Review Article

Patterns of lung fibrosis in patients with interstitial pneumonia with autoimmune features and connective tissue diseases-associated interstitial lung disease—a narrative review

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Background and Objective: Interstitial pneumonia with autoimmune features (IPAF) was defined in 2015 as a research statement of European Respiratory Society and American Thoracic Society. Connective tissue diseases (CTDs) manifest in the respiratory tract, the main manifestation being interstitial lung disease, which contributes to morbidity and mortality. This poses numerous clinical challenges and is a substantial burden on healthcare systems around the world. The objective of this narrative review was to provide readers with a comprehensive and extensive overview of such manifestations in the respiratory system, analysis of prevalence of specific manifestations in the lung and to characterize population of patients with IPAF.

Methods: We reviewed the current state of knowledge on radiological findings in interstitial lung diseases in course of convective tissue diseases and IPAF, a narrative review of PubMed database using Advanced Search Builder was performed. The search was conducted from 15.07.2021 to 03.04.2022. A total of 655 articles in English were reviewed.

Key Content and Findings: Similarities and differences between interstitial pneumonia in course of well-established CTDs and IPAF are discussed with special emphasis on required future research areas. Manifestations of CTDs in the respiratory system are overviewed, with the emphasis on interstitial lung disease, as despite clinical similarities of various connective tissue diseases, there is variability in their presentation in the respiratory system, radiological patterns and clinical outcomes. We would also like to draw readers' attention to clinical significance of interstitial lung abnormality both in the context of CTDs and lack of underlying autoimmune disorders.

Conclusions: There is need for prospective cohort studies regarding the natural course of IPAF, its clinical stability and its manifestations in the respiratory system. Prospective studies are also required to evaluate diagnostic and prognostic factors of IPAF. Interstitial lung disease associated with CTDs (CTD-ILD) is a significant factor impacting clinical outcomes and patient prognosis, therefore its diagnostic work-up is best performed by an experienced multidisciplinary team and with use of procedures of high diagnostic yield.

Keywords: Interstitial pneumonia; connective tissue disease (CTD); autoimmunity

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Introduction

Connective tissue diseases (CTDs) affect proteins forming organ structure through autoimmune-mediated inflammation and circulating autoantibodies. Although there are various manifestations of CTDs in the respiratory system, the most prevalent is interstitial lung disease (ILD) (1), leading to pulmonary function impairment. Among CTDs manifesting themselves in various ways in the respiratory system, the most prevalent are rheumatoid arthritis (RA), systemic sclerosis (SSc), mixed connective tissue disease (MCTD), Sjögren's syndrome (SS), systemic lupus erythomatosus (SLE) and polymyositis/dermatomyositis (PM/DM).

The prevalence of CTD-ILD understood as ILD occurring in patients with previously diagnosed CTD, ranges from 12.4% to 67.1% (1). CTD may also manifest itself in the respiratory system as airway disease, vasculopathy, lymphoproliferative disease and pleural pathology (2). This is why CTD patients should be evaluated and periodically reevaluated for ILD. ILD contributes to mortality and morbidity in individuals with CTD. Kocheril *et al.* (3) revealed 5-year survival rate of 43.4% of CTD-ILD patients. This statistic varies based on the fibrosis type and comorbidities.

A negative tendency of forced vital capacity (FVC) decline was impacted by introduction of anti-fibrotic agents such as nintedanib for patients with non-IPF fibrosing ILD; the effect on long-term survival in CTD-ILD remains to be determined in prospective studies (4).

In RA, occurrence of ILD is associated with significantly lower survival years; according to a large database analysis by Raimundo *et al.* (5), as the mortality rate for RA-ILD patients was found to be 35.9% at 5 years, and the median survival was calculated at 7.8 years (5).

According to Hyldgaard *et al.* (6) mean survival in RA-ILD is 5–8 years. We summarize the clinical presentation of RA-ILD in *Table 1*.

The occurrence of ILD in SSc, apart from increased hospitalization rates, is associated with significant morbidity, as 10-year mortality reaches 40% (20). Characterization of SSc-ILD is presented in *Table 2*. *Figures 1*,*2*, consecutively, are examples of nonspecific interstitial pneumonia (NSIP) and NSIP/organizing pneumonia (OP) overlap in course of SSc.

Mortality in SSc, apart from SSc-ILD, is associated with severe organ malfunction. Patients with diffuse skin involvement, FVC <55% (a surrogate for severe ILD), malabsorption syndrome, cardiac arrhythmia, congestive heart failure or renal failure had a 9-year survival rate of 38%, whereas those with mild organ involvement had a 9-year survival rate of 78% (35).

ILD is nowadays the leading cause of SSc-related mortality (36).

In inflammative myositis-associated ILDs (PM/DM-ILD) (overview provided in *Table 3*), overall mortality was 7.5% over a median follow-up period of 34 months as reported in a case series of 107 patients (38). Data on prognosis for SLE-ILD patients is scarce, however, the occurrence of ILD within 1 year is thought to be a death predictor. The death rate is circa 12.5% at a mean follow-up period of 4.3 years from the time of initial SLE diagnosis (49). We summarize the clinical characteristics of SLE-ILD in *Table 4*.

In MCTD-ILD, at a mean follow-up period of 4.2 years, the overall mortality was circa 7.9%. The mortality in MCTD patients with normal HRCT was around 3.3%, in comparison with 20.8% in patients with severe fibrosing ILD (59). Clinical characteristics of MCTD-ILD is summarized in *Table 5*.

In a study on primary SS-ILD (67), mean survival time was calculated at 9.0 years. The 10-year survival rate for all patients with pSS-ILD was 81.7%. Overview of SS-ILD course, prognosis and predictors is provided in *Table 6*. *Figure 3* is an example of lymphocytic interstitial pneumonia as pulmonary manifestation of SS, which is highly specific yet quite rare.

Pulmonary involvement usually follows CTD systemic manifestations, however, it may precede them by months or years (82).

Taken into account differences in the clinical presentation of ILD in relation to the underlying CTD, their thorough rheumatological diagnosis may optimize screening for ILD, follow-up, dedicated pharmacotherapy and eventually referral for lung transplantation. Severe refractory CTD-ILD, above all in the course of SSc or RA in patients without extrapulmonary contraindications

Table 1 General overview of CTDs—RA

Feature	Description
General information	Affects circa 1% of the worldwide population
	The most common CTD
	Affects primarily the synovial joints (female:male ratio, 3:1) (7)—articular manifestation more common in females, pulmonary symptoms more frequent in males (7)
	Pulmonary involvement: circa 10–20% of mortality overall (8) is the second most common cause of death (9)
	ILD: the most common form of pulmonary involvement (10)
	May involve airways, blood vessels, parenchymal tissue, pleura (unilateral pleural effusion and pleural thickening: the most frequent thoracic manifestation, is clinically relevant in 5% of cases but is found in 38% to 73% on autopsy (11)
	In circa 20% of patients, pulmonary symptoms may precede articular involvement (12)
Prevalence of RA-ILD	5.00% (13)
Radiological patterns of RA-ILD	UIP (the most common, in 41% of patients—unlike other CTDs)
	NSIP (30%), bronchiolitis (17%), and OP (8%) (14)
	Surgical lung biopsy: UIP described in 56% of patients, NSIP in 33% and OP in 11% (12)
	No survival difference between RA-UIP and IPF (15)
	Small airways manifestation: constrictive bronchiolitis, follicular bronchiolitis, evidence on HRCT (mosaic attenuation in inspiratory scans and air trapping in expiratory scans.) in up to 66 % of subjects with normal PFTs (16)
	Bronchiectasis, bronchial wall thickening: constrictive bronchiolitis (17)
	Necrobiotic lung nodules, from 0.5 to 5 cm in diameter, located in the mid and upper lung zones in up to 20%, of patients, usually asymptomatic: males, smokers and patients with high RF titer and subcutaneous nodules (18)
Predictors of RA-ILD	Male gender, active smoking, increasing age: associated with development of RA-UIP; similar patient profile as in IPF (19)

CTDs, connective tissue diseases; RA, rheumatoid arthritis; ILD, interstitial lung disease; HRCT, high resolution computed tomography; IPF, idiopathic pulmonary fibrosis; NSIP, non-specific interstitial pneumonia; OP, organizing pneumonia; PFTs, pulmonary function tests; RA-UIP, usual interstitial pneumonia in course of rheumatoid arthritis; UIP, usual interstitial pneumonia.

to transplantation, may be treated according to guidelines similar to those proposed for idiopathic ILD (83).

The term IPAF has been proposed in 2015 by Working Group consisting of pulmonologists and rheumatologists as a diagnosis concentrated on presence of a combination of clinical, morphologic and serologic features in patients who do not meet diagnostic criteria of specific CTDs, yet display hallmarks of underlying autoimmune processes leading to ILD development (84). These patients may benefit from use of immune suppressors, therefore thorough clinical assessment and differential diagnosis conducted by an experienced multidisciplinary team is needed (85). In this narrative review, we attempt to provide a summary of the available data regarding the prevalence and patterns of CTD-ILDs and IPAF and we aim to answer the following questions:

(I) What is the prevalence of specific types of pulmonary manifestations in course of CTDs?
(II) Is there a significant difference in survival and patient-related outcomes in CTD-ILDs and their idiopathic counterparts?
(III) Is it possible to characterize IPAF population, especially against CTD-ILDs and idiopathic ILDs?
(IV) Are there any specific radiological findings which may prompt clinicians to screen for a specific CTD?

We present the following article in accordance with the Narrative Review reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-21-3974/rc).

Table 2 General overview of CTDs—SSc

Feature	Description
General information	Autoimmune disease leading to fibrosis of the skin and multiple internal organs (21)
	Diffuse SSc: skin fibrosis of the face, trunk, shoulders, pelvis and proximal limbs
	Limited SSc: distal extremities, hands
	Small percentage of cases, presence of autoantibodies and internal organ involvement without skin fibrosis (SSc sine scleroderma)
Prevalence of ILD	65% of SSc patients in HRCT (22), but only up to 40% of them develop a clinically significant ILD, with a 10-year mortality of up to 40% (23)
Radiological patterns of SSc-ILD	Predominant pattern: NSIP, circa 77.5% of patients
	The second most common: UIP, circa 7.5% of patients, non-specific findings in the rest (24)
	Lung biopsy: NSIP in 69% of patients, UIP in 16% (25)
	Presence of pulmonary fibrosis on HRCT (i.e., traction bronchiectasis, reticulation) 92.9% of patients; 49.4% of whom had only ground glass opacities and 37.2% had honeycombing (26)
	Higher prevalence of honeycombing the course of limited SSc than in diffuse SSc (26)
	Other findings include dilated oesophagus, changes resulting from chronic aspiration, features of pulmonary hypertension (enlargement of pulmonary artery and right ventricular enlargement) (23)
Predictors of SSc-ILD	Internal organ involvement (high blood creatinine, cardiac involvement), hypothyroidism, vast areas of skin fibrosis (high skin scores), elevated creatinine phosphokinase level (27)
	Positive Scl-70 (anti-topoisomerase) associated with ILD occurrence (ILD in 60% of 3,656 Scl-70 positive patients in European League Against Rheumatism Scleroderma Trials and Research database) (28)
	Presence of anti-eIF2B antibodies, anti-U11/U12 ribonucleoprotein antibodies (29)
	No such association with anticentromere antibodies (only 21% of patients with anticentromere autoantibodies had SSc-ILD) (28)
	Other antibodies associated with increased occurrence of SSc-ILD: anti-U3 RNP, anti-RNA polymerase III, anti-U11/U12 RNP (30-32), Ro52 (33)
	Male sex, features of pulmonary hypertension on echocardiography, digital ulceration, presence ailfold capillary abnormalities, polymorphism in the HLA region (HLA-DRB1*11 HLA-DRB1*301) (23)
	Reduced FVC, reduced DLCO (34)

CTDs, connective tissue diseases; SSc, systemic sclerosis; HRCT, high resolution computed tomography; ILD, interstitial lung disease; NSIP, non-specific interstitial pneumonia; UIP, usual interstitial pneumonia; eIF2B, eukaryotic initiation factor 2B; HLA, human leukocyte antigen; RNP, ribonucleoprotein; HLA-DRB1*11 HLA-DRB1*301, human leukocyte antigen allele DRB1*11 HLA-DRB1*301; FVC, forced vital capacity; DLCO, diffusing capacity for carbon monoxide.

Methods

In this article, we reviewed 647 articles in total (PubMed database search 03.04.2022) on the subject of manifestation of various CTDs in the respiratory system and their radiological presentations and clinical/radiological presentation of IPAF. The latter was defined according to the official European Respiratory Society/American Thoracic Society research statement on interstitial pneumonia with autoimmune features published in 2015. The articles we reviewed included retrospective and prospective cohort studies as well as case reports. We searched the database using the following keywords: connective tissue disease (AND) interstitial lung disease, CTD (AND) ILD, interstitial pneumonia with autoimmune features, IPAF. We excluded studies on pediatric ILD, ILD of known ethology (smoking-related, hypersensitivity pneumonia, asbestosis, post-infectious ILD, etc.) as well as studies written in languages other than English. We focused on articles published within the last 5 years, however, we

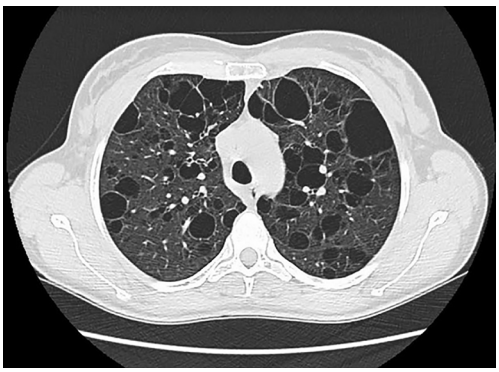

Figure 1 LIP in the coure of SjS-ILD. LIP, lymphocytic interstitial pneumonia; Sjs-ILD, Sjögren's disease- associated interstitial lung disease.

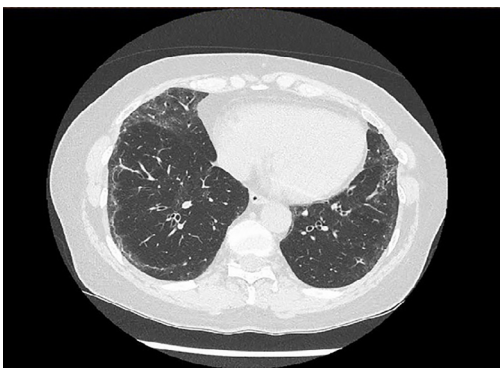

Figure 2 NSIP in course of Ssc-ILD. NSIP, non-specific interstitial pneumonia; SS-ILD, systemic sclerosis-associated interstitial lung disease.

decided to include some older case reports or case series provided on their important scientific or clinical impact, e.g., reports on rare unfavorable pulmonary manifestations, prospective studies or concise reviews.

We attach a table (*Table 7*) summarizing our search strategy and another one (*Table 8*) presenting detailed search strategy.

Results

Manifestations of CTDs in the respiratory system

The list of most common diseases in which pulmonary involvement is observed includes RA, SSc, MCTD, SLE, PM/DM, ankylosing spondylitis (AS) and SS.

Diagnosis of CTD is made in approximately 15% of patients with an already diagnosed ILD (86). Interstitial abnormalities of varying degrees have been reported in 20–60% of patients, and radiological progression in approximately 40% of these cases (87). A typical patient with CTD-ILD is a ≤50 years old female, however, various radiological patterns of CTD-ILD have been described in both genders regardless of age.

Radiological manifestations of CTD-ILD may mimic: acute lung injury (ALI) and OP, usual interstitial pneumonia (UIP), NSIP, fibrosing OP, diffuse alveolar damage (DAD), and lymphocytic interstitial pneumonia (LIP) (2).

Radiological findings in CTD-ILDs—overview

Early ILD in CTD

A serial HRCT follow-up of 40 patients with SSc-ILD (mean 40 months), revealed that the magnitude of lesions (honeycombing, reticulation) and general interstitium involvement increases with time (88). Moreover, the escalation of honeycombing was strongly associated with decrease of diffusing capacity for carbon monoxide (DLco) (88). Wells *et al.* early (89), reported differences in lung volume involvement: 42% in ILD in UIP-ILD and 20.8 % in SSc-ILD. Hartman *et al.* reported ILD progression in individuals with a UIP pattern and desquamative interstitial pneumonia (90). Initial extent of honeycombing was 12 % of lung volume and progressed to 18 % within 13-month follow-up, whereas Kim *et al.* (91), reported that honeycombing initially occupied 1.9% of lung volume and 5.0% approximately 3 years later as measured in consecutive HRCTs. The median monthly rate of honeycombing progression in patients with UIP pattern in SSc-ILD involved 0.4% of lung volume, whereas the rate of such progression was calculated at 0.07% (91).

CTD-ILDs are characterized by different patterns, however, NSIP is the most prevalent, especially in the course of SSc, PM/DM and MCTD (85). Presence of NSIP may precede the diagnosis of CTD for years (92). According to Kono *et al.* (92) occurrence of CTD in individuals being initially diagnosed with idiopathic NSIP reaches 17.1% during follow-up period ranging from 6 months to 10.5 years. Moreover, the authors noted that few individuals in the idiopathic NSIP group as well as in the ILD preceding diagnosis of CTD cohort had met the IPAF criteria at the time of NSIP diagnosis (92). A study dedicated to characterize subjects with CTD-ILD revealed that NSIP was the predominant pattern present in both HRCT (45%) and lung biopsy (27%). 15% of those individuals prospectively fulfilled the criteria for a definitive

Table 3 General overview of CTDs—polymoyositis/dermatomyositis

Feature	Autoimmune inflammatory myopathies; proximal skeletal muscles are affected
General information	CADM: circa 10–30% of all DM cases, skin involvement without muscle inflammation—ASS: the triad of myositis, ILD, arthritis
	Clinical symptoms: mechanic's hand, Raynaud's phenomenon, weight loss and fevers; cough, erythema, heliotrope rash, Gottron's sign, splinter hemorrhage, subungual erythema seen more often in presence of anti-MDA-5 which is also associated with decreased survival (37)
	Respiratory muscles involvement is rare, results in hypoventilation and atelectasis
	Pharyngeal muscles involvement—dysphagia, increased risk of aspiration pneumonia
Prevalence of Pm/Dm-ILD	Calculations elusive, prevalence varies among studies (38,39)
	Depends on myositis type
	Observed in majority of CADM individuals (40) and ASS patients (41)
Radiological patterns of Pm/Dm-ILD	Surgical lung biopsy: predominantly NSIP (82% of patient); other patterns less common (42)
	HRCT: co-existence of NSIP and OP, usually in ASS (43)
	NSIP: better survival than UIP (38,44)
	ILD may precede other symptoms
	More extensive GGO areas and lung tip consolidation in presence of MDA-5 (37)
	Airway, vascular or thoracic involvement is rare
Predictors of Pm/Dm-ILD	Older age
	Articular involvement
	Elevated serum CRP and ESR
	Presence of antiaminoacyl-tRNA synthetase antibodies or antisynthetase antibodies (i.e., anti-Jo-1, PL-7, PL-12, EJ, OJ), is also associated with an increased risk of ILD occurrence (45)
	Rapidly progressing ILD associated with anti-MDA-5 (46)
	Isolated ILD more common with anti-PL7, anti-PL12, and anti-EJ – clinically significant ILD associated with anti-EJ
	Clinical evolution to the complete triad: anti-Jo-1, anti-PL7, anti-EJ isolated ILD: PL12 (47)
	Presence of anti-MDA-5: increased risk of ILD development, acute clinical presentation, worse prognosis (48), greater extent of GGO, consolidation, and lung tip consolidation associated with decreased diaphragmatic excursion (37)
	Ro52 antibody often co-occurs with anti-synthetase antibodies and MDA-5 antibody associated with rapid ILD progression (48)
	Anti-Ku syndrome: overlap of myositis/SSc, associated with high occurrence of ILD (29)

CTDs, connective tissue diseases; CADM, clinically amyopathic dermatomyositis; DM, dermatomyositis; ASS, anti-synthetase syndrome; ILD, interstitial lung disease; anti-MDA-5, Melanoma Differentiation-Associated gene 5 antibody; NSIP, non-specific interstitial pneumonia; HRCT, high resolution computed tomography; OP, organizing pneumonia; UIP, usual interstitial pneumonia; GGO, ground glass opacity; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; SSc, systemic sclerosis.

CTD (93), therefore NSIP diagnosis justifies rheumatologic assessment (94). Kinder *et al.* (95) suggested that idiopathic NSIP is a pulmonary manifestation of undifferentiated CTD (UCTD). In this study 15 out of 18 showed an NSIP pattern based on surgical lung biopsy, which is significantly more prevalent in the control group that was classified as idiopathic interstitial pneumonia (2 subjects with NSIP on lung biopsy) (95). Furthermore, Suda *et al.* (96) revealed that among 47 individuals initially diagnosed with idiopathic NSIP who did not fulfill the criteria for a specific CTD, 22 had features of UCTD. Analysis of 5 years survival curves revealed that patients with UCTD-NSIP had better

Table 4 General overview of CTDs—SLE

Feature	Description
General information	Disorder affecting typically females of reproductive age with multisystem manifestations (hematological, neurologic, renal, pulmonary, musculoskeletal, cutaneous)
	Pleuritis or pleural effusion (uni- or bilateral, in up to 30–50% of cases, characterized by high ANA titer in the pleural fluid): the most frequent pulmonary manifestation (50)
	Acute lupus pneumonitis: 14% of cases (51), GGO or areas of patchy consolidation on HRCT with/without pleural effusion
	Mortality up to 50%, circa half of survivors develop chronic pulmonary abnormalities (51)
	DAH: rare but severe complication in 2% to 5.4% of patients (52)
Prevalence of SLE-ILD	4–13% of all cases; lower compared to other CTDs (53,54), hardly ever the first manifestation of SLE
Radiological patterns of SLE-ILD	Predominantly NSIP, also OP, LIP, UIP (55)
Predictors of SLE-ILD	Age, duration of disease: multicenter study of 513 SLE patients revealed ILD in 1% of patients at onset, 4% within 1 year and 8% by 12 years; ILD present in 2% of subjects <18 years, 7% of 18–49 years subjects and 18% of individuals ≥50 years (56)
	Male gender (56)
	Episodes of acute lupus pneumonitis
	Elevated serum CRP
	U1-RNP antibody presence
	Sunlight hypersensitivity, oral ulcers may have a protective effect (53,57,58)

CTDs, connective tissue diseases; SLE, systemic lupus eythematosus; ANA, antinuclear antibodies; GGO, ground glass opacity; HRCT, high resolution computed tomography; DAH, diffuse alveolar hemorrhage; NSIP, non-specific interstitial pneumonia; OP, organizing pneumonia; LIP, lymphocytic interstitial pneumonia; UIP, usual interstitial pneumonia; ILD, interstitial lung disease; CRP, C-reactive protein; U1-RNP, U1 small nuclear ribonucleoprotein.

Table 5 General overview of CTDs—MCTD

Feature	Description
General information	An overlap syndrome: features of SLE, SSc, and myositis, + presence of anti-U1-ribonucleoprotein (anti-U1-RNP) antibody which is involved in the pathogenesis (60)
Prevalence of MCTD-ILD	52–67% of all cases (59,61,62)
	Abnormalities in baseline PFTs: 51% of patients (63)
	ILD usually develops within the first 2–4 years of diagnosis (64)
Radiological patterns of MTCD-ILD	Predominantly NSIP
	78.1% of 144 MCTD patients had GGOs as the only symptom of pulmonary involvement and the rest of the patients had both GGO and pulmonary fibrosis (61)
	Study on 144 MCTD patients: 25% developed advanced pulmonary fibrosis within 4 years of initial diagnosis (62). Follow-up of 4.2 years: overall mortality circa 7.9%, mortality in no ILD group: circa 3.3%, mortality in advanced fibrosis 20.8% (59)
Predictors of MCTD-ILD	Dysphagia, Raynaud's phenomenon, seropositivity for anti-Smith, anti-Ro52 antibodies, and RF (64,65)
	High levels of RNP autoantibodies, immune complexes, total complement activity (CH50), C3 factor and serum CRP (61)
	Esophageal dilatation, esophageal motor dysfunction also associated with higher prevalence of ILD (66)

CTDs, connective tissue diseases; MCTD, mixed connective tissue disease; SLE, systemic lupus erythematosus; SSc, systemic sclerosis; MCTD-ILD, interstitial lung disease in course of mixed connective tissue disease; PFTs, pulmonary function tests; NSIP, non-specific interstitial pneumonia; GGO, ground glass opacity; ILD, interstitial lung disease.

Table 6 General overview of CTDs—SS

Feature	Description
General information	Autoimmune disease typically diagnosed in women between 50 and 70 years
	Affect salivary and lacrimal glands through lymphocytic inflammation, resulting in sicca syndrome
	SS may a primary condition (pSS) or an overlapping autoimmune disorder (secondary SS; sSS) (68,69)
	pSS-UIP often occurs before the onset of sicca syndrome in at first seronegative patients (70)
	Decreased saliva production revealed in 17.3% of ILD patients in a cohort of 313 patients with ILD, only circa 5,4% of them were diagnosed with definite SS (71)
	Pulmonary hypertension is common
	Amyloidosis may occurr (72)
	Rare pleural involvement, in secondary SS (with RA, SLE) (73)
Prevalence of SS-ILD	Estimated at 10–27% of all SS cases (68,74,75), more common in pSS
Radiological patterns of SS-ILD	Bronchiectasis/bronchiolar abnormalities (50%), ground glass opacity/interstitial lesions (49%), honeycombing (13%), septal thickening (23%), nodules (23%), cysts (22%) (76)
	Lung biopsy: NSIP (45% of cases), bronchiolitis in 25%, UIP in 16%, LIP in 15% and OP in 7% (76)
	Higher risk of lymphoma, which should be taken under consideration especially in case of, pulmonary nodules, lymphadenopathy (77)
Predictors of SS-ILD	Positive anti-Ro/SS-A or anti-La/SS-B antibodies
	Female gender, ≥60 years (68)
	Predictors of poor prognosis: higher $PaCO_2$, vast area of reticular abnormality on HRCT, increased activity of fibroblastic foci (79)
	BAL lymphocyte count >15% associated with ILD development, exacerbated respiratory symptoms and low TLC and DLCO (79)
	BAL lymphcytosis associated with need for treatment (80)
	Presence of BAL neutrophils may correlate with four times the normal rate of loss of DLCO (81)

CTDs, connective tissue diseases; SS, Sjögren's syndrome; pSS-UIP, usual interstitial pneumonia in course of primary Sjögren's syndrome; ILD, interstitial lung disease; RA, rheumatoid arthritis; SLE, systemic lupus erythomatosus; pSS, primary Sjögren's syndrome; NSIP, non-specific interstitial pneumonia; UIP, usual interstitial pneumonia; LIP, lymphocytic interstitial pneumonia; OP, organizing pneumonia; anti-Ro/SS-A, anti-Sjögren's-syndrome-related antigen A autoantibodies; $PaCO_2$, partial arterial pressure of carbon dioxide; HRCT, high resolution computed tomography; TLC, total lung capacity; DLCO, diffusing capacity of the lung for carbon monoxide; BAL, bronchoalveolar lavage.

survival (100%) *vs.* 58% in patients with idiopathic NSIP. HRCT findings typical for NSIP include: predominantly ground-glass opacities (GGO) with reticulation and traction bronchiectasis or bronchiolectasis present mostly in lower lobes in peribronchovascular area. The immediate subpleural zones are spared to some extent. Certain degree of subpleural sparing is reported in 20–64% of cases (97). Reticulation and traction bronchiectasis encounter with disease progression. Honeycombing is uncommon at early stages, but may occasionally develop in advanced fibrotic NSIP (93).

The second most common pattern of CTD-ILD is UIP, being at the same time the most common pattern of RA-ILD (93). Radiologic features of UIP in CTD-ILDs include reticulation in peripheral and lower lobes, traction bronchiectasis, and honeycombing. These features are similar to those described in IPF, however, fibroblastic foci occur less frequently than in IPF (98). Coronal reformatting is helpful to reveal this distribution. Honeycombing is characterized by peripheral conglomeration of cysts with clearly defined and shared walls which have direct contact with pleura. Emphysematous cystic spaces are

often located in upper lobes and retain blood vessels. The dilated bronchioles can be traced to proximal airways (99). OP may occur in any CTD, but it is mostly associated with PM/DM-ILD (100), where it frequently coexists with NSIP pattern. HRCT reveals peribronchial or peripheral consolidation with slight predilection to the lower lobes. Other features are patchy GGO, pronounced nodular consolidation, and GGO enclosed by ring- or crescent-shaped consolidation (reverse halo sign). Bronchial dilation may occur within consolidation area (100).

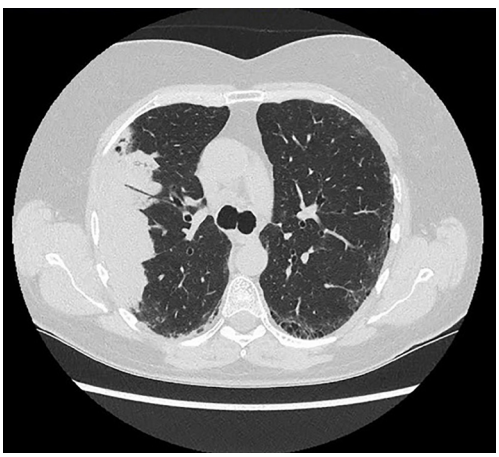

Figure 3 OP/NSIP overlap in course of Ssc-ILD. OP, organizing pneumonia; NSIP, nonspecific interstitial pneumonia; SSc-ILD, systemic sclerosis-associated interstitial lung disease.

LIP is an uncommon pattern. It may also be associated with immunodeficiencies. LIP is most closely associated with SS but may also occur in the course of SLE and RA (101). HRCT typically reveals basal-predominant GGO and thin-walled peribronchovascular cysts, perilymphatic nodules and interlobular septal thickening (102).

IPAF—differences and similarities to CTD-ILDs

IPAF is placed between the idiopathic ILD and defined CTD-ILDs. IPAF is a research classification proposed in 2015 by the ERS/ATS Task Force on Undifferentiated Forms of CTD-ILD (84). Aim of the Task Force was to identify and define in a systematic and consistent manner the ILD patient cohort who display some features of autoimmunity yet do not meet international diagnostic criteria for specific CTDs (2,84).

In the retrospective study by Oldham *et al.* (103), where 422 patients with ILD, either idiopathic or IL-CTD, 144 subjects (34%) met ERS/ATS IPAF diagnostic criteria. The IPAF cohort median age was 63.2 years, and consisted of females (52%) and former smokers (55%). The most common clinical symptom was Raynaud phenomenon (27.8%), with antinuclear antibodies (ANA) positivity in 77.6% subjects. Even though the most common radiological findings were NSIP pattern on HRCT in the entire ILD cohort (31.9%), the majority of the IPAF subgroup

Table 7 The search strategy summary

Items	Specification
Date of search (specified to date, month and year)	Mar 4, 2022
Databases and other sources searched	PubMed database, Elsevier, European Respiratory Society and American Respiratory Society official Internet pages (as of Mar 4, 2022)
Search terms used	Connective tissue diseases, autoimmune diseases, interstitial pneumonia with autoimmune features, interstitial lung disease, interstitial lung abnormality, CTD, ILD, IPAF
Timeframe	1970–2021, with focus on 2010–2021 period
Inclusion and exclusion criteria	Case reports (regarding rare/unfavourbale outcomes), prospective studies, retrospective studies; language: English; excluded: studies on pediatic ILD, ILD of known etiology
Selection process	Patrycja Rzepka-Wrona, Ewa Miądlikowska conducted the selection, all authors reached a consensus on significance of papers based on: study status, size of population studied, year of publication, whether rare/unfavorouble/patient outcomes mentioned in the article (case reports/case report series); especially if we felt that such knowledge may be beneficial in diagnostic work-ups

CTD, connective tissue disease; ILD, interstitial lung disease; IPAF, interstitial pneumonia with autoimmune features.

Table 8 Detailed search strategy of PubMed database

(connective tissue disease) AND (interstitial lung disease), (reumathoid arthritis) AND (interstitial lung disease), (systemic sclerosis) AND (interstitial lung disease), (Sjogren's) AND (interstitial lung disease), (mixed connective tissue disease) AND (interstitial lung disease), (CTD) AND (ILD), (MCTD) AND (ILD), (RA) AND (ILD), (SSc) AND (ILD), IPAF, interstitial pneumonia with autoimmune features

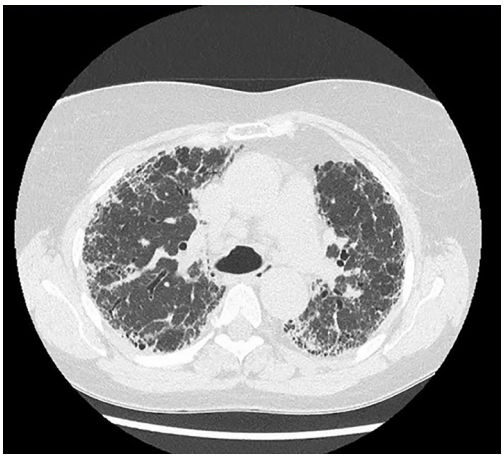

Figure 4 Probable UIP in course of IPAF (criteria from both serological and clinical domain fulfilled). UIP, usual interstitial pneumonia; IPAF, interstitial pneumonia with autoimmune features.

demonstrated a UIP pattern on HRCT (54.6%) and on surgical lung biopsy (73.5%) (104).

The mortality in IPAF patients was calculated at 39.6% over 100-months follow up period. In outcome analysis, individuals with UIP pattern on HRCT had comparable survival to those with IPF. However, subjects with other radiological patterns had comparable survival to patients with CTD-ILDs. Age and decreased DLCO were associated with an increase in mortality (104). The majority of IPAF patients were females (71%) but there was a predominance of non-smokers (68%). On HRCT, NSIP pattern was observed in 57%, NSIP and OP overlap in 18% and UIP pattern in only 8.8% of all IPAF patients. More patients in this study were diagnosed with clinical IPAF characteristics (63%) compared to other cohorts (104). This is most probably due to rheumatologist's involvement in the diagnostic work-up of every case (105).

In a European cohort study by Ahmad *et al.* (105) IPAF criteria were met in only 7.3% of subjects with idiopathic interstitial pneumonia. A modest male predominance was observed, and the majority were again non-smokers. In 53% of cases, an NSIP pattern was observed and in 28% of cases a UIP pattern was revealed (*Figures 4,5*), consecutively, demonstrate examples of a UIP and NSIP patterns in course of IPAF. In contrast with the aforementioned study by Oldham *et al.* (103), there was no significant difference in mortality between IPAF patients with UIP and NSIP (105).

In another study of patients with IPAF, 12.2% of individuals were finally diagnosed with a definite CTD, and 27.6% of patients died during a follow-up period of 4.5 years. The majority of patients in this cohort were female (58.2%) and non-smokers. The type of autoantibody was not associated with patient outcomes. NSIP pattern on HRCT was present in 64.3% of individuals and was associated with worse survival compared to those with OP (106).

In a prospective study of 45 patients with IPAF, morphological, clinical, and serological characteristics were present in 100%, 62%, and 49% of subjects, respectively. Female predominance (62%), NSIP pattern on HRCT (69%), ANA seropositivity (18%), and Raynaud phenomenon (31%) were observed (107).

The transformation of IPAF to a specific CTD was observed in only 13% of subjects in a prospective cohort of 52 subjects during a mean follow-up period of 45 months. The estimated 5-year survival was 69.5% in that cohort (108). An additional feature from both clinical and serological domains is needed to diagnose a patient with IPAF in case of UIP pattern on HRCT, whereas with other patterns only one additional characteristic is required. A small study analyzed patients' outcomes in case of IPAF defined as an UIP pattern on HRCT and only one additional feature, to an IPAF cohort. No significant difference was observed between the groups in the number of subjects who developed advanced ILD, progressed to a specific autoimmune disorder, or died, during a median follow-up period of 12–13 months (109).

Lim *et al.* (110) compared an IPAF cohort (54/305) with seronegative and seropositive IPF cohort (175/305), revealing better survival and less acute exacerbations (AE) in the follow up period repeatedly in year 1, 3, 5 in the first group. In this IPAF cohort, NSIP was the most common radiologic pattern (63%) whereas UIP (25,9%) on HRCT. Emphysematous lesions were observed in 9.3% of the IPAF cohort, which is significantly lower than in the CTD-ILD

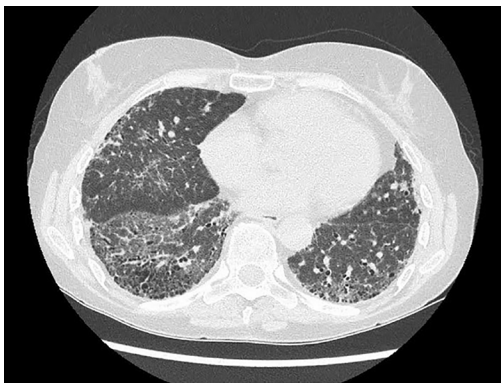

Figure 5 Fibrosing NSIP in course of IPAF (criteria from both serological and clinical domain fulfilled). NSIP, nonspecific interstitial pneumonia; IPAF, interstitial pneumonia with autoimmune features.

group, and the seropositive or seronegative IPF cohorts. The authors speculated that the UIP pattern on HRCT would worsen outcomes, as UIP pattern has been associated with poorer survival (111). On the other hand, Lim *et al.* have not confirmed poorer survival in IPAF patients with UIP pattern (110). Therefore, prospective studies aimed at characterization and comparison of these two specific subgroups are required to give further insight on diagnosis and treatment of those patients.

Mullticompartment involvement in IPAF

Multicompartment involvement (>2 compartments involved simultaneously) is often observed in IPAF patients (112). Taking this under consideration, multicompartment involvement was incorporated in the morphologic domain of IPAF criteria (84). This refers to changes associated with unexplained intrinsic airways disease (airflow obstruction, bronchiolitis, bronchiectasis) reflected by abnormal results of pulmonary function tests, radiologic or histopathologic findings; unexplained pulmonary vasculopathy (precapillary pulmonary hypertension, pulmonary arterial hypertension, pulmonary venoocclusive disease, pulmonary hypertension due to chronic pulmonary disease and/or hypoxia) revealed for the most part by cardiac hemodynamic tests; and unexplained pleural or pericardial effusion or thickening revealed by HRCT or ultrasound imaging or pleuritis on histopathology (84). Oldham *et al.* (103) reported that intrinsic airways disease was the most prevalent multicompartment involvement feature in IPAF which is followed by pleural pathology and pulmonary vasculopathy. According to Ahmad *et al.* pulmonary hypertension was observed in 17.5% IPAF patients (105), whereas Adegunsoye *et al.* (112) reported pulmonary vasculopathy as the most common feature present in 45 of 84 IPAF patients (53.6%). Yet, in terms of pulmonary vasculopathy IPAF patients did not significantly differ from the non-IPAF cohort (IPF, NSIP, COP, UCTD) (112). Additionally, IPAF with pulmonary vasculopathy was characterized by worse survival compared with the IPAF without vasculopathy. Analogous survival analysis was conducted in the non-IPAF cohort, and the concomitance of pulmonary vasculopathy was not linked with worse survival rates compared to individuals without such finding (112).

What are the radiologic differences between idiopathic ILD and CTD-ILD?

Additionally, an official ATS/ERS update of the international classification of idiopathic interstitial pneumonias, remarked on fibrosing OP, in course of which interstitial lesions do not resolve completely in spite of prolonged treatment and residual or progressive interstitial fibrosis is observed with or without recurring episodes of OP. The underlying cause for fibrosing OP is polymyositis or anti-synthetase syndrome.

OP usually occurs in the context of already diagnosed CTDs, however, it may also be the initial symptom of RA or SS (113).

According to Pan *et al.* (114) in 203 patients including CTD-ILD (31%), undifferentiated CTD (UCTD)-ILD (32%) and IPF, there was no significant differences in CT findings, but CTD-ILD patients had more positive autoantibody panels than UCTD-ILD and IPF groups. Nevertheless, a greater predominance of anterior upper lobe sign (visible at level of the aortic arch), vast regions of honeycombing and straight edge sign in patients with CTD-ILD and UIP pattern on HRCT than those with UIP in the course of IPF was reported (115). It was also suggested that honeycombing with predilection to the anterior upper lobe is distinctive of RA-ILD with UIP or UIP/NSIP mixed pattern. In SSc-ILD and PM/DM-ILD, the most predominant pattern was fibrosing NSIP without honeycombing (116).

AE of IPF is currently defined as acute worsening of the patient's general condition or development of progressive dyspnea that has a duration of less than 30 days and are characterized by high mortality (117). In case of CTD-ILD, AEs more likely occur in RA-ILD with UIP pattern and are usually associated with poor outcome (118).

IPAF *vs.* CTD-ILD

The aforementioned 2015 IPAF criteria (84) have been assessed in retrospective and prospective cohort studies. The scope of diagnostic process and the varying extent of rheumatologic involvement during the diagnostic work-up may contribute to the differences noted in various studies.

In a retrospective study by Tian *et al.* (119), 480 patients with CTD-ILD (412 subjects) and IPAF (68 subjects) were assessed.

In comparison with IPAF cohort, CTD-ILD subgroup was characterized by more pronounced female dominance, more frequent occurrence of joint pain, sicca syndrome and Raynaud's phenomenon. Regarding laboratory tests, erythrocyte sedimentation rate (ESR) and D-dimer levels were higher in the CTD-ILD cohort, whereas Hb and RBC were lower. CTD-ILD group was also characterized by a high RF titer and higher levels of seropositivity for autoantibodies [anti-cyclic citrullinated peptide antibodies (ACPA), anti-keratin antibody AKA, ANA and anti-melanoma differentiation-associated gene 5 anti-MDA5].

IPAF patients, on the other hand, were more likely to present with respiratory symptoms at early stages of the diagnostic process (non-productive or productive cough, dyspnea, Velcro crackles on auscultation) and fever. IPAF subgroup was also characterized by higher titers of anti-Ro52. On HRCT, there were higher incidences of reticulation, honeycombing, patchy opacities (predominant radiological feature in both cohorts) and pleural thickening.

Features associated with CTD-ILD were ANA, anti-CCP and anti-MDA52 seropositivity, high RF titer (>2 times the normal upper limit) and female sex.

Importance of interstitial lung abnormality (ILA) and its implications for CTD patients

Some patients with CTD who do not meet the radiologic criteria for an ILD diagnosis may exhibit some radiological features suggestive of interstitium involvement. It is disputed whether they will inevitably progress towards ILD. These findings in individuals with CTD have been gathered under a common name of ILA.

In the Fleischner Society Position Paper on ILA (120), CTD patients were not included, as this diagnosis is associated with increased risk of progressing to ILD in comparison with the general population. As might be expected, the approach towards CTD patients with HRCT features suggestive of ILA differs from that of individuals with ILA without CTD. However, individuals with ILA revealed incidentally on HRCT may be diagnosed with CTD after further rheumatological examination, which implies clinical questions such as: (I) how are non-specific interstitial lesions in the course of CTD defined differently from ILA without CTD? (II) When do such lesions evolve into CTD-ILD? And (III) what is the proper therapeutic approach towards them?

Other clinical implication may be that thorough rheumatological work-up of a patient with interstitial lesions on HRCT can help us distinguish individuals with IPAF and, among them, subjects with partial anti-synthetase syndrome. Due to rapidly evolving treatment regimens and use of antifibrotic agents in ILDs other than IPF such diagnostic work-up provides patients with an opportunity to start treatment early, which may in turn result in slower pace of functional deterioration over next months and years.

ILA is defined solely based on HRCT findings, therefore the definition of radiological features of ILA in subjects with CTD-ILA is the same as in ILA without CTD. It is assumed that the potential therapeutic approach shall be different in these two clinical settings. Diagnosis of CTD-ILD will be established in a similar way in individuals with CTD-ILA applying the following criteria: (I) respiratory symptoms or physical examination findings can be explained by presence of ILD; (II) substantial pulmonary involvement on CT defined by non-trivial abnormalities visible in at least three lung zones; and (III) decrease in pulmonary function or gas exchange that can be explained by an ILD. Due to known risks of progression from ILA to ILD in CTD patients, the monitoring approach in patients with CTD-ILA can be modified from that of pure ILA as follows: (I) all patients with CTD-ILA should be regularly monitored with repeated PFTs every 3–12 months; and (II) follow-up HRCT at 12–24 months, or sooner in case of clinical or physiologic progression.

Follow-up HRCTs of subpleural fibrotic pattern ILA seems of utmost importance, as individuals with subpleural reticulation located predominantly in lower lobes, or traction bronchiectasis (had a circa 6 times increase in the risk of HRCT progression than patients with other types of ILAs. This discrepancy remains even after adjusting for significant variables like age and smoking status (121).

Probable UIP or UIP patterns of ILA cases were all associated with progression to ILD over 5-year follow up period.

ILA in the context of CTD

ILD is diagnosed in 2–10% of patients with RA. However,

ILA of varying degrees occurs in an additional 20–60% of RA patients (122). ILA has been associated with decrease in functional parameters and worsening of clinical condition. Whereas clinically evident ILD is diagnosed in approximately 2–10% of individuals with RA, ILA of varying severity is reported in an additional 20–60% of patients with RA. The occurrence of ILA in RA patients and risk stratification should contribute to an improvement in RA-ILD outcomes (122). Moreover, 57% of RA-ILA patients display radiological features of progression over a 1.5-year period (123). The identification of progressing ILA should warrant clinical vigilance and may be associated with treatment commencement in order to minimize mortality and morbidity rate in RA-ILD.

Kawano-Dourado *et al.* (124) conducted a study with the goal to characterize risk factors for RA-ILA/ILD progression. Of 293 RA patients who had CTs performed, 22% displayed interstitial lesions (64 of 293; predominantly males with history of tobacco smoke exposure). Radiological features of disease progression were observed in 38%. Subpleural distribution and higher baseline ILA/ILD extent of interstitial tissue involvement were associated with progression.

Radiologic interstitial involvement features suggestive of an underlying CTD

According to a cohort study of 48 RA patients conducted by Lucchino *et al.* (125), there is early subclinical pulmonary involvement in the course of RA with anti-citrullinated proteins antibodies (ACPA), occurring even before the onset of articular symptoms.

Thirty individuals of this cohort (62.5%) displayed HRCT abnormalities, the most frequent being nodules (24, 50%), followed by evidence of fibrosis (14, 29.1%), consolidation (5, 10.4%), airway wall thickening (8, 16.6%), emphysema (8, 16.6%), and air trapping (4, 8.3%). As IPAF criteria encompass some dynamics and changes in clinical, radiological and serological presentation of a patient with a "rheumatological flavour", the following statements from Fleischner Society Position Paper seem to be of special significance during diagnostic work-up of these patients:

- Craniocaudal and axial distribution of interstitial lesions;
- Presence of GGOs or reticular abnormalities which have a predominant subpleural localisation, architecture distortion, traction bronchiectasis, honeycombing, and non-emphysematous cysts.

Discussion

Interestingly, ILD has not always been associated with CTD or viewed as primary symptom drawing clinical attention. For example, in a publication by Sharp *et al.* (126) from 1972, did not mention any symptoms from the respiratory system.

However, only 8 years later first reports on abnormalities in pulmonary function tests (PFTs) performed by subjects with MCTD were highlighted by Bennett *et al.* (127) in his clinicopathologic study on 20 individuals with this disease. Soon after, first reports on ILD as a common manifestation of MCTD in the respiratory system appeared (128).

In a study by Pan *et al.* (114), over 200 Chinese patients with ILD were retrospectively studied with purpose to analyze clinical and radiological features of MCTD-ILD, CTD ILD, IPF and UCTD-ILD. Surprisingly, all subjects in this study revealed UIP pattern on HRCT, as opposed to another retrospective cohort study on Chinese population by Tian *et al.* (119), where total of 412 CTD-ILD patients were studied, 68 of whom were diagnosed with IPAF.

In this study (119), even though UIP was revealed as a dominating pattern in a CTD-ILD and IPAF cohort, also NSIP, DIP, COP, LIP and overlap patterns were reported.

The reports by Pan *et al.* (114) show clearly, that HRCT scan itself is insufficient to distinguish between UCTD ILD, IPF, and CTD-ILD.

This highlights the importance of detailed medical history and further serological tests in establishing a proper diagnosis.

In contrast with MCTD-ILD, there are numerous studies on lung involvement in RA. What has lately sparked clinical interest is the occurrence of subclinical lung involvement in RA in context of the serological status.

Demoruelle *et al.* (129) reveals that in over 70% of ACPA positive individuals there is subclinical lung abnormality on HRCT. The study by Lucchino *et al.* (125) demonstrated that radiological features accumulate during the transition from systemic autoimmunity to fully developed RA.

This faces us with a few questions: should clinicians attempt early treatment of these abnormalities with the goal to stabilise the course of the disease? What is the potential harm of treatment of these subjects with anti-TNF agents?

Regarding the influence of serological status on ILD development, there is a need for prospective cohort studies.

Finally, there are some limitations to the study by Lucchino *et al.* (125) the most significant being lack of arterial blood gas performed during physical exercise.

This information is crucial to determine the relationship

between ventilatory insufficiency and the amount of CO_2 produced during physical exercise.

IPAF remains a relatively new disease, diagnosed according to the ERS/ATS working criteria from 2015 (16).

Ahmad *et al.* (105) attempted to assess the aforementioned research criteria by identifying 57 IPAF cases from a cohort of 778 ILD patients.

The goal of their work was to determine which domain (serologic, morphological or clinical) are the most prevalent. They noted that salivary gland biopsy or nailfold capillaroscopy results are not included in IPAF 2015 criteria. These tests contribute to the diagnosis of an established CTD in patients with autoimmunity symptoms (130,131).

The question arises, whether including nailfold capillaroscopy as a non-invasive and relatively easy diagnostic procedure would orient the diagnostic process in the direction of an established CTD, as, according to Ahmad *et al.* (105), the most prevalent clinical feature in IPAF patients is Raynaud's phenomenon.

We would also like to highlight another significant finding by Ahmad *et al.* (105), which is precapillary pulmonary hypertension (PH) diagnosed in 22% of IPAF patients.

The lung volumes remained within normal (or close to normal) range, which contrasted with such combination suggests vascular involvement as an underlying cause for PH.

Some IPAF patients with coexistence of PH displayed clinical features suggestive of SSc. Because of preserved lung volumes one may assume that PH results rather from the underlying autoimmune disease than chronic respiratory condition.

Nonetheless, the coexistence of PH and IPAF may affect management of IPAF patients, with the need to include transthoracic echocardiography as screening for PH at the time of diagnosis of IPAF and during follow up.

Some patients with IPAF have clinical and/or serological features suggestive of further development into a well-defined CTD, which may affect the choice of pharmacotherapy (e.g., systemic corticosteroids or immunosuppressants) and screening/monitoring approach.

As IPAF is an entity at the intersection of pulmonology and rheumatology and its criteria were proposed as a response to the needs of clinicians whose patients had an autoimmune "flavour" yet did not fully meet any criteria of well-defined CTDs, rheumatologists play a key role in the diagnostic process of IPAF patients. Many individuals on myositis spectrum, especially MDA5 disease, Pm/SCl overlap syndrome, non-Jo1 anti-synthetase syndrome) meet IPAF criteria. Subjects with the sole presence of anti-synthetase antibodies in serum who were classified as IPAF were characterized with the same outcomes as individuals with anti-synthetase antibodies meeting diagnostic criteria for PM/DM (132).

Does it mean that we should exclude these patients from IPAF cohort and treat them just like we would treat patients with Pm/Dm? This hypothetical approach should be tested in prospective cohort trials.

Due to relative novelty of IPAF criteria, other questions come to mind: do IPAF patients with a UIP pattern have always the same prognosis as patients with IPF? What is the clinical significance of immunological and clinical features in the presence of a UIP pattern? Will there be any differences in response to pharmacotherapy in different subsets of individuals with IPAF?

Multiple randomized prospective trials are needed to answer these questions, to adjust the current IPAF criteria and evolve an optimal diagnostic and therapeutic approach for these patients.

Multidisciplinary discussion (MDD) is nowadays seen as the reference standard for ILD diagnosis. In a retrospective observational study on management of 126 ILD (IPF and non-IPF) cases in a tertiary care referral centre, Ageely *et al.* (133) revealed that MDD altered the definitive diagnosis in 37% cases (47/126) and impacted management in 39%. Moreover, MDD also altered management in concordant-pre MDD cases. These observations highlight the importance of MDD in managing ILDs and determining prognosis.

De Lorenzis *et al.* (134) noted that, on average, the agreement between rheumatologists and other specialists during identification of alarming symptoms in the course of CTDs and progression assessment changed over time. The degree of multidisciplinary agreement improved over the 6-month observation period. Importantly, it was revealed that the aforementioned agreement increased in MDD of CTD-ILD cases can lead to an improvement in the diagnostic work-up and the assessment of ILD progression in comparison with single rheumatologist's or conventional multidisciplinary team (two pulmonologists, two radiologists with expertise in ILD assessment and, optionally, a pathologist). These findings may probably be extrapolated for the management of IPAF patients.

Novel diagnostic approaches are focused on reducing risks and simplifying procedures. Important indication for lung biopsy in subjects with diffuse infiltrations is exclusion of lung cancer, as adenocarcinoma often presents in form

of infiltrates mimicking ILD. Nowadays, in order to reduce risks associated with video-assisted thoracic lung biopsy (VATS-LB), such as prolonged air leaks or bronchopleural fistula, a biopsy with the use of a flexible cryoprobe has been introduced to obtain samples of endobronchial and transbronchial tissue samples. Moreover, such procedure may be undertaken under conscious sedation, without endotracheal intubation and with radial-EBUS guidance instead of fluoroscopy (135).

Ravaglia *et al.* (135) compared safety and diagnostic value of these methods in a large retrospective cohort study (447 ILD patients) and also performed a systematic review with metanalysis of literature. Safety and lower mortality or complication rates of cryobiopsy in comparison with surgical lung biopsy were confirmed.

These findings were confirmed in a prospective study on accuracy of TBLC in the diagnostic process of ILD (COLDICE) (136).

It was revealed that there is high level of conformity between cryobiopsy and surgical biopsy for both MDD diagnoses and histopathological results.

It may be concluded that cryobiopsy becomes a valid alternative to VATS-LB. However, during cryobiopsy it is more likely to obtain a probable UIP pattern on histopathological examination rather than a definite UIP pattern, due to the restricted access to sub-pleural lung parenchyma (137).

Areas for future research

ILD is a common clinical manifestation of CTDs. Despite clinical similarities of multiple CTDs, there is significant variability in the prevalence and clinical presentation. Due to scarcity of data and complex nature of the disease, many clinicians remain unaware of the clinical course CTD-ILD. In this review, we have recapitulated the available data and highlighted the differences in the prevalence, patterns, predictors, and patient prognosis of CTD-ILDs. In case of clinical uncertainty, feasible procedures with high diagnostic yield should be introduced to obtain tissue samples.

Conclusions

The clinical occurrence of CTD-ILD is high and each type has its distinctive radiological features. The lung is the location where symptoms of CTD can first arise. The extent of lung involvement is one of the most important predictors regarding future outcomes.

Based on currently available data we are also able to conclude that there are currently more questions than answers regarding IPAF radiological presentation and its impact on treatment and prognosis; therefore, future prospective studies in this field are required.

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Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://apm.amegroups.com/article/view/10.21037/apm-21-3974/rc

Peer Review File: Available at https://apm.amegroups.com/article/view/10.21037/apm-21-3974/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-21-3974/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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