Indian J Med Res 126, September 2007, pp 193-198

High resolution CT (HRCT) in miliary tuberculosis (MTB) of the lung: Correlation with pulmonary function tests & gas exchange parameters in north Indian patients

Pipavath S.N.J.*, S.K. Sharma, S. Sinha, S. Mukhopadhyay* & M. S. Gulati*

*Departments of Medicine & *Radiodiagnosis, All India Institute of Medical Sciences, New Delhi, India*

Received September 21, 2006

***Background & objectives*: High resolution computed tomography (HRCT) scans are known to be helpful in early diagnosis and management of patients with miliary tuberculosis (MTB). We made an attempt in this study to identify patterns of pulmonary MTB on HRCT and to correlate the HRCT disease extent with pulmonary function tests (PFT) and gas exchange analysis (GEA).**

***Methods*: A total of 16 non-HIV patients with MTB underwent HRCT of the chest, PFT and GEA. All the investigations in these patients were completed within 20 days of presentation. Evidence of TB was diagnosed by biopsy from lymph nodes (3/16), organ biopsy [skin, liver, bone marrow and lung (transbronchial) (6/16)]. In one patient fundoscopy revealed choroid tubercles. In 6 patients, diagnosis was confirmed by clinical/radiological improvement following anti-tuberculosis therapy. Radiological patterns of involvement on HRCT of the lungs were studied and disease extent was estimated in each case by consensus between two radiologists using specially devised visual scoring system. Disease extent was correlated with PFT and GEA. Spearman rank correlation was used for statistical analysis.**

***Results*: Findings on HRCT in MTB included miliary nodularity (16/16), alveolar lesions such as ground glass attenuation and/or consolidation (5/16), lymphadenopathy (8/16), peribronchovascular interstitial thickening (1/16), emphysema (1/16), pleural pathology (2/16), and pericardial effusion (2/16). A significant correlation was noted between disease extent score and forced vital capacity (FVC) (r = -0.76; *P*=0.003), forced expiratory volume in one second (FEV_1)(r = -0.74; *P* = 0.005), total lung capacity (TLC) (r = -0.66; *P* = 0.037), oxygen saturation in arterial blood (SaO_2) (r = -0.69, *P* = 0.01), diffusion capacity of the lung (DLco) (r = -0.8; *P* = 0.02).**

***Interpretation & conclusion*: Our findings showed that HRCT reliably diagnosed MTB, and thus could help in predicting derangement of pulmonary function tests and GEA in these patients.**

Key words Miliary tuberculosis - gas exchange analysis - high resolution computed - pulmonary function tests

Miliary tuberculosis (MTB) is a cause of significant morbidity and mortality in developing nations. Contrary to the developed world, in the developing world most of the new born receive BCG vaccination. In India, despite BCG vaccination, MTB is more common than in many other countries. It is known that MTB occurs due to a direct sequel of a primary infection/disease. However, secondary focus can also be responsible for haematogenous dissemination. Diagnosis of this entity earlier in its course helps in preventing a rapid course leading to possible respiratory failure and death[1]. Therefore, early diagnosis can decrease the morbidity associated with this disease. High resolution computed tomography (HRCT) is more sensitive than plain chest radiography in detecting this disease[2,3].

In pulmonary parenchymal tuberculosis the ventilation perfusion has been reported to be relatively normal[4]. Serious hypoxaemia is uncommon, occurring only when miliary or rarely fibrocavitary disease is complicated by acute respiratory distress syndrome (ARDS)[5,6] or when acute bronchogenic spread of TB results in "tuberculosis pneumonia"[7]. In the appropriate clinical situation, MTB may be suggested on HRCT[3]. Moreover, in cases with no evidence of miliary nodules on the chest radiograph, HRCT scan may depict miliary nodules in the lung parenchyma. HRCT features that potentially contribute in making a differential diagnosis are: (*i*) a peripheral distribution of nodules, an increased number of thickened interlobular septae, and a notable thickening of interlobar fissures, all of which are indicative of sarcoidosis; and (*ii*) multiple cyst-like lesions which should direct attention to tuberculosis or metastatic origin. The predominance of miliary nodules in relation to cephalocaudal axis, their margin and size are not helpful features to the differential diagnosis of diseases presenting with a miliary pattern[8]. Randomly distributed miliary nodules and areas of ground-glass opacities are the predominant HRCT findings in patients with MTB, and HRCT scans are helpful in the early diagnosis and proper management of patients with MTB[9].

Often the physicians face with a dilemma as to when and how to determine if the person on treatment is capable of returning to work. We attempted to address this problem by correlating pulmonary functions and HRCT features to see if HRCT can predict pulmonary function derangement. It is a unique attempt to see if HRCT can solely be used in determining the extent of pulmonary function test (PFT) derangement and replace the same in follow up.

Materials & Method

A total of 16 non-HIV patients with provisional diagnosis of MTB were studied at the Departments of Medicine and Radiodiagnosis, All India Institute of Medical Sciences (AIIMS) hospital, New Delhi, during January 1998 to November 1999. All patients fulfilling the inclusion criteria were included during the study period. Approval for study was obtained from ethics committee of AIIMS. Diagnosis of miliary tuberculosis was confirmed as described previously[6].

HRCT of the chest: Both postero-anterior and lateral chest radiographs were obtained in all the patients. HRCT of the chest was obtained in all the patients, using a Somatom plus 4 scanner (Siemens, Erlanger, Germany). Scans were obtained from apices to bases of the lungs using a standard HRCT protocol (l mm collimation at 10 mm intervals, scan time of 1-2 sec, high spatial frequency algorithm). All the scans were obtained in deep inspiration. Expiratory scans were also obtained. Consistent lung window with a mean of 600 to 700 HU and a width of about 1000-1500 HU was used. HRCT scans of the lungs were studied and disease extent was estimated in each case by consensus between the two radiologists using specially devised visual scoring system based on a study done by Muller *et al*[10]. Disease extent was correlated with PFT and gas exchange analysis (GEA). The overall disease extent was scored using a visual score on a continuous scale from 0-100 per cent.

Pulmonary functions: All patients underwent PFTs and gas exchange analysis. Forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), forced expiratory flow at 50 and 75 per cent of the vital capacity (FEF 50 and 75%), forced expiratory flow between 25 and 75 per cent of the vital capacity (FEF_{25-75}) total lung capacity (TLC) and residual volume (RV) data were obtained using constant volume variable pressure body plethysmograph (PK Morgan, Chatham, Kent, UK). Airway resistance and thoracic gas volumes were estimated according to the method of Du Bois[2]. Arterial blood gases (ABGs) were determined using a radiometer ABL3 blood gas analyzer (Radiometer, Copenhagen, Denmark)[2]. Pulmonary diffusion capacity was measured by the steady state technique, using a Rahn and Otis end tidal sampler for obtaining alveolar air[2].

Protocol for exercise test parameter: Following pulmonary function tests, subjects were familiarized

Table I. Lung volumes, maximum expiratory flow rates and gas exchange in patients with MTB

Lung volumes		Maximum expiratory flow rates		Gas exchange parameters	
Measurement	Mean value ±SD	Measurement	Mean value ±SD	Measurement	Mean value ±SD
FRC	91.0±33	FEV_1	78.1±16	PaO_2(mmHg)	85.2 ± 10
TLC	78.6±18.5	FEV_1/FVC(%)	81.7±7.1	$PaCO_2$(mmHg)	37.4 ± 8.3
FVC	79.2±14.6	FEF_{25-75}	83.3±32	SaO_2(%)	95.8 ± 1.3
				DLCO	59 ± 7.6

Values are mean ± SD (n=16)

Lung volumes, maximal expiratory flow rates are expressed as per cent predicted, unless specified otherwise. Forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), average forced expiratory flow between 25 and 75 per cent of vital capacity (FEF_{25-75}), total lung capacity (TLC), functional residual capacity (FRC), arterial oxygen saturation (SaO_2), arterial oxygen tension (PaO_2), arterial carbon dioxide tension ($PaCO_2$)

with exercise testing equipment. Exercise was carried out as described previously[11] using electrically breaked bicycle ergometer and data were acquired using Wyvern exercise software (PK Morgan Limited, UK). Calibration was done before starting the test. Resting data were recorded for initial two minutes, including end tidal carbon dioxide concentration.

Statistical analysis: Statistical analysis of data was done using Statistics version 4 software database program. Correlations between disease extent score on HRCT and pulmonary function derangement were evaluated using Spearman's rank correlation method. $P < 0.05$ was considered as statistically significant.

Results

Sixteen patients with MTB with age range 13-65 yr were studied. The majority of the patients presented with expected symptoms like fever (n=12, 75%), cough (n=8, 50%), weight loss (n=8, 50%), breathlessness (n=7, 43.7%), and anorexia (n=6, 37.5%). Less common modes of presentation were chest pain (n=2, 12.5%) and osteomyelitis secondary to dissemination to bones, with discharging sinuses (n=2, 12.5%). On physical examination signs of dissemination were evident in the form of peripheral adenopathy, hepatomegaly, splenomegaly and discharging sinuses in 2 patients each. On chest radiographs, 13 out of the 16 patients, showed typical miliary nodular pattern. Two showed reticulonodular pattern and one had normal pulmonary parenchyma with mediastinal widening. Details of TB diagnosis included: organ biopsy (6) (transbronchial lung, bone marrow, skin or liver biopsy), lymph node biopsy (3), and observation of choroid tubercles on opthalmoscopy (1) and/or response to anti-tuberculosis therapy (6).

Pulmonary Functions: Mean values of total lung capacity (TLC), forced vital capacity (FVC) forced residual capacity (FRC), residual volume (RV) and RV/TLC were normal or near normal (Table I). Maximum expiratory flow rates like forced expiratory volume in 1 sec (FEV_l), FEV_l/FVC (per cent), forced expiratory flow at 50 per cent of FVC, forced expiratory flow at 75 per cent of FVC and forced expiratory flow at 25-75 per cent of FVC were normal or near normal (Table I). Most of the mean values of gas exchange parameters were normal to near normal except for diffusing capacity of the lung. Changes in exercise parameters were noted and change in mean values are provided in Table II.

Table II. Mean change of parameters following exercise in patients with MTB (n=6)

Parameters	Mean
Δ SaO_2 (%)	3.8
$\Delta \dot{V}CO_2$ (ml/min)	523
$\Delta \dot{V}O_2$ (ml/min)	404

Arterial oxygen saturation (SaO_2), Arterial oxygen saturation change with exercise (Δ SaO_2), $\dot{V}CO_2$ change with exercise (Δ $\dot{V}CO_2$), $\dot{V}O_2$ change with exercise (Δ $\dot{V}O_2$)

HRCT features (Fig.1, Fig. 2 and Fig. 3: The predominant pattern of involvement on HRCT was diffuse miliary nodulation ranging from 1-3 mm in size in all patients. All of them showed typical random distribution. Some of these patients showed additional parenchymal abnormalities like alveolar space abnormality including both ground glass attenuation and consolidation (n=5, 31.2%), focal cystic abnormality, peribronchovascular interstitial thickening and parenchymal bands in one patient each (6.25%). The patient with focal cystic abnormality evolved to show frank emphysema on post-therapy CT. HRCT disease extent score based on a qualitative visual scoring ranged from 6-80 per cent, with a mean value of 22.5 per cent.

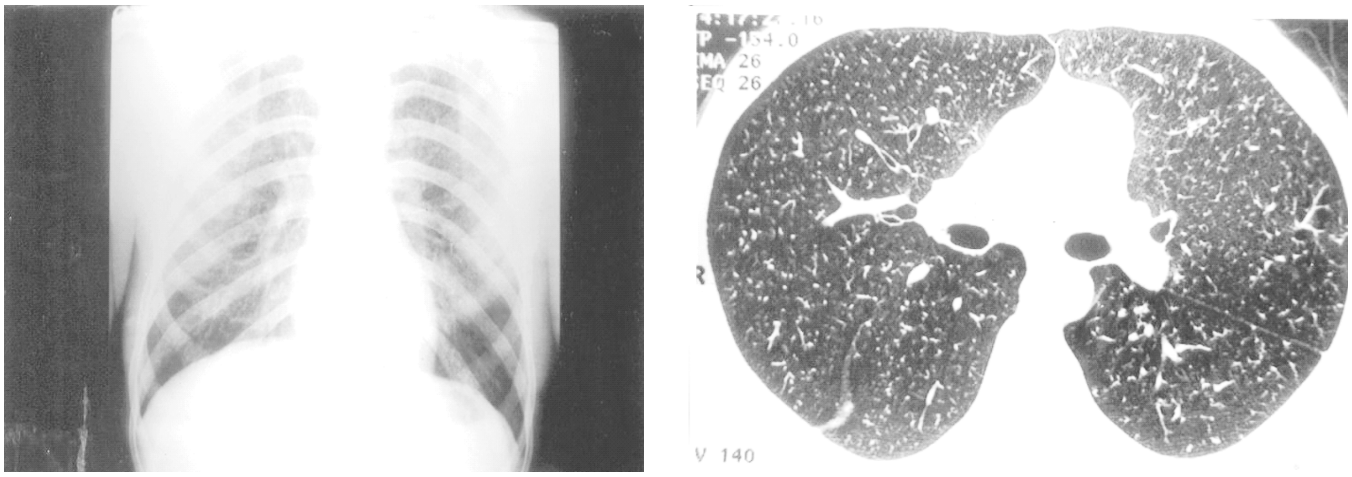

Fig. 1a. Chest radiograph showing bilateral diffuse miliary nodular lesions, **1b**. HRCT chest-lung window: Bilateral diffuse miliary nodular opacities showing random distribution.

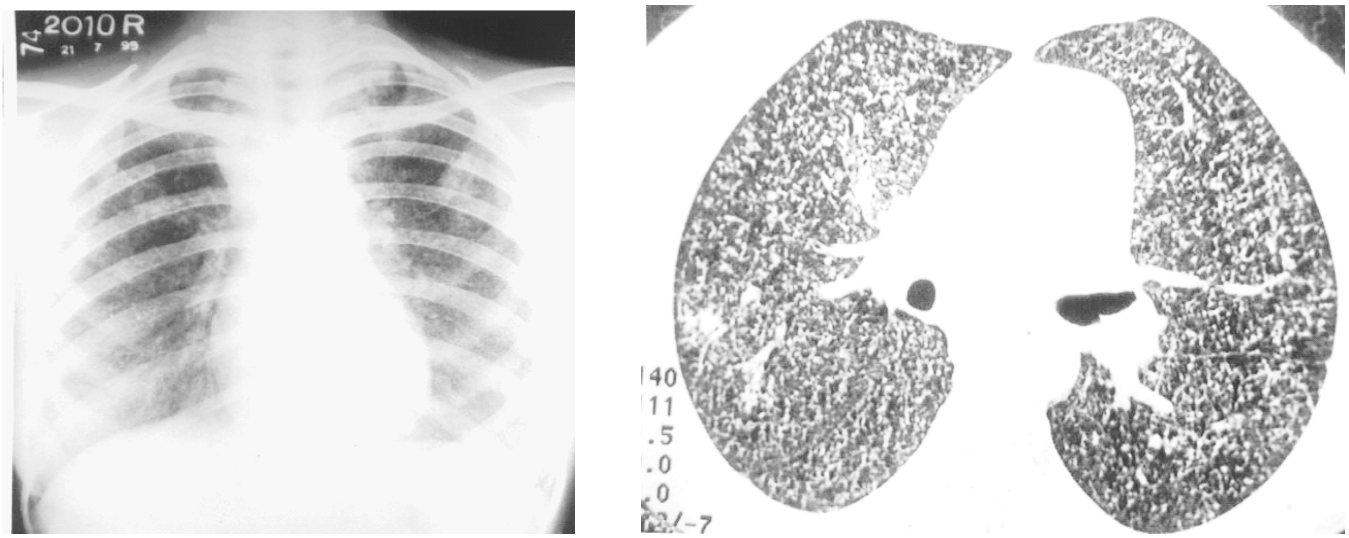

Fig. 2a. Chest radiograph showing bilateral diffuse miliary nodular lesions with conglomeration in the left upper lobe, and mediastinal widening suggestive of lymphadenopathy, **2b.** HRCT chest- lung window: Bilateral diffuse, randomly distributed miliary nodular lesions. Conglomeration of some nodules in the right lung.

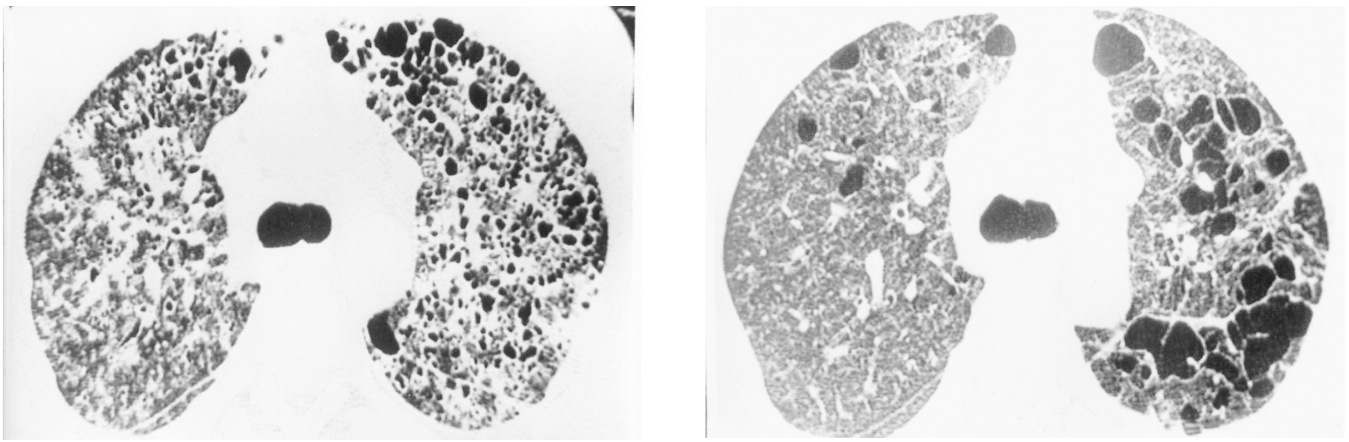

Fig. 3a. HRCT chest-lung window: Bilateral miliary nodular lesions (R>L), and multiple small cystic lesions seen in both the lung fields (L>R), **3b.** Post anti-tuberculosis treatment: HRCT chest- lung window: A significant resolution of nodules and ground glass opacities is seen. Centrilobular emphysema is now seen in some areas.

Table III. Correlations between HRCT score and pulmonary functions in patients with MTB

Parameters correlated with HRCT score	Correlation coefficient (r)	*P* value
FVC	-0.76	0.003
FEV_1	-0.74	0.005
TLC	-0.66	0.037
MVV	-0.68	0.04
SaO_2	-0.69	0.01
DLco	-0.811	0.02
$\Delta \dot{V}CO_2$	-0.670	0.048

Forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), total lung capacity (TLC), maximum voluntary ventilation (MVV), oxygen saturation (SaO_2), diffusion capacity of the lung for carbon monoxide (DLco), $\dot{V}CO_2$ change with exercise ($\Delta \dot{V}CO_2$)

Correlations with physiology: Total lung capacity (TLC), forced vital capacity (FVC), arterial blood oxygen saturation (SaO_2), diffusing capacity of the lung (DLco), forced expiratory volume in 1 sec (FEV_1), and change in $\dot{V}CO_2$ with exercise ($\Delta\dot{V}CO_2$) showed significant negative correlation with disease extent score, assessed on HRCT (Table III).

Discussion

In MTB haematogenous showers of *Mycobacterium tuberculosis* bacilli seed mostly the pulmonary interstitium and may secondarily involve the peribronchiolar areas. HRCT of the chest is a powerful tool in terms of being able to diagnose MTB both early and accurately in its course[2,3,9]. In a study done by Hong *et al*[9], 24 patients studied demonstrated miliary nodules, which varied in size from 1-5 mm. A high percentage of their patients had ground glass abnormality (GGA). They also pointed out that those who had dyspnoea showed large areas of GGAs, and two patients with impending adult respiratory distress syndrome revealed extensive GGAs. They concluded that miliary nodules and GGA are the predominant HRCT findings in patients with miliary tuberculosis. Fujita *et al*[12] identified the following patterns on HRCT (*i*) MTB (haematogenous dissemination), (*ii*) MTB with exudative reaction, (*iii*) bronchogenic spread, (*iv*) MTB mixed with bronchogenic spread, and (*v*) bronchogenic spread with multiple cavity formation. They concluded that the HRCT scan patterns described allow classification of disseminated TB according to the mechanism of spread (haematogenous and/or bronchogenic) and the degree of local lung involvement (reaction or cavitation).

In our study predominant pattern of involvement on HRCT was diffuse miliary nodulation ranging from 1-3 mm, similar to the finding of Hong *et al*[9]. All patients showed typical random distribution. In the present study a significant percentage of these patients showed additional parenchymal abnormalities like alveolar space abnormality including both ground glass attenuation and consolidation. Focal cystic abnormality, peribronchovascular interstitial thickening and parenchymal bands were unique. The patient with focal cystic abnormality evolved to show frank emphysema on post-therapy CT. Although cystic changes have been reported before in MTB[7], post-therapy emphysema has not been reported before.

In out study pulmonary function parameters like total lung capacity, forced vital capacity have shown significant negative correlation with the HRCT disease extent score. From this one can infer that as the disease extent increases, there is a progressive deterioration in these lung function parameters. This would also mean that increase in miliary nodules leads to increasing restriction of pulmonary functions. Sharma *et al*[2] showed that values of FVC, $FEF_{25-75\%}$, $FEF_{50\%}$, $FEF_{75\%}$ decrease, FRC, RV/TLC increase, and FEV_1/FVC (%) remains normal in patients with MTB. In the present study, however, these values were normal or near normal, while measures of gas exchange, particularly DLco, were reduced. These results are comparable to the few prior studies done to establish the physiology of this disease[2]. We showed that restriction in pulmonary function and gas exchange impairment increases with increasing disease extent score.

Limitations of the current study include a small sample size (n=16) and inter-observer variability in determining the HRCT disease extent score which was sorted out by arriving at a final score on consensus. However, we have demonstrated that the HRCT disease extent correlated well with restrictive physiology and impaired gas exchange. In addition to HRCT, certain pulmonary function parameters like TLC, FVC, DLco, SaO_2 and changes in exercise related parameters can be used for follow up.

References

1. Sharma SK, Mohan A, Pande JN, Prasad KL, Gupta AK, Khilnani GC. Clinical profile, laboratory characteristics and out come in miliary tuberculosis. *QJM* 1995; *88* : 29-37.
2. Sharma SK, Mukhopadhyay S, Arora R, Varma K, Pande JN, Khilnani GC. Computed tomography in miliary tuberculosis: comparision with plain film, bronchoalveolar lavage, pulmonary functions and gas exchange. *Australas Radiol* 1996; *40* : 113-8.

3. Oh YW, Kim YH, Lee NJ, Kim JH, Chung KB, Suh WH, *et al*. High-resolution CT appearance of miliary tuberculosis. *J Comput Assist Tomogr* 1994; *18* : 862-66.

4. Bromberg PA, Robin ED. Abnormalities of lung function in tuberculosis. *Adv Tuberc Res* 1963; *12* : 1-27.

5. Penner C, Roberts D, Kunimoto D, Manfreda J, Long R. Tuberculosis as a primary cause of respiratory failure requiring mechanical ventilation. *Am J Respir Crit Care Med* 1995; *51* : 867-72.

6. Sharma SK, Mohan A, Banga A, Saha PK, Guntupalli KK. Predictors of development and outcome in patients with acute respiratory distress syndrome due to tuberculosis. *Int J Tuberc Lung Dis* 2006; *10* : 429-35.

7. Rich AR. *The Pathogenesis of Tuberculosis* 2nd ed. Springfield, Ill: Charles C Thomas, 1951.

8. Voloudaki AE, Tritou IN, Magkanas EG, Chalkiadakis GE, Siafakas NM, Gourtsoyiannnis NC. HRCT in miliry lung disease. *Acta Radiol* 1999; *40* : 451-6.

9. Hong SH, Im JG, Lee JS, Song JW, Lee HJ, Yeon KM. High - resolution CT findings of miliary tuberculosis. *J Comput Assist Tomogr* 1998; *22* : 220-4.

10. Muller NL, Mawson JB, Mathieson JR. Sarcoidosis: Correlation of extent of disease at CT with clinical functional and radiographic findings. *Radiology* 1989; *171* : 613-8.

11. Sharma SK, Ahluwalia G. Effects of antituberculosis treatment on cardiopulmonary responses to exercise in miliary tuberculosis. *Indian J Med Res* 2006; *124* : 411-8.

12. Fujita J, Bandoh S, Kubo A, Ishii T, Kanaji N, Nakamura H, *et al*. HRCT shows variations in appearance in disseminated tuberculosis in adults. *Int J Tuberc Lung Dis 2006*; *10* : 222-6.

Reprint requests: Prof. S.K.Sharma, Chief, Division of Pulmonary, Critical Care and Sleep Medicine, Professor & Head Department of Medicine, All India Institute of Medical Sciences, Ansari Nagar, New Delhi 110029, India
e-mail: sksharma@aiims.ac.in