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New trajectories in the treatment of ILD: Treat the disease or treat the underlying pattern?

Julie Morisset[1], **Joyce S Lee**[2]

[1)]Département de Médecine, Centre Hospitalier de l'Université de Montréal, Québec, Canada

[2)]Department of Medicine, University of Colorado, Denver, Colorado, USA

Abstract

Purpose of review: A subset of patients with interstitial lung diseases (ILD), like rheumatoid arthritis (RA) associated ILD and chronic hypersensitivity pneumonitis (HP), will experience a disease course similar to patients with idiopathic pulmonary fibrosis (IPF). They also often have a usual interstitial pneumonia (UIP) pattern of fibrosis. While the standard of care for patients with RA-ILD and chronic HP is immunosuppression, the optimal treatment for patients with progressive disease and a UIP pattern remains unknown.

Recent findings: Recent research has highlighted shared risk factors, disease behavior and pathobiology between RA-ILD, chronic HP and IPF. The presence of a UIP pattern, in both RA-ILD and chronic HP, is associated with a worse prognosis. Moreover, genetic risk factors, previously well characterized in IPF, are increasingly being linked to RA-ILD and chronic HP. The *MUC5B* promoter variant rs5705950, telomerase complex mutations and short telomere lengths are also linked to an increased susceptibility to pulmonary fibrosis in RA and chronic HP.

Summary: IPF shares several clinical, genetic and biological features with other ILDs exhibiting the UIP pattern. The optimal pharmacologic management of these patients remains uncertain. Several on-going trials are evaluating the efficacy of antifibrotic medications in these other diagnoses and may change how we approach ILD treatment.

Keywords

interstitial lung disease; usual interstitial pneumonia; idiopathic pulmonary fibrosis; rheumatoid arthritis; hypersensitivity pneumonitis

Introduction

Interstitial lung diseases (ILD) form a heterogeneous group of diffuse parenchymal lung diseases of various etiologies, clinical course and prognosis[1]. The classical diagnostic approach to ILD heavily relies on the identification of the cause or trigger responsible for the development of ILD, including an underlying autoimmune condition (e.g. rheumatoid arthritis) and an environmental antigen (e.g. birds, mold). Patients are then classified, according to their clinical, radiological and pathological features, as having a diagnosis

Corresponding author: Joyce S Lee, University of Colorado, 1635 Aurora Ct, Aurora, Colorado, United Sates, 80045, Phone: 855-586-4824, joyce.lee@ucdenver.edu.

such as idiopathic pulmonary fibrosis (IPF), hypersensitivity pneumonitis (HP), connective tissue disease (CTD) related-ILD, or unclassifiable ILD[1–6].

This diagnostic framework shapes the subsequent medical management of patients with ILD. While antifibrotic medications, like pirfenidone and nintedanib, are being used to slow disease progression in IPF, corticosteroids and/or other immunosuppressive agents are frequently used in patients with HP and CTD-ILD[7–14]. Further, immunosuppression is avoided in patients with IPF given the increased morbidity and mortality observed with the use of combination therapy with prednisone, azathioprine and N-acetylcysteine (NAC)[15].

However, it is increasingly recognized that a proportion of patients with non-IPF ILD also progress in a manner very similar to that of IPF. Diseases in particular include rheumatoid arthritis associated ILD (RA-ILD) and chronic HP, specifically in those with the usual interstitial pneumonia (UIP) pattern of fibrosis. Recent work in these two disease states suggests that they share several clinical features and pathogenetic mechanisms with IPF[16,17]. While the optimal therapy for non-IPF ILDs such as RA-ILD and chronic HP remains unclear, the standard of care is immunosuppression. It has been hypothesized that these diseases could have more benefit and less risk from anti-fibrotic therapies, such as pirfenidone or nintedanib, rather than treatment with immunosuppression[18–20].

This review will highlight our current understanding of the UIP lesion in idiopathic (IPF) and other non-idiopathic forms of UIP (RA-ILD and chronic HP), explore the evidence and knowledge gaps regarding the various therapeutic options available for patients with ILD and discuss how research progress may challenge our current paradigms and change how we approach treatment in ILD.

The Usual Interstitial Pneumonia pattern

The pattern of usual interstitial pneumonia (UIP) was first recognized and described on surgical lung biopsies and autopsies by Dr Averill Liebow. The UIP pattern was the most prevalent pathological pattern in patients with idiopathic interstitial pneumonias (IIP)[21]. Further characterization of the UIP pattern on pathology and imaging occurred over the next several decades, shaping our current understanding of UIP and ILD pathogenesis[22].

Currently, the UIP pattern can be recognized in patients with ILD on high-resolution computed tomography (HRCT) and/or surgical lung biopsy. On HRCT, features of subpleural and basal predominance and honeycombing with or without peripheral traction bronchiectasis or bronchiolectasis are required to meet the UIP radiological pattern criteria[6] (Figure 1). On lung pathology, UIP is defined by the presence of dense fibrosis with architectural distortion, a subpleural predominance and/or pareseptal distribution, fibroblast foci and patchy involvement of the lung[6] (Figure 2). Although the UIP pattern is characteristic of IPF it is not pathognomonic and thus is also frequently encountered in patients with other forms of ILD, most commonly in RA-ILD and chronic HP[23,24].

Idiopathic UIP

Idiopathic pulmonary fibrosis (IPF)

IPF is a progressive fibrotic ILD characterized by the presence of the usual interstitial pneumonia pattern on imaging or on lung pathology in the absence of any other known cause of ILD (e.g. CTD, occupational or environmental exposure or drug toxicity)[6,25]. IPF is a disease of the aging population and is more common in men and former smokers[26]. Although the disease course of IPF is heterogeneous and unpredictable in individual patients, it is associated with a limited survival time of 3 to 5 years after diagnosis[25]. While still considered to be a rare disease, IPF is the most common and most studied ILD. In the past years, our understanding of IPF has evolved and is now considered a disease of epithelial cell dysfunction resulting from a complex interaction between genetic and environmental risk factors[27,28].

Several gene variants have been linked to an increased risk of IPF in sporadic and familial cases[26]. First, the presence of the *MUC5B* promoter minor-allele single nucleotide polymorphism (SNP) rs35705950 is strongly associated with an increase in IPF susceptibility[29,30]. When present, the variant allele rs35705950 SNP leads to an up-regulation of MUCB expression in the lungs, suggesting a role for airway mucins in the pathogenesis of IPF[29,31]. Paradoxically, this same MUC5B polymorphism has been found to be associated with better survival in patients with IPF[32]. Second, genome-wide association studies have identified the genetic variant rs5743890 in TOLLIP, an important regulator of innate immune responses. The TOLLIP mutation has also been associated with a higher risk of IPF[33,34]. Finally, telomere dysfunction and shortening is believed to play a role in the pathobiology of IPF with telomere attrition being one of the aging-associated processes playing a role in disease development[35]. Higher susceptibility to IPF was found in patients exhibiting mutations in the genes TERT, TERC, PARN and RTEL1, parts of the telomerase complex [35–39]. Short telomere length (TL) has also been found to be predictive of mortality among patients with IPF[40].

Disease behavior of progressive fibrotic ILD has also been observed in patients with other ILD diagnosis[3,41]. Most notably, this progressive disease phenotype has been observed and characterized in patients with rheumatoid arthritis-associated ILD (RA-ILD) and chronic HP [23,42,43].

Non-idiopathic Forms of UIP

Rheumatoid arthritis-associated interstitial lung disease (RA-ILD)

Rheumatoid arthritis (RA) is a connective tissue disease characterized by inflammatory arthritis and highly prevalent extra-articular and systemic manifestations[44,45]. ILD is one of the most common pulmonary manifestations in RA and the presence of ILD significantly impairs patient disease course, prognosis, and health-related quality of life[45–48]. Patients with RA-ILD often exhibit clinical characteristics similar to those of patients with IPF. Further, the prevalence of UIP pattern both on HRCT or surgical lung biopsy is higher in RA-ILD than in other types of CTD-ILD[23,49]. In RA-ILD, the UIP pattern of disease appears to be more frequent in older male patients with a positive history of smoking and

is associated with a poorer prognosis and a natural history similar to IPF[50–55]. Additionally, RA-ILD shares several risk factors for mortality with IPF[25,52,56]. Patient variables like age, male gender, pulmonary function tests (forced vital capacity and diffusion capacity of the lung for carbon monoxide), extent of fibrosis and presence of the UIP pattern are known to be significant predictors of mortality in both diseases[52,57–59].

RA-ILD also shares some genetic risk factors with IPF [55,60,61]. Whole exome sequencing in a cohort of patients with RA-ILD identified heterozygous mutations in the TERT, RTEL1, PARN and SFTPC coding regions[55,62]. Those mutations, previously described to be prevalent in patients with IPF, are similarly linked to ILD susceptibility in RA. Further, the prevalence of patients with short telomere length (TL), below the tenth percentile, is similar in patients with RA-ILD and IPF[61]. Last, the presence of the *MUC5B* promoter variant rs5705950 is a strong risk factor for RA-ILD and is associated with the radiological pattern of UIP among RA-ILD patients[60,61]. The *MUC5B* promoter variant could represent a shared risk factor for the UIP pattern and may be a more generalizable genetic risk variant across various ILD diagnoses[29,60,63].

Further, serum biomarkers that have been studied in IPF are being increasingly recognized in patients with RA-ILD[64,65]. For example, a peripheral biomarker signature combining matrix metalloproteinase (MMP7), pulmonary and activation-regulated chemokine (PARC) and surfactant protein D (SP-D) combined with clinical risk factors may enhance the detection of ILD in patients with RA[64].

Chronic hypersensitivity pneumonitis (chronic HP)

HP is a complex disease thought to result from an repetitive exposure to one of the various causative organic antigens known to initiate an inflammatory response in the lungs of individuals with a genetic predisposition[66]. While some patients with HP may experience a complete resolution of their lung disease, others will go on to develop pulmonary fibrosis and present chronic symptoms similar to those of IPF[43].

Historically, patients with HP were classified according to their clinical manifestations and symptom duration as having either acute, subacute or chronic HP[67,68]. More recently, it was proposed patients should instead be categorized into acute or chronic HP based on the absence or presence of fibrosis on radiology or lung biopsy[42,43]. The presence and extent of such fibrotic changes was found to represent a better surrogate of disease behavior in patients with HP since those who develop pulmonary fibrosis often experience chronic and progressive disease associated with a poorer prognosis[24,69,70]. Accordingly, presence of the UIP pattern on HRCT or surgical lung biopsy is known to be associated with an increased mortality among patients with chronic HP[24,71].

Further, the presence of short TL and the *MUC5B* promoter variant rs35705950 are known to be associated with extent of fibrosis, the histopathologic pattern of UIP and reduced survival in patients with chronic HP[63,72]. These recent findings suggest that among patients with chronic HP, individuals with short TL or *MUC5B* rs35705950 may be at higher risk to develop pulmonary fibrosis[63]. These data support a shared genetic risk profile, and consequently suggest a shared pathobiology between chronic HP and IPF[29,33].

Finally, on surgical lung biopsy and/or explanted lungs, patients with a UIP pattern of fibrosis and a diagnosis other than IPF (either chronic HP, CTD-ILD or unclassifiable ILD) also exhibit molecular markers of telomere dysfunction and senescence commonly found in IPF[73]. Interestingly, patients with non-IPF ILDs and a pathologic UIP pattern have shorter telomeres compared to age-matched healthy controls and show elevated levels of p16 and p21, 2 known molecular markers of senescence in alveolar type II cells[73].

Treatment of ILD

Idiopathic pulmonary fibrosis

The most recent international guidelines recommend the use of either pirfenidone or nintedanib for the treatment of patients with IPF[7]. Both medications have been shown to reduce the decline of forced vital capacity (FCV) by about 50% after 1 year on therapy [8,9,26]. Additionally, these drugs also improve other important outcomes: pirfenidone reduces the incidence of respiratory-related hospitalizations, nintedanib decreases the frequency of acute exacerbations and pooled analysis suggest they may also both reduce mortality [9,74–76].

Historically, prior to the era of antifibrotic medications, the recommended therapeutic approach for IPF was the combination of azathioprine, prednisone and N-acetylcysteine[5]. However, in the PANTHER-IPF trial, patients receiving this combination of drugs were found to be at increased risk of death and hospitalization compared to those on placebo[15]. A secondary data analysis of the PANTHER-IPF data has recently demonstrated that a high proportion of patients in the trial (62%) had a TL inferior to the tenth percentile. Further, in those receiving the combination of azathioprine, prednisone and N-acetylcysteine, having a short TL was associated with an increased risk of death, lung transplantation, hospitalization or lung function decline[77]. These results raise several questions relative to the safety of the use of immunosuppressive therapy in patients with other types of ILDs that exhibit shared clinical, genetic and biologic characteristics with IPF.

Rheumatoid arthritis-associated interstitial lung disease

Immunosuppressive therapy is considered a central part of the management of patients with RA-ILD[78,79]. Most of the evidence guiding the treatment of CTD-ILD and RA-ILD emerges from studies conducted in populations of patients with scleroderma-related ILD (Scl-ILD). Prospective randomized clinical trials have demonstrated the safety and efficacy of immunosuppressive therapies (i.e. cyclophosphamide and mycophenolate mofetil (MMF)) in Scl-ILD[12,13,80]. However, the improvement in lung function associated with both these medications remains modest. Additionally, several retrospective studies have shown lung function stabilization or improvement and reassuring tolerability in patients with various types of CTD-ILD receiving immunosuppressive medications[81–83]. Despite those favorable results, many patients with RA-ILD still experience disease progression associated with a significant impact on life expectancy[49,84]. The optimal medical management of these patients remains unknown and there is a pressing need for new therapeutic agents and a more comprehensive treatment algorithm. Recently, a phase 2 open-label study demonstrated pirfenidone can be well tolerated in patients with Scl-ILD and paved the way

for further research evaluating the use and efficacy of antifibrotics in patients with RA-ILD and other CTD-ILD[85].

Chronic hypersensitivity pneumonitis

Identification and removal of the causal antigen remains central to the medical management of chronic HP. However, many patients present with a high burden of symptoms or have disease progression despite antigen remediation and require additional therapy[42,43]. Unfortunately, few prospective studies have evaluated the different therapeutic approaches for HP. In patients with acute HP, corticosteroid use has been shown to alleviate symptoms, although it did not lead to better long-term outcomes when compared to antigen eradication alone[86,87]. The management of chronic HP remains even more challenging. Immunosuppressive agents like MMF and azathioprine (AZA) may be beneficial and help stabilize lung function, although further prospective studies are needed to validate their effectiveness in patients with chronic HP[10,11].

The way forward

Several unanswered questions remain regarding the optimal management of patients with ILD. Patients with various ILD diagnoses exhibiting a UIP pattern represent a huge challenge for clinicians and create a pressing need for the medical community. Considering the several shared attributes between IPF and other progressive forms of ILD with a UIP pattern, the available IPF medications may also represent effective therapies in these other diseases. Currently, there are several on-going trials evaluating the effectiveness of nintedanib and pirfenidone in non-IPF ILDs, including Scl-ILD, unclassifiable ILD, progressive fibrosing ILD, RA-ILD, and chronic HP (Table 1). If these studies yield positive results, the landscape for the management of patients with ILD will likely be greatly modified and antifibrotic medications may have relevance across various ILD subtypes. Perhaps future research will lead to changes in the diagnostic approach and management of ILD. One possibility includes moving away from the classification of ILD by specific etiology, to a more personalized approach involving the identification of the underlying pattern, genetic risk profile and disease behavior of the ILD. Nonetheless, some elements of the management will always remain specific to the clinical diagnosis of ILD, such as antigen remediation in HP and treatment of extra-pulmonary manifestations in patients with CTD-ILD.

Conclusion

Several ILDs, particularly in those with the UIP pattern, share common epidemiologic, genetic and pathobiologic features with IPF. The optimal management of these patients with the UIP pattern remains unclear and more evidence is needed to clarify the best treatment approach. Areas of treatment uncertainty include the role of immunosuppression and antifibrotic therapy in this patient population. On-going clinical trials are currently evaluating the effectiveness of antifibrotic medications in various ILD diagnoses and will likely shape how we approach ILD in the future.

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Conflicts of interest

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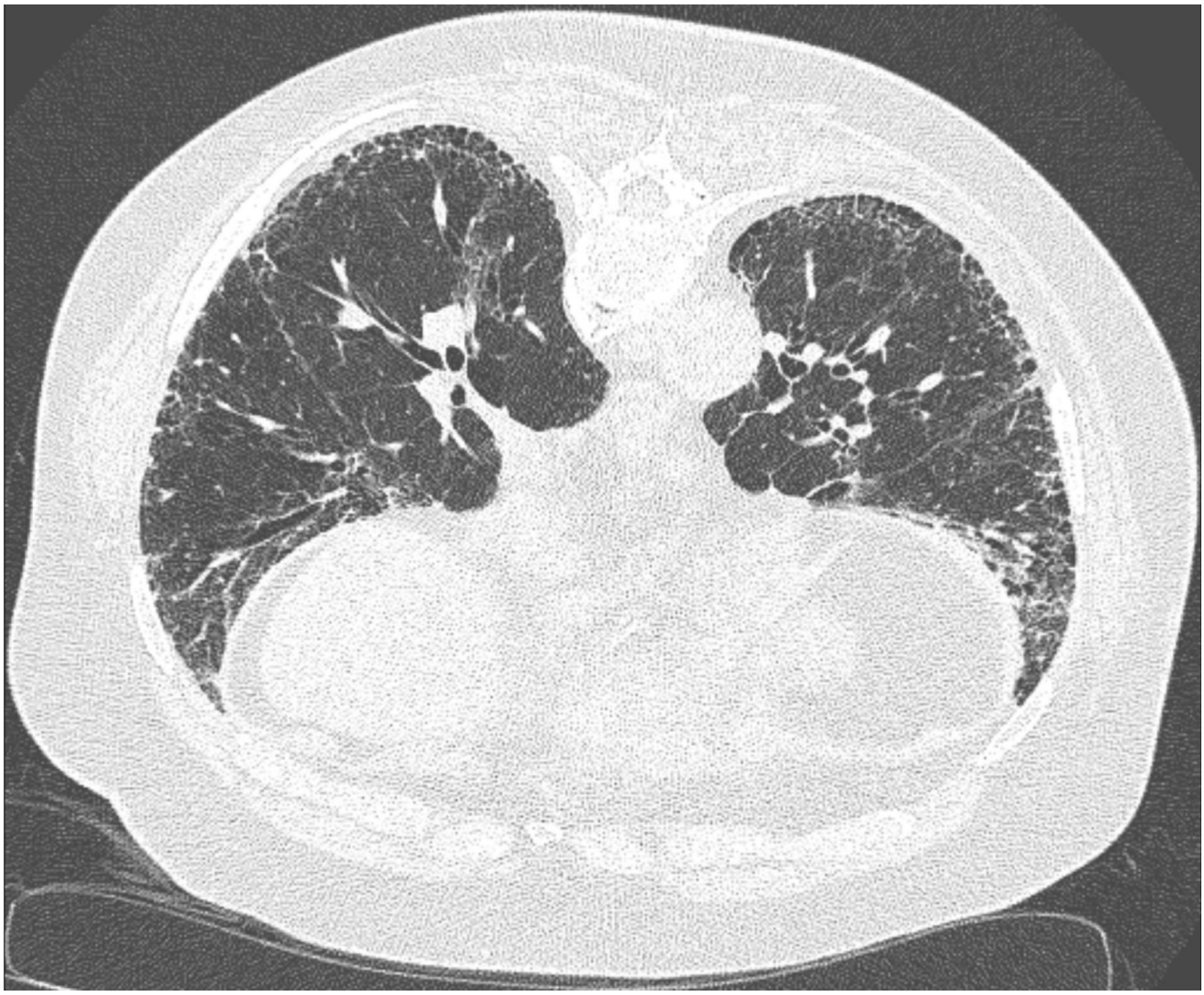
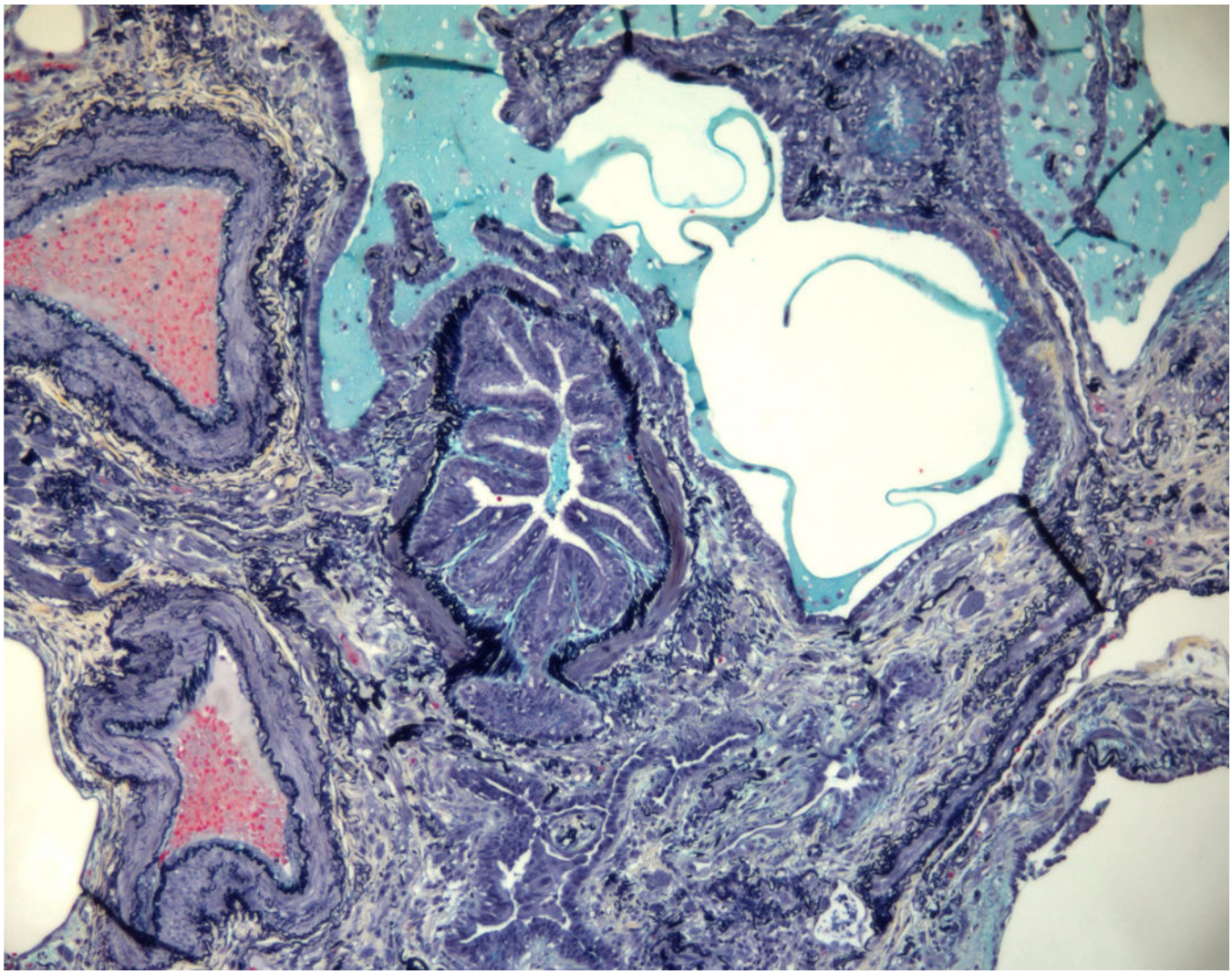
Key points:

- IPF shares several clinical, genetic and biological features with other ILD diagnoses such as chronic RA-ILD and chronic HP
- The UIP pattern of fibrosis is encountered in patients with RA-ILD and chronic HP and is associated with a worse prognosis.
- Genetic risk factors well characterized in IPF (e.g.*MUC5B* promoter variant rs5705950, telomerase complex mutations and short telomere lengths) are also linked to an increase susceptibility to pulmonary fibrosis in RA and chronic HP.





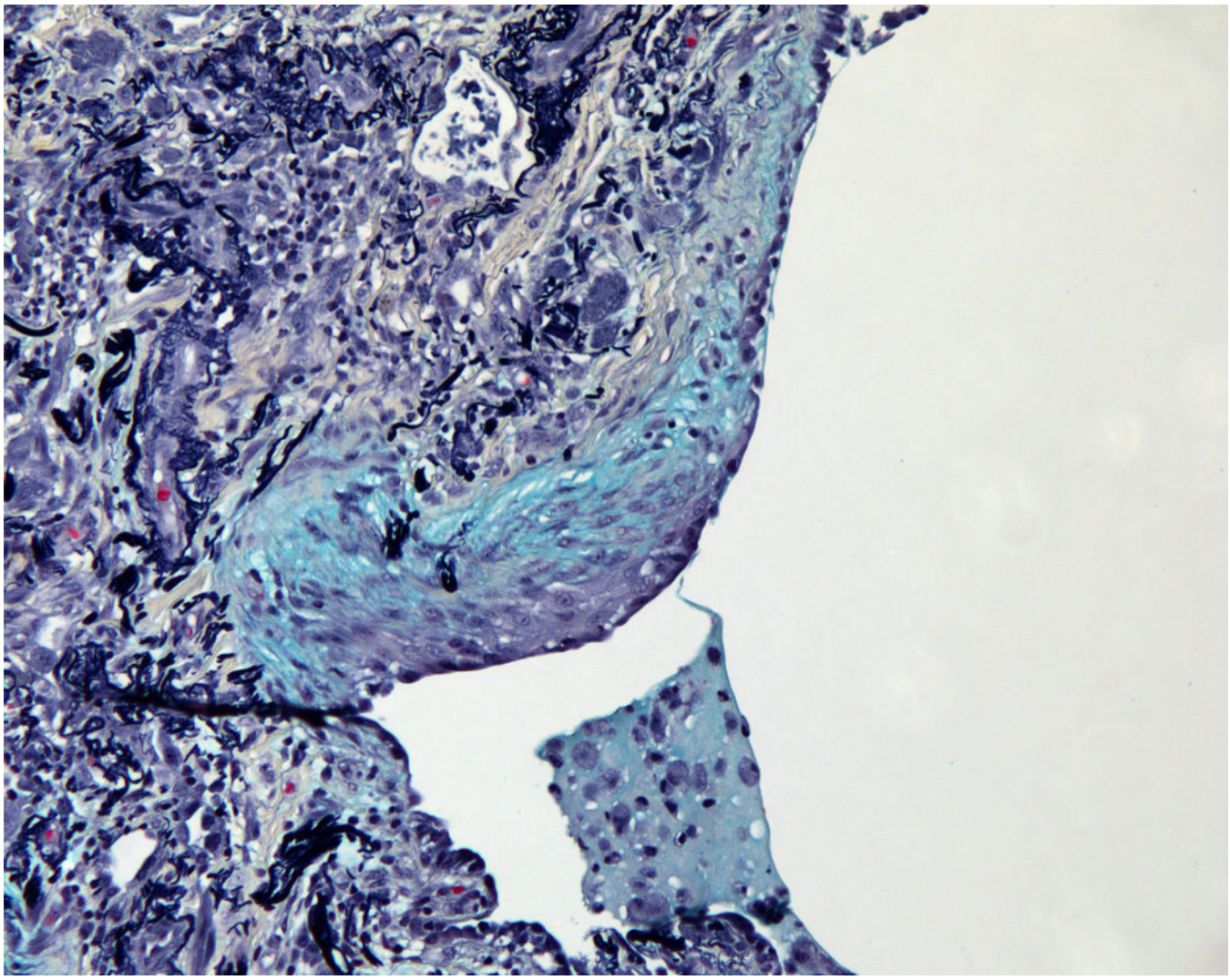
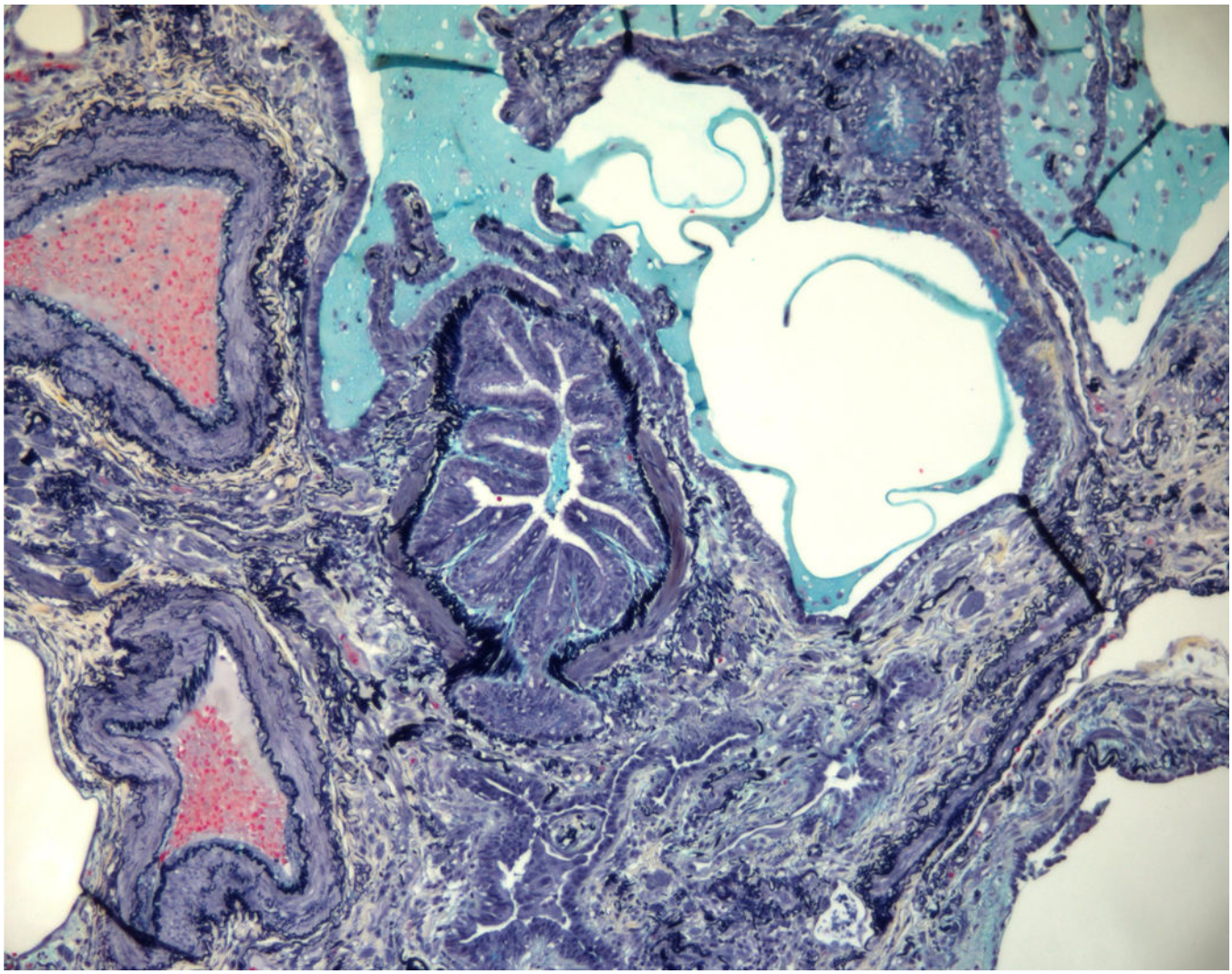


Figure 1:
High-resolution computed tomography image of usual interstitial pneumonia pattern - subpleural and basal predominance and honeycombing with or without peripheral traction bronchiectasis or bronchiolectasis.



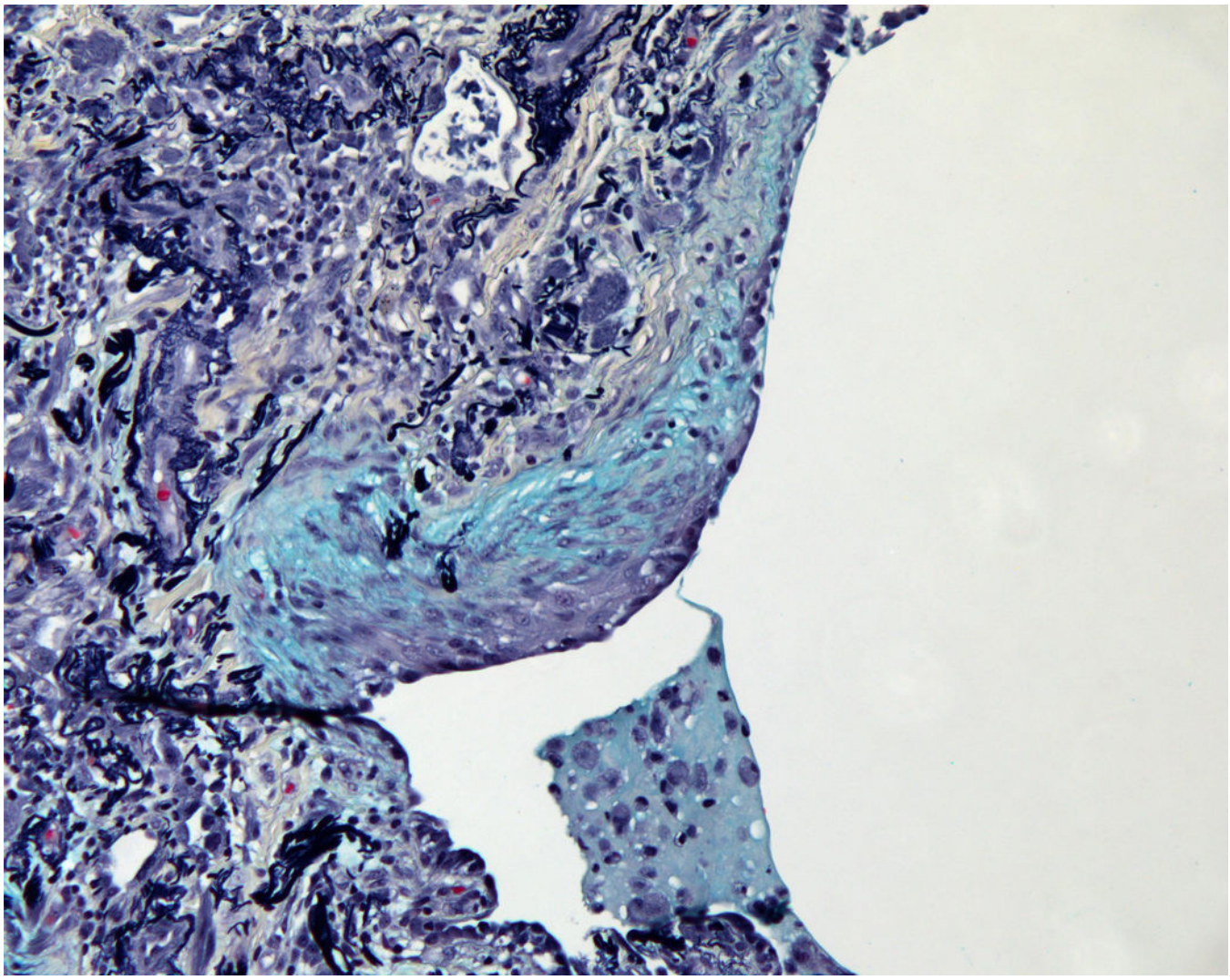


Figure 2:
(2A) Pentachrome (Movat) stain of peripheral honeycombed lung in a patient with usual interstitial pneumonia (courtesy of Dr. Carlyne Cool). The honeycomb spaces are filled with mucus and lined by bronchiolar-type epithelium. The pleura is at the bottom right. Black = elastic tissue; yellow = mature fibrosis; blue = mucopolysaccharides (including mucus and myofibroblastic/fibroblastic tissue); red = fibrin blood; purple = nuclei. (2B) Pentachrome (Movat) stain of fibroblast focus (blue). The focus is capped by cuboidal epithelial cells and overlies an area of dense fibrosis/elastic tissue.

Table 1:

Randomized clinical trials evaluating antifibrotics in interstitial lung disease other than idiopathic pulmonary fibrosis

	Study name	Trial Registration number	Patient population
SENSCIS	A randomized, placebo-controlled clinical trial of nintedanib in patients with systemic sclerosis-associated interstitial lung disease[88]	NCT02597933	SSc-ILD
SLS III	Scleroderma Lung Study III: combining the anti-fibrotic effects of pirfenidone with mycophenolate for treating scleroderma-related interstitial lung disease	NCT03221257	SSc-ILD
PF-ILD	A double-blind, randomized, placebo-controlled phase III trial of nintedanib in patients with progressive fibrosing interstitial lung disease[41]	NCT02999178	Progressive fibrosing lung disease
	Pirfenidone in patients with unclassifiable progressive fibrosing interstitial lung disease: design of a double-blind, randomized, placebo-controlled phase II trial[89]	NCT03099187	Fibrosing unclassifiable interstitial lung disease
TRAIL1	Phase II Study of Pirfenidone in Patients With RAILD	NCT02808871	RA-ILD
	A randomized, double-blind, placebo-controlled, study of efficacy and safety of pirfenidone in patients with fibrotic hypersensitivity pneumonitis	NCT02958917	Fibrotic hypersensitivity pneumonitis

Abbreviations

SSc-ILD: systemic sclerosis-associated interstitial lung disease

RA-ILD: rheumatoid arthritis-associated interstitial lung disease