

Clinico-radiological profile of connective tissue disease related-interstitial lung diseases from a tertiary care centre of India: a cross sectional study

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Abstract

Interstitial lung diseases (ILDs) are a frequently occurring pulmonary manifestation in patients of connective tissue diseases (CTD). Detailed understanding of this subset of lung dis-

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eases is vital, hence the study was conducted to analyze the clinico-radiological characteristics of CTD-ILD. The present study was conducted between March 2017 to February 2018 at a tertiary care teaching hospital from western India. A total of 100 patients having respiratory symptoms suggestive of ILD, who were either diagnosed cases of CTD or had clinical manifestations of underlying CTD, were included in the study. Twenty-seven percent of patients belonged to age group 41-50 years and 78% were females. Chief respiratory complaints were dyspnea and cough. Clubbing was present in 29% patients. The most common CTDs were rheumatoid arthritis (RA) (26%), systemic sclerosis (SS) (21%), mixed connective tissue disorder (MCTD) (19%) and Sjogren's syndrome (SS) (16%). Restrictive defect on spirometry was seen in 58% cases and was most significant among patients with RA (65%) and SS (62%). Pulmonary arterial hypertension was seen in 40% cases and was most evident in MCTD (78%) and SSC patients (58%). Chest radiograph was normal in 47% of subjects. Most common radiological pattern on high resolution computed tomography (HRCT) thorax was non-specific interstitial pneumonia (42%) followed by usual interstitial pneumonia (21%). ILD is a common manifestation of CTD. Work-up for an underlying CTD should be offered to all ILD patients and vice versa.

Introduction

Interstitial lung diseases (ILD) are a basket of 200 different disorders with diverse underlying etiological factors and with common features of varying degrees of fibrosis and inflammation of lung parenchyma and/or interstitium. Connective tissue diseases (CTDs) are inflammatory disorders with autoimmune mechanism and frequently involves the lung along with other organs of the body [1]. CTDs can involve any component of the respiratory system including the airways and pleura leading to ventilatory impairments, pulmonary vasculature resulting in vasculitis and/or pulmonary hypertension, and fibro-inflammatory parenchymal abnormalities [2]. Common CTDs presenting with ILDs include rheumatoid arthritis (RA), systemic sclerosis (SS), Sjogren's syndrome (SS), mixed connective tissue disorder (MCTD), systemic lupus erythematosus (SLE), and polymyositis (PM)/ dermatomyositis (DM). In majority of the cases, patients are already diagnosed with some form of CTD when ILD is recognized, however in a few subsets of CTDs pulmonary manifestations tend to precede the clinical signs and symptoms of CTDs [3]. CTD-ILDs carry a better overall prog-

nosis compared to other common ILDs like idiopathic pulmonary fibrosis (IPF) Hence, the present study, first of its kind from western India, was conducted to recognize the clinico-radiological profile of pulmonary involvement associated with different forms of CTDs, which may impact survival of these patients.

Materials and Methods

Study design and setting

The study was conducted between March 2017 and February 2018, in the department of pulmonary medicine of a tertiary care teaching hospital of western India. It was a prospective, cross-sectional, observational study. Subjects included in the study belonged to two categories. These include previously diagnosed cases of CTD who presented with pulmonary signs and symp-

toms of an underlying ILD and patients of ILD with a clinical suspicion of CTD which was later confirmed. Pregnant females, less than 18 years of age, patients with active infections and comorbidities including congestive heart failure, renal and liver failure and not giving informed written consent were excluded. After fulfilling the inclusion and having none of the exclusion criteria, a total of 118 patients were enrolled in our study. Five patients later withdrew consent, 8 patients with clinical suspicion of CTD were found to have infectious etiology, 2 had malignancy, 2 had only CTD without lung involvement/ILD and their respiratory symptoms were due to unrelated respiratory tract infection, 2 were lost to follow up and 1 succumbed due to massive pulmonary embolism. Finally, 100 patients were included (Figure 1). These patients after detailed clinical history and examination were evaluated by spirometry, body plethysmography, doppler echocardiogram, chest radiograph, HRCT thorax, and tests for immunological work-up were sent, as per requirement. HRCT

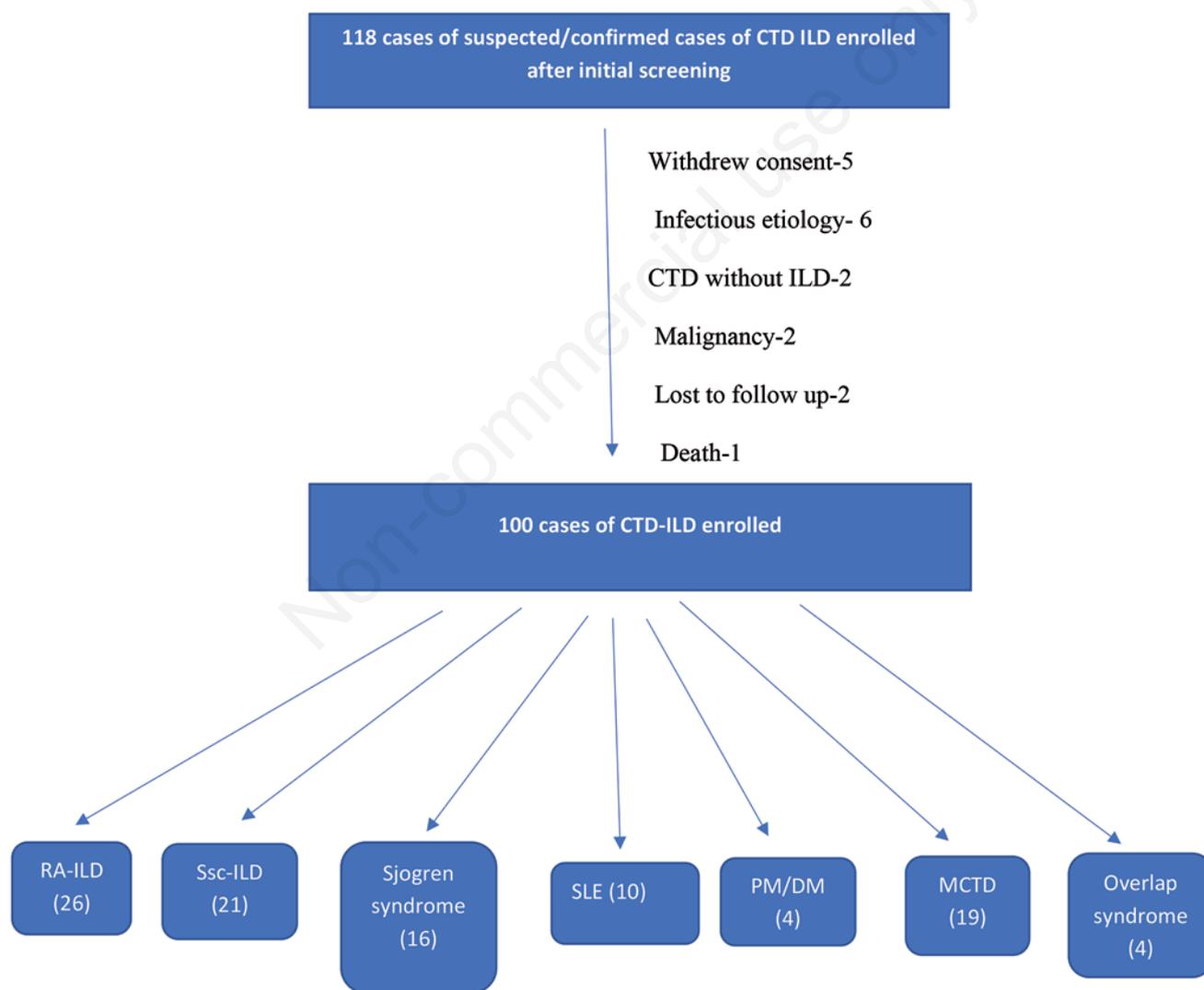


Figure 1. Flow chart depicting recruitment of cases and the various connective tissue diseases (CTD) - interstitial lung diseases (ILD) in our study population. RA, rheumatoid arthritis; SSC, systemic sclerosis; SLE, systemic lupus erythematosus; PM/DM, polymyositis/dermatomyositis; MCTD, mixed connective tissue disease.

thorax was done by Optima, General Electronics. Sixty-four slices with 1.25 mm thickness were acquired as per the recommended scanning protocol for interstitial lung disease [4]. Spirometry graph plotting was done with HELLO'S software which uses the same standardization values of the updated 1993 statement of the European Respiratory Society [5]. Doppler echocardiogram to calculate pulmonary artery systolic pressure (PASP) was done by tricuspid regurgitation (TR) peak velocity method. Symptomatology, signs, functional tests and type of pleuro-parenchymal disease were then correlated in context of background connective tissue disorder.

Definitions

- Obstructive ventilatory impairment in spirometry is defined by the ratio of forced expiratory volume in the first second (FEV_1)/forced vital capacity (FVC) <70 of lower limit of normal and FVC >80% of predicted.
- Restrictive ventilatory impairment was defined by FVC <80% of predicted in spirometry and total lung capacity (TLC) <80% of predicted via body plethysmography.
- Mixed ventilatory defect was given by FEV_1/FVC <70 as well as FVC and TLC less than 80% of predicted.
- Pulmonary hypertension was defined by PASP more than 35mmhg doppler echocardiogram by TR peak velocity method.

Statistical Analysis

Descriptive statistics were used to describe baseline characteristics. Quantitative variables were presented as mean and standard deviation. Dichotomous variables were presented as number and percentages. Chi square test was applied and p-value <0.05 was considered significant. All the statistical calculations were performed using STATA 12 [STATA Corp. TX, USA] statistical software.

Results

The majority of the patients (78%) in the study population were females and 50% patients belonged to age group between 40 to 60 years of age with a mean age of 45.69 ± 13.04 years. In our study, patients with SSC and SLE were all females while there were all males in PM/DM group (Figure 2). As depicted in Table 1, most frequent respiratory symptoms were dyspnea seen in all patients with RA, SSC, SS and PM/DM while cough was present in all patients with PM/DM, MCTD and overlap syndrome. Hemoptysis was seen in one patient with SLE while chest pain was most evident in patients with SLE (40%) and MCTD (36.8%).

Among the rheumatological symptoms (Table 1), joint pain was the most common in patients with RA (96.1%), PM/DM (75%) and overlap syndrome (75%). History of joint swelling (88.4%) and morning stiffness (80.7%) was most frequent among patients with RA. Ninety percent of patients with SSC had history of Raynaud's phenomenon. Muscle pain was mostly seen in patients with PM/DM (52.6%) and MCTD (50%) while 70% of patients with SLE had facial swelling. All these findings were statistically significant.

In physical examination (Table 1), 29% had clubbing, 69% had velcro crepitations on auscultation, some form of oral and skin lesions was seen in 30% and 27% of the patients, respectively. Majority of the patients (58%) had restrictive defect on spirometry and body plethysmography and was most frequent in patients with overlap syndrome (100%), RA (65.3%) and SS (62.5%), as depicted in Table 2. Raised PASP (>35 mmHg) was seen in 40% of study subjects and was most evident in MCTD (78.95%) and SSC (54.14%) groups (Table 2).

Chest radiograph was normal in 47% of study subjects. HRCT pattern among various CTDs is shown in Table 2. Non-specific interstitial pneumonia (NSIP) (42%) was the most common pattern followed by usual interstitial pneumonia (UIP)

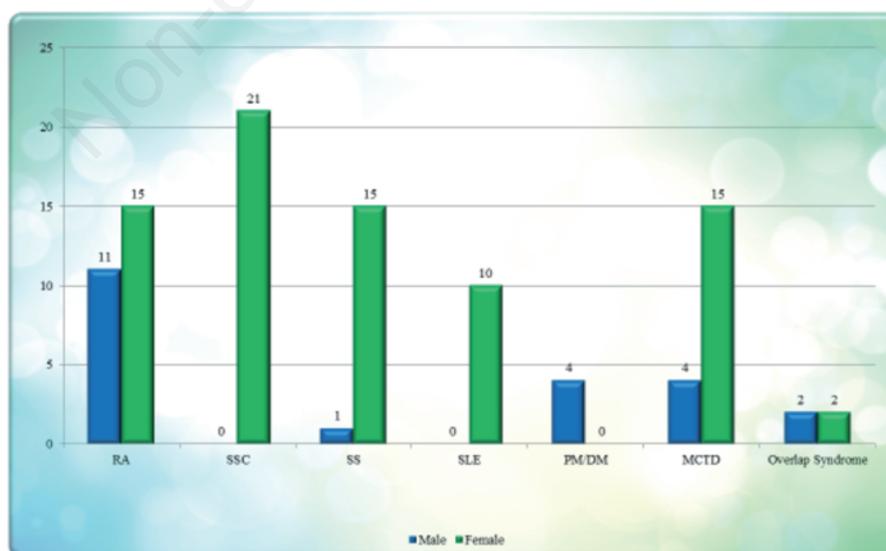


Figure 2. Gender distribution among various connective tissue diseases (CTD) in the study population. RA, rheumatoid arthritis; SSC, systemic sclerosis; SLE, systemic lupus erythematosus; PM/DM, polymyositis/dermatomyositis; MCTD, mixed connective tissue disease.

(21%). NSIP was commonly seen in patients with SSC (66.6%), MCTD (52.6%) and SS (43.7%) while UIP (38.4%) was the predominant pattern in patients with RA. Organizing pneumonia and bronchiolitis were the other patterns distributed among the study subjects. Seventy five percent of patients with PM/DM had

ground glass opacities with pleural effusion. Lymphocytic interstitial pneumonia (LIP) and necrobiotic nodules were seen in one patient each with Sjogren's and RA, respectively. Figure 3A-F: Figure 3 A-F shows HRCT thorax images of various ILD patterns associated with CTD seen in our patients.

Table 1. Respiratory, rheumatological symptoms and physical findings associated with various connective tissue diseases (CTD).

Parameters	RA (n = 26)	SSC (n = 21)	Sjogren's syndrome (n = 16)	SLE (n = 10)	PM/DM (n = 4)	MCTD (n = 19)	Overlap syndrome (n = 4)	p-value
Respiratory symptoms								
Cough	25 (96.1)	20 (95.2)	15 (93.7)	8 (80)	4 (100)	19 (100)	4 (100)	0.43
Dyspnea	26 (100)	21 (100)	16 (100)	9 (90)	4 (100)	18 (94.7)	3 (75)	0.06
Hemoptysis	0	0	0	1 (10)	0	0	0	0.18
Chest pain	3 (11.5)	2 (9.5)	0	4 (40)	0	7 (36.8)	0	0.019
Rheumatological symptoms								
Joint pain	25 (96.1)	9 (42.8)	5 (31.2)	4 (40)	3 (75)	12 (63.1)	3 (75)	<0.01
Joint swelling	23 (88.4)	1 (4.7)	0	4 (40)	0	4 (21)	2 (50)	<0.01
Morning stiffness	21 (80.7)	0	0	0	0	0	0	<0.01
Raynaud's	0	19 (90.4)	0	0	0	0	2 (50)	<0.01
Muscle pain	0	1 (4.7)	0	0	2 (50)	10 (52.6)	1 (25)	<0.01
Facial swelling	1 (3.8)	2 (9.5)	0	7 (70)	0	8 (42.1)	1 (25)	<0.01
Physical findings								
Clubbing	11 (42.3)	9 (42.8)	6 (37.5)	0	0	1 (5.2)	2 (50)	<0.05
Joint tenderness /deformity	1 (3.8)	0	0	0	0	0	0	>0.05
Oral cavity								
Microstomia	0	6 (28.5)	2 (12.5)	0	0	1 (5.2)	1 (25)	>0.05
Ulcers	0	7 (33.3)	4 (25)	2 (20)	0	3 (15.7)	2 (50)	>0.05
Stomatitis	0	2 (9.5)	0	0	0	0	0	
Cutaneous signs								
Rashes	1 (3.8)	8 (38)	3 (18.7)	3 (30)	1 (25)	0	1 (25)	>0.05
Dryness	0	2 (9.5)	5 (31.2)	0	0	1 (5.2)	0	>0.05
Hypopigmented patch	0	0	0	0	0	1 (5.2)	0	>0.05
Excoriation	0	0	0	0	0	1 (5.2)	0	0.05
Velcro crepitation	19 (73)	17 (80.9)	13 (81.2)	2 (20)	1 (25)	13 (68.4)	4 (100)	0.067
Xerophthalmia	0	0	2 (12.5)	0	0	0	0	0.13

RA, rheumatoid arthritis; SSC, systemic sclerosis; SLE, systemic lupus erythematosus; PM/DM, polymyositis/dermatomyositis; MCTD, mixed connective tissue disease; values in parenthesis indicates percentage.

Table 2. Spirometry, pulmonary hypertension and high-resolution computed tomography findings associated with various connective tissue diseases (CTD) in the study population.

Parameters	RA (n = 26)	SSC (n = 21)	Sjogren's syndrome (n = 16)	SLE (n = 10)	PM/DM (n = 4)	MCTD (n = 19)	Overlap syndrome (n = 4)	p-value
Pulmonary function abnormality								
Mixed defects	3 (11.5)	6 (28.5)	2 (12.5)	4 (40)	1 (25)	3 (15.7)	0	0.37
Restriction	17 (65.3)	13 (61.9)	10 (62.5)	3 (30)	1 (25)	10 (52.6)	4 (100)	0.18
Obstruction	6 (23)	2 (9.5)	4 (25)	3 (30)	2 (50)	6 (31.5)	0	0.43
Pulmonary hypertension								
Present	5 (19.23)	12 (54.14)	2 (12.5)	1 (10)	1 (25)	15 (78.95)	4 (100)	0.25
HRCT pattern								
UIP	10 (38.46)	3 (14.29)	2 (12.50)	0	0	3 (15.79)	2 (50)	0.05
Probable UIP	0	0	0	0	0	0	1 (25)	0.002
NSIP	8 (30.77)	14 (66.67)	7 (43.75)	1 (10)	1 (25)	10 (52.63)	1 (25)	0.05
Organizing pneumonia	4 (15.38)	4 (19.05)	5 (31.25)	2 (20)	0	4 (21.05)	0	0.73
Bronchiolitis	2 (7.8)	0	1 (6.25)	3 (30)	0	1 (5.26)	0	0.13
GGO with effusion	1 (3.8)	0	0	4 (40)	3 (75)	0	0	< 0.001
LIP	0	0	1 (6.25)	0	0	0	0	0.52
Necrobiotic nodule	1 (3.85)	0	0	0	0	0	0	0.84

RA, rheumatoid arthritis; SSC, systemic sclerosis; SLE, systemic lupus erythematosus; PM/DM, polymyositis/dermatomyositis; MCTD, mixed connective tissue disease; UIP, usual interstitial pneumonia; NSIP, non-specific interstitial pneumonia; GGO, ground glass opacity; HRCT, high-resolution computed tomography; LIP, lymphocytic interstitial pneumonia.

Discussion

The most common CTDs associated with ILD in our study were RA (26%) and SSC (21%). Several other studies also had RA and SSC as the most common CTDs associated with ILD [6-8]. Restrictive defect was seen in 58% of the patients. In a study by Verma *et al.*, 62.4% of patients of CTD with respiratory symptoms had restrictive pattern [7]. Similar observations were made by Gaude *et al.*, where 60% of the patients had restrictive defect [9]. NSIP pattern was the common pattern on HRCT thorax seen in nearly 40% of our study population. UIP pattern was the most common pattern in patients with RA (38.46%). Two landmark Indian studies of Singh *et al.* [10] and Kumar *et al.* [11] respectively had comparable results similar to our study. In study by Singh *et al.* they recruited a total of 1,084 patients with ILD from 27 centers across India, of these 151 (13.9%) were CTD-ILD. Among patients with CTD-ILD, the commonest presenting symptom was dyspnea (90.9%) while 82.2% experienced cough at presentation. Mean age was 50.8 years and most were women (73.5%). A total of 54.3% had NSIP, whereas 31.8% had UIP. Rheumatoid arthritis was the most common specific CTD (38.4%) followed by scleroderma (22.5%). Kumar *et al.* enrolled 289 patients with ILD in their study, of which 13 were diagnosed with CTD-ILD. Mean age at presentation was 44.24 years; females comprised 54.68% of the

patients. The most frequent presenting symptom cough (92.7%), followed by exertional dyspnea (79.2%). Of 13 patients, 6 cases were each of RA and SSC. NSIP was most common pattern of ILD on HRCT.

Among 26 patients with RA, predominant symptoms included cough, breathlessness, joint pain/swelling, and morning stiffness. Nearly two-third of RA patients had restrictive ventilatory defect. Prevalence of pulmonary hypertension was less (19.2%) among patients with RA. This is in line with previous studies which showed a lower prevalence of pulmonary hypertension in RA patients when compared with other CTDs-ILD [12,13]. Most common HRCT pattern among patients with RA was UIP (38%). Other studies are also in concordance with our findings [9,14]. Pleural effusion was present in 3.8 % of subjects. In a study by Shannon *et al.* they found incidence of pleural effusion to be around 5% in patients with RA [15].

Among the patients with SSC, nearly all patients had cough and breathlessness. Ninety percent patients had history of Raynaud's phenomenon. Raynaud's phenomenon was seen in 75% of SSC patients in a registry analysis [16]. Restrictive defect on spirometry was seen in 61.9% while pulmonary hypertension was present in 54% of cases. NSIP was the most common pattern (66.6%) observed on HRCT thorax. Similar findings were observed in previous studies from this part of the world [12,13].

NSIP was the most common pattern among patients with

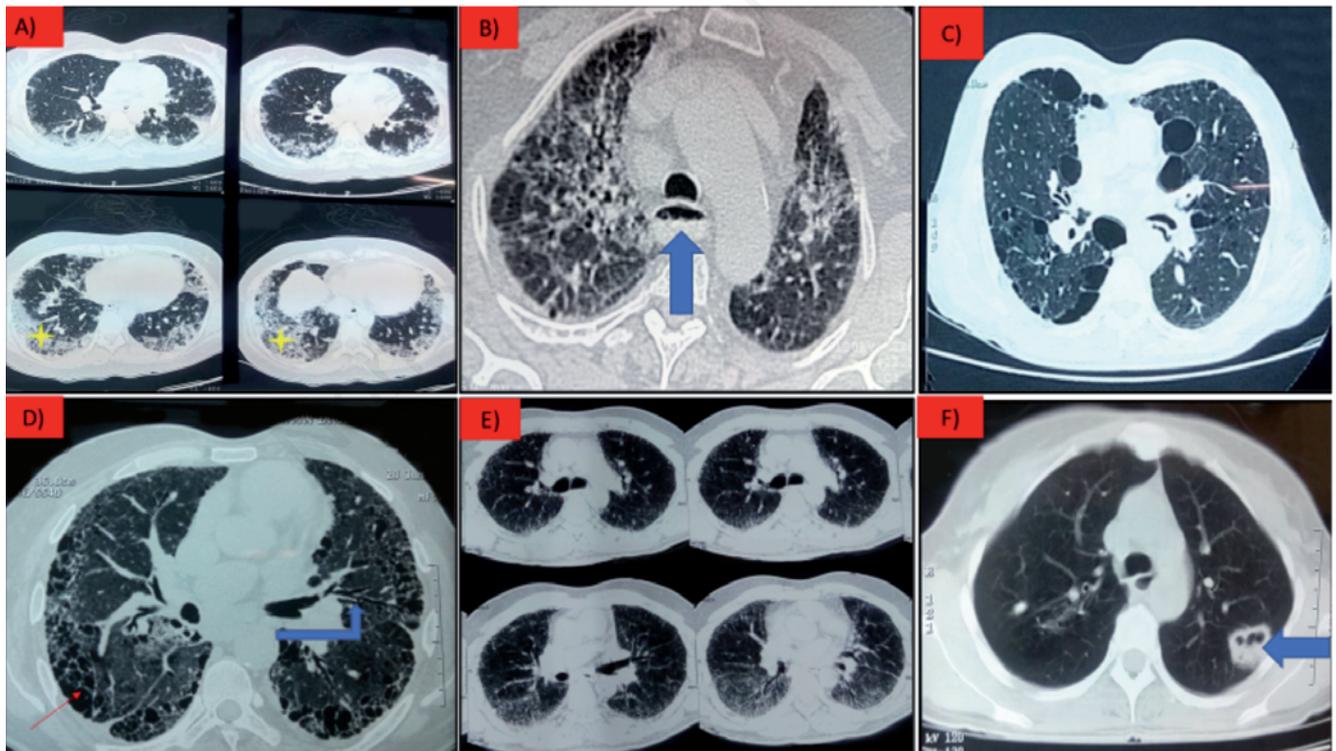


Figure 3. A) High-resolution computed tomography (HRCT) thorax axial reformatted images lung window shows bilateral patchy peripheral peribronchovascular subpleural consolidation and ground glass opacity (GGO) (yellow asterisk) in a case of polymyositis (PM) / dermatomyositis (DM) suggestive of organizing pneumonia. B) Dilated esophagus in a patient with systemic sclerosis (SSC) - interstitial lung disease (ILD) with fibrotic non-specific interstitial pneumonia (NSIP) pattern (blue arrow). C) Lymphocytic interstitial pneumonia (LIP) in a patient with Sjogren syndrome (SS). D) Usual interstitial pneumonia (UIP) pattern seen in a case of RA-interstitial lung disease (ILD); computed tomography (CT) axial reformatted images at the level of inferior pulmonary vein shows bilateral basal subpleural multilayered cysts stacked upon one another referred to as honeycombing (red arrow) and traction bronchiectasis (blue arrow). E) Depicting NSIP pattern in a case of SSC-ILD. F) Necrobiotic nodules in a patient with rheumatoid arthritis (RA) with a single nodule undergoing cavitation (blue arrow).

MCTD (52.6%) and SS (43.7%) in the present study. As per a previous study, this pattern is the most common radiologic and histologic pattern in patients with SSC, PM/DM and MCTD [17]. Among patients with SS, joint pain (31.2%) was the only rheumatological symptom while dry eyes were present in two patients. Misra *et al.* also observed sicca symptom and arthralgia as common presenting rheumatological features [18]. Incidence of PAH was very low (12.5%) while 62.5% had restrictive defect on spirometry in patients with SS. Organizing pneumonia was the most common pattern (31.2%) after NSIP (43.7%) while UIP pattern was seen in two and LIP in one patient. Similar observations were noted in a study by Ito *et al.* [19].

Along with cough and breathlessness, 40% of the patients with SLE also had chest pain as chief respiratory complaint. Facial swelling was present in 70% of the patients in our study. Restrictive ventilatory defect was seen in 30% cases. These findings are in concordance with studies by Kakati and Weinribet *et al.* [20,21]. Pulmonary hypertension was seen in 10% cases as was also seen in studies by Verma and Gaude *et al.* [7,9]. HRCT thorax showed ground glass opacity (GGO) with effusion in 40% cases and bronchiolitis in 30% cases. This is in contrast to findings of the study by Verma *et al.* where NSIP was the most common pattern on HRCT [7]. Quadrelli *et al.* in their study found pulmonary hemorrhage (25.5%) as the common feature on HRCT in SLE patients [22].

Cough and dyspnea were seen in all patients with PM/DM while joint pain was seen in 75% and myalgia in 50% of cases. All patients with PM/DM were males in our study. Douglas *et al.* also made similar clinical observations in their study of 70 patients with PM/DM [23]. Similar to SLE group, patients with PM/DM also had lesser incidence of pulmonary hypertension and restrictive abnormality, as was also seen in study done by Gaude *et al.* [9]. This group also had GGO with effusion as the common HRCT abnormality seen in 75% cases.

In MCTD group, nearly all patients had dyspnea and cough. Joint pain (63.1%), myalgia (52.6%), facial swelling (42.1%) and chest pain (36.8%) were other common symptoms. Both SSC and MCTD group had higher incidence of pulmonary hypertension (78.9%) and restrictive defect on PFT (52.6%) in our study. NSIP (52.6%) and organizing pneumonia (21%) were common HRCT patterns observed. Similar observations were seen in studies by both Verma and Gaude *et al.* [7,9].

Our study had few limitations. The sample size was relatively small and was a single centre experience. Diffusing lung capacity for carbon monoxide (DLCO) were not measured in our patients which could have helped in early identification of lung and pulmonary vascular involvement especially in those with apparently normal pulmonary function tests. Finally, in patients with organizing pneumonia radiological pattern, bronchoscopy was not performed to rule out active infection before labelling as ILD

Conclusions

The common symptoms of CTD-ILDs include dry cough and exertional dyspnea. Detailed history, symptom evaluation, physical examination, pulmonary function tests, and HRCT thorax aids in diagnosis of CTD-ILDs. Clinicians should keep a high index of suspicion for CTD-ILD as it is a potentially reversible entity and carries a better prognosis to appropriate therapy than idiopathic fibrosing ILDs which are generally associated with worse outcomes. NSIP pattern is the most common pattern observed in

CTD-ILDs, except in RA-ILD where UIP is the most common pattern. Incidence of pulmonary hypertension is higher in SSC and MCTD. LIP is seen in SS. Necrobiotic nodules are seen in RA.

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