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Original Research Article

High-resolution computed tomography as a non-invasive imaging biomarker for interstitial lung diseases: a tertiary center study

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ABSTRACT

Background: Interstitial lung diseases (ILD) are a heterogeneous group of non-neoplastic disorders resulting from damage to the lung parenchyma by varying patterns of inflammation and fibrosis. With high-resolution computed tomography (HRCT) the pattern of lung damage can be mapped accurately which may help to identify specific ILD.
Methods: 65 diagnosed cases of ILD by HRCT who were admitted to a tertiary care chest hospital, formed the study group. All these patients also underwent histopathological confirmation as per hospital protocol. The study was done over a period from August 2016 to July 2019. Clinical details, chest x-ray, HRCT and histopathological data was collected and analysed using 2x2 table for detecting sensitivity, specificity, positive predictive value (PPV) and negative predictive values (NPV).
Results: For diagnosing ILD like acute interstitial pneumonia (AIP), LIP and RB ILD the HRCT fared equally well in diagnostic utility as compared to histopathological examination. But in certain conditions like non-specific interstitial pneumonia (NSIP) the HRCT performed poorly in terms of PPV as compared to gold standard histopathology. In Bronchiolitis obliterans organizing pneumonia (BOOP) and usual interstitial pneumonia (UIP) again the HRCT performed fairly well as compared to gold standard.
Conclusions: HRCT shows good correlation with histopathological diagnosis in identifying a various subtype of ILD and may thus serve a useful non-invasive, imaging biomarker not only for diagnosing a particular ILD but for prognostication and response to treatment.

Keywords: HRCT, BOOP, NSIP, UIP, AIP, ILD

INTRODUCTION

Diffuse parenchymal lung diseases (DPLD) are also known as ILD are heterogeneous group of non-neoplastic disorders resulting from damage to the lung parenchyma by varying patterns of inflammation and fibrosis.[1] However, these disorders not only affect the interstitial which is the main site of injury but also involves the airspaces, peripheral airways and vessels along with their epithelial or endothelial lining.[1] The actual incidence of ILD remains unknown in the Indian population. The western literature from UK mentions the prevalence of all ILDs at 1 in 3000 to 4000 in the Europe.[1]

The classification of various disorders under ILD is standardized by the classification schemes of the ATS (American thoracic society)/ERS (European respiratory society), which proposed the classification which is used in this study. The classification of ILD is into (a) disorders of known cause (collagen vascular disorder or drug related), (b) idiopathic interstitial pneumonia (IIP), (c) granulomatous lung disorders and (d) other forms which include lymphangiomyomatosis, eosinophilic pneumonia.

IIP is further divided on the basis of clinical-radiological-pathologic diagnosis, into seven main sub categories:[1,2] Idiopathic pulmonary fibrosis (IPF), non-specific interstitial pneumonia (NSIP), cryptogenic organizing

pneumonia (COP), acute interstitial pneumonia (AIP), desquamate interstitial pneumonia (DSIP), lymphoid interstitial pneumonia (LIP) and respiratory bronchiolitis (RB ILD).

The diagnosis of ILD requires a team approach by the pulmonologist, radiologist and the pathologist. The approach to a patient with ILD comprises of detailed history, clinical examination, routine chest radiograph followed by pulmonary function test. After these initial tests the patient undergoes HRCT scan. The HRCT scan may also give clues to alternate diagnosis which may help in guided biopsies if needed.

Aim and objectives of the study were to evaluate interstitial lung by HRCT and correlation with histopathology. To assess pattern of distribution of abnormal findings on HRCT Scan in patients of ILD, study the histopathological findings in these patients and to correlate the HRCT and histopathological findings in patients of ILD.

METHODS

Study design

Diagnostic test evaluation study comparing HRCT with gold standard lung biopsy.

Sample size

A total of 65 confirmed cases of ILD by histopathology are included in the study during the period of 03 years from July 2016 to Jun 2019. Clinical details, chest x-ray, HRCT and tissue/blocks of 65 patients were analysed in this study. The study was done at army hospital (R and R), New Delhi after due clearance from institutional ethics committee.

Inclusion criteria

Only those patients were included in the study where both HRCT and lung biopsy-TBLB or open lung biopsy was done and histopathology diagnosis was confirmed.

Exclusion criteria

Patients of tuberculosis, bronchial asthma and pulmonary hypertension, patients with cough due to cardiac causes and other systemic diseases and if either HRCT or histopathology data not available were excluded.

Protocol of study

All patients with clinical suspicion of ILD will undergo both HRCT chest followed by tissue sampling. Two different set of codes will be given to each patient to maintain anonymity of data and for blinding purpose. The HRCT chest was reported by two radiologists with 05 years and 15 years of experience in a standard ILD reporting format for more objective evaluation. HRCT protocol included prone scan with breath hold and 0.625 mm thick sections with 10 mm inter slice gap. The thin sections were obtained with ultra-high frequency algorithm to obtain sharp images for pattern recognition. Data was analysed using SPSS software version 21.

RESULTS

Study included a total of 65 patients over a period of 3 years which comprised of 30 females and 35 males. The age group ranged from 32 years to 66 years with a median age of 44 years (SD ± 7 years). Other comorbidities like diabetes mellitus type 2 were present in 11 patient (05 females and 06 males) and hypertension in 15 patients (05 females and 10 males). Most common presenting clinical feature was dry cough (55 patients out of 65) followed by dyspnoea (45 out of 65). Digital clubbing was noted in 17 patients. Auscultatory crackles were present in all patients. Restrictive pattern on spirometry was noted in 60 patients out of 65 patients, 03 patients have normal spirometry and 02 patients have mixed obstructive and restrictive pattern on spirometry.

On HRCT findings the case load comprised of AIP (2 cases), BOOP (25 cases), LIP (2 cases), NSIP (14 cases), RB ILD (1 case) and UIP (21 cases) (Table 1).

Table 1: Case load as per HRCT findings.

HRCT findings		Positive
HRCT	AIP	2
	BOOP	25
	LIP	2
	NSIP	14
	RB_ILD	1
	UIP	21
Total		65

On histopathological examination the case distribution is AIP (2 cases), BOOP (24 cases), LIP (2 cases), NSIP (6 cases), RB ILD (1 case) and UIP (16 cases) as shown in the Table 2.

Table 2: Case load as per histopathological findings.

Findings		Positive
Histopathology	AIP	2
	BOOP	24
	LIP	2
	NSIP	6
	RB_ILD	1
	UIP	16
Total		51

The sensitivity, specificity, PPV and NPV of HRCT in detecting AIP as compared to gold standard histopathology is 100%, for each respectively.

For detecting BOOP the sensitivity, specificity, PPV and NPV of HRCT as compared to gold standard histopathology is 100, 97.5, 96 and 100% respectively.

For detecting LIP, the sensitivity, specificity, PPV and NPV of HRCT as compared to gold standard histopathology is 100%, each respectively.

In case of NSIP the sensitivity, specificity, PPV and NPV of HRCT as compared to gold standard histopathology is 83.34, 84.7, 35.72 and 98.04% respectively. HRCT has poor PPV in detecting NSIP as compared to histopathology because of wide range of presentation features of NSIP.

In RB ILD the sensitivity, specificity, PPV and NPV of HRCT as compared to gold standard histopathology is 100% each respectively.

As far as USIP is concerned, the sensitivity, specificity, PPV and NPV of HRCT as compared to gold standard histopathology is 93.75, 87.7, 71.4 and 97.7% respectively.

So, we can say that for conditions like AIP, LIP and RB ILD the HRCT fared equally well in diagnostic utility as compared to histopathological examination.

Table 3: AIP HRCT-histopathology 2x2 table.

Count		AIP histopathology		Total
		Positive	Negative	
AIP HRCT	Positive	2	0	2
	Negative	0	63	63
Total		2	63	65
HRCT parameters (%)				
Sensitivity	Specificity	PPV	NPV	
100.00	100.00	100.00	100.00	

Table 4: BOOP HRCT-histopathology 2x2 table.

Count		AIP histopathology		Total
		Positive	Negative	
BOOP HRCT	Positive	24	1	25
	Negative	0	40	40
Total		24	41	65
HRCT parameters (%)				
Sensitivity	Specificity	PPV	NPV	
100.00	97.50	96.00	100.00	

Table 5: LIP HRCT-histopathology 2x2 table.

Count		AIP histopathology		Total
		Positive	Negative	
LIP HRCT	Positive	2	0	2
	Negative	0	63	63
Total		2	63	65
HRCT parameters (%)				
Sensitivity	Specificity	PPV	NPV	
100.00	100.00	100.00	100.00	

Table 6: NSIP HRCT-histopathology 2x2 table.

Count		AIP histopathology		Total
		Positive	Negative	
NSIP HRCT	Positive	5	9	14
	Negative	1	50	51
Total		6	59	65
HRCT parameters (%)				
Sensitivity	Specificity	PPV	NPV	
83.34	84.70	35.72	98.04	

Table 7: AIP HRCT-histopathology 2x2 table.

Count		AIP histopathology		Total
		Positive	Negative	
RB ILD HRCT	Positive	1	0	1
	Negative	0	64	64
Total		1	64	65
HRCT parameters (%)				
Sensitivity	Specificity	PPV	NPV	
100.00	100.00	100.00	100.00	

Table 8: UIP HRCT-histopathology 2x2 table.

Count		AIP histopathology		Total
		Positive	Negative	
UIP HRCT	Positive	15	6	21
	Negative	1	43	44
Total		16	49	65
HRCT parameters (%)				
Sensitivity	Specificity	PPV	NPV	
93.75	87.70	71.40	97.7	

But in certain conditions like NSIP the HRCT performed poorly in terms of PPV as compared to gold standard histopathology. In BOOP and UIP again the HRCT performed fairly well as compared to gold standard.

DISCUSSION

ILD or DPLD are terms used to encompass a large group of disorders that primarily affect the lung parenchyma in a diffuse manner. The parenchyma of the lung includes the pulmonary alveolar epithelium, capillary endothelium and the spaces between these structures, together with the tissues within the septa including the perivascular and peri lymphatic tissues.[1] DPLD is increasingly in favor worldwide as a generic term for these disorders, in preference to terms such as ILD or diffuse lung disease. Both the terms are used interchangeably in this study. The term interstitial is misleading, since most of these disorders are also associated with extensive alteration of alveolar and airway architecture.

The concept of ILD has been described in the medical literature for over a century. In 1892, Osler described the lungs of patients with chronic interstitial pneumonia as having a fibrinoid change, for which he coined the term 'cirrhosis of lung'. Decades later, Hamman and Rich described 4 cases of acute diffuse interstitial fibrosis in which the lungs were the seats of a widespread connective tissue hyperplasia throughout the interstitial structures.[2] Over the next several decades progress was made in defining the aetiology of many ILDs.

The ATS/ERS international multidisciplinary consensus classification comprises the following clinicopathologic entities in the order of relative frequency: IPF/CFA, NSIP, COP/BOOP, AIP, RB-ILD, DIP, and LIP.

Overall, the prevalence of ILDs was 20% higher in males (80.9 per 100,000) than in females (67.2 per 100,000).[2] In another study by Roelandt et al done in Flanders, the overall incidence of ILDs was slightly more common in males (31.5 per 100,000/year) than females (26.1 per 100,000/year).[2]

Most of the interstitial disorders have a restrictive defect with reductions in total lung capacity (TLC), functional residual capacity (FRC), and residual volume (RV). Flow rates are decreased (FEV1 and FVC), but the changes are in proportion to the decreased lung volumes; thus, the FEV1/FVC ratio is usually normal or increased. The reductions in lung volumes become more pronounced as lung stiffness worsens with disease progression. A mixed pattern of restriction and obstruction (decreased FEV1/FVC ratio, elevated RV, lack of supranormal airflows on a flow-volume loop, or a significant response to bronchodilator) in the patient without coexisting emphysema may suggest sarcoidosis, hypersensitivity pneumonitis (HP), respiratory bronchiolitis-ILD (RB-ILD), lymphangioleiomyomatosis (LAM) and ILD associated with asthma (chronic eosinophilic pneumonia, Churg-Strauss syndrome).[2]

The common radiographic abnormalities on routine chest radiograph are reticular, nodular, or mixed patterns; normal radiographs are not unusual.[2] Unfortunately, the chest radiograph is normal in as many as 10% of patients with some forms of ILD, particularly those with hypersensitivity pneumonitis.

The accuracy of HRCT in determining specific aetiologies of ILD has been inconsistent in different series, and extrapolation of these data into routine clinical practice is difficult because of variability in radiologic experience

and scanning protocols at different centers. HRCT appears to provide greater diagnostic accuracy than plain films, but the extent to which this influences decision to obtain a tissue diagnosis is not well defined.[2] The utility of HRCT reflects the close relationship between macroscopic histopathological changes and HRCT abnormalities, evident in many diseases.[2]

Lung biopsy is indicated in cases with confusing HRCT picture and where treatment varies for different HRCT appearance or early diagnosis and treatment may reverse an ILD. In this study histopathology is available for all 65 patients. Now we will see a brief account of each entity:

Acute interstitial pneumonia

The pathology is described as an organizing form of diffuse alveolar damage (DAD) indistinguishable from the histologic pattern found in acute respiratory distress syndrome (ARDS) caused by sepsis and shock. When DAD is idiopathic, it is called AIP.

Radiology: The chest radiograph reveals bilateral airspace patchy ill-defined consolidation with air bronchograms in essentially all patients. Pleural effusions are uncommon. CT findings are areas of ground glass attenuation, bronchial dilatation, and architectural distortion.

Histological features: During the exudative (acute) phase, there is interstitial oedema, acute and chronic inflammation, type II cell hyperplasia, and hyaline membrane formation. Thrombi within small arteries are also common. During the organizing (healing) phase, the features are more similar to those of OP.

Although the course of ILD is variable, progression is common and often insidious. All treatable possibilities should be carefully considered. Since therapy does not reverse fibrosis, the major goals of treatment are permanent removal of the offending agent, when known and early identification and aggressive suppression of the acute and chronic inflammatory process, thereby reducing further lung damage

Non-specific interstitial pneumonia

Introduction: The concept of NSIP has helped to identify a group of ILDs with a more favourable prognosis and that need to be distinguished from IPF. Three major subgroups based on the amount of inflammation and/or fibrosis in the lung biopsies: group I, primarily with interstitial inflammation; group II, with both inflammation and fibrosis; and group III, primarily with fibrosis.

Radiological features: Radiographs shows pulmonary infiltrates predominantly in lower zones with ground glass opacities. On HRCT scan, temporal and spatial homogeneity along with ground glass attenuation is the predominant finding in the majority of cases with immediate subpleural sparing (Figure 1).

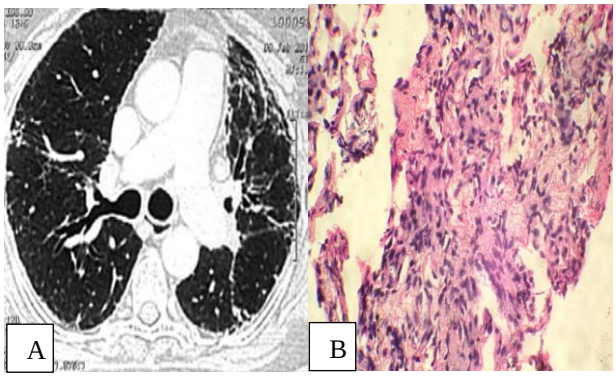

Figure 1: (A and B) A case of NSIP with peripheral ground glass opacities and immediate subpleural sparing. Histopathology of multiple inflammatory cells seen in uniform distribution.

Histological features: Temporal and spatial homogeneous interstitial and chronic inflammation, with or without fibrosis. Some cases have a primarily chronic inflammatory/cellular pattern ("cellular NSIP"), but most cases have a fibrotic pattern ("fibrotic NSIP"). NSIP may have significant fibrosis, but it is usually diffuse Fibroblastic foci and honeycombing, if present, are rare. These features are key in distinguishing NSIP from UIP.

Cryptogenic organizing pneumonia

Introduction: COP is the histologic pattern that indicates bronchiolitis obliterans organizing pneumonia (BOOP, also called cryptogenic organizing pneumonia) in the appropriate clinical setting.

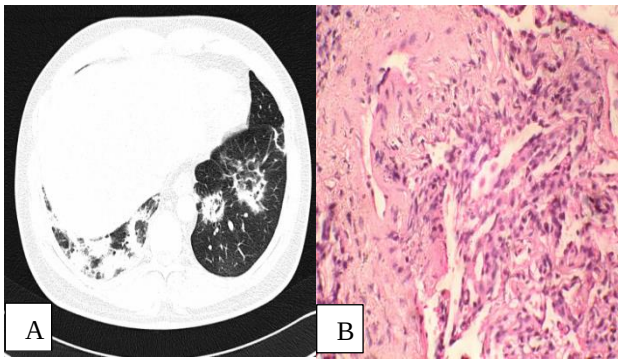

Figure 2: (A and B) Case of BOOP of irregular areas of consolidation, occurring in relation to bronchi. Air bronchograms are visible within the opacities. "Atoll" or "reverse halo" sign is seen. Histopathology showing alveolar ducts occupied by immature connective tissue with fibroblasts. Alveolar walls are expanded with inflammatory cells.

Radiological features: Chest radiograph shows bilateral or unilateral areas of consolidation. The distribution is usually patchy but may be confined to the subpleural region in a minority of cases. CT demonstrates patchy consolidation or ground glass opacities with subpleural or

peri bronchial distribution. Small nodules (10 mm) are usually seen along broncho vascular bundles. The large nodules or masses are irregular in shape. There can be focal or lobar consolidation. Mild cylindrical bronchial dilatation is commonly evident in areas of consolidation. "Atoll" or "reverse halo" sign en as ring shaped or crescentic opacities with ground glass opacities and no reticulation in center of the ring (Figure 2).

Histo-pathogical features: Histologically, there are numerous buds of granulation tissue within alveoli, often involving alveolar ducts and small airway. Foamy macrophages are commonly seen in the alveoli, presumably secondary to bronchiolar occlusion. Eosinophils and neutrophils are usually few in number, and severe fibrotic changes are unusual.

Respiratory bronchiolitis-associated interstitial lung disease

Introduction: RB ILD is a histopathologic lesion found in cigarette smokers and is characterized by the presence of pigmented intraluminal macrophages within first- and second-order respiratory bronchioles.

Radiological features: Chest radiograph shows thickening of the walls of central or peripheral bronchi and ground glass opacity. HRCT findings of RB-ILD include centrilobular nodules, patchy ground glass attenuation, and thickening of the walls of central and peripheral airways.

Histopathological features: It is a mononuclear inflammatory process involving the submucosa of the membranous and respiratory bronchioles; these changes may be associated with mild fibrosis that extends into the surrounding alveolar walls.

Desquamative interstitial pneumonia

Introduction: The name originated from the belief that the dominant histologic feature was desquamation of epithelial cells as originally thought by Liebow and Carrington. However, this is now recognized to be intra-alveolar macrophage accumulation rather than desquamation of epithelial cells.

Radiological features: The chest radiograph is usually normal. HRCT shows ground glass opacities in all cases of DIP. The distribution was diffuse and uniform. Irregular linear opacities and reticular pattern are frequent (59%) but usually confined to the lung bases. Honeycombing is seen in less than one-third of cases, and is usually peripheral.

Histopathological features: DIP is characterized by diffuse filling of alveoli by macrophages that have glassy eosinophilic cytoplasm and fine granular brown pigmentation. Fibrosis may also been present but it is generally mild.

Lymphocytic interstitial pneumonia

Introduction: The term lymphoid interstitial pneumonitis (LIP) was introduced by Liebow and Carrington to describe a diffuse lymphocytic interstitial infiltrate that was distinct from other patterns of interstitial pneumonitis.

Radiological features: Chest radiographs shows two patterns: basilar with an alveolar component and diffuse with associated honeycombing. HRCT finding is usually ground glass opacity. Perivascular cysts or perivascular honeycombing can also be seen. Reticular abnormality is seen in about half of cases. Lung nodules and widespread consolidation seen. Thin-walled cysts, thickening of the broncho vascular bundles, and interlobular septal thickening are the commonest findings.

Histopathological features: In LIP, there is a dense diffuse interstitial lymphoid infiltrate, similar to follicular bronchiolitis. LIP was previously considered be pre-neoplastic; however, it is now believed to be a reactive pulmonary lymphoid hyperplasia, similar to that seen in collagen vascular diseases or immunosuppression.

UIP: Honeycomb lung

Honeycomb lung is indicative of end-stage pulmonary fibrosis. Many disorders (e.g., IPF, sarcoidosis, hypersensitivity pneumonia, eosinophilic granuloma) can progress to end-stage fibrosis, but cannot be distinguished reliably by pathologists at this stage of the disease processes. Thus, biopsy of honeycomb lung is not helpful and should be avoided (Figure 1).

CONCLUSION

In our study, HRCT shows good correlation with histopathological diagnosis in identifying a various sub-type of ILD and may thus serve a useful non-invasive, imaging biomarker not only for diagnosing a particular ILD but for prognostication and response to treatment.

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