

A Clinico- Radiological Spectrum of Connective Tissue Disease Associated Interstitial Lung Diseases in a Tertiary Care Hospital

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Abstract

Background: The Pleuro-pulmonary manifestations frequently occur in patients with the connective tissue disorders (CTDs), ILDs being the most common pulmonary manifestation, and limited data are available on this topic from India.

Methodology: A total of 30 Patients diagnosed to have Connective tissue disease CTD associated ILD based on spirometry, HRCT and various Antibody studies associated to connective tissue diseases were taken.

Results: Females were more commonly affected (96.7%) and the mean age was 49.4 years Most common clinical presentations were cough (100%) and shortness of breath (100%), followed by fatigue (83.3%), skin dryness (63.3%) and Raynaud’s phenomenon (46.6%). Other symptoms include Joint pains (43.3%), Morning Stiffness (26.6%), Gastro-Esophageal Reflux Disease (23.3%), Dysphagia (23.3%) and Dryness of Mouth and eyes (3.3%).

Findings include clubbing (36.6%), skin thickening (36.6%), fish mouth (26.6%), joint deformities (23.3%). All the patients were found to have Velcro rales (100%). A Mean (SD) for SpO₂ of 92.5 ± 5.1 is observed. Non-Specific interstitial pneumonia was the most common pattern (73.3%) observed in HRCT. Most common pattern in Spirometry was Restrictive pattern (83.4%). Most commonly found Anti bodies were Anti-Nuclear Ab (100%), Anti-Scl70 Ab (36.6%), Anti-Centromere Ab (36.6%). Scleroderma was most commonly associated connective tissue disorder (36.7%) followed by Mixed connective tissue disorder (30%) and Rheumatoid Arthritis (23.4%).

Conclusion: Many pulmonary manifestations are common in patients with CTDs, ILD being the most common pulmonary involvement. Some of these manifestations may remain asymptomatic or can progress gradually resulting in morbidity and mortality.

All patients with CTDs should be systematically evaluated and monitored for pulmonary involvement so that early recognition and introduction of the therapy will help in preventing the morbidity and mortality.

Keywords: Interstitial Lung Disease; Connective Tissue Disorder; Restrictive Lung Disease; High Resolution Computed Tomography; Nonspecific interstitial pneumonia.

Introduction

Aims And Objectives

To study the clinical, radiological profile of Connective tissue disease associated interstitial lung diseases.

Methodology

Study design & period: Prospective observational study from October 2017 to September 2019.

Study population: 30 patients of connective tissue disease associated interstitial lung disease who attended to our hospital

Inclusion criteria

Previously diagnosed cases of connective tissue disease associated interstitial lung disease.

Patients with cough, Breathlessness on exertion with extra thoracic manifestations like arthralgia, skin rashes or pigmentation or tightness, dry mouth, dry eyes and features suggestive of Raynaud's phenomenon etc.

Connective tissue disease patients with velcro rales on respiratory system examination were further investigated and then included.

Exclusion criteria

Interstitial lung disease like infections e.g. Miliary tuberculosis and Pneumocystis jirovecii pneumonia (PJP).

Interstitial lung disease like malignancies e.g. Lymphangitis carcinomatosa or military carcinomatosa.

Study procedure

All the 30 patients were thoroughly examined with respect to history, physical examination of all systems, radiological examination, Spirometry and Laboratory investigations. The history included symptoms like cough, shortness of breath, chest pain, reflux symptoms, dry eyes, dry mouth, Raynaud's phenomenon, arthralgia, redness and pain at the joint sites etc.

Smoking history and Family history were taken in detail. Occupational history enquiring into any exposure to carpentry, automotive mechanics, painting, sand blasting, stone crushing, foundry work, welding, insulation, farming, heavy dust or smoke etc. History of any exposure to birds like pigeons, doves, ducks, hens, geese were taken. Any history of drug intake was also given importance.

A thorough Physical examination was done in all cases. Any positive findings like clubbing, peripheral lymphadenopathy, abnormal breath sounds and added sounds like Velcro crackles were noted. Examination of the cardiovascular system was done for any loud P2 and features of Cor-Pulmonale. Examination of the musculoskeletal system was done for detecting any abnormal joint manifestations. Examination of the nervous system, eye and GIT were done to look for any co-existent abnormalities. A special emphasis was laid in the examination of the skin to look for any cutaneous manifestations like rashes, subcutaneous nodules, skin tightening, pigmentation, and nail abnormalities.

Investigations

Routine laboratory Investigations were done in all cases that include Hemoglobin (gm%), Total leukocyte and Differential leukocyte counts, serum creatinine, AEC, RBS, and a complete urine examination. The following Antibodies were done to patients in whom these tests

were not done previously, which include Anti-Cyclic Citrullinated Peptide, Antinuclear Antibody, Anti Double-Stranded DNA, Rheumatoid Factor, Anti Ribonuclear Protein, Anti-Nuclear Ab, Anti-Scl70 Ab, Anti-Centromere Ab, Anti-Ro-Anti- La Ab, Anti-Smith Ab, Anti-Jo Ab and Anti-RNA Synthase Ab.

A 2-sample sputum examination for acid fast bacilli was done in all patients.

A chest x-ray and a HRCT were done in cases where it was not performed previously. Spirometry was done in all cases.

The patients were explained about the procedure before subjecting to the study. The baseline SpO2 was recorded when the patient is at rest. All the obtained data was analyzed using spss 20 software and results interpreted.

Results

In this study, most affected age group was 31 – 60 years with Mean age of 49.4 years. Out of 30 patients, only one (3.3%) was male and the remaining 29 (96.7%) were females. only 4 (13.3%) were smokers (1 male and 3 female), and the remaining 26 (86.7%) were non-smokers. Most common clinical presentations were cough and shortness of breath, which were present in all (100%), followed by fatigue (83.3%), dryness of skin (in 19 patients, 63.3%), Raynaud’s phenomenon (46.6%) Other symptoms in descending order include Joint pains (43.3%), Morning Stiffness (26.6%), Gastro-Esophageal Reflux Disease (23.3%), Dysphagia (23.3%) and Dryness of Mouth and eyes (3.3%) Most common Physical examination finding was pallor (in 26 patients, 86.6%). Other findings include clubbing (in 11 patients, 36.6%), skin thickening (in 11 patients, 36.6%), fish mouth (in 8 patients, 26.6%), joint deformities (in 7 patients, 23.3%). Malar rash was seen only in one patient (3.3%)

Most of the patients (in 21 patients, 70%) were having a saturation of $\geq 93\%$ with room air. Eight patients (26.7%) were having a saturation of $\leq 88\%$ with room air. One patient (3.3%) was having a saturation level between 89% to 92%. Mean SpO2 was 92.5 ± 5.1

All the patients (in 30 patients, 100%) were found to have Velcro rales on auscultation of Lungs.

Most common Chest X-ray findings in the present study were bilateral basal reticular pattern (100%) and Reduced lung volumes (100%). Infiltrates were seen in 5 (16%) patients.

HRCT Findings and Pattern

HRCT FINDINGS				
HRCT FINDINGS	Males	Females	Total	Percentage
IRREGULAR LINEAR OPACITIES	1	22	23	76.6%
GROUND GLASS OPACITIES	-	18	18	60%
RETICULAR PATTERN	-	12	12	40%
HONEY COMB APPEARANCE	1	6	7	23.3%
TRACTION BRONCHIECTASIS	1	6	7	23.3%
CONSOLIDATION	-	5	5	16.6%

Most common findings in HRCT include irregular linear opacities (in 23 patients, 76.6%) and ground glass opacities (in 18 patients, 60%) followed by Reticular pattern (in 12 patients,40%), Honey comb appearance (in 7 patients, 23.3%), Traction Bronchiectasis (in 7 patients, 23.3%) and Consolidation (in 5 patients,16.6%)

HRCT PATTERNS	Male	Female	Total	Percentage
NSIP	1	21	22	73.3%
UIP	-	6	6	20%
OP	-	2	2	6.7%

Most common pattern on High resolution computed tomography pattern (HRCT) was NSIP : Non-Specific interstitial pneumonia (in 22 patients, 73.3%), followed by UIP : Usual interstitial pneumonia (in 6 patients, 20%) and OP : Organizing pneumonia (in 2 patients, 6.7%).

Spirometry Findings

Most common pattern in the present study was Restrictive pattern (in 25 patients, 83.4%), followed by mixed pattern (in 4 patients, 13.3%). Spirometry was not done in one patient (3.3%) due to severe disability. Of the 25 patients found to have restrictive pattern in spirometry, 4 patients (16%) were having Very-severe restriction. Severe restriction is found in 4 patients (16%). Moderately-severe restriction is seen in 10 patients (40%). Moderate restriction is seen in 3 patients (12%) and Mild restriction was found in 4 patients (16%). For 25 patients with restrictive pattern, percentage predicted value was 53.4 ± 13.9

SEVERITY OF PAH IN 2D - ECHO				
SEVERITY OF PAH RVSP value	Male	Female	Total (n=23)	%
MILD (RVSP 35 – 45 mmHg)	-	3	3	13%
MODERATE (RVSP 46 – 60 mmHg)	-	12	12	52%
SEVERE (RVSP >60 mmHg)	1	7	8	35%

2 D Echo Findings

23 patients (76.7%) were found to have Pulmonary Artery hypertension in 2D-Echo. Other findings include Raised RVSP (in 23 patients, 76.7%) and Tricuspid Regurgitation (in 11 patients, 36.6%).

SEROLOGICAL PROFILE				
	Males	Females	Total	Percentage
ANTI-Scl70	-	11	11	36.6%
ANTI-CENTROMERE Ab	-	11	11	36.6%
ANTI-Ro Ab & ANTI-La Ab	-	-	1	3.3%
ANTI-SMITH Ab	1	-	1	3.3%
ANTI-RNP Ab	-	9	9	30%
RHEUMATIC FACTOR	-	7	7	23.3%
ANTI-CCP Ab	-	7	7	23.3%
ANTI-NUCLEAR Ab	1	29	30	100%
ANTI-Jo Ab	-	1	1	3.3%
ANTI-RNA-SYNTHASE Ab	-	1	1	3.3%

Of the 30 patients, 23 were found to have Pulmonary artery hypertension, eight patients (35%) were having severe PAH. Moderate and Mild PAH were found in 12

patients (52%) and 3 patients (35%) respectively. Mean of RSVP in the present study is 55.5 ± 8.4 .

Serological Findings

ASSOCIATED CONNECTIVE TISSUE DISORDERS				
	Male	Female	Total	Percentage
SCLERODERMA	-	11	11	36.7%
MIXED CTD	-	9	9	30%
RHEUMATOID ARTHRITIS	-	7	7	23.4%
SJOGREN'S	-	1	1	3.3%
SYSTEMIC LUPUS ERYTHEMATOSUS	1	-	1	3.3%
POLYMYOSITIS	-	1	1	3.3%

Most commonly found Anti bodies were Anti-Nuclear Ab (in 30 patients, 100%), Anti- Scl70 Ab (in 11 patients, 36.6%), Anti-Centromere Ab (in 11 patients, 36.6%), followed by Anti-Ro-Anti-La Ab (in 1 patient, 3.3%) and Anti-Smith Ab (in 1 patient, 3.3%). Other antibodies include Anti-RNP Ab (in 9 patients, 30%), Rheumatic Factor (in 7 patients, 23.3%), Anti-CCP Ab (in 7 patients, 23.3%), Anti-Jo Ab (in 1 patient, 3.3%) and Anti- RNA Synthase Ab (in 1 patient, 3.3%).

Associated Connective Tissue Disease

Scleroderma (in 11 patients, 36.7%) was the most commonly associated connective tissue disorder followed by Mixed connective tissue disorder (in 9 patients, 30%) and Rheumatoid Arthritis (in 7 patients, 23.4%). Sjogren's syndrome, Systemic Lupus Erythematosus and polymyositis were found in one patient (3.3%) each.

Discussion

Connective tissue disorders are a diverse group of immunologically mediated systemic disorders that often lead to pulmonary changes. There are huge differences between epidemiological studies based on ascertainment and selection criteria regarding the incidence of respiratory involvement due to connective tissue diseases. However, increased mortality and

morbidity develops due to pulmonary involvement due to connective tissue diseases. The diagnostic methods include clinical approach, pulmonary function tests, high-resolution computed tomography and Serology.

The present study is primarily aimed to study the profile of 30 patients with Connective tissue disease associated interstitial lung diseases. In all cases a clinical, radiological, spirometry, 2D-Echo and Serological results were obtained and analyzed to observe the trends in the disease.

Comparison of Mean age and sex distribution with Other Studies.

The Mean age in the present study is 49.4 years. According to a study done by Sheetu Singh et al. [2] which was conducted throughout India, CTD associated ILD cases were seen in 151 patients, where the mean age was 50.8 years which is significantly close to this study (49.4 years). The sex distribution was 40 males and 111 females, the variation may be due to small sample size and limited time period.

STUDY	CTD -ILD	Mean age	Males	Females
Present Study	30	49.4 Years	1	29
Sheetu Singh et al. [2]	151	50.8 Years	40	111
A Afeltra et al. [7]	81	57 Years	12	69
Rahul Sharma et al. [8]	28	56.9 Years	4	24
Lin Pan et al. [4]	63	57.2 Years	20	43
Joseph Jacob et al. [9]	203	58 Years	63	140

The variation seen with other studies may be due to geographical, racial and genetic factors

Comparison of Smoking Status with Other Studies.

The present study has a total number of smokers of 4 (13.3%) and the remaining 26 (86.7%) were non-smokers. In a study by Somenath kundu et al. [5] there were 6.9% of patients who were smokers. Similarly, Sheetu Singh et al. [2] study included 12.6% of patients as smokers, which can be comparable to the present study.

Study	Smokers
Present Study	13.3%
Somenath Kundu et al. [5]	6.9%
Sheetu Singh et al. [2]	12.6%
Lin Pan et al. [4]	24%
A Afeltra et al. [7]	24.6%
Joseph Jacob et al. [9]	37.4%

These variations in smoking are due to various factors, which include Geographical, Racial and environmental factors. Low socio-economic factor also plays an important role.

Comparison of clinical profile with Other Studies.

In the present study, cough and shortness of breath were the most common presentation for all the The variations from the present study may be due to early presentation and early access to the diagnostic and treatment modalities.

STUDY	Cough	Breathlessness	Fatigue	Skin Changes
Present Study	100%	100%	83.3%	63.3%
Somenath kundu et al. [5]	100%	96.5%	-	-
Sheetu Singh et al. [2]	90.8%	82.1%	-	17.2%
G S Gaude et al. [3]	54.8%	47.6%	-	-
Lin Pan et al. [4]	71%	56%	33%	22%

The variation in the skin symptoms may be due to negligence of the illiterate patients in the present study settings and probably due to late presentation to the hospital.

30 patients (100%) followed by fatigue (83.3%) and skin symptoms (63.3%).

Comparison of HRCT Patterns with Other Studies:

STUDY	Nonspecific Interstitial Pneumonia	Usual Interstitial Pneumonia	Organizing Pneumonia
Present Study	73.3%	20%	6.7%
Sheetu Singh et al. [2]	54.3%	31.8%	4%
Li Hailan et al. [6]	60.6%	36.2%	0.8%

Most common High resolution computed tomography pattern was Non-Specific interstitial pneumonia (73.3%), followed by Usual interstitial pneumonia (20%) and Organizing pneumonia (6.7%). These

findings were also comparable to present study based on the order of occurrence of the patterns.

Comparison of HRCT Findings with Other Studies.

STUDY	Irregular Linear Opacities	Ground Glass Opacities	Reticular pattern	Honey comb appearance	Consolidation
Present Study	76.6%	60%	40%	23.3%	16.6%
Lin Pan et al. [4]	94%	67%	-	44%	17%
G S Gaude et al. [3]	-	-	78%	14%	-
A. Afeltra et al. [7]	-	55.5%	-	29.65	-
Somenath Kundu et al [5]	-	44.8%	-	65.5%	-

Most common findings in HRCT include irregular linear opacities (76.6%) and ground glass opacities (60%) followed by Reticular pattern (40%), Honey comb appearance (23.3%) and Consolidation (16.6%).

Comparison of FEV1 with Other Studies.

Of the 25 patients found to have restrictive pattern in spirometry. Based on ATS/ERS grading of severity, 16% of patients were having Very-severe restriction. Severe restriction was found in 16% of the patients. Moderately-severe restriction was seen in 40% of the patients. Moderate restriction was seen in 12% of the patients. Mild restriction was found in 16% of the patients. For 25 patients with restrictive pattern, FEV1 percentage predicted value in the present study was 53.4 ± 13.9%.

STUDY	FEV1 < 80%
This Study	83.4% of patients
A Afeltra et al. [7]	21.7% of patients

Variation in the results may be due to late presentation in the present study probably because of low literacy rate and disease unawareness by the patients.

In 2D-Echo Pulmonary Artery Hypertension was found in 76.6% (23 patients) of the patients. Right Ventricular Systolic Pressure is useful in grading the severity of PAH. Of the 23 patients, 35% of the patients were having severe PAH. Moderate and Mild PAH were found in 52% and 13% of the patients respectively.

Mean (SD) of RVSP in the present study was 55.5 ± 8.4.

Comparison of Serological profile with Other Studies:

Most commonly found Anti bodies in the present study were Anti-Nuclear Ab (100%), Anti-Scl70 Ab (36.6%), Anti-Centromere Ab (36.6%). Other antibodies include Anti-Ro- Anti-La Abs (3.3%), Anti-Smith Ab (3.3%), Anti-RNP Ab (30%), Rheumatic Factor (23.3%), Anti-CCP Ab (23.3%), Anti-Jo-1 Ab (3.3%) and Anti-RNA Synthase Ab (3.3%).

STUDY	Present Study	Lin pan et al. [4]	Somenath Kundu et al. [5]
Anti-Nuclear Ab	100%	71%	58.6%
Anti-Scl70 Ab	36.6%	6%	51.7%
Anti-Centromere Ab	36.6%	5%	-
Anti-Ro-Anti-La Abs	3.3%	36.5%	-
Anti-Smith Ab	3.3%	3%	-
RNP	30%	10%	-
Rheumatic Factor	23.3%	42%	31%
Anti-CCP Ab	23.3%	13%	-
Anti-Jo-1 Ab	3.3%	3%	3.4%
Anti-RNA Synthase Ab	3.3%	-	-

The serological profile may be varied from study to study as the incidence of Connective tissue disorder is different for various geographical regions. The genetic susceptibility to various CTDs also differ due to racial factors

Comparison of Associated CTDs with Other Studies.

In the present study most commonly associated connective tissue disorder was Scleroderma (36.7%), followed by Mixed connective tissue disorder (30%) and Rheumatoid Arthritis (23.4%). Sjogren’s syndrome, Systemic Lupus Erythematosus and polymyositis were found in one patient (3.3%) each.

STUDY	Scleroderma	MCTD	RA	Sjogren’s	SLE	Polymyositis
Present Study	36.7%	30%	23.4%	3.3%	3.3%	3.3%
Sheetu Singh et al [2]	22.5%	7.9%	38.4%	4.6%	3.3%	3.3%
G S Gaude et al. [3]	6.6%	2.5%	61%	5.1%	16.4%	5.6%
A. Afeltra et al. [7]	16%	6.1%	38.2%	9.8%	20.9%	-

The variation in connective tissue disorders that are associated with Interstitial Lung diseases may be due to various factors including different geographical distribution of various connective

tissue disorders, Presenting age group, etc. An observer may get higher number of particular connective tissue disorders, which can again lead to varied profile.

Conclusion

Many pulmonary manifestations are common in patients with CTDs, ILD being the most common pulmonary involvement. Some of these manifestations may remain asymptomatic or can progress gradually resulting in morbidity and mortality. All patients with CTDs should be systematically evaluated and monitored for pulmonary involvement so that early recognition and introduction of the therapy will help in preventing the morbidity and mortality

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