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ORIGINAL INVESTIGATION

Use of High-Resolution Computed Tomography (HRCT) in Diagnosis of Sputum Negative Pulmonary Tuberculosis

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Abstract

OBJECTIVES: To study the role of high-resolution computed tomography (HRCT) in the diagnosis of pulmonary tuberculosis (PTB) in sputum smear negative patients and to design HRCT criterion to forecast the threat of pulmonary tuberculosis.

MATERIAL AND METHODS: We studied 69 patients having sputum smear negative for acid-fast bacilli (AFB) but still with clinical suspicion of PTB after taking written informed consent. We studied their medical characteristics, numerous separate HRCT-results and combination of HRCT findings to foresee the danger for PTB by utilizing univariate and multivariate investigation. Temporary HRCT diagnostic criteria were planned in view of these outcomes to find out the risk of PTB and tested these criteria on our patients.

RESULTS: Chronic cough and night sweats were highly linked to a greater risk of PTB among clinical features. On HRCT chest presence of cavity, centrilobular nodules, consolidation, ground glass opacity (GGO), lymphadenopathy, main lesion in S1, S2, S6, lobular consolidation, other minute nodules and tree in bud appearance was significantly linked to an elevated risk of PTB in linear regression analysis. While cavity, centrilobular nodules, interlobular septal thickening, pleural effusion and tree-in-bud appearance was significantly linked to a greater threat of PTB in multivariate regression analysis. Positioning of the patients utilizing our HRCT indicative criteria uncovered reliable sensitivity and specificity for PTB patients determining that HRCT is a useful tool in sputum negative PTB patients.

CONCLUSION: HRCT is useful in selecting individuals with greater chances of PTB in the sputum smear-negative setting.

KEYWORDS: Tuberculosis pulmonary, tomography, sputum

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INTRODUCTION

Tuberculosis is one of the oldest ailments having an impact on humankind, and is a noteworthy reason for mortality around the world. Causative agent of tuberculosis is *Mycobacterium tuberculosis* complex, and mostly influences the lungs. Other organs are affected in up to 33% of cases. Drug susceptible tuberculosis is curable in essentially all cases. In the event that it is left untreated, the malady may be deadly within a timespan of 5 years in 50-65% of cases [1]. Prevalence of tuberculosis in India was 2.6 million in 2013 [2]. The successful treatment of pulmonary tuberculosis (PTB) involves making an accurate diagnosis and starting timely anti-tuberculosis medications. In clinical practice, tuberculosis (TB) is treated based on patient symptoms, chest radiography (CXR) abnormalities and sputum bacteriological examination. Sputum smear test can find acid-fast bacilli (AFB) in almost 50-60% of cases of pulmonary tuberculosis [3]. Sadly, in some cases of current active pulmonary TB, neither bacteriological examination nor serial CXR unequivocally demonstrates the activity of disease. Such Patients (smear-negative TB patients) are although at a lesser risk of spreading the disease than the smear-positive patients, but still able to transmit the disease or infection. The relative transmission rate of smear-negative TB patients in contrast to smear-positive TB patients has been ascertained at 22% utilizing a molecular epidemiologic method [4]. A large portion of all patients (almost 50%) with TB can have negative sputum smear results, as a result of which the total contribution of smear-negative TB patients to the transmission of the disease is notable. Polymerase chain response (PCR) can quickly analyze sputum samples, however sensitivity is low [5]. As a result, clinicians often hesitate in starting anti-tuberculosis treatment for fear of the

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potential side-effects of anti-tuberculosis drugs. Then again, to confine the cost and potential hazards of empiric treatment correct identification of individualswho are unlikely to have TB is important as well. High Resolution Computed Tomography (HRCT) has been discovered to be more sensitive than chest x-ray in the identification of small exudative lesions, slight or occult parenchymal disease and in assessing disease activity in pulmonary TB. Moreover, sputum culture reports in sputum smear negative patients takes upto 6 to 8 weeks posing a clinical dilemma of whether to treat or not. Liquid culture methods and nucleic acid amplication methods like GeneXpert MTB/RIF (*Mycobacterium tuberculosis*/resistance to rifampicin) assay are costly and not widely available yet. In such situations, HRCT can help in providing provisional diagnosis of tuberculosis so that empirical therapy may be started and on the other hand selecting patients unlikely to have tuberculosis.

In this study, we investigated the function of a high resolution computed tomography (HRCT) scan of the thorax in the analysis of PTB in sputum smear-negative patients. We also designed criteria based on a mixture of HRCT findings to determine the threat of pulmonary tuberculosis.

MATERIAL AND METHODS

A protocol for study was constructed and approval taken from ethical board of our establishment. Permission in writing was taken from all patients. We studied 69 patients over a period of one year from June 2013 to May 2014 with suspicion of pulmonary tuberculosis taking into account the vicinity of one or a greater amount of the following symptoms: cough of at least 2 weeks or more; hemoptysis, constitutional symptoms such as loss of weight, fever, or night sweating with chest radiograph suggestive of tuberculosis. All patients had two consecutive sputum smears negative for acid fast bacilli (AFB) or they were unable to produce sputum after multiple attempts. The sputum samples were collected as per Revised National Tuberculosis control Program (RNTCP) norm and all sputum samples were sent for direct smear examination using Zeihl-Neelsen Stain. We excluded the patients who were sputum smear positive, pediatric patients and patients with only extra-pulmonary involvement.

Brief history was recorded including cough, hemoptysis, fever, decrease in weight, night sweats and time period of symptoms. Chest X-ray was performed followed by HRCT on 64 slice MDCT GE (General Electronics) LIGHT SPEED VCT Xte machine. Patient was said to have active pulmonary tuberculosis based on the presence of TB bacilli in bronchial washings/ broncho-alveolar lavage (BAL), cultures of sputum or bronchial washings/BAL, demonstration of non-caseating granuloma on FNAC or TBLB suggestive of TB or radiographic and clinical improvement after administration of anti-tubercular drugs for patients whose clinical and radiographic findings suggested a diagnosis of pulmonary tuberculosis. At least two experts from the Department of Radio-Diagnosis of our institute analysed the images obtained independently and any difference of opinions was solved by consensus.

We examined the accompanying HRCT discoveries: centrilobular nodules, other minute nodules, huge nodules, masses, fine granular pattern, lobular distribution of consolidation, interlobular septal thickening, consolidation, ground-glass opacities, cavitation, branching linear opacities, tree-in-bud appearance, bronchiectasis, pleural effusion, lymphadenopathy and the vicinity of a main lesion in bilateral upper lobes.

These findings were defined as follows. Centrilobular nodules and other nodules: the small nodules of < 8 mm were differentiated into centrilobular noduless and other nodules, that are interstitially or arbitrarily spread out. Huge Nodules: Nodules of ≥ 8 mm and < 30 mm were viewed as large nodules. Mass: A nodule of ≥ 30 mm was viewed as a mass. Fine granular pattern: fine nodular opacities connected with vessels or lymphatic lesions were viewed as a fine granular pattern. Lobular distribution of consolidation: Areas of consolidation outlined by sharp edges relating to 1 or 2 lobules. Regression analysis was used to find the blend of HRCT findings that foresee the threat of PTB. In view of these outcomes, a mix of HRCT findings was selected and positions were given based on these results to determine the threat for pulmonary tuberculosis as position 1, 2, 3 and 4. Specificity, sensitivity, positive likelihood ratio and negative likelihood ratio of distinctive positions were computed.

Statistical Analysis

The information collected was evaluated and studied further with SPSS statistical software version 20. Data are expressed in terms of means ± standard deviation. $p< 0.05$ shows a significant relationship. Regression analysis was used to determine the clinical components and HRCT discoveries linked or associated with the danger of PTB. Positive predictive values, negative predictive values, sensitivity and specificity were computed wherever relevant.

RESULTS

Analytical and Medical Characteristics

Age of participants varied between 18 to 85 years in our study. The average age was 35.7 ± 16.9 years. Out of 69 patients there were 38 men and 31 women. Forty one patients were found to have pulmonary tuberculosis. Among the 41 patients found to have tuberculosis, 18 were men and 23 were women. The average age of individuals affected by pulmonary tuberculosis was 31.5 ± 15.4 years. Twenty eight patients were found to have disease other than pulmonary tuberculosis. Among clinical findings chronic cough and night sweats were significantly linked to a greater possibility for PTB (Table 1).

HRCT Findings

On HRCT thorax, presence of cavity, lymphadenopathy, main lesion in S1, S2, S6, lobular consolidation, other minute nodules and tree in bud appearance centrilobular nodules, consolidation, ground glass opacity (GGO), was linked to higher chances of PTB in linear regression analysis significantly (Table 2). While cavity, pleural effusion, centrilobular nodules, interlobular septal thickening and tree-in-bud appearance was significantly linked or associated with a higher possibility of PTB in Multivariate regression analysis (Table 3). Positions were given from 1 to 4 according to HRCT findings (Table 4). Positive predictive value, negative predictive value, sensitivity and specificity were ascertained. When position 1 (Figures 1A,1B) alone was taken to be positive; negative predictive value, sensitivity and

Table 1. Multivariate regression analysis of demographic and clinical findings of sputum smear-negative PTB and Non-PTB patients

	PTB	Non-PTB	Coefficient	p-value
Age (years)	31.5	41.7	0.002	0.67
Cough	38	16	0.776	0.01
Chronicity of cough (duration, days)	31.1	37.4	0.013	0.02
Hemoptysis	5	12	-0.368	0.02
Fever	33	21	0.061	0.68
Male gender	18/41	20/28	-0.162	0.16

PTB: Pulmonary tuberculosis.

Table 2. Linear regression analysis of HRCT lesions

Variable	p-value
Centrilobular nodules	0.00
Other minute nodules	0.00
Huge nodules	0.37
Fine reticular pattern	0.33
Branching linear opacity	0.57
Tree-in-bud appearance	0.00
Lobular pattern of consolidation	0.00
Interlobular septal thickening	0.24
Consolidation	0.04
Ground-glass opacity	0.00
Cavity	0.00
Bronchiectasis	0.93
Pleural effusion	0.69
LAP	0.00
Main lesion in S1, S2 or S6	0.00

HRCT: High-resolution computed tomography.

specificity were 0.43, 53.6% and 100% respectively. When ≤ position 2 (Figures 2A, 2B) was taken to be positive; positive predictive value, negative predictive value, sensitivity and specificity were 23.22, 0.18, 82.9% and 96.43% respectively. When ≤ position 3 (Figures 3A,3B) was considered positive, these values were 1.56, 0, 100% and 35.7%, respectively (Table 5). The sensitivity and specificity of HRCT in sputum smear negative PTB patients in our research was 82.7% and 96.4% respectively.

DISCUSSION

Visualization of *M. tuberculosis* in sputum smear microscopy, culture of mycobacterium tuberculosis using solid or liquid culture media followed by drug susceptibility testing are considered standard for diagnosis of pulmonary tuberculosis [6]. Sputum smear examination can distinguish acid-fast bacilli (AFB) in up to 50-60% of instances of pulmonary tuberculosis. The rates of AFB detection are further lower in low-income economies due to lack of access to top notch microscopy services. Due to paucibacillary tubercular disease in HIV patients, the issue of the low sensitivity of smear examination is exaggerated further in nations with high pervasiveness of HIV/AIDS [3]. Delayed diagnosis can

Table 3. Multivariate variable regression analysis of HRCT lesions in sputum smear-negative PTB and Non-PTB

	PTB		Non-PTB		
	Number	Percentage	Number	Percentage	P value
Centrilobular nodules	35	85.4	5	17.8	0.00
Other minute nodules	35	85.4	14	50	0.43
Huge nodules	16	39	8	28.6	0.15
Fine reticular pattern	4	9.7	1	3.6	0.86
Branching linear opacity	4	9.7	4	14.3	0.61
Tree-in-bud appearance	27	65.8	0	0	0.01
Lobular pattern of consolidation	29	70.7	10	35.7	0.06
Interlobular septal thickening	2	4.9	0	0	0.00
Consolidation	26	63.4	11	39.3	0.51
Ground-glass opacity	33	80.5	12	42.8	0.11
Cavity	30	73.2	4	14.3	0.00
Bronchiectasis	7	17	5	17.8	0.71
Pleural effusion	2	4.9	2	7.1	0.00
LAP	41	100	23	82.1	0.07
Main lesion in S1, S2, S6	30	73.2	5	17.8	0.46

HRCT: High-resolution compudet tomography, PTB: Pulmonary tuberculosis.

Table 4. HRCT diagnostic criteria for diagnosing sputum smear-negative PTB

Position	HRCT diagnostic criteria	Findings
1.	Highly suspected PTB	Presence of at least 3 of the following findings: main lesion in upper lobes, apical lobes of lower lobes; tree-in-bud appearance; lobular consolidation; nodules (large or centrilobular).
2.	Probable PTB	Presence of at least 2 of the following findings: main lesion in upper lobes, apical lobes of lower lobes; tree-in-bud appearance; lobular consolidation; nodules (large or centrilobular)
3.	Nonspecific or difficult to differentiate from other diseases	No characteristic findings indicating other diseases or findings that are difficult to differentiate from other diseases.
4.	Other suspected diseases	Some findings indicating other specific diseases.

HRCT: High-resolution compudet tomography, PTB: Pulmonary tuberculosis.

Table 5. Sensitivity, specificity, positive likelihood ratio and negative likelihood ratio for each rank of HRCT diagnosis

	≤ Rank 3	≤ Rank 2	Rank 1
Sensitivity	100%	82.9%	53.6%
Specificity	35.7%	96.4%	100%
Positive likelihood ratio	1.56	23.22	-
Negative likelihood ratio	0	0.18	0.43

HRCT: High-resolution compudet tomography.

lead to the spread of infection in the society. Clinicians often face the difficulty of adding empirical treatment or waiting for up to 8 weeks for the culture results. Liquid media based culture methods like MGIT (Mycobacterial growth indicator tube) can provide culture reports as early as 2-3 weeks but at relatively high costs [7]. Disadvantages of culture methods are high degree of technical expertise required, high cost, non uniform availability and time required to obtain a result causing diagnostic delay. GeneXpert MTB/RIF assay is a nucleic acid amplication assay. It can provide results in less than two hours and can determine rifampicin resistance at the same time. Sensitivity of GeneXpert MTB/RIF assay in smear negative setting is 72.5% and specificity is 99.2% in diagnosis of pulmonary tuberculosis. But again it is expensive and not available in resource poor settings [8]. In spite of the fact that newer less time consuming analytic tests are accessible, they are expensive and yet are not considered standard of practice. In this research, we tried to determine the role of HRCT in sputum smear-negative PTB patients for early diagnosis and treatment of such patients. The average age of the individuals affected with pulmonary tuberculosis was 31.5 ± 15.4 years in our study which was slightly less as compared to other similar studies [5,6].

The younger mean age in our study could be explained by the fact that ours being developing country has much higher

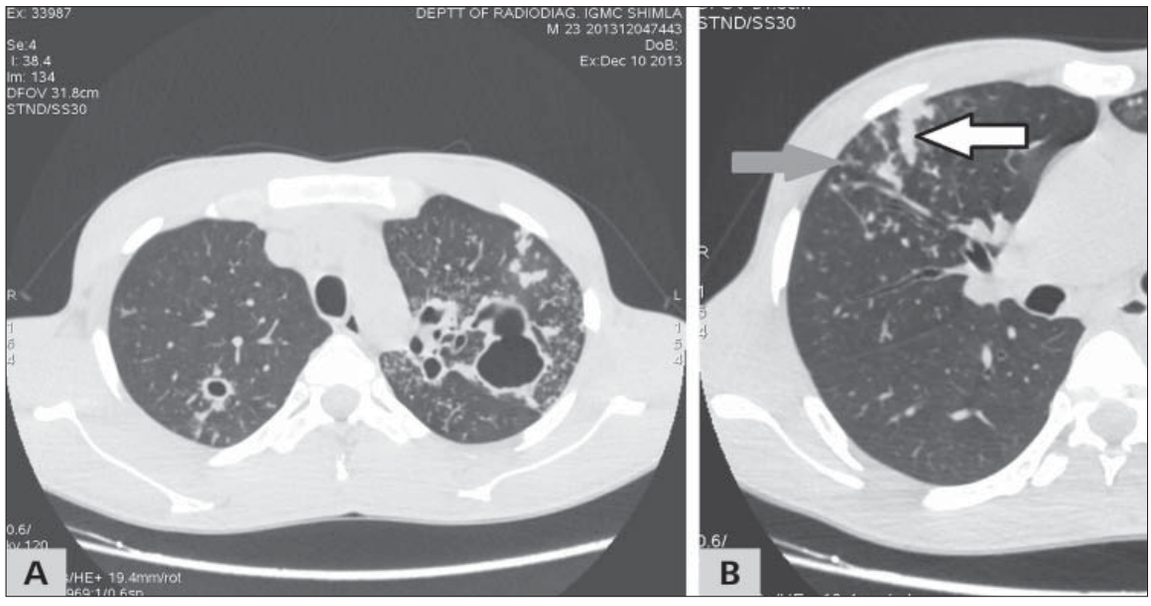

Figure 1. (A) Axial HRCT images of a twenty three year old male showing presence of cavitary lesions along with centrilobular nodules and consolidation in lobular pattern in the surrounding lung parenchyma in b/l upper lobes. **(B)** Magnified view of the same patient showing the centrilobular nodules, tree-in-bud appearance (dark arrow) and consolidation in lobular pattern (white arrow).This patient was given Rank 1 and proved to be tubercular on BAL examination.

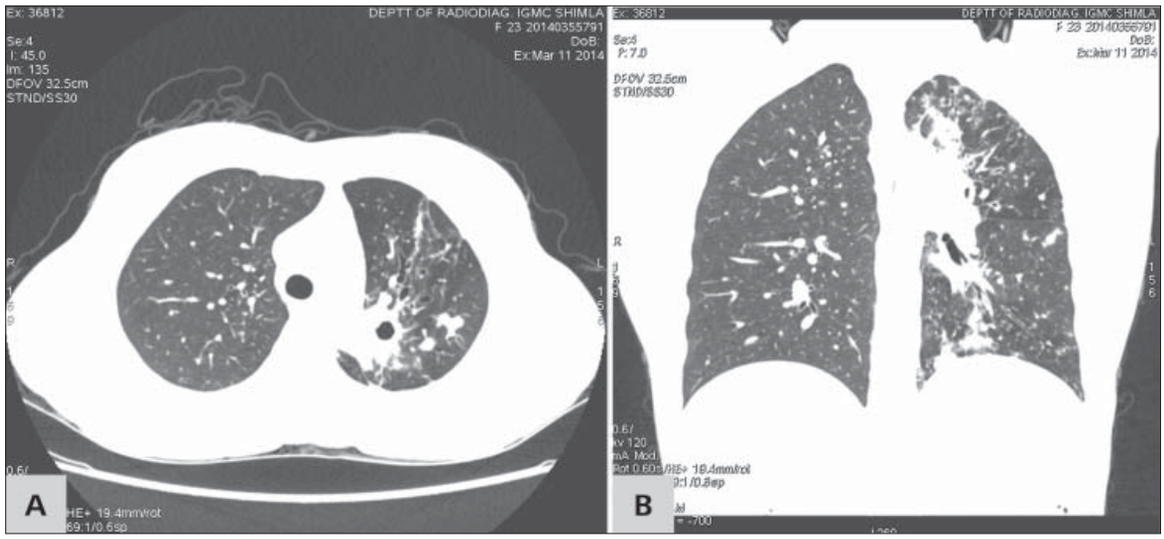

Figure 2. (A) Axial sections showing cavity, nodules and few centrilobular infiltrates with traction bronchiectasis in left upper lobe (anterior and apical segments). **(B)** Coronal sections showing the upper lobe distribution of main lesions. This patient was given Rank 2 and was proved tubercular on microbiological analysis.

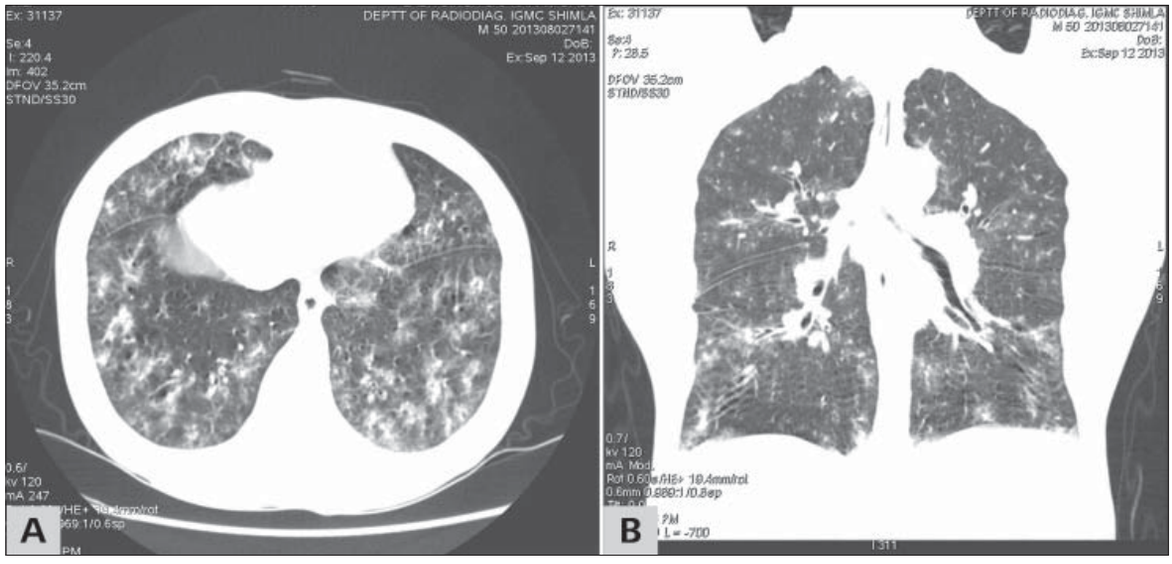

Figure 3. (A) Axial sections of HRCT chest of a fifty year old male patient showing diffuse patches of consolidation and surrounding ground glass haze, no specific apicobasal gradient seen. **(B)** Coronal sections also showing diffuse patches of consolidation and surrounding ground glass haze. This patient was given Rank 3. He responded to symptomatic treatment and recovered in 2 weeks.

exposure rate of tuberculosis and so TB occurs at a younger age as compared to the developed countries. Age and gender were not significantly associated with risk of tuberculosis. Among clinical features cough was the most common presenting complaint in our patients followed by fever, while chronic cough and night sweats were significantly associated with risk of pulmonary tuberculosis. A negative correlation was demonstrated with symptoms of hemoptysis i.e. hemoptysis was seen more in patients who were diagnosed non-tubercular. Out of the 17 patients with hemoptysis only 5 had tuberculosis and 12 patients were non-tubercular. A clarification for this result may be that moderately less quantity of bacilli in smear negative patients are not able to cause the pathological changes required to produce hemoptysis.

Tree in bud appearance, cavity, centrilobular nodules, consolidation, ground glass opacity (GGO), lymphadenopathy, main lesion in S1, S2, S6, lobular consolidation and other minute nodules were significantly linked with pulmonary tuberculosis on regression analysis. Causes of tree-in-bud appearance are respiratory infections with mycobacteria, bacteria or viruses, cystic fibrosis, allergic bronchopulmonary aspergillosis (ABPA), aspiration, and graft versus host disease. Tree-in-bud opacities arise from extensive bronchiolar mucoid impaction in the presence or absence of additional involvement of adjacent alveoli. Infectious bronchiolitis is the most significant differential diagnosis for this behavious of disease [10]. The specificity and sensitivity of this finding was 100% and 57% respectively in some previous studies [11]. In our study the specificity of this finding was 100% and the sensitivity was 65.8%. Centrilobular nodules can be found in hypersensitivity pneumonitis, respiratory bronchiolitis, immunodeficiency, mineral dust airway disease, pulmonary

Langerhans cell histiocytosis, respiratory bronchiolitis-interstitial lung disease, connective tissue disease (Sjögren syndrome, rheumatoid arthritis), and pulmonary infections. Specificity and sensitivity of centrilobular nodules were found to be 93% and 100% respectively in previous studies [10]. The sensitivity and specificity of centrilobular nodules was found to be 82% and 82.4% respectively in our study. Cavity can be found in tuberculosis, non-tuberculous mycobacterial infection, aspergillosis, lung abscess, wegener's granulomatoses, and metastatic neoplasm [12]. The sensitivity of the cavitatory lesions was 73% and the specificity was 85.7% in our study. Although individual findings are non-specific for diagnosis of tuberculosis, combination of HRCT findings can be helpful.

Positions were given based on combination of HRCT findings from 1 to 4 predicting the risk of tuberculosis. Position 1 was given to 22 patients (53.6%) and all of them were found to have pulmonary tuberculosis. Position 4 was found in 9 (32.1%) patients and all of them were found to have disease other than pulmonary tuberculosis. Thus patients with position 1 are more likely to have pulmonary tuberculosis and extensive work up for pulmonary tuberculosis can be undertaken in these patients.

We postulated that HRCT scan could not only diagnose PTB but also could exclude patients not having PTB. In our study the sensitivity and specificity of HRCT in sputum smear-negative PTB patients was 82.7%, and 96.4% respectively. The high specificity demonstrated in our study could be due to the high prevalence of tuberculosis in our set-up and the low sensitivity and specificity of the smear examination producing false-negative results. Also, the HRCT criteria takes into account a mixture of HRCT findings which becomes sufficiently reliable to anticipate the risk of PTB and could help isolate the patients highly suspected of having PTB.

Limitations

Utilization of HRCT to analyze PTB is not accessible at each center especially in developing countries. Immunocompromised patients were not evaluated in our study. The pathological response of pulmonary tissues to *Mycobacterium* could be altered in immunocompromised patients and simultaneous presence of other lung diseases in immunocompromised patients could interfere with diagnosis [13,14]. In this manner, the certainty of HRCT diagnosis for such patients stays ambiguous.

Conclusion

The main use of HRCT for diagnosing PTB in sputum smear negative patients is that the patient highly suspected for PTB can be selected among patients based on combination of characteristic HRCT findings. Thus it helps in selecting the patients for further invasive or advanced investigations besides excluding other diseases that can clinically mimic PTB.

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