Progression and prognosis of interstitial pneumonia with autoimmune features: a longitudinal, prospective, multi-centre study

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Abstract

Objective

To evaluate the rate of progression towards specific autoimmune diseases (SADs) of a prospective, multi-centre cohort of patients classifiable as interstitial pneumonia with autoimmune features (IPAF).

Methods

IPAF patients were enrolled based on specific research criteria, and jointly followed by rheumatologists and pulmonologists for at least one year with clinical check-ups, serological exams including autoimmunity, capillaroscopy and high-resolution computed tomography (HRCT). Diagnostic assessment was repeated at least once a year, or earlier when deemed useful.

Results

We enrolled 191 IPAF patients through 95 different combinations of IPAF criteria. Of these, 24.1% progressed towards SAD, mainly in connective tissue diseases but also in microscopic polyangiitis. The IPAF patients who progressed were younger than stable IPAF patients (63±10 years vs. 68±9 years, p=0.002) and had a longer follow-up (36.9±18.7 vs. 29.3±15.7 months, p=0.007), but similar severity. No parameters were associated with overall progression, but some parameters were associated with the development of specific diagnoses: Sjögren's syndrome with positivity for SSA (p=0.007, χ^2 7.4); idiopathic inflammatory myopathy with mechanic's hands (p=<0.0001, χ^2 12.6), organizing pneumonia pattern (p=0.01, χ^2 6.1), positivity for anti-Pm/scl (p=0.04 χ^2 4.1) and anti-MDA5 (p=0.04, χ^2 4.2); systemic sclerosis with palmar telangiectasias (p=<0.0001 ^{2} 18.3), positivity for anti-Scl70 (p=<0.0001 χ^2 12.5) and anti-PM/Scl (p=0.001 χ^2 10.1).

Conclusions

IPAF patients had a rate of progression towards SAD similar to that reported in previous studies on undifferentiated connective tissue diseases, thus including some patients in which lung involvement could represent the first or even the sole clinical manifestation of a SAD.

Key words

interstitial pneumonia with autoimmune features, progression, undifferentiated connective tissue disease, Sjögren's syndrome, idiopathic inflammatory myopathy

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Introduction

The term *interstitial lung disease* (ILD) refers to a pathological condition characterised by the deposition, in various degrees, of extracellular matrix and/or immune cells in the lung interstitium, causing a progressive damage of the pulmonary parenchymal architecture that may lead to respiratory failure (1). Although ILD can be caused by numerous conditions, global prevalence is relatively rare, ranging from 6.3 to 71 per 100000 people (1, 2). Connective tissue diseases (CTDs) are a relatively common cause of ILD, with a prevalence ranging from 7.5% to 33.3% of total ILD cases (2). However, several ILD patients show serological or clinical features of CTD not sufficient to be classified as a specific autoimmune disease (SAD). The definition of interstitial pneumonia with autoimmune features (IPAF) was proposed with the aim of providing a common research basis to follow these patients' natural history and prognosis (3).

IPAF classification requires at least one feature from two out of three domains (clinical, CD, serological, SD, and morphological, MD). As assessed by the authors, these criteria represent a platform for future research investigation aimed at creating a more uniform cohort (3). In the evaluation of IPAF patients it is reasonable to consider the possible stochastic association of an ILD and an autoimmune feature: for example, antinuclear antibody (ANA) ≥1:320 and Raynaud's phenomenon (RP) could be recognised in healthy subjects (4, 5). However, the possibility of including patients with an incomplete form of SAD, or at risk of developing a definite SAD, is interesting for scientific purposes.

These two possibilities resemble the concept of undifferentiated CTD (UCTD). Despite the lack of a validated definition, patients are considered UCTD in the case of an association of serological and clinical features not sufficient to meet classification criteria for SAD (6). These patients are considered "stable UCTD" if they do not develop other signs which could meet specific criteria for SADs within three years (7). In general, the progression towards SADs of UCTD patients was described in about 30% of patients during follow-up (8), and the possibility of achieving early recognition and exploiting a potential therapeutic "window of opportunity" allows the proposal of specific classification criteria for some conditions (for example, "Very Early Diagnosis of Systemic Sclerosis", VEDOSS) (9).

Patients selected with IPAF criteria, compared with the classic definition of UCTD, are of great interest for at least two reasons: the first is that ILD is rarely described in UCTD (10), and the second is the possibility of including patients despite the absence of seropositivity.

The main objective of the study is to evaluate the rate of progression towards SADs of a prospective cohort of IPAF patients jointly and longitudinally followed by rheumatologists and pulmonologists, while its secondary objective is to evaluate their prognosis.

Materials and methods

This is a multi-centre, longitudinal, prospective study, involving centres with an established, close collaboration between pulmonologists and rheumatologists in in the clinical assessment. The study was conducted from January 2017 to May 2022. The study complies with the Declaration of Helsinki, and it was approved by Ethical Committee "Catania 1", (n.0024182 TMP/10-2015). Written informed consent was obtained from all the patients enrolled in the study.

Inclusion and exclusion criteria

We included in the study only patients clinically evaluated multidisciplinary rheumatologists and pulmonologists expert in the management of ILDs and CTDs. We enrolled patients aged ≥18 years satisfying IPAF classification criteria (3). To improve specificity in the CD, the "polyarticular morning joint stiffness of at least one hour" was considered present only when associated with an abnormal level of C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR) (11, 12). ILD patients positive for anti-t-RNA synthetase antibodies (ARS) were not included because considered anti-synthetase syndrome (ASSD), in line with the papers

of the AENEAS collaborative group (13, 14). Finally, the MD of IPAF criteria allows the inclusion of patients with a radiological or histological pattern of nonspecific interstitial pneumonia (NSIP), organising pneumonia (OP), lymphocytic interstitial pneumonia (LIP) or NSIP+OP, while the authors clearly reported that the presence of a definite Usual Interstitial Pneumonia (UIP) pattern needs to satisfy both of the other two domains (3). However, the MD could also be satisfied by the presence of a section called "multicompartment involvement", including the presence of bronchiectasis. As bronchiectasis is very common in ILD, and in the same definition of typical and probable UIP (pUIP) pattern in high-resolution computed tomography (HRCT) (15), we considered the pUIP pattern sufficient to satisfy the morphological domain. On the contrary, UIP definite patients were enrolled, according to what reported in IPAF criteria, in the presence of at least one item from both the clinical and serological domains.

Patients were excluded from the study if they developed a SAD within the first three months from the baseline, and in the absence of a one-year follow-up check-up. Follow-up was considered stopped in the absence of a new check-up, or in the absence of the annual diagnostic assessment.

The following description of the diagnostic assessment was repeated at least once a year on all the patients, or earlier, depending on the new onset/worsening of signs and symptoms.

Clinical assessment

Enrolment of ILD patients depended on each centre's organisation. About two third of the patients were jointly evaluated by pulmonologists and rheumatologists. In the other cases, the two check-ups were performed within seven days from each other, starting from the pulmonology assessment. The pulmonologists were trained to recognise a specific checklist of previously published possible rheumatologic signs (16), and had a clinical questionnaire to be administered to patients (17, 18). The assessment of smoking habit was quantified using pack/years.

Serological assessment

All ILD patients assessed int the participating centres performed the same first-line laboratory assessment, that included the following exams: complete blood count, creatinine, ESR, CRP, urine test, complement fraction C3 and C4, serum protein electrophoresis, creatine phosphokinase (CPK), lactic dehydrogenase (LDH), aspartate and alanine transaminases (AST and ALT), myoglobin, aldolase, ANA in indirect immunofluorescence with description of the pattern, myeloperoxydase and proteinase 3 anti neutrophilic cytoplasm antibodies (MPO- and PR3-ANCA), rheumatoid factor (RF), anti-citrullinated protein antibody (ACPA), anti-extractable nuclear antigen (ENA) panel.

The latter panel includes anti-Sm, anti-Jo1, anti-RNP, anti-La, anti-SSA/Ro60Kd, anti-SSA/Ro52Kd, anti-Scl70, and was performed using Immunoblotting (due to its availability at each centre).

Second-line serological assessment, including testing for myositis-specific and myositis-associated antibodies (MSA/MAAs) was performed on all patients with suspected Idiopathic Inflammatory Myositis (IIM). This suspicion was raised by the presence of typical skin rashes, proximal weakness, increased muscle enzymes or dysphagia, however the exam was performed also on other patients when deemed useful (19). Also in these cases, the exam was performed using immunoblotting, including the following specificities: anti Mi2, MDA5, NXP2, SAE1, SRP, Tif1γ, EJ, OJ, PL7, PL12, Jo1, Ro52Kd, Pm/scl, Ku, RNP).

Instrumental assessment

HRCT was performed on all ILD patients at baseline and then yearly, or when deemed useful for the patients' management, with slices of 1.25 mm gap 0.6125. The images were interpreted by each centre's expert radiologists according to the current guidelines (15). A nailfold videocapillaroscopy was performed by rheumatologists on all patients with RP, puffy fingers, telangiectasias, suspected IIM, positivity for ANA, anti-Scl70, PM/Scl, MSAs or MAAs (20, 21).

Pulmonary function tests (PFTs) including spirometry, diffusion lung capacity for carbon monoxide (DLCO) and 6-minute walk test (6MWT) were performed at baseline and then at least yearly, or when deemed useful for the patients' management by pulmonologists according to the specific guidelines (22-24). Forced vital capacity (FVC) and DLCO are reported as a proportion of the predicted.

The functional exocrine gland assessment for the recognition of primary Sjögren's syndrome (pSS) was performed on all patients reporting sicca syndrome or with SSA positivity (25, 28).

Other instrumental exams were performed on ILD patients when deemed useful for diagnostic or prognostic purposes. These were: magnetic resonance imaging of the muscles, transthoracic echocardiogram, arterial gas sample, Electromyography, histological exams (mainly of the lung, muscles and minor salivary glands).

Criteria for the definition of SADs and prognosis

Diagnoses of SADs were made according to the current, validated criteria (13, 14, 27-35). In some patients the suspicion of IIM was raised during follow-up, and the recognition of ARS different than Jo1 was reported after the first visit. We considered the patients to have progressed towards ASSD on contemporaneous satisfaction of criteria for at least a probable IIM (31).

The progressive-fibrosing phenotype (PFP) of IPAF patients was considered based on the presence, within a period of 24 months of a relative FVC decline ≥10% or the presence of at least two of the following conditions: relative decline of FVC of 5–9%, clinical impairment, worsening of fibrosis on HRCT (36).

The need for oxygen (O_2) support was defined by the presence of PaO_2 <60mmHg in an arterial gas sample or a decline of saturation <90% at the 6MWT.

Statistical analysis

We used IBM SPSS Statistics for Windows, v. 20.0 (Armonk, NY, USA). For the sample size, we considered a global

prevalence of ILD of 50 per 100000 persons (1), and a prevalence of IPAF of 7% (37). Considering the population of the centres involved (3.7 million people), a confidence level of 95% and a confidence interval of 5%, we identified the need to enrol 101 patients.

We used a Shapiro-Wilk test to evaluate the distribution of the data. Based on the distribution of the variables, we used parametric (t-test and Fisher's exact test for continuous and dichotomic variables respectively) or non-parametric tests (Mann-Whitney U-test and χ^2 test). Data were presented in mean ± standard deviation (SD), or in proportion, *p*-value and 95% Confidence Interval (CI), considering to be statistically significant variables with a *p*-value <0.05.

Results

We enrolled a total of 191 IPAF patients, 62.8% females, with a mean age of 67.1±9.7 years, followed for a mean of 31.1±16.7 months. Current and former smokers made up 42.9%, whereas heavy smokers (at least 20 pack/years) made up 24.6%. The three domains were satisfied together by 52 (27.2%) patients. The CD+MD were satisfied by 38 (19.9%) patients, whereas 17 (8.9%) and 84 (44%) were classified due to the presence of CD+SD and SD+MD respectively. IPAF patients were enrolled through 95 different combinations of the criteria, but the majority showed the minimum of two criteria (51.3%). The number of IPAF items is reported in Figure 1, while Table I reports the IPAF patients' complete clinical presentation.

During the follow-up, 24.1% of patients developed a SAD. The specific diagnoses were the following: three patients with rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and microscopic polyangiitis (MPA), four patients with Polymyositis (PM) and ASSD, six with dermatomyositis (DM) and systemic sclerosis (SSc), twelve with pSS, and five cases of overlap syndromes (OS). The latter group was composed of two patients with SSc+PM, and a single patient with Sjögren's syndrome associated with DM and SSc, and SSc+SLE. The mean time of progression was 22±15.8 months (Fig. 2).

Among patients who progressed, 14 (30.4%) were enrolled satisfying all 3 domains, 16 (34.8%) SD+MD, 11 (23.9%) CD+MD, and 4 (10.9%) CD+SD. The number of IPAF criteria is similar between stable and progressed patients (2.6±0.8 *vs*. 2.9±1 respectively, *p*=0.07) (Fig. 3).

IPAF patients who progressed were younger than those with stable IPAF (63±10 years *vs*. 68±9 years, *p*=0.002 95CI 1.8–18.82) and had a longer follow-up (36.9±18.7 *vs*. 29.3±15.7 months, *p*=0.007 95CI 2.1–13.1), whereas the proportion of current/former smokers was similar (17.4% *vs*. 26.9% respectively, *p*=0.19).

The overall progression into established rheumatic diseases was not associated with specific items (Table II).

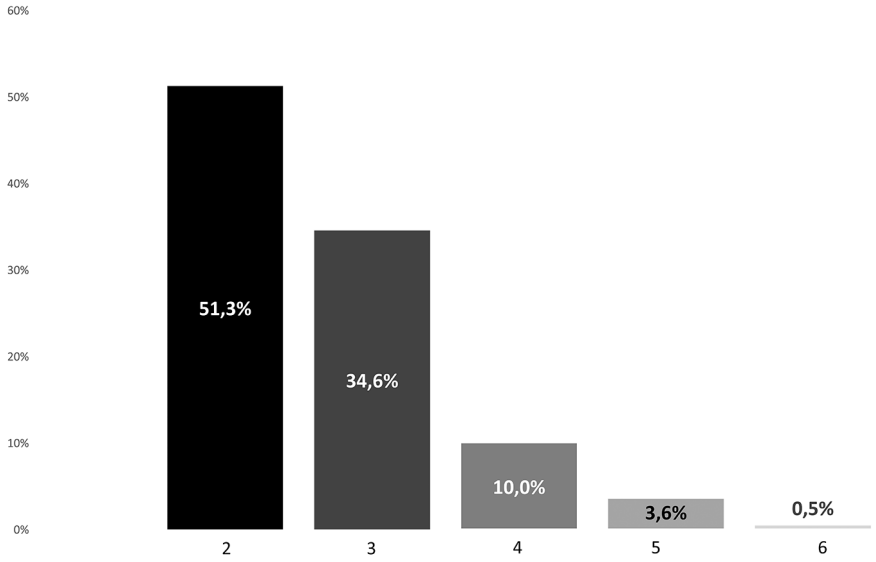

Fig. 1. Number of IPAF items in the whole cohort.

Table I. Clinical presentation of interstitial pneumonia with autoimmune features patients.

Clinical domain	56%	Serological domain	80.1%	Morphological domain	91.1%
MH	5.2%	RF	8.4%	NSIP	65.4%
DDTU	1.6%	ACPA	4.7%	OP	2.6%
IA	11.5%	DsDNA	3.7%	NSIP+OP	6.8%
PMJS	10.5%	Ro60Kd	3.2%	LIP	1.6%
IA+PMR	19.9%	Ro52Kd	15.7%	UIP	8.9%
PT	6.8%	Global SSA	16.8%	pUIP	14.7%
RP	26.2%	SSB	0%		
UDO	3.2%	RNP	3.2%		
GS	2.1%	Anti-Sm	1.1%		
		Anti-Scl70	2.6%		
		Pm/Scl	6.3%		
		MDA5	1.1%		
		ANA ≥1:320	56%		
		Homogeneous	10.5%		
		Speckled	31.9%		
		Nucleolar	18.3%		
		Centromeric	3.2%		
		Cytoplasmic	14.1%		
		Other patterns	6.3%		
		Global ANA	64.4%		

ACPA: anti citrullinated protein antibody; ANA: antinuclear antibodies; DDTU: distal digital tip ulceration; GS: Gottron's sign; IA: inflammatory arthritis; LIP: lymphocytic interstitial pneumonia; MH: mechanic's hands; NSIP: nonspecific interstitial pneumonia; OP: organising pneumonia; PMJS: polyarticular morning joint stiffness; PT: palmar telangiectasia; pUIP: probable UIP; RF: rheumatoid factor; RP: Raynaud's phenomenon; UIP: usual interstitial pneumonia.

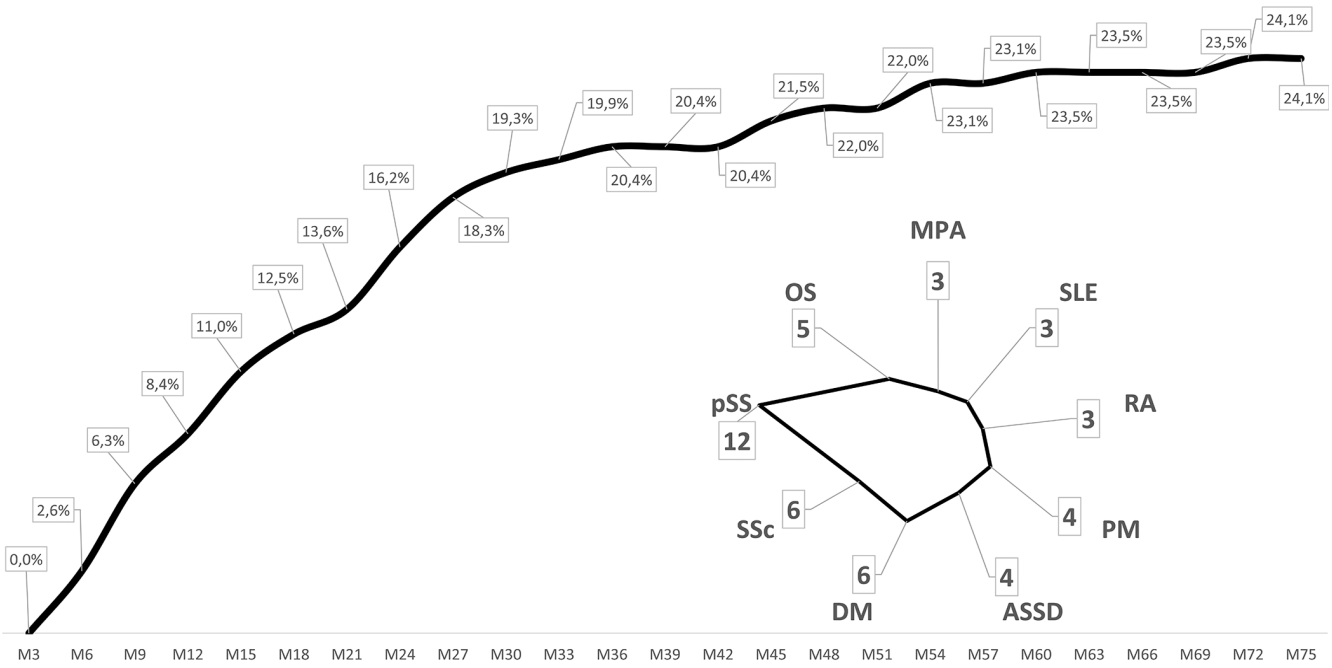

Fig. 2. Time to progression and diagnosis of IPAF patients progressed towards specific autoimmune diseases.
AS: antisyhnthetase syndrome; DM: dermatomyositis; MPA: micropolyangiitis; OS: overlap syndromes; pSS: primary Sjögren's syndrome; PM: polymyositis; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus.

However, when considering the specific rheumatic disorders, pSS appearance was associated with the overall positivity of anti-Ro antibodies (p=0.007, χ^2 7.4), of anti-Ro60kd (p=0.01 χ^2 6.2), of anti-Ro52Kd (p=0.03 χ^2 4.6), and with the presence of cytoplasmic positivity of the ANA test (p=0.01, ^{2} 5.8). Progression towards IIM was associated with the presence of Mechanic's hands (p=<0.0001, χ^2 12.6), OP pattern on HRCT (p=0.01, χ^2 6.1) and positivity for anti-PM/Scl (p=0.04 ^{2} 4.1) and anti-MDA5 (p=0.04, χ^2 4.2). Finally, progression towards SSc was associated with the presence of palmar telangiectasias (p=<0.0001 χ^2 18.3), positivity for anti-Scl70 (p=<0.0001 χ^2 12.5) and anti-PM/Scl (p=0.001 χ^2 10.1).

From a functional point of view, two patients were not able to perform PFTs due to their conditions. For the other 189 patients, the mean value of FVC was 88±23.8, DLCO 60.7±19.5. Stable IPAF showed a basal FVC of 86.1±20.6 and DLCO 59.7±20.5, whereas progressed IPAF had a basal FVC of 88.5±24.8 and DLCO of 63.8±15.8 (p=0.55 and 0.21, respectively).

A need for O_2 support was developed by 72 (37.7%) patients, in a mean time of 10.3±16.8 months, however 20.9% of patients needed O_2 support within three months of the first visit. The need for O_2 support was associated with smoking habit (p=0.01, χ^2 6.4) and ANA positivity (p=0.02, χ^2 5.3), mainly with titre ≥1:320 (p=0.005, χ^2 7.9), but not with progression towards SADs or HRCT patterns.

PFP was developed by 35.1% of patients in a mean time of 14.3±8 months. The development of PFP was associated with the ANA speckled pattern (p=0.04, χ^2 4) and a NSIP+OP pattern (0.04 χ^2 4.2), but not with a UIP-like pattern. The proportion of patients with O2 support and PFP was similar between stable and progressed IPAF.

Despite the relatively common need for O_2 and development of PFP, only 14 (7.3%) patients deceased due to a respiratory issue. The respiratory death was associated with the presence of RP (p=0.04, χ^2 4.4) and a NSIP + OP pattern (p=0.02, χ^2 5.1).

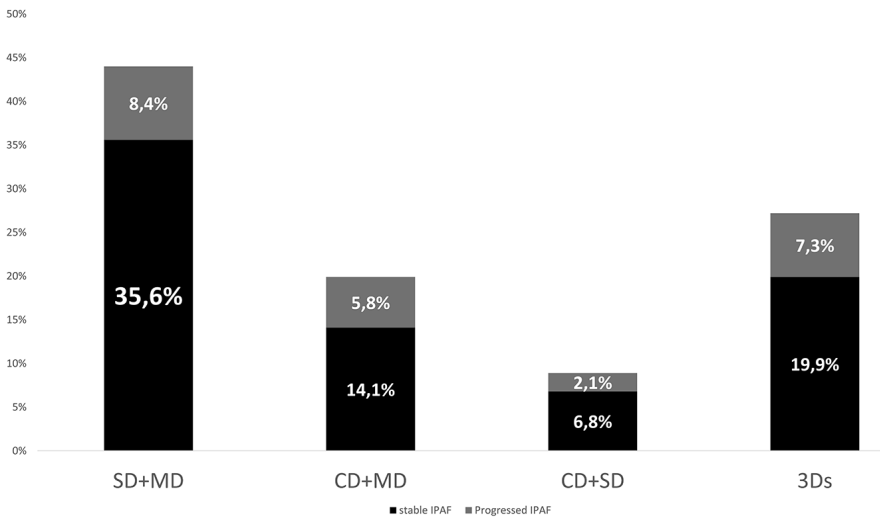

Fig. 3. Combination of domains in stable and progressed IPAF patients
3Ds: all three domains; CD: clinical domain; MD: morphological domain; SD: serological domain.

Table II. Clinical presentation of Stable and progressed IPAF patients.

MD	Stable IPAF	Progressed IPAF	*p*-value	SD	Stable IPAF	Progressed IPAF	*p*-value	MD	Stable IPAF	Progressed IPAF	*p*-value
MH	4.13%	8.7%	0.22	RF	7.6%	10.9%	0.67	NSIP	67.6%	58.7%	0.32
DDTU	2.1%	0%	0.32	ACPA	4.1%	6.5%	0.5	OP	1.4%	6.5%	0.06
IA	13.1%	6.5%	0.22	DsDNA	2.8%	6.5%	0.23	NSIP+OP	5.5%	10.9%	0.2
PMJS	9.7%	13%	0.51	Ro60Kd	13.8%	21.7%	0.13	LIP	2.1%	0%	0.32
IA+PMJS	20%	20%	0.94	Ro52Kd	2.1%	6.5%	0.19	UIP	9%	8.7%	0.95
PT	5.5%	10.9%	0.2	Global SSA	14.5%	23.9%	0.13	pUIP	14.5%	15.2%	0.9
RP	24.1%	32.6%	0.25	RNP	4.1%	0%	0.16				
UDO	3.4%	2.2%	0.67	Anti-Sm	1.4%	0%	0.42				
GS	2.1%	2.2%	0.97	Anti-Scl70	2.1%	4.3%	0.4				
				Pm/Scl	5.5%	8,7%	0.43				
				MDA5	0.7%	2.2%	0.38				
				ANA ≥1:320	57.2%	52.2%	0.34				
				Homogeneous	*11.7%*	6.5%	0.31				
				Speckled	*32.4%*	30.4%	0.8				
				Nucleolar	*20.7%*	10.9%	0.13				
				Centromeric	*2.8%*	4.3%	0.13				
				Cytoplasmic	*14.5%*	13%	0.8				
				Other	*8.3%*	0%	0.04 $X^2$4.1				
				Global ANA	66.9%	56.2%	0.2				

ACPA: anti citrullinated protein antibody; ANA: antinuclear antibodies; CD: clinical domain; DDTU: distal digital tip ulceration; GS: Gottron's sign; IA: inflammatory arthritis; IPAF: interstitial pneumonia with autoimmune features; LIP: lymphocytic interstitial pneumonia; MD: morphological domain; MH: mechanic's hands; NSIP: nonspecific interstitial pneumonia; OP: organising pneumonia; PMJS: polyarticular morning joint stiffness; PT: palmar telangiectasia; pUIP: probable UIP; RF: rheumatoid factor; RP: Raynaud's phenomenon; SD: serological domain; UIP: usual interstitial pneumonia.

Discussion

CTD-ILD deeply impact the survival of affected patients, although to a lesser extent than IPF (38). ILD represents a relatively common finding onset of CTD (14, 39). Despite the continuous progresses in the knowledge of CTD-ILD (40), the CTD diagnosis in ILD patients can be very difficult considering the commonly nuanced autoimmune signs/symptoms and the fact that collaboration between Pulmonologists and Rheumatologists is not yet widespread. The primary aim of this study is to evaluate the rate of progression of a prospective cohort of IPAF patients followed in centres with an established close collaboration between pulmonologists and rheumatologists.

As expected, our IPAF cohort proved to be heterogeneous, enrolling 191 patients with 95 different combinations of criteria. However, about a quarter of IPAF patients progressed towards SADs, developing, in different proportions, all the CTDs and in three cases, MPA. The progression is similar to that reported in previous cohorts of UCTD patients (9) but appears lower than that reported with VEDOSS criteria (52.4%) (41). It is of interest to highlight that the UCTD definition generally requires the association of a clinical sign with at least one positive autoantibody, whereas 23.9% of our progressed patients were seronegative at enrolment. Of course, VEDOSS criteria were designed solely for the early recognition of SSc. The patients who progressed in the cited study had a follow-up about two times longer and the proportion of seronegative patients among those who progressed was only about 5%.

None of the items included in the three IPAF domain proved to be associated with overall disease progression. This could again be explained by the heterogeneity of the patients, leading to progression towards different conditions.

Despite almost all the current RA criteria being included in IPAF (26), only three patients developed this condition. A possible explanation is the prevalent UIP pattern in RA not being included in the MD (3, 18). However, this could be questioned, considering that we have not found any association between progression and a specific HRCT pattern. Moreover, the association of a single domain from the clinical or serological ones with a UIP pattern proved to significantly increase the rate of progression towards SADs in IPF patients, with a proportion similar to classic IPAF (42, 43).

On the other hand, despite the exclusion of ANCA from the SD, three patients developed MPA. In view of this and considering the common lung onset of MPA (34), it could be appropriate to include these antibodies in future versions of IPAF criteria, as already suggested (44).

IPAF criteria also included almost all the items considered for the classification of SSc, therefore it is not surprising to see the development of a significant proportion of SSc (six primary forms and four overlap syndromes) (27). The progression was associated with telangiectasias, and positivity for anti-Scl70 and PM/Scl, all items highly suggestive for SSc in its primary or secondary form (18). However, it could be of interest to note that the majority of SSc patients had lung involvement in established disease (44), therefore it remains unclear whether these patients actually progressed towards a definite SSc or had an uncommon clinical presentation of an already established SSc. Similar discussions can be made regarding patients that developed SLE, considering that ILD is rarely associated with this condition (19). To improve the recog-

nition of this subgroup of patients, it could be useful to add other items suggestive for SLE (for example, fever to the clinical domain).

The most common progression was towards pSS, highlighted in 12 patients (but also in two patients with overlap syndromes), associated with positivity for anti-Ro antibodies. ILD can precede the diagnosis of pSS by years, and is commonly associated with mild sicca symptoms, therefore it is not surprising to see the development of pSS in IPAF patients despite the absence of sicca syndrome in the CD (45). Our IPAF patients who progressed towards pSS at the time of enrolment showed normal exocrine gland function and did not report significant sicca syndrome. We cannot exclude the possibility that some of these patients already had a suggestive minor salivary gland histology at enrolment, however in consideration of the absence of gland dysfunction, xerophthalmia and xerostomia, a biopsy was not performed. The latter two symptoms are considered entry criteria for the pSS classification (28), and the biopsy would not significantly change the therapeutic options for these patients. Despite ILD preceding pSS being generally reported with a UIP like pattern (44), we did not find this association. The data could be biased due to the difficulty in enrolling UIP patients according to IPAF criteria, which would suggest an opportunity to reconsider the presence of the MD, in order to limit the enrolment of a UIP pattern. Its exclusion could allow the early recognition of patients with a lung onset not only of vasculitides, but also CTD (mainly RA, IIM and pSS) (41, 42). We also found an association between the presence of cytoplasmic pattern of ANA and progression towards pSS. IPAF criteria allow the inclusion of patients with ANA positivity with a minimum titre of 1:320, or at any titre with a centromeric or nucleolar pattern (3). Cytoplasmic pattern is generally associated with the presence of MSAs, and in some cases with positivity for anti-Ro52Kd, both autoantibodies closely associated with ILD (19, 46, 47). Therefore, it could be reasonable to consider the inclusion of the cytoplasmic pattern in the IPAF SD.

Finally, primary IIMs were found in 14 patients (6 DM, 4 ASSD and PM), and 3 patients progressed towards overlap syndromes including an IIM (2 PM and 1 DM). It should be highlighted that patients with a probable IIM (31) or positivity for ARS were excluded from the study. The patients were considered to have progressed towards IIM according to specific criteria (29-31), and recognition of ARS during follow-up also required the satisfaction of IIM criteria. Therefore, we believe that our patients could actually represent a lung onset of the disease. Progression was associated with MH, PM/Scl and anti-MDA5 positivity, and an OP-HRCT pattern, all well-recognised parameters suggestive of IIM (19, 31).

From the functional point of view, we did not find differences in basal FVC and DLCO between stable and IPAF patients who progressed, and all patients generally had a good prognosis, confirming what was reported in the interesting study by Enomoto *et al*. (48). Respiratory-related death, as well as PFP, was associated with the presence of an NSIP+OP pattern. A possible explanation is an acute exacerbation, which could explain both the mortality and functional decline (on which the PFP definition is mainly based) (36, 49).

We are aware of the limitation of the study, as for example the lack of a central lecture of CT scans, the different laboratories involved in the blood samples analysis and that patients performed the PFTs in different machines. Moreover, the progression towards SADs seems to reach a plateau after 36 months, however we cannot exclude that other patients may progress in a longer follow-up. However, our study has also several strengths, as for example its prospective nature, the large number of patients enrolled and the established long-term collaboration between participating centres (14, 21, 50).

In conclusion, IPAF criteria, although improvable, could represent a lung-UCTD, being associated with a progression towards SADs in a quarter of patients, even when seronegative. Despite current treatment options for ILD are heading towards the radiological and functional findings of lung involvement and fibrosis progression (36), the appropriate diagnosis is fundamental. The recognition of the lung onset of SADs is useful to be aware of other possible visceral involvement. The tight collaboration between pulmonologists and rheumatologists required by the IPAF classification could improve the early recognition of SAD, favouring a progressive reduction of the proportion of ILD considered to be "idiopathic". The progresses in the diagnosis and classification of ILD patients allow to create more homogeneous group of ILD patients, with and without an underlying rheumatic disease, with potential benefits in clinical trials.

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