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Two sides of the same coin? A review of the similarities and differences between idiopathic pulmonary fibrosis and rheumatoid arthritis associated interstitial lung disease.

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Introduction

Rheumatoid arthritis (RA) is a common disease, characterized by an erosive and inflammatory synovitis, which affects 1% of the general population [1]. Interstitial lung disease is a frequent extra-articular manifestation of RA and causes significant morbidity and mortality [2]. While ILD in RA is common, our understanding of the pathogenesis of RA-ILD is limited [3]. There have been observations that certain subtypes of RA-ILD may be clinically similar to idiopathic pulmonary fibrosis (IPF) [4], a form of progressive ILD, histologically characterized by a usual interstitial pneumonia (UIP) pattern [5]. Recent work in the genetics of RA-ILD has uncovered shared genetic risk factors between RA-ILD and IPF [6-8], further supporting a possible connection between these two conditions.

The growing understanding of the overlap between RA-ILD and IPF has important pathobiological implications and, perhaps more importantly, has the potential to impact clinical care. To-date, treatment paradigms for IPF and RA-ILD are divergent. Immunosuppression-based therapy with prednisone, N-acetyl cysteine, and azathioprine is not recommended in patients with IPF [9]. This combination of therapy was not only found to be ineffective in slowing disease progression, but was associated with increased mortality in IPF [10]. In contrast, immunosuppression in RA is critical in order to achieve and maintain arthritis remission [11]. Further, systemic immunosuppression for RA-ILD is the current standard of care, based primarily on data extrapolated from studies in scleroderma associated ILD [12, 13]. However, the impact and efficacy of immunosuppression for ILD in RA is unknown. Other factors complicating RA-ILD treatment is the impact of RA disease activity [14] and its associated treatment (e.g. methotrexate) on risk for ILD development and progression [15-17].

Given the increasing data suggesting an overlap of these two diseases (Table 1), and the differing treatment paradigms with potential clinical impact, this review will compare and contrast what is currently understood about RA-ILD and IPF (Figure 1). We will also propose areas in need of additional investigation, including identification of targeted and novel biomarkers, as furthering our

understanding of these two conditions may have diagnostic, treatment and research implications in the field of ILD.

Epidemiology

RA is an inflammatory arthritis that affects nearly 1% of the general population [1]. The presence of RA significantly increases the lifetime risk for the development of ILD by 10% compared with the general population risk of 0.9% [2]. While the risk for development of ILD increases with a diagnosis of RA, the incidence of ILD within RA cohorts has been variable, ranging from 1 - 58% [18-24]. Estimates of the overall incidence of RA-ILD is also likely underreported, given the wide variance in diagnostic imaging techniques (e.g. chest x-ray vs. computed tomography (CT)) and studies of RA cohorts demonstrating rates of sub-clinical RA-ILD from 26% - 58% [24, 25]. As the treatment paradigm for RA advances and clinical outcomes in RA are improving (such as mortality), it is hypothesized that the incidence of RA-ILD will increase [26].

In comparison, IPF has a lower annual incidence between 4.6 and 16.3 per 100,000 people [27, 28]. However, the incidence of IPF is increasing, due to higher detection and aging of the general population [29], similar to what has been observed in RA-ILD [30].

Natural history and clinical characteristics

RA-ILD has a significant impact on quality of life and survival [30, 31]. The presence of ILD increases mortality when compared to those RA patients without ILD [2]. Median survival in RA-ILD varies, but has been reported to range from 2.6 years to 10.3 years, depending on the population studied [2, 31, 32].

The RA-ILD clinical course can also include the development of acute exacerbations, which are similar to what is observed in IPF [33-35]. Acute exacerbation in RA-ILD, characterized by acute hypoxemic respiratory failure and increased ground glass opacities on CT imaging, appears to be

more common among RA patients with a UIP pattern when compared to those with a non-UIP pattern of ILD [33].

Among those with RA-ILD, patients with a UIP pattern of disease have a worse outcome with more rapidly progressive disease and increased mortality when compared to those with a non-UIP pattern of disease [36, 37]. In fact, the natural history of RA-ILD patients with a UIP pattern of disease appears to mimic that of IPF [38], however there are some conflicting data [39]. Further, a prognostic model that was derived and validated in IPF (i.e. the GAP model, which relies on four variables: Gender (G), Age (A) and lung physiology (P) variables (forced vital capacity (FVC) and diffusing capacity for carbon monoxide (DLCO)) [40], has similar discrimination and calibration among a multi-national cohort of RA-ILD patients [4].

One of the most significant clinical differences between RA-ILD and IPF, besides the articular disease, is the myriad pulmonary manifestations that can occur aside from ILD in patients with RA. While IPF is an isolated parenchymal disease, RA can affect all compartments of the lung, including the pleura (e.g. pleuritis, pleural effusion) [41] and airways (e.g. follicular bronchiolitis, constrictive bronchiolitis) [42], and is associated with other non-fibrotic parenchymal lung diseases (e.g organizing pneumonia [43], diffuse alveolar hemorrhage [44], or nodules [18]).

Radiologic and histologic patterns

In RA-ILD, several radiologic patterns can be observed, however the most common pattern in RA-ILD is the UIP pattern (Figure 2), making RA-ILD unique amongst all of the other connective-tissue ILDs (CT-ILD). In other CT-ILDs, such as scleroderma-ILD or myositis-ILD, the most common ILD pattern is non-specific interstitial pneumonia (NSIP) (Figure 3). In RA-ILD, the UIP pattern on chest CT is seen in 40-62% of the cases [37], while the rest are made up of NSIP and organizing pneumonia. Similar to IPF, the radiologic pattern of UIP in RA-ILD is highly specific for the UIP pattern on surgical lung biopsy (Figure 4) [5, 45]. However, it is worth noting that the current diagnostic paradigm for RA-ILD,

and all CT-ILDs, does not include the determination of the underlying radiologic and/or histopathologic pattern.

IPF is defined by the presence of the UIP pattern in all cases, either radiographically or histologically [46], without an identifiable cause. The histologic findings of UIP in IPF are identical to UIP in RA-ILD with the exception of findings that includes the presence of more extensive lymphoid aggregates, organizing pneumonia and bronchiolitis.

Genetic susceptibility

Recent work in the genetics of RA-ILD suggests a common genetic susceptibility to the development of both IPF and RA-ILD. A whole exome sequencing study, followed by a restricted analysis to familial pulmonary fibrosis-linked genes [47-54], found similar genetic mutations in *TERT, RTEL1, PARN and SFTPC* in a French RA-ILD cohort [8], although these findings were limited by the lack of comparison to RA subjects without ILD. Subsequently, the *MUC5B* gain of function single nucleotide polymorphism in rs35705950 was also found to be significantly associated with RA-ILD [7]. The *MUC5B* promoter variant has been shown to be a significant genetic risk factor for the development of IPF [6, 55-58] and this recent work finds that the promoter variant accounts for a similar risk for ILD in RA patients [59]. Further, the *MUC5B* association with ILD in RA appears to be driven by those with a radiologic UIP or possible UIP pattern of disease [7]. This association between *MUC5B* and ILD in RA is more predictive than any other previously reported clinical risk factor or association including smoking [7]. This relationship has not been observed in other connective-tissue disease associated ILDs (e.g. scleroderma, myositis) [60, 61], but has been observed in another ILD with a higher prevalence of the UIP pattern, fibrotic hypersensitivity pneumonitis [62]. Last, exploratory analyses have demonstrated similar associations between other common variants identified in IPF [63] in RA-ILD [59], though this study was not powered to confirm these common variants as genetic risk factors.

Risk factors for development of ILD

Despite the female preponderance in RA, males are more commonly affected by RA-ILD. Similar to IPF, RA-ILD affects men nearly two times as often as women [3, 64, 65]. The other common associations with the development of ILD in RA are RA disease activity, age and smoking status, [14, 59, 65]. Most patients with RA-ILD are diagnosed with ILD in their fifth or sixth decades of life and age has repeatedly been shown to be an independent risk factor for development of ILD in RA populations [30]. Additionally, there is a clear preponderance for the development of IPF with aging, for instance in one study the prevalence of IPF increased from 4 in 100,000 in persons aged 18-34 to 227.2 per 100,000 in those aged greater than 75 years [28]. Other risk factors specific for RA-ILD include the duration of RA and older age at RA onset [2, 66, 67]. In both IPF and RA-ILD the most common environmental risk factor is smoking. The odds ratio for development of ILD in RA for those who smoked > 25 years was 3.8 (CI 1.59, 8.88) [68]. Similarly, the odds ratio for development of IPF in heavy smokers (21 to 40 pack years) is 2.3 (CI 1.3, 2.9) [69].

Other co-morbidities and risk factors, such as gastroesophageal reflux disease (GERD) and obstructive sleep apnea (OSA), have been described in IPF and may have implications on development and/or progression of the disease [70-76]. However, the relationship of these co-morbidities in RA-ILD is less clear. Further investigation into these associations would be clinically relevant as both GERD and OSA have clinical interventions that are effective.

Nomenclature and diagnosis

The diagnosis of RA-ILD requires the presence of RA and radiologic findings compatible with interstitial lung disease. Currently, the diagnostic paradigm does not require the identification of the underlying histopathologic pattern (e.g. UIP vs. NSIP), however should include the exclusion of other causes of lung disease in an RA patient (e.g. drug toxicity, opportunistic infection), particularly if the imaging is not compatible [77]. In contrast, IPF is diagnosed by the presence of the UIP pattern on

radiology and/or histopathology with the exclusion of other diseases that can lead to the UIP pattern, including RA and chronic hypersensitivity pneumonitis [46]. By virtue of this, a patient with RA cannot be diagnosed with IPF.

Given the clinical and genetic similarities that are being uncovered, some have questioned this construct. While there are risk factors specifically related to RA that appear to be risk factors for ILD in this population, as discussed above, there are other scenarios, albeit less common, that suggest this may not always be the case (e.g. concurrent presentation of RA and ILD and development of RA after the diagnosis of ILD) [5]. The majority of the data does not distinguish between these sub-phenotypes of clinical presentation and more work needs to be done to determine if UIP in RA is concurrent IPF or an extra-articular manifestation of RA.

Molecular markers of disease

Biomarkers may have diagnostic or prognostic functions in disease states. In addition, with ongoing development of therapeutic targets in ILD, biomarkers may also play a theragnostic role in quantifying or anticipating response to therapy. And, while an exhaustive discussion of biomarkers currently under study in both of these conditions is beyond the scope of this review, we will highlight a few candidate biomarkers identified as a result of data from one or both conditions. See Table 2 for a more exhaustive list of candidate molecular markers which have been shown to have diagnostic or prognostic ability in RA-ILD and/or IPF.

Biomarkers associated with alveolar epithelial cell dysfunction: telomere length

Telomeres are a repetitive region of DNA-protein structure found at both ends of chromosomes and function to protect the chromosomes and genomic structures from nucleolytic degradation [78]. Disease states associated with short telomeres often are associated with mutations in the telomerase complex, which restores telomere length. Mutations in telomerase reverse transcriptase (TERT) and telomerase RNA (TERC) lead to telomere shortening and are found in 8% of patients with

familial pulmonary fibrosis [49]. In sporadic IPF, short telomeres are found in the circulating leukocytes of 23% of patients, even in the absence of a known telomerase mutation [79]. These data suggest that aberrant telomere repair and resultant cellular senescence may be involved in the development of IPF.

Recent data suggests that telomere length in in RA-ILD is shorter than that seen in other CT-ILDs and that this group had poorer outcomes when compared to the other CT-ILDs in terms of survival and pulmonary function indicating a possible prognostic role for telomere length in RA-ILD [80]. Higher rates of mutations in genes encoding for telomere maintenance (e.g. *TERT, RTEL1, PARN*) have been found in RA-ILD when compared with controls. Those with the mutations had shorter leukocyte telomere lengths compared with controls. [8] Shortened telomeres have previously been thought to play a role in the increased age propensity for RA, where CD4 T-cells in RA exhibit ineffective up-regulation of TERT, increasing apoptosis and limiting clonal expansion [81]. Immune senescence has long been a feature of RA, and some investigators have hypothesized that this lack of telomere maintenance through TERT-mediated telomerase down-regulation plays a role in the pathogenesis of immune dysregulation in RA [82].

Further understanding of telomere biology in RA-ILD may have therapeutic implications and telomere length should be further explored as a prognostic and potentially theragnostic marker.

<u>Biomarkers associated with extracellular matrix remodeling and fibroproliferation: matrix metalloproteases</u>

Matrix metalloproteases (MMPs) play a role in extracellular matrix (ECM) turnover regulation. MMPs are endopeptidases whose primary role is to degrade ECM proteins [83]. MMP-1 and MMP-7 levels (in plasma and bronchoalveolar lavage fluid) were significantly higher in IPF than controls, which included subjects with acute and chronic hypersensitivity pneumonitis (HP), and other fibrotic lung conditions such as sarcoidosis [84]. Aside from distinguishing IPF from chronic ILDs, MMP may also

be a prognostic biomarker. MMP-7 levels in IPF have been shown to be negatively correlated with diffusing capacity and positively correlated with the GAP scoring system [85]. In addition, MMP-7 values change over time in individuals with IPF and this change has been shown to correlate, within individuals, with worsening lung function [86].

In RA synovial disease, the underlying pathogenesis is also related to abnormal deposition of ECM proteins as well as cartilage destruction which is mediated by these endopeptidases, among others [87]. Expression of several MMPs (1, 2, 3, 9, 13) have been shown to be elevated compared to control cohorts in RA patients and inhibitors of these enzymes have been proposed as a potential therapeutic target for RA synovial disease [87]. In RA-ILD, MMP-7 levels are elevated when compared to those with RA without ILD [88]. Additionally, in US cohorts of RA-ILD, the value of MMP-7 has been shown to be negatively correlated with markers of pulmonary function (FVC and DLCO) and with worse dyspnea scores [88].

Biomarkers associated with immune dysfunction: citrullinated proteins

Citrullination is the post-translational modification of a peptide that is catalyzed by peptidyl arginine deiminase (PAD), which converts an arginine to a citrulline. This formational and structural alteration fundamentally changes the way the immune system interacts with the protein. Having been altered, the immune system now recognizes the protein as foreign. As such, auto-antibodies are subsequently generated to the "citrullinated" protein, known as anti-citrullinated protein antibodies (ACPA). ACPAs are implicated directly in the pathogenesis of RA and antibodies detected in serum, such as anti-cyclic citrullinated protein (anti-CCP), are highly predictive of RA development and are useful diagnostic biomarkers [89].

In RA-ILD, an association between ILD and the presence of APCAs has been observed. Studies have shown significantly higher levels of ACPA in those patients with RA-ILD when compared to RA without lung disease, even after matching for disease severity and age [90-92]. Levels of ACPA titer

have also been associated with the presence of restrictive physiology or diffusion capacity limitations in patients with RA and the likelihood of having ILD [90]. This association between RA-ILD and APCA titer raises the possibility that ACPA generation could be related to the pathogenesis of RA-ILD.

In IPF, a disease not currently thought to have any significant component of autoimmunity, there are higher rates of ACPAs detectable in explanted lung tissue than those of controls (46% vs. 20%) [67]. Rates of citrullinated proteins in explanted IPF lung tissue were as high as those found in patients with RA-ILD [67]. Further, in a cohort of patients with IPF, rates of serum anti-CCP (IgA isotype) were 21% compared to 6% in the control cohort [93]. While both IPF and RA-ILD have ACPAs in their serum, ACPA has been clearly linked to the pathogenesis of synovial RA. While in IPF and RA-ILD, the association with ACPA and presence of pulmonary fibrosis is seen, it remains to be understood how these serum and lung ACPAs are generated and what, if any, role they may play in pathogenesis of the condition.

Future directions in understanding pathogenesis of RA-ILD and IPF

The biomarkers described above are obvious candidate biomarkers based on our current understanding of RA, RA-ILD and IPF. These biomarkers may help us better understand the pathophysiology of RA-ILD and its seeming overlap with IPF. However, other approaches could also identify novel biomarkers for either or both of these disease states that could be equally, if not more, informative.

The advancing field of -omics holds the promise of identifying a “molecular endotype”, which may provide new insights into the link between these two conditions. Additionally, given that IPF and RA-ILD are heterogeneous disorders that can funnel into a common histopathologic pathway of UIP, the application of an –omics approach may shed light on common or disparate biologic pathways and processes that lead to the fibrotic phenotype of UIP in these conditions.

Further, comparisons across fibrotic diseases affecting different organs (e.g. liver, skin, kidney) is another strategy that could be employed to elucidate common fibrotic pathways which may not be conserved to IPF. For example, in an analysis of the lung and skin tissue of scleroderma patients with ILD, a deep proteomics profiling strategy identified a shared high prevalence of MZB1-positive plasma B cells in both the lung and skin [94]. The presence of an antibody-producing plasma cell signature in fibrotic models of disease further lends credence to the theory of antibody mediated-fibrotic mechanisms, which could be another mechanistic trait connecting IPF and RA-ILD.

Summary

While the presence of an underlying autoimmune disease such as RA has impacted the diagnostic approach and approach to treatment in ILD, it may be that we can learn important lessons from IPF. This review has outlined the similarities and differences in clinical presentation, appearance and outcomes in RA-ILD and IPF. The recent finding of a shared genetic susceptibility between IPF and RA-ILD has sparked additional interest in this relationship. Further investigation of candidate and novel biomarkers that are similar or dissimilar in RA-ILD and IPF will better elucidate common biologic mechanisms between these two conditions. The drive to better understand RA-ILD in the context of what we know in IPF is underscored by our divergent treatment paradigms for these conditions and the concern for potential harm. As a result of advancing our understanding of the links between IPF and RA-ILD, current strategies for diagnosis, screening, and treatment of ILD may fundamentally change in the coming years. Until then, clinicians face difficult clinical questions regarding the co-management of the articular disease and the ILD in RA and treatment decisions should be made in a multi-disciplinary format with collaboration between pulmonologists and rheumatologists.

Figure Legend

Figure 1: This schematic illustration highlights the similarities and differences between idiopathic pulmonary fibrosis (IPF) and rheumatoid arthritis associated interstitial lung disease (RA-ILD). The yellow section identifies clinical features unique to IPF: (1) the usual interstitial pneumonia (UIP) pattern is seen in all cases, (2) treatment in IPF is anti-fibrotics and not immunosuppression, and (3) IPF is a lung-limited condition. The blue section identifies clinical features unique to RA-ILD: (1) UIP is the most common pattern of ILD in RA but other patterns exist, (2) the treatment strategy in RA-ILD is based on immune suppression, and (3) RA is a multi-system disease where ILD is one of many possible manifestations of RA. The green section includes areas of overlap between IPF and RA-ILD: both are diseases of the aging population, affect men more than women, risk factors include smoking and genetics, and are associated with poor survival and acute exacerbations.

Figure 2: This is a representative computed tomography image of the chest from a patient with rheumatoid arthritis associated interstitial lung disease. Radiologic usual interstitial pneumonia (UIP) pattern is defined as basilar, sub-pleural distribution of reticulation and traction bronchiectasis with honeycombing without features incompatible with UIP [95]. This radiologic pattern is highly specific for the UIP pattern on surgical lung biopsy [57].

Figure 3: Representative CT image of NSIP (non-specific interstitial pneumonia. Radiographic NSIP pattern is defined by bilateral and symmetric ground-glass opacities. There can be fine peripheral reticulations and evidence of fibrosis by traction bronchiectasis. In this image there is also an example of sub-pleural sparing. Image courtesy of Tami Bang, MD.

Figure 4: This is a low power (2A) and high power (2B) view of a lung biopsy from a patient with rheumatoid arthritis associated interstitial lung disease. Usual interstitial pneumonia (UIP) on histopathology is characterized by subpleural fibrosis, spatial and temporal heterogeneity, fibroblast foci and microscopic honeycombing [96]. This biopsy has features of UIP, but also has an abundance of lymphoid aggregates. Biopsy images courtesy of Carlyne Cool, MD.

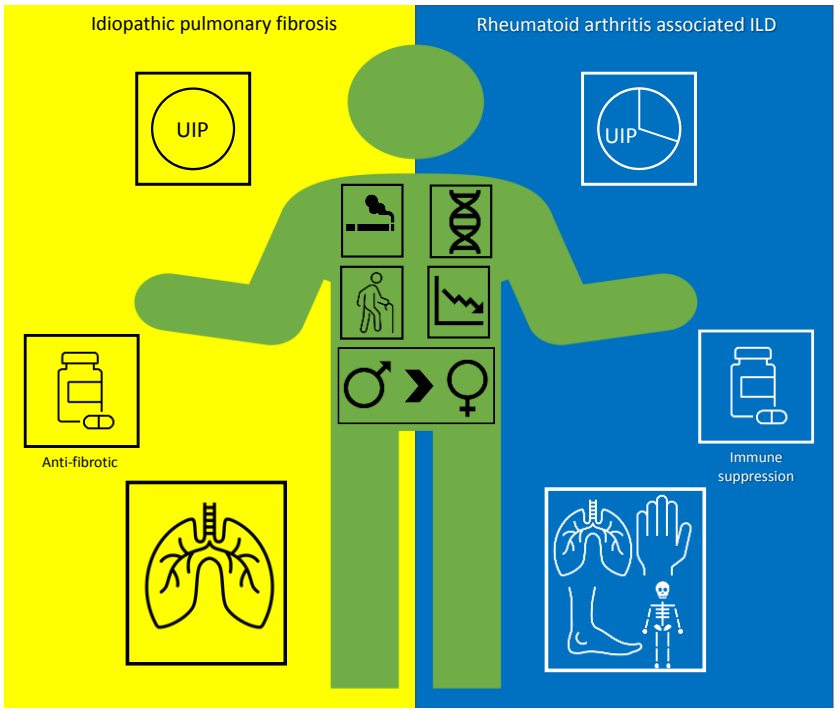
Idiopathic pulmonary fibrosis
Rheumatoid arthritis associated ILD
UIP
UIP
Anti-fibrotic
Immune suppression

Figure 1

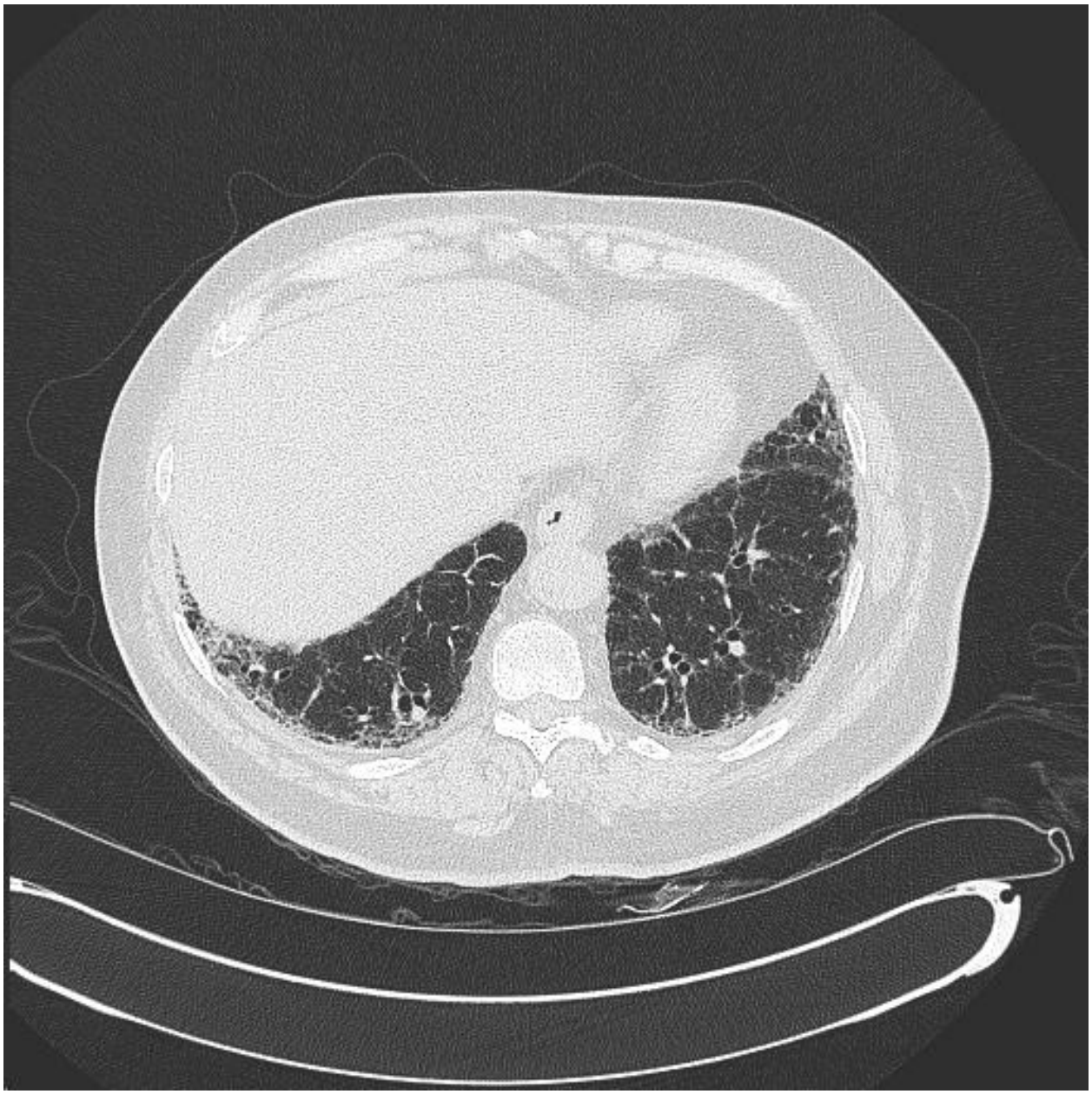

Figure 2

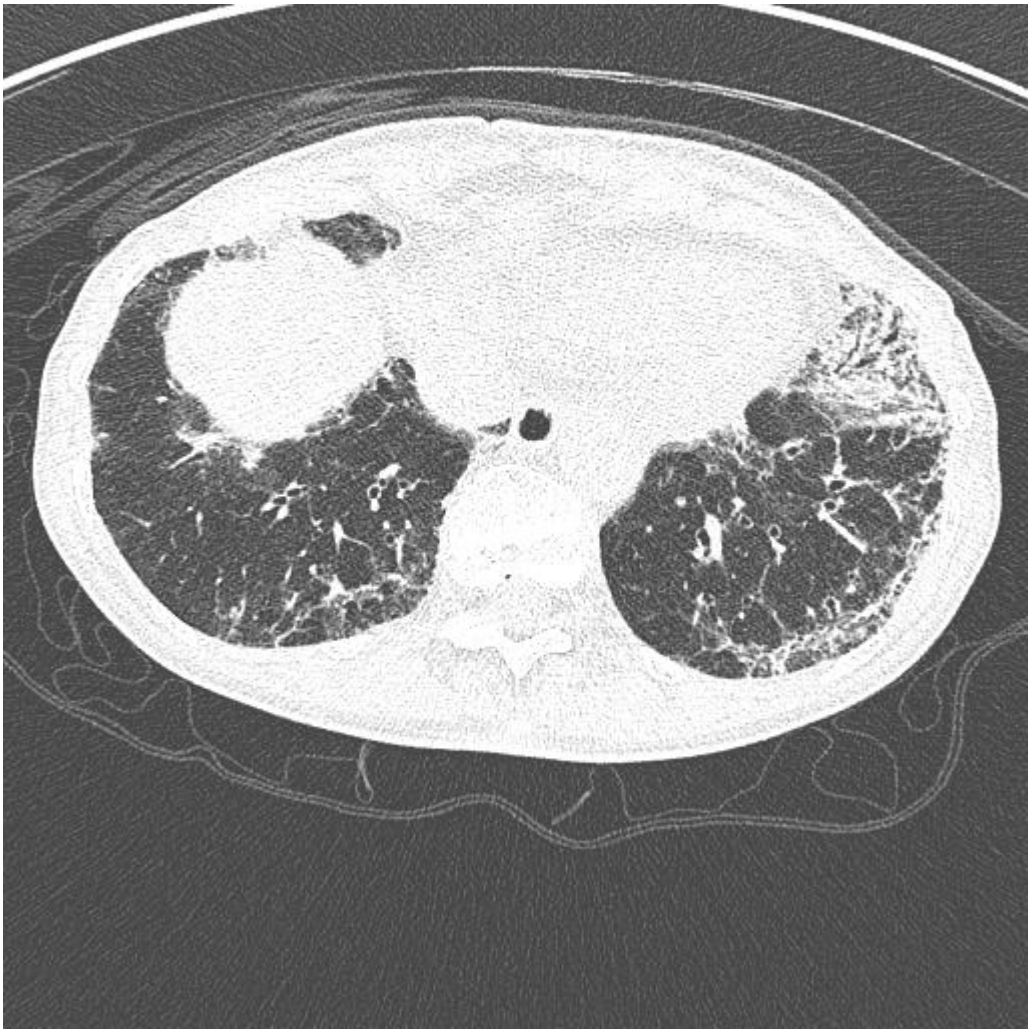

Figure 3

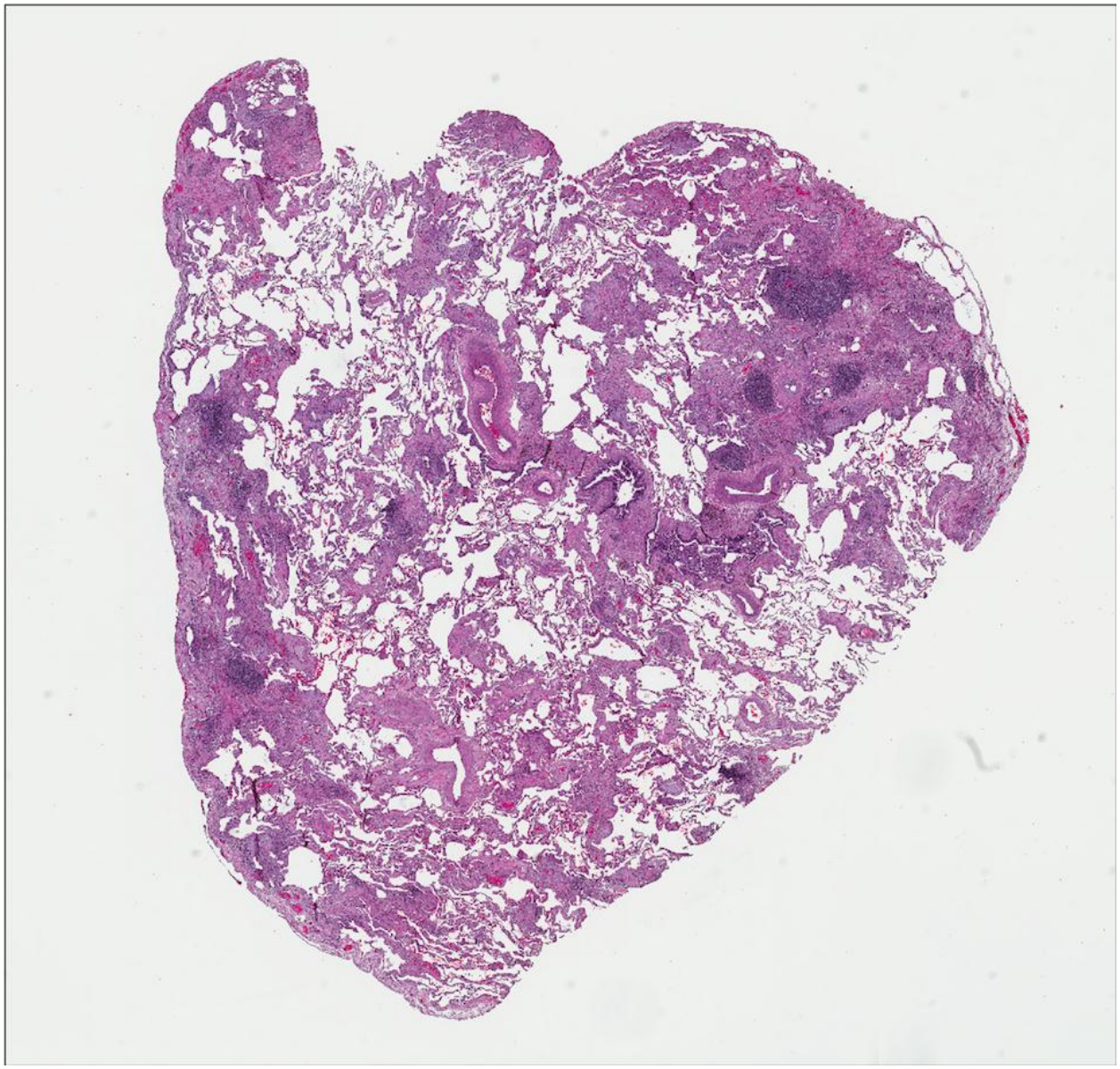

Figure 4A

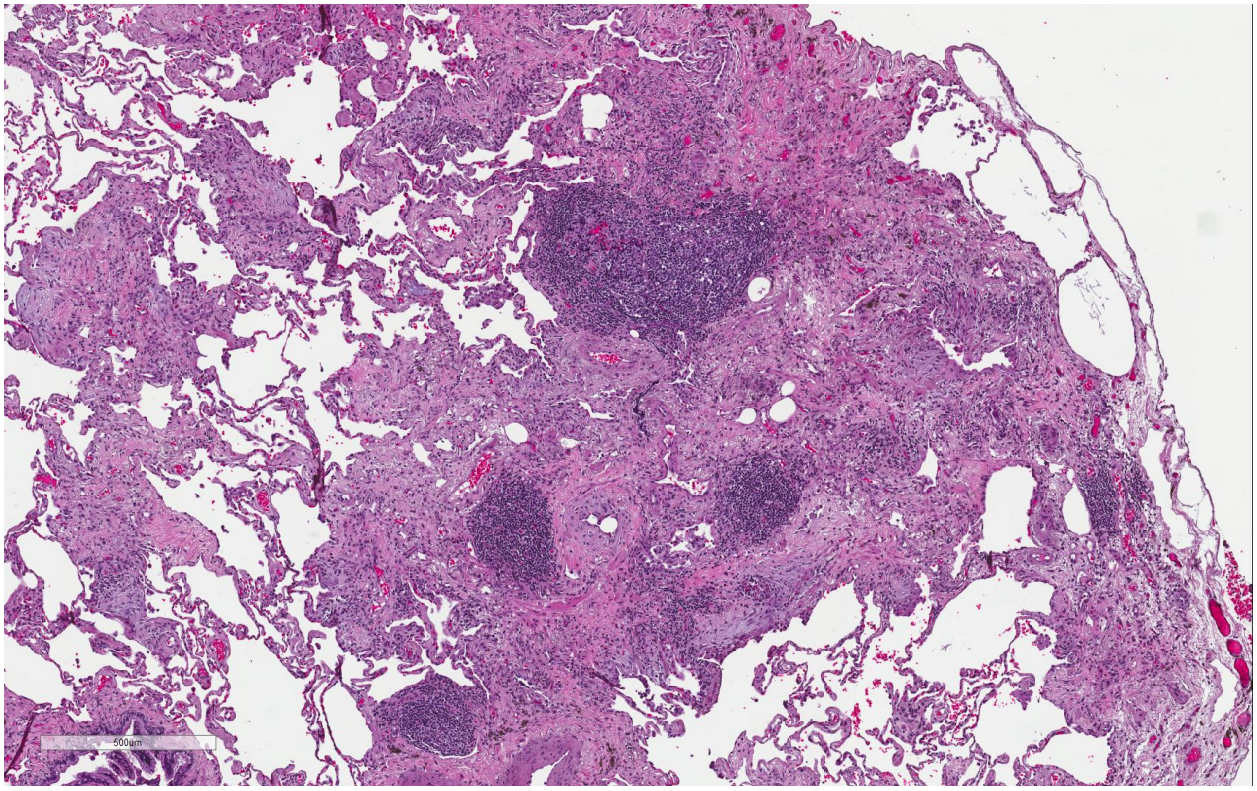

Figure 4B

Table 1. Clinical features of RA-ILD and IPF

	Rheumatoid arthritis interstitial lung disease	**Idiopathic pulmonary fibrosis**
Age	Most commonly diagnosed in 6th decade of life, age is an independent risk factor for development of ILD in cohorts of RA [30, 65]	Incidence highest in ages 70-79 [27]
Sex	More common in men (2:1 ratio) [3, 64]	More common in men (2:1 ratio) [27, 28]
Cigarette smoking	Odds ratio for development of RA-ILD for those who smoked > 25 years is 3.8 (CI 1.59, 8.88) [68]	Odds ratio for developing IPF amongst heavy smokers (21 to 40 pack years) is 2.3 (CI 1.3, 2.9) [69]
Genetic risk	*MUC5B* promoter variant polymorphism significantly associated with RA-ILD and UIP phenotype [7] Telomere maintenance gene mutations associated with RA-ILD [8]	*MUC5B* promoter variant polymorphism significantly associated with IPF, confers up to 30% of the risk of development of IPF [6, 55, 56, 97] Shortened telomeres related to telomerase and telomere maintenance gene mutations associated with IPF and worse survival [62]
UIP pattern	Seen in > 50 % of cases [37]	Required for diagnosis of IPF [46]
Gastroesophageal reflux	Unknown association	Known association with IPF [98] role of medical or surgical treatment is unclear [70, 99]
Obstructive sleep apnea	Association with RA but no studies in RA-ILD [100, 101]	Known association with IPF but the impact of treatment is unknown [74, 75, 102]
Acute exacerbation	Acute exacerbations of ILD occur, however only reported in the UIP phenotype of RA-ILD [33]	Acute exacerbation in IPF has a 1 and 3-year incidence of 14.2 and 20.7% respectively [34, 103]
Survival	Median survival 2.6 years among those with a UIP pattern [2]	Median survival 3.5 years [27]
Immune suppression based treatment strategy	Unknown efficacy, but is the standard of care [104]	Combination therapy with prednisone, azathioprine and N-acetylcysteine has been associated with higher morbidity and mortality [10]

Anti-fibrotic treatment strategy	Patients with RA-ILD made up 12.7% of the intervention group (and 14.2% of the placebo arm) in the INBUILD trial of anti-fibrotic use in progressive fibrotic ILDs, which was associated with slower decline in lung function compared to placebo [105]	Associated with slower decline in lung function [106, 107]

GER – gastroesophageal reflux , ILD – interstitial lung disease, IPF – idiopathic pulmonary fibrosis,

OSA – obstructive sleep apnea, RA – rheumatoid arthritis, UIP – usual interstitial pneumonia

Table 2. Molecular markers of disease in RA-ILD and IPF

Marker	Observation in RA-ILD	Observation in IPF
Telomere length	Shortened telomeres associated with RA-ILD and associated with worse survival [63].	Shortened telomeres associated with IPF and associated with worse survival [62]
MMP-7	Differentiates RA-ILD from RA without ILD and correlated with worse pulmonary function and diffusing capacity [71]	Differentiates IPF from controls and correlated with worse pulmonary function and diffusing capacity [68, 69]
ACPA	Differentiates RA-ILD from RA without ILD and correlated with worse pulmonary function and diffusing capacity [73, 75, 76]	Higher rates in IPF than seen in controls [91], unclear association with pulmonary function
IP-10/ CXCL10	Differentiates RA-ILD from RA without ILD and correlated with worse pulmonary function and diffusing capacity [71]	Not reported in IPF. Currently under investigation as therapeutic target, given effects seen in murine models of IPF [108]
Rheumatoid Factor	Levels of RF increased in RA-ILD when compared to RA without ILD; with higher levels in sub-clinical lung disease than clinically-evident RA-ILD [25]	Not reported in IPF
Surfactant proteins	SP-D differentiates RA-ILD from RA without ILD as a part of a diagnostic model when combined with MMP-7, PARC and clinical risk factor score [25]	SP-A/D differentiate IPF from normal controls and correlated with worse survival [109]
KL-6	Associated with deterioration in RA-ILD, additionally KL-6 levels decreased with successful treatment of RA-ILD indicating possible role of KL-6 as theragnostic biomarker [110]	Elevated KL-6 levels in IPF were associated with poorer prognosis and serial increases in KL-6 also portend more rapid decline in pulmonary physiology and increased mortality [111]
CCL-18	CCL-18 levels higher in the BALF of RA-ILD subjects than controls, and CCL-18 levels in BALF predicted mortality during hospitalization [112]	Baseline levels of CCL-18 predicted decline in FVC and DLCO at 6 months and baseline CCL-18 level in IPF correlated with worse survival [113]
LOXL2	Serum LOXL2 levels in RA-ILD higher than those in control subjects, LOXL2 was highest in those RA-ILD patients with shorter duration of lung involvement (< 3 months compared to > 3 months) and	In IPF cohorts, higher serum LOXL2 levels were correlated with worse pulmonary physiology and greater risk for mortality and disease progression [115]

	LOXL2 was correlated with worse FVC and DLCO [114]	
Periostin	Not reported in RA-ILD	Associated with IPF disease progression [116]
IL-8	Not reported in RA-ILD	Correlated with worse FVC and DLCO and predicts disease activity [117]
Heat shock proteins	Autoantibodies to HSP-90 differentiated RA-ILD from IPF and differentiated RA-ILD patients from RA patients without ILD, unclear association with disease activity [118]	Patients with IPF who have autoantibodies to HSP-70 have worse near-term decline in FVC and DLCO and worse mortality [119]
CXCL-13	Not studied in RA-ILD	Higher levels of CXCL-13 in IPF are associated with worse prognosis [120]
CA-125	Differentiates RA-ILD patients from RA without ILD patients, not clear if has prognostic ability in RA-ILD [121, 122]	Differentiates IPF from CT-ILDs, correlated with disease progression and worsened survival, also associated with lung cancer in IPF [123, 124]
YKL-40	Not studied in RA-ILD	Differentiates IPF patients from controls and idiopathic NSIP, serum and BALF levels associated with worsened survival [125, 126]

ACPA – anti-citrullinated protein antibodies, ILD – interstitial lung disease, IPF – idiopathic pulmonary fibrosis, MMP – matrix metalloproteinase, RA-ILD – rheumatoid arthritis associated interstitial lung disease, FVC – forced vital capacity, DLCO – diffusing capacity for carbon monoxide, SP-D – surfactant protein D, PARC – pulmonary and activation-regulated chemokine, KL-6 – Krebs von den Lungen-6, BALF – bronchoalveolar lavage fluid, LOXL2 – Lysyl oxidase-like 2, IL-8 – Interleukin-8, HSP – Heat shock protein-70, CXCL-13 – C-X-C motif chemokine 13, CT-ILDs – connective tissue associated interstitial lung diseases, NSIP – nonspecific interstitial pneumonia

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