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Internal Medicine Section

Clinico-radiological Difference between Primary and Secondary MDR Pulmonary Tuberculosis

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ABSTRACT

Introduction: Multidrug Resistant Tuberculosis (MDR-TB) is classified into primary and secondary type depending upon history of Anti-TB drug received in past. MDR-TB generally remains undetected in newly detected TB cases as the index of suspicion is low.

Aim: To compare the clinical and radiological features of primary and secondary MDR-TB.

Materials and Methods: This was a hospital based retrospective observational study on 74 MDR Pulmonary Tuberculosis (PTB) patients seen in the pulmonary medicine department of a tertiary hospital of Bihar, India between 1st January 2016 and 31st December 2017. Because of the lack of conventional culture or Line Probe Assay (LPA) facilities at the institute, rifampicin resistance on GeneXpert was taken as a surrogate marker for MDR-TB.

Results: A total of 85 patients were diagnosed as having MDR PTB in the study period. Eleven patients were excluded from the study due to non-availability of clinical details. Out of the 74 patients, 19 (25.67%) were primary MDR cases and 55 (74.33%) were secondary. The mean age of primary MDR-TB was 24.2±13.8 years and secondary MDR-TB was 27.8±13.13 years. A 78.9% of primary MDR and 81.8% of secondary MDR patients were male. Patients were symptomatic for a mean duration of 4.5 months in primary and 11.9 months in the case of secondary MDR-TB before the diagnosis. Haemoptysis as a presenting symptom was more common in primary MDR-TB (47.3%) than in secondary MDR-TB (20%) ($p<0.05$). On the other hand breathlessness was more common in secondary MDR tuberculosis (52.7% vs 15.7%) ($p<0.05$). Moderate lesion on Chest X-ray (CXR) was most common in both primary and secondary MDR-TB (73.68% vs 45.54%) ($p<0.05$).

Conclusion: Haemoptysis was more common in primary MDR than secondary MDR PTB patient, while breathlessness occured more frequently in secondary MDR PTB; bilateral and moderate lesion in chest radiograph was seen more with primary MDR PTB.

Keywords: Chest X-ray, GeneXpert, Multidrug resistant tuberculosis

INTRODUCTION

Tuberculosis is a major health problem globally, more so in developing countries like India. Multidrug-Resistant Tuberculosis (MDR-TB) refers to tuberculosis infection caused by Acid-Fast Bacteria (AFB) organisms resistant to at least two drugs, isoniazid and rifampicin [1]. In May 2016, World Health Organisation (WHO) issued guidelines that people with TB resistant to rifampicin, with or without resistance to other drugs, should also be treated with MDR-TB treatment regimen. This group of patients is sometimes referred to as MDR/RR-TB [2]. According to the Global TB Report 2017 released by the WHO, India topped the list of seven countries, accounting for 64% of the over 10 million new Tuberculosis (TB) cases worldwide in the year 2016 [3]. MDR-TB is a major challenge in TB control programmes. It has been spreading rapidly across the globe, and in recent years an estimated 3.5% of new cases and 20.5% of previously treated TB cases have MDR-TB [4].

MDR-TB is divided into primary MDR-TB and secondary (or acquired) MDR-TB. Secondary MDR-TB refers to resistance developed during or following chemotherapy in patients who had previously been regarded as having Drug Sensitive Tuberculosis (DS TB) [5]. In India, due to the limited availability of Molecular method like Line Probe Assay (LPA) and conventional culture media and Drug Sensitivity Test (DST) most of the MDR-TB is generally labelled on the basis of rifampicin resistance detected by GeneXpert.

Imaging has an important role in diagnosis of TB, especially because of the lack of availability and poor sensitivity of microbiological tests. There are various studies which compare the radiological features of drug sensitive TB and MDR-TB. But there is limited literature comparing the clinical and radiological features of primary and secondary MDR-TB. The suspicion of MDR in new PTB case is generally low and so continues transmission of infection before getting diagnosed. Studies have shown that multiple cavities and signs of chronicity, fibrosis and bronchiectasis are especially common in secondary MDR-TB [6,7].

This study was designed to assess the clinical and radiological differences between primary and secondary MDR-TB.

MATERIALS AND METHODS

This was a hospital based retrospective observational study of MDR PTB patients diagnosed in the pulmonary medicine department of a tertiary hospital of Bihar, India between 1st January 2016 and 31st December 2017.

Approval was obtained from the institutional ethics committee (Serial no 72, IEC No 75 dated 30 Nov 2017). The patients' case records were examined to extract detailed history, baseline demographic characteristics, clinical findings, radiological findings and reports of routine laboratory investigations like complete blood count, random blood sugar and retroviral status etc. Patients with no record of baseline characteristics and laboratory findings were excluded from the study. Patients who had been diagnosed as MDR outside of institute or already getting treatment were excluded from the study. Because of the lack of conventional culture or LPA facilities at the institute, rifampicin resistance on GeneXpert was taken as a surrogate marker for MDR-TB.

Plain posteroanterior Chest Radiographs (CXR) were taken for all the patients. The CXR was classified using the criteria used by the National Tuberculosis Association of USA [8,9].

Minimal lesions are the ones which have slight to moderate density but do not contain demonstrable cavitation. They may involve a

small part of one or both lungs, but the total extent, regardless of distribution, should not exceed the volume of lung on one side that occupies the space above the second chondro-sternal junction and the spine of the fourth or body of the fifth vertebra.

Moderately advanced lesions are defined as lesions which may be present in one or both lungs, but the total extent should not exceed the following limits: disseminated lesions of slight to moderate density that may extend throughout the total volume of one lung or the equivalent in both lungs; dense and confluent lesions limited in extent to one third the volume of one lung; total diameter of cavitations, if present, <4 cm.

Lesions which are more extensive than moderately advanced are defined as far advanced lesions.

Other features on CXR such as unilateral or bilateral involvement, the predominant type of lesion, viz., consolidation, cavitation and fibrosis and pleural effusion were also recorded.

STATISTICAL ANALYSIS

All the data were entered in Microsoft excel 2016. We have used IBM SPSS statistics for windows, version 21.0 Armonk, NY, USA, IBM corporation software for analysis. The quantitative data were represented as mean±SD and qualitative data as proportion in the form of percentage. Unpaired t-test was used for comparison of means and proportions between two groups. A two-sided p-value less than 0.05 was considered as statistically significant.

RESULTS

A total of 85 patients were diagnosed as having MDR-TB during that study period. Eleven patients were excluded from the study due to non-availability of clinical details. Out of the 74 patients included, 19 (25.67%) were new cases (Primary MDR PTB) and 55 (74.33%) were previously treated (Secondary MDR PTB).

[Table/Fig-1] shows the clinical and demographic characteristics of MDR-TB. The mean age of primary MDR-TB was younger than secondary MDR-TB (24.2±13.8 years vs 27.8±13.13 years). Males were predominant in both groups (78.9% of primary MDR and 81.8% of secondary MDR patients). Patients were symptomatic for a mean duration of 4.5 month in primary and 11.9 months in the case of secondary MDR-TB before getting diagnosed.

Characteristics	Primary (n=19) (100%)	Secondary (n=55) (100%)	p-value*
Age (years, mean±SD)	24.2±13.8	27.8±13.13	0.3125
Male percentage	15 (78.9)	45 (81.8)	0.7809
Below Poverty Line (BPL)	13 (68.4)	24 (43.6)	0.0623
Total Duration of Illness in months (TDI)	4.5±4.0	11.9±7.3	0.0001
Cough	19 (100)	55 (100)	
Fever	14 (73.6)	48 (87.2)	0.1664
Haemoptysis	9 (47.3)	11 (20)	0.0209
Shortness of Breath (SOB)	3 (15.7)	29 (52.7)	0.005
Anorexia	11 (57.8)	18 (32.7)	0.0533
Weight loss	5 (26.3%)	16 (29%)	0.8218

[Table/Fig-1]: Base line characteristics of MDR PTB patients.
*p-value based on t-test for comparison of means and proportions between two group

Haemoptysis as a presenting symptom was more common in primary MDR-TB (47.3%) than in secondary MDR-TB (20%) (p<0.05). On the other hand breathlessness was more common in secondary MDR-TB (52.7% vs 15.7%) (p<0.05).

The CXR findings of primary and secondary MDR-TB are summarised in [Table/Fig-2]. Cavities were more frequently observed in primary MDR-TB (47.3%) than in secondary MDR-TB (40%). In contrast fibrosis was more commonly seen in secondary MDR-TB (38.18%) compared to primary MDR-TB (21.05%). Patients of secondary MDR-TB were more likely to have bilateral involvement (73.6%) compared to primary MDR-TB (58.1%). According to the criteria used by the National Tuberculosis Association of USA, moderate lesion is common in both primary and secondary MDR-TB (73.68% and 45.54% respectively) (p<0.05).

	Primary (n=19)	Secondary (n=55)	p-value*
Bilateral	14 (73.68%)	32 (58.18%)	0.2229
RT:Lt	3:2	18:5	
Cavity	9 (47.36%)	22 (40%)	0.5746
Consolidation	15 (78.94)	44 (80%)	0.9216
Fibrosis	4 (21.05%)	21 (38.18%)	0.1735
Chest X-ray classification			
Minimal	2 (10.52%)	9 (16.36%)	0.5375
Moderate	14 (73.68%)	25 (45.54%)	0.0336
Advanced	3 (15.78%)	21 (38.18%)	0.0722

[Table/Fig-2]: Comparison of chest X-ray between primary and secondary MDR PTB.
*p-value based on t-test for comparison of means and proportions between two group

On blood investigations mild leucocytosis with neutrophilia was noted in both types of MDR-TB. Majority of the patients were sputum positive for acid fast bacilli at the time of diagnosis [Table/Fig-3].

Parameter	Primary (n=19)	Secondary (n=55)	p-value*
HB	10.8±1.56	10.71±1.43	0.8129
TLC	13060±5607	11710±2170	0.1372
Neutrophil	75.9±6.8	75.72±6.85	0.9215
ESR	32.8±16.8	31.24±14.84	0.7037
RBS	119.133.2	125.72±39.09	0.5113
Sputum AFB positive	13 (68.42%)	39 (70.09%)	0.8379

[Table/Fig-3]: Comparison of blood and sputum result in primary and secondary MDR PTB.
*p-value based on t-test for comparison of means and proportions between two group

DISCUSSION

There is no previous study which compares clinical and radiological features of primary and secondary MDR PTB. The ratio between primary and secondary MDR-TB in this study was noted to be 1:4. This high proportion of primary MDR is one of the important findings and could be related to the efficacy of TB control programme in the region, study population, sample size and methods used to measure drug resistance. While prevention of the development of drug resistance is of paramount importance for controlling TB, early detection and immediate enrolment as well as completion of an effective treatment regimen are keys to interrupting the on-going transmission, preventing deaths and reducing post tuberculosis sequelae. Studies with larger sample size are needed to find out the actual prevalence of primary and secondary MDR-TB in the region.

This study also looked at the difference in presenting symptoms and radiological findings between primary and secondary MDR-TB. Primary MDR-TB patients were younger than the patients with secondary MDR-TB. There was no significant difference in the gender composition of the two groups. Cough was present in all patients but haemoptysis and anorexia were more frequently reported by patients with primary MDR-TB. Patients with secondary MDR-TB presented more frequently with breathlessness. This may be due to sequalae of previous treatment leading to impaired pulmonary function; however pulmonary function was not checked in this study. Previous studies [6] have compared the CXR findings between drug sensitive TB to MDR-TB but we couldn't find any studies comparing the radiological findings of primary and secondary MDR PTB. The presence of cavities has been noted to

be more common in primary MDR than drug sensitive TB [7,10]. However, none of these studies have assessed the difference between primary MDR and secondary MDR-TB. Poor penetration of drug into cavities, which contain large numbers of mycobacteria, is believed to contribute to the development of acquired MDR-TB [7,11]. In our study, cavities were more frequently observed in primary MDR-TB than in secondary MDR-TB. On the other hand, fibrosis was more common in secondary compared to primary MDR-TB. This could be due to sequelae of previous treatment. Patients of secondary MDR-TB have more bilateral involvement compared to primary MDR-TB.

LIMITATION

Multi-drug resistance was labelled on the basis of rifampicin resistance detected by GeneXpert. The sample size was small. As it was a hospital based study, conclusions cannot be drawn about the prevalence of primary and secondary MDR-TB.

CONCLUSION

Haemoptysis along with bilateral and moderate lesion in chest radiograph was more common in primary MDR, while breathlessness was seen more frequently in secondary MDR PTB. Our index of suspicion for MDR-TB is low as patients are not symptomatic for about 4-5 months before getting diagnosed.

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