

Correlation between Imaging Features of High-resolution Computed Tomography and Histopathology of Connective Tissue Diseases associated Interstitial Lung Disease in Chinese Population: Avoid Lung Biopsy in Those Patients?

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Abstract

Objective: By analysis the correlation between images of high-resolution computed tomography (HRCT) and histopathology patterns of different connective tissue diseases associated interstitial lung diseases (CTD-ILDs), we aimed to investigate the feasibility of deduce the histopathology pattern from HRCT imaging and thereby avoid lung biopsy in such patients.

Methods: Patients with a diagnosis of CTD in Guangdong General Hospital from November 2008 to June 2014 were screened and those with a diagnosis of ILD were enrolled in this study. The clinical data and findings on HRCT of those patients were reviewed; histopathology patterns of lung biopsy samples from 43 patients obtained by CT guided percutaneously transthoracic approaches were analyzed and compared with their HRCT images.

Results: 2320 patients were screened and 325 of those were enrolled. Three major imaging patterns were identified: usual interstitial pneumonia (UIP)(76 patients), non-specific interstitial pneumonia (NSIP) (121 patients) and indeterminate (128 patients). UIP and NSIP were more common in SSc-ILD patients, and rarely in SLE/PM-ILD patients. Histopathology patterns from 43 lung biopsies could also be divided to three types: UIP (20 samples), NSIP (20 samples), undefined (3 samples).

Statistical analysis showed positive correlation between histopathology patterns and imaging features on HRCT in CTD-ILD patients ($P < 0.05$).

Conclusion: Fibrosis is the main finding of HRCT in patients with SSc/RA-ILD and which is rarely seen in SLE/PM-ILD. Since there was a very good correlation between HRCT imaging findings and histopathology results, HRCT features of those patients with CTD may be a good indication of ILD and may avoid lung biopsy in those patients.

Introduction

PET/CT images. We also recognize that are small number of cases of tumour recurrence after radiotherapy treatment suitable for the training of ANNs. In this study, we proposed an ANNs scheme for limited samples that simulated the decision process of radiologist for recognizing recurrent NPC on 18F-FDG PET/CT images [1].

According to the American Thoracic Society/European Respiratory Society (ATS/ERS) consensus classification, histopathology patterns of ILD are divided into seven subtypes: idiopathic pulmonary fibrosis (IPF/UIP), non-specific interstitial pneumonia (NSIP), respiratory bronchiolitis interstitial lung disease (RBILD), acute interstitial pneumonia (AIP), desquamative interstitial pneumonia (DIP), cryptogenic organizing pneumonia (COP), lymphocytic interstitial pneumonia (LIP). The classification of CTD-ILD follows the ATS/ERS consensus classification criteria and all the subtypes of ILD histopathology can present in CTD-ILD, even multiple subtypes of histopathology can coexist in an individual patient's lung [2]. Although lung biopsy is the golden criteria for diagnosis subtypes of ILD, its application in clinical practice is limited because of its possible complication of pulmonary hemorrhage and pneumothorax. In the other hand, without histopathology diagnosis from lung biopsy, it may be difficult to provide correct therapies for those patients.

High resolution computed tomography (HRCT) is a major modality to diagnosis ILD without lung biopsy. Huang Wenqun reported that the diagnosis rate of SLE-ILD through HRCT might be up to 77%

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while the routine chest X-ray was only 38%, 3 Lin Li reported that the sensitivity and specificity of HRCT in diagnosis of ILD exceeded 95%.⁴ Moreover, the different imaging characteristics, such as ground glass opacity, reticulation, consolidation, nodular shadow, emphysema and bronchiectasis can be clearly distinguished.⁵ In this study, we aimed to identify the correlation between images features on HRCT and histopathology patterns on lung biopsy, thereby avoiding lung biopsy in those patients based on the correlation.

Patients and Methods

Patients

325 patients with a diagnosis of ILD in Guangdong General Hospital from November 2008 to June 2014 were enrolled after screening 2320 CTD patients. We used American College of Rheumatology (ACR)

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criteria for the diagnosis of RA, SSc, pSS, and SLE. For the diagnosis of DM and MCTD, we used Bohan/Peter and Sharp criteria.

ILDs were diagnosed according to the combination of clinical symptoms, imaging findings, lung function test and pathology results. Patients who had three of the following items would have a diagnosis of ILD: (1) dyspnea at rest or activity; (2) dry cough or Velcro rales in the lungs on auscultation; (3) interstitial lung changes on images (chest X-ray or HRCT) such as ground glass opacities, honeycombing, pleural incassation thickening of interlobular septa and mixed pattern; (4) restrictive ventilation disorder or dysfunction of lung ventilation on lung function tests; Exclusive criteria were patients with pregnancy; malignant tumor, active lung infection, pulmonary hypertension, congenital heart disease, pulmonary veno-occlusive disease, chronic obstructive pulmonary disease and right or left heart failure. Patients with environmental toxic exposures or other known causes of ILD and patients with familial idiopathic pulmonary fibrosis were also excluded.

Methods

The following data were collected from the enrolled patients' records: gender; age at diagnosis of ILD; the age at diagnosis of CTD; the duration of respiratory symptom, the time elapsed between the diagnosis of CTD and the diagnosis of ILD; findings on imaging tests, results of lung function tests and results of histopathology. Each patient underwent HRCT in three days after being admitted to hospital, some of them had lung functions tests and about 15% of patients had lung biopsy.

ILD was divided into several subtypes when they were identified by HRCT. The HRCT images were read by two experienced chest radiologists. Diagnosis of the ground glass opacities, reticulation, consolidation, nodular shadow, emphysema and bronchiectasis were according to the terms of pulmonary HRCT imaging defined by Fleischner Commission on Nomenclature. 6 CTD-ILDs were grouped into three patterns according to the ATS/ERS consensus classification: usual interstitial pneumonia (UIP), fibrotic non-specific interstitial pneumonia (NSIP) and indeterminate (lack of characteristic, mixed pattern or difficult to specify).

Lung samples were obtained by CT guided percutaneous transthoracic biopsy. Samples were sliced into 4µm pieces after being fixed with alcohol solution and paraffin embedding, then underwent hematoxylin and eosin staining and observed under a microscopy. Several special staining was employed for observation of specific substances: Masson staining for accumulation of collagen; PAS and gomori methenamine silver staining for fungus; acid-fast staining for fungus and acid-fast bacilli. All ILD lung samples were divided into histopathology subtypes according to 2002 ERS consensus classification.

Statistical analysis were performed using SPSS software (SPSS for windows, Release 13). The Kolmogorov-Smirnov test was used to check the goodness of fit. The enumeration data were described by constituent ratio and proportion detected by χ^2 test, Fisher exact method and Rank test. The enumeration data were expressed as means±SD when subject to the normal distribution and comparisons between groups were tested by One Way ANOVA. The data were summarized as median and interquartile range when not subject to the normal distribution and comparisons between groups were tested by Kruskal-Wallis Test. A p-value<0.05 was considered significant in all cases.

Results

325 ILD patients were diagnosed by HRCT from 2320 CTD patients and the general incidence rate was 14%, the incidence rate of SSc-ILD was high up to 59.3% and the rates for other CTDs were listed below: DM-ILD, 53.2%; PM-ILD, 42.2%; pSS-ILD, 16.9%; RA-ILD, 9.9% and SLE-ILD, 4.5%. 78.5% of CTD presented before ILD. SSc-ILD was the most common ILD in this situation; 15.7% of CTD presented at the same time as that of ILD and most of those patients were DM-ILD; 5.8% of CTD appeared after diagnosis of ILD and in this sequence, SLE-ILD was the most common one. There were statistically significant differences among any of those groups ($p<0.001$) (table 1).

Imaging characteristics and subtypes of chest HRCT

Unenhanced HRCT images of 325 CTD-ILD patients showed that more than two imaging features coexisted in individual patients and each types of CTD had specific imaging features. For example, honeycombing features were common in SSc/RA-ILD but rarely appeared in SLE-ILD; reticulation was common in DM/SSc/RA-ILD but rarely SLE-ILD; consolidation was more common in PM/SLE-ILD but rarely appeared in SSc-ILD. There were statistically significant differences in comparison of those three imaging features mentioned above among those different CTDs. 325 CTD-ILD patients can be divided into three subtypes based on their imaging patterns: 76 patients with UIP, 121 patients with NSIP and 128 patients with indeterminate (table 2). The UIP and NSIP subtypes were mainly observed in SSc-ILD while few SLE/PM-ILD patients presented the UIP and NSIP patterns.

Correlation of histopathology with CTD-ILDs

47 out of 325 CTD-ILD patients underwent CT guided lung biopsy and 43 of them were diagnosed of CTD-ILD based on the histopathology result. In line with ATS-ERS subtypes criteria: 20 patients had NSIP, 20 patients had UIP and 3 patients had indeterminate (coexist of inflammation and fibrosis, lack of characteristics or mixed patterns or difficult to specify). NSIP were more frequently associate with DM-ILD and UIP were more common in SSc-ILD but there was no statistical difference. Four CTD patients suspected having ILDs by HRCT were confirmed subsequently having other lung diseases: 1 tuberculosis, 1 rorulosis, 1 tuberculosis atypical adenomatous hyperplasia and 1 congenital cystic adenomatoid malformation of the lung.

Correlation of HRCT with histopathology patterns

The results of the matching analysis of HRCT features and histopathology of these 43 patients shown that: 17 patients were diagnosed with NSIP by HRCT out of the 20 patients diagnosed by histopathology and the other 3 patients were diagnosed with UIP; in the 20 patients with confirmed UIP by histopathology were also mainly diagnosed UIP by HRCT previously (14 UIP, 4 NSIP, 2 indeterminate). There were no significantly statistical difference between these two diagnosis methods in diagnosis of those patients ($p=1.00$). These two methods were in good agreement with linear correlation coefficient by Kappa Concordance Test and have significantly statistical difference ($\kappa =0.63$, $p =0.00$) (table 3). The result indicated that the ILD histopathology pattern could be deduced from HRCT features in clinical practice without lung biopsy.

CTD-ILD	Ground grass opacity (%)	reticulation(%)	honeycombing (%)	consolidation (%)	fiberopticcable (%)	thickening of interlobular septa (%)	Small lung nodules (%)
DM	35.6	42.4*	22	50.8	32.2	45.8	25.4
PM	24.0	16.0	12.0	76.0*	32.0	48.0	4.0
pSS	27.6	22.4	19	41.4	36.2	24.1	22.4
RA	23.8	42.9*	34.9*	44.4	33.3	39.7	15.9
SLE	21.3	8.5	6.4	78.7*	40.4	42.6	17
SSc	32.9	50.7*	32.9*	28.8	30.1	50.7	13.7
p	0.506	<0.001	0.002	<0.001	0.899	0.057	0.184

Table 1: Comparison of HRCT Characteristics of Different CTD-ILD (%)

* there are statistically difference comparing other groups

	NSIP (N=121)	UIP(N=76)	Indeterminate (N=128)
DM	23(19%)	13(17.1%)	23(18%)
PM	11(9.1%)*	4(5.3%)*	10(7.8%)
pSS	20(16.5%)	11(14.5%)	27(21.1%)
RA	19(15.7%)	22(28.9%)	22(17.2%)
SLE	16(13.2%)	3(3.9%)*	28(21.9%)
SSc	32(26.4%)*	23(30.3%)*	18(14.1%)

Table 2: Correlation of HRCT Subtypes and CTD-ILDs.

In different CTDs, NSIP diagnosed by HRCT were mostly seen in SSc and seldom seen in PM, UIP diagnosed by HRCT were also mostly seen in SSc and seldom seen in SLE, there are statistically significant difference comparing these groups ($P=0.006$).

	NSIP diagnosed by histopathology (N=20)	UIP diagnosed by histopathology (N=20)	P
NSIP diagnosed by HRCT	17	4	1.00#
UIP diagnosed by HRCT	3	14	
Indeterminate diagnosed by HRCT	0	2	
Ground grass opacity	12(60%)	7(35%)	0.113
Honeycombing	4(20%)	13(65%)	0.004
SSc	3(15%)	7(35%)	0.144

Table3: Correlation of HRCT and Histopathology Patterns.

$P=1.00$ there are no significant statistical different between these two diagnostic methods. Applying of Kappa Concordance Test shown that these two methods are in good agreement with linear correlation coefficient and have significant statistical difference ($k=0.630$, $P=0.000$) the coincidence is of the ordinary probability distribution ($0.7 > k \geq 0.4$).

Discussion

Lung and pleura are the most common organs involved in CTDs. The involvement of respiratory system is an indicator for significant poor prognosis, therefore it is crucial to early diagnosis and manage those patients.⁷ According to literatures, the general incident rate of CTD-ILD is 15%^{8, 9} but the incident rate of ILD caused by different CTDs is different. Our data showed that the general incident rate

of CTD-ILD is 15%^{8, 9} but the incident rate of ILD caused by different CTDs is different. Our data showed that the general incident rate of CTD-ILD was 14% with SSc-ILD the highest (59.3%), and SLE-ILD the lowest (4.5%). This difference may be due to the different pathogenesis patterns of the primary disease. The basic pathological change of SSc is activation of fibroblasts while SLE is mainly inflammatory exudation. Fibrosis is seldom occurred in SLE. Due to the varieties of pathologic changes of ILDs caused by different CTDs, the imaging features of ILDs are also varied as well as their therapeutic response and prognosis. For example, treatment of UIP should give priority to anti-fibrosis as fibrosis is the main pathogenesis in UIP and the glucocorticoid steroids and immune-suppressors has less value in treatment of UIP. It is thought that ground glass opacity/consolidation changes in HRCT images are caused by exudations which have good therapeutic response to glucocorticoid treatment [10,11]. Therefore, it is important in clinical practice to select the correct treatment based on different histopathology patterns.

A non-invasive diagnostic method could be used to deduce the histopathology pattern and to avoid invasive lung biopsy and its possible complications. Some literature reported that there might have some relation between HRCT imaging appearances and histopathology patterns, therefore CT findings could be used to diagnosis of UIP without pathologic diagnosis.¹² For example, the characteristic of honeycombing in HRCT, a manifestation of pleural incarcination thickening of interlobular septa caused by fibrosis, and mainly belongs to UIP. On the other hand, the characteristics of ground grass opacity and consolidation mainly belongs to NSIP, those are respectively caused by edema and infiltration of inflammatory cells in pulmonary alveoli or exudation of cells filled in pulmonary alveoli.

This study divided the 325 CTD-ILD patients into three subtypes by the different appearances on HRCT images according to the revised classification of idiopathic interstitial pneumonia. The results shown that ground grass opacity was mainly observed in NSIP and reticulation and honeycombing were mainly in UIP, which was consistent with the results as reported by others; we also found that characteristics of HRCT was varied among different CTD-ILDs, for instance, honeycombing and reticulation were more common in SSc/RA-ILD on HRCT imagers. Imaging features on DM-ILD patients were likely to associate with reticulation. Consolidation was more common in PM/SLE-ILD. Imaging findings of pSS-ILD patients were usually nonspecific. The further analysis of imaging features shown that UIP and NSIP subtypes were mainly observed in patients with SSc-ILD and very rarely appeared in patients with SLE/PM-ILD.

These results indicated that the pathology process form the basis for the characteristics and subtypes of HRCT images and further provide the foundation for selection of treatment.

Irreversible fibrosis in patients with ILDs can be prevented by glucocorticoid steroids and immune-suppressors therapy during the early phase of inflammatory cells infiltration. But, those drugs don't work in UIP because the histopathology of UIP is mainly fibrosis, not inflammation. As the histopathology pattern is a key for patients' treatments, it would be a great value that the CTD-ILD histopathology pattern can be deduced from HRCT imaging analysis to void lung biopsy and its complications. Therefore, we have matched imaging features on HRCT and histopathology patterns of CTC-ILD patients using the result from of lung biopsy. In this study, 43 patients with ILD were identified by lung biopsy. Among those, 20 patients had diagnosis of NSIP. 17 patients of the 20 patients could be diagnosed by HRCT alone making the HRCT diagnosis rate of HRCT 80%. This result shown that HRCT had a good agreement with the histopathology result ($p=0.000$), therefore, histopathology patterns could be deduced from HRCT features of some patients. This could be a great value to avoid lung biopsy and a greater value for patients who are contraindicated for lung biopsy. Furthermore, correct medications could be selected based on appearances on images without lung biopsy.

previous studies and indicated that ANNs may be helpful for readers with limited clinical experience [7, 8,15]. It could be reasonably suggested that the ANN would help clinicians with less clinical experience in recognition of significant PET/CT features of recurrent NPC by alerting them to reconsider certain diagnostic features through careful interpretation of radiological features, arriving at a correct diagnosis (Table 2). One the other hand, while our result suggested that ANN was helpful for readers with limited clinical experience, we believed that further study is required to determine the usefulness of ANN in the evaluation of recurrent NPC based on PET/CT images for radiologists with different levels of experience.

This study also suggested that ILD was one of adverse outcomes of the progression of the CTD. Most patients with ILD had no symptoms to suggest ILD when their CTD symptom appeared: 78.5% of patients with ILD developed symptoms long time after diagnosis of CTD, 15.7% of patients with ILD had symptoms at the same time when CTD was diagnosed. Missing diagnosis of ILD could happen if frequently HRCT follow-up was not performed. Only 5.8% of patients with ILD had symptoms before the diagnosis of CTD. Those patients might be easily to be misdiagnosed as IPF. In this study, 47 out of 325 patients with CTD-ILD had CT guided percutaneous transthoracic biopsy and 43 of them were diagnosed with CTD-ILD according to the histopathology results but there was no statistical significance of the histopathology patterns among different CTDs and this might be due to the small number of the samples. The rest 4 CTD patients who initially thought to have ILDs by their HRCT were subsequently confirmed to have other lung diseases indicated the value of CT guided percutaneous transthoracic biopsy in rule out a small percentage of patients who had other than ILDs.

In conclusion, though the incident rates, clinical characteristics and imaging featurers of ILDs are different in different CTDs, HRCT is the most effective modality in diagnosis CTD-ILD and also images features of HRCT correlate very well with the histopathology diagnosis. Therefore, HRCT might be used to diagnosis of those patients with lung biopsy, though further multiple center investigation is needed.

In this study, the ANN was developed with 21 radiological features without any clinical parameters as input data. To further enhance the practical application of this diagnostic model in the future, some useful clinical data, such as infection of Epstein-Barr virus (EBV), stage of primary NPC and dietary habits, could be included as input data. Higher diagnostic performance of the ANNs obtained with a combination of clinical parameters and radiological findings as input data was reported by previous studies [15, 18]. It is therefore expected that with the combination of clinical parameters and radiological features as input data, the performance of the diagnostic model can be further enhanced for practical use. Although the number of cases for our study was quite limited, our attempt to construct a computer-aided diagnostic scheme using ANNs that was proven to be useful.

Conclusion

ANNs showed a high performance in evaluation of recurrent NPC based on 18F-FDG PET/CT images. Its outputs can provide a second opinion to improve the accuracy and efficiency for clinicians in diagnosis. In addition, we have established a diagnostic model based on CAD for evaluation of recurrent NPC based on 18F-FDG PET/CT images.

Competing Interests

The authors have no competing interests with the work presented in this manuscript.

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