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ORIGINAL ARTICLE

Progressive pulmonary fibrosis in patients with connective tissue disease-associated interstitial lung disease: An explorative study

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ABSTRACT

Objectives: The aim of this study was to identify differences and similarities between connective tissue disease (CTD) patients with and without progressive pulmonary fibrosis (PPF) by applying the new guidelines.

Patients and methods: Patient characteristics and disease courses from medical records of 50 CTD-associated Interstitial lung disease (ILD) patients (33 females, 17 males; mean age: 60.1±12.9 years) were longitudinally studied between January 2018 and May 2022. Respiratory involvement in CTD patients was described, and differences in CTD patients who developed PPF compared to those who did not were identified by the 2022 ATS (American Thoracic Society)/ERS (European Respiratory Society)/JRS (Japanese Respiratory Society)/ALAT (Asociación Latinoamericana de Thórax) Guidelines on Idiopathic Pulmonary Fibrosis and Progressive Pulmonary Fibrosis in Adults.

Results: In the majority (74%) of patients, CTD was diagnosed before ILD onset. Nonspecific interstitial pneumonia was the most common high resolution computer tomography pattern, followed by the usual interstitial pneumonia pattern. On pulmonary function test, 38% had a restrictive pattern at baseline. Patients without PPF tended to have worse lung function at baseline and increased macrophage count in bronchoalveolar lavage than patients with PPF.

Conclusion: In patients without PPF, disease progression may be missed, resulting in inadequate management. Interdisciplinary management of patients with CTD with the participation of pulmonologists and precise lung function diagnostics is recommended.

Keywords: Bronchoalveolar lavage, connective tissue disease, high-resolution computer tomography, interstitial lung disease, progressive pulmonary fibrosis, pulmonary function test.

Interstitial lung disease (ILD) encompasses a heterogeneous group of diseases, including idiopathic interstitial pneumonia and lung diseases associated with environmental/occupational exposures or systemic diseases.[1] Connective tissue disease (CTD) is one of the common systemic disorders associated with ILD.[2] Moreover, growing evidence has underscored a significant lifetime risk of ILD development in CTD.[3] However, diagnostic delay is a common problem for patients with fibrotic ILD.[4] This is further complicated since a subset of patients present with progressive pulmonary fibrosis (PPF), which is characterized by a rapid deterioration in symptoms, decline in lung function, or progressive fibrosis on high-resolution computed tomography (HRCT).[5] Moreover, PPF is associated with a reduction in quality of life and high morbidity and mortality.[2] Since no serum biomarkers have been validated for monitoring disease progression, scores based on clinical examination, HRCT, and pulmonary function testing (PFT) parameters have been developed to assess the disease progression.[6] The definition of PPF has not been clear for a long time, and the literature contains variously used references.[7] Recently, the American Thoracic Society (ATS), European Respiratory Society (ERS), Japanese Respiratory Society (JRS), and Asociación Latinoamericana de Thórax (ALAT)

published a guideline with new reference values for the definition of PPF.[8]

In the present study, we examined data from 50 patients with confirmed CTD-associated ILD (CTD-ILD) and described the course of these patients. The focus of the work was to describe pulmonary involvement in CTD patients. By applying the new 2022 ATS/ERS/JRS/ALAT guidelines, we aimed to identify differences and similarities between CTD patients with and without PPF, with emphasis on time since symptom onset, diagnosis of CTD, and diagnosis of ILD.

PATIENTS AND METHODS

This retrospective longitudinal study was performed at the Cologne Merheim Hospital, Kliniken der Stadt Köln gGmbh, Faculty of Health/School of Medicine, Witten/Herdecke University, Department of Pneumology. Fifty patients (33 females, 17 males; mean age: 60.1±12.9 years) with a diagnosis of CTD-ILD who were treated in the department between January 2018 and May 2022 and presented to the multidisciplinary ILD board were included. Diagnostic and classification criteria used for CTD were as follows: the 2013 American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatism (EULAR) classification criteria for systemic sclerosis (SSc), 2019 EULAR/ACR classification criteria for systemic lupus erythematosus (SLE), 2016 EULAR/ACR classification criteria for primary Sjögren's syndrome (pSS), 2017 EULAR/ACR criteria for idiopathic inflammatory myopathies (IMMs), and 2010 EULAR/ACR criteria for rheumatoid arthritis (RA). Mixed connective tissue disease (MCTD) was diagnosed according to Alarcon-Segovia et al. Others were classified as ILD with undifferentiated CTD.

Demographical, clinical, laboratory, radiological, and pulmonary function data as well as treatment history and current therapies were retrieved from medical records. PFTs were performed, comprising spirometry, full body plethysmography (ZAN 500 Bodyplethysmographie; ZAN Austria, Winkling, Austria), and 6-min walking tests. The diffusing capacity for carbon monoxide (DLCO) was measured using the single-breath method (ZAN 500 Bodyplethysmographie; ZAN Austria, Winkling, Austria). Values were expressed as the percentage of the predicted value. Restrictive lung disease was defined as total lung capacity (TLC) Z-Score<lower level of normal (LLN) and obstructive lung disease as Tiffeneau index (forced expiratory volume in 1 sec [FEV1]/forced vital capacity [FVC]<LLN).[9,10] PPF was defined as ≥5% decline in FVC of percent predicted or ≥10% decline in DLCO of percent predicted during one year of follow-up according to the previously published criteria.[8] Contrarily, a change in FVC of <5% or DLCO of <10% was defined as stable disease.

High-resolution computed tomographies were evaluated at baseline and after follow-up. HRCT patterns were classified by an experienced radiologist during multidisciplinary discussion according to the classification for idiopathic interstitial pneumonia, listing them as consistent with usual interstitial pneumonia (UIP), probable UIP, or alternative diagnosis. The consistent UIP and probable UIP were summarized as UIP. The alternative diagnosis category was then classified as nonspecific interstitial pneumonia (NSIP), lymphocytic interstitial pneumonia, organizing pneumonia, or combined pulmonary fibrosis and emphysema. The predominant HRCT patterns were categorized into fibrotic patterns (UIP, fibrotic NSIP, and combined pulmonary fibrosis and emphysema) or inflammatory patterns (cellular and mixed NSIP, lymphocytic interstitial pneumonia, and organizing pneumonia). Progression in HRCT was defined according to Raghu et al.[8] *(i)* increased extent or severity of traction bronchiectasis and bronchiolectasis; *(ii)* new ground-glass opacity with traction bronchiectasis; *(iii)* new fine reticulation; *(iv)* increased extent or increased coarseness of reticular abnormality; *(v)* new or increased honeycombing; *(vi)* increased lobar volume loss.

Statistical analysis

All statistical analyses were performed using Jamovi version 2.3.21.0 (the jamovi project, 2021), retrieved from https://www.jamovi.org (accessed on September 6, 2022). All data were descriptively analyzed. Data were tested for normal distribution using the Shapiro-Wilk test. The Mann-Whitney U test (nonparametric) or the unpaired t-test (parametric) was performed for continuously distributed variables. For categorical

Table 1. Characteristics of 50 CTD-ILD patients

	All patients (n=50)			Without PPF (n=27)			With PPF (n=23)			
	n	%	Mean±SD	n	%	Mean±SD	n	%	Mean±SD	*p*
Sex										
Male	17	34.0		8	29.6		9	39.1		
Female	33	66.0		19	70.4		14	60.9		
History and physical exam										
History of smoking	22	44.0		12	44.4		10	43.5		
Bilateral fine end-inspiratory crepitations	28	77.8		11	40.1		17	73.9		
Disease course										
Age Dx CTD (year)			60.1±15.9			59.6±17.1			60.7±14.7	0.81
Age Dx ILD (year)			64.6±12.9			64.5±11.8			64.1±14.2	0.91
Duration since Dx CTD (year)			6.7±9.0			7.7±10.3			5.7±7.3	0.57
Duration since Dx ILD (year)			2.5±3.1			2.6±3.4			2.4±2.7	0.94
Pathology										
Lung biopsy performed	13	26		10	37.1		3	13.1		
BAL performed	33	66		20	74.1		13	56.5		
Cell count (mio/L)			71.2±43.9			74.8±46.1			64.8±41.0	0.56
Lymphocytes (mio/L) (%)			18.5±20.5 23.41±18.04			17.2±16.0 23.3±16.6			20.9±27.4 23.5±20.8	0.90
Macrophages (mio/L) (%)			41.1±28.2 65.0±20.3			43.6±30.5 61.1±20.3			36.3±23.8 72.1±19.2	0.17
Baseline HRCT pattern (n=50)										
NSIP	20	40		10	37.0		10	43.5		
UIP	18	36		9	33.3		9	39.1		
OP	5	10		1	3.7		4	21.7		
LIP	3	6		3	11.1		0	0.0		
CPEF	4	8		2	7.4		2	8.7		
Baseline lung function test (n=50)										
FEV1-L (%)			2.1±0.7 76.8±15.6			1.9±0.7 73.5±15.0			2.3±0.8 81.4±15.4	0.06
FVC-L (%)			2.5±0.9 75.9±15.8			2.5±0.9 74.0±16.0			2.7±1.0 78.2±15.5	0.35
FEV1/FVC			80.4±10.4			76.5±19.6			80.8±8.5	0.28
Raw tot (%)			121.3±50.3			120.5±52.7			122.2±48.6	0.91
RV (%)			94.3±39.8			98.5±43.9			89.7±35.2	0.53
TLC-L (%)			4.6±1.6 82.9±21.3			4.5±1.5 82.0±22.3			4.78±1.7 84.0±20.5	0.74
TLCO (%)			51.4±17.1			46.3±16.3			57.1±16.6	0.03*
KCO (%)			73.2±24.5			64.5±17.1			83.3±28.1	0.01*
Baseline 6MWT (n=26; 13 *vs.* 13)										
Distance			395.4±116.9			446.6±92.0			344.15±119.7	0.02*
PaO_2 decrease			6.4±10.5			7.0±11.0			5.7±10.4	0.74

CTD: Connective tissue diseases; ILD: Intersitial lung disease; PFF: Progressive pulmonary fibrosis; SD: Standard deviation; BAL: Bronchoalveolar larvage; Dx: Diagnosis; HRCT: High-resolution computed tomography; NSIP: Nonspecific pneumonia; UIP: Usual interstitial pneumonia; OP: Organizing pneumonia; LIP: Lymphocytic interstitial pneumonia; CPEF: Combined pulmonary fibrosis and emphysema; FEV1: Forced expiratory volume per second; FVC: Forced vital capacity; Raw tot: Resistance; RV: Residual volume; TLC: Total lung capacity; TLCO: Transfer factor of the lung for carbon monoxide; KCO: Carbon monoxide transfer coefficient; 6MWT: 6 minute walk test; PaO_2: Partial pressure of oxygen. Duration since diagnosis of CTD (Dx CTD) and since diagnosis of ILD (Dx ILD) was defined as the time from diagnosis to final evaluation of patient data. Baseline time point was defined as the time of patient referral to our pulmonology specialty outpatient clinic. At this time point, patients were enrolled in the study.

variables, either the chi-square test or Fisher exact test was performed. A p-value of <0.05 was considered statistically significant.

RESULTS

Detailed patient characteristics and subgroups consisting of the 50 CTD-ILD patients with or without PPF are displayed in Table 1. In 37 (74%) patients, CTD preceded ILD onset by 5.2±9.1 years. In 13 (26%) patients, however, ILD was primarily diagnosed, and CTD was diagnosed consecutively. CTDs included 19 (38%) RA, seven (14%) SSc, seven IIMs, three (6%) MCTD, three pSS, one (2%) spondyloarthritis, one SLE, and nine (18%) undifferentiated CTD. Immunosuppressants or immunomodulatory treatment for CTD or ILD at time of inclusion into the study was used in 32 (64%) patients. Seven (14%) patients received antifibrotic therapy with nintedanib.

Concerning PFT at baseline, 19 (38%) had a restrictive pattern on PFT, and an obstructive pattern was found in three (6%) patients. At baseline, the mean FVC and DLCO were 76.0±15.8 and 51.4±17.1 percent predicted, respectively. After 12.7±11.7 months of follow-up, PFT was recorded for 39 (78%) patients. In 15 patients (30%), the decline in PFT met the criteria for progressive ILD. FVC improved in 21 (54%), stabilized in nine (23%), and declined in nine patients. DLCO improved in 23 (59%), stabilized in eight (20.5%), and declined in eight patients. At baseline HRCT, 76% of patients had a predominant fibrotic pattern and 34% had a predominant inflammatory pattern. After 10.2±10.8 months of follow-up, HRCT was available for 38 (76%) patients. During the period of follow-up, 14 patients showed progressive fibrosis on HRCT.

According to PFT and HRCT criteria, 23 (46%) patients met the criteria for PPF (Table 1). Six patients showed PPF in both PFT and HRCT. Patients with PPF tended to have a shorter course of CTD compared to patients without PPF (Table 1). At baseline PFT, patients without PPF showed a significantly reduced DLCO and carbon monoxide transfer coefficient and tended to have a reduced FEV1 compared to patients who developed PPF during follow-up. None of the patients with PPF had an obstructive pattern in PFT. In bronchoalveolar lavage, macrophages tended to be increased in patients without PPF during follow-up. The presence of relevant emphysema could be excluded for all patients on CT.

DISCUSSION

In the present study, we retrospectively analyzed data from 50 patients with CTD-ILD and applied the newly published definition of PPF for the first time. Accordingly, clinical, functional, and radiologic characteristics and differences between patients with and without PPF were compared. The main results can be summarized as follows. First, in about a quarter of the patients, ILD was the first clinical organ involvement of CTD. Second, the time between symptom onset and diagnosis of ILD was not different between patients with and without PPF. Third, about half of the patients showed a progressive course of the ILD, and fourth, patients without PPF had worse lung function at baseline than patients who developed PPF during follow-up.

Interstitial lung disease is a common complication of CTDs with up to 85% of SSc patients, 20 to 30% of RA patients, 20 to 50% of IMMs, up to 20% of pSS, 2 to 8% of SLE, and 20 to 60% of MCTD patients developing ILD.[2,11] Many patients diagnosed with CTD-ILD already have a classifiable CTD at the time ILD is recognized, but lung disease can also predate extrapulmonary CTD manifestations by several years.[1,12] In our study, 26% of patients were diagnosed with ILD before CTD. This is in line with previous findings of Hu et al.,[13] who found that 32% of patients in their cohort developed ILD prior to CTD.

Previous studies already showed that after developing ILD, more than half of all patients with ILD have stable disease or even improvements in respiratory function.[1] However, the risk of progressive ILD and the prognosis is associated with the underlying entity, and the longitudinal disease course varies individually.[1] A subset of ILD patients will develop PPF.[5] The term PPF, also known as progressive fibrotic ILD (PF-ILD), has recently been popularized and describes a high-risk process in patients

with ILD. Progression manifests as deterioration in pulmonary symptoms, imaging, and lung function. However, as previously described by Chiu et al.,[7] different criteria for PPF were used in literature.[8] In 2022, the ATS, ERS, JRS, and ALAT have issued a joint guideline on idiopathic pulmonary fibrosis and PPF in adults, including PFT threshold values to define PPF.[8] Thus, the current cohort of 50 CTD-ILD patients was studied using more clearly defined criteria, as established by a broad consensus.

Previous studies have suggested that in patients with fibrosing ILDs, the presence of a UIP-like fibrotic pattern on HRCT is associated with more rapid disease progression.[5,14] Accordingly, in this cohort, 50% of patients with a UIP pattern on HRCT showed a progressive disease.

Chiu et al.[7] studied clinical predictors for poor outcome in CTD-ILD. Interestingly, the authors did not find a significant difference in baseline lung function between patients with and without PPF. In both groups of the current cohort, however, a significant reduction of lung volumes and diffusion disturbances were evident at baseline. Of note, patients without PPF had worse respiratory function compared to PPF patients, and this was shown to be statistically significant for FEV1, transfer factor of the lung for carbon monoxide, and carbon monoxide transfer coefficient. Although it might appear to be somewhat deceptive, this finding suggests that deterioration of respiratory function has already occurred in those patients with nonprogressive patterns at baseline, assuming that further formal disease progression is less likely, while PPF-patients had less impaired respiratory function, allowing for more predominant disease progression during actualy observed follow-up.

Furthermore, macrophage count, as assessed by bronchoalveolar lavage, tended to be higher in patients without PPF during follow-up. Macrophages are known to play a role in the development of fibrosis, and the increase of these cells in the group without PPF supports the hypothesis that the fibrotic process has already occurred in this group. Overall, from the current data, it can be hypothesized that early ILD diagnosis is inevitably needed to maintain all treatment alternatives aimed at slowing down pulmonary disease progression. In this regard, an interdisciplinary approach, including both rheumatological and pulmonary expertise, is considered to be beneficial.[3,15] According to our findings that in some patients the active fibrotic process is missed and that some patients even have ILD as an initial symptom of their CTD, it should be demanded that this interdisciplinary approach is established not only in the course of the patient's treatment but right at the beginning of the diagnosis.

To our knowledge, this is the first study evaluating the new guidelines in a well characterized CTD-ILD cohort. However, this study has several limitations related to the relatively small number of patients and its design: It is a medical record review study in nature; hence, observations remain to be confirmed in a prospective longitudinal study. Second, clinical symptoms were not systematically scored in our cohort. A prospective study design combining physician global scores and patient-reported outcomes may provide more evidence on the risk stratification of clinical symptoms. Third, follow-up HRCT was only available for 40 patients. Furthermore, although information on the use of immunosuppression and antifibrotic therapy were collected, we did not pursue cause-effect analyses due to the certainty of confounding by indication and challenges in analyzing such data in this cohort and set of data. Moreover, as patients in our registry were recruited from a tertiary care academic referral center, it is possible that referral bias may have led to an overestimation of the prevalence of PPF or even non-PPF.

In conclusion, progression of CTD-ILD is common, and early diagnosis is difficult. However, early detection of CTD-ILD and, if necessary, the initiation of adequate therapy are important to stabilize the disease. The current study suggests that pulmonary disease progression in CTD-ILD has already occurred prior to the first examination in those patients who are formally nonprogressive according to clearly defined criteria. Therefore, greater awareness of CTD-ILD is needed, and systematic workup for lung involvement, including spirometry, full body plethysmography, and measurements of diffusion capacity in addition to HRCT, should be considered in CTD patients, even as early

as at the time of the initial diagnosis. Future longitudinal studies are needed to identify baseline markers for patients at risk for PPF and further insights into the epidemiology, natural history, and immunobiology of CTD-ILD.

Ethics Committee Approval: The study protocol was approved by the Witten/Herdecke University Ethics Committee (date: 05.10.2022, no: S-180/2022). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Study design: J.H., M.W.S., W.W., M.B.; Data collection: J.H., M.W.S., M.B.; Data analysis: J.H., M.W.S., M.B.; Data interpretation: J.H., M.W.S., F.S., E.S., W.W., M.B.; Drafting manuscript: J.H., M.W.S., M.B.; Revising manuscript content: E.S., F.S., W.W.; All authors reviewed the results and approved the final version of the manuscript.

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