

DIFFICULT TO TREAT MDR-TB

Afsar Khan

Programmatic Management of Drug Resistance TB Unit, Lady Reading Hospital, Peshawar - Pakistan

Address Correspondence:

Afsar Khan

Programmatic Management of Drug Resistance TB Unit, Lady Reading Hospital, Peshawar - Pakista

E-mail:
afsarafridik@yahoo.com

ABSTRACT

Tuberculosis (TB) is a major infectious disease killing nearly two million people, mostly in developing countries, every year. The increasing incidence of resistance of *Mycobacterium tuberculosis* strains to the most-effective (first-line) anti-TB drugs is a major factor contributing to the current TB epidemic. Drug-resistant strains have evolved mainly due to incomplete or improper treatment of TB patients. Resistance of *M. tuberculosis* to anti-TB drugs is caused by chromosomal mutations in genes encoding drug targets. Multidrug-resistant (resistant at least to rifampin and isoniazid) strains of *M. tuberculosis* (MDR-TB) evolve due to sequential accumulation of mutations in target genes. Emergence and spreading of MDR-TB strains is hampering efforts for the control and management of TB. The MDR-TB is also threatening World Health Organization's target of tuberculosis elimination by 2050. Proper management of MDR-TB relies on early recognition of such patients. Several diagnostic methods, both phenotypic and molecular, have been developed recently for rapid identification of MDR-TB strains from suspected patients and some are also suitable for resource-poor countries. Once identified, successful treatment of MDR-TB requires therapy with several effective drugs some of which are highly toxic, less efficacious and expensive. Minimum treatment duration of 18–24 months is also long, making it difficult for health care providers to ensure adherence to treatment. Successful treatment has been achieved by supervised therapy with appropriate drugs at institutions equipped with facilities for culture, drug susceptibility testing of MDR-TB strains to second-line drugs and regular monitoring of patients for adverse drug reactions and bacteriological and clinical improvement.

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CASE REPORT

A 27 years old well educated gentleman, experienced with extensive cerebral capabilities, who was referred by a pulmonologist to programmatic management of drug resistant TB (PMDT) site Lady Reading Hospital Peshawar. Before we discuss his present illness we want to divulge his past history.

In March 2006, he was diagnosed as smear positive PTB patient by a chest specialist at Peshawar. And was started on 1st line anti tb drugs (2RHEZ/6RHE). Despite taking 1st line ATT, after six months his sputum c/s showed resistance to RHEZ and sensitivity to S,Eto and Ofx, on the basis of which, he was switched on to

Streptomycine (S) Ofloxacin (Ofx), Ethionamide (Eto), hiocitazone (Ctz) and PAS in private sector.

After two months he defaulted and did not return for follow up due to side effects of 2nd line drugs.

After 5 months interruption, he returned back realizing that he has no other option except 2nd line drugs. His sputum was sent for AFB c/s (Later on result showed resistance to RHE) and restarted on

Kanamycine (Km), Levofloxacin (Lfx), Ethionamide (Eto), Cycloserine (Cs), Para-amino cyclohexyl carboxylic acid (PAS) and Pyridoxine (B6). After 6 months in December 2007 a pulmonologist at Karachi stopped Km and Lfx switching him to continuation phase and continued Eto, Cs and PAS.

In the period of 8 months (Jan-Aug 2008) due to positivity of AFB culture, several times DST was requested which showed resistance to RHE, RHZ and RHEZ respectively. On the basis of AFB culture positivity Km, ofx and (ctz) reintroduced to the regimen and Cs stopped due to side effects. After 6 months his physician stopped Km due to AFB culture conversion, and continued the rest of regimen (Ofx, Eto, Ctz, PAS and B6) but he was still symptomatic despite taking this regimen for almost 18 months. And in the last days of 2010 he was referred from

Karachi to a well-known pulmonologist at Peshawar. Keeping in view the previous history and recent AFB culture/DST results, he was declared as treatment failed and after sending AFB culture sensitivity to AKU Lab, started on Amikacin, Ethambutol, Levofloxacin, Ethionamide, Cycloserine, PAS and B6. Later on Levofloxacin was replaced by Moxifloxacin when his DST showed resistance to RHEZS and FQ. After taking the above mentioned regimen of almost seven months, he was still AFB culture positive and DST showed resistance to RHEZS, FQ, Km and Am, a step forward to XDR-TB. That was the time to take some extra measures for him. Therefore a skilled thoracic surgeon did left pneumonectomy (most probable cause of this chronic infection) on the recommendation of chest physician, as well as at this stage another sample was sent for AFB culture and DST, which showed the growth of MOTT (Mycobacterium other than TB) and his treatment was changed to RHE, Clr (Clarithromycin) and Lfx.

In the 1st month of 2014 he completed the treatment of MOTT for 2 years with significant improvement and few negative AFB cultures during this time period. He was very aware of his illness and did AFB culture twice in the next period of eight months which were negative.

After eight months of the completion of his MOTT treatment, we received him at our PMDT site with the complaints of Productive cough, Fatigue, Fever, Breathlessness, significant weight loss and death dreams.

His baseline biochemistry was normal, WBC count was 11500/cmm and ESR was 85 mmHg 1st hour. Audiometry showed bilateral high frequency sensory neural loss (due to excessive use of aminoglycosides in his previous regimen) On psychological assessment he was mildly depressed with death phobias.

His sputum smear was 3+ and Xpert MTB/MTB RIF assay showed MTB as well as RIF resistance detection. We sent his sample for AFB culture and DST. Later on result showed resistance to RHZ. We reassured and enrolled him as a cat IV relapse PTB case, but the challenge was to design the treatment regimen for him because he had used mostly available second line drugs.

According to National and WHO guidelines we selected the following maximum available regimen for him.

Capriomycin, Pyrazinamide, Moxifloxacin, Ethionamide, Cycloserine, Clofazimine, Linezolid,

Clarithromycin, Amoxi/Clave and B6. Although he passed away within a month of initiating this regimen but the aim behind this case report is to be aware, like such challenging cases in future, which will be discussed in discussion.

SUMMARY

Tuberculosis (TB) is a major infectious disease killing nearly two million people, mostly in developing countries, every year. The increasing incidence of resistance of Mycobacterium tuberculosis strains to the most-effective (first-line) anti-TB drugs is a major factor contributing to the current TB epidemic. Drug-resistant strains have evolved mainly due to incomplete or improper treatment of TB patients. Resistance of M. tuberculosis to anti-TB drugs is caused by chromosomal mutations in genes encoding drug targets. Multidrug-resistant (resistant at least to rifampin and isoniazid) strains of M. tuberculosis (MDR-TB) evolve due to sequential accumulation of mutations in target genes. Emergence and spreading of MDR-TB strains is hampering efforts for the control and management of TB. The MDR-TB is also threatening World Health Organization's target of tuberculosis elimination by 2050. Proper management of MDR-TB relies on early recognition of such patients. Several diagnostic methods, both phenotypic and molecular, have been developed recently for rapid identification of MDR-TB strains from suspected patients and some are also suitable for resource-poor countries. Once identified, successful treatment of MDR-TB requires therapy with several effective drugs some of which are highly toxic, less efficacious and expensive. Minimum treatment duration of 18–24 months is also long, making it difficult for health care providers to ensure adherence to treatment. Successful treatment has been achieved by supervised therapy with appropriate drugs at institutions equipped with facilities for culture, drug susceptibility testing of MDR-TB strains to second-line drugs and regular monitoring of patients for adverse drug reactions and bacteriological and clinical improvement.¹⁻⁴

The prevalence of NTM lung disease is increasing worldwide, even in immunocompetent individuals. NTM lung disease is becoming a greater public health problem and the financial costs are substantial, particularly in elderly patients. Because NTM is a ubiquitous pathogen, isolation from a respiratory specimen does not necessarily indicate NTM lung disease. Clinical, microbiologic, and radiographic criteria should all be met to make a diagnosis of NTM lung disease.

Treatment regimen and response rates differ accord-

ing to NTM species; therefore, molecular methods for identification of NTM species and DST for optimal treatment regimens are ultimately needed. The diagnosis of NTM lung disease depends on meeting established diagnostic criteria; however, treatment decisions are difficult and still require considerable clinical judgment.⁵ Management of NTM lung disease is mainly carried out by medical therapy, a lengthy, expensive, and time-consuming process. Macrolides remain the most effective agents available against SGM and some RGM. Multiple drug therapy with a macrolide, ethambutol and a rifamycin is recommended, and an initial 2–3 months of aminoglycosides may be needed depending on the disease severity of MAC lung disease. Although optimal therapeutic regimens have yet to be established and effective agents are lacking, with frequent side effects in MABC lung disease, treatment with a macrolide and two parenteral agents (amikacin plus cefoxitin or imipenem) has shown favorable outcomes in species of *M. abscessus* erm (41) C28 sequevar or *M. massiliense* species with nonfunctional erm(41) gene. There is a lack of evidence and few randomized clinical trials to guide the management for refractory NTM lung disease, macrolide-resistant NTM, or *M. abscessus* erm(41) T28 sequevar with activeerm(41) gene, resulting in inducible resistance to macrolides. However, multiple combination regimens with inhaled amikacin following initial treatment with parenteral aminoglycosides, tigecycline and other promising oral antibiotics such as linezolid, clofazimine, and bedaquiline, and surgical intervention in selected cases have shown promising results. A multidisciplinary approach is important in the diagnosis and treatment of NTM lung disease and improved management of NTM lung disease allows for more comprehensive care. Newer antimicrobial agents and clinical trials are needed in order to improve patient management.

Treatment for nontuberculous mycobacteria will depend on the specific bacteria causing infection. Treatment may be difficult because NTM bacteria may be resistant to many common types of antibiotics. For some patients, the same drugs used to treat tuberculosis (TB) will be recommended.⁷

In ours' setup the treatment of NTM is experienced base, like some chest physicians are treating ntm with, RE(H)+Clr+Lfx with the initial cover of 3Km(3Am), total duration of treatment upto 18 months, if resistance pattern not available. we has experience that almost 80% patients recovered with this treatment.⁸

One can align the treatment according to the DST resistance pattern.

CONCLUSION

Before 2010 there was no specialist programmatic management unit, nor proper guidelines to treat MDR-TB patients. Chest physicians were treating DR-TB patients on their individual capabilities with no proper monitoring follow ups. This patient made himself a rolling stone with poor compliance. On the other hand he was miss treated for NTM during the course of MDR-TB Treatment, which may grow anytime due to diseased lung.

Key Message from this case is to refer all DR-TB cases to specialist programmatic management units of DR-TB, functional almost in every region of Pakistan for proper free of cost management with regular follow ups.

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