Review Article

Difficult to Treat Tuberculosis: A Challenging Vignette in Indian Context

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The magnitude of TB disease, including drug resistance, is huge and alarming in India, being the highest-burden country. The steps taken during the initial decades after getting independence in 1947 were slower and not very effective which is reflected in the timeline depicting changes (from NTP to RNTCP and then NTEP) in India's TB control policies. India has been proactive for the last couple of years with strong scientific, political and financial support in its battle against TB with the 'WHO End TB Strategy'. To achieve an ambitious goal of eliminating TB by 2025, the program has adopted a multifaceted approach that includes early detection of DSTB and DRTB cases with the genexpert diagnostics, use of potent regimen and preventive care of household contacts. However, a simultaneous multi-dimensional uplift of socioeconomic, educational, nutritional status, personal health and hygiene etc., of the community is not to be ignored. A vignette case of TB with multiple complicating events during management is included to highlight the problem of managing difficult-to-treat TB cases. The role of multidisciplinary specialist expert committee support to deal with adverse drug reactions (ADR) due to newer anti-TB (Bedaquiline, delamanid/pretomanid), use of repurposed antibiotics and efficacious management of comorbidities is also being recognized to strengthen the program. Potent new anti-TB drugs to shorten the duration of treatment, quick diagnostics tools, and effective preventive vaccine with a strong infrastructure laboratory network are the urgent needs of the day

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Introduction

Tuberculosis is not only a problem of mankind. It equally affects animals, birds and marine creatures. The human type strain (H37Rv) is the most common to produce TB disease while the *Mycobacterium africanum* strain is common in West African countries. However, both strains respond well to the first-line drugs (RHZE regimen). Apart from this enormous variants and species of mycobacterium tuberculosis are detected even in the environment known as non-tubercular mycobacterium (NTM) having a similar morphology. These atypical mycobacteria, or NTM, are also capable of producing PTB and extra-pulmonary TB, especially in immunocompromised individuals, as an opportunistic infection, but the treatment is different. Thus, it becomes mandatory to identify NTM (Mycobacteria). The saprophytic or rapid grower (on culture) is another group of NTM that is sometimes unable to produce disease but physical presence may mislead as false positives also need to be considered.

The lungs are the most vulnerable organ (85%) to be affected through inhalation of droplets/ aerosols generated during coughing or sneezing of a patient suffering from PTB to the other people in contact. TB infection may spread to extra-pulmonary organs of the body in 15% of cases via blood, lymphatics, or by direct contiguity to other parts of the body.

Magnitude of TB

Tuberculosis has remained for a long time the infectious disease of mankind, responsible for huge morbidity and mortality. In the Indian population, the case detection and mortality rate of TB remained at 199 per lakh and 23 per lakh, respectively, during the post-Covid year of 2023. Moreover, the 63,939 cases of multidrug-resistant TB (MDR-TB) were also diagnosed in the year.[1] The primary drug resistance in new TB cases and secondary/ acquired drug resistance in previously treated cases were 2.84 and 11.60 percent, respectively, with an overall total of

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1.7 lakh or 6.2% MDR cases diagnosed among the total TB cases detected during the year 2023. The MDR-TB cases are likely to have a poor outcome, i.e., nearly 60% success rate and many multi-fold increases in cost to treatment with socioeconomic impact on the family [(2)]. India has the highest, i.e., more than one-fourth of the world's magnitude of TB cases, with about 27% of global drug resistance cases.[2,3] The emergence and spread of HIV and the problem of multiple drug resistance (MDR), extensively drug-resistant (XDR) and Total Drug Resistant (TDR) TB has further drastically affected the epidemiology of TB in India [(4)]. However, in the past decade, momentum has been seen toward improvement due to intense multi-dimensional actions by the central TB Division (CTD) and the World Health Organization (WHO).

The natural epidemiologic curve of TB over centuries shows a declining trend, while a simple intervention beginning in 1750 as an industrial revolution had improved the hygiene and healthcare conditions, helped regions of Europe and North America to put a dent in a downward decline of the epidemiological curve.[4] However, it was also supported with improved nutrition, bed rest, fresh air, sunlight and isolation (as sanatorium movement) with some surgical interventions such as resection (Pneumonectomy/ lobectomy) or compressing the diseased lung in the form of Thoracoplasty/ Phrenic crush or lung collapse therapy.[4] The epidemiologic decline of TB had happened even before the discovery of precise anti-TB drugs (like Streptomycin, PAS, and INH). The developed countries who had shifted the resources toward eradication have reached near the goal of control defined as<10 TB cases per 100000 population in a year.[5] Thakur G. *et al*. mentioned that if we eradicate poverty and undernourishment, educate the masses, improve hygiene, and eliminate the stigma attached to TB, we can achieve a disease-free future.[6] He further mentioned that the current Coronavirus pandemic in 2020 has also given us an excellent opportunity to create awareness pertaining to TB among the community at large. Worldwide, TB is the number one cause of death from a preventable infectious disease, has been stated to the WHO. Marco Schito opined that to achieve the 'WHO End TB Strategy, 'bold leaders providing strong political support based on the scientific ground and adequate financial funding are urgently required. However, he also mentioned to date, only Smallpox (1980) and Rinderpest (2011) have been successfully eradicated.[5]

A timeline depicting changes in India's TB control policies (a period after getting freedom in 1947) has been well complied with and summarized by Aliabbas A. Husain.[3] Starting from 1961 when for the first time, the National Tuberculosis Program (NTP) was launched after completing the national sample survey in 1955-1958. It was reviewed and revised as RNTCP (1997) with DOTS (a WHO strategy) as a step towards controlling the situation. The programmatic management of drug-resistant tuberculosis (PMDT) was launched to improve drug-resistant tuberculosis (DR-TB) care in India as RNTCP-2 (2007). The first national drug resistance survey (NDRS-2014) was conducted by the government of India[7] and has come up with alarming and eye-opening information on drug resistance. Thereafter, a cartridge-based nucleic acid amplification test (CBNAAT/ TrueNAT) a molecular assay, was endorsed and included as an integral part in 2019 to further strengthen the program. These tests enabled rapid diagnosis of mycobacterium within 2 hours and its resistance against at least the most potent drug, rifampicin. Once again, the program was renamed in 2020 as the National Tuberculosis Elimination Program (NTEP), towards achieving the goal of the WHO End TB Strategy.[3] India is proactive in its battle against TB to achieve an ambitious goal of eliminating TB by 2025-30 so it has adopted a multifaceted approach that includes early detection of rifampicin susceptible TB (RSTB) and resistant (RRTB) cases with the use of genexpert diagnostics. A new, safer, shorter, more efficacious and more tolerable drug regimen is needed to shorten the period of infectiousness and potent vaccine.[5]

Achieving tuberculosis eradication/ elimination requires a sensitive sputum-based and or non-sputum-based diagnostic tool capable of diagnosing latent tuberculosis and enable of predicting the risk of progression to active disease.[8] The initiation and implementation of policies regarding hospital/ domestic infection control and to identification of household contact transmission and TB preventive treatment (TPT) for already infected or those who harbor latent TB infection detected by MT and or IGRA is also monitored under NTEP. Naidoo K. *et al*. had given a panel of ongoing studies/ trials reflecting the advance in the upcoming future.[8] However, 40% of the total Indian population is infected with TB and among them, only about 10% will likely to suffer from active TB disease during their lifetime. This subgroup of latent TB (which act as a reservoir of future disease) requires an effective and potent drug against intermittently multiplying or non-replicating bacilli is another challenge.[9]

There are so many factors for drug failure or inability that adversely affect the treatment outcomes. The mycobacterium has an inherent or intrinsically resistant to many antibiotics due to its thick, lipid-rich, waxy, hydrophobic cell wall, which prevents permeability. In some of the antibiotics, even after crossing the MTB cell wall (called as first line of defense), they become inactivated by enzymatic action, e.g., by methylation or acetylation, which renders them ineffective. The chromosomal mutations of mycobacterium with varying mechanisms are the next issue for difficult to treat TB. Gygli *et al*., gave a comprehensive list of the most common targets of chromosomal mutation conferring drug resistance in M. tuberculosis.[10] Some of the example for rifampicin is rpoB drug targ*et al*teration, for Isoniazid katG abrogated prodrug activation and inhA as drug targ*et al*teration. These mutations can be detected by LPA examination of the sputum sample of an MDR case; thus, accordingly appropriate MDR regimen can be prescribed.

Disseminated and extra-pulmonary TB is an additional challenge and diagnostic dilemma to be considered. A multi-specialty (Respiratory, Psychiatry, Gynaecology, Pediatrics, General Medicine, Dermatology, Surgical, Radiological and Public health expertise, etc) consultation body known as "TB Consilium" or expert committee also been formed to manage comorbidities and difficult-to-treat TB cases, thus lowering the risk of making mistakes to enable to improve clinical outcome.[11,12] The duration of treatment for resistant TB is prolonged, with a success rate of merely around 60%. The incidence of drug toxicity or adverse drug reaction (ADR) with the use of new (Bedaquiline, Delamanid/ pretomanid) and repurposed drugs is more frequent and likely to further increase especially with the presence of special conditions/situations (i.e., pregnancy and lactation, HIV, renal impairment, pre-existing liver disease, seizure disorders and psychiatric illness) and along with associated comorbidities. These situations require a customized drug regimen and rebuilding of a treatment plan; thus, a dedicated team of trained healthcare personnel are also needs to be present at secondary and peripheral health facilities**.**

A classic vignette case as an example to the readers of the difficult to treat TB case is presented below. This difficult-to-treat TB cases (DTTTC) are discussed on the national and state levels in the ECHO clinics to promote increased awareness of similar activities among them to share their experience is a good initiative by the Central TB Division (CTD).

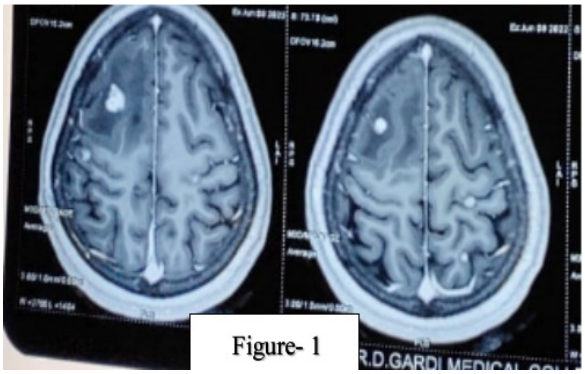

Figure 1: MRI of multiple ring-enhancing lesions

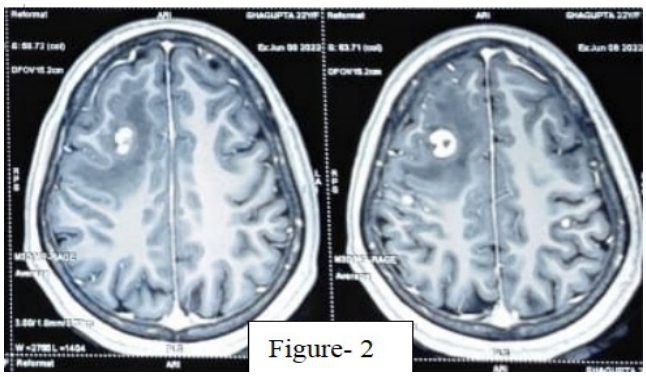

Figure 2: No improvement on repeat MRI

Case Presentation

A 19-year-old housewife was admitted with complaints of pain abdomen, low-grade fever, headache and generalized body pain for the past 15 days. She had a history of contact with an active case of TB with her mother, who had died a year back. Her chest examination was essentially normal, but her abdomen was tender with splenomegaly and a palpated mass in the right iliac region. USG revealed omental thickening (biopsied) with minimal ascites. Histopathology report favored TB with necrotic granular debris; hence ATT (RHZE) started. She was non-diabetic and non-reactive for HIV with a normal chest x-ray. After 2 weeks, a modified ATT regimen (Injection SM, Tab Ethambutol & Levofloxacin) was given due to deranged LFT with anorexia and vomiting. An episode of seizure with numbness in the left hand developed during 4th month of treatment, so an MRI brain was done, which depicted multiple ring-enhancing lesions (Figure 1). Injection SM (for 2 months), Levofloxacin and steroids were added to the regimen and continued for next 1 year. However, in the mean the USG abdominal lesion reported clearing with symptomatic improvement. Somehow, there was no improvement

on repeat MRI (Figure 2) after two years of treatment, so an expert committee, including the opinion of the Neurophysician, decided to give the MDR regime (All Oral Longer) on a clinical basis. Again, after 2 months, she presented with anemia (Hb 8.2 g%) due to linezolid induced, which required a transfusion of 2 units of RCC and the dose of linezolid was reduced (due to ADR) to 300 mg. A repeat MRI at the end of treatment showed a marked reduction in size and disappearance of the lesion.

Discussion

It is not easy to treat and manage a patient of tuberculosis, especially one drug-resistant, using multiple drugs that too for a longer duration without infrequent adverse events. There could be many factors responsible for the difficulty in treating TB, firstly the patient and their relatives have a lack of knowledge of TB symptoms and ADR, stigmatization, associated comorbidities, delay in diagnosis due to distance from a health facility, lack of periodic follow-up monitoring, non-adherence to the prolonged treatment period, loss of household income and poor family support, etc. Secondly, it also depends upon the behavioral attitude of staff, record maintenance, prompt medicine supply and information, education, and communication (IEC) skills of the medical team or fraternity. Thirdly related to the drugs that is over or dosing, use of scientifically constituted drug regimen, drug intake regularity of patient without default, well-maintained uninterrupted logistics, periodic recording of intolerance/ ADR, and periodic monitoring with an evaluation of developing Drug Resistant-TB (primary or acquired) with change of appropriate drugs, all are needed to ensure better outcomes.[2] The expected cure rate in DR-TB cases is very low (near 60%), even with the use of newer anti-TB drugs. The annual TB report 2023-2024 (1) has reported that 30% 0f the expected DRTB cases are still not notified and this is alarming, as they are a source of infection of DRTB in the community and risk of complications to their ownselves.

Conclusion

The magnitude of the problem of tuberculosis is huge, with an increasing trend of drug-resistant cases. It has created enormous management hurdles. The goals of the WHO End TB Strategy could be achieved with a consistent effort toward the discovery of new anti-TB drugs. The drugs should be potent, least toxic, cost-effective and enable to decrease the duration of treatment. They can also eliminate persisters or latent TB and NTM infections. Let us hope that the new shorter six-month BPaLM regimen for drug-resistant TB can bring better compliance and outcomes. A preventive vaccine and quick diagnostics tools with a strong infrastructure laboratory network are the urgent needs of the day. The improvement of socioeconomic and educational status with adequately trained health care personnel, consistent, proactive political will and support is also required.

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