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Case Series

Orthopaedics Section

Improvement in Outcomes with a New Bedaquiline-based Regimen in Postoperative Cases of Drug-resistant Tuberculosis of the Spine: A Case Series

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ABSTRACT

The incidence of drug-resistant strains of Tuberculosis (TB) is rising at an alarming rate. With the emergence of newer drug-resistant strains, managing the disease with existing antitubercular agents is becoming increasingly difficult. Few studies exist regarding the treatment of drug-resistant TB of the spine using a Bedaquiline-based regimen. Therefore, the efficacy of shorter regimens with novel drugs such as Bedaquiline and Delamanid in drug-resistant TB of the spine must be analysed. The present case series highlights the outcomes of a newer Bedaquiline-based antitubercular regimen in postoperative cases of drug-resistant TB of the spine. All three cases discussed in this study-54-year-old female, 12-year-old female, and 19-year-old female patients-had a clinical and radiological diagnosis of TB of the spine with significant neurodeficits. They underwent decompression and instrumentation surgery. Postoperatively, all three were diagnosed with drug-resistant TB and were started on a Bedaquiline-based antitubercular regimen. Subsequently, all the patients showed significant improvement in neurodeficits with no radiological evidence of recurrence. Therefore, Bedaquiline might play an important role in the future management of drug-resistant spinal TB.

Keywords: Antitubercular agents, Bacterial infection, Koch's spine, Multidrug resistance

INTRODUCTION

Drug-resistant strains of tuberculosis are emerging as a serious health problem in both developed and developing countries. Spinal TB is a paucibacillary infection that is deep-seated, and the demonstration of Acid-fast Bacilli (AFB) with Ziehl-Neelsen (ZN) staining is possible in only 10-30 percent of cases [1]. Drug resistance is suspected in cases showing no clinicoradiological improvement or the appearance of new osteoarticular lesions of TB despite being on Antitubercular Treatment (ATT) for a minimum of five months [1]. The prevalence of drug resistance in spinal tuberculosis patients is reported to be 28.6%, out of which 4.6% were MDR TB, 6% were pre-extensively Drug-resistant TB (XDR-TB), and 2.7% were XDR-TB; the rest (15.3%) exhibited monodrug resistance [2].

Drug resistance can manifest in various types. Resistance to any of the single first-line anti-TB drugs is known as monodrug resistance, while resistance to more than one first-line anti-TB drug, other than Isoniazid (INH) and Rifampicin (RIF), is known as polydrug resistance. Rifampicin Resistance (RR) is resistance to RIF detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs. Multidrug Resistance (MDR) is resistance to both INH and RIF. XDR is considered when resistance is present to both INH and RIF with resistance to atleast 1 of the 3 second-line injectable drugs (capreomycin, kanamycin, and amikacin) and any Fluoroquinolone (FQ). Recently, a newer term has been introduced as pre-XDR, which is resistance to both INH and RIF with resistance to FQ or 1 of the 3 second-line injectable drugs [2].

There is inadequate data in the literature regarding the treatment of XDR-TB spine; therefore, the efficacy of shorter regimens with novel drugs such as Bedaquiline and Delamanid in drug-resistant TB of the spine needs to be analysed [3]. The aim of the present study was to assess the outcome of a newer Bedaquiline-based antitubercular regimen in cases of postoperative drug-resistant TB of the spine and to evaluate the effectiveness of this regimen, the improvement of neurological function postsurgery with Bedaquiline, and radiological improvement postsurgery with this regimen using serial radiographs.

CASE SERIES

Case 1

A 54-year-old female patient presented at the orthopaedic Outpatient Department (OPD) with complaints of upper back pain and weakness in both lower limbs over the past two weeks. The pain had an insidious onset and gradually progressed. She also experienced paraesthesia, difficulty in passing urine, and recent weight loss. The patient had a history of pulmonary tuberculosis six years prior, which was successfully treated with a six-month regimen of antitubercular drugs, leading to a cure. She did not report any history of fever or other medical illnesses.

Upon examination, the patient exhibited 2/5 power in bilateral hip and knee, and 1/5 power in bilateral ankle and toes. There was an 80% loss of sensation below the level of the xiphisternum. Deep tendon reflexes in the bilateral lower limbs were exaggerated, with well-sustained ankle clonus. Spasticity was observed in both lower limbs, and the plantar response showed an extensor reflex. An X-ray revealed the collapse of the D4 vertebra. Magnetic Resonance Imaging (MRI) indicated D4-D5 Koch's spine with the collapse of the D4 vertebra and an abscess compressing the cord.

Based on these findings, urgent decompression and instrumentation with interbody fusion were performed, and an intraoperative sample was sent for bacterial, fungal, AFB culture and sensitivity, Mycobacteria Growth Indicator Tube (MGIT), GeneXpert TB, and histopathological examination. The patient was started on a four-drug antitubercular regimen based on the clinical and radiological findings mentioned above. The AFB smear report was negative, the MGIT report was

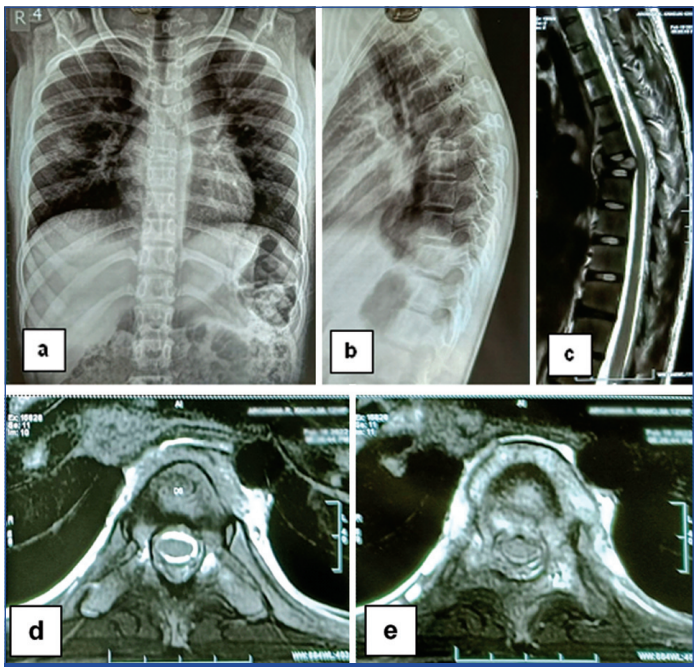
positive for Mycobacterium tuberculosis complex, and GeneXpert showed RIF resistance. Subsequent Line Probe Assay (LPA) showed resistance against both RIF and INH. Full Drug Sensitivity Testing (DST) confirmed resistance to both RIF and INH. Therefore, a Bedaquiline-based regimen was initiated, including Bedaquiline, Levofloxacin, Clofazimine, Pyrazinamide, Ethambutol, and a high dose of INH. Bedaquiline was administered for six months, while Levofloxacin, Clofazimine, Pyrazinamide, Ethambutol, and the high dose of INH were continued for 18 months. The patient is currently under treatment.

Monthly follow-up and routine examinations, including radiographs, Electrocardiography (ECG), and blood parameters, were done. Eight months following the surgery, the patient reported no pain, and X-rays did not show any recurrence of the lesion or abscess. Additionally, weight gain and appetite were restored. The patient exhibited full power (5/5) in bilateral hip and knee, but bilateral ankle, Extensor Hallucis Longus (EHL), and Flexor Hallucis Longus (FHL) had a power of 4/5. Sensation was restored in the bilateral lower limbs, and while deep tendon reflexes were exaggerated, clonus and spasticity were absent. The plantar response was not observed, and bowel and bladder habits remained unaltered. The C-reactive Protein (CRP) and Erythrocyte Sedimentation Rate (ESR) were recorded at 1.2 and 8, respectively.

Case 2

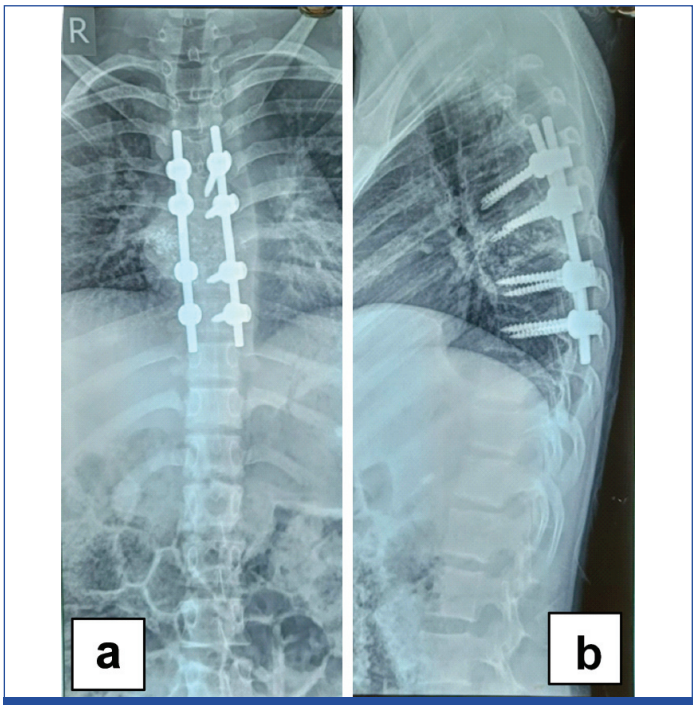
A 12-year-old female patient presented with complaints of back pain and difficulty walking for the past three months. She had a known case of TB spine and had been under a standard antitubercular regimen for the last six months. However, her condition deteriorated, and she became bedridden due to worsened back pain over the last three months.

On examination, she had a power of 3/5 in all muscles of the bilateral lower limb, except the right Extensor Hallucis Longus (EHL), which had a power of 4/5. Bilateral deep tendon reflexes were absent, and plantar reflexes were mute. Sensations in the bilateral lower limbs were intact. Tone and nutrition were normal. There was no bladder or bowel involvement. The X-ray and MRI suggested complete collapse of the D6 vertebral body with marrow oedema at D5 and D7 levels. Abnormal prevertebral and paravertebral collections were seen at D5-7 levels, with a maximum thickness of 1.5 mm. An anterior epidural collection was also noted at this level [Table/Fig-1a-e].



[Table/Fig-1]: (a) Preoperative antero-posterior; and (b) Lateral view X-ray radiograph showing collapse of D6 vertebra; (c) Sagittal Magnetic Resonance Imaging (MRI) Radiograph showing collapse of D6 vertebral body and prevertebral collection at D6 level; (d) Axial MRI radiograph showing collapse of D6 vertebral body; (e) Prevertebral and paravertebral collection at D6 level.

She underwent decompression and instrumentation with interbody fusion [Table/Fig-2a,b], and intraoperative specimens were sent for bacterial, fungal, AFB culture and sensitivity, GeneXpert TB, MGIT, and histopathological examination. The AFB smear was negative. The histopathological report suggested chronic inflammatory pathology, possibly TB. On GeneXpert, RIF resistance was detected. Therefore, a Bedaquiline-based regimen was started for six months. Later, LPA suggested resistance to all first and second-line antitubercular agents, and thus XDR-TB was diagnosed. Therefore, Para aminosalicylic Acid (PAS) was added to the previous regimen, replacing levofloxacin. Finally, the DST report showed resistance against all antitubercular agents except Clofazimine and PAS. She had taken Bedaquiline for 6 months, and Clofazimine, Cycloserine, Linezolid, and PAS were given for 12 months. She is currently continuing the above regimen. She was routinely followed-up on a monthly basis for the assessment of neurological recovery and monitoring of blood parameters.



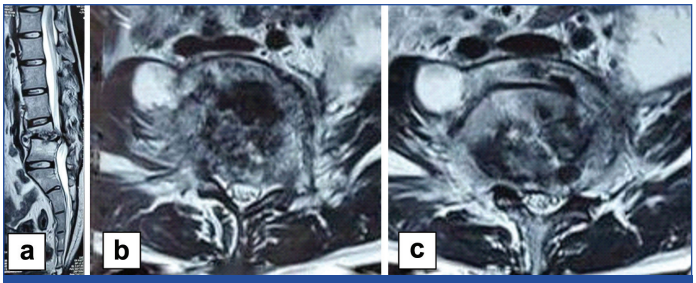
[Table/Fig-2]: Immediate postoperative: (a) Anteroposterior; and (b) Lateral x-ray radiograph showing instrumentation done at D4-8 levels.

After seven months of surgery, the patient had full neurological recovery. Power in the bilateral lower limb was found to be normal, i.e., 5/5 in the bilateral hip, knee, ankle, and toes. Deep tendon reflexes were found to be normal. Bilateral plantar reflexes showed a flexor response bilaterally. Sensation and tone were also normal bilaterally. The Erythrocyte Sedimentation Rate (ESR) and C-Reactive Protein (CRP) values at the end of five months were 11 and 3.46, respectively, and the patient had gained a significant amount of weight (12 kg).

Case 3

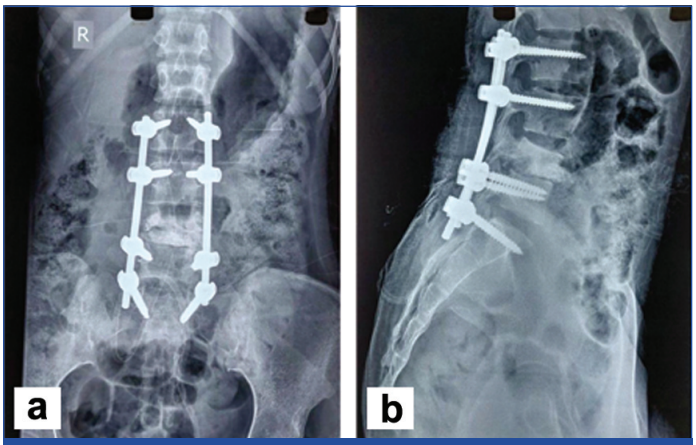
A 19-year-old female patient presented at the orthopaedic OPD with a complaint of low back pain and weakness in both lower limbs for the last 1.5 months. The pain had an insidious onset and was gradually progressive in nature. She had no history of any blunt trauma, falls, or lifting heavy weights. There was no history of tingling, numbness, paraesthesia, or any other joint pain, nor any history of Kochs' or Koch's contact, fever, or weight loss.

On examination, power in bilateral hips and knees was 3/5, the right ankle and toes were 2/5, and the left ankle and toes were 0/5. Deep tendon reflexes and the plantar reflex were absent in the bilateral lower limbs. Clonus was absent in both lower limbs. Both lower limbs were flaccid, and there was 20% sensory loss below L2 bilaterally. MRI suggested discitis at the L4-L5 level with destruction of the L4 vertebra and a prevertebral collection [Table/Fig-3a,b].



[Table/Fig-3]: (a) Sagittal MRI; and (b) Axial MRI radiograph suggestive of discitis at L4-L5 level with destruction of L4 vertebra; and (c) prevertebral collection.

She underwent decompression and instrumentation with interbody fusion, and intraoperative specimens [Table/Fig-4a,b] were sent for bacterial, AFB, and fungal culture and sensitivity, GeneXpert TB, MGIT, and histopathological examination. The AFB smear report was negative. The histopathological report suggested chronic inflammatory pathology, possibly Tuberculosis. On GeneXpert, RIF resistance was detected, and she was put on the Bedaquiline-based regimen, which contained Bedaquiline, Levofloxacin, Clofazimine, Pyrazinamide, Ethambutol, and a high dose of INH. Following positivity in MGIT, LPA was done, which showed resistance against both RIF and INH. She continued with the above regimen. Full DST confirmed resistance to both RIF and INH, diagnosing it as MDR TB of the spine. Therefore, she continued with the regimen containing Bedaquiline (for six months) and Levofloxacin, Linezolid, Clofazimine, and Cycloserine for eight months. She is currently continuing this regimen. She was routinely monitored using radiographs, ECG, and blood parameters on monthly follow-up.



[Table/Fig-4]: Immediate postoperative: (a) anteroposterior; and (b) lateral X-ray radiograph showing instrumentation done at L2-S1 levels.

She was regularly followed-up, and three months following surgery, she had power in bilateral hips and knees at 5/5 and bilateral ankles and toes at 4/5. Deep tendon reflexes were absent, and plantar reflexes showed a flexor response. Sensation, tone, and nutrition were normal in bilateral lower limbs. X-rays didn't show any recurrence of the lesion. ESR and CRP were 9 and 4.2, respectively.

DISCUSSION

Among the three cases discussed above, two of them had MDR-TB, and one had XDR-TB. All three of them showed significant neurological recovery several months after surgery with this new Bedaquiline-containing regimen. According to previous literature, the four main causes of drug resistance [1,3] are incomplete or inadequate treatment [4], non adherence to ATT [5], genetic predisposition to develop drug resistance [6,7], and Human Immunodeficiency Virus (HIV) co-infection [8,9]. In the present case series as well, Case-1 and Case-2 were known cases of pulmonary TB and spine TB, respectively, and showed failure of treatment with the traditional ATT regimen.

The treatment of drug-resistant tuberculosis comes at a terrible price. It is expensive, takes a longer time to treat, disrupts lives, and has potentially life-threatening side-effects, including depression or psychosis, hearing loss, hepatitis, and kidney impairment [10]. Hence, proper diagnosis and timely management are crucial. Current GeneXpert and LPA techniques provide a quick diagnosis of drug resistance in Tuberculosis. Culture remains the gold standard in the diagnosis and drug susceptibility testing of tuberculosis [11].

In the context of drug-resistant TB, a bedaquiline-based regimen should include bedaquiline and atleast four effective second-line drugs. The choice of drugs should be based on the DST pattern in descending order and should form the Other Background Regimen (OBR), including a Second Line Injectable (Kanamycin/Capreomycin), a fluoroquinolone (Levofloxacin/Moxifloxacin), two bacteriostatic drugs (Ethionamide, Cycloserine, Para aminosalicylic Acid), and other medications such as Linezolid, Clofazimine, high-dose INH, and Pyrazinamide, if sensitive.

The dosages are as follows:

(i) Weeks 0-2: Bedaquiline 400 mg daily + OBR;

(ii) Weeks 3-24: Bedaquiline 200 mg thrice a week (with atleast 48 hours gap between doses) + OBR;

(iii) Week 25 (start of the seventh month) until the end of the treatment: Continue with other second-line anti-TB drugs as per the sensitivity pattern and the National Tuberculosis Education Program (NTEP) recommendations, which were recently updated in June 2023 [12].

Similar treatment regimens were planned for all cases in the present case series after proper testing by LPA and DST patterns for the best outcomes, and all three cases responded well.

Delamanid and Bedaquiline are associated with cardiac side-effects like QT prolongation and hence need to be monitored using Echocardiography (ECG) [13]. In the present case series, all three cases were followed-up for varying periods of 5 to 8 months after treatment with proper follow-up reports to check for outcomes and prevent any late side-effects. Although a past study has also suggested the effectiveness of a Bedaquiline-based regimen in treating MDR-TB spinal infection without any severe adverse effects [14].

Very few studies are available worldwide regarding the effectiveness of a Bedaquiline-based regimen in the treatment of drug-resistant tuberculosis. According to a case reported very recently in 2022 by De Vito A et al., a similar outcome was observed in a 21-year-old male patient with MDR TB spine managed with a Bedaquiline-based regimen. A Computed Tomography (CT) scan done 1.5 years after starting therapy confirmed the cure [14]. Follow-up radiographs in the present case series for all three cases also showed signs of neurological recovery, with no new lesions or abscesses seen.

CONCLUSION(S)

The newer Bedaquiline-based regimen is effective in treating drug-resistant tuberculosis of the spine and warrants further study to objectively determine the efficacy of this regimen. With the emergence of newer strains with drug resistance, management with the existing antitubercular agents is becoming difficult. Newer drugs need to be added to the existing armamentarium. Bedaquiline and Delamanid are definitely going to play an important role in the management of drug-resistant spine tuberculosis in the future.

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