Characterization of CT scan in Birt-Hogg-Dubé syndrome compared with non-BHD diffuse cysts lung diseases in Chinese Patients

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Research

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Abstract

Background and objective: The purpose of this study was to create a practical CT-based algorithm to differentiate Birt-Hogg-Dubé (BHD) syndrome from other diffuse cystic lung diseases (DCLD).

Methods: The study was a retrospective review of the CT images of 18 patients with BHD syndrome, 18 patients with LAM, and 16 patients with NBNL (non-BHD and non-LAM) DCLD patients. On the basis of the data collected, the CT images were reviewed again to evaluate the characteristics (size, number, distribution, morphology) of pulmonary cysts.

Results: Lower lung–predominant cysts were prone to be found in patients with BHD syndrome than in patients with LAM, but there is no difference between BHD and NBNL DCLD group. In the axial distribution, 9 of 18 patients in BHD-group had cysts predominance near the mediastinum, relatively, all the patients in the non-BHD group have diffuse cysts. The appearance of fusiform cysts was easier observed in patients of BHD group. Most patients in BHD-group had less than 50 lung cysts, while all patients in non-BHD group had more than 50 lung cysts. The maximum cyst located in the lower lobe in 16 of 18 patients in BHD-group, while 6 of 18 patients in LAM group and 8 patients in NBNL DCLD group had the maximum cyst in the lower lobe.

Conclusion: The pulmonary cysts in patients with BHD tend to be fusiform, less numerous, and have a predominance in the lower lobe and near the mediastinum. These radiologic pulmonary features could assist physicians differentiating BHD from other DCLDs.

Introduction:

Birt-Hogg-Dubé syndrome (BHD) is a rare autosomal dominant disorder manifested by multiple pulmonary cysts by recurrent pneumothorax, fibrofolliculomas, and renal tumors. BHD is caused by germline mutation in the folliculin (FLCN) gene on chromosome 17p11.2 (1), a tumor suppressor gene known to be involved in the signaling of mammalian target of rapamycin (mTOR). Reports and characterization of BHD in Chinese are rare (2).

Pulmonary cysts have been described in most patients with BHD, and pneumothorax has a 33%-38% incidence to happen among them (3). Lung involvement is often the earliest phenotypical manifestation to appear, most affected patients are asymptomatic (4, 5).Though previous research has demonstrated the difference between BHD and lymphangioleiomyomatosis (LAM) (6), BHD needs to be distinguished from other conditions associated with diffuse cysts lung diseases (DCLD) including LAM, Langerhans cell histiocytosis (LCH), lymphocytic interstitial pneumonitis (LIP), et al. Computed tomography (CT) gives us an intuitive manner to observe the cyst distribution and properties in thorax. In BHDs, cysts are typically located in the lower lung regions, bilaterally. Some researchers concluded the chest CT findings of patients with BHD syndrome were multiple thin-walled pulmonary cysts of various sizes, predominantly distributed to and sub-pleural regions of the lung. However, no studies concluded the

statistical significance of the thoracic CT findings of lung cysts characteristics in BHD compared with other DCLDs in China.

The purposes of this study were to quantify pulmonary cysts in CT of patients with BHD and to identify the independent parameters that help us to diagnose BHD syndrome from non-BHD DCLDs, which will decrease the misdiagnosis and under-diagnosis of DCLD.

Methods:

Study population

This single-center, retrospective, observational study received institutional review board approval. Patients' confidentiality was strictly maintained. We searched the computerized medical record system for patients with diagnosis of DCLD at Peking Union Medical College Hospital from January 2014 to February 2017. However, those patients who had pneumothorax and chylothorax on CT scans were excluded. Eighteen cases of BHD syndrome, eighteen cases of LAM, and sixteen cases of other DCLD were enrolled in this study. Patients with BHD syndrome were all diagnosed by genetic testing. Sixteen BHD patients were reported in our previous study(7), the remaining two patients were their relatives, also diagnosed by genetic testing. Given that the relative high incidence of LAM and to avoid the selection bias of the control group, we randomly selected 18 cases using random number table method from 108 patients with definite LAM in the DCLD cohort at Peking Union Medical College Hospital during the same period as BHD patients. We selected all the non-BHD and non-LAM (NBNL) patients who have definite diagnosis in the same period and got 16 NBNL DCLD patients. The diagnosis of LAM is based on the American Thoracic Society/Japanese Respiratory Society Clinical Practice Guideline (8). Other etiologies of DCLDs include 12 cases of sjögren syndrome (SS) related DCLD, 2 cases of pulmonary LCH (PLCH), 1 case with LCH and 1 case of Castleman’s Disease. Other DCLD were diagnosed by pulmonary physicians according to the clinical review of DCLD published in Am J RespirCrit Care Med, 2015(9, 10).

CT scan analysis of BHD & Control

For 39 of 52 patients (75%), high resolution CT scans of the chest were available, with a slice thickness of 3 mm or less. For the remaining 13 patients (25%), CT scans were available, with a slice thickness of 4–5 mm. All CT images were evaluated by two pulmonologists (WX and ZX) and one radiologist separately (XS). The pulmonary cyst was defined as an air-filled space with a sharply demarcated thin wall. The total number of lung cysts in each patient was assessed as few if there were fewer than 10 cysts, several for 10–20, numerous for 20–50, or abundant if there were more than 50 cysts. This kind of stratification will change the continuous variables into categorical variables, and decrease the uncertainty as much as possible. Cyst distribution was classified for both cranial-caudal distribution (as upper lung predominant, lower lung predominant or diffuse) and axial distribution (as near peripheral pleura, near mediastinum, or diffuse), the predominance was defined as more than 50% of cysts (11). The special fusiform shape of cysts was noted in all CT scans. The size and craniocaudal distribution of the biggest pulmonary cyst were also recorded in both BHD and non-BHD patients.

Statistical method

Data were analyzed using SPSS for Windows version 24.0 (IBM Corp., USA) and are reported as the mean ± SD or IQR (interquartile range). The unpaired t-test or Mann-Whitney U-test was used to compare continuous variables. Categorical variables were compared using Fisher's exact test. For all analyses, two-sided tests and a significance level of 0.05 was used.

Results:

Demographic features of all patients

Comparison of gender ratio, age of diagnosis, smoking history, pneumothorax and family history were listed in Table 1. All patients from different families were of Chinese Han origin. Female was predominant in all group. Compared with NBNL group, patients with BHD syndrome were more likely to have past medical histories of pneumothoraces (p = 0.003), but there is no difference between BHD and LAM (BHD 10/18 [55.6%] vs LAM 9/18 [50%], p = 1.000). Significant difference was noted in family history of pneumothoraces between BHD and either LAM or NBNL group. Smoking history has no significant difference between BHD and either LAM or NBNL group. (Table 1)

Table 1
Demographic features of the BHDs and non-BHD groups

Characteristic	BHD	LAM	NBNL DCLD§	P*	P**
	N = 18	N = 18	N = 16		
Female, N (%)	17 (94.4)	18(100)	13 (81.3)	1.000	0.323
Age of Diagnosis, Mean ± SD	48 ± 12	36 ± 9	41 ± 14	0.001	0.131
PMH of PTX, N (%)	10 (55.6)	9 (50)	1 (6.3)	1.000	0.003
Smoking history, N (%)	1 (5.6)	0 (0)	4 (25)	1.000	0.164
Family history, N (%)	16 (88.9)	0 (0)	0 (0)	< 0.001	< 0.001
*P values are for comparison between BHD and LAM group.					
**P values are for comparison between BHD and NBNL DCLD group.					
§NBNL (no-BHD and no-LAM) DCLD group includes 12 cases of lymphocytic interstitial pneumonia associated with sjögren syndrome (SS), 2 cases of pulmonary Langerhans cell histiocytosis (PLCH), 1 case with Langerhans cell histiocytosis (LCH) and 1 case of Castleman Disease.					
The P value was calculated with the use of the unpaired t-test for compare continuous variables.					
The P value was calculated with the use of Fisher's exact test for categorical variables.					
Abbreviations: BHD: Birt-Hogg-Dubé syndrome, DCLD: diffuse cystic lung disease, PMH: past medical history, PTX: pneumothorax. NBNL: no-BHD and no-LAM; SD: standard deviation.					

Radiologically feature of pulmonary cysts in BHD and non-BHD

Cysts were bilateral in all patients. Lower lung–predominant cysts were prone to be found in patients with BHD syndrome (56% of patients) than in patients with LAM (none of patients), who were more likely to have diffuse cysts. Significant difference was also found in the axial distribution of pulmonary cysts. All cysts were diffuse in the non-BHD group, 9 of 18 patients (50%) in BHD-group had cysts predominance near the mediastinum ($p = 0.001$).

The morphology of the pulmonary cysts was variable within individual patients. The appearance of fusiform cysts was observed in 13 patients of BHD group (72%), only 5 cases were observed fusiform cysts in LAM group (28%, $p = 0.018$) and 5 patients in NBNL group (31%, $p = 0.037$).

In terms of the number of cysts, most patients in BHD-group have less than 50 lung cysts (89%), while all patients in LAM group and 75% patients in NBNL group had more than 50 lung cysts ($p < 0.001$).

The distribution of the maximum cyst was different. The maximum cyst located in the lower lobe in 16 of 18 patients (89%) in BHD-group, while 6 of 18 patients (33%) in LAM group and 8 patients (50%) in NBNL group had the maximum cyst in the lower lobe. When comparing the diameter of maximum cysts

between patients in two groups, the median length was 40 mm in the BHD-group, and 16.5 mm in LAM group. Significant difference in the distribution of the diameter of maximum cysts were noted between BHD and LAM groups ($p < 0.001$), but no difference between BHD and NBNL group ($p = 0.545$). Table 2.

Table 2
Radiologically characteristic of pulmonary cysts in BHD and non-BHD

Characteristic	BHD N = 18	LAM N = 18	NBNL DCLD N = 16	P*	P**
Cranial-caudal distribution					
Upper lung, N (%)	2 (11)	0 (0)	2 (12)	0.486	1.000
Lower lung, N (%)	10 (56)	0 (0)	6 (38)	< 0.001	0.327
Diffuse, N (%)	6 (33)	18 (100)	8 (50)	< 0.001	0.487
Axial distribution					
Mediastinum, N (%)	9 (50)	0 (0)	0 (0)	0.001	0.001
Peripheral pleural, N (%)	2 (11)	0 (0)	0 (0)	0.486	0.487
Diffuse, N (%)	7 (39)	18 (100)	16 (100)	< 0.001	< 0.001
Fusiform Cysts, N (%)	13 (72)	5 (28)	4 (25)	0.018	0.015
No. of Lung Cysts					
10, N (%)	2 (11)	0 (0)	0 (0)	0.486	0.487
10–20, N (%)	3 (17)	0 (0)	0 (0)	0.229	0.230
20–50, N (%)	11 (61)	0 (0)	4 (25)	< 0.001	0.045
50, N (%)	2 (11)	18 (100)	12 (75)	< 0.001	< 0.001
Maximum Cyst					
Lower lung, N (%)	16 (89)	6 (33)	8 (50)	0.002	0.023
Diameter of Max cyst,IQR	40(30, 50)	16.5(10,20)	37(23,50)	< 0.001	0.545
*P values are for comparison between BHD and LAM group.					
**P values are for comparison between BHD and NBNL DCLD group.					
The P value was calculated with the use of Fisher's exact test for categorical variables.					
The P value was calculated with the use of the Wilcoxon rank-sum test for compare continuous variables.					

Discussion:

This is a retrospective study focusing on the thoracic CT findings of lung cysts characteristics in BHD compared with other DCLD in Chinese. We used quantified methods to confirm that the pulmonary cysts in patients with BHD tend to be fusiform, less numerous, and have a predominance in the lower lobe and near the mediastinum compared with other DCLD.

BHD was always confused with other kinds of DCLD in clinic not only because of its low prevalence but its low awareness as well. Most of our BHD patients were referred to our hospital because of suspected as other kinds of DCLD, such as LAM since our clinic is the largest LAM/TSC centre in China. Among the patients with BHD, almost half of patients were misdiagnosed with primary spontaneous pneumothorax. The longest misdiagnosis duration for patients with BHD was 38 years. The average misdiagnosis delay for patients with BHD was 7.73 years. Extra-pulmonary abnormalities including kidney and skin manifestations are rare in Chinese (7) compared with Caucasians, and respiratory symptom may be the only symptom observed in Chinese BHD patients. So, it is important to recognize the radiologic features of lung in BHD and to differentiate from other diffuse cystic lung diseases. Some researchers believed that pulmonary cysts predominantly localizing the medial and lower zones in BHD compared with other DCLD, nevertheless, the majority of which were based on experiences from specialists (10, 12, 13).

Abundant studies focused on the descriptive characteristics of pulmonary cyst of BHD, whereas, statistical comparison of the lung cysts between BHD and other DCLDs were rare. Tobino and colleagues made a quantitative analysis of pulmonary cysts on CT between BHD and LAM(6). They found that compared with patients with LAM, the cysts in BHD patients had a more irregular shape, more septation, lower and more peripheral distribution, larger maximum size, and more attachment to the pleura. As we all know, it’s not too difficult to differentiate BHD from LAM as the later has more homogeneous cysts compared with BHD. Whether or not the characteristics of pulmonary image of BHD will be different from that of NBNL patients is not determined. In our study, for the first time, we are trying to distinguish BHD from other kinds of NBNL group based on digitalized radiologic pulmonary feature. We verified the speculation suspected by the previous study(6) that the cysts in BHD patients had a more irregular shape, more septation, lower and more peripheral distribution, and larger maximum size compared with LAM. Meanwhile, we also found that NBNL DCLDs have the similar morphology and distribution, and have less fusiform, peripheral, and para-mediastinal cysts. Those findings are consistent with the prior study, which reported that compared with patients with LIP or LAM, patients with BHD syndrome were significantly more likely to have elliptical (floppy) para-mediastinal cysts or a disproportionate number of para-mediastinal cysts(14). Our study also found that compared with patients with NBNL DCLDs or LAM, patients with BHD syndrome have less cysts ,the cysts in most of patients range from 20 to 50, and the largest cyst often located in lower lobe. Therefore, pulmonary cysts in BHD has specific radiologic feature that can different from other kind of DCLDs. However, we found that BHD and NBNL DCLDs have the similar diameters of largest cyst, and both are bigger than the diameters of largest cyst in LAM. As the result, the diameters of largest cyst could not be used to distinguish BHD from NBNL DCLDs.

The pathogenesis of lung cysts distribution is still unknown. There were hypothesises explaining it from the effect of the mutation in FLCN on the epithelial layer at the inside of the pleural cysts. The down-

regulation of folliculin was followed by increased cell-cell adhesion(15). It is much more likely to believe that the development and recurrence of pneumothorax in BHD is related to the lack of epithelial layers to stretch, but a therapeutic study is needed(16).

Our study may have several limitations. First, the number of patients with BHD included is relatively small. Second, three-dimensional reconstruction of lung cysts is hard to achieve, the number and distribution of cysts were observed in the horizontal direction, causing some deviation in the data collection. However, two professional respiratory physicians and one radiologist worked independently and in random order to assess the thoracic CT results in patients to decrease the possible counting deviation.

Conclusion:

In conclusion, our study provides an evidence that fusiform para-mediastinal cysts of various sizes with bilateral lower lung zone predominance, and number of lung cysts less than 50 are characteristic CT findings to distinguish BHD from other cystic lung diseases, making it possible to take a detailed evaluation of pulmonary cysts on thoracic thin-section CT. Molecular analysis of FLCN gene should be systematically conducted in patients with cystic lung diseases in such cases.

Declarations

Ethics approval and consent to participate

The study was part of LAM registry study of Peking Union Medical College Hospital. The protocol of this study was approved by the Ethical Committee of Peking Union Medical College Hospital. All subjects included in this study signed informed consent documents.

Consent for publication

Consent for publication was obtained from all participants.

Availability of data and materials

The datasets used and analysed during the current study area available from the corresponding author.

Competing interests

No competing interests were declared.

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Authors contributions

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Xue Zhang: study design

Kai-Feng Xu: study design

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Figures

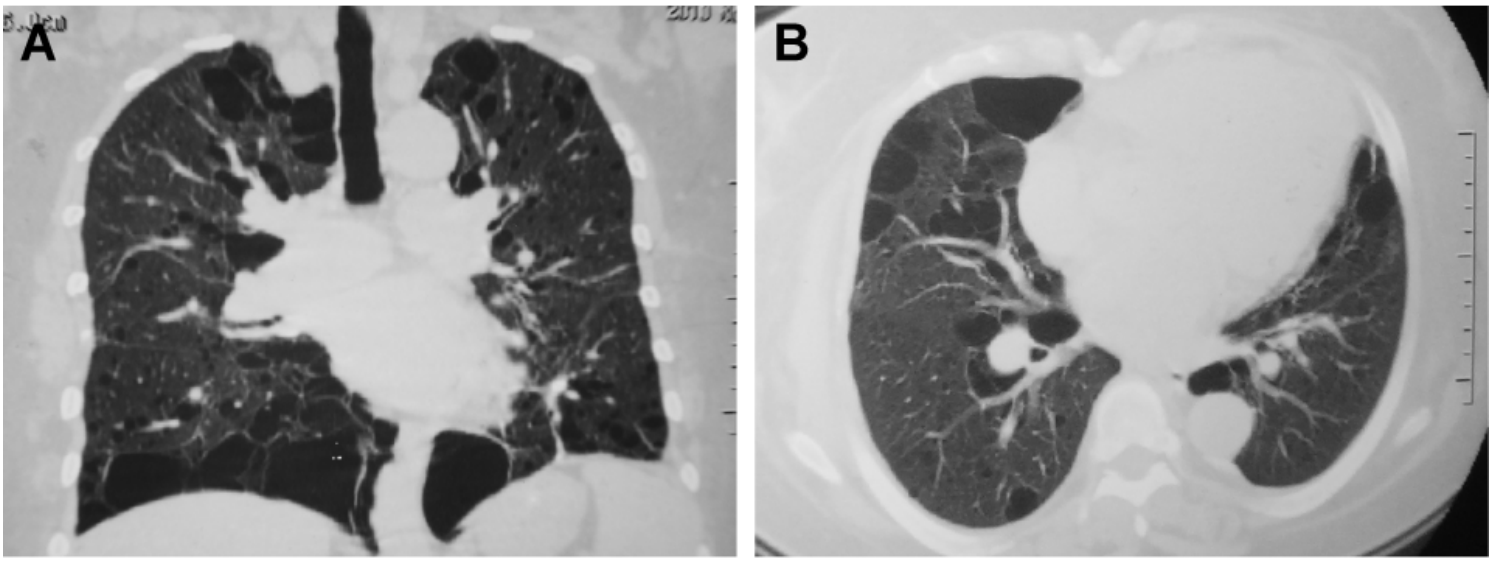

Figure 1

Thoracic CT findings of patients with BHD A: Coronal reformatted image of high-resolution chest CT images show lower lung predominant, para-mediastinal, and fusiform cysts in BHDs; B: Axial high-resolution chest CT images through lower lungs

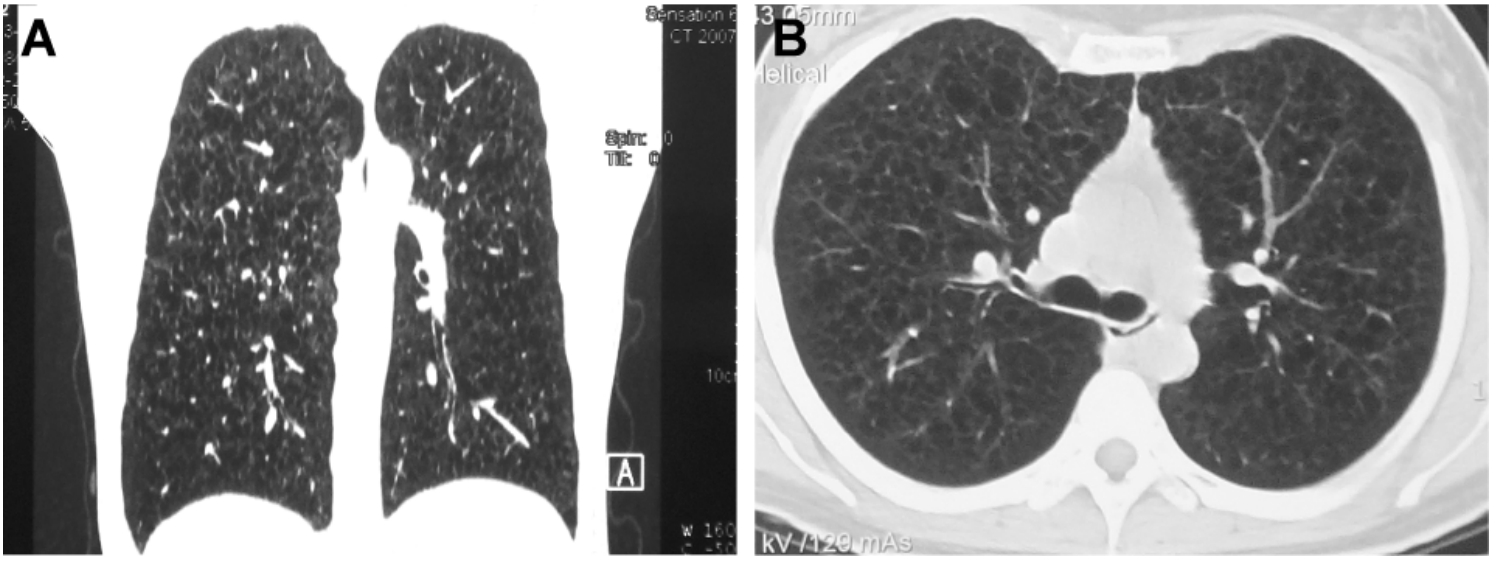

Figure 2

Thoracic CT findings of patients with LAM A: Coronal reformatted image of high-resolution chest CT images in a patient with LAM shows diffuse cysts; B: Axial high-resolution chest CT images through upper lungs

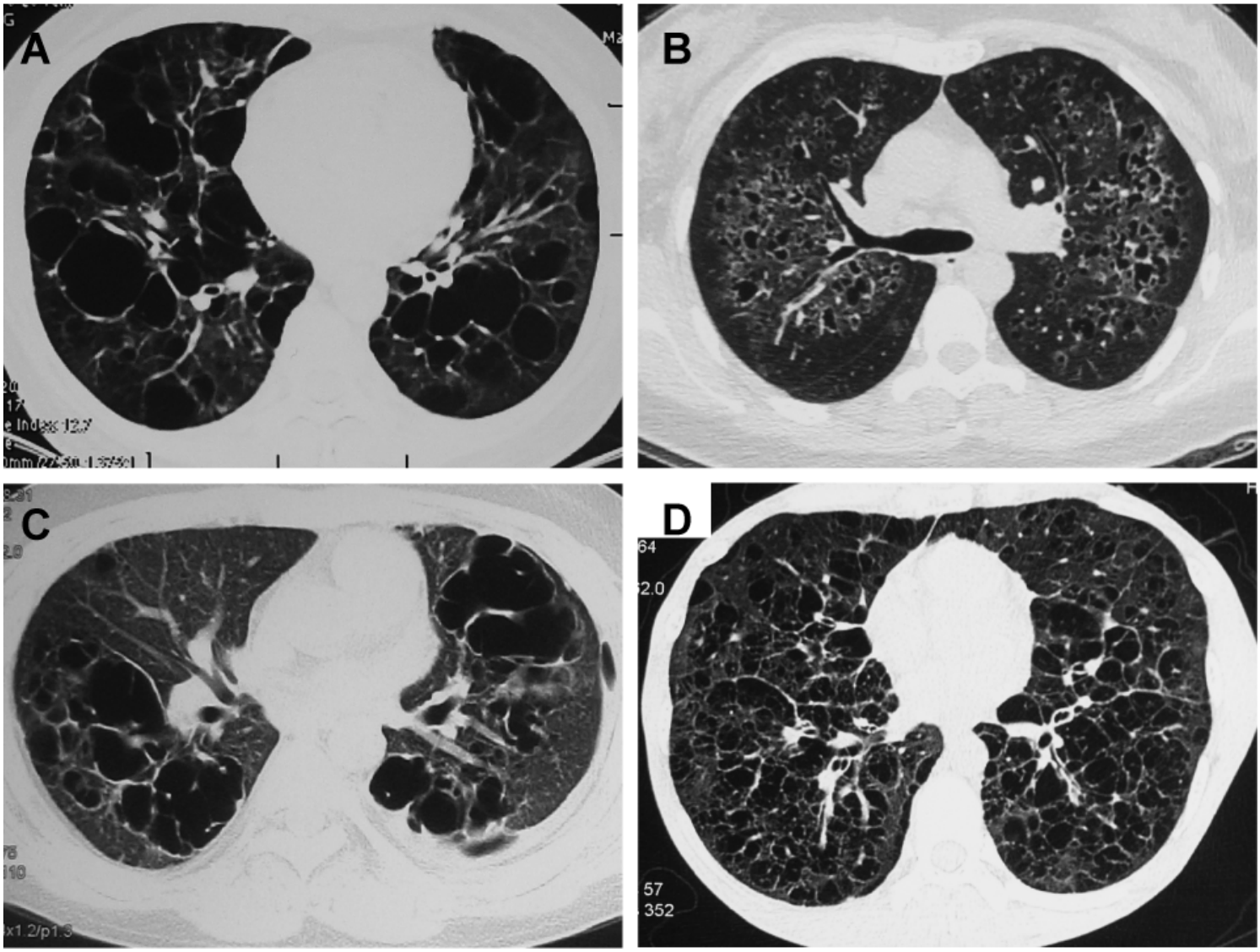

Figure 3

Thoracic CT findings of patients with non-BHD and non-LAM (NBNL) DCLDs A: CT images of patients with sjögren's syndrome; B: CT images of patients with Pulmonary Langerhans Cell Histiocytosis; C: CT images of patients with Langerhans Cell Histiocytosis; D: CT images of patients with Castleman’s disease.