CASE STUDY

XDR-TB: An outcome of programmatic management of TB in India

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Abstract

A significantly strengthened Revised National Tuberculosis Control Programme (RNTCP) is currently operational in India. In this case-based commentary, we describe the plight of a patient who developed extensive drug-resistant tuberculosis (XDR-TB) despite having received treatment under the RNTCP for a long period. Our aim is to analyse the programmatic management of tuberculosis in India by highlighting and discussing various issues related to the treatment received by the patient. Further, the article explores whether there is a need to incorporate an ethical element into the RNTCP as it stands today.

Introduction

India has the highest burden of tuberculosis (TB) in the world, accounting for 26% of the global incidence of TB (1). A significantly strengthened Revised National Tuberculosis Control Programme (RNTCP) is currently operational in India. The whole of India was covered by the RNTCP by March 2006 (2). The development of Programmatic Management of Drug-Resistant Tuberculosis (PMDT) is the latest move in the RNTCP's battle against the menace of drug-resistant tuberculosis. There is, however, a need for ethical introspection on the part of the RNTCP to evaluate whether, over the years, patients have been provided the best possible treatment under the programme. To fight the problem of drug-resistant TB, it is necessary to ensure that all TB cases are managed in the best possible way during the initial period and that their management is in line with the existing guidelines. The process of continuous updating is crucial to the success of any programme. Unfortunately, the current state of TB management in India is far from satisfactory, as reflected in a recent statement made in an editorial in the Indian Journal of Medical Research: "…Early and effective TB treatment and control is difficult in India with its current tools and systems"(3). The provision of quality healthcare services to patients is the ethical responsibility and obligation of the system. Under the RNTCP, the health system, and not the patient, is responsible and accountable for cure (4). Drug-resistant TB is a man-made problem (5). If this problem is growing day by day, something is seriously wrong somewhere. In this context, one of the important factors is the treatment administered to TB patients.

Recently, a patient was initiated into the regimen for extensive drug-resistant TB (XDR-TB) at our DOTS Plus site under PMDT. The case is presented here, with the aim of analysing the treatment she received during the course of her illness. The objective of the discussion is to analyse programmatic management of TB in India by highlighting and discussing various issues related to the management of the patient. Further, the article explores whether there is a need to incorporate an ethical element into the RNTCP as it stands today.

Table 1
Drugogram or past history of intake of anti-tuberculosis drugs

Sr. No.	Dates	Source (government /private)	Regimen	Duration	Regular / irregular	If irregular, reasons	Sputum AFB smear report pre- and post-treatment	Outcome
1	13.09.06 to 19.03.07	Government	CATEGORY I	6 months	Regular	--------	Pre- treatment: scanty 8 AFB +Post-treatment: 1+	Failure 19.03.07
2	21.03.07 to 12.11.07	Government	CATEGORY II	8 months	Regular	--------	Pre treatment: 1+Post-treatment: negative	Cured 12.11.07
3	28.02.08 to 16.12.08	Government	CATEGORY II	8 months	Regular	--------	Pre-treatment: 2+Post-treatment: 1+	Failure 16.12.08
4	20.12.08 to 03.09.09	Government	CATEGORY II	9 months	Regular	--------	Pre-treatment: 1+Post-treatment: 2+	Failure 3.09.09
5	22.10.09 to 02.07.10	Government	CATEGORY II	8 months	Regular	--------	Pre-treatment: 2+Post-treatment: 1+	Failure 2.07.10
6	05.07.10 to 9.11.10	Government	CATEGORY II	4 months	Regular	--------	Pre-treatment: 1+	Shifted to regime for MDR-TB
7	16.11.10 to 01.02.13	Government	CATEGORY IV	27 months	Regular	--------	Pre-treatment: 1+	Shifted to regime for XDR-TB

Case report

A 19-year-old unmarried woman college student complained that she had been suffering from cough and breathlessness, which had been occurring on and off, for the past six years. There was associated fever, anorexia and weight loss. She was admitted as a diagnosed case of XDR-TB under PMDT. The history of her intake of anti-TB drugs is presented in Table 1. Table 2 shows the results of her drug sensitivity tests (DST), carried out in an accredited laboratory under PMDT as per the norms of the World Health Organization (WHO).

Family history: She had a history of contact with TB patients in the family. Her father had taken category I anti-TB treatment for pulmonary TB in 2008. He had been irregular in adhering to the six months' course, to which there was no clinical response. On March 30, 2009, he was started on category II anti-TB treatment. His adherence was again irregular and he expired on April 7, 2009, due to respiratory disease. Her father was a labourer and a chronic alcoholic, who had been consuming approximately 180 ml country liquor per day for 30 years. He was also a smoker, and had been smoking one bundle of bidis every day for 30 years.

Socioeconomic history: Her socio-economic status as per the modified Kuppuswami socioeconomic scale was lower-middle (III) socio-economic class.

Personal history: The patient was a college student and had no other disease.

Findings of examinations: The general examination revealed that the patient was underweight, her body mass index being 13.78. There was noticeable pallor. An examination of her respiratory system revealed features of volume loss on the right side. The breath sounds were also reduced on the right side.

Investigations. Her sputum smear and culture were positive for TB. The results of the DSTs were suggestive of XDR-TB. Her chest X-ray showed right-sided pleuroparenchymal fibrosis, ie her right lung was totally "destroyed". Table 3 gives the salient aspects of this case.

Table 2
Drug sensitivity testing results of the patient

Date	Drug	Sensitivity report
20.10.10	INH	Resistant
20.10.10	Rifampicin	Resistant
20.10.10	Ethambutol	Sensitive
20.10.10	Streptomycin	Sensitive
28.06.12	Amikacin	Resistant
28.06.12	Kanamycin	Resistant
28.06.12	Capreomycin	Sensitive
28.06.12	Ofloxacin	Resistant

Table 3
Salient aspects of the case

Salient aspects of the case:

The patient always took her anti-TB medication regularly.

Throughout the course of her illness, she had taken treatment from the government sector and was treated as per the existing guidelines of the Revised National Tuberculosis Programme in India.

When the patient failed the Category I* regimen for the first time, she was put on the Category II** regimen, which meant the addition of a single drug (streptomycin) to the failed regimen.

The patient received the same Category II regimen five times till November 9, 2010. After the first time, she was declared cured on the basis of the sputum acid-fast bacilli smear-negative report. After that, the Category II regimen was declared to have failed for three consecutive times and after the fifth time, a regimen for the treatment of MDR-TB was initiated as she was diagnosed to be a case of MDR-TB.

The patient was first registered under the RNTCP on September 13, 2006 and was diagnosed with MDR-TB on October 20, 2010. She was further diagnosed as an XDR-TB case on June 28, 2012.

Though diagnosed with XDR-TB on June 28, 2012, the patient was started on a regimen for XDR-TB only on February 1, 2013.

As for her socioeconomic class, the patient came from the lower middle (III) class.

The patient's family history included a history of contact with a TB patient, i.e. her father, who had taken Category I anti-tuberculosis treatment under the RNTCP in 2008. He was a chronic alcoholic, a heavy smoker, and a suspected case of MDR TB. He had died of a TB relapse in 2009, just one month after starting on the Category II anti-TB regimen.

Throughout the course of her illness, the patient continued with her routine activities, such as going to college and public places.

*CAT I is now known as the regimen for new patients. **CAT II is now known as the regimen for previously treated patients.

Discussion

Background of TB programme in India

Before discussing the various issues related to the case, we will briefly describe India's RNTCP so as to enable the reader to understand the programmatic management of patients more clearly.

The Indian RNTCP initiative

The RNTCP (4) is the state-run TB control initiative of the Government of India. The two regimes under the RNTCP are detailed in Table 4.

PMDT (6) case definitions

MDR-TB case: An MDR-TB case is defined as one whose sputum is culture-positive for *Mycobacterium tuberculosis* and resistant in vitro to isoniazid and rifampicin, with or without other anti-tubercular drugs, on the basis of DST results from an RNTCP-certified culture and DST laboratory.

XDR-TB case: An XDR-TB case is a case of multi-drug resistant TB (MDR-TB) whose recovered M. *tuberculosis* isolate is resistant

Table 4
RNTCP treatment regimes

Treatment groups	Type of patient	Regimen	
		Intensive phase (IP)	Continuation phase (CP)
New	Sputum smear-positive Sputum smear-negative Extra-pulmonary Others	$2H_3R_3Z_3E_3$	$4H_3R_3$
Previously treated	Smear-positive relapse Smear-positive failure Smear-positive treatment after default Others*	$2H_3R_3Z_3E_3S_3$ / $1H_3R_3Z_3E_3$	$5H_3R_3E_3$

The number before the letters refers to the number of months of treatment. The subscript after the letters refers to the number of doses per week. The drugs are as follows: isoniazid (H), rifampicin (R), pyrazinamide (Z), ethambutol (E), and streptomycin (S).

**In rare and exceptional cases, patients who are sputum smear-negative or who have extra-pulmonary disease can have Relapse or Failure. This diagnosis in all such cases should always be made by an Medical Officer and should be supported by culture or histological evidence of current, active TB. In these cases, the patient should be categorized as 'Others' and given Category II treatment.*

to at least isoniazid, rifampicin, a fluoroquinolone (ofloxacin, levofloxacin, or moxifloxacin) and a second-line injectable anti-TB drug (kanamycin, amikacin, or capreomycin) on the basis of results from an RNTCP-certified culture and DST laboratory. Table 5 lists the cases that can be suspected to have MDR-TB, as per the current programme guidelines. As the table shows, for all practical purposes, all retreatment cases, HIV-TB cases, and new cases which are smear-positive at two months or later can be suspected to have MDR-TB. The two regimes for MDR-TB and XDR-TB under PMDT are presented in Table 6. Patients with diagnosed MDR-TB or rifampicin-resistant TB are started on regimes for MDR-TB (previous category IV). Patients in whose case the MDR-TB regimen fails or whose culture is positive at the fourth month are investigated for XDR-TB. If they are diagnosed with XDR-TB, a regimen for XDR-TB may be initiated.

Issues to be considered in this case

1. The patient was very regular with the anti-TB treatment provided to her under the RNTCP and not once did she deviate from it. Thus, through no fault of her own, she ended up being a case of XDR-TB. We, who are ourselves part of the healthcare system in this country, are at a loss for words when trying to explain to such patients why they have developed drug-resistant TB.
2. The patient's father had received all his anti-TB medication from the government sector until his death while under treatment. He was a chronic alcoholic and smoker, and his adherence to the regimen was irregular. For these reasons, co-morbidities such as alcoholic liver disease could not be excluded as contributory factors to his illness. These were also risk factors for the development of drug resistance. He was an MDR-TB suspect since he was sputum smear-positive at the start of the retreatment regime (6). Thus, our patient was exposed to a patient who was an MDR-TB suspect, which placed her at risk of developing drug-resistant TB. Social evils such as addiction to smoking and alcohol do have this ugly face, and it need to be recognised and tackled. Also, even though the father was an MDR-TB suspect, he was never investigated for the same under the RNTCP to address the matter. What is more, there is no provision for the isolation of such cases to prevent transmission. The fact that the practices of isolation and segregation are not advocated under the RNTCP could have led to either of them contracting the disease from the other, since the transmission of TB is aerosol-based and the disease spreads through the air we breathe.
3. Adding a single drug to a failing regimen is against the basic principle of TB chemotherapy (5), and Category II is nothing but the addition of a single drug to the failed regimen of Category I. Also, during the course of the illness, the patient had been put on the same Category II regimen five times! And she had not responded to it. These are again factors which are responsible for drug resistance. She was probably resistant to the drugs in the regimen at this stage itself.
4. Throughout the course of her treatment, the patient was given intermittent chemotherapy with first-line anti-TB drugs, until she ultimately became a case of MDR-TB. The WHO treatment guidelines recommend daily instead of intermittent chemotherapy, as patients receiving a thrice-weekly regime under the RNTCP have a high risk of developing resistance (7). Intermittent therapy could be a contributory factor to the development of drug-resistant TB in the patient. Given such instances, the question arises as to how far we are ethically and morally right in referring patients diagnosed with TB to a programme (ie the RNTCP) which has an inbuilt risk factor (ie intermittent therapy) that is proven to cause drug resistance. Are we not pushing our patients into the jaws of drug-resistant TB, a more serious form of the illness they are already suffering from? These questions need to be considered and answered by us individually, as well as collectively, as we are an integral part of this healthcare system. The RNTCP needs to adopt the daily anti-TB regimen as early as possible. If the programme can provide a daily regime (under PMDT) with a larger number of drugs for a longer duration of treatment, incurring more expenditure as compared to first-line regimes (viz CAT I and CAT II), then there should be no operational problems in shifting the alternate day first line regimes (under RNTCP) to the optimal and

WHO-recommended daily regimes (6,7). It has already been three years since the guidelines first endorsed daily chemotherapy, and a further delay will result in disastrous outcomes.

5. The diagnosis of drug-resistant TB was inordinately delayed in our patient. Though she was suspected to have MDR-TB, each time the treatment failed and she was found to be sputum smear-positive, she was started on the same treatment regimen. Further, the patient was diagnosed with MDR-TB as late as October 20, 2010, ie four years into the course of her illness. It was only on June 28, 2012, almost six years into the course of her illness, that she was diagnosed with XDR-TB. Had all her first-and second-line culture DSTs been carried out at an earlier stage, when she had first become an MDR-TB suspect, the diagnosis would probably not have been delayed so long. This might have led to early intervention and a better outcome. A good part of the reason for this state of affairs is the delayed incorporation by RNTCP of the guidelines recommended by WHO. The delay in the incorporation of the WHO guidelines on the management of drug-resistant TB is reflected in the following facts. The Guidelines for establishing DOTS-Plus pilot projects for the management of multidrug-resistant tuberculosis were published by WHO in the year 2000 (8). Also, the Category IV regime was described in the WHO publication by Toman in 2004 (5). Gujarat was the first state to initiate DOTS-Plus services in India. This was in August 2007 (9), seven years after WHO had first come out with its guidelines on the subject. The need of the hour is for the RNTCP to waste no time in implementing the programme and making decisions on the basis of standard international guidelines. It should keep itself regularly up to date with the management protocols and function in line with the emerging evidence. Perhaps, if the DOTS-Plus guidelines had been implemented at an earlier stage, many patients such as ours could have been diagnosed and treated accordingly.

6. In the context of isolation and other infection control issues, the patient was never advised isolation throughout the course of her illness. Whether isolation of drug-resistant TB suspects is required needs to be explored. On the basis of the results of the Chennai trial, the RNTCP does not recommend isolation or admission to a sanatorium (5,10). However, it needs to be mentioned that drug-resistant TB cases were excluded in that study and hence, the results should not be applied to these cases. In its policy on TB infection control, WHO recommends: "While culture-positive, XDR-TB patients should be isolated at all times, and any person in contact with a culture-positive XDR-TB patient should wear a particulate respirator" (11). Compulsory isolation or detention is a very difficult decision, but the health risk to the community at large due to such cases needs to be considered. As set forth in the Siracusa principles, this means that such measures must be in accordance with the law; based on a legitimate objective; strictly necessary in a democratic society; the least restrictive and intrusive; and not arbitrary, unreasonable, or discriminatory (12). Also, as per the recent guidance provided by WHO on the ethics of the prevention, care and control of TB, isolation or detention should be limited to exceptional circumstances, when an individual is known to be contagious and refuses treatment, and all reasonable measures to ensure adherence have been attempted and proven unsuccessful; or is known to be contagious, has agreed to ambulatory treatment, but lacks the capacity to institute infection control in the home; or is highly likely to be contagious (on the basis of the symptoms and evidence of epidemiological risk factors) but refuses to undergo assessment of his/her infectious status (13). We need to give some thought to the ethical issues involved in this matter to determine the weightage that should be given to the patient's rights vis-a-vis the health risk faced by the community at large (due to unrestricted movement of these infective cases).

7. Apart from providing free management of TB, the programme does not recognise the patient's other needs, such as psycho-emotional and socio-economic support. Medication can cure drug-resistant TB only if the patient does not interrupt or abandon the treatment. The management of drug-resistant TB requires much more than medication. It involves the provision of socio-economic and psycho-emotional support to patients (14). Some of the problems confronting our patient might have been as follows. (i) There was only one earning member (her brother) in a family of four; (ii) The fact that her father died of TB could have given rise to the fear that TB is incurable and ultimately leads to death. Her father's death could also have created a void in her life. The fact that she had been afflicted with the disease for so long could have made her feel that she was a burden to her family. Her studies had been interrupted. Psychological and emotional needs of this sort have to be recognised and tackled at the earliest. This requires a proper psychological support system. The patient should be given professional psychological counselling, which should be built into the system. (iii) The patient might have been stigmatised by society on account of her illness, as is very often the case with those suffering from TB for a long period. (iv) There is no system in the RNTCP for countering social issues such as alchoholism among TB patients. The existence of such a system might have helped the patient's father and consequently, the patient herself. The role of medical social workers in the programme needs to be expanded. Thus, the programme should include a strong psycho-socio-economic component to tackle the issues mentioned above, as this is vital for attaining the ultimate goal of curing the patient in toto. The RNTCP has no such component at present.

8. There is an urgent need for capacity-building of PMDT services (15). The RNTCP plans to expand diagnostic facilities and management services, but this needs to be done on a priority basis so that patients like the one

Table 5
MDR-TB suspect criteria as per current programme guidelines

MDR-TB suspect criteria as per current programme guidelines*:
Criteria A
All failures of new TB cases
Smear +ve previously treated cases who remain smear +ve at 4th month onwards
All pulmonary TB cases who are contacts of known MDR TB case
Criteria B – in addition to Criteria A
All smear +ve previously treated pulmonary TB cases at diagnosis
Any smear +ve follow up result in new or previously treated cases
Criteria C – in addition to Criteria B
All smear -ve previously treated pulmonary TB cases at diagnosis,
HIV TB co-infected cases at diagnosis
**The graded criteria for suspecting MDR TB will be scaled up gradually from criteria A to criteria C. It is expected that all districts in the country would be implementing Criteria B by 2012-2013, and Criteria C by 2015.*

mentioned here are detected at an earlier stage and benefit from early management.

Conclusion

The case discussed in this article sheds light on the programmatic management of TB in India. The patient had, throughout the duration of her illness, shown full faith in the public healthcare system. For no apparent fault of her own, the patient ended up being a case of XDR-TB. This definitely leaves us with some questions to answer.

Was the patient managed in the best possible manner?

The answer is no. Had all her cultures and DSTs been carried out at an earlier stage, the scenario would have been different. Also, the repeated prescription of an intermittent regime before the patient was diagnosed with drug-resistant TB has been linked with acquired drug resistance, and is not recommended now even in programmatic conditions. If drug-resistant TB is a "man-made" phenomenon, and if the patient is not responsible for its development, then who is? The development of drug resistance in this case seems to be a matter of "programme-induced drug resistance". The healthcare system has the ethical obligation to provide appropriate treatment to patients. That the programme was not brought up to date in accordance with the standard evidence-based recommendations definitely played a role in the genesis of drug resistance in the present case. PMDT should aim to reduce the factors that lead to drug resistance, one of them being the initial prescription of intermittent therapy to all patients under the RNTCP.

Table 6
Regimens under PMDT

Regimens under PMDT	**Intensive phase (IP)***	**Continuation phase (CP)****	**Reserve/ substitute drugs**
Regimen for MDR-TB	6–9 Km, Lvx, Eto, Cs, Z, E	18 Lvx, Eto, Cs, E	PAS, Mfx, Cm
Regimen for XDR-TB	6–12 Cm, PAS, Mfx, high-dose H, Cfz, Lzd, Amx/Clv	18 PAS, Mfx, high-dose H, Cfz, Lzd, Amx/Clv	Clarithromycin, Thiacetazone

**Intensive phase for MDR-TB: 6 to 9 months. Intensive phase for XDR-TB: 6 to 12 months.*

***Continuation phase for MDR-TB and XDR-TB: 18 months.*

Drugs: Km - kanamycin, Lvx - levofloxacin, Eto - ethionamide, Cs - cycloserine, Z - pyrazinamide, E - ethambutol, PAS - para amino salicylic acid, Mfx - moxifloxacin, Cm - capreomycin, H- isoniazid, Cfz - clofazimine, Lzd - linezolid, Amx/Clv - amoxyclav

Need for inculcating a sense of ethics in the RNTCP

As a programme, the most important asset of the RNTCP is its 100% coverage in a densely populated country like ours. The fact that it provides free anti-TB drugs to all types of TB patients registered under it speaks of a great effort and the programme needs to be lauded for this. However, every patient under the RNTCP deserves the best and most effective and appropriate treatment for his /her illness and the RNTCP has an ethical obligation to provide such treatment to its patients. According to the recent guidance provided by WHO on ethics in TB, individuals undergoing testing and treatment for TB should be given complete and accurate information on the risks and benefits involved, as well as the alternatives available to them (13). What the case discussed in this article seeks to highlight is the lack of "alternative" treatment options, which are the optimal treatment options for such TB patients, under the RNTCP. Non-maleficence –"first, do no harm" (primum non nocere) – is one of the basic principles of medical ethics (16). In this case, the very principle of non-maleficence was breached, with the patient developing drug-resistant TB that was "programme-induced". The RNTCP should engage in some ethical introspection and, in consonance with the basic principles of medical ethics, improve its management of all such cases.

Indeed, incorporating the element of ethics into the management of this disease will help our healthcare system far more than merely following a target-based approach which focuses primarily on numbers and not on the needs of individual patients.

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