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Interstitial pneumonia with autoimmune features: clinical and demographic features, clinical history and survival

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Footnote for abbreviations: IPAF: interstitial pneumonia with autoimmune features; CTD: connective tissue diseases; IPF: idiopathic pulmonary fibrosis; ILD: interstitial lung disease; UCTD: undifferentiated connective tissue diseases; PFTs: pulmonary function tests; HRCT: high-resolution computerized tomography; UIP: usual interstitial pneumonia; NSIP: nonspecific interstitial pneumonia; OP: organizing pneumonia; LIP: lymphoid interstitial pneumonia; FVC: forced vital capacity; DLCO-SB: Single-breath diffusing capacity of the lung for carbon monoxide; DLCO-VA: diffusing capacity of the lung for carbon monoxide adjusted by the alveolar volume; IQR: interquartile range; CI: confidence intervals; ANA: antinuclear antibodies; ACPA: anti-citrullinated peptides antibodies;

Abstract

Background and objective. Recently the term "interstitial pneumonia with autoimmune features" (IPAF) has been proposed to identify patients with interstitial lung disease and autoimmune characteristics, not fulfilling the criteria for specific connective tissue diseases (CTD). Only few data are available about the clinical and serological features of IPAF patients, their survival and the possible evolution in a CTD.

The aims of the study were to investigate the demographic and clinico-serologic features of patients with IPAF, their relationship to survival, and the possible evolution in a definite CTD.

Patients and methods. Fifty-two patients were consecutively enrolled and prospectively followed for 45±31.6 months. Data about disease onset, serological, clinical and therapeutic features, pulmonary function tests and high-resolution computed tomography were periodically repeated. The survival of patients with IPAF was compared with that of 104 patients with idiopathic pulmonary fibrosis (IPF).

Results. The clinical domain for IPAF was satisfied in 44 patients, serological domain in 49 and the morphological domain in 29 patients. During the follow-up, a definite CTD was diagnosed in 7

patients, in particular Sjogren's syndrome in 4 patients, rheumatoid arthritis in 2, and polymyositis in the last.

The estimated 5-year survival of IPAF patients 69.5±7.8%, significantly higher than survival observed in IPF patients, and the baseline value of FVC and DLCO were the only factors associated to death

Conclusions. IPAF seems to a distinct entity, with a low tendency to evolve in a definite CTD. Nevertheless, further studies are needed to better define the clinical evolution and the outcome of IPAF.

Key words: connective tissue diseases (CTD), interstitial lung disease (ILD), interstitial pneumonia with autoimmune features (IPAF), idiopatic pulmonary fibrosis (IPF), survival.

1. Introduction

The European Respiratory Society and American Thoracic Society (ERS/ATS) research statement has recently proposed the term "interstitial pneumonia with autoimmune features" (IPAF) to identify patients who have interstitial lung disease (ILD) with autoimmune features, but not fulfill the specific criteria for connective tissue diseases (CTD). This classification is based on a combination of clinical, serological, and morphological domains [1].

The term IPAF generally describes a heterogeneous group of patients, including both subjects with undifferentiated CTD (UCTD) complicated by ILD (for definition not fulfilling the criteria for a definite CTD), and interstitial pneumonia with nonspecific rheumatic symptoms and antinuclear antibodies (ANA). ILD is one of the most frequent clinical manifestations of CTD [2,3] and may represent the first sign of a CTD, which may precede the onset of the rheumatic disease by many years [4,5].

As expected for UCTD, the evolution in a definite CTD has been described in some cases of IPAF; however , only few studies have described the clinical and serological characteristics of patients classified as IPAF, their survival and the possible evolution in a CTD [6–11].

The aim of this prospective follow-up study was to investigate the demographic, clinical and serologic features of patients with IPAF, their relationship to survival and the possible evolution to a definite CTD.

2. Patients and methods

In our study, we enrolled all consecutive patients referred to our rheumatologic-pneumological Center, who had a diagnosis of IPAF. The study was approved by the local ethical committee and all patients signed an informed consent.

Since 2009 our multidisciplinary team of the university-based Center for Rare Pulmonary Diseases at Modena Hospital is cooperating in the clinical assessment and management of patients affected by

ILDs or systemic autoimmune disorders complicated by lung involvement. Trained pulmonologists and rheumatologists are involved in the center, together with radiologists, cardiologists, thoracic surgeons, and pathologists. All patients with ILD are evaluated by a pulmonary/rheumatology multidisciplinary team. We provide to all patients with ILD a standardized screening and a comprehensive evaluation using a core set of clinical and laboratory investigations. The initial patient's assessment is followed by a prospective periodical patient's re-evaluation and all data are prospectively collected. [12–23].

This prospective study includes all patients satisfying the current research criteria for IPAF-referred to our Center from 2009. After the publication of 2015 ERS/ATS research statement for the classification of IPAF, we reviewed the diagnosis of all patients with lung-dominant CTD or UCTD with ILD diagnosed from 2009 to 2015 and prospectively followed since 2009 to evaluate if they met at diagnosis the new 2015 criteria for IPAF. Among them, 43/74 patients satisfied criteria for IPAF.

Starting from 2015, we have directly started to apply the new criteria.

Therefore, our cohort of consecutive IPAF patients diagnosed over an 8-year period and prospectively followed from 2009 to 2017 includes 52 patients, 43 patients reclassified as IPAF and diagnosed in the period 2009-2015, and 9 diagnosed after the publication of IPAF criteria.

According to the current research criteria, to be classified as IPAF, patients with suspected idiopathic interstitial pneumonia must have at least one feature from at least two of clinical, serologic, morphologic domains [1].

2.1 *Data collection*

Data about disease onset, serological, clinical and therapeutic features of the patients were recorded at baseline and every 3 months according to the protocol.

At baseline for every patient were recorded:

- demographic findings and specific patients' findings potentially responsible for some variants of secondary ILDs [13, 24];

- a wide panel of signs and symptoms of either lung involvement and possible underlying CTDs or rheumatoid arthritis [12–18];
- laboratory and instrumental investigations, including pulmonary function tests (PFTs) and high-resolution computerized tomography (HRCT). [12–23].

Clinical and serological evaluations and PFTs were repeated every 6 months; HRCT was repeated every 2 years or when a deterioration of clinical status occurred.

The initial patient's assessment was followed by a periodical re-evaluation until June 30th 2018, when the vital status of all enrolled subjects was re-evaluated. The survival of patients with IPAF was compared with that of 104 patients with idiopathic pulmonary fibrosis (IPF), randomly selected from a population of 153 patients at a 2:1 ratio to IPAF patients evaluated in the same study period (female/male 23/81; mean age at diagnosis 66.7±6.3 years).

2.2 *Assessment of lung involvement*

ILD was diagnosed by HRCT. At baseline all patients performed chest HRCT in supine position at end inspiration; all images were scored by a thoracic radiologist (GDC) experienced in ILD, classifying them as definite, possible or inconsistent with usual interstitial pneumonia (UIP) pattern [25]. If inconsistent with UIP pattern, the pattern was furtherly classified in nonspecific interstitial pneumonia, organizing pneumonia or lymphoid interstitial pneumonia [26, 27]. Based on the proposed criteria [26, 27], nonspecific interstitial pneumonia (NSIP) pattern was defined as basal predominant reticular abnormalities with traction bronchiectasis, frequently associated with ground-glass attenuation; organizing pneumonia (OP) pattern was defined as bilateral patchy areas of consolidation and/or ground-glass opacities with a subpleural and lower lung zone predominance or peri-bronchovascular distributions; and UIP pattern was defined as basal honeycombing opacities associated with reticular abnormalities and traction bronchiectasis [24]. Finally, lymphoid interstitial pneumonia (LIP) was defined as ground-glass opacity accompanied by scattered, thin-walled, perivascular cysts [26, 27].

The results of pulmonary function tests were expressed as percentages of the predicted value of each parameter and corrected for age, gender and height. Pulmonary function was considered abnormal if forced vital capacity (FVC) was <80% of predicted values. Single-breath diffusing capacity of the lung for carbon monoxide (DLCO-SB) and DLCO adjusted by the alveolar volume (DLCO-VA) were used to assess gas transfer. A worsening of FVC ≥10% or DLCO ≥ 15% were considered clinically significant [24]

2.3 *Statistical analysis*

Continuous variables were reported as median and interquartile range (IQR) and were compared using unpaired or paired nonparametric tests (Mann-Whitney or Wilcoxon test, respectively). The Kaplan-Meier curve and two-sided log-rank test were used for univariate survival analysis. The Cox proportional hazards model was used for univariate and multivariate survival analysis to calculate the hazard ratios (HR) and corresponding 95% confidence intervals (CI). Variables significantly associated to death at univariate analysis (≤0.05) were included in the multivariable Cox model. Survival time was calculated from the date of initial diagnosis to death from any cause. For patients lost to follow-up, survival time was censored at the last follow-up date. A p value less than 0.05 was considered significant [28]. Statistical analyses were performed using the SPSS statistical software, version 17.0 (SPSS Inc., Chicago, IL, USA).

3. Results

Demographic, clinical and serological features of the patients are reported in table 1. Seven patients were lost at follow-up after a mean period of 27 months (range 2-55).

The female/male ratio was 1.26 and the mean age 68 years (IQR 14). About half patients were never-smoker. The mean follow-up was 44.5 months (IQR 53).

Forty-four (84.6%) patients satisfied the clinical domain for the classification of IPAF, showing at least one clinical symptom, mainly polyarticular morning joint stiffness more than 60 min or

Raynaud's phenomenon (table 1). Distal digital ulceration, palmar telangiectasias, digital edema and Gottron's sign were not observed in any patients. Despite not included in IPAF criteria, sicca syndrome and serositis were recorded in a significant percentage of patients (46.8%, 35.6%, and 15.6% for oral dryness, eye dryness, and serositis, respectively).

Moreover, serological domain was satisfied in 94.2% of patients (49 subjects), in particular antinuclear antibodies (ANA) were detected in 72.3% of patients. No patients showed anti-DNA or anti-citrullinated peptides antibodies (ACPA).

Finally, the morphological domain for IPAF classification was recorded in 29 patients (55.8%). Forty-eight or all patients satisfied morphological domain. In particular, UIP pattern at HRCT were described in 23 patients (44.2%), NSIP in 17 (32.7%), OP in 8 (15.4%), while in 4 patients (7.7%) HRCT pattern was not classifiable. Only 2 patients underwent to lung surgical biopsy that found an UIP pattern in both cases.

Thirty-three patients were treated with steroids, generally low doses of prednisone (5-10 mg daily), while 15 patients were treated with immunosuppressants (namely cyclophosphamide in 4, azathioprine in 5, and mycophenolate mofetil in 5), all but 1 in combination therapy with steroids. Six patients underwent to antifibrotic therapy (namely nintedanib or pirfenidone), in 4 cases associated to low dose of prednisone. Finally, 16 patients didn't take any therapies.

3.1 *Evolution of the clinical manifestations*

During the follow-up, sicca syndrome appeared in 4 patients (eyes and mouth dryness), while a fifth patient reported only mouth dryness. The occurrence of Raynaud's phenomenon was recorded in 3 patients, photosensitivity in 1, arthralgias with prolonged morning stiffness in 4, while an overt arthritis appeared in 3 cases.

Among serological data, ANA became positive in 4 patients during the follow-up, while in one case ANA disappeared; rheumatoid factor and ACPA appeared in one patient. No variations were observed regarding antisynthetase antibodies.

Finally, 7 of 52 (13.5%) patients developed a definite CTD during the follow-up. After a mean time of 31 months (range 7-71), 4 patients fulfilled the classification criteria for Sjogren's syndrome, 2 for rheumatoid arthritis, and the last for polymyositis.

In one patient with sicca syndrome and Raynaud's phenomenon who developed SS, anti-SSA antibodies and the biopsy of minor salivary glands were negative at baseline. This patients developed anti-SSA antibodies 2 years later, on this occasion a new biopsy of minor salivary glands showed a focus score 2 [13, 29]. In another one, rheumatoid arthritis was diagnosed after the appearance of rheumatoid factor and ACPA, both tests were negative at the first visit.

3.2 *Evolution of lung function*

Lung function declined progressively during the follow-up in a high percentage of patients. In particular, FVC worsened (≥10% of predicted) in 34.4% of patients during the first 12 months and in 87% of patients at the end of the follow-up, while a reduction of DLCO ≥15% was recorded in 34.3% of patients in the first 12 months and in 57.6% at the end of follow-up. On the other hand, DLCO improved after 12 months in 31.4% of cases and in 10.5% at the end of follow-up, while FVC improved only in 6.3% and 10.5% of patients during the first 12 months and at the end of follow-up, respectively (the evolution of lung function is reported in figure 1).

3.3 *Survival*

During the study, 15 patients died (28.8%).

The overall mean survival of our population was 94.2 months (CI95% 77.5, 110.9) [median: 94 months (CI95% 67.1-120.8)], while the estimated 5-year survival was 69.5±7.8% (figure 1).

The only factors associated to death at univariate analysis were the baseline value of FVC (HR 0.97, CI95% 0.94-0.99 for each point of FVC; p=0.012) and DLCO (HR 0.93, CI95% 0.88-0.98 for each point of DLCO; p=0.009), also confirmed as independent predictors of death at Mantel-Cox

multivariate analysis. No differences were observed according to the HRCT pattern of the patients (Table 2).

Finally, we compared the population of patients with IPAF with a cohort of 104 patients with IPF. The overall mean survival of this population was 55.7 months (CI95% 43.7-67.6) [median: 40 months (CI95% 29-51)], while the estimated 5-year survival was 36.8±5.9%, significantly lower than IPAF ($p<0.001$ at Mantel-Cox Log-rank, see figure 2).

4. Discussion and Conclusions

In the present study, we analysed 52 patients classified as IPAF and prospectively followed with a standardized approach by a single Center multidisciplinary team

The main clinical features of our patients were represented by Raynaud's phenomenon, arthralgias and sicca syndrome. Of interest, the clinical status was stable during the time, and we observed only few changes, mainly due to the appearance of Raynaud's phenomenon, sicca syndrome and arthritis. A similar trend was observed for the autoimmune serology, with the appearance of ANA in 4 patients only.

In less than 15% of patients a definite CTD was diagnosed during the follow-up. According to literature data, Sjogren's syndrome and rheumatoid arthritis were the main diagnoses. In these two conditions ILD has been described as the only presentation by many Authors, and lung involvement can be the only clinical manifestation of the disease for many years [2–5].

The term IPAF, proposed in 2015 by an expert international panel of pulmonologists, rheumatologists, thoracic radiologists and pathologists, has the advantage of removing previous confounding nomenclatures, but it is not completely able to identify a homogeneous subgroup of patients [1,6–10].

The lack of a rheumatologist in the multidisciplinary team for the clinical assessment of ILD patients has been reported as a limitation in some published studies. Some articles reported the presence of an

expert rheumatologist in the diagnostic process, whereas in other studies this role was not involved in diagnosis, partially explaining the reason of the heterogeneity of the published data [6–11].

In fact, some cohorts have features and outcomes similar to CTD [8], whereas patients in other published studies have features and outcomes more similar to IPF [6], causing difficulties in comparing different cohorts of patients. According to our results, Sambataro et al. showed a different phenotype in patients with IPAF compared with IPF; in fact, IPAF patients were younger, with better performances in PFTs, less necessity of O_2 support and predominance of female sex and NSIP pattern [30].

The main advantage of our study is the multidisciplinary approach to our patients and the longitudinal prospective design. All patients underwent the same assessments at baseline and periodically during the follow-up and the data collection was the same since 2009; then, we prospectively observed the natural history of a population of patients with IPAF.

As in other studies, we cannot exclude the inclusion of patients with idiopathic pneumonia or with early stages of CTDs [6–10, 31]. However, IPAF shows low tendency to evolve in a definite CTD and, although the prognosis was severe, the observed significantly higher survival when compared to IPF suggests that IPAF is a well-defined clinical entity by itself.

Recently, a better survival and less episodes of acute exacerbation were described also in Korean patients with IPAF when compared to IPF [11]; moreover, the IPAF group tended to have a longer survival than IPF group, despite the presence of an UIP pattern [11]. On the other hand, other Authors suggest that patients with IPAF and features of UIP have similar poor outcomes comparable to IPF [6]. Furthermore, Ahmad et al. diagnosed IPAF in 57 patients, 19 (33%) of whom were found to have UIP features, and found no differences in survival between IPAF and IPF in their series. For this reason, some Authors affirm that the presence of UIP pattern could be a confounding factor in differential diagnosis between IPAF and IPF, suggesting the exclusion of patients with UIP pattern [9, 31].

According to Ito and Lim [7, 11], our data did not confirm these results, observing a better prognosis for patients with IPAF, without differences on the basis of radiological pattern. Moreover, UIP represents a frequent pattern in many CTD [4] and its exclusion could be arbitrary.

Currently, no studies are available about the possible therapeutic approach of patients with IPAF. The majority of our patients received an immunosuppressive treatment, overall corticosteroids and mycophenolate mofetil; however, some patients with UIP pattern were treated with antifibrotic agents. Only studies on large populations could better define the correct treatments for these patients, defining the usefulness of antifibrotic or immunosuppressive therapy. A combination therapy with immunosuppressant and antifibrotic drugs could be considered in some cases, in particular for patients with UIP pattern [32-34].

The current study has some limitations, but also some strengths. All patients were prospectively followed-up and all diagnoses were made in a homogeneous, rigorous, and multidisciplinary approach, including experienced clinicians and dedicated thoracic radiologists. Also the relatively long follow-up period (mean duration: almost 4 years) represents a strength of this study. This approach provides a more reliable perspective of the clinical spectrum of IPAF than previous retrospective and smaller series followed for a shorter period Limitations are represented by the relatively small number of patients which could underestimate the effect of some variables, as HRCT pattern, on survival, possible referral bias of cases, and the lack of tissue at diagnosis in almost all patients.

The present study suggests that IPAF could represent a distinct clinical entity from IPF, with a low tendency to evolve in a definite CTD, similarly to that observed for UCTD. Further larger studies with long-term follow-up are needed to better define the clinical features and the outcome of IPAF. In particular, the actual research criteria partially fail to differentiate between patients with IPF and positivity of autoantibodies, and patients with early or undifferentiated CTD with or without UIP pattern [6–10, 31]. Finally, a better definition of IPAF criteria could help to define the correct therapeutic approach to these patients.

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Table 2. Univariate and multivariate Cox regression. Predictive factor of death

	Univariate Hazard Ratio (CI95%)	p	Multivariate Hazard Ratio (CI95%)	p
Dicotomic variables				
Male sex	1.60 (0.58-4.45)	ns		
Smoke	1.25 (0.84-1.84)	ns		
Raynaud' s phenomenon	2.56 (0.79-8.37)	ns		
Arthralgias	0.83 (0.34-3.84)	ns		
Arthritis	1.80 (0.38-8.35)	ns		
HRCT pattern UIP/non-UIP	1.53 (0.54-4.31)	ns		
Antinuclear antibodies	1.71 (0.53-5.48)	ns		
ENA	2.16 (0.66-7.08)	ns		
Rheumatoid factor	3.71 (0.92-15.04)	ns		
Anti-synthetase antibodies	1.36 (0.16-11.42)	ns		
Continuous variables				
Age (years)	1.00 (0.95-1.05)	ns		
Forced vital capacity (%)	0.97 (0.94-0.99)	0.012	0.97 (0.94-0.99)	0.032
Diffusion lung CO (%)	0.93 (0.88-0.98)	0.009	0.92 (0.87-0.98)	0.006

Legend to the figure 1

Evolution of lung function after 12 months and at the end of follow-up. Data are reported as median of forced vital capacity and diffusion lung capacity of CO

Legend to the figure 2

Five-year survival of patients with interstitial pneumonia with autoimmune features (IPAF) and idiopathic pulmonary fibrosis (IPF).

Highlights

- IPAF is a well-defined clinical entity by itself
- IPAF has distinct characteristics that remain stable during the time
- IPAF has a low tendency to evolve in a definite CTD
- IPAF shows a better survival when compared to IPF