Analysis of Interstitial Lung Disease in Connective Tissue Disease by High Resolution Computerised Tomography and Diffusing Capacity for Carbon Monoxide

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ABSTRACT

Introduction: Interstitial Lung disease (ILD) frequently occurs in patients with the connective tissue diseases (CTD) referred to as CTD-ILD. The purpose of this study was to correlate HRCT spectrum with spirometry and the diffusing capacity for carbon monoxide (DLCO) values in patients of CTD-ILD.

Material and Methods: In this prospective study, we enrolled 36 patients with various CTD - ILD. After completing the physical examination and HRCT of those who have fulfilled the criteria, patients were subjected to pulmonary function tests including spirometry and DLCO.

Results: Out of 36 patients 66.67% were females, 33.33% were males with a mean age of 44 years. Systemic sclerosis was the most common CTD (44.44%) followed by rheumatoid arthritis (33.33%), Mixed connective tissue disease (8.33%), systemic lupus erythematosus (5.56%) Polymyositis/Dermatomyositis (5.56%) and Sjogrens syndrome (2.28%). In individual HRCT pattern, Reticular pattern is the most frequent presentation (80.6%) followed by Nodular pattern (58.3%) and GGO pattern (50%). In various combinations of HRCT pattern ReticuloNodular pattern forms the most common presentation (38.9%). In 36 cases of study population, 28 presented with restriction pattern(75%) except 8 who presented with Normal FVC in spirometry.

Conclusion: CTD - ILD remains innocuous at an early stage as most of the rheumatic patients have restricted mobility manifesting with subtle or nil respiratory symptoms. It is better to opt on for(on) alternate non invasive procedures like HRCT, spirometry and DLCO as CTD patients are in real respiratory compromise. DLCO may be the first and only abnormality found in early stage of ILD. DLCO when compared with HRCT is the best index of the extent of the ILD but couldn't be elicited on large scale because of the limited sample size.

Key words: Connective Tissue Diseases, Spirometry, ILD, Diffusing Capacity for Carbon Monoxide, DLCO, HRCT.

INTRODUCTION

Approximately 15% of the patients who present with Interstitial Lung disease have an underlying connective tissue diseases[1]. The association of connective tissue disease and Interstitial lung disease (ILD) is well established[2]. High Resolution Computerised Tomography (HRCT) scanning is best for imaging chest with a very good spatial resolution and also provides a detailed Lung anatomy similar to that seen by gross histopathological examination. By pulmonary function test (PFT) the severity of physiologic disarrangements in ILD correlate well with the overall extent of pathologic abnormalities[3]. Connective tissue diseases (CTD) are immunologically mediated diverse group of inflammatory diseases. We might have known that, by reason of their ample blood supply and abundant connective tissue, the lungs are frequently involved in these Connective tissue diseases. Consequently, CTD affect all areas of the lung (i.e., the airways, parenchyma, pleura and vascular system), and do so in various degrees and combinations[4] due to autoimmune processes. ILD is characterised by deteriorating parenchymal fibrosis and gas exchange. It remains harmless in the early stage as most of the rheumatic patients have restricted mobility manifesting with subtle or nil pulmonary symptoms. Hence the respiratory physician should be prudential in diagnosing the cases as early as possible. As pulmonary physician often involved in care of these patients, a comprehensive understanding of Connective tissue diseases and usual course of ILD is important. This has led to the increasing use of HRCT scans in conjunction with through clinical assessment[5]. In addition DLCO may be the first and only abnormality found in early stage of ILD. Our study figures out the importance of non invasive procedures rather than the invasive procedures. Since most of the patients afraid of procedures like bronchoscopy or surgical biopsy as they are in real respiratory compromise, it is better to opt on for alternate procedure like CT chest, Diffusing capacity for carbon monoxide (DLCO) and spirometry which are frequently done nowadays as an adjunct to aid the diagnosis.

MATERIAL AND METHODS

In our 11 months study 60 patients in tertiary care hospital were screened for Interstitial Lung Disease with Connective tissue disease (ILD –CTD). Out of which 36 patients were

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How to cite this article: G. Sangamithra, D. Nancy Glory. Analysis of interstitial lung disease in connective tissue disease by high resolution computerised tomography and diffusing capacity for carbon monoxide. International Journal of Contemporary Medical Research 2018;5(5):E34-E38.

DOI: http://dx.doi.org/10.21276/ijcmr.2018.5.5.24

taken up for the study after satisfying eligible criteria. Inclusion criteria include serologically positive CTD patients, clinically and radiologically confirmed cases of ILD, Age > 12 years, Sex- Both genders and patients who were able to perform spirometry and diffusion capacity with breath holding period of atleast 10 seconds. All were nonsmokers. Remaining patients were excluded from the study group based on exclusion criteria. Exclusion criteria include patient associated with history suggestive of Infection, Allergy and immunosuppression or associated with another respiratory disease, cardiovascular disease and malignancy, smokers and ILD due to other known cause or unknown cause. In this prospective study, we have done HRCT in 36 patients with various CTD. This study was approved by the local ethical committee. Procedures had been explained to all patients and written informed consent was obtained from all participants. Medical history was taken with special reference to previous cardiopulmonary disease, cough, dyspnoea, sputum, chest pain and risk factors for pulmonary disease, such as smoking. Then followed by exhaustive review of past medical, social, medication use, family and occupational histories with an exploration of all potential environmental exposures were done. The patients were then subjected to High-resolution computed tomography (HRCT) in supine position, holding a breath at deep inspiration, without contrast medium. Individual pattern and various combinations of patterns studied in HRCT. After completing the physical examination and HRCT of those who have fulfilled criteria, were subjected to pulmonary function tests including spirometry and DLCO. DLCO was measured using a single-breath technique. The DLCO was routinely adjusted for haemoglobin (DLCOHb) if the value was outside the normal range. Measurements of DLCO were made with a Collins automated system using a gas mixture that contained 10% helium tracer gas and 0.3% carbon monoxide. The breath holding time was 10 s and the washout volume to 0.75 L. Diagnosis and assessment of Interstitial lung disease can be done with Forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), FEV_1/FVC ratio, diffusing capacity of carbon monoxide is corrected for Haemoglobin concentration called as DLCOHb. The values are interpreted as follows: DLCOHb: Normal (>80% predicted) Mild diffusion defect (65-80%), Moderate diffusion defect (45-65%) and severe diffusion defect (<45%). FVC:Normal (>80% predicted), Mild Reduction (60-80%), Moderate Reduction (40-60%), Severe Reduction (<40%). A multidisciplinary approach involving pulmonologists, radiologists and rheumatologists was implemented on all ILD patients before a final diagnosis was rendered.

Age Group (Years)	No of Patients	Percentage (%)
<35	9	25
36-45	11	30.56
46-55	7	19.44
>55	9	25
Total	36	100

Table-1: Age

Disease	No of patients	Percentage (%)
SS	16	44.44
RA	12	33.33
MCTD	3	8.33
SLE	2	5.56
PM/DM	2	5.56
Sjogren's	1	2.78
Total	36	100

Table-2: Disease classification

STATISTICAL ANALYSIS

The data were entered in MS Excel. Descriptive statistics, i.e., means, standard deviations, frequencies, and percentages, were used to describe the study variables. The following statistical analyses were performed to assess the strength of association between the variables of the study by using Chi-Square Test. HRCT pattern and DLCOHb in ILD groups were compared by Mantel-Haenszel test for linear association and a *P* value of <0.05 was considered significant.

RESULTS

Our study principally focuses on characterisation of HRCT pattern of ILD analysed by comparing with Spirometry and Diffusing capacity for Carbon monoxide (DLCOHb). In this study group most of them fall in late fourth decade. In our study 55 patients were screened for CTD - ILD. Out of which 36 patients were taken up for the study after satisfying eligible criteria. In our study population age group ranges from 16-74 years. Maximum number of patients present presented between the ages of 36-45 years. The mean age distribution found in our study is 44 ± 13.79.Hence 95% of confidence interval lies in the range of 44± 4.5, indicating that most of them fall in late fourth decade (Table1). The selected patients consisted of 66.67% Females and 33.33% males. Female predominance is noted in ILD with connective tissue disease patients. Male: Female sex ratio is 1:2. Rheumatoid arthritis and Progressive systemic sclerosis form the bulk of the study population. Both constitute more than 75% of the cases. Followed by 3 cases of Mixed Connective Tissue Disease, 2 cases each from systemic lupus erythematosus, Polymyositis/Dermatomyositis,

Forced Vital capacity (FVC)	No	%	Diffusing capacity DLCOHb	No	%
Normal	8	22.22	Normal	5	13.89
Mild restriction	6	16.67	Mild diffusing capacity	7	19.44
Moderate restriction	18	50	Moderate diffusing capacity	6	16.67
Severe restriction	4	11.11	Severe diffusing capacity	18	50
Total	36	100	Total	36	100

Table-3: Spirometry and Diffusing capacity DLCOHb

HRCT pattern	Normal		Mild diffusing capacity		Moderate diffusing capacity		Severe diffusing capacity		Total	
	No	%	No	%	No	%	No	%	No	%
RGHT	-	-	-	-	-	-	5	100	5	13.89
RN	2	14.3	3	21.4	3	21.4	6	42.9	14	38.9
RGH	-	-	-	-	-	-	1	100	1	2.8
RNG	1	16.7	-	-	1	16.7	4	66.7	6	16.7
RH	-	-	-	-	1	16.7	2	66.7	3	8.3
GGO	2	33.3	3	50	1	16.7	-	-	6	16.67
Normal	-	-	1	100	-	-	-	-	1	2.8
R-Reticular, G-Ground glass, H-Honey combing, T-Traction bronchiectasis, N-Nodular										

Table-4: HRCT Vs DLCOHb

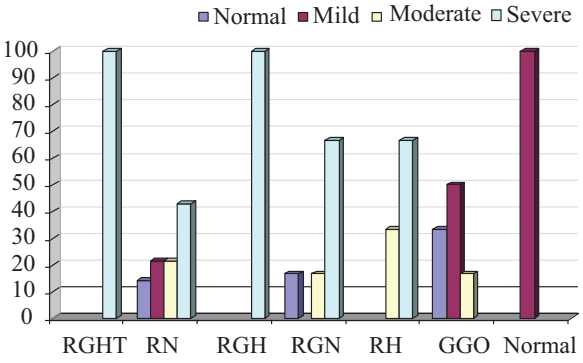

Figure-1: HRCT Vs DLCOHb

SLE and 1 case of Sjogrens syndrome (Table 2). In our study population various combinations of Reticular (R), Ground glass opacity (GGO), Honey combing (H), Traction bronchiectasis, and Nodular (N) patterns seen (Fig 1). When individual pattern is concerned 29 patients have Reticular Pattern which is the most frequent presentation (80.6%) and has significant association of p value 0.007 with DLCO Hb. But on combinations of HRCT spectrum ReticuloNodular (RN) pattern forms the most common presentation (38.9%). Less common being the Reticular, Ground glass, Honey combing pattern (RGH) and normal pattern one case each (Table 3). The predominant symptom found in majority of the study cases were Exertional dyspnoea, followed by cough and chest pain. Exertional dyspnoea found in 32 patients (88.89%) followed by Cough in 18 patients (50%) and Chest pain in 9 patients (25%). Bibasilar crackles heard in 16 cases out of 36 cases. In spirometry, FVC presented as either restriction or Normal FVC. In 36 cases of study population 28 presented with restriction pattern (75%) except 8 who presented with Normal FVC in spirometry. Forced vital capacity suggestive of Moderate restriction constitutes 50% of study population followed by Normal FVC. In DLCOHb Severely reduced diffusing capacity (>50%) is the most common presentation in study population followed by Moderately reduced diffusing capacity and then by equal presentations of Normal diffusing capacity and Mildly reduced diffusing capacity. When comparing HRCT pattern with DLCOHb, the following results were obtained (Fig 1). 5 cases of RGHT (Reticular, Ground glass opacity, Honeycombing and Traction bronchiectasis) pattern present only in Severely reduced diffusing capacity. 14 cases of RN (Reticulo Nodular) pattern present in all forms of diffusing capacity with predominant in severely reduced diffusing capacity (6 Cases).1 case of RGH (Reticular, Ground glass opacity, Honeycombing) pattern present in severely reduced diffusing capacity. 6 cases of RGN (Reticular, Ground glass opacity, Nodular) pattern 4 were present in severely reduced diffusing capacity. 3 cases of RH (Reticular, Honeycombing) pattern 2 cases present in severely reduced diffusing capacity.6 cases of GGO 3 cases in mildly reduced diffusing capacity 2 as Normal and 1 in Moderately reduced diffusing capacity. 1 case with Normal HRCT pattern present in Mildly reduced diffusing capacity.

Statistical analysis showed Significant p value (<0.05) association occurs between the above mentioned HRCT patterns and DLCOHb at 5% level by using Chi- Square Mantel - Haenszel test for linear association.Significant p value association occurs between the above mentioned HRCT patterns and FVC at 1% level by using Chi- Square Mantel-Haenszel test for linear association. Significant p value association occurs between FVC Vs DLCO Hb (p value 0.003) at 1% level by using Chi- Square Mantel Haenszel test for linear association.

DISCUSSION

Interstitial lung diseases (ILD) commonly complicate the management of connective tissue diseases. Moreover respiratory symptoms like cough, breathlessness or signs of ILD may precede the clinical presentation of CTD by five years or more[6]. Certainly it may result in significant morbidity and mortality.

In Systemic sclerosis (SSc) Lung is the fourth most commonly affected structure after skin, vessel and oesophageal involvement[7]. The predominant abnormalities on high-resolution CT consist of areas of ground-glass attenuation, poorly defined subpleural nodules, reticular pattern of attenuation, honeycombing, and traction bronchiectasis[8]. In Kim et al study[9] of longitudinal CT series of 40 patients with SS, a variety of radiological features were found including GGO (100%), irregular linear opacity (90%), small nodules (70%), honeycombing (33%), traction bronchiectasis (68%), bilateral pleural thickening (45%), and enlarged mediastinal lymph nodes (15%). In our study, Systemic sclerosis (SSc) is the CTD with the largest percentage 44.44% of all CTD patients and Reticulonodular pattern is the most common

presentation. In SSc spirometry have shown a restrictive pattern with a decreased total lung capacity (TLC), vital capacity (VC), forced vital capacity (FVC) and residual volume in most of the studies. DLCO in SSc impairment of the transfer factor (or diffusing capacity) for carbon monoxide (DLCO) is present. With progression of the ILD, the restrictive pattern is paralleled by the decrease in gas exchange. In Demosthenes Bouros, Athol U. Wells et al study in SSc Outcome is linked more strongly to disease severity at presentation and serial DLCO trends than to histopathologic findings. The percent predicted DLCO best reflects the extent of ILD in SSc, and therefore should be measured in routine evaluations[10].

While Rheumatoid Arthritis (RA) occurs more commonly in females (female to male ratio 3:1), RA-ILD is more frequent in males. RA-ILD most commonly presents as Reticulation, traction bronchiectasis and honeycombing and less commonly as ground-glass opacity and nodular pattern. HRCT findings of RA-ILD presents with irregular linear hyperattenuation due to a combination of intralobular lines and irregular thickening of interlobular septa[11]. Honeycombing is seen more markedly near the diaphragm. HRCT demonstrates interstitial lung disease in patients with and without clinical evidence of the disease (69%–80% and 20%–29%)[11]. In a study by Akira et al[12], three major radiographic patterns of disease have been identified in symptomatic patients who developed lung disease prior to or following the diagnosis of RA. These included reticulation with or without honeycombing (n=19), centrilobular branching lines with or without bronchial dilatation (n=5), and consolidation (n=5). Spirometry of rheumatoid Interstitial Lung Diseases is identical to the other fibrosing lung diseases[13]. Abnormalities of gas transfer, including a low DLCO are present in RA. In Systemic lupus erythematosus (SLE) multiple HRCT patterns have been reported.

In a study of HRCT imaging among 50 patients with Sjogren syndrome, there is an increased prevalence of lymphocytic interstitial pneumonitis, which is seen radiographically as a reticulonodular pattern predominantly involving the lower lobes[14] Bariffi and colleagues studied 18 female non-smokers with Sjögren's syndrome. They found that 13 of the 18 had an FEV_1/FVC ratio of less than 80% and 7 of 18 had anFEV_1 of less than 80[15].

HRCT of chest in Mixed connective tissue diseases (MCTD) have been characterized as the presence of ground-glass attenuation, nonseptal linear opacities, with a peripheral and lower-lobe predominance. The frequency of pulmonary abnormalities varies considerably in different series. In a review of the CT findings in 41 patients with MCTD, Kozuka et al found ground glass, subpleural micronodules, non septal linear and reticular abnormality were all found in more than 50% of cases. Pulmonary function abnormalities include a reduction of the DLCO, a decreased VC, TLC, and FEV_1.Abnormal PFTs and chest radiographs are frequent; impaired DLCO has been reported in 67%, and restrictive lung volumes in 50%. DLCO appears to be the most sensitive single parameter in evaluating pulmonary dysfunction in MCTD.

To date, only a few investigators have assessed long-term outcome of ILD in PM/DM patients, although ILD is still considered to have a high morbidity due to decreased functional pulmonary status. These patients usually have evidence of a restrictive spirometry pattern with reductions in FVC. In addition, the DLCO may also be reduced.

Our HRCT study can suggest the underlying pathologic category in the absence of FNAC/Biopsy material and has assumed a greater role in the diagnosis and management of CTD-ILD. Reticulonodular pattern was frequently observed in our study. Though there were various HRCT combination patterns, GGO alone in the absence of honeycombing was predominant next to RN pattern. Honey combing Pattern has significant association with DLCOHb. The percent predicted DLCOHb best reflects the extent of GGO which can be considered as inflammatory index in CTD, hence should be measured early for advance in management of ILD. Ground-glass opacities are usually considered to represent a higher degree of cellularity and suggest the disease is potentially more responsive to treatment**.** The percent predicted DLCOHb best reflects the extent of Honeycombing considered as fibrotic index in CTD, and therefore should be measured in routine evaluations. Reticulation, traction bronchiectasis and honeycombing reflect fibrotic changes and more advanced ILD.

Significant p value association occurs between the above mentioned HRCT patterns and DLCO Hb at 5% level by using Chi-Square Mantel-Haenszel test for linear association. As demonstrated by WELLS et al.[10], DLCO is the best index of the extent of the ILD when compared with HRCT as the "gold standard", our study also confirmed the same. The main limitations of our study were the small number of subjects and only CTD - ILD patients were included. DLCO when compared with HRCT is the best index of the extent of the ILD could not be elicited in large scale because of the limited sample size.

CONCLUSION

Our study points to the lung as the target organ for the development of complications from connective tissue diseases. ILD in this study was mainly diagnosed by chest HRCT, which can be used to distinguish different patterns, in the absence of pathologic material and pulmonary function tests including spirometry and DLCOHb. The percent predicted DLCOHb correlated better with extent of disease on HRCT. Overall, DLCOHb is the most sensitive parameter to detect the early interstitial changes in patients with CTD. Specific monitoring of pulmonary disease is necessary because the course of ILD does not always follow systemic disease activity.Therefore, it is imperative for physicians to look for early ILD pattern to assess favourable outcome pertaining to morbidity and mortality in CTD - ILD.

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Source of Support: Nil; **Conflict of Interest:** None

Submitted: 01-05-2018; **Accepted:** 02-06-2018; **Published:** 13-06-2018