Rare interstitial lung diseases: a narrative review

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Background and Objective: Interstitial lung diseases (ILDs) encompass over 200 entities. Among them, fibrosing lung diseases, have recently generated special interest due to the emerging therapies for their management. However, it is important to deepen our knowledge of other less prevalent ILD, since many of them are associated with a poor prognosis. This narrative review aims to provide a practical and up-to-date description of some poorly recognized ILD. It covers rare idiopathic interstitial pneumonias and their histologic patterns, genetic disorders with interstitial lung involvement (Hermansky-Pudlak syndrome), and ILD associated with benign proliferation of pulmonary lymphoid tissue, namely follicular bronchiolitis and granulomatous-lymphocytic interstitial lung disease.

Methods: Electronic searches of PubMed and Google Scholar using specific keywords were conducted. Articles underwent screening for relevance, covering review articles, meta-analyses, systematic reviews, case series, prospective studies, society guidelines, editorials in peer-reviewed journals; scientific books on the subject. The data included was limited to English and Spanish publications.

Key Content and Findings: Despite the low prevalence of these diseases, the increased recognition of radiological patterns, pathological features, and diagnostic procedures, have permitted their better characterization. This review highlights epidemiology, clinical presentation, diagnosis, natural history, and treatment.

Conclusions: Lesser-studied ILD represent a diagnostic and therapeutic challenge and can be frequently misdiagnosed. Also, due to the lack of randomized controlled trials, there are no well-established therapeutic options. Further studies or registries are needed to improve accurate diagnosis and management.

Keywords: Rare idiopathic interstitial pneumonias; acute fibrinous organizing pneumonia (AFOP); Hermansky-Pudlak syndrome (HPS); granulomatous-lymphocytic interstitial lung disease (GLILD)

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Introduction

Interstitial lung diseases (ILD) encompass a wide group of entities that affect the alveolar-capillary unit and, in some cases, the small airways and pulmonary vasculature (1). The heterogeneity of ILD and emerging descriptions of novel disorders and histological patterns have led to updated consensus of their classification and management by international scientific societies (2,3).

A specific ILD diagnosis usually requires a comprehensive, multidisciplinary clinical, radiological and/or histopathological approach. Its evaluation involves a detailed assessment of the patient's current and past medical history, environmental exposures, a physical exam, and the integration of several investigations (imaging, laboratory and pulmonary function testing). In some cases, further invasive testing such as bronchoscopy with bronchoalveolar lavage (BAL), and bronchoscopic or surgical lung biopsies may be required. However, despite all the currently available diagnostic tools, up to 25% of patients with ILD remain unclassified (4).

For epidemiological and practical purposes, ILD can be divided into three main groups: (I) idiopathic interstitial pneumonias (IIPs); (II) ILD due to a known cause, which includes systemic autoimmune diseases, those caused by therapeutic interventions (e.g., ILD due to drugs or radiation therapy) and disorders linked to environmental exposures [e.g., pneumoconiosis, hypersensitivity pneumonitis (HP)]; and (III) primary disease-related ILD, such as sarcoidosis (1).

Among the over than 200 causes of ILD, there is a group of entities that are less well-known and less prevalent. Recent studies have revealed that some of these entities, such as pleuroparenchymal fibroelastosis (PPFE), are more common than initially thought (4,5). Therefore, acknowledging the importance and characteristics of these diseases will lead to their proper identification from others with similar clinical or radiological presentations. The correct diagnosis of these ILD has management and prognostic implications. In this review, we provide an overview of several of these less-studied ILD, focusing on their clinical presentation, diagnosis, clinical course, and treatment. We present this article in accordance with the Narrative Review reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-450/rc).

Methods

For this review, all authors agreed to include as "rare" ILDs with low prevalence in the published literature and based on the author's own experience. We conducted a comprehensive search of relevant articles published between January 2000 and January 2024 inclusive (except those mentioning or describing the disease for the first time). Databases used for the search included PubMed and Google Scholar. The keywords used to perform the search were: "Rare idiopathic interstitial pneumonias", "Lymphocytic interstitial pneumonia", "Pleuroparenchymal fibroelastosis", "Acute Fibrinous Organizing Pneumonia", "Bronchiolocentric Interstitial Pneumonia", "Follicular Bronchiolitis", "Hermansky-Pudlak syndrome", "granulomatous-lymphocytic interstitial lung disease". This review encompassed review articles, meta-analyses, systematic reviews, case series, prospective studies, society guidelines, editorials in peer-reviewed journals; scientific books on the subject. Key data on the following aspects were collected: epidemiology, clinical features, diagnostic approach and management. The search was restricted to capture only full manuscripts published in English and Spanish. Information used to write this paper was collected from the sources listed in *Table 1*.

Rare IIPs

In 2002, a panel of experts from the European Respiratory Society and the American Respiratory Society published a consensus document in which IIPs were classified and defined for the first time (2). In 2013, this consensus was updated with the introduction of PPFE and lymphocytic interstitial pneumonia (LIP), which were both included in the section of rare IIPs (3). In this updated classification, two new histological patterns were also described: acute fibrinous organizing pneumonia (AFOP) and bronchiolocentric interstitial pneumonia.

LIP

LIP is a clinical-pathological entity that is part of the spectrum of non-neoplastic lymphocytic pulmonary diseases (3,6-8). LIP was first described in 1969 by Carrington and Liebow (9) and it is characterized by a polyclonal lymphocytic infiltration of the interstitium by B and T cells, which distinguishes LIP from lymphoma; there can also be hyperplasia of bronchus associated lymphoid tissue and occasional non-necrotizing granulomas, but they are usually inconspicuous (10,11). Cysts in LIP may result from ischemia due to vascular obstruction, post-obstructive

Table 1 The search strategy summary

Items	Specification
Date of search	December 4, 2023 and January 02, 2024
Databases and other sources searched	PubMed and Google Scholar
Search terms used	"Rare idiopathic interstitial pneumonias", "Lymphocytic interstitial pneumonia", "Pleuroparenchymal fibroelastosis", "Acute Fibrinous Organizing Pneumonia", "Bronchiolocentric Interstitial Pneumonia", "Follicular Bronchiolitis", "Hermansky-Pudlak syndrome", "granulomatous-lymphocytic interstitial lung disease"
Timeframe	From 02 Jan 2000 to 02 Jan 2024 (except those mentioning or describing the disease for the first time)
Inclusion and exclusion criteria	Inclusion criteria: review articles, meta-analyses, systematic reviews, case series, prospective studies, society guidelines, editorials in peer-reviewed journals; scientific books on the subject. The material included comprised both English and Spanish language sources
	Exclusion criteria: articles from news media and online blogs
Selection process	The selection process was conducted independently by all authors. The consensus was reached through discussions among the researchers. The included data were chosen based on our expertise

bronchiolectasis, or bronchiolar compression by lymphoid tissue resulting in focal lung hyperinflation due to a check-valve mechanism (8). LIP was included in the 2002 consensus as one of the seven IIPs. However, the experience accumulated in recent years shows that LIP is very rare. For this reason, the updated classification placed LIP in the rare IIPs section (3).

The incidence and prevalence of LIP are unknown (6-8). LIP is idiopathic in less than 20% of cases. The majority of cases have been associated with an underlying disease, such as Sjögren's syndrome (up to 25% of cases), rheumatoid arthritis, systemic lupus erythematosus, Hashimoto's disease, autoimmune hemolytic anemia, primary biliary cirrhosis, human immunodeficiency virus (HIV) infection, and in common variable immunodeficiency (CVID) and granulomatous-lymphocytic interstitial lung disease (GLILD) (4,6-9,12,13). LIP has also been associated in case reports or series to chronic hepatitis, allogeneic bone marrow, transplant-related graft versus host disease, and amyloidosis (12,14-16).

This disease is more frequent in women. The average age of presentation has been reported between 30 and 50 years of age (4,6-8). It may be seen as an incidental finding in imaging studies but it is usually associated with insidious exertional dyspnea and dry cough. It can also manifest with pleuritic pain and systemic symptoms such as arthralgias, weight loss, fever, night sweats, and fatigue. On physical examination, crackles and prolonged expiration have been described (12,13). Clubbing is infrequent with this entity (8).

Most patients with LIP have a restrictive ventilatory pattern with decreased carbon monoxide diffusing capacity (DLco) in pulmonary function tests (12). High-resolution computed tomography (HRCT) findings include ground-glass opacities, thin-walled cysts, poorly defined centrilobular nodules, and nodular thickening of the interstitium along the lymphatic ducts (*Figure 1A,1B*). Pulmonary cysts are smaller than 30 mm, randomly distributed, and occupy less than 10% of the lung parenchyma (4,8,14). They have been described in up to 80% of cases and their presence can help to differentiate LIP from other entities such as lymphoma (4,6,7).

On BAL there is usually lymphocytosis, which is a non-specific finding common to other ILD such as HP, drug-related ILD, and sarcoidosis, but the clinical and radiological picture in these conditions usually differs from that in LIP (4). A definitive diagnosis of LIP requires a surgical lung biopsy (3). Histologically, LIP is characterized by extensive polyclonal interstitial lymphocytic infiltration into the alveolar septa with T lymphocytes, plasma cells, histiocytes, and macrophages (*Figure 1C,1D*) (7). Immunohistochemical and/or molecular techniques may need to be performed to exclude alternative diagnoses such as lymphoma (9,11).

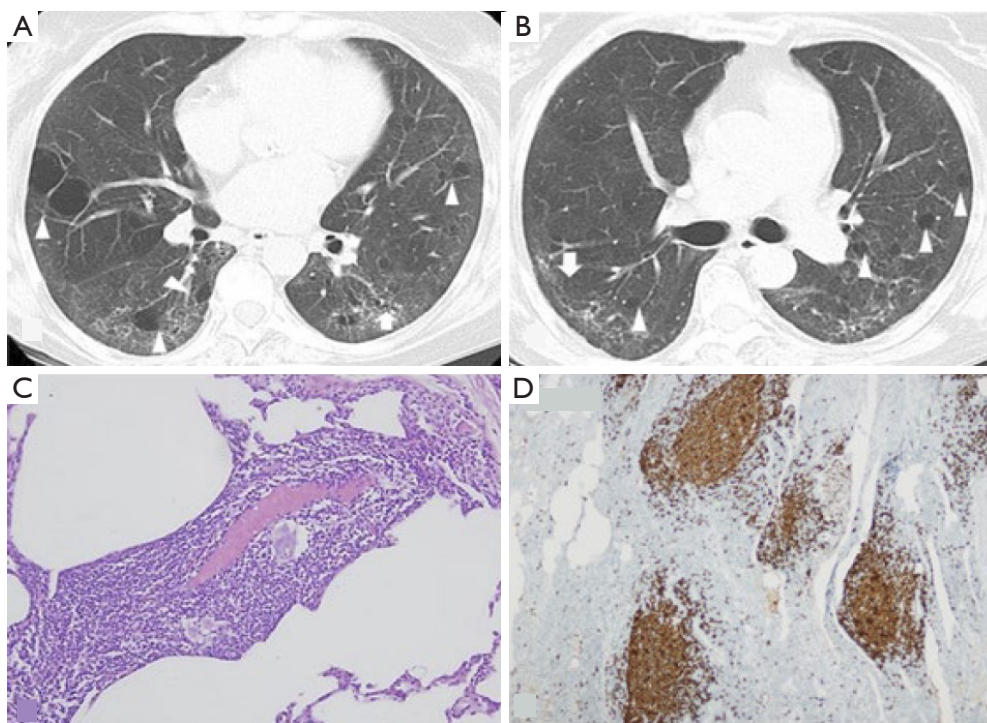Once the diagnosis of LIP is established, underlying

Figure 1 Lymphoid interstitial pneumonia. (A,B) HRCT views showing scattered randomly distributed thin-walled cysts (arrowheads) and interspersed patches of ground glass-opacification (arrows). (C) The biopsy shows thickened septa with chronic inflammation and the presence of abundant mature lymphocytes (hematoxylin eosin staining, ×2) and (D) CD20 (immunohistochemical staining, ×2). Courtesy of Dr. J. L. Mate. HRCT, high-resolution computed tomography.

conditions should be investigated through serology testing: cell blood count, anti-Ro/Sjögren's syndrome antigen A (SSA), anti-La/Sjögren's syndrome antigen B (SSB) antibodies, antinuclear antibodies, double-stranded DNA antibodies, rheumatoid factor, anti-citrullinated peptide antibodies, liver function tests, serum immunoglobulins (Igs), T3, T4, thyroid stimulating hormone (TSH), HIV-1/HIV-2 immunoassay, and when appropriate, rheumatology referral.

Data from published series on the natural history of LIP are heterogeneous. It can vary from asymptomatic presentation and resolution without treatment to progressive disease, with the development of pulmonary fibrosis with respiratory failure and death. Close follow-up is recommended for asymptomatic patients. It has been reported that 5% of cases can progress to lymphoma (4,6), however, the frequency of this progression is difficult to assess because low-grade lymphomas may mimic LIP (17). The estimated median survival of LIP is 11.5 years (6,12).

Regarding therapeutic management, the main objective is to control the subjacent disease associated with LIP. There are no controlled clinical trials in the literature and data on treatment comes from case reports or case series; hence the treatment for LIP is not well established. The most widely used treatment has been oral corticosteroids (prednisone or equivalent) at a dose of 0.75 to 1 mg/kg/day for 8 to 12 weeks, followed by a progressive taper to 0.25 mg/kg/day over 6 to 12 weeks (4,6-8). Stabilization has been reported in up to 60% of patients. Pneumocystis jiroveci prophylaxis is recommended. As an alternative treatment, or to reduce the dose of corticosteroids, various immunosuppressants (cyclophosphamide, azathioprine, mycophenolate, and rituximab) have been used with variable responses (6). The use of antiretroviral drugs has led to successful treatment in patients with secondary LIP due to HIV infection (17).

PPFE

PPFE is an entity with very particular clinical, radiological, and histological features. This entity was formally labeled PPFE in 2004 by Frankel *et al.* (18). Its real prevalence and incidence are not known, probably due to misdiagnosis (19).

PPFE is characterized by fibrosis and elastosis of the visceral pleura and subpleural parenchyma predominantly affecting the upper lobes (*Figure 2A,2B*). Its pathogenesis is unknown, although it has been suggested that PPFE is the result of the interaction of various factors such as immunological dysfunction, infections, environmental, occupational and/or pharmacological exposures that act as triggers in genetically susceptible individuals (20,21). There is no clear gender predominance. It affects young adults more frequently, although in the published series there is a wide age range, and it has also been described in children (20-23). Smoking is not associated with the development of the disease, while chronic or recurrent bronchopulmonary infection (especially by *Aspergillus* and non-tuberculous mycobacteria), exposure to asbestos, aluminum or organic antigens can act as risk factors (5,24).

Aside from its idiopathic presentation, PPFE may have a familial distribution. There are cases associated with idiopathic pulmonary fibrosis, telomeric syndromes, and gene mutations related to telomere maintenance, such as telomerase reverse transcriptase (TERT), telomerase RNA component (TERC), regulator of telomere elongation helicase 1 (RTELI) (25,26). Non-idiopathic PPFE is associated with a wide variety of conditions, including HP, lung transplant (LT), bone marrow haematopoietic stem cell transplantation, autoimmune diseases, radiotherapy, and chemotherapy (especially with alkylating agents) (24,27). Some authors consider that PPFE is a new pathological phenotype within the spectrum of chronic graft dysfunction (21,24).

Clinically, it shares common symptoms with IIPs, such as dyspnea on exertion, dry cough, and weight loss. Clubbing and dry crackles on auscultation are rare, although they may appear when the disease progresses or when PPFE coexists with other fibrosing interstitial pneumonias (5,19,21,24,27,28). A decrease in the anteroposterior diameter of the rib cage or "flattened chest" (platy thorax) is a common sign that is associated with disease progression (19,28-31). In some patients, the suprasternal notch deepens noticeably (19) (*Figure 2C*). It has also been described that patients with PPFE usually have a low body mass index (BMI) (27-29). Spontaneous or iatrogenic pneumothorax is a frequent complication of this disease (18-21).

Similar to most IIPs, there is a restrictive pattern in pulmonary function tests with a decrease in DLco. However, an increase in the residual volume (RV) and the total lung capacity (TLC) ratio is also described, likely due to compensatory hyperinflation in the lower lobes as a result of the volume loss caused by fibrosis in the upper lobes (21,28). An RV/TLC ratio of ≥115% of the predicted value has recently been proposed as a diagnostic criterion for PPFE (30). Another suggested criterion was the association of the RV/TLC ≥80% with a BMI ≤20 kg/m^2 (32). These two parameters have been demonstrated to be useful in differentiating PPFE from other ILD such as idiopathic pulmonary fibrosis (IPF) (30-32).

Radiological findings are essential in the diagnosis of this entity. Irregular pleural thickening and fibrotic changes are observed in the subpleural parenchyma in the superior lobes (18,27-33). As the disease progresses, subpleural reticular and nodular opacities, platy thorax, ascending hilar retraction and diaphragmatic elevation can be observed, reflecting lung volume loss (21) (*Figure 2D,2E*). The presence of bullae or cysts in the upper lobes and bronchopleural fistulas are a risk factor for the development of pneumothorax (19) (*Figure 3A*). The signs of fibrosis (reticulation, traction bronchiectasis and architectural distortion) can progress and spread to the remaining lung fields (21,24,27).

The most relevant histological findings of PPFE are visceral pleural fibrosis and parenchymal and subpleural intra-alveolar fibroelastosis, predominantly in the upper lobes (5,18,30). Elastosis is more profuse than in other IIPs such as IPF (24). The transition between lesions and the normal parenchyma is usually abrupt (*Figure 3B*). There may be some fibroblastic foci and a variable amount of lymphocytic infiltrate (24,30). As with the radiological findings, the coexistence of other histological patterns, such as usual interstitial pneumonia (UIP), can be observed (19,31). When PPFE presents as a complication of LT or bone marrow haematopoietic stem cell transplantation, it can be accompanied by findings of bronchiolitis obliterans/ obliterative bronchiolitis (OB) or acute alveolar damage (18,33).

Although the accurate diagnosis of PPFE requires histological evaluation, a diagnosis of PPFE is most commonly achieved by identifying characteristic abnormalities on HRCT, avoiding the risks related to surgical lung biopsy (19). Hence, the importance of making multidisciplinary ILD teams aware of the clinical, functional, and radiological features of PPFE (22-24). Cryobiopsy emerges as a safe technique that can be useful for reaching a diagnosis with the relevant staining techniques (29) (*Figure 3D*). Regarding BAL findings, Oda *et al.* reported normal cell counts with slight lymphocyte elevation (34), however, no characteristic cell patterns have been described in other series (29,31).
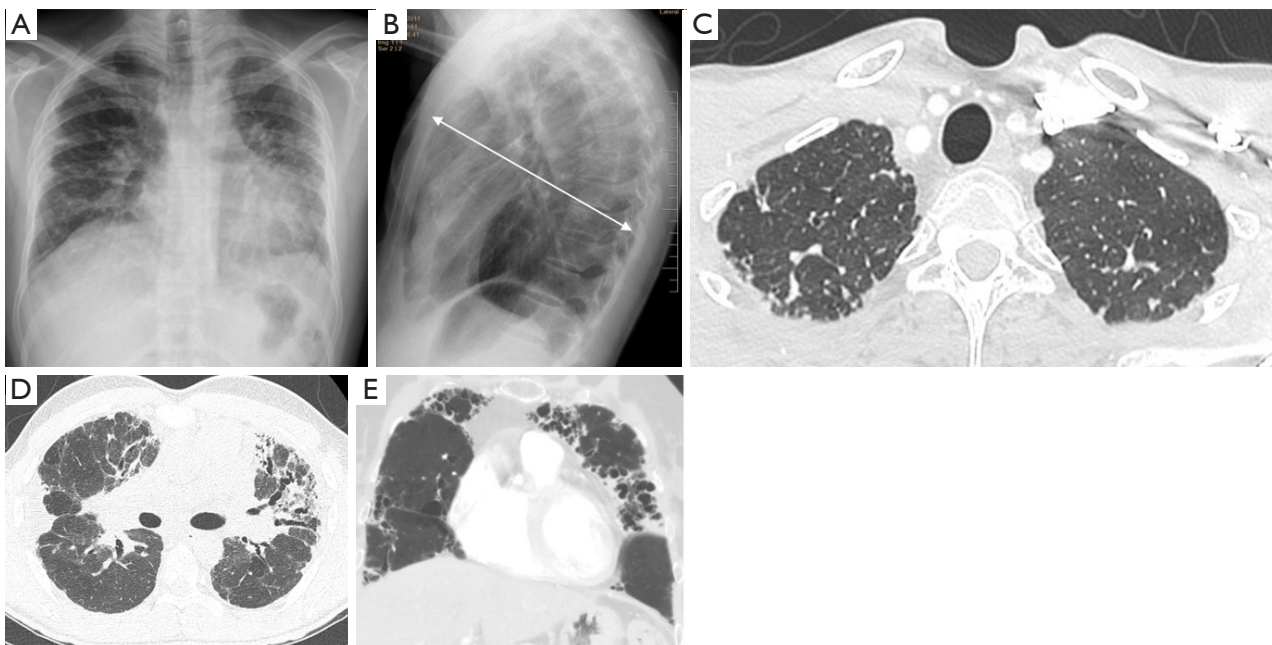
Figure 2 Pleuroparenchymal fibroelastosis. (A) Chest radiography shows upper-lobe volume loss, distortion of the pulmonary hila, as well as biapical pleural thickening. (B) Lateral view shows flattening of the chest, observed by the decreased anteroposterior diameter of the rib cage (arrow). (C) A prominent supra-sternal notch due to decreased volume in the upper thoracic region and ongoing weight loss (arrowhead). (D) HRCT and (E) HRCT coronal reconstruction section show pleural thickening and signs of pulmonary fibrosis, mainly in the left upper lobe, with multiple traction bronchiectasis, superimposed with ground-glass opacities. HRCT, high-resolution computed tomography.
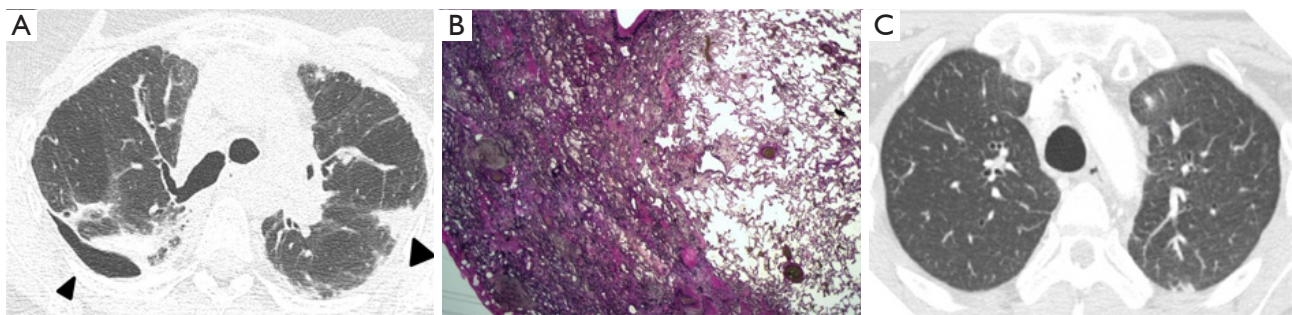

Figure 3 Pleuroparenchymal fibroelastosis. (A) HRCT demonstrates pleural thickening and right pneumothorax (arrowheads). (B) Microscopic examination of explanted lung demonstrates dense pleural and subpleural fibrosis with abrupt transition to non-affected pulmonary parenchyma Weigert-Van Gieson stain ×4. Courtesy of Dr. I. Sansano. (C) HRCT after lung transplantation. HRCT, high-resolution computed tomography.

PPFE is generally a progressive disease and occasionally progresses rapidly causing respiratory insufficiency and death. Patients with idiopathic or familial PPFE and those with a UIP pattern, HP, other ILD, or history of chemotherapy have a particularly poor prognosis (19,31-34). Treatment with corticosteroids and immunosuppressive therapy have been used empirically without presenting satisfactory results (31). Functional stabilization after treatment with pirfenidone or nintedanib has been reported (27,35-37). However, a significantly faster decline in forced vital capacity (FVC) has been described in patients with PPFE and UIP pattern on antifibrotic treatment compared with IPF patients (36). Non-pharmacological measures, such as vaccination, rehabilitation, and oxygen therapy,

should be part of the management of patients (*Figure 3C*). LT is a viable option in cases that meet the corresponding criteria, however, the follow-up and prognostic data in this regard are still very limited (38). According to case reports published to date, long-term outcomes are similar to those of patients with other transplanted ILD (29,39-41).

Histological patterns

AFOP and bronchiolocentric interstitial pneumonia are considered rare histological patterns and were not included as separate clinical entities in the 2013 classification (3). This is because they were not sufficiently well characterized, and it was thought that they could be variants of other interstitial pneumonias or be associated alterations (4).

AFOP

Since its description by Beasley *et al.* in 2002 in a series of 17 patients, more than a hundred cases have been published in the literature, which has deepened our knowledge regarding the particularities of AFOP (42-53). It is considered to be a histological pattern within the spectrum of acute or subacute lung injuries (42). It is characterized by the deposition of intraalveolar fibrin associated with organizing changes that more frequently affect the lower lobes. In its original description, the mortality rate was 53%, which is similar to that of adult respiratory distress syndrome (42). Recently it has generated interest because it is a pattern described in patients with coronavirus disease 2019 (COVID-19) and has previously been reported in other epidemics such as severe acute respiratory syndrome (SARS) (46,47).

AFOP can be idiopathic or secondary to a wide variety of entities, including autoimmune diseases, infections, malignancies, organ transplantation, environmental and pharmacological exposures (*Table 2*) (42-53).

According to published cases, there is a slight predominance in men than in women (49). There is a wide range in the age of presentation, but the age group most frequently described is between 50 and 70 years of age, although there have been also cases reported in children (49).

Clinically, there are two forms of AFOP: one with severe onset and rapid progression to respiratory and multi-organ failure with a high risk mortality; the other with semi-severe and less aggressive presentation (42-53). Symptoms are nonspecific and include cough which can be either dry or productive, dyspnea, fever, and chest pain. Radiological

findings are variable, the presence of patchy or mass-like airspace consolidation is the most frequent pattern (52). Ground-glass opacities, reticular and linear opacities, and nodules with air bronchograms or with a miliary pattern have also been described (43-47,52) (*Figure 4A-4C*). BAL findings might vary according to the underlying cause of AFOP, but no characteristic pattern has been described. Since both clinical and radiological findings are nonspecific and can be confused with common processes such as community-acquired pneumonia, obtaining a histological tissue sample is essential for an accurate diagnosis (3,42,49). In addition to transbronchial biopsy or surgical lung biopsy by video-assisted thoracoscopy (VATS), other techniques, such transbronchial lung cryobiopsy can be used (48,49,51,52). Endobronchial ultrasound (EBUS) or computed tomography (CT)-guide biopsy may occasionally lack adecuacy for an accurate diagnosis.

The main histopathological characteristics of AFOP are the presence of intra-alveolar fibrin "balls", organizing changes similar to those observed in organized pneumonia (OP), and an irregular distribution within the lung parenchyma (42-44,51) (*Figure 4D*). These alterations can comprise up to 90% of the alveolar spaces in a tissue sample (48). Other features include inflammatory changes in the alveolar walls surrounding the fibrin areas, in the myxoid connective tissue in the alveolar septum, type II pneumocyte hyperplasia, and minimal changes in areas of lung tissue where there is no fibrin. AFOP often shows a more diffuse and uniform distribution throughout the lung parenchyma compared to the patchy distribution seen in OP. There are no hyaline membranes or eosinophilic inflammation, which distinguishes AFOP from diffuse alveolar damage (DAD) and eosinophilic pneumonia, respectively. Although fibrin deposition can be observed in DAD, it is not the most representative alteration, nor it is the presence of intra-alveolar fibrin "balls". Furthermore, there are diffuse changes in DAD, while AFOP presents with an irregular distribution (42,50). There are no granulomas or abscess formation.

Although AFOP is not a clinical diagnosis, patients with this histopathologic pattern have been treated with various therapeutic regimens, mainly with medium or high dose corticosteroids (prednisone or methylprednisolone) (42-53). Although there is no consensus on the treatment or its duration, an early start is important, especially in the severe presentation that has a worse prognosis (44,46,48,49,52). Patients requiring invasive mechanical ventilation have a mortality rate close to 100% (48).

Macrolides and immunosuppressants, such as cyclosporine,

Table 2 Causes associated with acute fibrinoid pneumonia (42-53)

Autoimmune diseases

  Inflammatory myopathies

  Anti-synthetase syndrome

  Systemic lupus erythematosus

  Sjogren's syndrome

  Undifferentiated connective tissue disease

  Ankylosing spondylitis

  Primary biliary cirrhosis

Infections

  Acinetobacter baumannii

  Aspergillus fumigatus

  Chlamydia pneumoniae

  Cytomegalovirus

  H1N1 influenza

  Haemophilus influenzae

  HIV

  Legionella pneumonia

  Penicillium citrinum

  Pneumocystis jirovecii

  Pulmonary tuberculosis

  SARS-CoV

  SARS-CoV-2 (COVID-19)

Hematologic disorders

  Lymphoma

  Leukemia

  Myelodysplastic syndrome

  Aplastic anemia

Transplant

  Lung transplant

  Allogeneic hematopoietic cell transplant

Occupational exposures

  Avian exposure

  Asbestos

  Coal

  Herbicides

Chronic diseases

  Poorly controlled diabetes mellitus

  Chronic kidney disease on dialysis

  Alcoholism

Table 2 (*continued*)

Table 2 (*continued*)

Drugs

  Amiodarone

  Bleomycin

  Everolimus

  Busulfan

  Nivolumab

  Decitabine

  Abacavir

  Trimethoprim/sulfamethoxazole

  Minocycline

HIV, human immunodeficiency virus; SARS-CoV, severe acute respiratory syndrome coronavirus; COVID-19, coronavirus disease 2019.

cyclophosphamide, and mycophenolate, have also been used with variable response (41-44,47,52). Surgical resection has been described, and LT has been used in cases refractory to medical treatment (51-53). There are insufficient data on long-term evolution of these patients.

Bronchiolocentric interstitial pneumonia

Since its first description by Yousem and Dacic in 2002 (54), the histopathologic pattern of airway-centered interstitial fibrosis (ACIF) has been labeled with different terms, including bronchiolocentric interstitial pneumonia, centrilobular fibrosis, and peribronchiolar metaplasia (54-60). Because the histological alterations are observed along the airways, Kuranishi *et al.* proposed the term ACIF as the most appropriate (60).

Published series are scarce and most included a small number of patients. To date, the largest series, with 68 patients, described ACIF being more frequent in non-smoking women with a mean age of 57 years (60). It has been related to environmental exposure to organic and inorganic agents, the presence of gastroesophageal reflux and in the context of HP or connective tissue diseases (54,60).

The main clinical findings are cough and dyspnea on exertion, usually a restrictive and sometimes obstructive or mixed ventilatory pattern, decreased DLco on pulmonary function tests, and arterial oxygen desaturation during exercise (54-63).

A wide variety of radiological signs have been described in chest HRCT, such as ground-glass opacities with
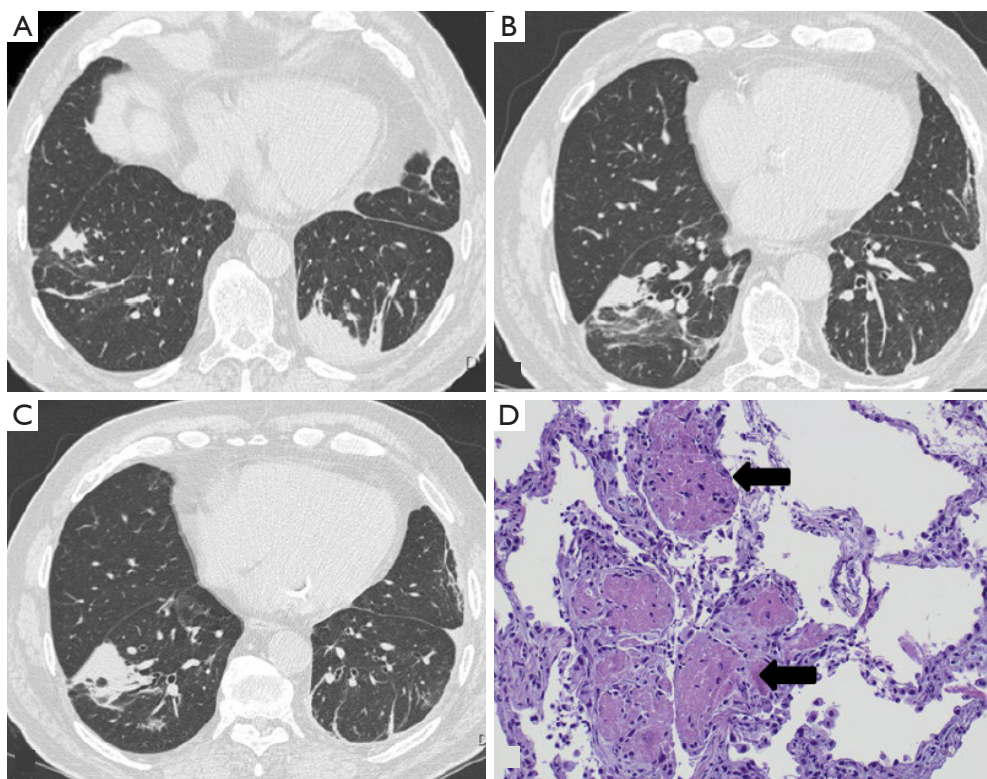
Figure 4 Acute fibrinous organizing pneumonia. (A-C) High-resolution computed tomography showing bilateral consolidations in lower lobes. (D) The biopsy shows mainly intra alveolar fibrin "balls" (black arrows). Hematoxylin-eosin staining ×2. Courtesy of Dr. López-Vilaró.

peribronchovascular distribution, thickening of the bronchiolar walls, bronchiectasis, reticulation, mosaic pattern, gas trapping, and in some cases, honeycombing. Conversely, HRCT can be normal in some cases (55-57,63). Histopathological findings consist of fibrosis and/or inflammation limited to the alveolar interstitium and bronchioles, superimposed with peribronchial metaplasia. These changes can extend around the central airways (3,53-60,64).

The differential diagnosis of ACIF includes diseases affecting small airways such as HP, respiratory bronchiolitis associated ILD (RB-ILD), OB, and diffuse panbronchiolitis (DPB). In HP granulomas are usually present, RB-ILD is characterized by the accumulation of pigmented macrophages within the respiratory bronchioles, OB causes bronchiolar obstruction/obliteration without extensive changes in the alveolar walls; and DPB is characterized by transmural lymphocytic and plasmocytic bronchiolar infiltrate, and lipid-laden "foamy" macrophages in respiratory bronchioles without alveolar wall involvement (54,56). OB and DPB usually cause an obstructive pattern on pulmonary function tests (occasionally a mixed or a restrictive pattern); and DPB

affects mainly Japanese individuals, frequently causes sinusitis and the disease responds to macrolides (65).

ACIF seems to be corticosteroid resistant, with inevitable loss of lung function and a high mortality rate in the absence of lung transplantation. Interestingly, one case report found that ACIF stabilized with clarithromycin after failure of systemic corticosteroids (66). The presence of cough, low oxygen saturation at rest, and histological findings such as fibroblastic foci and microscopic honeycombing, have been reported as predictors of worse survival (60).

Hereditary diseases with interstitial lung involvement

Hermansky-Pudlak syndrome (HPS)

HPS is a genetic disorder, named in 1959, with an autosomal recessive inheritance that belongs to the group of disorders of synthesis, trafficking and homeostasis lysosome. Ceroid lipofuscin, an amorphous, autofluorescent, lipid-protein material, accumulates in lysosomes in patients with HPS and has been identified in multiple organs including alveolar
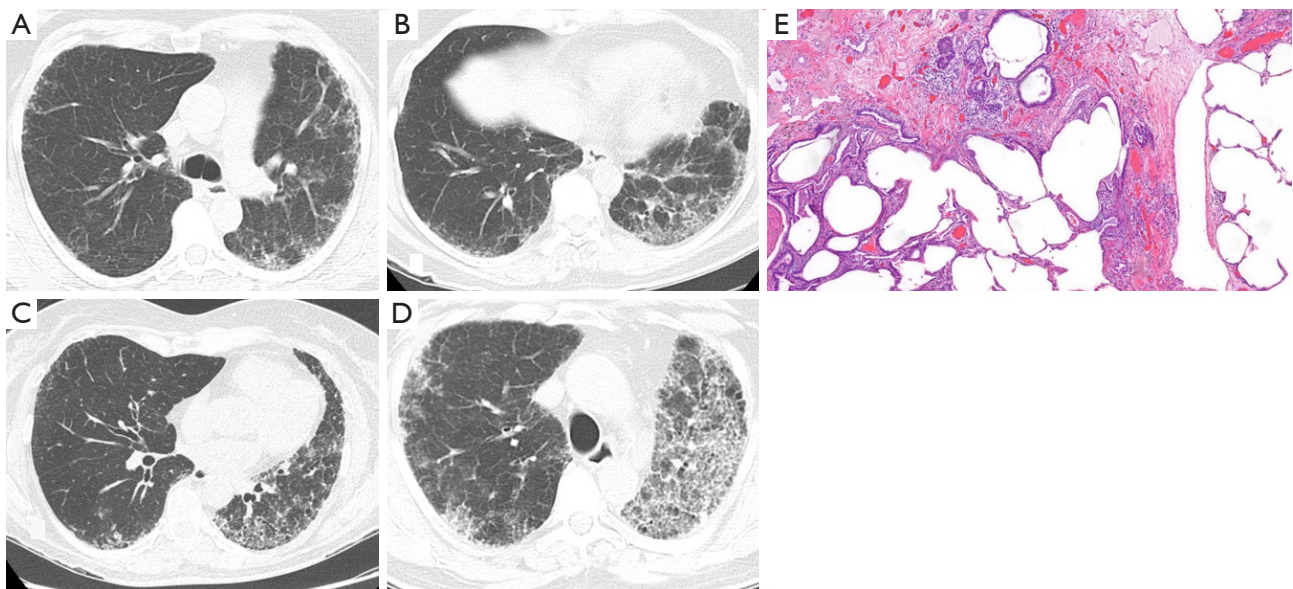
Figure 5 Hermansky-Pudlak syndrome. (A,B) HRCT shows subpleural reticulation (mainly in left lung), with traction bronchiectasis and honeycombing changes. (C,D) The patient presented acute exacerbation of pulmonary fibrosis. HRCT revealed patchy ground-glass infiltrates superimposed on fibrotic changes. (E) Left lower lobe lung biopsy: unspecific changes, normal areas alternating with others with inflammation and lax fibrosis with collagenized fibrosis. Hematoxylin-eosin staining ×2. Courtesy of Dr. J. L. Mate. HRCT, high-resolution computed tomography.

macrophages, lymph nodes, liver, spleen, bone marrow, the gastrointestinal tract, and the heart (67). It is characterized by oculocutaneous albinism, haemorrhagic diathesis due to platelet dysfunction, and in some cases, pulmonary fibrosis and granulomatous colitis (68-70).

Its prevalence is estimated at between one and two cases per million individuals worldwide, while in Puerto Rico its prevalence is estimated to be approximately one in every 1,800 people (68). To date, 10 HPS genetic subtypes [1–10] have been described in the medical literature (71). Subtypes 1, 2 and 4 are associated with the development of pulmonary fibrosis, which determines the prognosis and premature mortality in these patients (72).

Pulmonary fibrosis in HPS presents clinical, functional and radiological characteristics that are similar to IPF, but it usually debuts in the third decade of life, or during adolescence (70). Patients present with cough, exertional dyspnea and velcro crackles on pulmonary auscultation (72). HRCT shows subpleural and central infiltrates, ground-glass and diffuse opacities. Fibrosing radiological signs such as reticulation, traction bronchiectasis and honeycombing may be present as the disease progresses (73) (*Figure 5A,5B*). Acute exacerbations of pulmonary fibrosis have also been

described in HPS (69,71,74) (*Figure 5C,5D*). Although no typical pattern has been described in BAL of patients with HPS, Rouhani *et al.* (75) observed significantly higher concentrations of total BAL cells and alveolar macrophages in subjects with HPS-1 compared with healthy volunteers. This study also found high lung concentrations of cytokines and chemokines. Alveolar macrophages may show yellow-brown staining of ceroid accumulation (76,77). The diagnosis of HPS is established by its clinical signs, in particular, albinism (patients may have white or reddish hair, white or tan skin, and light blue, green, or hazel eyes), early onset nystagmus, and the absence of dense bodies in the platelets on electron microscopy (67-73). The platelet dense bodies play a role in platelet aggregation and their absence predisposes to bleeding diathesis (72). Lung surgical biopsy is not recommended due to the risk of bleeding (69). In cases in which the biopsy or pathological evaluation of the resected lung has been analyzed, the histopathological pattern is similar to that of UIP (73,74). It has been described fibroblastic foci, patchy dense fibrosis with alveolar architectural distortion due to the proliferation of fibromuscular tissue and infiltration of numerous inflammatory cells (78) (*Figure 5E*). In HPS patients,

features of pulmonary fibrosis include the apoptosis and dysfunction of alveolar type II epithelial cells which appear foamy because of the formation of giant lamellar bodies (79). A genetic study is useful to identify the mutation and to establish the prognosis (68-74).

Although no medications are currently approved for HPS pulmonary fibrosis treatment, pirfenidone and nintedanib have shown benefits in slowing the progression of pulmonary fibrosis in small series (77-80). LT is a therapeutic option, with satisfactory outcomes despite the risk of bleeding (79,80).

ILD associated with the proliferation of lung lymphoid tissue

Follicular bronchiolitis

Follicular bronchiolitis was first described in 1979 by Epler *et al.* (81) and is characterized on histopathology by hyperplastic lymphoid follicles along the walls of the bronchioles that encroach upon or obliterate the bronchiolar lumen. If the lymphoid follicles extend along the alveolar septa, the pathologic pattern is more consistent with lymphoid interstitial pneumonia. Both follicular bronchiolitis and lymphoid interstitial pneumonia represent a spectrum of reactive pulmonary lymphoid disorders suspected to be a result of repetitive antigen stimulation and polyclonal lymphoid expansion. Accordingly, follicular bronchiolitis is a common finding in airway inflammatory diseases, including bronchiectasis, cystic fibrosis, asthma, and chronic aspiration (82). Follicular bronchiolitis is also associated with conditions stimulating the immune system, including autoimmune diseases (particularly Sjogren's syndrome, rheumatoid arthritis, and systemic lupus erythematosus), immunodeficiency syndromes (particularly common variable immune deficiency and HIV), and infections (83). Rarely, follicular bronchiolitis can occur without any underlying etiology (11,84).

Follicular bronchiolitis can occur at any age. The idiopathic form usually occurs in middle-aged individuals, as does the form associated with connective tissue diseases, while the form associated with immunodeficiency tends to appear in young adults (83,84). Symptoms are usually nonspecific, taking the form of asthenia and weight loss. Respiratory symptoms include cough, progressive dyspnea, fever, and recurrent respiratory infections. Pulmonary function tests can show restrictive, obstructive or mixed patterns, or may be normal (84).

The main finding on chest radiography is bilateral nodular or reticulonodular involvement, but there can also be signs of air trapping such as hyperinflation. The most characteristic findings in HRCT consist of 1–12 mm centrilobular nodules associated with patchy, diffuse, bilateral ground-glass opacities (85) (*Figure 6A,6B*). Other findings are tree-in-bud pattern, bronchial dilation and wall thickening. Mosaic pattern, honeycombing and pleural effusion are rare findings in this entity (86-88).

BAL shows lymphocytosis and it may be useful in excluding others disorders such as infections or malignancy. One study analyzed the BAL fluid cytokine profiles in a pediatric population and showed increased inflammatory cytokines, specifically interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1), and interleukin 1 receptor antagonist (IL-1ra), whom are thought to play a role in the formation of the germinal centers near the airway that characterize follicular bronchiolitis (89).

A histological exam is required to achieve diagnosis. Lung surgical biopsy has proven to be the most reliable technique compared to transbronchial biopsy or other endoscopic techniques, due to the patchy distribution of the disease (87). Characteristic histopathological findings include lymphoid hyperplasia numerous lymphoid follicles associated with germinal centers along the bronchi and bronchioles, which are occasionally associated with an interstitial inflammatory infiltrate in the adjacent alveolar septa (87) (*Figure 6C,6D*). Nonspecific findings include foci of organizing pneumonia, obstructive pneumonia, or an intraluminal bronchiolar neutrophil infiltrate (87-90). A differential diagnosis must be made with LIP, lymphoid nodular hyperplasia and low-grade BALT lymphoma. Differentiating between these entities can be difficult and is usually based on the extent of the infiltrate (in follicular bronchiolitis the distribution is peribronchial or peribronchiolar, while in LIP this distribution is diffuse) (84). Histologically, lymphoid nodular hyperplasia is characterized as single or multiple masses, with a proliferation of germinal centers that tend to confluence, together with interfollicular plasma cells. Low-grade BALT lymphoma manifests with well-defined or multiple solid masses, and an infiltrate composed of monoclonal B lymphocytes. In some cases, there may be germinal centers (11).

The treatment and prognosis of follicular bronchiolitis depend primarily on the cause. In idiopathic cases, treatment is usually based on high-dose corticosteroid therapy. Macrolides have also been used and the prognosis is usually favorable (88,90,91). Some authors have proposed
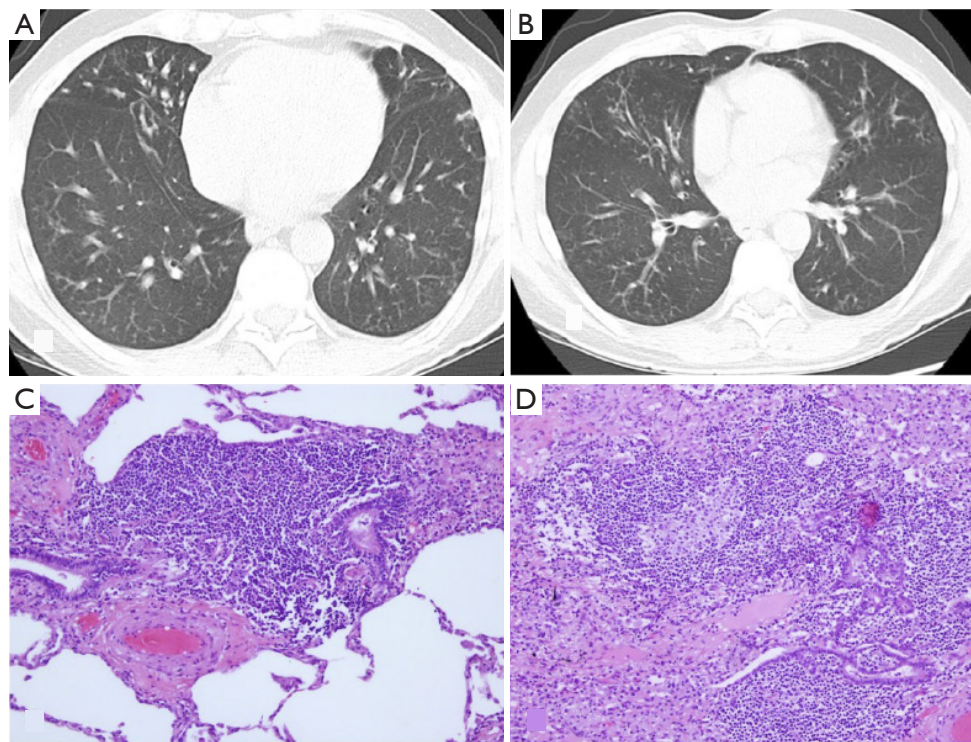
Figure 6 Follicular bronchiolitis. (A,B) The high-resolution computed tomography shows centrilobular nodules and peribronchiolar opacities with a "tree-in-bud" distribution. (C,D) The lung biopsy reveals lymphocytic infiltrates in germinal centers distributed around the bronchioles and extending to the interlobular septa, avoiding the alveolar septa. Hematoxylin-eosin staining ×4 and ×2. Courtesy of Dr. A. Hernández Gallego.

immunosuppressants such as azathioprine, methotrexate, or rituximab as an alternative to corticosteroid therapy in some patients (88). In patients with a known cause, treatment is that of the underlying disease such as autoimmune diseases or immunodeficiency syndromes. The prognosis in these cases is variable and depends on the underlying condition and its response to treatment (82,88,90,91).

GLILD

GLILD, first reported in 2004 by Bates *et al.* (92) in a retrospective review of 69 patients with CVID is the most common immunodeficiency in adults, with a prevalence of approximately one in every 25,000 individuals. CVID is characterized by persistently reduced serum concentrations of IgG, along with low IgA and/or IgM and poor or absent response to immunizations, in the absence of another immunodeficiency condition (13,93-95). The main immune defect is B-cell dysfunction but one third of patients have defects in T-cell function; however, the cause of these immune defects remains unclear (96). As a result of the immunodeficiencies, repeated respiratory

tract infections and bronchiectasis are the most frequent clinical-radiological manifestations of CVID. However, 10–30% of patients with CVID have pulmonary interstitial involvement with the histological features of GLILD (94), the most common ILD in patients with CVID and the one with the worst prognosis (94,97,98). GLILD has also been reported in patients with immunodeficiency associated with specific gene mutations (96).

Although asymptomatic cases have been described, GLILD usually manifests with exertional dyspnea and cough (94). Diffuse lymphadenopathy and splenomegaly (sometimes hepatomegaly) are frequent features on physical exam (93).

Pulmonary function tests can be normal or patients can have a restrictive pattern with decreased DLco. Periodic (e.g., annual) monitoring of pulmonary function tests is essential to assess disease progression and response to treatment. A change in DLco can be an early sign of GLILD, in fact, a change of 20% has been proposed as clinically significant 3 months after starting therapy (92-95).

The most frequent findings related to HRCT are nodules (varying from <5 to >5 mm) with a random distribution. Nodules frequently have a perilymphatic (peribronchovascular) distribution. These nodules can be solid or ground-glass, and can vary over time (94,96). Reticulation (septal thickening) (*Figure* 7*A*, 7*B*) and ground-glass opacities and areas of consolidation are also observed, predominantly in the lower lobes (96,97). There is typically hilar and mediastinal lymphadenopathy found on chest CT in patients with GLILD. Abdominal CT scan is indicated as GLILD patients frequently have diffuse adenopathy and splenomegaly and are at increased risk of developing lymphoma (93). Bronchiectasis is less frequent and fibrosis may appear if there is progression (97-100). Fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) imaging is a promising tool in the evaluation of GLILD. In a study performed by Fraz *et al.*, the patients with progressive GLILD had significantly greater pathologic features and more prominent pulmonary inflammation on HRCT and ^{18}F-FDG PET/CT scans as compared to patients with stable disease (101).

GLILD is an underdiagnosed entity and it may resemble other diseases such as sarcoidosis, granulomatous infections, ILD associated with autoimmune diseases (e.g., Sjögren syndrome or rheumatoid arthritis), HP, and lymphomas (98). Surgical lung biopsy, particularly video-assisted thoracoscopic surgery is the recommended diagnostic test due to a higher yield than transbronchial biopsy and lower complication rates than open lung biopsy (94-96). Transbronchial lung cryobiopsy has recently been described as a less invasive approach to diagnosing GLILD (102,103). Performing BAL is recommended to rule out other entities (94,104). In a systematic review conducted by Bintalib *et al.* significant lymphocytosis >20% was seen among 78% of patients (105). Furthermore, in cases where lymphocyte phenotyping was conducted a higher percentage of B cells was revealed, particularly CD21low. In sarcoidosis, there is no elevation in B cells. Sarcoidosis and GLILD can be easily distinguished by assessing serum immunoglobulins, which are elevated in sarcoidosis and reduced in GLILD (93-104). If histopathology is worrisome for malignancy, B cell clonality studies should be performed to exclude lymphoma.

GLILD histology is characterized by lymphocytic interstitial pneumonitis, non-necrotizing granulomas, follicular bronchiolitis, peribronchiolar lymphocytic inflammation and/or organizing pneumonia (*Figure* 7*C*). Interstitial fibrosis has also been reported (94,106).

GLILD is associated with reduced survival in patients with CVID. As a result, early detection and ongoing follow-up with pulmonary function tests and chest HRCT are the preferred monitoring approaches (94-96). A recent consensus statement of the British Lung Foundation/United Kingdom Primary Immunodeficiency Network recommended immunoglobulin replacement therapy for GLILD in symptomatic patients, as well as in asymptomatic patients with abnormal or deteriorating lung function (94). While immunoglobulin replacement therapy aimed to maintain normal serum IgG levels reduces recurrent infections, there is no evidence that it prevents the development of GLILD or other autoimmune/inflammatory conditions associated with CVID (107). Other therapeutic strategies for GLILD are heterogeneous and essentially based on expert consensus and data from small case series or case reports (108). Oral corticosteroids such as prednisone at doses of 0.1–1.0 mg/kg/day have been suggested as first line treatment (94) (*Figure* 7*D*). Smits *et al.* (109), observed that induction therapy with high-dose corticosteroids (≥0.3 mg/kg prednisone equivalent) improved HRCT scans and pulmonary function test in 56 patients with GLILD. However, most series have reported that although GLILD may initially respond to glucocorticoids, relapses frequently occur when doses are reduced, and side effects are common (108-110). Various drugs such as azathioprine, mycophenolate, methotrexate, cyclosporine and infliximab have been used as a second line treatment, with variable responses, when corticosteroids fail to induce remission, or they cause significant side effects. Some cases have a satisfactory response to rituximab (110-112).

Combination therapy with rituximab and either azathioprine or mycophenolate has been reported as a potentially useful treatment regimen in patients with CVID and GLILD (110).

There is still controversy about the optimal treatment of GLILD. Recently, the European GLILD network (e-GLILDnet) (113) published a survey to determine the most important areas for research in GLILD. The survey revealed disparities in follow-up and criteria for initiating immunosuppressive therapy in these patients. Clinicians treating GLILD often do not have access to standardized protocols, leading to variations in the use of steroids for remission-induction and maintenance therapy. Additionally, the survey found that there were disparities in defining the optimal time interval for follow-up and how to follow asymptomatic patients not requiring therapy. This
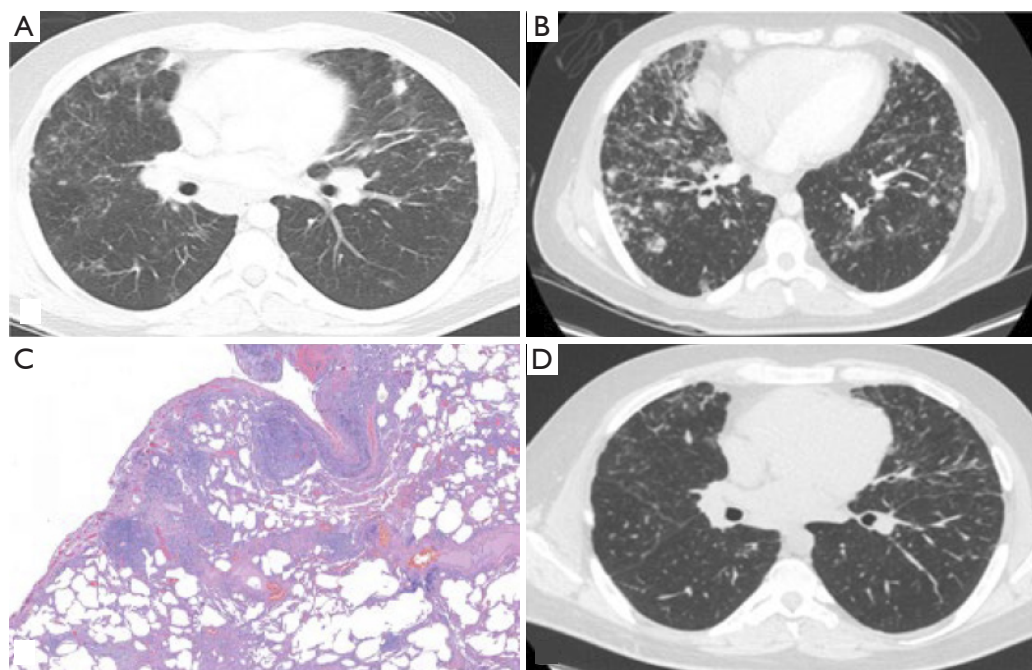
Figure 7 GLILD. (A,B) HRCT shows multiple bilateral nodular images and ground-glass opacities with peribronchovascular distribution. (C) Lung biopsy. Peribronchiolar and interstitial lymphocytic infiltration in GLILD. There are nodular lymphoid aggregates associated with bronchioles and dense, nodular and diffuse interstitial lymphocytic infiltration. Hematoxylin-eosin staining ×4. Courtesy of Dr. J. L. Mate. (D) HRCT 6 months after starting treatment with immunoglobulins replacement and prednisone showing improvement of ground glass opacities and interstitial infiltrates in the lungs. GLILD, granulomatous-lymphocytic interstitial lung disease; HRCT, high-resolution computed tomography.

highlights the need for clear guidelines and standardized protocols for the management of GLILD to ensure consistent and effective treatment for patients.

Conclusions

The rare ILDs described in this review represent a diagnostic and therapeutic challenge. Because of their low prevalence and shared clinical and radiological features with other more common ILD, they can be frequently misdiagnosed. In addition, due to the lack of randomized controlled trials, there are no well-established therapeutic options.

This review provides clinicians with a summary of the most clinically useful features of rare ILDs and available therapeutic options. Achieving an early and accurate diagnosis is very important, especially since some of them are associated with a poor prognosis. Regarding the treatment, clinicians depend mostly on experts' opinions and a small series of reports as the available data is scarce and heterogeneous. Further studies or registries are needed to improve the understanding of these entities and enable clinicians to establish better diagnostic and management strategies.

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Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-450/rc

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