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RESEARCH ARTICLE

Evolving Concepts and Controversies in Interstitial Lung diseases: Update in 2023

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ABSTRACT

Recent studies elicited evolving concepts and controversies in interstitial lung diseases and proposed substantial changes in diagnostic and therapeutic approaches to interstitial lung diseases. Dr. Averill A. Liebow first coined the term usual interstitial pneumonia (UIP) in 1960's as distinct pathologic pattern of fibrosis in idiopathic pulmonary fibrosis (IPF), the prototype of progressive fibrosing interstitial lung disease with poor prognosis. Advances in omics led to a better understanding of molecular pathogenesis of UIP and shed light on various types of familial pulmonary fibrosis as well as familial IPF. The concept of progressive pulmonary fibrosis was introduced to acknowledge additional types of progressive fibrosing interstitial lung diseases with the clinical and pathologic phenotypes very similar to those of UIP/IPF. As such, some authors have proposed a paradigm shift by considering UIP as a stand-alone diagnostic entity to encompass other fibrosing interstitial lung diseases that undergo the same relentless progression as IPF. Cicatricial organizing pneumonia is a variant of organizing pneumonia that can be reminiscent of UIP on histopathology but usually follows a stable clinical course unlike UIP. There has been significant disconnection in fundamental understanding as well as diagnostic criteria of lymphocytic interstitial pneumonia among pathologists, pulmonologists and radiologists, which needs to be resolved. The concept and histopathologic criteria of granulomatous and lymphocytic interstitial lung disease are also elusive and require clarification as well. In this review, these topics will be covered based on current literature.

Keywords: idiopathic pulmonary fibrosis (IPF), usual interstitial pneumonia (UIP), familial pulmonary fibrosis, progressive pulmonary fibrosis, cicatricial organizing pneumonia (CiOP), lymphocytic interstitial pneumonia (LIP), granulomatous and lymphocytic interstitial lung disease (GLILD), American Thoracic Society (ATS), European Respiratory Society (ERS), Japanese Respiratory Society (JRS), Asociacion Latinoamericana de Torax (ALAT)

Introduction

Usual interstitial pneumonia (UIP) was first introduced by Liebow and Carrington over 50 years ago.[1] The early histologic classification distinguished 5 diffuse interstitial pneumonias which included UIP, desquamative interstitial pneumonia (DIP), bronchiolitis obliterans with interstitial pneumonia (BIP), lymphoid interstitial pneumonia (LIP) and giant cell interstitial pneumonia (GIP). The "usual" aspect of UIP indicated that it was the most common type of these interstitial pneumonias. Katzenstein and Myers eloquently described the histologic features of UIP in 1998,[2] which were incorporated into an international consensus statement in 2000[3] and laid the foundation for the current histopathologic criteria for diagnosing UIP.

The first international consensus on interstitial lung diseases (ILDs) was summarized by the 2000 ATS/ERS statement on the diagnosis and treatment of idiopathic interstitial pneumonias (IIPs),[3] which helped better understanding of ILDs and initiating the advances in omics (genomics, epigenomics, transcriptomics, proteomics and metabolomics) and opened the era of drug development. The first effective medications for IPF were approved in 2014 and now there are many promising drugs in phase 2 or 3 trials. The nomenclature for IIP classification facilitated effective communication in the setting of non-IIPs; use of UIP, nonspecific interstitial pneumonia (NSIP), DIP, organizing pneumonia (OP), and acute interstitial pneumonia (AIP) patterns for description of the similar findings in ILDs associated with underlying conditions (e.g. connective tissue disease, exposure-related, etc.) helped not only in research setting but also in clinical application by expanding antifibrotic therapy approved for UIP/IPF to other ILDs.

In the past, pathologic examination was the gold standard to classify ILDs but the role of high-resolution computed tomography (HRCT) emerged since the second ATS/ERS statement in 2013, which led to a significant decrease in the frequency of lung biopsies for diagnosing ILDs. Many typical cases of UIP now bypass histopathologic evaluation and the cases undergoing lung biopsies are mostly atypical and complex ones, causing challenges to pathologists. A recent official practice guideline by ATS/ERS/JRS/ALAT made a conditional recommendation regarding transbronchial lung cryobiopsy as acceptable alternative to surgical lung biopsy in centers with appropriate expertise.[4] Genetic profiling using transbronchial biopsy specimens has been introduced that completely bypasses morphologic evaluation.[5,6] No recommendation was made for or against this type of genomic classifier testing due to lack of consensus among the committee members.

Moreover, concept of certain ILDs has been changing. Some proposed to make UIP as a stand-alone diagnostic category regardless of the underlying cause.[7] A concept of progressive pulmonary fibrosis (PPF) has been also proposed. Familial ILD is now well recognized. Cicatricial organizing pneumonia (CiOP) is more recently reported variant of organizing pneumonia (OP), which is important to differentiate from UIP given its very different prognostic implication. There have been attempts to clarify the significant disconnections between pathology and radiology arenas under the terminology of LIP and granulomatous and lymphocytic interstitial lung diseases (GLILD).

This review will cover selected clinically relevant topics in ILDs including evolving concepts in UIP, familial ILD, PPF and CiOP and controversies around LIP and GLILD based on current literature through primarily pathologists' point of view.

Selected Topics

I. *Usual Interstitial Pneumonia: Past, Present and Beyond*

Description of cardinal histologic features of UIP by Katzenstein and Myers[2] in 1998 served as the backbone of an international consensus statement in 2000, which paved the way to establish the current histopathologic criteria for diagnosing UIP.[3] The histopathologic criteria used to diagnose UIP by biopsy in the most current ATS/ERS/JRS/ALAT clinical practice guideline include a combination of the following: 1) patchy, dense fibrosis with architectural distortion (i.e., destructive scarring and/or honeycombing); 2) fibrosis that is predominantly subpleural and/or paraseptal in distribution; 3) the presence of fibroblast foci; and 4) absence of features to suggest an alternate diagnosis (such as granulomas, hyaline membranes, organizing pneumonia, airway-centered changes, lymphoid infiltrates, and/or chronic pleuritis).[4] If all criteria are met in a biopsy, it is considered diagnostic of UIP, while the presence of only some of these features is considered "probable UIP" in the absence of features to suggest an alternative diagnosis. This type of categorization has not been widely applied in routine pathology practice but may be useful in the clinical trial setting to recruit patients.

Idiopathic pulmonary fibrosis is currently understood to be a chronic, fibrosing interstitial pneumonia associated with histologic (and radiologic) features of UIP.[4] The term IPF should be reserved for cases of UIP, the most common IIP. Patients with IPF may undergo occasional episodes of acute respiratory worsening, referred to acute exacerbations, that manifest histologically as

diffuse alveolar damage or, less commonly, organizing pneumonia.[8]

The natural history of IPF is characterized by a progressive decline in pulmonary function with eventual death from either respiratory failure or a complicating comorbidity, with a median survival of 2 to 3 years from the time of diagnosis.[9] Early treatment attempts were based on the hypothesis that inflammation was a driving factor leading to lung injury and fibrosis; therefore, corticosteroids and immunosuppressive agents were given with the hope that they may slow disease progression but were eventually shown to have no benefit in patients with IPF. There was no compelling evidence for the use of any pharmacologic therapy in IPF patients until the early 2010s, when randomized control trials showed potential benefits in patient outcomes (disease progression and rate of FVC decline) in IPF patients treated with either nintedanib, a tyrosine kinase inhibitor,[10,11] or pirfenidone, an inhibitor of transforming growth factor beta associated collagen synthesis.[12,13] These two medications, both often referred to as "antifibrotics," are conditionally recommended for use in IPF patients as of the 2015 treatment guidelines.[14]

Based on the ATS guidelines, UIP is exclusively intended to be the correlate of IPF; histologic findings that indicate other diseases (e.g. fibrotic HP, connective tissue disease (CTD)-related ILD) are considered not consistent with UIP.[15] This often leaves pathologists in a difficult position when they have to determine whether the degree of chronic inflammation, airway centered changes, and/or rare poorly formed granulomas would be acceptable for UIP or not in the cases demonstrating otherwise characteristic features of UIP.

Recently, a proposal has been made to consider UIP as a stand-alone diagnostic entity, whether in its primary form (IPF) or as a secondary process, based on either the radiologic or histopathologic findings.[7] The basis of this argument is that UIP pattern can be seen in other ILDs, especially fibrotic HP and CTD-associated ILD, and show similar clinical outcomes with a poor IPF-like prognosis.[16] Similarly, acute exacerbations of ILD are known to occur in the setting of rheumatoid arthritis-associated ILD[17] and fibrotic HP[18], with similar outcomes to acute exacerbations of IPF. They argued that such a lumping would be justified because there are striking similarities between primary and secondary UIP in the morphological or radiological appearance, clinical behavior, pathogenic pathways and the efficacy of anti-fibrotic therapy. Of note, a radiologic study showed that the presence of honeycombing alone on CT was sufficient to predict an IPF-like mortality in patients with fibrotic HP, CTD-ILD and unclassifiable ILD.[19]

II. *Familial Pulmonary Fibrosis*

Hereditary factors have long been suspected to play a role in the development of IPF with descriptions of familial cases of IPF dating back to 1907.[20] From then until the first ATS consensus statement on IPF in 2000, no specific genetic markers were identified.[3] As studying these familial clusters of IPF would potentially provide insight into the pathogenesis and possible treatment strategies for IPF, 'familial IPF' was formally defined in the 2000 ATS statement as at least two members of a primary biological family (parent, child, sibling) having clinical features of IPF and histologic confirmation; the histologic requirement appears to have subsequently been dropped but is not overtly stated in later ATS statements.

Other fibrosing interstitial lung diseases have also been observed to show clustering within families and are often included in studies looking at the hereditary aspect of these diseases. Idiopathic interstitial pneumonias, for example, have been reported in closely related family members in 2-20% of cases.[21-24] Additional terminology used to describe this broader cohort of fibrosing lung diseases includes the terms 'familial interstitial pneumonia', 'familial pulmonary fibrosis', 'familial/inherited interstitial lung disease', and, if limited to idiopathic lung diseases, 'familial idiopathic interstitial pneumonia.' This abundance of nomenclature has led to some cloudiness in the literature, but for the purposes of this paper, the term familial pulmonary fibrosis (FPF) will be used broadly to describe a familial pedigree that includes any form of pulmonary fibrosis (including IPF) and may include diseases and syndromes with systemic manifestations (e.g. Hermansky-Pudlak syndrome), in contrast to familial IPF, which only includes familial pedigrees with IPF, as previously defined.

Through this muddied lens, it is reported that the frequency of FPF may be as high as 20% of patients with pulmonary fibrosis.[24-26] When specifically assessed based on the subtype of fibrotic ILD, 20% to 25% of patients with IPF, 14% to 17% of patients with chronic HP, and 3% to 8% of patients with CTD-related ILD have a family history of pulmonary fibrosis.[27-29] Interestingly, relatives in the same family can show different subtypes of fibrotic ILD.[30,31] In addition, the burden of FPF may be greater than suspected as evidenced by radiographic screening of the asymptomatic relatives of patients with pulmonary fibrosis, which found subclinical lung disease in 15 to 31% of cases.[32-34]

The widespread application of molecular testing in recent years has aided the study of diseases including those associated with pulmonary fibrosis. Many genetic risk variants have been identified that implicate a variety of disease pathways in pulmonary fibrosis and are particularly relevant to familial cases. The variants associated with pulmonary fibrosis can be placed into two broad categories based on their frequency in the population: common genetic variants, which are typically single nucleotide polymorphisms (SNPs), and rare genetic variants. The frequency of a variant within the population is inversely proportional to its impact on disease risk; therefore, the common variants confer a smaller effect size than the rare variants.[35] The result is that SNPs may contribute to overall risk but are insufficient to cause disease on their own, whereas cosegregation of rare variants are often found in FPF kindreds, suggesting a causal relationship.

Numerous common genetic variants associated with IPF have been identified, primarily through linkage analysis and genome-wide association studies. The most widely recognized is in the promoter region of the MUC5B gene, gain-of-function promoter variant rs35705950, whose association with pulmonary fibrosis was first described by Seibold et al in 2011 in a study that identified this genetic variant in 34% of their subjects with familial IIP, 38% of those with sporadic IPF, and 9% of their control subjects.[36]

The first reports of rare genetic variants in pulmonary fibrosis were those associated with dysfunctional surfactant metabolism, including variants in SFTPC, SFTPA1/2 and ABCA3.[37] The pattern of inheritance is autosomal dominant for SFTPC and SFTPA1/2 and autosomal recessive for ABCA3.[38] Families with a rare surfactant-related gene variant may show a wide range of disease onset, from infancy to late adulthood, and can show varied histologic and radiologic patterns of fibrosis including UIP, NSIP, and DIP.[37,39,40] As surfactant production is limited to the lung, these rare variants do not result in any extrapulmonary manifestations.

The other major biologic pathway implicated in FPF through rare genetic variants is telomere maintenance, estimated to be found in approximately 25% of FPF kindreds and includes variants in TERT, TERC, and numerous other genes.[41,42] Damaging variants in telomere-related genes are associated with systemic manifestations and are collectively referred to as telomeropathies, short telomere syndromes, or telomere biology disorders. Approximately 90% of individuals who carry an inherited mutation in a telomere maintenance gene develop chronic lung disease, typically pulmonary fibrosis but sometimes emphysema.[43] The most well-known telomeropathy is dyskeratosis congenita (DC), a pediatric disorder whose classic manifestations include nail dystrophy, abnormal skin pigmentation, and oral leukoplakia.[44] Bone marrow failure occurs in over 80% of patients with DC and is the leading cause of death; pulmonary fibrosis develops in approximately 20%, typically in early adulthood. Dyskeratosis congenita is often due to homozygous telomere-related gene mutations resulting in extreme telomere shortening and a younger age of onset; those with heterozygous telomere-related gene mutations typically present in adulthood with pulmonary fibrosis as the most common manifestation. Extrapulmonary manifestations similar to those in DC can be seen in these patients or relatives and include bone marrow dysfunction, liver disease and premature graying of hair.[45] The pulmonary fibrosis phenotype associated with telomere-related gene variants is variable but 50% develop IPF, whereas others develop chronic hypersensitivity pneumonia (7%-12%), connective tissue disease-associated ILD (2%-3%) or other IIPs (14-18%).[31,46]

It is noteworthy that patients with various forms of adult-onset sporadic pulmonary fibrosis are also enriched for rare telomere-related gene variants, having been found in approximately 10% of sporadic IPF, chronic HP, and rheumatoid arthritis-related ILD cases.[47-50] Short age-adjusted telomere length, which is often found in patients with FPF, has also been associated with sporadic cases of pulmonary fibrosis when compared to control subjects, which implicates short telomere length as a potential cause of pulmonary fibrosis.[51]

While there has been substantial progress in characterizing FPF through the identification of subgroups with characteristic genetic features, detailed studies of the pathologic features of FPF are sparse. In 2005, Steele et al reported on a study of families with idiopathic interstitial pneumonias[30] which included histopathologic assessment in some cases. They found considerable heterogeneity within families, with more than one histopathologic subtype of IIP identified in 45% of family pedigrees.

No histopathologic features that might differentiate familial and sporadic IIP cases have been identified until 2012, when Leslie et al performed a histopathologic study to characterize the features of familial IIP,[52] primarily focusing on familial IPF. They found that most of the patients had some histopathologic features commonly associated with UIP, but 60% of their cases did not qualify as UIP, mainly due to lack of temporal heterogeneity, and were considered to represent a form of unclassifiable fibrotic lung disease. This

study suggests there are histopathologic features that may differentiate sporadic and familial fibrotic lung disease, although prior to this study, familial IPF and sporadic IPF were thought to be clinically and histologically indistinguishable, apart from familial IPF possibly developing at an earlier age.[9] The implications of this study are that a pathologist should consider raising the possibility of FPF (or familial IPF) when a surgical lung biopsy shows an unclassifiable pattern of lung fibrosis. Secondly, if a patient with suspected familial IPF undergoes a surgical lung biopsy, then the histopathologic features could still be compatible with familial IPF even if classic features of UIP are not present.

III. *Concept of Progressive Pulmonary Fibrosis*

Fibrosing interstitial lung diseases are a diverse group of lung disorders characterized by interstitial fibrosis, of which IPF is often considered the prototype.[53] The remaining fibrosing ILDs may include other idiopathic interstitial pneumonias, autoimmune ILDs (e.g., rheumatoid arthritis-associated ILD), exposure related ILDs (e.g., HP, occupational exposures, medications), ILDs associated with cysts and/or airspace filling (e.g Langerhans cell histiocytosis) and sarcoidosis.[4] These other ILDs have typically been studied independently based on the underlying ILD subtype which, in contrast to IPF, often have less defined lung pathology that may or may not include interstitial fibrosis in all cases. There has been recent interest in studying fibrosing interstitial lung diseases as a group, as there is considerable overlap in the clinical, imaging and histopathologic features of these diseases. In particular, a subset of non-IPF fibrosing ILDs has been found to develop a progressive phenotype similar to IPF, with worsening of respiratory symptoms, decline in lung function and early mortality, often despite conventional treatment.[54-56] Initially described in 2017 as "progressive fibrosing ILDs",[57] the term "progressive pulmonary fibrosis" (PPF) was instead adopted in the 2022 ATS/ERS/JRS/ALAT clinical practice guideline.[4] Progressive pulmonary fibrosis was formally defined in that statement as occurring in patients with an ILD of known or unknown etiology, other than IPF, who have radiologic evidence of pulmonary fibrosis and satisfy specific criteria based on worsening respiratory symptoms, physiological evidence of disease progression, and/or radiological evidence of disease progression, occurring within the past year.[4] The authors stated that PPF is not considered a diagnosis and the criteria have only been associated with prognosis.

The idea of studying the disease characteristic (or phenotype) of progressive fibrosis without regard for the specific underlying ILD led to clinical trials evaluating the utility of antifibrotics, which had already proven of benefit in patients with IPF. In the INBUILD trial in patients with PPF, antifibrotic therapy with nintedanib resulted in a significant reduction in disease progression measured as the annual decline of FVC.[58] Pirfenidone was also found to reduce FVC decline in some patients with PPF based on the meta-analysis of two randomized control trials.[59,60] As a result of these trials, the subsequently published 2022 ATS clinical practice guidelines gave a conditional recommendation for nintedanib for the treatment of PPF in patients who have failed standard management, while further research was suggested to evaluate the utility of pirfenidone, as the findings of benefit from pirfenidone were considered very low quality evidence.

The idea of treating ILD based on the disease behavior without regard for the specific underlying ILD is novel and may have greater implications in the approach to patients with ILD. The authors of the ATS clinical practice guideline on PPF did explicitly state that they did not want to discourage clinicians from "rigorously trying to identify the underlying type of ILD before the initiation of therapy," but in practice this new treatment approach is likely to reduce the incentive of pursuing surgical lung biopsy to establish a definitive diagnosis of the underlying ILD. There have been efforts made to analyze the clinical trials data based on specific ILD subgroups within PPF, but these studies did not have enough power to provide evidence of benefit.[61,62]

Although the definition of PPF does not include criteria that involve pathologic findings, a question that may be worth evaluating is whether there are any pathologic findings that correlate with progressive fibrosis. The obvious candidate is the UIP histopathologic pattern, as there is already compelling evidence that patients with non-IPF ILDs showing UIP pattern may follow the same disease course as IPF, but the direct association with the PPF phenotype has yet to be established.[7]

IV. *Cicatricial Organizing Pneumonia: A Mimicker of UIP or other Fibrosing ILDs*

Organizing pneumonia (OP) is characterized histologically by the accumulation of mucopolysaccharide-rich plugs of proliferating fibroblasts in distal air spaces (bronchioles, alveolar ducts, and alveoli). These plugs (or polyps) are sometimes referred to as Masson bodies. Organizing pneumonia is a non-specific pattern of acute lung injury; it can be seen in a wide variety of clinical settings including aspiration, various infections, adverse drug reactions, reaction to radiotherapy, following inhalation of toxic

compounds, systemic connective tissue diseases and distal to obstruction.[63-75] OP can occasionally be seen at the periphery of other disease processes such as neoplasms and infarcts.[64,65,69]

When OP is the primary pathologic finding in the idiopathic setting, it is referred to as cryptogenic organizing pneumonia (COP). Cryptogenic organizing pneumonia is listed as a major type of idiopathic interstitial pneumonia (IIP) in the most recent official statement on IIP classification by the ATS/ERS and has characteristic clinical, radiologic, and pathologic features.[76]

Cryptogenic organizing pneumonia typically presents in middle aged adults as a subacute illness of short duration (usually less than 3 months) with cough and dyspnea.[77-80] Radiographically, COP is characterized by patchy and often migratory consolidation and/or ground glass opacities in a peripheral or peribronchial distribution without evidence of honeycomb change or traction bronchiectasis. Pathologically, COP is characterized by OP, as described above, but other important features include preservation of the underlying lung architecture and a uniform temporal appearance; pertinent negatives include findings that would suggest other diagnoses such as interstitial fibrosis, granulomas, necrosis or hyaline membranes.

The majority of patients with COP have both symptomatic and radiologic resolution of the disease with corticosteroid therapy.[64,77] Between 10-20% of patients with COP have progressive disease.[76,81-83] A poor outcome in COP has been tied to an assortment of clinical findings, as well as reticulonodular/nodular disease on radiology, but pathologic assessment of these unresponsive cases has not been well defined.[77,84,85]

In 1997, Yousem et al performed a small study on biopsies from patients with steroid non-responsive COP[86] and noted they were more likely to have some degree of thickening and fibrosis or alveolar septa; as well, most of these patients showed dense hyalinization and fibrosis of the central cores of the organizing pneumonia. Yousem returned to this observation in 2017 when he retrospectively examined cases of COP to find those that showed dense lamellar intraluminal collagen (which he described as having a "tendinous" appearance) replacing the loose fibromyxoid tissue typically at the center of the plugs of organizing pneumonia[87]; he called this the "cicatricial variant" of COP. Of the 12 cases he identified, 7 had progressive or persistent radiographic disease despite corticosteroid therapy.

Shortly thereafter, Churg et al. published a case series of what they described as cicatricial OP mimicking a fibrosing interstitial pneumonia.[88] Their cases involved areas of conventional OP, as well as bands and nodules of dense collagen or densely organizing granulation tissue in air spaces that did not resemble OP and vaguely resembled fibrotic non-specific interstitial pneumonia (fNSIP); this was noted by the authors to be slightly different morphology than what Yousem described in his studies. The bands/nodules were occasionally associated with metaplastic bone. Of the 6 cases with clinical follow-up available, 5 patients were treated with steroids and improved or stabilized while 1 other patient was not treated and clinical stable one year later. The study concluded that cicatricial OP is a variant of OP and does not imply progressive disease.

Additional reports followed in which cicatricial OP, similar to that described by Churg et al, was observed as an incidental finding in 3 patients undergoing pulmonary resection for metastatic colon cancer who had received chemotherapy prior to resection, and was also seen in up to a third of specimens in a study of the late complications of COVID-19 infection.[89,90]

A larger systematic histopathologic review of cicatricial organizing pneumonia was performed by Woge et al in 2020.[91] It included cases with the morphology first described by Yousem with organizing pneumonia showing intraluminal collagen deposition, as well as the morphology observed by Churg et al and subsequent reports, which also showed densely fibrotic linear bands or fibrotic small nodules that partly mimicked fNSIP. The review included cases of COP as well as secondary OP due to other causes such as aspiration and rheumatoid arthritis. They found that patients with cicatricial OP still seemed to follow an indolent and favorable course.

Overall, the findings suggest that cicatricial OP represents a morphologic variant of OP without definite clinical implication. The importance of this finding is to correctly identify it as OP and not mistake it for a fibrotic interstitial lung disease, which could be especially challenging on a small biopsy such as a transbronchial cryobiopsy.

The histopathologic assumption with classic OP is that the underlying lung architecture is preserved during the healing process and essentially returns to normal. In cases of cicatricial OP, the plugs of organizing pneumonia show maturation to irreversible dense eosinophilic scar tissue within lumens of airways and airspaces that may persist indefinitely, but do not appear to have clinical significance. It is worth noting that some radiologic cases of COP appear to progress to NSIP,[76,85] however, pathologic confirmation of that process has not been established and warrants further study.

V. *Lymphocytic Interstitial Pneumonia: Differing Ideas Between Pathologists and Radiologists*

Lymphoid (or lymphocytic) interstitial pneumonia (LIP) was first described in 1966 by Carrington and Liebow in 5 patients with pulmonary disorders who had massive lymphoid infiltrates in the lung.[92] Lymphocytic interstitial pneumonia was subsequently included as one of the five interstitial pneumonias described in Liebow and Carrington's 1969 classification.[1] The use of the term has persisted as a pathologic and radiologic pattern-based diagnosis to present day, although universally accepted diagnostic criteria were not established until the publication of the 2002 ATS/ERS classification of the IIPs, which included idiopathic LIP,[76] and the 2013 update which listed it as a rare IIP.[93]

The key histologic features of LIP according to the ATS/ERS consensus statement are a diffuse interstitial infiltrate comprised mostly of T lymphocytes, plasma cells, and macrophages in a predominantly alveolar septal distribution, often associated with lymphoid hyperplasia.[93] The pertinent negative findings include absence of features of lymphoma and necrotizing granulomas. Distinguishing malignant from benign pulmonary lymphoid infiltrates remains a significant challenge even at present, but it seems probable that many cases originally characterized as LIP may have represented lymphomas, especially extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) which was first characterized in the 1990s.[94,95]

Another significant change that affected the concept of LIP was the introduction of nonspecific interstitial pneumonia (NSIP) as a category of IIP,[96,97] as many cases previously diagnosed as LIP were now classified as cellular NSIP.

With the exclusion of cases of NSIP and lymphoma, LIP has become a relatively uncommon diagnostic histopathologic pattern and cases of idiopathic LIP are quite rare.[98] The LIP histopathologic pattern still shows established associations with connective tissue diseases such as Sjogren syndrome, systemic lupus erythematosus and rheumatoid arthritis; and immunodeficiency states, such as common variable immunodeficiency (CVID) and acquired immunodeficiency syndrome (AIDS), but the spectrum of histopathologic findings in the lungs of patients with these conditions is more diverse than LIP. Consequently, the utility of LIP and its place amongst the IIPs has been called into question.

An additional area of uncertainty with regards to LIP is whether there is correlation between histopathologic and radiologic features. For example, the ATS/ERS consensus statements list "curious" perivascular cysts and "striking cyst formation" amongst possible radiologic features of LIP, although cysts are not mentioned in the histologic features.[76,93]

A recent study by Fraune et al provided some much-needed insight into the current landscape of LIP.[98] They performed histopathologic assessment of cases meeting current criteria for LIP by either histologic criteria ("pathologic LIP") or cystic cases meeting radiologic criteria ("radiologic LIP"), in addition to cases showing other diffuse benign lymphoid proliferations not meeting histologic criteria for LIP. They showed that there was poor correlation between pathologic and radiologic LIP, in that most cases of pathologic LIP did not show radiologic LIP on imaging, and vice versa. However, radiologic LIP was often associated with pulmonary lymphoid infiltrates showing patterns such as follicular bronchiolitis and micronodular lymphoid hyperplasia; and the vast majority also showed cystic changes on pathology. Pathologic LIP was found to be associated with autoimmune disorders and immunodeficiency, while radiologic LIP was only seen with autoimmune disorders. No cases of idiopathic LIP were identified. The authors conclude that LIP should be dropped as a pathologic and radiologic diagnosis, based on the rarity of the idiopathic form and the findings in their study that show minimal overlap in pathologic findings between pathologic LIP and radiologic LIP.

A practical takeaway from this study is that pathologists evaluating lung biopsies from patients with radiologic features of LIP should not expect to see "classic" histologic of LIP; in these cases, a descriptive diagnosis including patterns of any lymphoid infiltrates and noting the presence of cyst should be considered, with an appropriate differential diagnosis provided in a comment.

VI. *Granulomatous and Lymphocytic Interstitial Pneumonia: Elusive Relationship with Immunodeficiency*

The term 'granulomatous-lymphocytic interstitial lung disease' (GLILD) was first used in 2004 by Bates et al in a study examining noninfectious pulmonary disease in patients with combined variable immunodeficiency (CVID).[99] Out of 69 patients with CVID, 18 were found to have chronic respiratory symptoms associated with diffuse lung abnormalities on chest imaging. All 18 of these patients underwent surgical lung biopsy, and the term GLILD was applied to the 13 patients whose biopsies showed "granulomatous disease" and/or various patterns of lymphoid infiltrates including one case of B-cell lymphoma; the remaining 5 cases with diffuse lung abnormalities on imaging showed either organizing pneumonia,

hypersensitivity pneumonitis, or metastatic gastric carcinoma. In evaluating survival data from these patients, the study found that CVID patients with GLILD had a median survival of 13.7 years compared to nearly 30 years for those without GLILD. Perhaps due to the significance of this finding, or our affinity for acronyms in the study of interstitial lung disease, the term 'GLILD' has persisted in the literature to the present day although it has remained unclear whether it should be defined with specific histopathologic features.

A subsequent study by Rao et al in 2015 sought to further characterize the histopathologic features of GLILD[100] by examining surgical lung biopsies from 16 patients with CVID. Similar to the previous study, lymphoid infiltrates and granulomatous inflammation were common findings. They also identified organizing pneumonia and interstitial fibrosis in 87.5% and 75% of cases, respectively, and included these features within the pathologic spectrum of GLILD.

A definition for GLILD was proposed in 2017 by Hurst et al as part of the British Lung Foundation/United Kingdom Primary Immunodeficiency Network consensus statement as "a distinct clinico-radio-pathological ILD occurring in patients with CVID, associated with a lymphocytic infiltrate and/or granuloma in the lung, and in whom other conditions have been considered and where possible excluded".[101] They noted that GLILD occurs in a background of multisystem granulomatous/inflammatory involvement that could include lymphadenopathy, splenomegaly and granulomatous inflammation in a variety of organs.

Although defining GLILD is useful to raise awareness that interstitial lung disease is a possible complication of immunodeficiency, with reported frequencies in CVID patients of 10% to 20%, the associated pathologic features were still poorly characterized and their relation to GLILD remained uncertain.[102] In addition, using a term that includes pathologic features in its name (i.e., 'granulomatous' and 'lymphocytic') creates confusion, particularly when the presence of both features is not required for diagnosis, but also because it falsely gives the impression that this is diagnosis primarily based on pathologic findings.

A recent article by Larsen et al proposes abandoning the term GLILD in favor of using descriptive pathologic diagnosis in the setting of CVID and IgAD.[103] They evaluated the histopathologic features in surgical lung biopsies from 34 patients with CVID, the largest case series to date, in addition to 4 patients with immunoglobulin A deficiency (IgAD). They also evaluated the utility of the term GLILD by determining the frequency that histopathologic findings in CVID and IgAD satisfy criteria for that diagnosis and evaluating differences in patient outcomes between those with and without GLILD.

Their study found that granulomas were present in 68% of biopsies from patients with CVID and 50% of patients with IgAD. The granulomas were usually non-necrotizing, located in air spaces and tended not to show a lymphangitic distribution; the granulomas were reminiscent of sarcoidosis, with concentric peripheral lamellar fibrosis, in a few cases. Benign lymphoid infiltrates were seen in 95% of the CVID cases and 75% of the IgAD cases. The pattern of the lymphoid infiltrates included LIP, follicular bronchiolitis, peribronchiolar lymphoid infiltrates, diffuse lymphoid hyperplasia, nodular lymphoid hyperplasia (mass lesions), and NSIP.

A mixture of patterns was often seen in one biopsy. Plasma cells were readily apparent in 26% of CVID cases and 75% of IgAD cases. Organizing pneumonia was present in 75% of CVID cases and 50% of IgAD cases. Only one case showed significant fibrosis, which was in an NSIP-like pattern. Applying their pathologic definition of GLILD, which required the presence of both a lymphoid proliferation and granulomas, 75% of CVID cases and 50% of IgAD cases would qualify as GLILD; and there was no obvious outcome differences between those that would qualify as GLILD and those that would not, although all patients their study had excellent survival.

They conclude that GLILD is not a useful concept, at least from a pathologic perspective as it does not accurately reflect the spectrum of histopathologic changes that can occur in patients with CVID and IgAD. In lung biopsy specimens from patients with a known history of CVID or IgAD, they suggest listing the pathologic findings in a comment and stating that the findings are compatible with CVID or IgAD, while in patients with no known history, making a comment suggesting clinical workup for these disorders when compatible histologic changes are seen. What constitutes compatible histologic changes remains open to interpretation but primarily seems to be based on a benign lymphoid infiltrate, possibly with non-necrotizing granulomas and organizing pneumonia, but perhaps the greater emphasis should be placed on excluding other etiologies as this is likely the reason for obtaining a lung biopsy.

As the spectrum of pathologic findings in CVID and IgAD disease is broad, so too is the histologic differential diagnosis. Cases showing dense lymphoid infiltrates should undergo evaluation for lymphoma. Otherwise, it's notable that the histopathologic findings would show significant overlap with LIP-pattern, especially the expanded spectrum of LIP described in the most recent paper

by Larsen, and would share the same possible list of etiologies (autoimmune disease and adverse drug reactions).

In cases with granulomas, infection should be excluded with appropriate stains and cultures. The presence of necrotizing granulomas would strongly favor infection. Hypersensitivity pneumonia and sarcoidosis would also be in the differential diagnosis.

The significance of diffuse interstitial fibrosis in lung biopsies from patients with CVID and IgAD disease is uncertain. It was a common finding in Rao's study yet uncommon in Larsen's study and it is difficult to account for this difference. It is possible that patients with immunodeficiency-related ILD can progress to fibrotic lung disease, although Larsen's paper suggests that this is an uncommon event and should warrant consideration of other etiologies.

Conclusion

Usual interstitial pneumonia/idiopathic pulmonary fibrosis, the prototype of fibrosing ILD, has a poor prognosis but recent advances in antifibrotic therapy have improved its clinical course. Surgical lung biopsy for histopathologic examination used to be the gold standard in the diagnosis of UIP/IPF but the roles of smaller biopsy (especially transbronchial cryobiopsy) and HRCT have been emphasized in the past decade. Progressive pulmonary fibrosis is not a specific diagnosis and many fibrotic lung diseases other than UIP/IPF can manifest PPF. An international committee defined PPF with physiological, radiological and histopathological features and addressed the issue of antifibrotic treatment. Usual interstitial pneumonia pattern of fibrosis can be seen in many diseases other than IPF, following the course of PPF comparable to IPF, which led to a proposal of UIP as a standalone diagnostic entity. Recent molecular studies helped to elucidate genetic and molecular background of many ILDs that may contribute to development of newer therapeutic agents. Differentiation from UIP is crucial for CiOP given its prognostic and therapeutic implications. Clarification of biologic concept as well as diagnostic criteria is needed for LIP and GLILD by further discussion among pathologists, radiologists and pulmonologists.

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