Respiratory Medicine 119 (2016) 150–154

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: www.elsevier.com/locate/rmed

Clinical features and natural history of interstitial pneumonia with autoimmune features: A single center experience

Sandra Chartrand [a], Jeffrey J. Swigris [b, c], Lina Stanchev [c], Joyce S. Lee [c], Kevin K. Brown [b, c], Aryeh Fischer [c, *]

[a] Department of Medicine, Hôpital Maisonneuve-Rosemont affiliated to Université de Montréal, Montréal, Québec, Canada
[b] Department of Medicine, National Jewish Health, Denver, CO, USA
[c] Department of Medicine, University of Colorado School of Medicine, Aurora, CO, USA

ARTICLE INFO

Article history:
Received 24 May 2016
Accepted 1 September 2016
Available online 3 September 2016

Key indexing terms:
Interstitial pneumonia with autoimmune features
Interstitial lung disease
Connective tissue disease
Idiopathic interstitial pneumonia

ABSTRACT

Objective: To describe the clinical phenotype and natural history of a cohort of patients with interstitial pneumonia with autoimmune features (IPAF).
Methods: A retrospective, single center study of 56 patients with IPAF evaluated between February 2008 and August 2014. All clinical data were extracted from the electronic medical record and longitudinal changes in forced vital capacity (FVC) were analyzed with mixed-effects, piecewise linear regression models that considered time as a continuous factor.
Results: All patients fulfilled classification criteria for IPAF. The majority were women (71%) and never smokers (68%). The most frequently identified clinical features were Raynaud's phenomenon (39%), distal digital fissuring (29%), Gottron's sign (18%) and inflammatory arthropathy (16%). The most frequently identified serologies were antinuclear antibody (ANA) (48%), anti-Ro (SSA) (43%) and anti-tRNA-synthetase antibodies (36%). Nonspecific interstitial pneumonia (NSIP) (57.1%) followed by NSIP with organizing pneumonia (18%) were the most common radiologic patterns, while usual interstitial pneumonia was identified in only 9%. All but one patient was treated with immunosuppression: prednisone (82%) and mycophenolate mofetil (76%) were the most frequently used agents. During a follow-up period of 284.9 ± 141.3 days, modeled longitudinal FVC% was stable (slope = 0.69/year) and no deaths were observed in the cohort.
Conclusions: In this single center study, patients with IPAF were predominately non-smoking women with high-resolution computed tomography scans that suggested NSIP. Their pulmonary physiology was stable, and during limited follow-up, no deaths were observed. Prospective and multi-center studies are needed to better inform our understanding of IPAF.

1. Introduction

Some patients considered to have an idiopathic interstitial pneumonia (IIP) possess certain, often subtle, clinical features that suggest an underlying autoimmune process; however, they do not meet established diagnostic criteria for any connective tissue disease (CTD) [1,2]. In many of these patients, such features occur in the absence of serologic positivity, while in others, a highly-specific autoantibody is the only finding pointing toward autoimmunity. In other patients, radiologic or histopathologic features suggest underlying CTD, but the absence of extra-thoracic (including serologic) findings precludes classification of these patients as anything other than an IIP.

Differing, but overlapping, criteria and terms have been used to describe these patients, including "undifferentiated CTD-associated interstitial lung disease (ILD)" (UCTD-ILD) [3–5] "lung-dominant CTD" (LD-CTD) [2], or "autoimmune-featured ILD" (AIF-ILD) [6]. With an aim to achieve consensus around how to label, define, and study cohorts of these patients, the European Respiratory Society (ERS) and American Thoracic Society (ATS) convened a Task Force on Undifferentiated Forms of CTD-associated ILD [1]. They proposed that individuals with interstitial pneumonia, and a combination of certain clinical, serologic, and/or morphologic features

* Corresponding author. Department of Medicine, University of Colorado School of Medicine, 1775 Aurora Court, Box B115, Aurora, CO 80045, USA.
E-mail address: aryeh.fischer@ucdenver.edu (A. Fischer).

http://dx.doi.org/10.1016/j.rmed.2016.09.002
0954-6111/

that raise suspicion for the presence of an underlying systemic autoimmune disease, be labeled as having *"interstitial pneumonia with autoimmune features"* (IPAF) and developed consensus-derived classification criteria (Table 1) [1].

This study had two objectives: 1) to describe the characteristics of a cohort of patients that fulfill classification criteria for IPAF; and 2) to evaluate the natural history of IPAF by examining longitudinal pulmonary physiology and survival.

2. Materials and methods

Cohort identification. All patients in this cohort received clinical care from a rheumatologist experienced in ILD (AF) between 2008 and 2014. All were confirmed to have ILD by thoracic high resolution computed tomography (HRCT) and/or surgical lung biopsy (when available). Based on a combination of clinical, serologic, radiologic or pathologic features, each patient was considered by AF to have an autoimmune basis for their ILD. None had a defined CTD or alternative etiology to account for the presence of ILD (e.g., infection, drug, environmental or occupational exposure). Clinical data captured between February 2008 to August 2014 were extracted from the comprehensive electronic medical record and used to determine whether each patient fulfilled classification criteria for IPAF (Table 1). AF and three other authors of this manuscript (JSL, JJS, KKB) were part of the ERS/ATS Task Force [1].

Serologic autoantibody testing was performed as part of a standardized clinical evaluation for all of the patients. For each patient, a broad panel of autoantibodies was tested, including myositis-associated and myositis-specific autoantibodies. Serial pulmonary function testing (PFT) was performed as part of usual clinical care as previously described [7]. Forced vital capacity (FVC) and diffusing capacity of the lung for carbon monoxide (DLco) were expressed and analyzed as percentages of sex-, age- and height-specific predicted values (i.e., FVC % or DLco %, respectively). We recorded data from the earliest thoracic HRCT scans in the medical record. Each scan was interpreted by an expert thoracic radiologist at our center, and pattern determinations of usual interstitial pneumonia (UIP), non-specific interstitial pneumonia (NSIP), respiratory bronchiolitis-interstitial lung disease (RB-ILD), organizing pneumonia (OP), desquamative interstitial pneumonia (DIP), or hypersensitivity pneumonitis was based on current accepted criteria, definitions and guidelines [8,9]. Similarly, surgical biopsy specimens were reviewed by lung pathologists at our center and data from the histopathologic determinations were recorded. For the assessment of multi-compartment criteria within the morphologic domain of the IPAF criteria (Table 1): unexplained intrinsic airways disease was determined by FEV1/FVC ratio of <70% predicted, evidence by HRCT of air-trapping or mosaicism, or by histopathologic evidence of airways inflammation, pulmonary vasculopathy was determined by findings of pulmonary arterial hypertension with right-heart catheterization, or with histopathologic evidence of pulmonary vasculopathy, pericardial disease was determined by either echocardiographic or HRCT findings, and pleural disease was based on HRCT findings of pleural inflammation, thickening, or effusion or histopathologic evidence of acute or chronic pleuritis.

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. Data are presented as counts or means with standard deviations. We analyzed longitudinal changes in FVC% with mixed-effects, piecewise linear regression models (Proc Mixed procedure in SAS) that considered time as a continuous factor. The covariance structure was specified with the "unstructured" option in PROC MIXED, as this provided the best fit. These models used least-squares to fit curves to the data to generate estimates for the mean FVC% as a function of time.

Table 1
Classification criteria for interstitial pneumonia with autoimmune features (IPAF) [1].

1. Presence of an interstitial pneumonia (by HRCT or surgical lung biopsy) AND,
2. Exclusion of alternative etiologies AND,
3. Does not meet criteria of a defined CTD AND,
4. At least one (1) feature from at least two (2) of these domains:

A. Clinical domain	B. Serologic domain	C. Morphologic domain
1. Distal digital fissuring (i.e. 'mechanic hands')	1. ANA, either diffuse, speckled, or homogeneous patterns at >1:320 titer OR ANA nucleolar pattern at any titer OR ANA centromere pattern at any titer	1. Suggestive radiology patterns by HRCT:
2. Distal digital tip ulceration	2. RF > 2 × ULN	a. NSIP
3. Inflammatory arthritis or polyarticular morning joint stiffness >60 min	3. Anti-CCP	b. OP
4. Palmar telangiectasia	4. Anti-dsDNA	c. NSIP with OP overlap
5. Raynaud's phenomenon	5. Anti-Ro (SS-A)	d. LIP
6. Unexplained digital edema	6. Anti-La (SS-B)	2. Histopathology patterns or features by surgical lung biopsy:
7. Unexplained fixed rash on the digital extensor surfaces (i.e. 'Gottron's sign')	7. Anti-ribonucleoprotein	a. NSIP
	8. Anti-Smith	b. OP
	9. Anti-topoisomerase (Scl-70)	c. NSIP with OP overlap
	10. Anti-tRNA synthetase (eg, Jo-1, PL-7, PL-12, EJ, OJ, KS, Zo, tRS)	d. LIP
	11. Anti-PM-Scl	e. Interstitial lymphoid aggregates with germinal centers
	12. Anti-MDA5 (CADM-40)	f. Diffuse lympho-plasmacytic infiltration (with or without lymphoid follicles)
		3. Unexplained multi-compartment involvement[a]:
		a. Pleural effusion or thickening
		b. Pericardial effusion or thickening
		c. Intrinsic airways disease
		d. Pulmonary vasculopathy

HRCT = high-resolution computed tomography scan; ILD = interstitial lung disease; IPAF = interstitial pneumonia with autoimmune features; LIP = lymphocytic interstitial pneumonia; NSIP = nonspecific interstitial pneumonia; OP = organizing pneumonia; RTX = rituximab; SD = standard deviation; UIP = usual interstitial pneumonia.

[a] Either by: thoracic imaging, lung histopathology, right heart catheterization, pulmonary physiology.