel A, Drummond D, Abou Taam R, *et al.* Alveolar proteinosis of genetic origins. *Eur Respir Rev* 2020; 29: 200187.
8 Bonella F, Bauer PC, Costabel U, *et al.* Pulmonary alveolar proteinosis: new insights from a single-center cohort of 70 patients. *Respir Med* 2011; 105: 1908–1916.
9 Jouneau S, Ménard C, Lederlin M. Pulmonary alveolar proteinosis. *Respirology* 2020; 25: 816–826.
10 Kreuter M, Costabel U, Herth F, *et al.* (Eds.). Seltene Lungenerkrankungen. Berlin Heidelberg, Springer, 2016.
11 Kitamura T, Tanaka N, Nakata K, *et al.* Idiopathic pulmonary alveolar proteinosis as an autoimmune disease with neutralizing antibody against granulocyte/macrophage colony-stimulating factor. *J Exp Med* 1999; 190: 875–880.
12 Trapnell BC, Carey BC, Suzuki T, *et al.* Pulmonary alveolar proteinosis, a primary immunodeficiency of impaired GM-CSF stimulation of macrophages. *Curr Opin Immunol* 2009; 21: 514–521.
13 Inoue Y, Trapnell BC, Tazawa R, *et al.* Characteristics of a large cohort of patients with autoimmune pulmonary alveolar proteinosis in Japan. *Am J Respir Crit Care Med* 2008; 177: 752–762.
14 Holbert JM, Costello P, Rogers RM. CT features of pulmonary alveolar proteinosis. *AJR Am J Roentgenol* 2001; 176: 1287–1294.

15 Costabel U, Guzman J, Oshimo S, *et al.* Bronchoalveolar lavage in other interstitial lung diseases. *Semin Respir Crit Care Med* 2007; 28: 514–524.
16 Milleron BJ, Costabel U, Akoun GM, *et al.* Bronchoalveolar lavage cell data in alveolar proteinosis. *Am Rev Respir Dis* 1991; 144: 1330–1332.
17 Kitamura T, Uchida K, Nakata K, *et al.* Serological diagnosis of idiopathic pulmonary alveolar proteinosis. *Am J Respir Crit Care Med* 2000; 162: 658–662.
18 Uchida K, Nakata K, Suzuki T, *et al.* Granulocyte/macrophage-colony-stimulating factor autoantibodies and myeloid cell immune functions in healthy subjects. *Blood* 2009; 113: 2547–2556.
19 Campo I, Luisetti M, Griese M, *et al.* A global survey on whole lung lavage in pulmonary alveolar proteinosis. *Chest* 2016; 150: 251–253.
20 Campo I, Luisetti M, Griese M, *et al.* Whole lung lavage therapy for pulmonary alveolar proteinosis: a global survey of current practices and procedures. *Orphanet J Rare Dis* 2016; 11: 115.
21 Michaud G, Reddy C, Ernst A. Whole-lung lavage for pulmonary alveolar proteinosis. *Chest* 2009; 136: 1678–1681.
22 Alberti A, Luisetti M, Braschi A, *et al.* Bronchoalveolar lavage fluid composition in alveolar proteinosis. Early changes after therapeutic lavage. *Am J Respir Crit Care Med* 1996; 154: 817–820.
23 Trapnell BC, Inoue Y, Bonella F, *et al.* Inhaled molgramostim therapy in autoimmune pulmonary alveolar proteinosis. *N Engl J Med* 2020; 383: 1635–1644.
24 Tazawa R, Ueda T, Takahashi A, *et al.* Inhaled GM-CSF for pulmonary alveolar proteinosis. *N Engl J Med* 2019; 381: 923–932.
25 Seymour JF, Presneill JJ. Pulmonary alveolar proteinosis: progress in the first 44 years. *Am J Respir Crit Care Med* 2002; 166, 215–235.
26 Garber B, Albores J, Neville TH, *et al.* A plasmapheresis protocol for refractory pulmonary alveolar proteinosis. *Lung* 2015; 193: 209–211.
27 Borie R, Debray MP, Crestani B, *et al.* Rituximab therapy in autoimmune pulmonary alveolar proteinosis. *Eur Respir J* 2009; 33: 1503–1506.
28 Kavuru MS, Malur A, Thomassen MJ, *et al.* An open-label trial of rituximab therapy in pulmonary alveolar proteinosis. *Eur Respir J* 2011; 38: 1361–1367.
29 Soyez B, Borie R, Crestani B, *et al.* Rituximab for auto-immune alveolar proteinosis, a real life cohort study. *Respir Res* 2018; 19: 74.
30 McCarthy C, Lee E, Carey BC, *et al.* Statin as a novel pharmacotherapy of pulmonary alveolar proteinosis. *Nat Commun* 2018; 9: 3127.
31 Flaherty KR, Wells AU, Brown KK, *et al.* Nintedanib in progressive fibrosing interstitial lung diseases. *N Engl J Med* 2019; 381: 1718–1727.
32 Ishii H, Tazawa R, Nakata K, *et al.* Clinical features of secondary pulmonary alveolar proteinosis: pre-mortem cases in Japan. *Eur Respir J* 2011; 37: 465–468.
33 Ishii H, Seymour JF, Nakata K, *et al.* Secondary pulmonary alveolar proteinosis complicating myelodysplastic syndrome results in worsening of prognosis: a retrospective cohort study in Japan. *BMC Pulm Med* 2014; 14: 37.
34 Borie R, Danel C, Crestani B, *et al.* Pulmonary alveolar proteinosis. *Eur Respir Rev* 2011; 20: 98–107.
35 Harbitz, F. Extensive calcification of the lungs as a distinct disease. *Arch intern Med* 1918; 21, 139.
36 Kosciuk P, Meyer C, McCormack FX, *et al.* Pulmonary alveolar microlithiasis. *Eur Respir Rev* 2020; 29: 200024.
37 Castellana G, Castellana G, Resta O, *et al.* Pulmonary alveolar microlithiasis: review of the 1022 cases reported worldwide. *Eur Respir Rev* 2015; 24: 607–620.
38 Corut A, Senyigit A, Tolun A, *et al.* Mutations in SLC34A2 cause pulmonary alveolar microlithiasis and are possibly associated with testicular microlithiasis. *Am J Hum Genet* 2006; 79: 650–656.
39 Jönsson ÅLM, Bendstrup E, Mogensen S, *et al.* Eight novel variants in the SLC34A2 gene in pulmonary alveolar microlithiasis. *Eur Respir J* 2020; 55: 1900806.
40 Ferreira FA, Pereira e Silva JL, Marchiori E, *et al.* Pulmonary alveolar microlithiasis. State-of-the-art review. *Respir Med* 2013; 107: 1–9.
41 Castellana G, Gentile M, Lamorgese V, *et al.* Pulmonary alveolar microlithiasis: clinical features, evolution of the phenotype, and review of the literature. *Am J Med Genet* 2002; 111: 220–224.
42 Jönsson ÅL, Hilberg O, Simonsen U, *et al.* SLC34A2 gene mutation may explain comorbidity of pulmonary alveolar microlithiasis and aortic valve sclerosis. *Am J Respir Crit Care Med* 2012; 185: 464.
43 Deniz O, Ors F, Tozkoparan E, *et al.* High resolution computed tomographic features of pulmonary alveolar microlithiasis. *Eur J Radiol* 2005; 55: 452–460.
44 Sumikawa H, Johkoh T, Müller NL, *et al.* Pulmonary alveolar microlithiasis: CT and pathologic findings in 10 patients. *Monaldi Arch Chest Dis* 2005; 63: 59–64.
45 Gasparetto EL, Tazoniero P, Sakamoto D, *et al.* Pulmonary alveolar microlithiasis presenting with crazy-paving pattern on high resolution CT. *Br J Radiol* 2004; 77: 974–976.

46 Barnard NJ, Crocker PR, Levison DA, *et al.* Pulmonary alveolar microlithiasis. A new analytical approach. *Histopathology* 1987; 11: 639–645.
47 Lauta VM. Pulmonary alveolar microlithiasis: an overview of clinical and pathological features together with possible therapies. *Respir Med* 2003; 97: 1081–1085.
48 Tachibana T, Hagiwara K, Johkoh T. Pulmonary alveolar microlithiasis: review and management. *Curr Opin Pulm Med* 2009; 15: 486–490.
49 Ozcelik U, Yalcin E, Kiper N, *et al.* Long-term results of disodium etidronate treatment in pulmonary alveolar microlithiasis. *Pediatr Pulmonol* 2010; 45: 514–517.
50 Klikovits T, Slama A, Hoda MA, *et al.* A rare indication for lung transplantation – pulmonary alveolar microlithiasis: institutional experience of five consecutive cases. *Clin Transplant* 2016; 30: 429–434.
51 Enemark A, Jönsson ÅLM, Bendstrup E, *et al.* Pulmonary alveolar microlithiasis – a review. *Yale J Biol Med* 2021; 94: 637–644.
52 Frankel SK, Cool CD, Lynch DA, *et al.* Idiopathic pleuroparenchymal fibroelastosis: description of a novel clinicopathologic entity. *Chest* 2004; 126: 2007–2013.
53 Piciucchi S, Tomassetti S, Casoni G, *et al.* High resolution CT and histological findings in idiopathic pleuroparenchymal fibroelastosis: features and differential diagnosis. *Respir Res* 2011; 12: 111.
54 Watanabe K, Nagata N, Kitasato Y, *et al.* Rapid decrease in forced vital capacity in patients with idiopathic pulmonary upper lobe fibrosis. *Respir Investig* 2012; 50: 88–97.
55 Khiroya R, Macaluso C, Montero MA, *et al.* Pleuroparenchymal fibroelastosis: a review of histopathologic features and the relationship between histologic parameters and survival. *Am J Surg Pathol* 2017; 41: 1683–1689.
56 Reddy TL, Tominaga M, Hansell DM, *et al.* Pleuroparenchymal fibroelastosis: a spectrum of histopathological and imaging phenotypes. *Eur Respir J* 2012; 40: 377–385.
57 Becker CD, Gil J, Padilla ML. Idiopathic pleuroparenchymal fibroelastosis: an unrecognized or misdiagnosed entity? *Mod Pathol* 2008; 21: 784–787.
58 Nakatani T, Arai T, Kitaichi M, *et al.* Pleuroparenchymal fibroelastosis from a consecutive database: a rare disease entity? *Eur Respir J* 2015; 45: 1183–1186.
59 Shioya M, Otsuka M, Yamada G, *et al.* Poorer prognosis of idiopathic pleuroparenchymal fibroelastosis compared with idiopathic pulmonary fibrosis in advanced stage. *Can Respir J* 2018; 2018: 6043053.
60 Tanizawa K, Handa T, Kubo T, *et al.* Clinical significance of radiological pleuroparenchymal fibroelastosis pattern in interstitial lung disease patients registered for lung transplantation: a retrospective cohort study. *Respir Res* 2018; 19: 162.
61 Pakhale SS, Hadjiliadis D, Howell DN, *et al.* Upper lobe fibrosis: a novel manifestation of chronic allograft dysfunction in lung transplantation. *J Heart Lung Transplant* 2005; 24: 1260–1268.
62 Mariani F, Gatti B, Rocca A, *et al.* Pleuroparenchymal fibroelastosis: the prevalence of secondary forms in hematopoietic stem cell and lung transplantation recipients. *Diagn Interv Radiol* 2016; 22: 400–406.
63 Oda T, Ogura T, Kitamura H, *et al.* Distinct characteristics of pleuroparenchymal fibroelastosis with usual interstitial pneumonia compared with idiopathic pulmonary fibrosis. *Chest* 2014; 146: 1248–1255.
64 Kato M, Sasaki S, Kurokawa K, *et al.* Usual interstitial pneumonia pattern in the lower lung lobes as a prognostic factor in idiopathic pleuroparenchymal fibroelastosis. *Respiration* 2019; 97: 319–328.
65 Sugino K, Ono H, Shimizu H, *et al.* Treatment with antifibrotic agents in idiopathic pleuroparenchymal fibroelastosis with usual interstitial pneumonia. *ERJ Open Res* 2021; 7: 00196-2020.
66 Fujisawa T, Horiike Y, Egashira R, *et al.* Radiological pleuroparenchymal fibroelastosis-like lesion in idiopathic interstitial pneumonias. *Respir Res* 2021; 22: 290.
67 Gudmundsson E, Zhao A, Mogulkoc N, *et al.* Pleuroparenchymal fibroelastosis in idiopathic pulmonary fibrosis: Survival analysis using visual and computer-based computed tomography assessment. *EClinicalMedicine* 2021; 38: 101009.
68 Jacob J, Odink A, Brun AL, *et al.* Functional associations of pleuroparenchymal fibroelastosis and emphysema with hypersensitivity pneumonitis. *Respir Med* 2018; 138: 95–101.
69 Bonifazi M, Sverzellati N, Negri E, *et al.* Pleuroparenchymal fibroelastosis in systemic sclerosis: prevalence and prognostic impact. *Eur Respir J* 2020; 56: 1902135.
70 Kang J, Seo WJ, Lee EY, *et al.* Pleuroparenchymal fibroelastosis in rheumatoid arthritis-associated interstitial lung disease. *Respir Res* 2022; 23: 143.
71 Enomoto Y, Nakamura Y, Colby TV, *et al.* Radiologic pleuroparenchymal fibroelastosis-like lesion in connective tissue disease-related interstitial lung disease. *PLoS One* 2017; 12: e0180283.
72 Beynat-Mouterde C, Beltramo G, Lezmi G, *et al.* Pleuroparenchymal fibroelastosis as a late complication of chemotherapy agents. *Eur Respir J* 2014; 44: 523–527.
73 Lee JH, Chae EJ, Song JS, *et al.* Pleuroparenchymal fibroelastosis in Korean patients: clinico-radiologic-pathologic features and 2-year follow-up. *Korean J Intern Med* 2021; 36: S132–S141.
74 Ricoy J, Suárez-Antelo J, Antúnez J, *et al.* Pleuroparenchymal fibroelastosis: clinical, radiological and histopathological features. *Respir Med* 2022; 191: 106437.

75 Enomoto Y, Nakamura Y, Satake Y, *et al.* Clinical diagnosis of idiopathic pleuroparenchymal fibroelastosis: A retrospective multicenter study. *Respir Med* 2017; 133: 1–5.
76 Ishii H, Watanabe K, Kushima H, *et al.* Pleuroparenchymal fibroelastosis diagnosed by multidisciplinary discussions in Japan. *Respir Med* 2018; 141: 190–197.
77 von der Thüsen JH, Hansell DM, Tominaga M, *et al.* Pleuroparenchymal fibroelastosis in patients with pulmonary disease secondary to bone marrow transplantation. *Mod Pathol* 2011; 24: 1633–1639.
78 Kono M, Nakamura Y, Enomoto Y, *et al.* Pneumothorax in patients with idiopathic pleuroparenchymal fibroelastosis: incidence, clinical features, and risk factors. *Respiration* 2021; 100: 19–26.
79 Esteves C, Costa FR, Redondo MT, *et al.* Pleuroparenchymal fibroelastosis: role of high-resolution computed tomography (HRCT) and CT-guided transthoracic core lung biopsy. *Insights Imaging* 2016; 7: 155–162.
80 Kusagaya H, Nakamura Y, Kono M, *et al.* Idiopathic pleuroparenchymal fibroelastosis: consideration of a clinicopathological entity in a series of Japanese patients. *BMC Pulm Med* 2012; 12: 72.
81 Sverzellati N, Zompatori M, Poletti V, *et al.* Small chronic pneumothoraces and pulmonary parenchymal abnormalities after bone marrow transplantation. *J Thorac Imaging* 2007; 22: 230–234.
82 Travis WD, Costabel U, Hansell DM, *et al.* An official American Thoracic Society/European Respiratory Society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. *Am J Respir Crit Care Med* 2013; 188: 733–748.
83 Kronborg-White S, Ravaglia C, Dubini A, *et al.* Cryobiopsies are diagnostic in pleuroparenchymal and airway-centered fibroelastosis. *Respir Res* 2018; 19: 135.
84 Shiiya H, Nakajima J, Date H, *et al.* Outcomes of lung transplantation for idiopathic pleuroparenchymal fibroelastosis. *Surg Today* 2021; 51: 1276–1284.
85 Shiiya H, Sato M. Lung transplantation for pleuroparenchymal fibroelastosis. *J Clin Med* 2021; 10: 957.
86 Nasser M, Si-Mohamed S, Turquier S, *et al.* Nintedanib in idiopathic and secondary pleuroparenchymal fibroelastosis. *Orphanet J Rare Di*. 2021; 16: 419.
87 Kinoshita Y, Miyamura T, Ikeda T, *et al.* Limited efficacy of nintedanib for idiopathic pleuroparenchymal fibroelastosis. *Respir Investig* 2022; 60: 562–569.
88 Calado RT, Young NS. Telomere diseases. *N Engl J Med* 2009; 361: 2353–2365.
89 Savage SA, Niewisch MR. Dyskeratosis congenita and related telomere biology disorders. *In*: Adam MP, Mirzaa GM, Pagon RA, *et al.*, eds. GeneReviews. Seattle, University of Washington, 1993.
90 Armanios M. Telomerase and idiopathic pulmonary fibrosis. *Mutat Res* 2012; 730: 52–58.
91 Niewisch MR, Savage SA. An update on the biology and management of dyskeratosis congenita and related telomere biology disorders. *Expert Rev Hematol* 2019; 12: 1037–1052.
92 Giri N, Ravichandran S, Wang Y, *et al.* Prognostic significance of pulmonary function tests in dyskeratosis congenita, a telomere biology disorder. *ERJ Open Res* 2019; 5: 00209-2019.
93 Cronkhite JT, Xing C, Raghu G, *et al.* Telomere shortening in familial and sporadic pulmonary fibrosis. *Am J Respir Crit Care Med* 2008; 178: 729–737.
94 Tsakiri KD, Cronkhite JT, Kuan PJ, *et al.* Adult-onset pulmonary fibrosis caused by mutations in telomerase. *Proc Natl Acad Sci U S A* 2007; 104: 7552–7557.
95 Armanios MY, Chen JJ, Cogan JD, *et al.* Telomerase mutations in families with idiopathic pulmonary fibrosis. *N Engl J Med* 2007; 356: 1317–1326.
96 Stuart BD, Choi J, Zaidi S, *et al.* Exome sequencing links mutations in PARN and RTEL1 with familial pulmonary fibrosis and telomere shortening. *Nat Genet* 2015; 47: 512–517.
97 Petrovski S, Todd JL, Durheim MT, *et al.* An exome sequencing study to assess the role of rare genetic variation in pulmonary fibrosis. *Am J Respir Crit Care Med* 2017; 196: 82–93.
98 Alder JK, Chen JJ, Lancaster L, *et al.* Short telomeres are a risk factor for idiopathic pulmonary fibrosis. *Proc Natl Acad Sci U S A* 2008; 105: 13051–13056.
99 Juge PA, Borie R, Kannengiesser C, *et al.* Shared genetic predisposition in rheumatoid arthritis-interstitial lung disease and familial pulmonary fibrosis. *Eur Respir J* 2017; 49: 1602314.
100 Daniali L, Benetos A, Susser E, *et al.* Telomeres shorten at equivalent rates in somatic tissues of adults. *Nat Commun* 2013; 4: 1597.
101 Alder JK, Guo N, Kembou F, *et al.* Telomere length is a determinant of emphysema susceptibility. *Am J Respir Crit Care Med* 2011; 184: 904–912.
102 Borie R, Tabeze L, Thabut G, *et al.* Prevalence and characteristics of *TERT* and *TERC* mutations in suspected genetic pulmonary fibrosis. *Eur Respir J* 2016; 48: 1721–1731.
103 Savage SA, Bertuch AA. The genetics and clinical manifestations of telomere biology disorders. *Genet Med* 2010; 12: 753–764.
104 Newton CA, Batra K, Torrealba J, *et al.* Telomere-related lung fibrosis is diagnostically heterogeneous but uniformly progressive. *Eur Respir J* 2016; 48: 1710–1720.
105 Diaz de Leon A, Cronkhite JT, Katzenstein AL, *et al.* Telomere lengths, pulmonary fibrosis and telomerase (TERT) mutations. *PLoS One* 2010; 5: e10680.

106 Hoffman TW, van Moorsel CHM, Borie R, *et al.* Pulmonary phenotypes associated with genetic variation in telomere-related genes. *Curr Opin Pulm Med* 2018; 24: 269–280.
107 Mackintosh JA, Pietsch M, Lutzky V, *et al.* TELO-SCOPE study: a randomised, double-blind, placebo-controlled, phase 2 trial of danazol for short telomere related pulmonary fibrosis. *BMJ Open Respir Res* 2021; 8: e001127.
108 Ohsumi A, Nakajima D, Yoshizawa A, *et al.* Living-donor lung transplantation for dyskeratosis congenita. *Ann Thorac Surg* 2021; 112: e397–e402.
109 Povedano JM, Martinez P, Serrano R, *et al.* Therapeutic effects of telomerase in mice with pulmonary fibrosis induced by damage to the lungs and short telomeres. *Elife* 2018; 7: e31299.
110 Zhang D, Newton CA. Familial pulmonary fibrosis: genetic features and clinical implications. *Chest* 2021; 160: 1764–1773.
111 Hamvas A, Deterding RR, Wert SE, *et al.* Heterogeneous pulmonary phenotypes associated with mutations in the thyroid transcription factor gene NKX2-1. *Chest* 2013; 144: 794–804.
112 van Moorsel CHM, Van der Vis JJ, Grutters JC. Genetic disorders of the surfactant system: focus on adult disease. *Eur Respir Rev* 2021; 30: 200085.
113 Borie R, Kannengiesser C, Sicre de Fontbrune F, *et al.* Management of suspected monogenic lung fibrosis in a specialised centre. *Eur Respir Rev* 2017; 26: 160122.
114 Li J, Hosia W, Hamvas A, *et al.* The N-terminal propeptide of lung surfactant protein C is necessary for biosynthesis and prevents unfolding of a metastable alpha-helix. *J Mol Biol* 2004; 338: 857–862.
115 Hawkins A, Guttentag SH, Deterding R, *et al.* A non-BRICHOS SFTPC mutant (SP-CI73T) linked to interstitial lung disease promotes a late block in macroautophagy disrupting cellular proteostasis and mitophagy. *Am J Physiol Lung Cell Mol Physiol* 2015; 308: L33–L47.
116 Pobre-Piza KFR, Mann MJ, Flory AR, *et al.* Mapping SP-C co-chaperone binding sites reveals molecular consequences of disease-causing mutations on protein maturation. *Nat Commun* 2022; 13: 1821.
117 Atochina-Vasserman EN, Beers MF, Gow AJ. Review: chemical and structural modifications of pulmonary collectins and their functional consequences. *Innate Immun* 2010; 16: 175–182.
118 Brasch F, Schimanski S, Muhlfeld C, *et al.* Alteration of the pulmonary surfactant system in full-term infants with hereditary ABCA3 deficiency. *Am J Respir Crit Care Med* 2006; 174: 571–580.
119 Shulenin S, Nogee LM, Annilo T, *et al.* ABCA3 gene mutations in newborns with fatal surfactant deficiency. *N Engl J Med* 2004; 350: 1296–1303.
120 Nogee LM, Dunbar AE, 3rd, Wert S, *et al.* Mutations in the surfactant protein C gene associated with interstitial lung disease. *Chest* 2002; 121: Suppl. 3, 20S–21S.
121 Abou Taam R, Jaubert F, Emond S, *et al.* Familial interstitial disease with I73T mutation: A mid- and long-term study. *Pediatr Pulmonol* 2009; 44: 167–175.
122 Doan ML, Guillerman RP, Dishop MK, *et al.* Clinical, radiological and pathological features of ABCA3 mutations in children. *Thorax* 2008; 63: 366–373.
123 Epaud R, Delestrain C, Louha M, *et al.* Combined pulmonary fibrosis and emphysema syndrome associated with ABCA3 mutations. *Eur Respir J* 2014; 43: 638–641.
124 Cottin V, Cordier JF. SFTPC mutations in patients with familial pulmonary fibrosis: combined with emphysema? *Am J Respir Crit Care Med* 2011; 183: 1113.
125 Kroner C, Wittmann T, Reu S, *et al.* Lung disease caused by ABCA3 mutations. *Thorax* 2017; 72: 213–220.
126 Huizing M, Malicdan MCV, Gochuico BR, *et al.* Hermansky–Pudlak syndrome. *In:* Adam MP, Mirzaa GM, Pagon RA, *et al.*, eds. GeneReviews. Seattle, University of Washington, 1993.
127 Yokoyama T, Gochuico BR. Hermansky–Pudlak syndrome pulmonary fibrosis: a rare inherited interstitial lung disease. *Eur Respir Rev* 2021; 30: 200193.
128 Santiago Borrero PJ, Rodriguez-Perez Y, Renta JY, *et al.* Genetic testing for oculocutaneous albinism type 1 and 2 and Hermansky–Pudlak syndrome type 1 and 3 mutations in Puerto Rico. *J Invest Dermatol* 2006; 126: 85–90.
129 Seward SL, Jr., Gahl WA. Hermansky–Pudlak syndrome: health care throughout life. *Pediatrics* 2013; 132: 153–160.
130 Shotelersuk V, Gahl WA. Hermansky–Pudlak syndrome: models for intracellular vesicle formation. *Mol Genet Metab* 1998; 65: 85–96.
131 Trimble A, Gochuico BR, Markello TC, *et al.* Circulating fibrocytes as biomarker of prognosis in Hermansky–Pudlak syndrome. *Am J Respir Crit Care Med* 2014; 190: 1395–1401.
132 Mahavadi P, Korfei M, Henneke I, *et al.* Epithelial stress and apoptosis underlie Hermansky–Pudlak syndrome-associated interstitial pneumonia. *Am J Respir Crit Care Med* 2010; 182: 207–219.
133 Anderson PD, Huizing M, Claassen DA, *et al.* Hermansky–Pudlak syndrome type 4 (HPS-4): clinical and molecular characteristics. *Hum Genet* 2003; 113: 10–17.
134 Gochuico BR, Huizing M, Golas GA, *et al.* Interstitial lung disease and pulmonary fibrosis in Hermansky–Pudlak syndrome type 2, an adaptor protein-3 complex disease. *Mol Med* 2012; 18: 56–64.
135 Witkop CJ, Almadovar C, Pineiro B, *et al.* Hermansky–Pudlak syndrome (HPS). An epidemiologic study. *Ophthalmic Paediatr Genet* 1990; 11: 245–250.

136 Gahl WA, Brantly M, Troendle J, *et al.* Effect of pirfenidone on the pulmonary fibrosis of Hermansky–Pudlak syndrome. *Mol Genet Metab* 2002; 76: 234–242.
137 O'Brien K, Troendle J, Gochuico BR, *et al.* Pirfenidone for the treatment of Hermansky–Pudlak syndrome pulmonary fibrosis. *Mol Genet Metab* 2011; 103: 128–134.
138 O'Brien KJ, Introne WJ, Akal O, *et al.* Prolonged treatment with open-label pirfenidone in Hermansky–Pudlak syndrome pulmonary fibrosis. *Mol Genet Metab* 2018; 125: 168–173.
139 Benvenuto L, Qayum S, Kim H, *et al.* Lung transplantation for pulmonary fibrosis associated with Hermansky–Pudlak syndrome. A single-center experience. *Transplant Direct* 2022; 8: e1303.
140 Lederer DJ, Kawut SM, Sonett JR, *et al.* Successful bilateral lung transplantation for pulmonary fibrosis associated with the Hermansky–Pudlak syndrome. *J Heart Lung Transplant* 2005; 24: 1697–1699.
141 Bode SFN, Rohr J, Müller Quernheim J, *et al.* Pulmonary granulomatosis of genetic origin. *Eur Respir Rev* 2021; 30: 200152.
142 Cazzato S, Omenetti A, Ravaglia C, *et al.* Lung involvement in monogenic interferonopathies. *Eur Respir Rev* 2020; 29: 200001.
143 Burkhalter JL, Morano JU, McCay MB. Diffuse interstitial lung disease in neurofibromatosis. *South Med J* 1986; 79: 944–946.
144 Tanita K, Sakura F, Nambu R, *et al.* Clinical and immunological heterogeneity in Japanese patients with gain-of-function variants in STAT3. *J Clin Immunol* 2021; 41: 780–790.
145 Borie R, Crestani B, Guyard A, *et al.* Interstitial lung disease in lysosomal storage disorders. *Eur Respir Rev* 2021; 30: 200363.
146 Mauhin W, Habarou F, Gobin S, *et al.* Update on lysinuric protein intolerance, a multi-faceted disease retrospective cohort analysis from birth to adulthood. *Orphanet J Rare Dis* 2017; 12: 3.
147 Rebaine Y, Nasser M, Girerd B, *et al.* Tuberous sclerosis complex for the pulmonologist. *Eur Respir Rev* 2021; 30: 200348.
148 Torre O, Elia D, Caminati A, *et al.* New insights in lymphangioleiomyomatosis and pulmonary Langerhans cell histiocytosis. *Eur Respir Rev* 2017; 26: 170042.
149 McCarthy C, Gupta N, Johnson SR, *et al.* Lymphangioleiomyomatosis: pathogenesis, clinical features, diagnosis, and management. *Lancet Respir Med* 2021; 9: 1313–1327.
150 Harknett EC, Chang WY, Byrnes S, *et al.* Use of variability in national and regional data to estimate the prevalence of lymphangioleiomyomatosis. *QJM* 2011; 104: 971–979.
151 Elia D, Torre O, Vasco C, *et al.* Pulmonary Langerhans cell histiocytosis and lymphangioleiomyomatosis have circulating cells with loss of heterozygosity of the TSC2 gene. *Chest* 2022; 162: 385–393.
152 Rodrigues DA, Gomes CM, Costa IM. Tuberous sclerosis complex. *An Bras Dermatol* 2012; 87: 184–196.
153 Ryu JH, Moss J, Beck GJ, *et al.* The NHLBI lymphangioleiomyomatosis registry: characteristics of 230 patients at enrollment. *Am J Respir Crit Care Med* 2006; 173: 105–111.
154 Taveira-DaSilva AM, Steagall WK, Rabel A, *et al.* Reversible airflow obstruction in lymphangioleiomyomatosis. *Chest* 2009; 136: 1596–1603.
155 Kirchner J, Stein A, Viel K, *et al.* Pulmonary lymphangioleiomyomatosis: high-resolution CT findings. *Eur Radiol* 1999; 9: 49–54.
156 Yano S. Exacerbation of pulmonary lymphangioleiomyomatosis by exogenous oestrogen used for infertility treatment. *Thorax* 2002; 57: 1085–1086.
157 Gupta N, Lee HS, Ryu JH, *et al.* The NHLBI LAM registry: prognostic physiologic and radiologic biomarkers emerge from a 15-year prospective longitudinal analysis. *Chest* 2019; 155: 288–296.
158 McCormack FX, Gupta N, Finlay GR, *et al.* Official American Thoracic Society/Japanese Respiratory Society clinical practice guidelines: lymphangioleiomyomatosis diagnosis and management. *Am J Respir Crit Care Med* 2016; 194: 748–761.
159 Johnson SR, Cordier JF, Lazor R, *et al.* European Respiratory Society guidelines for the diagnosis and management of lymphangioleiomyomatosis. *Eur Respir J* 2010; 35: 14–26.
160 McCormack FX, Inoue Y, Moss J, *et al.* Efficacy and safety of sirolimus in lymphangioleiomyomatosis. *N Engl J Med* 2011; 364: 1595–1606.
161 Harari S, Spagnolo P, Cocconcelli E, *et al.* Recent advances in the pathobiology and clinical management of lymphangioleiomyomatosis. *Curr Opin Pulm Med* 2018; 24: 469–476.
162 Harari S, Torre O, Elia D, *et al.* Improving survival in lymphangioleio-myomatosis: a 16-year observational study in a large cohort of patients. *Respiration* 2021; 100: 989–999.
163 Goldberg HJ, Harari S, Cottin V, *et al.* Everolimus for the treatment of lymphangioleiomyomatosis: a phase II study. *Eur Respir J* 2015; 46: 783–794.
164 Khawar MU, Yazdani D, Zhu Z, *et al.* Clinical outcomes and survival following lung transplantation in patients with lymphangioleiomyomatosis. *J Heart Lung Transplant* 2019; 38: 949–955.
165 Daccord C, Good J-M, Morren M-A, *et al.* Brit–Hogg–Dubé syndrome. *Eur Respir Rev* 2020; 29: 200042.
166 Muller ME, Daccord C, Taffe P, *et al.* Prevalence of Birt–Hogg–Dubé syndrome determined through epidemiological data on spontaneous pneumothorax and Bayes theorem. *Front Med* 2021; 8: 631168.

167 Vocke CD, Yang Y, Pavlovich CP, *et al.* High frequency of somatic frameshift BHD gene mutations in Birt–Hogg–Dubé-associated renal tumors. *J Natl Cancer Inst* 2005; 97: 931–935.

168 Gupta N, Kopras EJ, Henske EP, *et al.* Spontaneous pneumothoraces in patients with Birt–Hogg–Dubé syndrome. *Ann Am Thorac Soc* 2017; 14: 706–713.

169 Tobino K, Gunji Y, Kurihara M, *et al.* Characteristics of pulmonary cysts in Birt–Hogg–Dubé syndrome: thin-section CT findings of the chest in 12 patients. *Eur J Radiol* 2011; 77: 403–409.

170 Johannesma PC, van de Beek I, van der Wel T, *et al.* Renal imaging in 199 Dutch patients with Birt–Hogg–Dubé syndrome: screening compliance and outcome. *PLoS One* 2019; 14: e0212952.

171 Kahle B, Hellwig S, Schulz T. Multiple mantleomas in Birt–Hogg–Dubé syndrome: successful therapy with CO_2 laser. *Hautarzt* 2001; 52: 43–46.

172 Emile JF, Abla O, Fraitag S, *et al.* Revised classification of histiocytoses and neoplasms of the macrophage-dendritic cell lineages. *Blood* 2016; 127: 2672–2681.

173 Vassallo R, Ryu JH, Schroeder DR, *et al.* Clinical outcomes of pulmonary Langerhans'-cell histiocytosis in adults. *N Engl J Med* 2002; 346: 484–490.

174 Watanabe R, Tatsumi K, Hashimoto S, *et al.* Clinico-epidemiological features of pulmonary histiocytosis X. *Intern Med* 2001; 40: 998–1003.

175 Tazi A, de Margerie C, Naccache JM, *et al.* The natural history of adult pulmonary Langerhans cell histiocytosis: a prospective multicentre study. *Orphanet J Rare Dis* 2015; 10: 30.

176 Badalian-Very G, Vergilio JA, Degar BA, *et al.* Recurrent BRAF mutations in Langerhans cell histiocytosis. *Blood* 2010; 116: 1919–1923.

177 Mourah S, How-Kit A, Meignin V, *et al.* Recurrent NRAS mutations in pulmonary Langerhans cell histiocytosis. *Eur Respir J* 2016; 47: 1785–1796.

178 Hogstad B, Berres ML, Chakraborty R, *et al.* RAF/MEK/extracellular signal-related kinase pathway suppresses dendritic cell migration and traps dendritic cells in Langerhans cell histiocytosis lesions. *J Exp Med* 2018; 215: 319–336.

179 Benattia A, Bugnet E, Walter-Petrich A, *et al.* Long-term outcomes of adult pulmonary Langerhans cell histiocytosis: a prospective cohort. *Eur Respir J* 2022; 59: 2101017.

180 Elia D, Torre O, Cassandro R, *et al.* Pulmonary Langerhans cell histiocytosis: a comprehensive analysis of 40 patients and literature review. *Eur J Intern Med* 2015; 26: 351–356.

181 Brauner MW, Grenier P, Tijani K, *et al.* Pulmonary Langerhans cell histiocytosis: evolution of lesions on CT scans. *Radiology* 1997; 204: 497–502.

182 Seely JM, Salahudeen S, Sr., Cadaval-Goncalves AT, *et al.* Pulmonary Langerhans cell histiocytosis: a comparative study of computed tomography in children and adults. *J Thorac Imaging* 2012; 27: 65–70.

183 Poellinger A, Berezowska S, Myers JL, *et al.* The octopus sign-a new HRCT sign in pulmonary Langerhans cell histiocytosis. *Diagnostics* 2022; 12: 937.

184 Vassallo R, Harari S, Tazi A. Current understanding and management of pulmonary Langerhans cell histiocytosis. *Thorax* 2017; 72: 937–945.

185 Singla A, Kopras EJ, Gupta N. Spontaneous pneumothorax and air travel in pulmonary Langerhans cell histiocytosis: a patient survey. *Respir Investig* 2019; 57: 582–589.

186 Shaw B, Borchers M, Zander D, *et al.* Pulmonary Langerhans cell histiocytosis. *Semin Respir Crit Care Med* 2020; 41: 269–279.

187 Mogulkoc N, Veral A, Bishop PW, *et al.* Pulmonary Langerhans' cell histiocytosis: radiologic resolution following smoking cessation. *Chest* 1999; 115: 1452–1455.

188 Grobost V, Khouatra C, Lazor R, *et al.* Effectiveness of cladribine therapy in patients with pulmonary Langerhans cell histiocytosis. *Orphanet J Rare Dis* 2014; 9: 191.

189 Diamond EL, Durham BH, Ulaner GA, *et al.* Efficacy of MEK inhibition in patients with histiocytic neoplasms. *Nature* 2019; 567: 521–524.

190 Dauriat G, Mal H, Thabut G, *et al.* Lung transplantation for pulmonary Langerhans' cell histiocytosis: a multicenter analysis. *Transplantation* 2006; 81: 746–750.