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Review

Interstitial pneumonia with autoimmune features and undifferentiated connective tissue disease
Our interdisciplinary rheumatology–pneumology experience, and review of the literature

Clodoveo Ferri [a,*], Andreina Manfredi [a], Marco Sebastiani [a], Michele Colaci [a], Dilia Giuggioli [a], Caterina Vacchi [a], Giovanni Della Casa [c], Stefania Cerri [b], Pietro Torricelli [c], Fabrizio Luppi [b]

[a] Chair and Rheumatology Unit, Centre for Rare Pulmonary Diseases (MaRP), University of Modena and Reggio Emilia, Medical School, Azienda Ospedaliero-Universitaria, Policlinico di Modena, Modena, Italy
[b] Respiratory Disease Unit, Centre for Rare Pulmonary Diseases (MaRP), University of Modena and Reggio Emilia, Medical School, Azienda Ospedaliero-Universitaria, Policlinico di Modena, Modena, Italy
[c] Radiology Unit, Centre for Rare Pulmonary Diseases (MaRP), University of Modena and Reggio Emilia, Medical School, Azienda Ospedaliero-Universitaria, Policlinico di Modena, Modena, Italy

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ABSTRACT

Background: Interstitial lung diseases (ILDs) are a heterogeneous group of disorders characterized by inflammation and/or fibrosis of the lungs, varying from idiopathic interstitial pneumonias to secondary variants, including the ILDs associated to connective tissue diseases (CTDs). In addition, a number of patients are recognized as unclassifiable ILD (U-ILD), because of the inability to reach a definite diagnosis; some of them show autoimmune manifestations not fulfilling the classification criteria of a given CTD. The term interstitial pneumonia with autoimmune features (IPAF) has been recently proposed for this particular ILD subset.
Methods: Here, we report our experience resulting from the integrated — pneumology/rheumatology — approach to patients with suspected ILDs or CTDs referred to our university-based Center for the Rare Pulmonary Diseases and Rheumatology Unit, from January 2009 to June 2015, with particular attention to the above-mentioned U-ILD, IPAF, and undifferentiated connective tissue disease (UCTD). The comparative analysis of these clinical variants was carried out; moreover, the observed findings were compared with the results of the updated review of the literature.
Results: After the first clinical assessment, the U-ILD were identified in 50 patients; afterwards, on the basis of clinico-serological and radiological findings U-ILD group was subdivided into 2 subgroups, namely U-ILD without any clinical extra-thoracic manifestations and/or immunological alterations (15 pts) and IPAF according to the above-mentioned classification criteria (35 pts). Patients with either IPAF or U-ILD were compared with a series of 52 stable UCTD (disease duration ≥3 years), followed at our Rheumatology Unit. Some important differences were evidenced among the 3 series of U-ILD, IPAF, and UCTD: firstly, female gender was more frequent in patients with UCTD (86%) or IPAF (69%) compared with U-ILD (60%) or idiopathic pulmonary fibrosis (24%; $p = 0.001$). In addition, UCTD patients were younger and showed longer disease duration. More interestingly, both UCTD and IPAF series show a comparable prevalence of various clinical manifestations, with the exception of the interstitial lung involvement detectable in a very small percentage of UCTD patients.
Concordantly, the review of the literature evidenced two main subsets of U-ILD, one is characterized by isolated unclassifiable interstitial pneumonia and another one composed by subjects with clinically prevalent lung involvement in the setting of not definite CTD, the recently proposed IPAF.
Conclusion: We hypothesize that IPAF and UCTD might represent two clinical variants of the same systemic autoimmune disorders. The marked difference regarding the prevalence of ILD, which is the clinical hallmark of IPAF but very rare in UCTD, may at least in part reflect a selection bias of patients generally referred to different specialist centers, i.e. pneumology or rheumatology, according to the presence/absence of clinically dominant ILD, respectively. Well-integrated, interdisciplinary teams are recommended for the assessment and management of these patients in the clinical practice. Finally, the cooperation between multidisciplinary groups with

* Corresponding author at: Chair and Rheumatology Unit, Dept of Internal Medicine, University of Modena and Reggio E., Policlinico di Modena, Via del Pozzo, 71, 41100 Modena Italy. Tel.: +39 059 4222279; fax: +39 059 4223007.
E-mail address: clferri@unimore.it (C. Ferri).

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different experiences may be advisable for a validation study of the proposed nomenclature and classification criteria of these indefinable ILD/CTD variants.

Contents

1. Introduction

Interstitial lung diseases (ILDs) represent a heterogeneous group of clinical conditions characterized by inflammation and/or fibrosis of the lungs; it encompasses a spectrum of different subtypes and phenotypes [1–3]. In particular, ILDs include idiopathic interstitial pneumonias, and a number of variants secondary to environmental and occupational exposures, sarcoidosis, pulmonary Langherans cell hystiocytosis, lymphangioleiomyomatosis, connective tissue diseases (CTDs), as well as a miscellanea of less frequent forms such as ILDs associated with systemic vasculitides, including diffuse alveolar hemorrhage, eosinophilic pneumonia, etc [1–3]. In addition, various clinico-pathological studies on ILD patients' series referred at tertiary respiratory units focused on the presence of unclassifiable ILD (U-ILD); this is a newly proposed and poorly definite entity that seems to represent 10–15% of the whole ILDs [4–8]. Some inconsistencies in the U-ILD definition and the lack of conclusive classification criteria represent a challenging problem in the clinical practice in term of correct diagnosis and patients' management [4–8]. Thus, several authors emphasized the importance of a multidisciplinary approach to the complex of ILDs, including U-ILD [4,9,10]. In addition to clinical, radiological, and pathological features of lung involvement, the patient's assessment should also include a clinico-immunological evaluation by expert rheumatologists, considering the incidence of phenotypes with overlapping features of both ILDs and systemic autoimmune disorders [4,9,10]. Very recently, a task force of pulmonologists and rheumatologists was formed to develop a consensus regarding these difficulties; the team of investigators proposed the introduction of a novel entity termed interstitial pneumonia with autoimmune features (IPAF), along which the preliminary classification criteria based on the combination of features from clinical, serological, and morphological domains [11]. At our university-based Center for Rare Lung Diseases (MaRP), a similar multidisciplinary approach have been directed at patients referred to our tertiary units because of the presence of suspected ILDs and/or systemic autoimmune diseases. The

Table 1
Clinical assessment of patients with interstitial lung diseases (ILDs).

General data	Signs/symptoms[a]	Laboratory examinations	Instrumental investigations
Demografic	Arthralgias	***First line***	
Occupational	Arthritis	ANA ≥1:320 titer	Chest HRCT
Environmental	Morning stiffness	Anti-ENA	PFTs (including DLco)
Avocational	Puffy fingers	ESR (>2 times normal)	
Medication	Raynaud's phen.	Abnormal CRP	
Smoking	Myalgias	Routine blood chemistry	
	Muscle weakness	Urinalysis	
	Rash	Infections	
	Photosensitivity	(HCV, HBV, HIV, EBV)	
	Alopecia	RF	
	Dermatitis	***Second line***	
	Mechanics' hand	Anti-CCP	Surgical lung biopsy
	Gottron's sign	Complement C3/C4	Doppler echocardiography
	Skin ulcers	AMA	Joint echography
	Oral/genital ulceration	ASMA	Nailfold capillaroscopy
	Oral dryness	ANCA	Schirmer's test
	Ocular dryness	Anti-phospholipid Ab/LAC	Salivary gland echography
	Dysphagia	Organ-specific autoAb	Minor salivary gland biopsy
	Recurrent fever	24 h-proteinuria	Muscle biopsy
	Weight loss		Electromyography
	Serositis		Skin biopsy
	Dyspnoea on exertion		
	Dry cough		

ANA: anti-nuclear antibodies; anti-ENA: anti-extractable nuclear antigen; (antibodies: anti-Scl-70, anti-Ro, anti-La, anti-dsDNA, anti-Smith, anti-RNP, anti-PM-Scl, and/or anti-tRNA synthetase); ESR: eritrocyte sedimentation rate; CRP: C-reactive protein; HCV: hepatitis C virus; HBV: hepatitis B virus; HIV: human immudeficiency virus; EBV: Epstein-Barr virus; RF: rheumatoid factor; anti-CCP: anti-cyclic citrullinated peptide antibodies; AMA: anti-mitochondrial antibodies; ASMA: anti-smooth muscle antibodies; ANCA: antineutrophil cytoplasmic antibodies; LAC: lupus anticoagulant; HRCT: high-resolution computed tomography; PFTs: pulmonary function tests; DLco: diffusion lung capacity for carbon monoxide.
[a] Past and/or present.