Original Article

Multidrug resistance in tubercular mediastinal adenopathy diagnosed by endobronchial ultrasound-transbronchial needle aspiration

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ABSTRACT

Background: Drug resistance in tuberculosis (TB) is a major public health problem. It is easy to assess for drug resistance in pulmonary samples, but the resistance pattern of TB in the mediastinal nodes has not been studied. The aim of this study is to assess the incidence of multidrug resistance in tubercular mediastinal adenopathy with the help of endobronchial ultrasound (EBUS)-guided transbronchial needle aspiration. **Materials and Methods:** This was a prospective study at a tertiary care teaching hospital in New Delhi where 102 patients with positive mycobacterial cultures from mediastinal lymph node aspirates taken with the help of EBUS were enrolled over 24 months and their drug sensitivity to the first-line antitubercular drugs analyzed. **Results:** There were 30 cases of drug resistance of 102 culture-positive cases. Of them, 8 patients had multidrug resistant TB (MDR-TB), 16 cases had only single drug resistance, and the remaining 6 cases had more than one drug resistance pattern but not MDR. In our study, the overall incidence of MDR-TB is 7.8% (8/102), although the incidence of MDR-TB in new and re-treatment cases is 2.2% (2/89) and 46.1% (6/13), respectively. **Conclusion:** Such a high percentage of drug-resistant patients is common in tertiary care hospitals; however, similar percentages may be found in other settings as well. Therefore, all efforts should be made to take samples for *Mycobacterium tuberculosis* culture from the involved nodes before commencing therapy to avoid treatment failures.

KEY WORDS: Drug-resistant tuberculosis, endobronchial ultrasound, mediastinal lymphadenopthy, tuberculosis

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Submitted: 10-Sep-2019 **Revised:** 09-Dec-2019 **Accepted:** 11-Dec-2019 **Published:** 27-Feb-2020

INTRODUCTION

Multidrug-resistant tuberculosis (MDR-TB), defined as resistance to at least isoniazid (H) and rifampicin (R), has become a significant public health problem worldwide and an obstacle to the effective global control of TB. India is one of the high-burden countries for TB as well as drug resistance. As per the WHO's "Global TB Report, 2018," 10 million people developed TB in 2017, and India accounted for 27% of these cases. Of around 500,000 new MDR-TB cases, 24% were reported from India. Globally, 3.5% of new TB cases and 18% of previously treated patients had MDR/rifampicin-resistant TB.[1]

Access this article online

Quick Response Code:

Website: www.lungindia.com

DOI: 10.4103/lungindia.lungindia_421_19

How to cite this article: Dhamija A, Goyal S, Guliani A, Raveendran R, Basu AK. Multidrug resistance in tubercular mediastinal adenopathy diagnosed by endobronchial ultrasound-transbronchial needle aspiration. Lung India 2020;37:130-3.

An estimate of drug resistance is extremely important in the epidemiology and control of TB. An assessment of the magnitude of drug resistance in extrapulmonary TB is not very well described globally, and data remain scantier for India. The emergence of drug resistant, MDR and extensively drug-resistant TB has emphasized the importance of establishing the drug susceptibilities of *Mycobacterium tuberculosis* (MTB) before starting antitubercular therapy (ATT).[2] The literature currently estimates the incidence of pulmonary drug-resistant TB only as sampling is easy. There are no estimates available for drug resistance in TB mediastinal adenopathy, as diagnostic assessment of the mediastinal lymph nodes was difficult and invasive. With the advent of a minimally invasive technique of endobronchial ultrasound (EBUS) in the past decade, the accessibility to these nodes has increased. The role of EBUS–transbronchial needle aspiration (TBNA) in the staging of lung cancer[3] and diagnosis of sarcoidosis[4,5] has been evaluated before. The past few years have seen growing use of EBUS in the developing world; many centers have reported the utility of EBUS for the diagnosis of tubercular mediastinal adenopathy.[6-8] Till date, no study on the incidence of drug-resistant TB in mediastinal lymphadenopathy has been published.

In the present study, we intend to evaluate the incidence of MDR in tubercular mediastinal adenopathy with the help of EBUS TBNA from the affected mediastinal lymph nodes, to compare the incidence of MDR in patients who have a history of prior ATT and new cases, and to look for resistance rates for each of the drugs tested, i.e., H, R, ethambutol (E), and streptomycin (S).

MATERIALS AND METHODS

This study was conducted by the departments of pulmonary medicine and microbiology at a tertiary care teaching hospital in New Delhi, India. The study population included cases from both the outpatient and inpatient subgroups, who were TB suspects with mediastinal lymphadenopathy as detected on chest X- ray/computed tomography (CT) of the thorax. It was a prospective study conducted over a period of 2 years (from September 2013 to September 2015) after approval by the Hospital's Ethics Committee (Approval number – EC/02/14/632).

The inclusion criteria for the present study were (1) patients with clinical features suggestive of TB with intrathoracic lymphadenopathy on chest X-ray or CT scan, (2) pyrexia of unknown origin with intrathoracic lymphadenopathy, and (3) intrathoracic lymphadenopathy without any symptoms. The exclusion criteria were (1) patients in whom an alternative diagnosis is established to explain adenopathy, (2) uncorrected coagulopathy, and (3) any contraindications to bronchoscopy or EBUS-TBNA.

Each patient was duly counseled and informed consent was obtained. A detailed study pro forma was filled out taking history from each patient. Emphasis was laid on history of TB in the past and drug history in patients who have received any form of ATT in the past.

EBUS-TBNA was carried out as an outpatient/inpatient procedure under local anesthesia with sedation/general anesthesia. The procedure was performed with an endobronchial bronchoscope (BF-UC180F, processer-EU ME1, light source-CV 150, Olympus, Japan). Aspirate obtained was sent as air-dried and alcohol fixed slides for cytological examination and in normal saline for microbiological analysis. All specimens were subjected to direct fluorescent staining using auramine and rhodamine stains and were cultured by Bact/Alert three-dimensional (3D) (Biomerieux Durham, North Carolina, USA) and Lowenstein–Jensen (LJ) media. Positive growths in either media were identified using the Accuprobe molecular identification system (Gen-Probe, San Diego, California, USA). All the MTB isolates were subjected to drug susceptibility testing (DST). Susceptibility testing to H, R, E, and S was carried out by an automated liquid culture system Bact/Alert 3D system (1% proportion method according to the manufacturer's instructions). The critical concentrations used were 0.1 mcg/ml for H, 1 mcg/ml for R, 1 mcg/ml for S, and 2.5 mcg/ml for E.

Only patients who had a positive culture for MTB were finally included in the study, and the sample was processed for DST for first-line drugs.

A diagnosis of MDR was made if DST showed resistance to both R and H. The rate of MDR and isolated single and polydrug resistance (more than one drug other than H and R resistance together) was calculated.

Continuous variables were presented as mean ± standard deviation (SD) or median if the data are unevenly distributed. Categorical variables were expressed as frequencies and percentages. Nominal categorical data between the groups were compared using the Chi-square test or Fisher's exact test as appropriate. For all statistical tests, $P < 0.05$ was taken to indicate a significant difference.

RESULTS

A total of 856 procedures were carried out by the operators in the above-mentioned period, and the samples were sent for mycobacterial culture. A total of 102 patients who had a positive mycobacterial culture in whom drug sensitivity was subsequently done were enrolled for the study. There were 53 females and 49 male. The age range was 13–78 years with a mean of 37.3 years (SD – 15.1), most being in 31–40 years age group (26.5%). Fever was the most common symptom followed by cough and weight loss than the rest of clinical features (breathlessness, hemoptysis, and chest pain) [Table 1].

More than one lymph node was targeted in most patients, the subcarinal and right paratracheal being the most common [Table 2].

Since Bact/Alert 3D was used instead of LJ medium, most of the cultures came positive in 2–4 weeks (>60%). Nearly 8% had a rapid growth within 2 weeks also [Table 3].

Overall, we found 30 cases of any drug resistance of 102 tubercular mediastinal adenopathy cases. Of 30 cases, there were 8 cases of MDR-TB (resistant to H and R), 16 cases had only single drug resistance, and the remaining 6 cases had polydrug resistance pattern but not MDR-TB cases. Among the individual drugs, 24 patients showed resistance to S, 17 to H, 11 to E, and 8 to R. All those resistant to R were resistant to H also [Table 4].

History of prior antitubercular therapy

Thirteen patients had a history of ATT intake prior to enrolment. Of 8 MDR cases, 6 patients had a history of taking ATT previously and 2 cases were MDR without a history of taking ATT. Therefore, the overall incidence of MDR-TB is 7.8% (8/102), although the incidence of MDR-TB in new and previously treated cases is 2.2% (2/89) and 46.1% (6/13) [Table 5].

DISCUSSION

This study attempted to assess the problem of MDR in tubercular mediastinal adenopathy. To the best of our knowledge, this is the first study assessing the incidence of MDR in mediastinal lymph node aspirates taken with the help of EBUS. EBUS has been available in the country for the past 10 years now and has proven to be very useful in the diagnosis of tubercular mediastinal adenopathy.[6-10]

Most of the people confirmed with tubercular mediastinal adenopathy in the current study were in the productive age group with no specific gender predilection. With the use of Bact/Alert 3D for MTB culture, most of the growths were obtained within the first 4 weeks, thereby reducing the time taken for positivity than in conventional culture by LJ medium.

According to the "Global TB Report," the incidence of MDR is 3.5% in new pulmonary TB cases and 18% in previously treated. In our study, the overall incidence of MDR-TB in the mediastinal nodes is 7.8%, although the incidence of MDR-TB in new and previously treated cases is 2.2% and 46.1%, respectively. The incidence of MDR in a study done by Ranganath *et al*. was 25.6% in previously treated cases.[11] Sharma *et al*. found 1.1% incidence of MDR in new cases, a study done in New Delhi.[12] As compared to the above two studies on pulmonary samples, our data suggest a much higher incidence of MDR, but the limiting factor could be the small sample size of our study. Much larger-scale multicenter studies will be required to assess the problem in the general population.

TB can affect any mediastinal lymph node. In this study, the subcarinal and right paratracheal nodes were most commonly sampled. It is similar to the study done by Navani *et al*.[13] (44% subcarinal and 29% right paratracheal) and Sun *et al*.[14] (36% subcarinal and 20% right paratracheal). Most of the nodes involved are easily accessible with EBUS. However, since the subcarinal and the right paratracheal are the most commonly involved nodes, they are easily sampled by conventional TBNA as well. Therefore, even in centers where EBUS is still not available, conventional TBNA must be done to take a sample for culture and drug sensitivity before commencing the therapy.

Table 1: Clinical features

Clinical features	Frequency (%)
Fever	58 (56.9)
Cough	56 (54.9)
Weight loss	53 (52)
Breathlessness	26 (25.5)
Hemoptysis	14 (13.7)
Chest pain	11 (10.8)
No symptoms	4 (3.9)

Table 2: Targeted Lymph node frequency

Targeted lymph node	Frequency
Subcarinal (station 7)	62
Right paratracheal (station 4R)	52
Left paratracheal (station 4L)	9
Right hilar (station 11R)	8
Left hilar (station 11L)	8

Table 3: Time to culture positivity

Time to culture positivity (weeks)	Frequency
Within 2	8
2-3	37
3-4	32
4-6	22
6-8	3

Table 4: Individual drug resistance pattern

Resistance to individual drug	Frequency	Percentage of cases with resistance	95% CI (%)
Isoniazid	17	16.7	10.6-25.2
Rifampicin	8	7.8	3.8-14.9
Ethambutol	11	10.8	6.0-18.4
Streptomycin	24	23.5	16.3-32.7

CI: Confidence interval

Table 5: Effects of prior history of antitubercular therapy on multidrug resistance

H/O ATT	Non-MDR	MDR	OR	95% CI	*P*
No	87	2	37.3	6.3-220.2	<0.0001*
Yes	7	6			
Total	94	8			

ATT: Antitubercular therapy, TB: Tuberculosis, MDR: Multidrug resistant TB, CI: Confidence interval, OR: Odds ratio, H/O: History of

We found 30 cases of drug resistance of 102 tubercular mediastinal adenopathy cases. There were 8 cases of MDR-TB, 16 cases had only single drug resistance, and the remaining 6 cases had more than one drug-resistance pattern but not MDR. Twenty-three percent cases showed the resistance to S followed by H (16.7%), E (10.8%), and R (7.8%). Costa *et al*.[15] in their article on the treatment success of TB treatment at a DOTS center in India have reported the overall treatment success rate in sputum-smear-positive TB, sputum-smear-negative TB, and extrapulmonary TB cases as 73.4%, 77.3%, and 84.2%, respectively, indicating a significant number of cases are at potential risk for MDR-TB. Desai and Joshi[16] in their recent study on 1743 cases of extrapulmonary drug-resistant TB at a TB center in Mumbai, India, found that 53.9% had MDR-TB and 6.6% had extensively drug-resistant TB on DST. Approximately 51.3% of these patients had lymph node TB. Sharma *et al*. found resistance rates to be 6.2% for H, R: 1.1%, pyrazinamide: 0%, E: 3.4%, and S: 2.3%.[12]. The resistance pattern found by Ranganath *et al*. was 31.2%, 28%, 17.6%, and 21.6% for resistance to H, R, E, and S, respectively.[11] All the above studies highlight the fact that single and polydrug resistance is a major concern for any form of TB and it could be the reason for the failure of standard first-line therapy in many patients.

CONCLUSION

These results prove that drug resistance is a serious problem in tubercular mediastinal adenopathy, as it is in the pulmonary form. It often goes unnoticed and MDR patients are treated by prolonged courses of first-line drugs and various combinations of second-line drugs in the absence of drug sensitivity pattern due to limited means to sample these nodes. As these cases are not contagious and do not pose a public health risk, none of the national and international TB programs have focused on this problem. However, as our results show, all efforts should be made to sample these nodes and to ascertain the drug sensitivity pattern before the commencement of treatment, as resistance rates are very high in these nodes as well.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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