Characteristics of connective tissue diseases associated interstitial lung diseases – a single centre study in Sri Lanka

Prasanjanie Jayasinghe[1], Nuwan Wickramasinghe[2], Prathapan Krishnakumar[1], Aflah Sadikeen[1], Amitha Fernando[1]

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Abstract

Introduction Interstitial lung diseases are the major cause of mortality in connective tissue diseases.

Objectives Our aim is to describe patients with interstitial lung disease associated with connective tissue diseases (CTD-ILD) in the Chest Clinic, Colombo 08.

Methods We conducted a descriptive cross-sectional study at the Central Chest Clinic, Colombo, Sri Lanka and data of all patients attending the Clinic were analysed.

Results The sample consisted of 83 consecutive patients diagnosed with CTD-ILD. The age ranged from 24 to 72 years with mean (SD) age of 55.6 (10.6) years. The majority was female patients (n=70, 88.6%). The majority 53.0% (n=44) had RA and SSc was the second commonest CTD-ILD (n=22, 26.5%). NSIP 51(61.9%) was the most frequently observed HRCT pattern in our cohort whereas UIP was the second commonest.

RA-ILD subgroup demonstrated female (n=37, 86.0%) preponderance. NSIP (n=24, 55.8%) was the commonly observed HRCT pattern followed by UIP (n=15, 34.9%) pattern. Among RA-ILD patients, 28 (65.1%) had positive Rheumatoid factor. Majority of (n=20, 90.9%) SSc-ILD were females. Sixteen (72.7%) of them had NSIP pattern in HRCT analysis followed by UIP (n=6, 27.3%).

Conclusion RA-ILD was the most frequent type of CTD-ILD followed by SSc. More importantly; the present study revealed the predominant NSIP pattern and clear female preponderance in RA-ILD compared to global data. We recommend prospective multicenter studies to be carried out and prospective disease registries to be established to explore the epidemiological, clinical, radiological and prognostic characteristics of CTD-ILD in Sri Lanka.

Introduction

The connective tissue diseases (CTDs) are multi-systemic rheumatological diseases characterized by autoimmune mediated disease process causing multiorgan dysfunction. Among the multiple causes leading to mortality in CTD patients, interstitial lung diseases (ILD) are identified as the main cause [1].

CTDs associated ILDs (CTD-ILD) have been described in rheumatoid arthritis (RA), systemic sclerosis (SSc), Inflammatory myositis (IM), primary Sjögren's syndrome (pSS) and mixed connective tissue disease (MCTD) [2]. In addition, there is another entity called interstitial pneumonitis with autoimmune features (IPAF) [3], which is described recently. Nonspecific pneumonia (NSIP) and usual interstitial pneumonia (UIP), organizing pneumonia (OP), diffuse alveolar damage (DAD) and lymphocytic interstitial pneumonia (LIP) are the main histopathological subtypes identified in CTD-ILD [4].

Identification of the type of ILD is necessary to decide on definitive treatment and more importantly to prognosticate the disease. Interestingly, most of the time High Resolution CT scan (HRCT) patterns reflect the underlying histopathological subtypes [4]. Studies have shown that in UIP, HRCT diagnosis has excellent concordance with the histological diagnosis [5]. Lung biopsy is recommended only in atypical cases [6]. Thus, identification of the pattern of HRCT is mandatory to decide definitive treatment and assess the prognosis.

It is Important to note that limited studies have been conducted regarding histological and radiological pattern of CTD-ILD in Sri Lanka [7]. Available data also being obtained from the studies conducted in the other countries [8]. In practice, these findings are extrapolated to various clinical settings across the globe including Sri Lanka. However, it is important to generate local evidence base in the Sri Lankan population in order to identify any possible differences compared to the western population.

[1]*Central Chest Clinic and National Hospital of Sri Lanka,* [2]*Faculty of Medicine and Allied Sciences, Rajarata University of Sri Lanka.*

Correspondence: PJ, *e-mail: <p_jayasinghe@yahoo.com>. Received 16 January 2021 and revised version 17 March 2021 accepted 20 March 2021.*

Many sociodemographic and immunological factors are identified as risk factors of developing ILD [8]. As an example, male gender, severity of the RA, older age, presence of rheumatoid factor, anti CCP antibody and smoking carry risk for developing RA-ILD [9]. This further emphasizes the necessity of data from our population, which has many sociodemographic differences compared to European countries. Hence, it is important to identify which subtype of ILD is predominant in the Sri Lankan population. Accordingly, the available diagnostic and treatment facilities could be further developed to cater the needs of the local setting.

Methods

We conducted a descriptive cross-sectional study at Central Chest Clinic, Colombo, Sri Lanka, which is the largest chest clinic in the country. CTD-ILD patients, who met 2010 American College of Rheumatology and European League Against Rheumatism (ACR/EULAR) classification criteria for RA, 2013 ACR/EULAR classification criteria for SSc, 2017 ACR/EULAR classification criteria for DM/PM, 2016 ACR/EULAR classification criteria for pSS and 2015 ERS diagnostic criteria for IPAF were included in the study. Diagnosis of ILD was made on the basis of the HRCT findings.

Information on socio-demographic data, clinical features and autoantibodies were recorded by reviewing patient medical records. All HRCT findings, which were evaluated at the multidisciplinary team meeting by an experienced Radiologist and a Consultant Chest Physician were documented.

Data was collected after obtaining the ethical clearance from Medical Research Institute (MRI) in Sri Lanka, informed written consent of the patient and permission from the hospital director.

Data analysis was carried out using SPSS version 25.0. Descriptive statistics including mean [Standard Deviation (SD)], median [Inter-quartile range (IQR)] and frequency distributions were used to present study variables. Fisher's exact test was used to compare the differences of categorical variables between subgroups.

Results

Sample characteristics

The sample consisted of 83 consecutive patients diagnosed with CTD-ILD attending the Central Chest Clinic Colombo 08. The age ranged from 24 to 72 years and the mean (SD) age was 55.6 (10.6) years. Mean age of female and male were 55.0 and 58.7 respectively. The majority was female patients (n=70, 88.6%).

Time of the initial diagnosis was recorded in 55 subjects. CTD was diagnosed before ILD in 53 (96.4%) of them, with a median (IQR) interval of 4 (2-8) years separating the two diagnoses. ILD was diagnosed first only in two (3.6%) patients.

Distribution of CTD-ILD

The distribution of the CTD-ILD in the sample is given in Table 1. The majority 53.0% (n=44) had RA and SSc was the second commonest CTD-ILD (n=22,26.5%).

HRCT patterns of ILD

NSIP (n=51, 61.9%) was the most frequently observed HRCT pattern among the CTD-ILD patients, whereas UIP was the second commonest pattern (n=25, 30.8%) Details of the HRCT patterns are given in Table 2.

Table 1. Distribution of CTD-ILD in the sample

CTD-ILD	Number	Percentage
Rheumatoid arthritis	44	53.0%
Systemic sclerosis	22	26.5%
Mixed connective tissue diseases Overlap syndrome	3	3.6%
Inflammatory myositis	4	4.8%
Systemic lupus erythematosus (SLE)	2	2.4%
Interstitial pneumonias with autoimmune features (IPAF)	3	3.6%

Table 2. HRCT patterns of CTD-ILD

HRCT Pattern	Number	Percentage
NSIP	51	61.9
UIP	25	30.8
HP	3	3.7
OP	1	1.2
CPEF	1	1.2

Clinical features

Shortness of breath and cough were the commonest presenting symptoms found in 55 (66.3%) and 49 (59.0%) patients respectively. Fine crepitations on auscultation of lungs was noted among 43 (51.8%) of the sample. One fifth of the sample had fatigue (n=17, 20.5%).

Pulmonary function test interpretation

Records on pulmonary function tests done at initial presentation were available in 55 patients. Restrictive pattern 47(85.4%) (FVC and FEV1 being <80% predicted with FEV1/FVC >70%) was observed in the majority. Six (10.9%) of them had normal spirometry followed by obstructive (n=1, 1.8%) and mixed pattern (n=1, 1.8%).

Characteristics of patients with common ILDs

Rheumatoid arthritis

RA-ILD subgroup demonstrated female (n=37, 86.0%) preponderance. NSIP (n=24, 55.8%) was the commonly observed HRCT pattern followed by UIP (n=15, 34.9%) pattern. In this sub-group, there were three patients with hypersensitive pneumonitis as well.

Shortness of breath (n=28, 65.1%) and cough (n=20, 46.5%) were documented as the common presenting symptoms. Among RA-ILD patients, 28 (65.1%) had positive rheumatoid factor.

Comparison of RA-ILD [RA (+)] group with other CTD-ILD [RA (-)] group

The mean (SD) age of the RA (-) and RA (+) groups were 52.3 (11.3) years and 58.7 (8.9) years respectively. There was a statistically significant difference in the mean age between the two groups (t(77)=-2.824, p=0.006).

There were no statistically significant associations between RA and gender, HRCT patterns or symptomatology (p>0.05). However, there was a statistically significant association between RA and rheumatoid factor positivity (Chi (1) = 24.8675 p<0.001).

Systemic sclerosis

Majority of (n=20, 90.9%) SSc-ILD were females. Sixteen (72.7%) of them had NSIP pattern in HRCT analysis followed by UIP (n=6, 27.3%). Most of them had shortness of breath (n=16, 72.7%) and cough (n=13, 59.1%) on presentation. Majority (n=15, 68.2%) had bilateral fine end-inspiratory crepitations on examination.

Comparison of SSc-ILD [SS (+)] group with other CTD-ILD [SS (-)] group

The mean (SD) age of the SS (-) and SS (+) groups were 57.8 (9.7) years and 49.9 (10.8) years respectively. There was a statistically significant difference in the mean age between the two groups (t(77)=3.128, p=0.002).

There were no statistically significant associations between SSc and gender, HRCT patterns or symptomatology (p>0.05). However, there were statistically significant associations between SSc and rheumatoid factor positivity [Chi (1) = 10.9691, p=0.001] and SSc and ANA positivity [Chi (1) = 0.9568, p=0.005].

Table 3. Comparison of RA-ILD [RA (+)] group with other CTD-ILD [RA (-)] group

Characteristic	RA (-)n (%)	RA (+)n (%)	Statistical significance
Gender			
Male	4 (44.4)	5 (55.5)	Chi (1) = 0.754
Female	33 (47.1)	37 (52.8)	p=0.460
HRCT			
NSIP	27 (57.9)	24 (47.0)8	Chi (1) = 5.8903
UIP	10 (4)	15 (6)	p=0.207
HP	0	3 (100)	
OP	1 (100)	0	
CPEF	0	1 (100)	
Shortness of breath			
Absent	12 (42.8)	16 (57.1)	Chi (1) = 0.2895
Present	27 (49.0)	28 (50.9)	p=0.647
Cough			
Absent	20 (58.8)	14 (41.1)	Chi (1) = 3.2388
Present	19 (38.7)	30 (61.2)	p=0.080
Fatigue			
Absent	30 (45.4)	36 (54.5)	Chi (1) = 0.3942
Present	9 (52.9)	8 (47.8)	p=0.599
Bilateral fine end-inspiratory crepitations			
Absent	18 (4)	22 (5)	Chi (1) = 0.1225
Present	21 (48.8)	22 (51.1)	p=0.827
Rheumatoid factor			
Absent	35 (68.6)	16 (31.3)	Chi (1) = 24.8675
Present	4 (12.5)	28 (87.5)	p<0.001

Table 4. Comparison of SSc-ILD [SSc (+)] group with other CTD-ILD [SSc (-)] group

Characteristic	SSc (-) n (%)	SSc (+) n (%)	Statistical significance
Gender			
Male	8 (88.8)	1 (11.1)	Chi (1) = 1.2457
Female	50 (71.4)	20 (28.5)	p=0.432
HRCT			
NSIP	35 (68.6)	16 (31.3)	Chi (1) = 2.4480
UIP	19 (76.0)	6 (24)	p=0.784
HP	3 (100)	0	
OP	1 (100)	0	
CPEF	1	0	
Rheumatoid factor			
Absent	31 (60.7)	20 (39.2)	Chi (1) = 10.9691
Present	30 (93.7)	2 (6.2)	p=0.001
ANA			
Absent	53 (81.5)	12 (10.4)	Chi (1) = 0.9568
Present	8 (44.4)	10 (55.5)	p=0.005
Ex SOB			
Absent	22 (78.5)	6 (21.4)	Chi (1) = 0.5592
Present	39 (70.9)	16 (29.0)	p=0.601
Cough			
Absent	25 (73.5)	9 (26.4)	Chi (1) = <.001
Present	36 (73.4)	13 (26.5)	p=1
Fatigue	48 (72.7)	18 (27.2)	Chi (1) = 0.0972
Absent	13 (76.4)	4 (23.5)	p=1
Present			
Bilateral fine end-inspiratory crepitation			
Absent	33 (82.5)	7 (17.5)	Chi (1) = 3.2147
Present	28 (65.1)	15 (34.8)	p=0.086

Discussion

CTD-ILDs were responsible for vast majority of secondary ILD in Sri Lanka [7]. This is the first study to describe the characteristics of CTD-ILD patients attending to lung specialized tertiary care centre in Sri Lanka.

The mean age of 55.6 years of our sample was similar to available literature [8,10,11,12]. Female preponderance was demonstrated as expected since the CTD was well known to occur in female gender [7,8,11,12].

Evidence suggests that in some instances, ILD is the initial clinical manifestation of CTD [10,12]. There were two patients who initially presented with ILD in our sample as well. However, the date of the initial diagnoses was recorded only in 55 patients. RA was the most prevalent subtype of CTD-ILD followed by SSc. RA-ILD was recognized as the commonest type in many studies

conducted globally [12,13]. A recent study conducted in Sri Lanka reported similar findings [7]. However, a descriptive study conducted in Portugal reported SSc as the commonest CTD-ILD subtype [8].

In consistent with the existing literature, our study reveals that the predominant pattern of HRCT in CTD-ILD group was NSIP followed by UIP [8,12]. As expected, shortness of breath and cough were the commonest presenting symptoms found in patients [11]. At the same time, it is important to note significant proportion did not have expected symptoms, which signifies the importance of screening with LFT and HRCT even in asymptomatic group.

Pulmonary function test which is widely used as a screening tool in detecting ILD, revealed predominant restrictive pattern as reported in literature [7,8].

RA-ILD is an important entity that carries higher mortality than RA patients without ILD [14]. RA-ILD patients, who comprised the majority of our sample, reported clear female preponderance. Despite female predominance in RA, the largest RA-ILD study conducted in the UK has revealed almost equal gender distribution [9]. On the other hand, there were some studies showing female preponderance as well [14,15] emphasizing the importance of conducting local research to identify epidemiological variations.

Globally, many studies demonstrated UIP pattern as the predominant HRCT pattern in RA-ILD [2,9,14,16,17,18]. In contrast, the majority of our patients had NSIP pattern in HRCT followed by UIP in approximately one third of patients. Recent study conducted in Sri Lanka also reported NSIP pattern as the commonest HRCT pattern closely followed by UIP [7]. There were few cases of drug induced HP and organizing pneumonia. Though it is rare [19] we reported one case with CPFE Combined pulmonary fibrosis and emphysema as well.

RA-UIP pattern carries poorer prognosis and increases all-cause mortality in RA patients [9]. Since the NSIP pattern is the commonest type, our RA-ILD patients may have better overall survival in contrast to other countries, which we have not addressed in our study.

Our study demonstrated statistically significant difference in the presenting age of RA-ILD and other CTD-ILD. RA-ILD presented in late fifties compared to other CTD-ILDs, which presented in early fifties.

It is an already known fact that high levels of Rheumatoid Factor (RF) and titers of anti-CCP increase the risk of ILD development in RA [8,9,20,21]. Confirming this, the majority of our RA-ILD patients had positive RF and that association was statistically significant. We have not analyzed Anti-CCP as it was available only in few patients, since it is not freely available in the government sector.

SSc-ILD is the major cause of mortality in SSc [22,23]. The mean age of the SSc-ILD was significantly lower than that of other CTD-ILD groups. This showed the early presentation of SSc ILD compared to other group. Female preponderance was clearly observed in our sample similar to other studies [2,14,24]. The majority of SSc-ILD group was symptomatic at the time of presentation. Similar to global evidence NSIP was the predominant HRCT pattern [2,14,24].

Limitations

The present study was a single-center retrospective study; hence, generalizing the findings of the study needs to be done cautiously. Since evidence suggest that there are substantial differences in data obtained from prospective disease registries compared to single-center retrospective studies [12], we believe it is important to establish prospective disease registries and conduct future studies to explore the potential associations further. Since this study involved retrospective data, some of the relevant data could not be retrieved due to misplacement of reports and records as well as deficiencies in record keeping.

Conclusions

To the best of our knowledge this is the first study to describe CTD-ILD patients in Sri Lanka. Comparison of the present study findings with evidence from other countries revealed both similarities and differences. RA-ILD was the most frequent type of CTD-ILD observed in our center followed by SSc. The most striking finding is that the predominant NSIP pattern and clear female preponderance in RA-ILD compared to global data.

We recommend prospective multicenter studies to be carried out and prospective disease registries to be established to explore the epidemiological, clinical, radiological and prognostic characteristics of CTD-ILD in Sri Lanka.

Abbreviations

Connective Tissue Diseases associated ILD (CTD-ILD)

Rheumatoid arthritis (RA)

Systemic sclerosis (SSc)

Inflammatory myositis (IM)

Primary Sjögren's syndrome (pSS)

Mixed connective tissue disease (MCTD)

Interstitial Pneumonitis with Autoimmune Features (IPAF)

Nonspecific pneumonia (NSIP)

Usual interstitial pneumonia (UIP)

Organizing pneumonia (OP)

Diffuse alveolar damage (DAD)

Lymphocytic interstitial pneumonia (LIP)

High Resolution CT scan (HRCT)

Declarations

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