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Lung Involvement in Undifferentiated Connective Tissue Diseases: A Rheumatology Perspective

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Abstract

Objectives: Studies pointing out the occurrence of Interstitial Lung Diseases (ILD) in Undifferentiated Connective Tissue Diseases (UCTD) have been so far derived from patients admitted to Respiratory Medicine Units. We undertook the present prospective study to investigate for the presence of lung involvement, patients admitted to a Rheumatology Unit and diagnosed as UCTD.

Materials and Methods: Eighty-one consecutive UCTD patients were enrolled in the study. Each patient underwent history and physical examination, routine laboratory investigations, antinuclear antibody (ANA) profiling, B-mode echocardiography and lung function study according to previously reported methods. Moreover patients giving a further consent, underwent a high resolution computed tomography (HRCT) of lungs.

Results: Six patients (7.4%) referred dyspnea grade II at history. Out of them 3 presented a DLCO ranging from 42 to 55% of the predicted value; and a HRCT documented ILD with a Non-Specific Interstitial Pneumonia (NSIP) pattern. The other 3 patients suffered from cardiac disease accounting for their symptoms.

Out of the 75 asymptomatic patients, nobody presented relevant findings at physical examination, 26 resulted to have a DLCO <80% (<70% in 10 cases). Thirty out of these 75 patients accepted to undergo lung HRCT, that pointed out a NSIP-ILD in 3 cases.

Conclusion: Six out of the 81 investigated were found to present a definite ILD which was symptomatic in half cases. A higher percentage of patients resulted to have a reduced DLCO, the meaning of which awaits to be investigated (preradiographicILD? Preechocardiographic pulmonary vascular disease?).

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Introduction

Interstitial lung disease(ILD) represents a distinct manifestation of many connective tissue diseases (CTDs), reaching the higher prevalence in Systemic Sclerosis (SSc), but also occurring in a significant percentage in patients with Mixed Connective Tissue disease (MCTD), Systemic Lupus Erythematosus (SLE), Sjögren's Syndrome(SS), Polymyositis-Dermatomyositis (PM/DM) and Rheumatoid Arthritis(RA) [1,2].

In the last few years, a number of reports have pointed out that some ILD patients present features suggestive of an autoimmune origin even if they do not satisfy classification criteria for any major CTDs. Such a condition has been considered as ILD secondary to Undifferentiated CTD (UCTD) [3,4] and otherwise referred to as Lung dominant CTD [5], autoimmune featured ILD (AIF-ILD) [6], Interstitial pneumonia with autoimmune features (IPAF) [7].

Studies pointing out the existence of ILD secondary to UCTD have been derived from series of patients admitted to Respiratory Medicine Units for the evaluation of an ILD and investigated for the presence of features consistent with either a major CTD or UCTD. This thesis is devoted to define if the UCTD patient must be routinely investigated for lung involvement. To this aim, we studied patients admitted to a Rheumatology Unit and diagnosed as UCTD.

Materials and Methods

Patients

UCTD patients consecutively admitted to the outpatient clinic of the Rheumatology Unit of the

Table 1: Main baseline demographic and clinical features of the 81 UCTD patients enrolled.

Demographic and clinical features	
Female, n (%)	73 (90.1%)
Age, yrs, median (range)	40 (33-48)
Disease duration from the first symptom, yrs, median (range) Smokers	6 (5-11) 20 (24.6%)
Clinical features	
Arthralgias/Arthritis, n (%)	57(70.3%)
Raynaud's Phenomenon, n (%)	40 (49.3%)
Oral and/or ocular dryness, n (%)	35 (43.2%)
Carpal tunnel syndrome, n (%) Bibasilar crackles Estimated sPAP> 40 mmHg Impaired left ventricular function	21 (25.9%) 3 (3.7% 1 (1.2%) 24 (29.6%)
Dyspnea at presentation, n (%)	6 (7.4%)
Laboratory features	
Antinuclear positivity, n (%)	86 (100%)
Anti-SSA positive , n (%)	16 (19.7%)
ESR≥30mm/h and/or CRP>1mg/dl, n (%)	14 (17.2%)
Hypocomplementemia, n (%)	10 (12.3%)
Leucopenia, n (%)	4 (4.9%)
Lymphopenia, n (%)	1 (1.2%)
Thrombocytopenia, n (%)	1 (1.2%)
Physiology and Imaging	
FVC<80%, n (%) DLCO<80%, n (%)	1 (1.2%) 31 (38.2%)
DLCO<70%, n (%)	13 (16%)
ILD at HRCT, n (%)	6 (7.4%)

Yrs: Years; **ESR:** Erythrocyte Sedimentation Rate; **CRP:** C-Reactive Protein.

Second University of Naples from 1st January 2013 to 31st December 2015, were enrolled in the study, after giving a written informed consent.

UCTD was diagnosed according to Mosca et al. [8] and Doria et al. [9]. Briefly, patients had to: a) presentsigns and symptoms suggestive of a CTD with out fulfilling the criteria of any definite CTD [8]; b) be anti-nuclear antibodies (ANA) positive; c) do not have either any CTD marker autoantibody (i.e. anti-dsDNA, anti-Sm, anti-ribosomal P protein, anti-Scl-70, anti centromere, anti-La/SSB, anti-Jo1, anti-Mi-2) or any manifestation distinctive of any major CTD (i.e. malar rash, subacute CLE, chronic CLE, skin sclerosis, heliotrope rash, Gottron's plaques, erosive arthritis, alopecia) [9]; d) have a diseasedurationasassessed from the onset of the 1st symptom/ sign ≥ 3 years.

Routine assessment

According to standard clinical practice and to ensure a correct classification, each patient with a suspected UCTD underwent a detailed history and an accurate physical examination devoted to identify any of the previously referred featurespreventing enrolment in the study [8,9] as well the presence of symptoms/signs of ILD, namely dyspnea, graded according to NYHA and bibasilar crackles; routine laboratory investigations including blood cell count, urinalysis, blood urea nitrogen (BUN), serum creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), erythrosedimentation rate (ESR), serum protein electrophoresis, serum C3 and C4 concentration; nailfold videocapillaroscopy (NVC), antinuclear antibody (ANA) screening and profiling, B-mode echocardiography and lung function.

Autoantibody profile assessment

Autoantibodies were investigated in sera collected at the first visit, stored at −20°C and heated at 56°C for 30 min before testing. ANA and ACA were determined by IIF on HEp-2 cells (Astra srl, Pavone Canavese, Italy), using fluorescent anti-human gamma globulin as conjugate, using a 1:160 serum dilution as cut-off value. Anti-Scl-70, anti-SSA, anti-SSB, anti-Sm, anti-Jo1 and anti-U1RNP were identified with commercially available ELISA kits (Chematil srl, Angri, Italy), using 25 U/ml as cut-off value. Anti-RNA polymerase III, anti-fibrillarin and anti-Pm-Scl were investigated by EliA Varelisa Phadia test (Germany) using 150 U/ml as cut-off value. Anti-Th/To were investigated by western blotting technique (Arnikasrl, Milan, Italy). Anti-DNAds antibodies were identified by IIF on *Crithidialuciliae* at a serum dilution of 1:10 (Astra srl) [10].

Nailfold videocapillaroscopy assessment

Patients were investigated for typical microvascular alterations (megacapillaries and/or avascular areas) by nailfold Videocapillaroscopy (NCV). NCV was carried out while the patients were seated with their hands positioned at heart level, and at a room temperature of 22–25°C. A drop of immersion oil was applied to the nailfold to increase the translucency of the keratin layer. All the fingers were examined by the same physician (R.I.) who is experienced in NCV using a video capillaroscope (Video cap 25-DS Medica; Freiburg, Germany) with optical probes of ×200. The degree of capillary enlargement on a scale of 0–3 and capillary loss (Grades A–D) were considered. Megacapillaries (capillary enlargement ≥2) and/or avascular areas (capillary loss Grade ≥C) were considered a scleroderma pattern [11].

Assessment of internal organ involvement

All patients underwent B-mode echocardiography and lung function study. Echocardiographic examination was performed as described elsewhere [12]. The detection of either a diffusing lung capacity for CO (DL_{CO}) or a forced vital capacity (FVC) <80% of the respective predicted values in the absence of smoking, obstructive lung disease and/or cardiac involvement was considered indicative of possible ILD [13,14].

Moreover, patientsgiving a further consent underwent a high resolution computed tomography of lungs (Lung HR-CAT). Chest HRCT images were obtained with 1-mm collimation and 10-mm intervals at maximal end- inspiratory phase with the patient in a supine position using a high spatial frequency algorithm. If needed, prone scans were added to distinguish gravity-related changes from structural abnormalities. According to Fischer et al. [15], the presence of a non-specific interstitial pneumonia (NSIP), usual interstitial pneumonia (UIP), organising pneumonia (OP), lymphoid interstitial pneumonia (LIP) wereconsidered consistent with a diagnosis of ILD.

Statistical analysis

We used the SPSS for Windows software (version 16.0) for statistical analysis. Categorical data were analyzed by contingency table (Chi square). A p value <0.05 was considered significant. The study was approved by the ethics committee of the Second University of Naples.

Results

From January 1st, 2013 to December 31st, 2015, 81consecutive

Caucasian UCTD patients were enrolled in the study after giving a written informed consent. They were mostly female (90.1%), with a median age of 40(from 33-48) years and a median disease duration of 6 (from 5-11) years.

Table 1 summarizes the main demographic, clinical and laboratory features of the patients enrolled. The most frequent clinical manifestations related to CTD were arthralgias/arthritis (70.3%), asthenia (51.8%), Raynaud's phenomenon (49.3%), myalgias (46.9%), ocular and/or oral dryness (43.2%).

Six patients presented effort dyspnea, all of them grade II. Out of them, 3 presented bibasilar crackles, were found to have normal FVC values, DLCO value of 42, 44 and 55% respectively, and presented a bibasilar NSIP pattern at lung HRCT. These 3 patients, accounting for 3.7% of our series were considered as symptomatic ILD secondary to UCTD. The other 3 dyspnoic patients did not present either basilar crackles or ILD findings at HRCT or a DLCO < 70% of the predicted value and were each affected by cardiac disease accounting for effort dyspnea.

Out of the remaining 75 UCTD asymptomatic patients, nobody presented relevant findings at physical examination, all had a FVC > 80%; 26 resulted to have a DLCO <80%, that was <70% in 10 cases. Out of these patients, 16 presented findings putatively accounting for the reduced DLCO (11were smokers, 4 presented pulmonary vascular disease detected by echocardiography, 1 of them had chronic obstructive pulmonary disease). The remaing 10 did not present any other explaining feature including smoke, obstructive lung disease, clinically and echocardiography detected pulmonary vascular disease.

In conclusion, a definite i.e. HRCT-documented ILD was pointed out in 6 out of 81 consecutive UCTD patients (7.4%), 4 of whom presenting a DLCO <70% as the only altered physiologic parameter. On the other hand, an altered DLCO, unexplained by any other cause was detected in 10 further patients, 2 of whom presented a DLCO value < 70%.

Relationships between lung alterations and other disease findings

We tried to investigate for relationships between lung involvement features i.e. HRCT documented ILD or isolated DLCO, and any disease feature including disease duration, Raynaud's phenomenon, anti-SSa positivity and altered inflammation indexes, but failed to detect any association.

Discussion

At the best of our knowledge, this is the first study devoted to investigate the presence of lung disease in patients affected with UCTD and admitted to a Rheumatology Unit.

Kinder et al. first investigated 75 ILD patients admitted to a ILD Center, out of whom 28 presented features consistent with a UCTD diagnosis. These Authors reported that UCTD-ILD presented more frequently than idiopathic ILD a ground-glass pattern consistent with a NSIP and that 88% of patients admitted to the center and found to have a ILD with a NSIP pattern at lung HRCT, presented autoimmune features consistent with a UCTD diagnosis.

Suda et al. [16] compared the lung features detected in 22 patients with UCTD-NSIP with those registered in 25 patients with primary NSIP and found a female preponderance and a predominantly lymphocyte infiltration as detected by bronchoalveolar lavage analysis in the former. These evidence point out the occurrence of UCTD in patients admitted to Respiratory Units for the evaluation of a ILD and underline the demographic and cellular features of UCTD-ILD.

We investigated UCTD patients admitted to a Rheumatology Unit. Our patients presented lung symptoms, signs, physiologic and imaging findings milder than those detected in patients admitted to Pneumology Units [3-7]. Actually, upon a circumstantial request, 6 only declared a grade II effort dyspnoea. Out of them, 3only resulted to be affected by ILD consisting in a NSIP pattern at HRCT and characterized by a definite reduction of DLCO in all the 3 cases.

Out of the 75 remaining patients, HRCT was carried out in 30 and pointed out the presence of ILD in further 3 patients in whom FVC was > 80% of the predicted value in all and DLCO was < 70% in one case only. Therefore, a ILD was pointed out in 3 out 6 symptomatic patients and 3 out of 75 asymptomatic ones accounting for a prevalence of 7.4%.

Unexpectedly, we found in further 10 patients (further 18.5%), a decreased DLCO unexplained by any other condition including smoke, obstructive pulmonary disease and clinically or echocardiographycally detected cardiac or pulmonary vascular disease.

DLCO is not considered a parameter strictly reflecting ILD since it can be influenced by vascular pulmonary disease, smoking and obstructive disease [13]. Nevertheless, it is worth noting that 20 out of the 73 patients with systemic sclerosis (SSc) (27%) admitted to Pittsburgh Unit with an isolated reduction of DLCO developed a restrictive pattern during the follow-up and, more importantly, 22% of them already presented pulmonary fibrosis as detected by chest x-ray at baseline and 43% were found to present this feature at the end of a 5.4-year follow-up [14]. In that regard, moreover, DLCO has been recently demonstrated to provide the best overall estimate of HRCT-measured SSc-ILD disease in the absence of pulmonary hypertension [17]. In that context, we detected a pre radiographic alveolitis in 13/29 patients with SSc, presenting with a reduced DLCO as the only altered parameter and investigated by bronchoalveolar lavage analysis [18]. Differences in the evolution between SSc-ILD [17-20] and UCTD-ILD [2,4] induced us to choose a wait and watch strategy in our UCTD patients. Moreover, data from SSc patients cannot be extrapolated to UCTD. Nevertheless, the presence of pre radiographic alveolitis in UCTD patients presenting with an isolated reduction of DLCO deserves to be investigated in the future.

Recently Ferri et al. [21] compared demographic and clinical data of patients with IPF and IPAF admitted to a Respiratory Unit with those of UCTD patients followed at a Rheumatology Unit and hypothesized that IPAF and UCTD might represent two clinical variants of the same systemic autoimmune disorders, the marked difference in the prevalence of ILD being at least in part dependent on the selection bias between patients referred to different specialities.

Nosographic controversies are still present in this topic point of view, the same condition having be labelled as ILD secondary to Undifferentiated CTD (UCTD) [3,4], Lung dominant CTD [5], autoimmune featured ILD (AIF-ILD) [6], or as proposed by a European Respiratory Society/American Thoracic Society Committee Interstitial pneumonia with autoimmune features (IPAF) [7]. Nevertheless, from a clinical point of view, our data support the need to investigate for lung involvement patients with UCTD admitted to Rheumatology Units. Moreover, from a pathophysiologic point of

view, the finding of an isolated reduction of DLCO deserves to be investigated in the near future for its origin (vascular, alveolar wall infiltration), the clinical impact and the need, if any, of a therapeutic intervention.

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