Navigating challenges in management of drug resistant tuberculosis: Case experience from Nepal

Avatar Verma,[1] Narendra Bhatta,[1] Deebya Raj Mishra,[1] Achyut Bhakta Acharya,[1] Rejina Shahi,[1] Sion Hangma Limbu,[1] Srijan Katuwal[1]

[1] Department of Pulmonary, Critical Care and Sleep Medicine, B. P. Koirala Institute of Health Sciences, Dharan, Nepal

ABSTRACT

Drug resistant tuberculosis (DR TB) a severe form of TB is a disease of concern. Its treatment requires multiple toxic drugs for prolonged duration because of which, often have complicated course requiring close supervision, continuous encouragement from physician, management of side effects and modification of drug regimen for successful outcome. In this report, we are presenting a case of diabetic patient suffering from DR TB highlighting key diagnostic and management challenges.

Keywords: Adverse effect of drugs, Challenges, Drug resistant tuberculosis, Drug Regimen

INTRODUCTION

TB is one of the leading infectious cause of death, killing about one and half million people annually.[1] Adding to that there are more than four hundred thousand cases of DR TB and about two hundred thousand deaths were noted in 2019.[2] Worst thing about DR TB is that only one of three has access to treatment and has treatment success rate of only 59%.[1] A clinician face many challenges in managing DR TB because of long treatment course, adverse effect of drugs (AEDs), managing co-morbidities, etc. Hereby, presenting a case report of a patient suffering from DR TB, focusing various management difficulties.

CASE HISTORY:

40 years gentleman, an accountant, a reformed smoker with history of smear positive pulmonary tuberculosis six years back, diabetes mellitus three years back and underlying depression presented with productive cough of five days duration to our hospital in Eastern Nepal. Chest x-ray revealed a left upper radio-opacity. While the sputum microscopy was negative, Xpert MTB/Rif detected Mycobacterium tuberculosis with Rifampicin resistance.

As per the preference of patient at the time, he was put on Short Treatment Regimen (STR) (Fig. 1). In the meanwhile, sputum sample was also sent to referral laboratory (situated in the capital city of Nepal) for molecular testing for resistance to second line drugs (LPA SL- GenoType MTBDRsl).

In April 2019, LPA showed resistance to fluoroquinolones (gyr A mutation) signifying pre extensively drug resistant TB (Pre-XDR). His treatment was modified to Bedaquiline (Bdq), Amikacin (Am), Linezolid (Lzd), Ethionmaide (Eto), Clofazimine (Cfz), Pyrazinamide (Z). Cycloserine (Cs) was not initially started taking into account his underlying depression.

Four months into the new regimen, patient developed tinnitus and joint pain involving small joints of hands bilaterally. For tinnitus, Pure Tone Audiometry (PTA) was performed that revealed Sensorineural Hearing Loss (SNHL) for high frequency sounds. Am was withdrawn and Cycloserine (Cs) initiated in place.

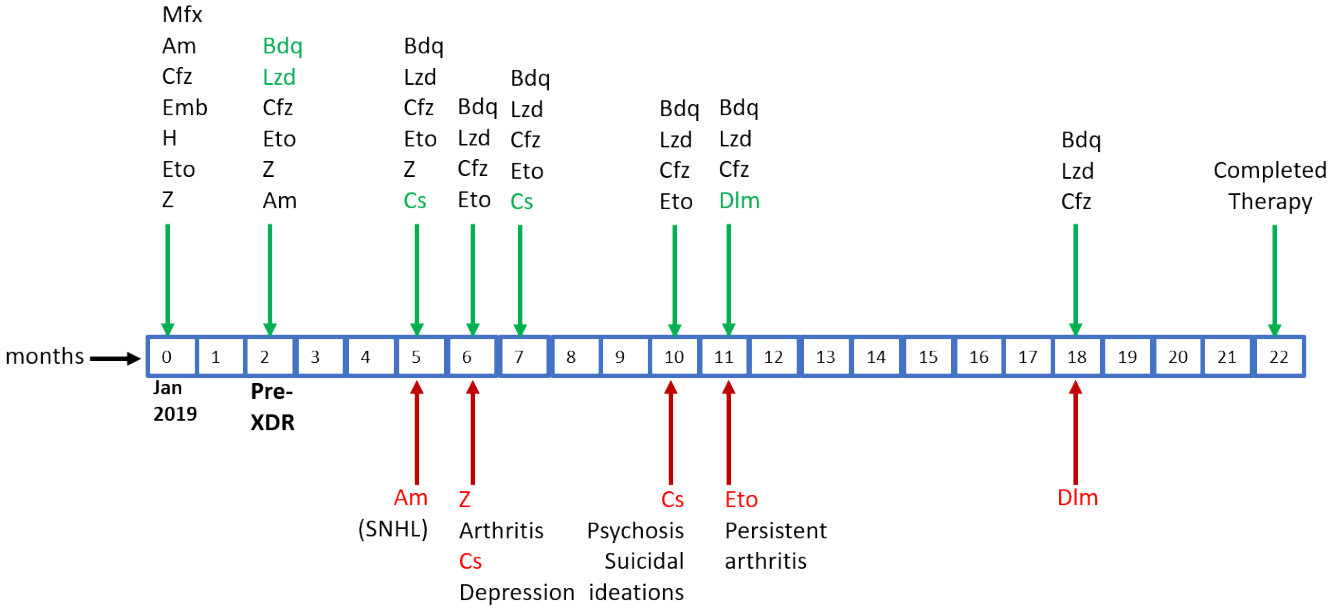
For joint pain, his C-reactive protein was raised while all other markers such as rheumatoid factor, anti-cyclic citrullinated peptide and extractable nuclear antigen panel of tests were negative. As pain persisted despite symptomatic treatment, Z was stopped in the sixth month (Fig. 1).

The patient continued having features suggestive of depression. Cs was temporarily withdrawn for about a month, and subsequently restarted once his symptoms were a little bit better. However, patient again presented to hospital in the ninth month of treatment with suicidal ideations and violent behavior. This time he was admitted, Cs stopped and treatment for drug induced psychosis started as guided by Psychiatry team.

While his psychosis improved, he continued having small joint pain specially in left hand progressing to limitation of

Corresponding author:
Avatar Verma
avatar4ktm@yahoo.com

Fig 1. Timeline of treatment



movement. MRI cervical spine and brachial plexus was done which were normal. Despite exhaustive investigation and rheumatologic and orthopedic review, as no obvious cause was found, Eto was also stopped on suspicion.

By this time, the patient was only on three drugs with questions about the strength of regimen. Incidentally Delamanid (Dlm) had just been brought in to Nepal. After permission from relevant authorities, Dlm was started from the eleventh month of his treatment in December 2019. Keeping in mind the propensity of QT prolongation with Bdq, Dlm and Cfz, ECG monitoring was done on a weekly basis. The QT interval remained within 470 milliseconds throughout.

In the subsequent months, his joint pain got better, psychosis and blood sugar were under control. Consequent sputum cultures were negative and CT chest revealed only chronic fibro-bronchiectatic changes in left upper lobe. Subsequently, after 20 months of therapy, treatment for DRTB was stopped. Till date, the patient is doing well with another repeat CT chest on July 2021 showing no additional findings.

DISCUSSION

The treatment of drug resistant TB has undergone a paradigm shift. From the initial days of conventional regimen to the present all oral regimen, the treatment landscape has changed dramatically.[3–6]

On the back of the rapid communication released by WHO in 2018, with due discussion with the patient, he was started on Short Treatment Regimen (STR) with Amikacin as the injectable in place of Capreomycin.[4] Following the report of FQ resistance, patient was started on Bdq. The subsequent development of SNHL is in fact a common occurrence in DRTB drug regimen. A recent meta-analysis points out that the reported incidence of hearing loss is 28.3% (95%CI 23.4-33.1) in those using the injectables in DRTB and it is more so with Amikacin (33.4%, 95%CI 18.2-48.6).[7] Thus, the shift to all oral regimen in the newer guidelines is well warranted.

Incidence of depression is already high in cases of tuberculosis in general and DRTB in particular with a prevalence of 52.34% (95% CI 38.09–66.22) DRTB and 43.47% (95% CI 35.88–51.37) non-MDR-TB.[8] The situation is made more tricky by the use of Cs with known side effects of psychosis and suicidal ideation.[9] Cs was started as second Group B drug in place of Am despite underlying depression to maintain the strength of the regimen on the background of FQ resistance as per guidelines.[4]

At the same time persistent arthritis led to withdrawal of pyrazinamide and ethionamide. Thus, adjustments to the regimen are actually very common and more so with older regimens. Constant need to balance the regimen to the side effects limits the number of active drugs and thus raises questions on the strength of regimen. For similar reasons, the patient was put on Dlm. The combined use of Bdq and Dlm was one of the earlier instances of use in Nepal. While initially there were many concerns about the combination of these drugs, recent data review suggests that there is no additional safety concerns for the combined use.[6] While Dlm was used for six months, Bdq was continued throughout the regimen. The use of Bdq for more than six months still remains "off label".[6] At the same time, Bdq can still be used for longer periods following best practices in "off-label" use.10 In our patient, we continued using Bdq for 20 months without any side effects. Similarly, Lzd was also continued for the entire duration of the treatment without any reported attributable side effects.

All the treatment decisions were made keeping in mind the evolving guidelines at the time in the absence of culture-based

drug susceptibility testing (DST). While molecular DST did help in decision making, the absence of culture-based DST to other drugs in the regimen leaves much on the judgement of the clinician to decide on the mix of the regimen. At the same time, with rapidly changing guidelines and long treatment regimens, an ongoing regimen might feel like "not current" as can be thought of in this case with the 2020 WHO guidelines paving the way for BPaL regimen.[6,11] With the NeXT trial also being completed, the DRTB field is indeed in an exciting phase.[12] However, the challenge remains for the programmatic management to catch up with the rapid changes and perhaps make life easier for patients as illustrated in this case.

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