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Original Research Article

A Hospital Based Observational Research to Evaluate Diagnostic Value of Connective Tissue Disease Related CT Signs in Usual Interstitial Pneumonia Pattern of Interstitial Lung Disease

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Abstract

Aim: The aim of this study was to evaluate diagnostic value of connective tissue disease related CT signs in usual interstitial pneumonia pattern of interstitial lung disease.

Methods: The present study was conducted at Department of Radio-diagnosis, Indira Gandhi Institute of Medical Sciences, Patna, Bihar, India and retrospective search was done among all CT thorax studies done for nine months for cases which fulfilled UIP pattern as per ATS/ERS/JRS/ALAT guidelines. 100 patients were included in the study.

Results: A total of 100 patients were included in the study, 50 (50%) had CTD. Majority of the study subjects were females (53.2%). The mean age for the cohort was 55.85 ±15 years. Comparison of demographic characteristics and CT sign distribution between CTD-related UIP and non-CTD related UIP. There was significant difference in gender distribution, females being more common in CTD-related UIP. Patients with CTD-related UIP were significantly younger than those without CTD in our study. Rheumatoid arthritis (RA) (60%) was the most common subtype of CTD.

Conclusion: The presence of SE, AUL, and EHC signs in cases with UIP pattern are specific imaging markers to diagnose underlying CTD; however, due to its low sensitivity, the absence of these signs cannot exclude the same. Because of its excellent interobserver agreement, these signs are reliable in the evaluation of CTD-related ILD.

Keywords: Usual Interstitial Pneumonia, Connective Tissue Disease, Computed Tomography.

Introduction

A usual interstitial pneumonia (UIP) pattern on chest CT scans is highly suggestive of UIP pathologic findings; has varied causes, being idiopathic pulmonary fibrosis (IPF), connective tissue disease (CTD), chronic hypersensitivity pneumonitis (HP), asbestosis, and drug toxicity; the most common cause of UIP is idiopathic pulmonary fibrosis (IPF) . [1]

(ALAT) are used for the diagnosis of UIP patterns on chest CT. [2] Differentiating IPF from secondary UIP has substantial therapeutic and prognostic implications. A number of radiological and histological clues may help distinguish IPF from other conditions with a UIP pattern of fibrosis, but their appreciation requires extensive expertise in interstitial lung disease (ILD) as well as an integrated multidisciplinary approach involving pulmonologists, rheumatologists, radiologists, and pathologists. Some of the imaging findings which suggest a possible secondary cause for UIP include the presence of pleural plaques, dilated esophagus, distal clavicular erosions, and pleural effusions/thickening. The connective tissue disease (CTD)-associated ILD can also commonly present with a UIP pattern in a chest CT examination, especially in patients with rheumatoid arthritis. Current understanding is that the pattern of fibrosis in UIP related to CTD is similar to that in IPF. [3,4]

Usual interstitial pneumonia (UIP) pattern on chest computed tomography (CT) has varied causes, with the common causes being idiopathic pulmonary fibrosis (IPF), connective tissue disease (CTD), chronic hypersensitivity pneumonitis (HP), asbestosis, and drug toxicity. [1] The clinical practice guidelines put forward in 2018 by the American Thoracic Society (ATS), the European Respiratory Society (ERS), the Japanese Respiratory Society (JRS), and the Latin American Thoracic Association (ALAT) are used for the diagnosis of UIP patterns on chest CT. [2] Differentiating IPF from secondary UIP has substantial therapeutic and prognostic implications. A number of radiological and histological clues may help distinguish IPF from other conditions with a UIP pattern of fibrosis, but their appreciation requires extensive expertise in interstitial lung disease (ILD) as well as an integrated multidisciplinary approach involving pulmonologists, rheumatologists, radiologists, and pathologists. Some of the imaging findings which suggest a possible secondary cause for UIP include the presence of pleural plaques, dilated esophagus, distal clavicular erosions, and pleural effusions/thickening.2

Chung et al[6] in a study done in an ILD clinic in University of Chicago had identified three CT signs which were significantly more common in CTD-related UIP than in IPF-related UIP. The CT signs studied were anterior upper lobe (AUL) sign, straight edge (SE) sign, and exuberant honeycombing (EHC) sign. They concluded that the index of suspicion for CTD related ILD should be raised in the case of patients with any of the three CT signs. The aim of this study was to evaluate the diagnostic value of each of these findings in differentiating CTD UIP and IPF UIP.

Materials & Methods

The present study was conducted at department of Radio-diagnosis Indira Gandhi Institute of Medical Sciences, Patna, Bihar, India and retrospective search was done among all CT thorax studies done for nine months for cases which fulfilled UIP pattern as per ATS/ERS/JRS/ALAT guidelines. 100 patients were included in the study. Patients with probable UIP pattern or indeterminate for UIP pattern and other types of ILD was excluded. In our institute, the final diagnosis in each case of ILD is made by multidisciplinary discussion, and cases with clinical and/or serological evidence of autoimmunity will be evaluated by a rheumatologist to diagnose and characterize CTDs using established criteria. Hence, we assessed the clinical records of subjects with UIP pattern through hospital information system, and the study subjects were grouped into CTD-related UIP and non–CTD-related UIP. Any case with clinical and/or serological evidence of autoimmunity but fall short of diagnosis of a specific CTD was classified as

undifferentiated CTDs. They were excluded from the study.

CT Assessment

CT scan was performed in one of these three multislice. CT scanners were available at our institution. Contiguous helical acquisition of CT scans was performed. CT scans were considered diagnostic quality if whole of thorax in full inspiration is covered. All the CT scans were viewed in 1 to 2 mm high spatial algorithm, reconstructed in different planes. A chest radiologist (A.A.) who was blinded to multidisciplinary discussion (MDD) diagnosis and study grouping assessed the CT images for the presence of the three CT signs as described by Chung et al.[5]The AUL sign is concentration of fibrosis in anterior aspect of upper lobes with relative sparing of rest of the upper lobes along with concomitant lower lobe involvement. EHC sign is extensive honeycomb-like cyst formation in more than 70% of fibrotic portion of lungs. SE sign is fairly straight and abrupt interphase between fibrotic lung bases and normal lung without extension along the lateral margins of lung on coronal images.

A random selected subset of 60 patients was chosen to assess interobserver agreement in detecting the CT signs. The CT of these patients was reviewed independently by another chest radiologist (L.R.V.) who was blinded to MDD diagnosis or study grouping, to look for the presence of the three CT signs.

Statistical Analysis

Categorical variables were presented as frequency and percentage, and continuous variables as mean and standard deviation. Continuous variables were compared among CTD related ILD and non-CTD-related ILD using independent t test. Categorical variables were compared using chi-square test. The sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio for each of the signs in diagnosing CTD-related ILD were calculated. Interobserver agreement was estimated by calculating intraclass correlation coefficient (ICC).

Results

Table 1: Demographic characteristics and CT sign distribution between CTD-related UIP and non-CTD-related UIP

	Non-CTD UIP (n =50)	CTD UIP (n =50)	Total	p-Value
Mean age (y)	61.39 ± 12	50.0 ±15	55.85 ± 15	<0.001
Sex				
Male	32 (71.12%)	13 (28.88%)	45	<0.001
Female	15 (2.27%)	40 (72.73%)	55	
Smoking history				
Present	18 (75%)	6 (25%)	24	<0.001
Absent	19 (25%)	57 (75%)	76	
Anterior upper lobe sign				
Present	9 (34.61%)	17 (65.38%)	26	0.015
Absent	42 (56.75%)	32 (43.24%)	74	
Exuberant honeycombing sign				
Present	20 (35.1%)	37 (64.9%)	57	0.002
Absent	60 (60.6%)	39 (39.4%)	99	
Straight edge sign				
Present	11 (31.43%)	24 (68.57%)	35	0.001
Absent	40 (61.53%)	25 (38.47%)	65	
Any sign positive (one or more)				

Present	20 (36.36%)	35 (63.64%)	55	<0.001
Absent	31(68.88%)	14 (31.12%)	45	
More than one sign positive (two or more)				
Present	9 (32.15%)	19 (67.85%)	28	0.003
Absent	45 (62.5%)	27 (37.5%)	72	
All signs positive				
Present	2 (20%)	8 (80%)	10	0.015
Absent	49 (54.44%)	41 (45.56%)	90	

A total of 100 patients were included in the study, 50 (50%) had CTD. Majority of the study subjects were females (53.2%). The mean age for the cohort was 55.85 ±15 years. Comparison of demographic characteristics and CT sign distribution between CTD-related UIP and non-CTD related UIP. There was significant difference in gender distribution, females being more common in CTD-related UIP. Patients with CTD-related UIP were significantly younger than those without CTD in our study.

Table 2: Subtypes of CTD in cohort

Subtype of CTD–ILD	Count (%)
Rheumatoid arthritis	30 (60)
Systemic sclerosis	9 (18)
Mixed connective tissue disease	6 (12)
Systemic lupus erythematosus	3 (6)
Sjogren's syndrome	2 (1)
Total	50 (100)

Rheumatoid arthritis (RA) (60%) was the most common subtype of CTD.

Table 3: Performance of CT signs in the diagnosis of CTD-related UIP

	AUL	EHC	SE	Any positive	> 1 positive	All positives
Sensitivity	35.6	48.2	38.2	69.5	38.2	14.7
Specificity	82.8	75.0	85.0	62.8	83.6	96.4
LRþ	2.06	1.90	2.54	1.90	2.40	3.87
LR—	0.75	0.65	0.73	0.50	0.75	0.85

When any one of the three signs being positive is considered for diagnosis, the sensitivity was higher (69.5%) and the specificity is lower than that for any individual signs. When more than one sign being positive are considered, the sensitivity and specificity were 38.2 and 83.8%, respectively. Sensitivity further decreased to 14.5% and specificity increased to 96.2% when all the three positivity signs were considered for diagnosis.

Discussion

Although many cases of CTD-ILD are diagnosed in patients who have a rheumatologic diagnosis of a well-defined CTD, a substantial minority of patients, including those with UIP, present with ILD first and CTD is diagnosed at a later date. [7-12] Moreover, a substantial number of patients with ILD have clinical and serologic features suggestive of an underlying autoimmune disease but do not meet strict criteria for a specific CTD. [13-15] In addition, radiologists often interpret chest CT scans without access to the patient's clinical record and may not be aware that a patient has a diagnosis of

CTD. The specific CT signs evaluated in this study are additional tools that the radiologist or pulmonologist can use to help differentiate CTD-ILD from IPF in patients who have a CT UIP pattern.

The imaging patterns of ILD in CTD have been described according to the radiologic and pathologic classification of the idiopathic interstitial pneumonias. [16] Although not formally tested, in many cases, this classification is appropriate and affords accurate characterization of CTD-related ILD. In clinical practice, however, a UIP pattern at CT is often equated with IPF. Recognition that a substantial minority of cases of UIP are secondary to an underlying disease or exposure is critical for accurate diagnosis. [2] Radiologists are encouraged to define imaging patterns mirroring pathologic diagnosis given that ultimately the goal of imaging is to reflect the pathologic finding as closely as possible. However, in patients with ILD, neither pathologic examination, clinical workup, nor imaging is the reference standard in diagnosis. Multidisciplinary diagnosis including radiologists, pathologists, and clinicians is the reference standard for achieving accurate diagnosis of ILD.

Some of the previous studies which included all types of ILD have found conflicting results with IPF as the most common ILD in some of the studies, whereas CTD-related ILD was the most common in a few others. [17–20] One of the largest prospective registries for ILD performed in a similar population as the present study has found HP to be the most common cause of ILD, followed by CTD-related ILD and then IPF. [21] In the same registry, among cases with UIP pattern on CT, majority of cases (51.6%) were IPF, and only 18.75% were CTD related. In the study by Chung et al, [6] which studied CT features of UIP, 32% of cases were CTD related and the rest IPF. The incidence of CTD-related UIP is higher in our sample as the study was done in a multispecialty institute with a larger proportion of patients being referred from Clinical Immunology and Rheumatology Department. Hence, our results may not represent the proportion of such diagnosis in other hospital settings or general population.

RA is the most common CTD to cause ILD, and the most common pattern of ILD in RA is UIP followed by nonspecific interstitial pneumonia. [6,21,22] Our cohort of CTD-related UIP cases also showed similar trend with RA being the most common (60%) followed by systemic sclerosis (18%), mixed CTD (12%), systemic lupus erythematosus (6%), and Sjogren's syndrome (1%). All the three CT signs described in CTD-related UIP had lower sensitivity individually (35.5–48.7%) but good specificity (75–85%) in diagnosing CTD-related UIP. With increasing number of signs being considered for diagnosis, the sensitivity for the detection of CTD decreased, whereas the specificity increased. [23] Our results showed a similar trend as the previous study by Chung et al [10] which compared the performance of these CT signs in patients with IPF and CTD- related UIP. The sensitivity was slightly lower and specificity was slightly higher in the study by Chung et al. [7] In their study, the highest sensitivity was for AUL sign and SE sign and the highest specificity was for EHC sign and SE sign (both had 94% specificity), whereas in our study, the highest sensitivity was for EHC sign and highest specificity was for SE sign. These difference may be partly due to the difference in the study group selection, as our comparison group had all cases with UIP pattern which are non–CTD related (includes IPF as well as other secondary causes of UIP other than CTD).

The limitation of our study was its retrospective design and the limited number of subjects. Also, as the study is done in a single tertiary referral center with an established rheumatology

department, the proportion of each diagnosis may not be a representative sample in the general population. Undifferentiated CTD cases were not addressed in our study and were excluded from our cohort as they may represent an overlap between the groups. The number of such cases was also small for deriving any conclusion. Further multicentric, prospective studies on larger sample will be helpful.

Conclusion

Radiologists should actively look for AUL sign, EHC sign, and SE sign when evaluating UIP pattern on CT as these are significantly common in CTD-related ILD with UIP pattern. EHC sign was the most sensitive sign and SE sign was the most specific sign. Inclusion of more than one sign increases the specificity of diagnosis of CTD-related UIP; however, the sensitivity decreases. These signs can be used as specific imaging markers to diagnose underlying CTD; however, due to its low sensitivity, the absence of these signs cannot exclude the same. Because of its excellent interobserver agreement, these signs are reliable in the evaluation of CTD-related ILD.

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