Original Article ISSN (O):2395-2822; ISSN (P):2395-2814

To Study Clinico-Radiological Profile of Multi-Drug Resistant Tuberculosis Patients

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Received: February 2019
Accepted: February 2019

ABSTRACT

Background: Drug resistance is a threat to TB control program worldwide. Patient infected with multiple drug resistant strains are less likely to become cured. Management of resistant cases is complex and presents therapeutic limitations. Patients with multidrug resistant strains are more prone to treatment failure, progresses to more chronic forms of the disease and death. In most areas of the world, the routine use of drug susceptibility tests, let alone cultures to diagnose tuberculosis or multidrug resistant tuberculosis is beyond the scope of health care resources. According to Global Tuberculosis Report 2015, about 3.3% of newly diagnosed patients had multidrug resistant tuberculosis and 20% of previously treated Tuberculosis cases were estimated to have Multidrug resistant Tuberculosis (MDR-TB). This present study was conducted in the department of chest and TB, Government medical college, Amritsar, with an aim to study the clinico-radiological profile of patients with multidrug resistant tuberculosis. **Methods:** A prospective study was conducted at the Chest and TB hospital, Amritsar which included 100 diagnosed patients of Multidrug Resistant Tuberculosis. Clinico-radiological profile of these patients was determined. **Results:** Out of 100 study population, maximum number of patients belonged to the age group of 21-30 years i.e. 26% followed by 22% in the age group of <20 years. Most common symptom was cough with expectoration which was present in 94 (94%) patients. 97 (97%) patients were having previous history of ATT, 3 (3%) patients were not having any previous history of ATT. On radiology unilateral disease was present in 48 (48%) patients, bilateral disease present in 52 (52%) patients. Parenchymal infiltration was present in 79 (79%) patients. Cavitation was present in 23 (23%), Fibrocavitary disease was present in 37 (37%) study subjects. Previous history of ATT had significant association with extent of lesion on chest x- ray ($p < 0.05$). **Conclusion:** clinico-radiological characteristics should always be determined where appropriately administered drugs have not achieved necessary drug levels to deal with all the population of mycobacteria, to timely modify and strengthen the national programs, and evaluation of trends in drug resistance pattern.

Keywords: Tuberculosis, MDR, CBNAAT, Drug-Resistance.

INTRODUCTION

Tuberculosis, a disease caused predominantly by Mycobacterium tuberculosis.[1] Tuberculosis (TB) is an old disease – studies of human skeletons showed that it has affected humans for thousands of years.[2] As per India TB report 2018, Global incidence of TB is (including HIV) 1,04,00,000 and incidence of TB in India is 27,90,000 i.e. 211 cases per lakh population.[3] In 2017, TB caused an estimated 1.3 million deaths (range, 1.2–1.4 million) among HIV-negative people, and there were an additional 300 000 deaths from TB (range, 266 000–335 000) among HIV-positive people.[4] Strains of Mycobacterium tuberculosis resistant to both isoniazid and rifampicin with or without resistance to other drugs have been termed multidrug resistant tuberculosis. Drug-resistant TB is a persistent threat, with 490 000 million cases of multidrug-resistant TB (MDR-TB) emerging in 2016 and an additional 110 000 cases that were susceptible to isoniazid but resistant to rifampicin (RR-TB), the most effective first-line anti-TB drug. WHO estimated incidence of Rifampicin (R) and MDR-TB in India is estimated to be around 147000. This translates to around 11 patients per 100 000 population annually as per the Global TB Report, 2017.[5]

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Clinical characteristics of patients have also been recognized where appropriately administered drugs have not achieved necessary drug levels to deal with all populations of mycobacteria. Exposure to a single drug — due to irregular drug supply, inappropriate prescription or poor adherence to treatment — suppresses the growth of susceptible bacilli to that drug but permits the multiplication of drug-resistant organisms.[6]

This research is believed to contribute to identifying the potential risk factors for MDR-TB, so that the management of patients will also be strengthened through preventing these factors, alongside patient treatment which will have a positive impact on successful treatment outcome, and decrease the burden of the disease as a whole. The treatment of MDR-TB is extremely challenging owing to the complexity of chemotherapy regimens, the toxicity of alternative drugs, and the high cost of these drugs. Therefore, it is particularly important to identify the risk factors associated with DR-TB.

There is a paucity of studies on patients with multidrug resistant tuberculosis. In this study we present data regarding the clinico-radiological characteristics of MDR-TB patients.

MATERIALS AND METHODS

The present observational prospective study was carried out in the department of Chest and Tuberculosis, Government Medical College, Amritsar. The study included 100 diagnosed patients of Multidrug Resistant tuberculosis (MDR-TB) from an RNTCP-Certified Laboratory after taking informed consent. Patients who were not multidrug resistant (MDR) but have Rifampicin- resistance were also included in the study. It is to be noted that R resistance is quite rare without H resistance. Majority of DST results with R resistance will also be H resistant, i.e., MDR-TB. This has been substantiated in the National Drug Resistance Survey (2014-16). Therefore, RNTCP has taken the programmatic decision that patients, who have any R resistance, should be managed as if they are an MDR-TB patient and this is in line with WHO global guidelines for PMDT.5The approval of institutional thesis and ethics committee was taken before the start of study.

Inclusion criteria:

1. Patients with documented evidence of drug resistance through CBNAAT (Cartridge Based Nucleic Acid Amplification)
2. Patients with documented evidence of drug resistance through Line Probe Assay (LPA).
3. Age more than 18 years.

Exclusion criteria:

1. Multidrug resistance suspects.
2. Critically ill or moribund patients.
3. Patients having extra-pulmonary tuberculosis
4. Mono-resistant to isoniazid.
5. Patients with extensively drug resistant tuberculosis XDR-TB

All diagnosed Patients of Multidrug resistant Tuberculosis (MDR-TB) were admitted for Cat-IV treatment under PMDT-RNTCP in DOTS PLUS ward, department of TB & Chest, Government Medical College, Amritsar for pre-treatment evaluation for a minimum duration of seven days. The protocol was clearly explained to patient/care provider before enrolment and informed consent was taken from each patient.

Demographic characteristics, complete detailed clinical history regarding total duration of illness, smoking history, drug/alcohol abuse, mental illness, diabetic history, previous anti tuberculosis therapy, family history of anti- tuberculosis therapy and any contact with tuberculosis patients was taken from the patients. All patients were subjected to chest radiograph.

The data thus obtained was analysed statistically and compiled to reach valid conclusions.

RESULTS

This study was conducted in the Department of Chest and Tuberculosis, Government Medical College, Amritsar, which included 100 patients who were microbiologically confirmed cases of MDR-TB either through Cartridge Based Nucleic Acid Amplification Technique or Line Probe Assay. Study included rifampicin- resistant and rifampicin-isoniazid resistant cases. In our study maximum number of patients belonged to the age group of 21-30 years i.e. 26% followed by 22% in the age group of <20 years. Minimum patients were in age group >60 years i.e. 6%. Mean age was 35.56 years. Maximum patients were males (66%), while females contributed (34%) of patients. Out of 100 patients, 45 (45%) patients were from rural population and 55 (55%) patients belonged to urban areas. Among 100 cases, most of the patients 62 (62%) were married; 36 (36%) were unmarried, 1(1%) was divorced and 1 (1%) was widow. Most of the patients were Labourers 30 (30%), followed by students 23 (23%). Twenty two (22%) patients were Housewives; six (6%) patients were Farmers. Four (4%) patients were Drivers, and two patients (2%) were Teachers and three (3%) were unemployed in this study. Out of 100 cases, 57 (57%) patients were Rifampicin mono resistant and 43 (43%) were Rifampicin-isoniazid (RH) resistant cases in this study.

Table 1: Frequency of Presenting Symptoms

Symptoms	Number Of Cases	Percentage
Cough with Expectoration	94	94%
Fever	66	66%
Breathlessness	53	53%
Hemoptysis	11	11%
Loss of Appetite	56	56%
Weight loss	57	57%

Most of the patients taken in the study were having more than one complaint for more than one month and most common symptom was cough with expectoration which was present in 94 (94%) of cases followed by fever which was present in 66 (66%) cases. Weight loss was present in 57 (57%) of cases, loss of appetite in 56 (56%) of patients, breathlessness was present in 53 (53%) of cases and hemoptysis was present in 11 (11%) of cases.

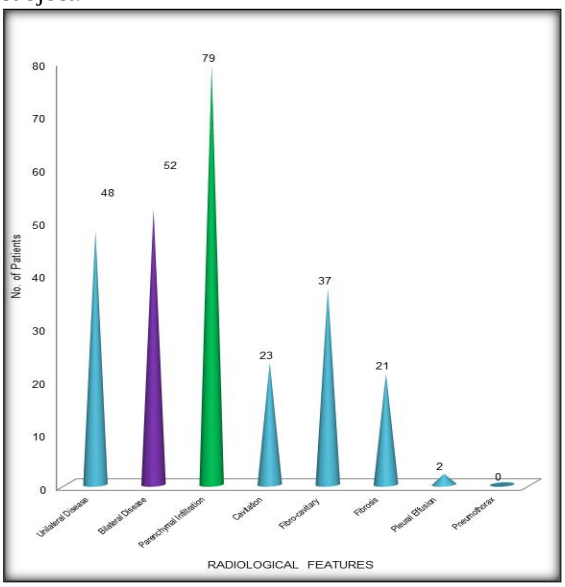
In our twenty seven 27 (27%) patients were Diabetic. Out of 100 patients, 3 (3%) were diagnosed cases of HIV/AIDS. Among comorbidities other than diabetes and HIV, most common comorbid condition was COPD present in 8 (8%) which was smoking related, followed by Hypothyroidism in 5 (5%) of cases. Hypertension in 3 (3%), depression in 1 (1%), hydro-pneumothorax in 1 (1%), sick euthyroid syndrome in 1 (1%). Most common addiction was alcoholism, present in 25 (25%) of study subjects, followed by smoking which was present in 20 (20%) of the cases and heroin addiction was present in 1 (1%) of cases. 3 (3%) of the cases were having other types of drug addiction and 47 (47%) of study subjects were not having any drug addiction. Out of 100 study subjects, 97 (97%) patients were having previous history of ATT, 3 (3%) patients were not having any previous history of ATT. Previously treated cases included patients with recurrent TB (15%) and loss to follow up (9%).

History of contact was present in 32 (32%) patients. Among these 32 patients history of contact with pulmonary TB case was present in 25 (25%) of patients and contact history with MDR-TB case was present in 7 (7%) of the study subjects. 68 (68%) of cases were not having any history of contact with TB case. Most of the patients taken in the study were having more than one sign. Pallor, clubbing and lymphadenopathy were present in 89 (89%), 17 (17%), 26 (26%) of the patients respectively.

Table 2: Radiological Features –Wise Distribution of Cases

Radiological Findings	Number Of Patients	Percentage
Unilateral Disease	48	48%
Bilateral Disease	52	52%
Parenchymal Infiltration	79	79%
Cavitation	23	23%
Fibro-cavitary	37	37%
Fibrosis	21	21%
Pleural Effusion	2	2%
Pneumothorax	0	0

In most of the patients taken in the study more than one finding was present in chest x-ray. Above table shows that unilateral disease was present in 48 (48%) patients, bilateral disease present in 52 (52%) patients. Parenchymal infiltration was present in 79 (79%) patients. Cavitation was present in 23 (23%), Fibrocavitary disease was present in 37 (37%) study subjects. On the other hand fibrosis was present in 21 (21%) study subjects. 2 (2%) patients were having pulmonary as well as extra-pulmonary involvement i.e. pleural effusion was present. Pneumothorax was not seen in any of the study subject.

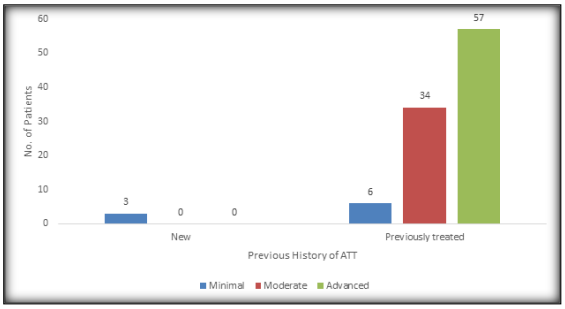


In our study, 9 (9%) patients were having minimal disease. 34 (34%) and 57 (57%) patients were having moderate and far advanced disease respectively.

Table 3: Association of Previous History of Att with Extent of Lesions

Previous H/O ATT	Extent of lesion			Total
	Minimal	Moderate	Advanced	$\chi 2$ = 31.27 df = 2, p < 0.05
New	3 (100.0%)	0 (.0%)	0 (.0%)	
Previously treated	6 (6.2%)	34 (35.1%)	57 (58.8%)	

From above table it is evident that previous history of ATT had significant association with extent of lesion on chest x- ray ($p < 0.05$).



DISCUSSION

Drug resistant TB has been known from the time Anti-TB drugs were first introduced for the treatment of TB. The problem of DR-TB cannot be addressed completely by standalone systems for detection and treatment of drug resistance. Strong

system to detect, successfully treat and ensure long-term disease free status of TB patients, are required to prevent emergence of resistance. In clinical settings, an inadequate or poorly administered treatment regimen allows drug resistant mutants to become the dominant strain in a patient infected with TB. Therefore, clinico-radiological characteristics should always be recognized where appropriately administered drugs have not achieved necessary drug levels to deal with all the population of mycobacteria.

According to RNTCP status report 2011, TB primarily affects people in their most productive years of life. Almost 70% of TB patients are aged between the ages of 15-54 years of age and more than 50% of the female cases occur before 34 years of age. This is almost in accordance with our data where majority of the patients are in 21-30 years of age.[7] Udwadia and Moharil, Sharma et al; also reported prevalence of younger age group among MDR-TB patients with the mean age of their study groups being 29.7 years and 33.25 years respectively.[8] High level of drug resistance among younger patients may be due to more exposure to drug-resistant cases. In our male dominating society males have more access to health facilities as compared to female.

The main predictor of resistance to a particular drug is the demonstration of its prior use in monotherapy for more than 1 month. To obtain evidence of possible inadvertent or direct monotherapy, it is essential to be meticulous in obtaining the history of anti-TB treatment in all presumptive cases of MDR-TB. In our study 57 (57%) patients were Rifampicin mono resistant and 43 (43%) were Rifampicin-isoniazid (RH) resistant. In study by Dr Nirmalya Manna, 53.7% patients were found to be resistant to Rifampicin only, 46.3% to both Rifampicin and Isoniazid.[9]

Among 100 patients taken in the study, most common symptom was cough with expectoration present in 94% of cases followed by fever in 66%. Weight loss in 57% and loss of appetite in 56% of patients. Breathlessness was present in 53% and hemoptysis in 11% of cases. Majority of patients who were taken in the study had more than one symptom for more than one month.

Among 100 cases, 27% patients were diabetic, 73% were non- diabetic and 3% were HIV positive. Diabetes is a one of the important risk factor for active tuberculosis. In our study diabetes mellitus was most common comorbidity. Among comorbidities other than diabetes and HIV, most common comorbid condition was COPD present in 8%. Study done by More et al; reported that, out of 96 MDR-TB patients, 27 (28.13%) patients had a self-reported comorbidity which included 6 (29.62%) patients with diabetes mellitus and 2 (7.40%) patients with diabetes mellitus and hypertension, 3 (14.81%) patients who were HIV positive and 1 (3.70) had HIV with anemia.10 Datta et al; reported 1.9% HIV seropositivity among MDR -TB cases.[11]

In our study, 97 (97%) patients were having previous history of ATT, 3 (3%) patients were not having any previous history of ATT. Previously treated cases included patients with recurrent TB (15%) and loss to follow up (9%). In our study previous history of ATT had significant relation ($p < 0.05$) with extent of lesion on chest x-ray. Study showed that majority of the patients with MDR-TB had acquired drug resistance. Study done by Akshata et al; out of 69 patients, 55 patients re-treatment (Cat-II) failure and 14 patients (20.3%) were Cat-I failure. 3 patients had a history of treatment with 2 or more second line drugs for more than one month.[12] Previous history of ATT is a strong risk factor for emergence of drug resistance, reason could be non-compliance or non-adherence to treatment, repeated hospitalizations which leads to exposure to drug resistant strains, use of anti-TB drugs as monotherapy, addition of one anti-TB drug to failing regimen, intolerance to drugs or adverse effects leading on to default behaviour may lead to emergence of drug resistance.

In our study history of contact was present in 32% patients. Among 32% patients, 25% and 7% of cases had history of contact with pulmonary TB and MDR-TB patients respectively. Study by Mulu et al; reported that out of 153 MDR-TB cases, 44 (28.8%) had history of contact with MDR- TB patients.[13]

In our study most of the patients taken were having more than one finding on chest x-ray. 48 (48%) and 52 (52%) patients were having unilateral and bilateral disease respectively. Parenchymal infiltration was present in 79 (79%) patients. Cavitation, fibrocavitary and fibrosis, pleural effusion was present in 23 (23%), 37 (37%), 21 (21%), 2 (2%) respectively. Among 100 study subjects 9 (9%), 34 (34%) and 57 (57%) patients were having minimal, moderate and far advanced disease. Mishra et al; reported similar findings, out of 244 patients, 224 (91.8%) patients had bilateral lung involvement, whereas 20 (8.2%) patients had unilateral lung involvement, along with it, 209 (85.7%) patients had cavitatory lung disease and 35 (14.3%) patients had non cavitatory lung disease. Of these patients, 130 (58.04%) had bilateral far advanced disease, 89 (39.7%) patients had bilateral moderately advanced disease and 5 (2.2%) patients had bilateral minimal lung disease.[14]

A study done by Icksan et al; which compares chest X-ray findings of two groups of patients, involving 183 DS-TB patients and 183 MDR-TB patients. MDR-TB group have 177 (96%) patients with large lesions, 6 (4%) with medium lesions, and no small lesions. DS-TB group have 55 (30%) patients with small lesions, 78 (43%) with medium lesions, and 50 (27%) with large lesions.[15]

The limited drug penetration into the cavity that harbour large mycobacterial load and a greater number of Acid fast bacilli (AFB) in moderately advanced or far advanced disease is believed to contribute to drug resistance. Change in size of cavities and increase in the size of existing lesions and appearance of new lesions are signs of disease progression and activity. Although radiological worsening is not a very reliable indicator for predicting drug resistance, it serves to compliment the clinical and bacteriological evidence of the disease.

CONCLUSION

MDR-TB is a cause of great concern around the world. Not only does the emergence of MDR-TB signal that control strategies are failing; MDR-TB itself could become an obstacle to effective anti-tuberculosis treatment. So clinico-radiological characteristics should always be determined where appropriately administered drugs have not achieved necessary drug levels to deal with all the population of mycobacteria, to timely modify and strengthen the national programs, and evaluation of trends in drug resistance pattern. Therefore early detection of drug resistance among re-treatment cases is required.

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How to cite this article: Pandhi N, Kajal NC, Malhotra B, Kaur L, Singh A, Kaur G, Shukla AK, Dadra R, Neki NS. To Study Clinico-Radiological Profile of Multi-Drug Resistant Tuberculosis Patients. Ann. Int. Med. Den. Res. 2019; 5(2):TB25-TB29.

Source of Support: Nil, **Conflict of Interest:** None declared