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Interstitial pneumonia with autoimmune features: Clinical, radiologic, and histological characteristics and outcome in a series of 57 patients☆

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ABSTRACT

Background: Interstitial pneumonia with autoimmune features (IPAF) has recently been defined by an international Taskforce to characterize interstitial lung disease associated with systemic manifestations limited to subtle serological and clinical autoimmune abnormalities and not fulfilling the international criteria for the diagnosis of a given connective tissue disease.
Objective: to report on a series of patients with IPAF, and to compare their outcome to that of a cohort of patients with idiopathic pulmonary fibrosis (IPF).
Methods: Retrospective analysis of consecutive patients in a single institution over a 3-year period.
Results: Out of 778 consecutive patients with interstitial lung disease, 55% had idiopathic interstitial pneumonia (including 20.1% with IPF), 21.5% had connective tissue disease, and 7.3% had IPAF. Patients (49% of females) had a mean FVC of 64% and a mean DLco of 49%. Serologic criteria for IPAF were the most frequent (93%), followed by "morphologic" criteria (79%), and clinical criteria (47%). Fifty three percent of patients had a NSIP pattern on CT. Nailfold capillaroscopy found giant capillaries in 13/30 patients tested (23%). No significant was found in overall survival between patients with IPAF and those with IPF.
Conclusion: The recently defined criteria for IPAF are fulfilled by a significant proportion of patients referred for interstitial lung disease. As compared to those with IPF, patients with IPAF are more frequently females, have distinctive characteristics, have relatively frequent abnormalities at nailfold capillaroscopy, with no difference in age or in overall survival. Prospective studies are needed to guide the management of IPAF.

1. Introduction

Interstitial lung disease (ILD) occurs with varying frequency and severity in all connective tissue diseases (CTDs) [1], mainly systemic sclerosis, rheumatoid arthritis, inflammatory myopathies (dermatomyositis, polymyositis), Sjögren syndrome, systemic lupus erythematosus, and mixed CTD. It is recommended at initial evaluation of patients presenting with ILD to seek symptoms and physical signs related to CTD and to test for auto-antibodies. A CTD is more frequently present in females, subjects younger than 50 years of age [2,3], those with a radiologic or pathologic pattern of nonspecific interstitial pneumonia (NSIP), organizing pneumonia (OP), NSIP/OP overlap (particularly in dermatomyositis), and sometimes lymphoid interstitial pneumonia (LIP). Conversely, the pattern of usual interstitial pneumonia (UIP) is less often associated

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with CTDs [4], with the notable exception of rheumatoid arthritis. In patients with a histologic pattern of UIP, some features may denote association with CTD, such as the presence of lymphocytic infiltration with lymphoid nodules, perivascular collagen deposition, pleural thickening, or lymphocytic or follicular bronchiolitis [1,4–6]. Diagnosing a CTD in patients with ILD is highly relevant, because it is associated with a better prognosis than that of idiopathic ILD [7,8], and it has an impact on management [9,10].

Although ILD is generally found in patients already diagnosed with a given CTD, ILD can be the first manifestation of a CTD, with systemic manifestations of the underlying CTD being limited to subtle serological and clinical autoimmune abnormalities, not fulfilling the international criteria for the diagnosis of a given CTD [2,3,6,11]. Different nomenclatures and sets of criteria have been used to describe this condition, e.g. “undifferentiated CTD-associated ILD”, “lung-dominant CTD” and “autoimmune-featured ILD” [2,3,6,11]. Recently, a consensus set of criteria has been proposed by an international taskforce of the American Thoracic Society and the European Respiratory Society, with a consensus terminology of “interstitial pneumonia with autoimmune features” (IPAF) [12], and a proposed set of criteria, with the aim of facilitating further research.

Here, we report on a series of patients with IPAF defined according to the recently proposed diagnostic criteria, and describe their clinical, serologic, thoracic imaging, and histological features, and compared their outcome to that of a cohort of patients with IPF.

2. Patients and methods

2.1. Study design and data collection

This retrospective study was carried out in the department of respiratory diseases and national reference center of rare pulmonary diseases, Louis Pradel University Hospital, Lyon, France. All consecutive patients with a diagnosis of idiopathic ILD or CTD-ILD were identified from the hospital discharge database (*Programme de Médicalisation des Systèmes d'Information* [PMSI]), using the International Classification of Diseases, 10th revision (ICD-10) codes of J841 (idiopathic interstitial pneumonia), and J848 (CTD-ILD), either as the main diagnosis or as a significant associated diagnosis. The study period was between January 1st, 2012 and December 31st, 2014. Data collection ended on October 1st, 2015. Patients' charts were then reviewed for the diagnosis of ILD and diagnostic criteria for CTDs. IPAF was defined as published [12]. Briefly, a diagnosis of IPAF was made by having one positive findings in at least two of the three domains: clinical, serologic and morphologic (imaging/pathology). “Multi-compartment involvement” was defined by the presence of unexplained airways, vascular, pleural or pericardial abnormalities in addition to the interstitial pneumonia. The IPAF score was defined as the cumulative number of IPAF criteria in each patient. To assess survival, the overall survival of incident (new) cases in the IPAF cohort was compared to that of incident cases of IPF seen at the same institution over a 3-year period (January 1st, 2012 to December 31st, 2014). IPF was diagnosed following international guidelines [13].

The study was approved by the Institutional Review Board of the *Société de Pneumologie de Langue Française*. The database was anonymous and complied with the requirements of the *Commission Nationale Informatique et Libertés*. According to the French legislation, patient consent is not required for retrospective observational studies of patients with routine clinical care. Patients received information attesting to their unrestricted rights to ask for the deletion of their data from the database.

2.2. Data collection and assessments

A standard form was used to systematically collect data from the medical files (printed and electronic). Data collected included clinical features (gender, age at ILD diagnosis, tobacco smoking history, symptoms, pulmonary function tests at diagnosis, bronchoalveolar lavage differential cell count if performed), autoimmune, chest imaging pattern, histologic pattern if available, and treatment received. This set of data is systematically present in patients' medical files. Clinical features collected included subtle clinical features as confirmed by a rheumatologist when appropriate. The autoimmune biology assessed at the time of ILD diagnosis in all patients included antinuclear antibodies (titer, immunofluorescence pattern), specific antibodies against soluble nuclear antigens, rheumatoid factor (considered significant if titer $\geq 2 \times$ upper limit of normal), anti-cyclic citrullinated peptide antibodies (anti-CCP), and anti-synthetase antibodies. Anti-tRNA synthetase other than Jo-1, PL-7 and PL-12, anti-PM-Scl, and anti-MDA-5 antibodies were obtained only if requested by the clinicians.

For the morphologic domain, thoracic CT images were reviewed for pattern classification by a thoracic radiologist with 10 years of experience (DG), and classified by patterns (NSIP, UIP, OP, NSIP/OP, LIP and others), as per international recommendations. The pathologic pattern was defined according to international criteria, following pathological analysis by two pathologists with 15 and 30 years of experience, respectively (Dr Lara Chalabreysse, FTB), as reported following multidisciplinary meeting during which pathologic pattern was critically reviewed. Pulmonary hypertension (PH) was defined by a mean pulmonary artery pressure of 25 mmHg or higher at right heart catheterization as per international guidelines [14], and severe PH by a mean arterial pulmonary pressure greater than 35 mmHg and/or cardiac index lower than 2.5 L/min/m^2. Treatment of PH was left to the discretion of the physician and followed standard of care guidelines.

2.3. Statistical analysis

All results were expressed as mean ± standard deviation for continuous variables and number (percentage) for categorical variables, unless stated otherwise. The assumption of a normal distribution of the quantitative variables was checked with a Kolmogorov Smirnov test and graphically checked with a histogram. Continuous variables were compared using the Student *t*-test, after checking for variance equality, or by non-parametric Wilcoxon test in the absence of normality. Categorical variables were compared by the Chi^2 test or by the Fisher's exact test when conditions to use the Chi^2 applying were not met. The duration of follow-up was calculated using the Kaplan Meier method, from the time of diagnosis to death or lung transplantation, or to the last follow-up visit. Comparison between groups was performed using the Log-Rank test. After checking the proportionality of the risks, predictors of mortality were determined using the Cox semi-parametric model with a univariate model. Results were considered significant for $p < 0.05$. The IBM SPSS Statistics 20 software was used.

3. Results

3.1. Study population and characteristics of patients with IPAF

Among a cohort of 778 patients with ILD, 426 had idiopathic ILD, including 156 diagnosed with IPF, and 167 had ILD associated with one of the well-defined CTD (systemic sclerosis: 81, dermatomyositis or polymyositis: 31, rheumatoid arthritis: 28, Sjögren syndrome: 10, systemic lupus erythematosus: 9, and overlap CTD: 8)