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INTERSTITIAL LUNG DISEASE

Clinical Characteristics and Natural History of Autoimmune Forms of Interstitial Lung Disease: A Single-Center Experience

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Abstract

Objective To describe the phenotypic characteristics and natural history of patients with autoimmune forms of interstitial lung disease (ILD).

Methods Retrospective, descriptive, single-center study of patients with autoimmune forms of ILD evaluated between February 2008 and August 2014. All data were extracted from the electronic medical record. Longitudinal changes in forced vital capacity (FVC%) and diffusion capacity for carbon monoxide (DLco%) in percent predicted were analyzed and time-to-event analyses for death were performed using Cox regression.

Results Of the entire cohort ($n=243$), systemic sclerosis (SSc)-associated ILD ($n=88$, 36%), interstitial pneumonia with autoimmune features (IPAF, $n=56$, 23%), rheumatoid arthritis (RA)-associated ILD ($n=42$, 17%), and idiopathic inflammatory myopathy (IIM)-associated ILD ($n=26$, 11%) were the most common phenotypes. The SSc-ILD, IIM-ILD, and IPAF groups had similar features: average age in the mid-50s, strongly female predominant and more likely to have nonspecific interstitial pneumonia (NSIP). In contrast, RA-ILD patients were older, gender balanced, more likely to be past smokers and were UIP predominant. Adjusted longitudinal lung function was stable during a median follow-up period of nearly 4 years and the independent predictors for death were older age ($p=0.003$), male sex ($p=0.019$), and lower FVC ($p=<0.001$).

Conclusions The predominant phenotypes of autoimmune ILD were SSc-ILD, IPAF, RA-ILD, and IIM-ILD. In contrast to the other subsets, those with RA-ILD may be older, gender balanced, with more smoking history, and higher proportion of UIP. Longitudinal lung function was stable among the groups and younger age, female gender, and better lung function were associated with improved survival.

Keywords Interstitial lung disease · Connective tissue disease · Interstitial pneumonia with autoimmune features · Prognosis · Survival

Introduction

Interstitial lung disease (ILD) is a common manifestation associated with the spectrum of connective tissue disease (CTD) and often associated with significant morbidity and mortality [1]. Although ILD has the highest prevalence in systemic sclerosis (SSc), the advent of the thoracic high-resolution computed tomography scan has led to a greater appreciation, awareness, and recognition that ILD is highly prevalent in other forms of CTD such as rheumatoid arthritis (RA) and the idiopathic inflammatory myopathies (IIM) [2]. Furthermore, some patients with an idiopathic interstitial pneumonia (IIP) have certain, often subtle, features that suggest an underlying autoimmune process and are considered to have "interstitial pneumonia with autoimmune features" (IPAF) [3]. Because of the heterogeneity of the

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CTD-ILD population, and the potentially unique natural history of each CTD-ILD, precise phenotyping and study of each subset may impact prognostication and therapeutic strategies. The objective of this study was to add to what is known about autoimmune forms of ILD by describing the phenotypic characteristics and natural history of a cohort of patients with diverse forms of autoimmune ILD evaluated in a multidisciplinary ILD referral center.

Materials and Methods

Cohort Identification

All patients in this cohort were evaluated and managed at a tertiary multidisciplinary ILD referral center and under the clinical care of a rheumatologist experienced in ILD (Aryeh Fischer, MD). Each patient was confirmed to have ILD, by thoracic high-resolution computed tomography (HRCT) in all patients and surgical lung biopsy when available. All either had a clinical diagnosis of a specific CTD as defined by current rheumatologic classification/diagnostic schema with an associated ILD or fulfilled classification of IPAF [3]. The specific characteristics and natural history of the IPAF cohort have been reported elsewhere [4, 5] and is included in this study to compare with the groups that had characterizable forms of CTD-ILD. All clinical data from February 2008 to August 2014 were extracted from the electronic medical record and the average follow-up period of the cohort was 3.95 years. A broad panel of serologic autoantibody testing was performed as part of a standardized clinical evaluation. Serial pulmonary function testing (PFT) was performed according to current guidelines and as part of usual clinical care. The earliest thoracic HRCT scan of diagnostic quality for ILD in the medical record was reviewed and pattern determination was based on clinical interpretation by expert thoracic radiologists based on current guidelines [5, 6]. Similarly, histopathologic findings from surgical lung biopsy specimens were recorded as based on interpretation by expert pulmonary pathologists based on current guidelines [5, 6].

This study was retrospective, HIPAA-compliant, and approved by the National Jewish Health institutional review board (protocol HS-2917).

Statistical Analysis

Descriptive statistics were generated for baseline data. We analyzed longitudinal changes in percent predicted forced vital capacity (FVC%) and percent predicted diffusion capacity for carbon monoxide (DLco%) using linear mixed-effects models that considered time as a continuous factor. These models were adjusted for potential confounders including age, sex, and smoking history. Survival time was calculated from initial visit until the primary outcome was achieved (i.e., death). Patients were censored if they did not meet the primary outcome after review of the medical record or on query of the Social Security Death Index. Kaplan–Meier curves were constructed for each diagnosis and compared using the log-rank test. Predictors of death were analyzed using unadjusted Cox proportional hazards regression analyses and multivariate analysis adjusting for diagnosis, age, sex, and FVC. STATA Version 14 (Stata Corp, College Station, Texas) was used for all the statistical analyses.

Results

Phenotypic Characteristics (Table 1)

The cohort included 243 patients with varied forms of autoimmune ILD. The predominant phenotypes observed were SSc-ILD ($n=88$, 36%), IPAF ($n=56$, 23%), RA-ILD ($n=42$, 17%), and IIM-ILD ($n=26$, 11%). The remainder of the cohort consisted of primary Sjogren's ($n=14$, 6%), systemic lupus erythematosus ($n=7$, 3%), and overlap forms of CTD (including mixed CTD) ($n=10$, 4%). The SSc-ILD, IIM-ILD, and IPAF groups had similar demographics: mean age in the mid-50s and strong female predominance. In contrast, those with RA-ILD had a mean age of 64 and an equal male-to-female ratio. A higher proportion of the RA-ILD patients were past smokers (54.8%) compared with IIM-ILD (42.3%), SSc-ILD (40.9%), or IPAF (32.1%).

Radiologic pattern suggesting nonspecific interstitial pneumonia (NSIP) was the predominant pattern in SSc-ILD (58.0%), IIM-ILD (53.8%), and IPAF (48.2%). In contrast, for the RA-ILD cohort, radiologic UIP pattern was suggested in 45.2% and NSIP in only 28.6%. A minority of the patients in each group had a lung biopsy and the pathologic patterns were diverse (Table 1).

All patients were treated with chronic immunosuppressive medications. The majority received corticosteroids (68.2% in the SSc-ILD group, 96.2% in the IIM-ILD), and each was also treated with a corticosteroid sparing agent, including mycophenolate mofetil, azathioprine, cyclophosphamide, tacrolimus, or rituximab (Table 1).

Natural History

Longitudinal Lung Function (Tables 1 and 2)

Baseline PFT values of the overall cohort demonstrate that most had a mild reduction in FVC% with moderate reduction in DLco% (Table 1). On unadjusted analysis, there appeared to be differences in longitudinal change in FVC% for the different groups (Table 2). Patients with

Table 1 Cohort characteristics

	SSc-ILD $n=88$	IIM-ILD $n=26$	RA-ILD $n=42$	IPAF $n=56$
Age at diagnosis, years (mean ± SD)	57.3 ± 9.6	54.7 ± 9.6	64.3 ± 10.2	55.1 ± 10.5
Female, *n* (%)	63 (71.6)	18 (69.2)	21 (50.0)	40 (71.4)
Race, *n* (%)				
White	86 (97.7)	23 (88.5)	42 (100)	50 (89.3)
African-American	1 (1.1)	2 (7.7)	0 (0.0)	4 (7.1)
Asian	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)
American native or Alaskan native	1 (1.1)	1 (3.8)	0 (0.0)	1 (1.8)
Tobacco status, *n* (%)				
Never smokers	50 (56.8)	15 (57.7)	18 (42.9)	38 (67.9)
Ever smokers	36 (40.9)	11 (42.3)	23 (54.8)	18 (32.1)
Current smokers	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)
Unknown	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)
PFT parameters at baseline, in percent predicted (mean ± SD)				
FVC%	71.0 ± 15.1	61.5 ± 16.4	74.9 ± 14.3	68.4 ± 16.0
FEV-1%	73.1 ± 15.0	61.8 ± 15.7	76.8 ± 17.1	72.7 ± 16.3
TLC%	87.3 ± 19.5	79.1 ± 20.8	91.5 ± 20.1	80.1 ± 13.7
DLco%	52.3 ± 20.7	49.1 ± 18.3	56.3 ± 17.7	52.2 ± 15.9
Thoracic HRCT scan, *n* (%)				
NSIP	51 (58.0)	14 (53.8)	12 (28.6)	27 (48.2)
NSIP + OP	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
UIP	15 (17.0)	0 (0.0)	19 (45.2)	3 (5.4)
LIP	0 (0.0)	0 (0.0)	2 (4.8)	1 (1.8)
OP	0 (0.0)	1 (3.8)	1 (2.4)	1 (1.8)
Undefined	22 (25.0)	8 (30.8)	7 (16.7)	16 (28.6)
Immunosuppressive therapy, *n* (%)				
Prednisone	60 (68.2)	25 (96.2)	40 (95.2)	45 (80.4)
Mycophenolate mofetil	31 (35.2)	9 (34.6)	5 (11.9)	42 (75.0)
Azathioprine	60 (68.2)	22 (84.6)	18 (42.9)	20 (35.7)
Cyclophosphamide	22 (25.0)	11 (42.3)	21 (50.0)	13 (23.2)
Tacrolimus	3 (3.4)	6 (23.1)	0 (0.0)	4 (7.1)
Rituximab	2 (2.3)	3 (11.5)	7 (16.7)	2 (3.6)

PFT pulmonary function testing, *FVC%* forced vital capacity in percent predicted, *FEV-1* forced expiratory volume in 1 s in percent predicted, *TLC* total lung capacity in percent predicted, *DLco%* diffusion capacity of the lung for carbon monoxide in percent predicted, *CTD* connective tissue disease, *HRCT* high-resolution computed tomography scan, *ILD* interstitial lung disease, *IIM* idiopathic inflammatory myopathy, *IPAF* interstitial pneumonia with autoimmune features, *LIP* lymphocytic interstitial pneumonia, *NSIP* nonspecific interstitial pneumonia, *OP* organizing pneumonia, *RA* rheumatoid arthritis, *SSc* systemic sclerosis, *UIP* usual interstitial pneumonia

Table 2 Unadjusted lung function analysis per group

Group	Change in FVC%/month		Change in DLco%/month	
	%predicted/month (95% CI)	*p* value	%predicted/month (95% CI)	*p* value
SSc-ILD	−0.099% (−0.165% to −0.033%;)	0.0035	−0.144% (−0.209% to −0.08%)	< 0.001
IIM-ILD	+0.124% (+0.009% to +0.239%;)	0.0341	+0.152% (+0.04% to +0.264%)	0.0079
RA-ILD	−0.102% (−0.198% to −0.007%)	0.0361	−0.063% (−0.157% to +0.031%)	0.1891
IPAF	+0.068 (−0.019 to +0.156%)	0.1236	+0.109% (+0.022% to +0.197)	0.0141

DLco% diffusion capacity of the lung for carbon monoxide in percent predicted, *FVC%* forced vital capacity in percent predicted, *ILD* interstitial lung disease, *IIM* idiopathic inflammatory myopathy, *IPAF* interstitial pneumonia with autoimmune features, *RA* rheumatoid arthritis, *SSc* systemic sclerosis

IPAF and IIM tended to have stable to improved FVC%, while patients with RA and SSc had decline in FVC% over time. After adjustment for age, sex, and smoking history, longitudinal change in FVC% was not statistically different over the average follow-up period of 3.95 years. A similar pattern, for both unadjusted and adjusted analyses, was observed for change in DLco%.

Survival (Fig. 1)

During an average follow-up of 3.5 years for SSc-ILD, 4.1 years for IIM-ILD, 3.6 years for RA-ILD, and 3.1 years for IPAF, there were 21 deaths (23.9%) in the SSc-ILD group, 10 deaths (23.8%) in the RA-ILD group, 4 deaths (15.4%) in the IIM-ILD group, and no deaths in the IPAF group. The overall log-rank p value across the different groups was 0.012. Unadjusted predictors of death were older age ($p=0.016$), male sex ($p=0.015$), lower baseline FVC% ($p=0.025$), lower baseline DLco% ($p=0.02$), and UIP pattern on thoracic HRCT scan ($p=0.042$). A diagnosis of IPAF was associated with a better outcome ($p=0.019$). On multivariate analysis adjusting for diagnosis, age, sex, and FVC, the independent predictors for death in the entire cohort were age ($p=0.003$), sex ($p=0.019$), and FVC ($p=<0.001$). Diagnosis was not an independent predictor for death ($p=0.357$).

Discussion

In this single-center study, we describe the phenotypic characteristics and natural history of a cohort of patients with diverse forms of autoimmune ILD. The largest subsets identified were SSc, RA, IIM, and IPAF. Certain similarities were identified in those with SSc-ILD, IIM-ILD, and IPAF: similar age (mid-50s), strong female predominance, and NSIP as the predominant ILD pattern observed. In contrast, those with RA-ILD appear to be older (mid-60s), gender balanced, and more likely to be past smokers and UIP predominant.

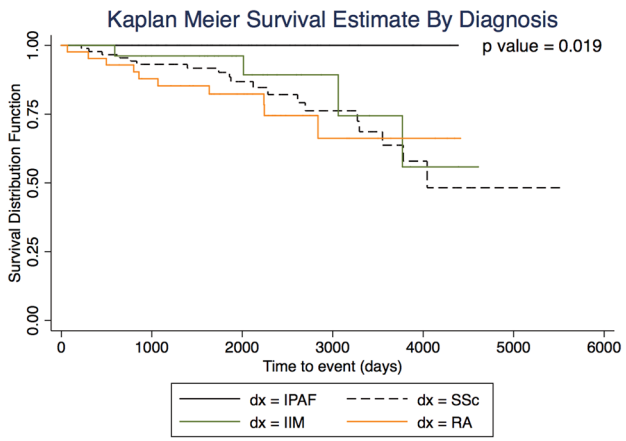

Fig. 1 Kaplan–Meier survival curve for each group. Note the average follow-up of 3.5 years for SSc-ILD, 4.1 years for IIM-ILD, 3.6 years for RA-ILD, and 3.1 years for IPAF. *Dx* diagnosis, *ILD* interstitial lung disease, *IIM* idiopathic inflammatory myopathy, *IPAF* interstitial pneumonia with autoimmune features, *RA* rheumatoid arthritis, *SSc* systemic sclerosis

After adjustment for age, sex, and smoking history, no changes in longitudinal lung function were observed between groups during the follow-up period of 4 years. Similar survival was seen in those with RA, SSc, and IIM, while no deaths were observed in the IPAF subset. After adjusting for diagnosis, age, sex, and FVC, the independent predictors for death in the entire cohort were older age, male sex, and lower FVC.

These data affirm what previous studies have shown about unique characteristics of RA-ILD, whereby older age, male gender, and UIP pattern predominates, and a high proportion are former smokers [7–9]. They also affirm the phenotypes aspects typical of SSc-ILD and IIM-ILD whereby most patients are women and NSIP predominates. In contrast to a different single-center study [10], our SSc-ILD cohort had similar—not better—natural history compared with other forms of autoimmune ILD. Further, given that gender, age, and lung function were the only variables identified as independent predictors of survival on adjusted multivariate analysis, these data extend on previous studies that have shown that the GAP model used for prognostication in idiopathic pulmonary fibrosis [11] is also useful in other forms of ILD [12], including autoimmune ILD [12]. Although other series have suggested that survival with RA-ILD may be worse than other forms of CTD-ILD [13], the small sample sizes in this study preclude ability to draw firm conclusions about the natural history of individual cohorts.

As discussed in our earlier publication of the IPAF subset in this cohort [4], these data add to what we know about the IPAF phenotype. Although it is logical to predict that some patients with IPAF may evolve into a defined CTD [14], none of the patients in our cohort did so over the roughly four-year mean follow-up. However, as discussed in our earlier publication of the IPAF subset [4], we acknowledge that some of these patients could be considered to have partial or early presentations of characterizable forms of CTD. For example, those with a positive tRNA synthetase antibody might be considered as definite for IIM-ILD yet others might consider such patients as compatible with IPAF in the absence of more characteristic features of IIM. As all were taking chronic immunosuppression for ILD, it is possible that this prevented the development of additional extra-thoracic manifestations of a characterizable CTD (e.g., synovitis or myositis). Perhaps due to the high prevalence of NSIP and/or OP, or the

effectiveness of immunosuppressive therapy, we observed no decline in FVC% or deaths over the follow-up period. Prospective, multicenter studies are needed to more reliably determine the natural history of IPAF and the potential role for immunosuppression of these patients.

This study has limitations. Its retrospective design limits the ability to draw firm conclusions about natural history. Furthermore, unfortunately we were unable to reliably ascertain cause of death in this cohort, thus limiting ability to draw conclusions regarding progression of ILD as the etiology. It is from a single tertiary referral center, which introduces referral bias and limits the ability to generalize our findings. The cohort selection may be biased because the investigative team was intrinsically involved in the generation of the IPAF definition [3]. The very small sample sizes preclude ability to draw firm conclusions about the phenotypic characteristics of these cohorts or about their natural history. As such, although we observed apparent differences among groups with respect to demographics, smoking status, and patterns of lung injury, studies with larger cohorts of patients are needed to definitely affirm whether true differences exist among these subsets and to more definitely assess for differences in natural history. HRCT scans and histopathologic specimens were interpreted for clinical purposes, not by strict research protocols. These limitations notwithstanding, these data add to what we know about the phenotypes and natural history of diverse forms of autoimmune ILD.

Conclusion

In this single-center study, the most frequently encountered forms of autoimmune ILD are SSc, IIM, RA, and IPAF. While SSc, IIM, and IPAF appear to be characterized by female gender and NSIP, the RA subset in this study was more gender balanced, a bit older, and UIP predominant. No appreciable differences in natural history were observed among specific phenotypes, but older age, male gender, and lower lung function were associated with worse survival.

Compliance with Ethical Standards

Conflict of interest All authors declare that they have no conflict of interest.

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