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A Comparison of Chest Computed Tomographic Findings in Multi - Drug Resistant Tuberculosis and Drug Sensitive Tuberculosis

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Abstract
Objectives*: 1.To illustrate the spectrum of radiological findings of multi-drug resistant tuberculosis (MDR-TB) in computerized tomography (CT) of chest. 2. To compare the CT findings of MDR-TB with those of drug sensitive tuberculosis (DS – TB) and to determine the characteristic radiological findings of MDR-TB, which would serve as signs to raise the suspicion of MDR-TB in a patient with pulmonary tuberculosis. Hence, they can be referred to gene expert for early diagnosis and treatment.*
Materials and Methods*: Total of 52 MDR-TB patients (cases) and 200 drug sensitive-TB patients (controls), who had undergone CT chest during the study period were included in the study. Age, sex, history of anti-TB treatment and CT chest findings of both groups were analysed.*
Results: *Multiple cavities, thick walled cavities and cavitary consolidation were more commonly observed in MDR-TB patients as compared to the drug sensitive TB cases, with a P value of less than 0.001. When these findings were present, they were numerous and extensive, involving multiple lobes as opposed to the controls in whom predominantly the upper lobes were involved. Pleural effusion was also commonly seen in the multi-drug resistant group with a P value of 0.025. There was no significant statistical difference in incidence of consolidation and pleural thickening while it was statistically higher among incidence of atelectasis, bronchiectasis and fibrosis in multi drug resistant group. While single cavity was found to be a common feature in drug sensitive cases particularly involving right and left upper lobes.*
Conclusion;*The finding of multiple cavities, thick walled cavities, cavitary consolidation especially when seen extensively involving multiple lobes of both lungs should highly raise the suspicion of multi-drug resistance and those patients should be promptly referred to gene-expert to confirm the diagnosis and appropriate treatment can be given.*
Keywords: *Tuberculosis, multi drug resistant, computed tomography*

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I. Introduction

Tuberculosis is one of the most common cause of mortality among infectious disease next only to AIDS(Acquired immunodeficiency syndrome).[1]In a global statistics done in 2009 about 1.7 million people died from tuberculosis (TB) and around ten percent them died due to multidrug resistant- TB (MDR-TB).[2]Mycobacterium tuberculosis is the sole agent seen in more than 95% of these pulmonary TB infections[3.]Also rise in incidence of HIV (Human Immuno- defeciency Virus) co-infection there is increase in prevalence of MDR-TB. Not only these also irregular and inadequate treatment of TB made drug resistance more frequent among TB, one another reason is point mutation in mycobacterium genome. Also patients who are immunocompromised due to solid organ or stem cells transplant and patients with lymphoma or leukemia and patients under corticosteroid treatment are more susceptible to MDR-TB. According to recent WHO(World Health Organisation) definition of MDR-TB is defined as infections caused by mycobacterium resistant to isoniazid and rifampin.[2]Lung is the most common site of involvementin MDR-TB.[4]Since pathologic findings of MDR-TB and drug sensitive TB like granulomatous inflammation and even cavity are very similar, it is hard to differentiate them. Also, findings in chest radiography and CT-scan are similar.[5]Diagnosis of drug sensitive TB and MDR-TB starts with identifying acid fast bacilli (AFB) from sputum but to consolidate the diagnosis sputum culture is mandatory which often takes at least 2–3 weeks[6,7]Similar failure to first line anti-TB treatmentin MDR-TB and drug sensitive TB lead to misdiagnosis and deferred treatment with rise in pathogen spread.[5,8]So we are in need an alternative way of early diagnosis and treatment. This study aims to analyse the spectrum of the CT findings of MDR- TB and to make a comparison between CT findings of MDR-TB and drug sensitive TB. The main aim of this comparison is to identify those radiological findings that are more often found in patients with MDR-TB, which could serve as a potential tool in early diagnosis of MDR-TB.

II. Materials and methods

This prospective case-control study assesses the tuberculosis patients referred for CT-Chest to department of radio diagnosis,Coimbatore medical college hospital for a period of one year from June 2016 to June 2017. Cases are those patients infected with multi-drug resistant bacilli. Controls are the patients with drug-sensitive pulmonary tuberculosis who were referred for CT chest by the physician when clinically indicated. Patients who had history of cough with expectoration, whose sputum is positive for mycobacterium tuberculosis, primary Multi-drug resistant TB patients, who had never received any Anti-tuberculosis drugs (ATT) or who had received ATT for less than one month, Acquired MDR-TB, who had received ATT for one month or more in the past. Drug sensitive pulmonary TB patients were includes in study while patients with history of who are sputum negative for TB. Old treated and cured (inactive) pulmonary tuberculosis patients, HIV positive patients, and diabetic patients were excluded.268 patientswho fulfilled the inclusion criteria were enrolled in the study. MDR-TB was confirmed in 68, and drug sensitive TB in 200 patients. TOSHIBA Multi-slice (4 slice) CT was used for all the cases. Initially both groups were assessedin terms of age, gender and anti-TB treatment.Table 1 demonstrate variables and results. Additionally all these CT findings were for difference in lobar distribution.Descriptive statistical analysis was conducted for all variables.Variables were compared by the chi-square test and*p*-value less than 0.05 was considered statistically significant.Data analysis was carried out using SPSS version 21.This study was approved by the ethical committee of Coimbatore medical college hospital.

III. Results

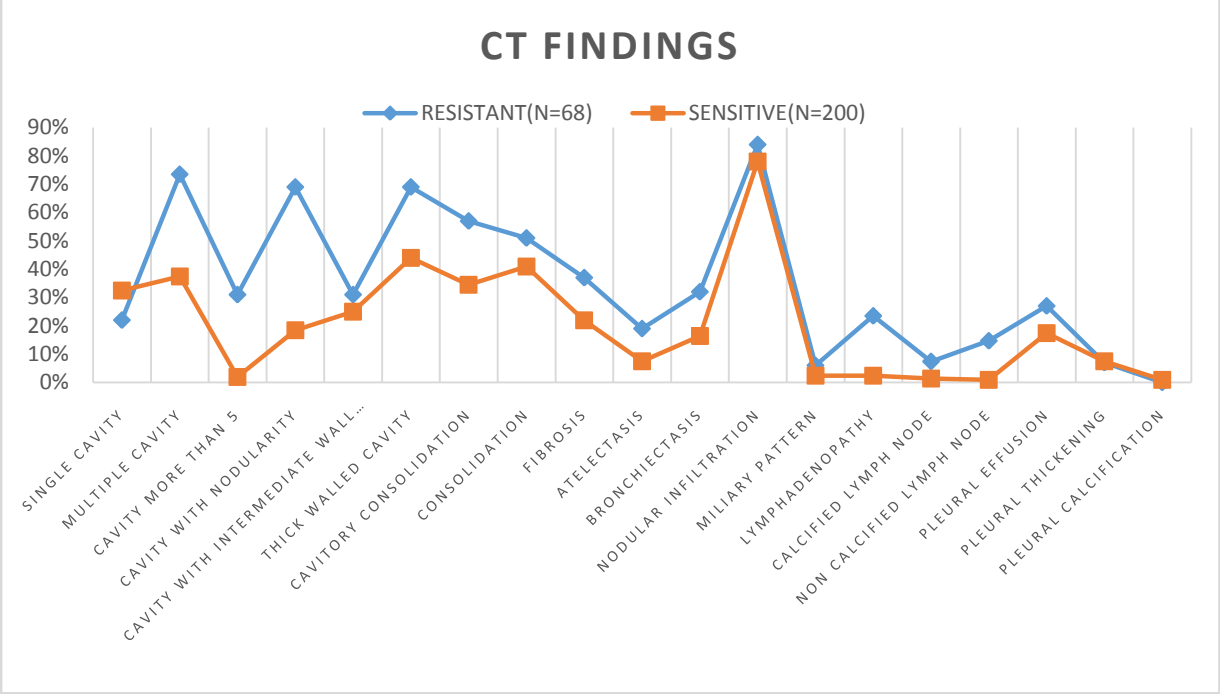
After performing culture for 268 patients suspected ofMDR-TB, 68 cases proved to be MDR-TB and 200 cases drug sensitive TB.CT-scan changes in general and lobe wise are presentedin Tables 1 and 2. There were no significantdifferences in terms of age and gender with more common incidence of disease in third and fourth decade and maleto female ratio of 2.39:1; however,history of previous anti-TB treatment was significantly morecommon in the MDR group with an odds ratio of 8.05. Most common CT-scan findings in MDR patients in orderof prevalence were: Multiple cavity particularly thick walled, Cavitary consolidation, bronchiectasis, nodular infiltration and fibrosis. In the drug sensitive TB group the more common findings were thin walled cavity, nodular infiltration and consolidation. Chronic changes like atelectasis, and pleural effusion were significantly more common in MDR-TB patients.

Table 1: Group wise distribution of all CT findings

CT FINDINGS	TUBERCULOSIS		P VALUE
	MDR-TB(N=68)	DS-TB(N=200)	
SINGLE CAVITY	15 (22%)	65 (32.5%)	0.104
MULTIPLE CAVITIES	50 (73.5%)	75 (37.5%)	0.001
CAVITY WITH NODULARITY	47 (69%)	37 (18.5%)	0.001
CAVITY WITH INTERMEDIATE WALL THICKNESS	21 (31%)	50 (25%)	0.342
THICK WALLED CAVITY	47(69%)	88(44%)	0.001
CAVITARY CONSOLIDATION	39(57%)	69(34.5%)	0.001
CONSOLIDATION	35 (51%)	82(41%)	0.133
FIBROSIS	25(37%)	44(22%)	0.016
ATELECTASIS	13(19%)	15(7.5%)	0.007
BRONCHIECTASIS	22 (32%)	33(16.5%)	0.005
NODULAR INFILTRATION	57 (84%)	156(78%)	0.304
MILIARY PATTERN	4(6%)	5(2.5%)	0.181
LYMPHADENOPATHY	16(23.5%)	5(2.5%)	0.001
CALCIFIED LYMPH NODE	5(7.4%)	3(1.5%)	0.014
NON CALCIFIED LYMPH NODE	10 (14.7%)	2(1%)	0.001
PLEURAL EFFUSION	18(27%)	35(17.5%)	0.015

PLEURAL THICKENING	5(7%)	15(7.5%)	0.258
PLEURAL CALCIFICATION	0(0%)	2(1%)	0.469

Chart 1: Groupwise distribution of all CT findings



Cavities were commonly seen in MDR-TB and mostly in multiple patterns inboth group of patients.Thick wall cavities were significantly more common in theMDR group when compared to drug sensitive TB group. Similarly multiple cavities are also more common in MDR-TB patients, withsignificant difference between these two groups. Multiplecavities in the MDR group cavities were significantlymore common in not only right upper lobe (RUL) also in all other lobes. Whereas single cavity which is commonly seen in drug sensitive patient is frequent in Right upper lobe(RUL).No considerable difference in prevalence ofpleural thickening,military pattern and nodular infiltration were seen between these groups. However, in the MDR group bronchiectasis weremore common in middle and lower lobes on right lung significantly. Similarly fibrosis was also significantly higher in MDR patients.Prevalence and distribution pattern of consolidationbetween the two groups were not significantly different.Pleural effusion was significantly higher in MDR-TB patients. Lymph node involvement, calcifiedor non-calcified were of significant difference between the two groups with more prevalence in MDR patients.

Table 2: Lobewise distribution

SINGLE CAVITY	RUL	RML	RLL	LUL	LINGULA	LLL
RESISTANT	2	1	1	10	1	2
SENSITIVE	52	0	1	17	2	2
P VALUE	0.001	0.049	0.303	0.026	0.757	0.143
MULTIPLE CAVITIES						
RESISTANT	35	10	5	25	8	12
SENSITIVE	54	7	1	22	8	4
P VALUE	0.001	0.001	0.001	0.001	0.003	0.004
CAVITY IMD WALL THICKNESS						
RESISTANT	7	3	3	9	1	3
SENSITIVE	41	2	2	11	3	2
P VALUE	0.25	0.028	0.028	0.005	0.828	0.028
THICK WALLED CAVITY						
RESISTANT	27	7	2	21	9	8
SENSITIVE	65	14	5	31	5	5
P VALUE	0.01	0.133	0.599	0.001	0.001	0.001

CAVITARY CONSOLIDATION						
RESISTANT	20	9	2	20	8	7
SENSITIVE	54	12	5	14	8	4
P VALUE	0.106	0.009	0.599	0.001	0.003	0.001
CONSOLIDATION						
RESISTANT	9	5	6	6	8	15
SENSITIVE	38	14	4	31	15	9
P VALUE	0.78	0.525	0.002	0.472	0.079	0.001
FIBROSIS						
RESISTANT	12	2	3	5	3	2
SENSITIVE	36	0	1	11	2	5
P VALUE	0.406	0.005	0.007	0.278	0.028	0.599
ATELECTASIS						
RESISTANT	6	5	4	1	1	2
SENSITIVE	10	0	0	7	3	0
P VALUE	0.085	0.001	0.001	0.563	0.828	0.005
BRONCHIECTASIS						
RESISTANT	6	7	6	1	2	2
SENSITIVE	24	5	1	7	1	0
P VALUE	0.927	0.001	0.001	0.563	0.047	0.005
NODULAR INFILTRATION						
RESISTANT	37	32	30	32	30	26
SENSITIVE	124	82	68	97	58	49
P VALUE	0.221	0.008	0.002	0.094	0.001	0.001

We also did an sub analysis of Cavity with nodularity where among MDR-TB patients 65 had any type of cavity either single or multiple and among that 47(72%) had cavity with nodularity whereas among the Drug sensitive TB patients 130 patients had any type of cavity and among them 37 (28%) had nodularity.This difference was also statistically significant with P value of 0.001.

Similarly we also compared the impact of ATT intake on presence of cavity with nodularity which showed among 112 patients on ATT 52(46%) had nodularity whereas among 156 who were not on ATT 32(20%) had nodularity, there was also statistically significant difference among them with more prevalence in patients on ATT.

IV. Discussion

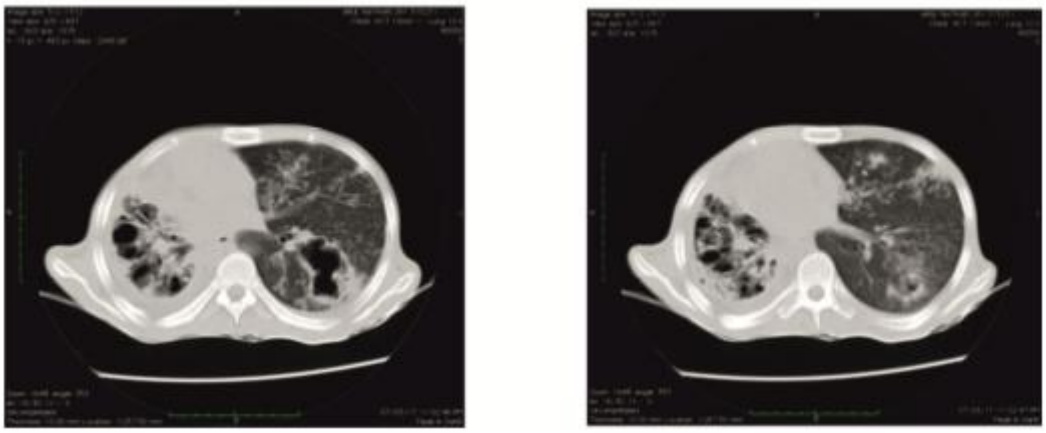
The main aim in this study was to demonstrate the imaging findings in CT chest in MDR-TB and to compare the imaging findings with those of drug-sensitive TB. The mean age of patients with MDR-TB was parallel to drug-sensitive TB (46 years versus 43 years). Patients commonly were from third and fourth decade and there was no significant difference in terms of age distribution between resistant and sensitive group which is similar to previous study done by Shahram Kahkoueeet al[9]. Male patients were common in this study with a ratio of 2.39:1. This was analogousto that of previous studies done by Koh WJ et al[10].Next we assessed the history of ATT, This history of previous ATT was significantly more common in the MDR-TB patients with P value of 0.001 and with an odds ratio of 8.05. It is thus clear that a patient who has previous history of ATT has approximately 8 times higher risk of becoming resistant to drugs compared to the group who have not taken ATT which was also similar to the study done by Koh WJ[10].

The frequentlydetected CT findings in MDR patients were multiple cavities, that to more than five, thick walled cavity, cavitary consolidation, atelectasis, pleural effusion and lymphadenopathy. The distribution of the imaging findings were most commonly seen in the upper lobes of lung, predominantly involving the right upper lobe. Multiple cavities were more prevalent in MDR-TB where 73.5% of patients had multiple cavities in MDR group compared to 37.5% in drug sensitive patients which was also statistically significant P value < 0.05 and odds ratio of 7.7. Similarly, the incidence of five and more cavities is also higher in MDR group, which was also statistically significant with P value of 0.010 and an odds ratio of 6.5.

Thick walled cavities is one of the commonest CT finding in MDR-TB patients compared to non MDR group with a statistical significance of 0.001 and odds ratio of 2.8. In MDR-TB patients with history of ATT intake, multiple and thick walled cavities were commonly seen, also cavity with nodularity were more common. Lobe wise multiple cavities were commonly seen in right upper lobe followed by left upper lobe in MDR-TB patients. We also did statistical analysis on difference in the individual lobe wise distribution of multiple cavities with drug susceptibility. MDR had significantly common occurrence of multiple cavities compared non MDR

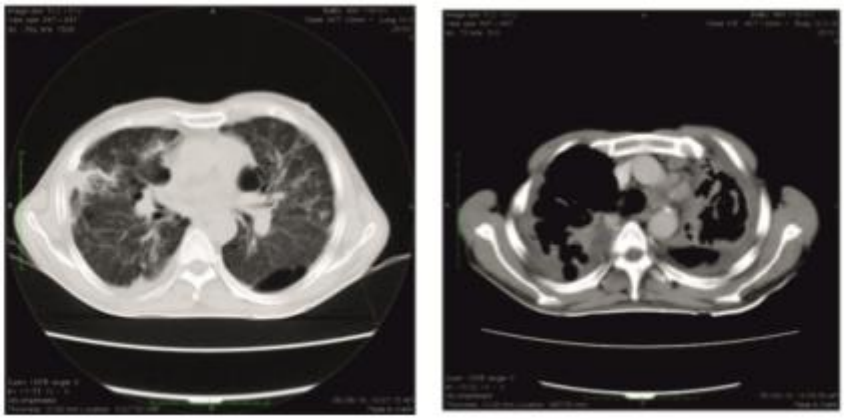
with P value less than 0.5 in all lobes which correlated with the study by Chung et al. Cavities form the key means of spread of disease. The cavity wall reduces the penetration of bactericidal drugs and promotes the growth and multiplication of bacilli. Hence, a large number of bacilli are harboured within the cavities. Also the therapeutic concentration of the bactericidal drug may not be attained within the bacilli that survive within the cavity which further promotes the occurrence of mutations leading to drug resistance. This, explains the higher incidence of multiple and thick walled cavities. The presence of cavities in a patient renders the patient highly infectious and increases the spread of infection to the general population. Hence, prompt diagnosis and treatment of these patients are utmost essential. These observations correlated well with the study conducted by Cha JH et al[12] in which they had proved that multiple and thickwalled cavities were significantly more commonly seen in MDR-TB. Also in another study done in Iran multiple cavities turned out as important characteristic of MDR-TB since TB bacilli can settle there rising the risk of MDR-TB. Another study by Zahirifardet al[13] manifested that multiple cavities were even more common in MDR-TB than in drug-sensitive TB: 40% in MDR-TB versus11% in drug-sensitive TB which also correlates with our study.

Figure 1: Multiple thick walled cavities



Cavitary consolidation is one another finding commonly seen in MDR group in our study which is also statistically significant with P value of 0.001 and odds ratio of 2.55. Cavitary consolidation is a common feature in right upper lobe and left upper lobe while there is statistical difference between MDR and non MDR in left upper lobe, there is no such statistical difference in right upper lobe. It was observed that drug sensitive patients had thin walled cavities mostly with adjacent nodular infiltration in the related segment, but MDR-TB cavities are mostly seen surrounded by area of pulmonary consolidation with thick walls. This feature seen in the study by Scott M et al is also seen in our study with predominance of thick wall cavities with surrounding consolidation in drug resistant cases[14].

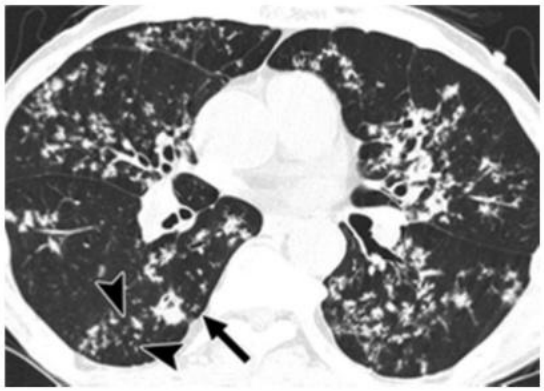
Figure 2: Cavity with consolidation



Atelectasis or volume loss is one another important chronic finding seen in TB particularly in MDR patients. There significant difference in prevalence of atelectasis in MDR patients with P value of 0.007 and an odds ratio of 2.9. In MDR-TB atelectasis was commonly seen in right upper lobe and middle lobe with significant difference in right middle lobe as compared to controls.

Lymphadenopathy was predominantly seen in MDR-TB patients with a prevalence rate of 23.5% compared to that of 2.5% in DS-TB patients.This difference was statistically significant with P value of 0.001 and an odds ratio of 12. Lymphadenopathy in CT due to TB may be both calcified and non-calcified. Calcified lymph node is seen more commonly in MDR group than in drug sensitive group. Similarly non calcified lymph nodes were also seen commonly in MDR-TB patients with a statistically significant difference and P-value of 0.001. Our study correlated well with the finding of ShahramKahkoueeet al[9] and Zahirifard et al[10]. In these studies also the incidence of lymphadenopathy was commonly seen MDR-TB cases.

Figure 3: Centriacinar nodule with tree in bud appearance

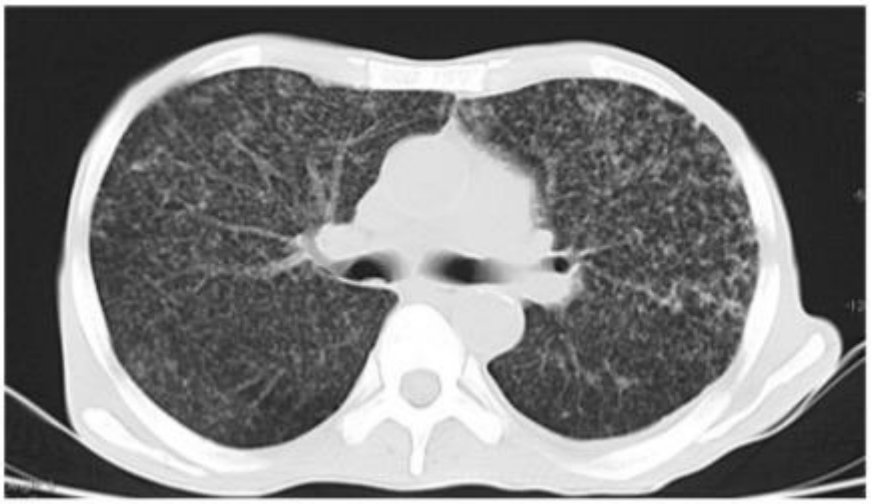


Pleural effusion is a common finding in MDR-TB patients with double the prevalence to that of DS-TB cases. The difference is statistically significant with P-value of 0.015 and odds ratio of 3.7. Contrary to the previous studies done, which didn't show any significant difference between drug sensitive and resistant patients[15].

Single cavity was commonly seen in drug-sensitive group with a prevalence rate of 32.5% as compared to 22% in MDR-TB. Single Cavity which was predominantly seen in DS-TB patients was commonly seen in right upper lobe while in MDR patients single cavity was commonly seen in left upper lobe. They were statistically significant, with P-value less than 0.05 in both situations.

Miliary pattern of TB is seen in very few number of cases. In our study, only 6 cases had miliary TB among them all belonged to the drug-sensitive group.

Figure 4: Miliary pattern

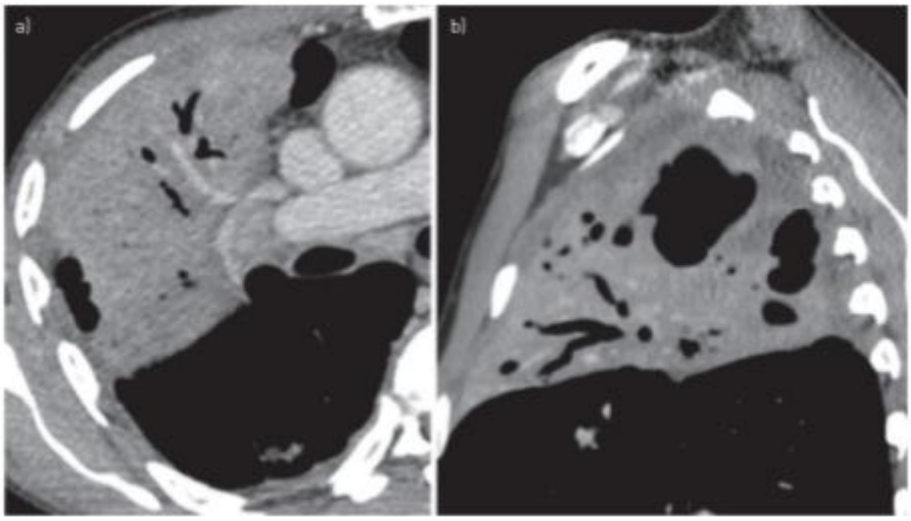


Nodular infiltration is a common CT finding in TB patients, seen in both drug resistant and sensitive groups. About 84% of MDR patients and 78% of non MDR patients had features of nodular infiltration in CT and hence there was no statistically significant difference between both groups with P-value of 0.304. Though the distribution was seen in almost all lobes, there was significant difference between MDR and non MDR patients with statistically significant difference seen in middle lobe, lingula and lower lobes.

There was also no statistically significant difference between both the groups with regard to the presence of thin walled cavities and cavities with intermediate wall thickness.

Consolidation was seen in 51% of cases and 41% of controls. There was no significant statistical difference in the presence of consolidation between these two groups. Consolidation was commonly seen in left lower lobe in MDR patients with statistically significant difference over DS-TB patients. While in drug-sensitive patients consolidation was commonly seen in right upper lobe. This was contrary to previous studies which did not detect significant differencebetween lobes[12]. There was no statistically significant difference between both groups with P value more than 0.05 (0.133).

Figure 5: Consolidation of right upper lobe



Chronic changes like fibrosis were also analysed. Fibrosis was seen in 37% of cases and 22% of controls. Fibrosis or fibro-destruction of lung is seen commonly in upper lobe of right lung in both groups, followed by left upper lobe. This finding in our study did not correlate with the study done by ShahramKahkoueeet al[9], in which fibrosis was seen in 65.1% of MDR-TB patients.But there was significant difference between the groups with p value of 0.016

There was significant difference in association of bronchiectasis between these groups with P value of 0.005. There were 32% of MDR-TB patients had bronchiectasis, compared to that of 16.5% in drug sensitive-TB cases. While bronchiectasis is seen commonly in right middle lobe and lower lobe followed right upper lobe. There was significant difference between MDR and non MDR group in middle lobe and lower lobe of right lung with p value of 0.001 in both lobes. The same results were also seen in a study done by Shahramkhokee et al [9] which explains the reason behind this pattern. It seems that bronchiectasis in the MDR-TB group often occurs in the presence of fibro-destructive changes which clarifies why superior lobes are more commonly affected.

While pleural thickening and pleural calcification are seen in few cases, there was not much of statistical difference between both the groups. The prevalence was too less among our study group patients which is not similar to previous studies which showed a statistically significant predominance of pleural thickening in MDR patients.[16]

The limitation of our study is selection bias. Not every patient with MDR-TB and DS-TB undergo CT. Patients with severe symptoms such as haemoptysis, or when there is suspicion of bronchiectasis or collapse or those with atypical clinical manifestations tend to undergo CT. Therefore, our study may have a selection bias for patients who had severe or atypical manifestations of TB.

V. Conclusion

There are certain unique thoracic computed tomographic findings more commonly observed in patients with MDR-TB. Multiple cavities especially thick walled cavities affecting almost all lobes but predominantly upper lobes suggest high possibility of MDR-TB. Cavitary consolidation, atelectasis, bronchiectasis and

lymphadenopathy are the other predominant features in our study which suggest the possibility of MDR-TB. While single cavity is a common feature in drug sensitive cases particularly involving the upper lobes, there is no significant difference in the incidence of centriacinar nodules and consolidation between the two groups namely MDR-TB and DS-TB. Knowledge of the typical CT findings of MDR-TB prompts earlier evaluation for drug sensitivity which is useful for selecting proper anti-TB treatment in infected patients before reaching a definitive diagnosis based on bacteriology. This, together with good therapeutic compliance is the best strategy for controlling this important public health problem of MDR-TB.

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