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Case report

Acquired bedaquiline and fluoroquinolones resistance during treatment follow-up in Oromia Region, North Shewa, Ethiopia

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ABSTRACT

Background: Bedaquiline (BDQ) is an effective drug currently used for multidrug-resistant or rifampicin-resistant TB (MDR/RR-TB) and pre-extensively drug-resistant TB (pre-XDR-TB) treatment. However, resistance to this new drug is emerging. We discussed the characteristics of the first patient in Ethiopia who acquired BDQ and fluoroquinolones (FQs) resistance during treatment follow-up.

Case report: In this case report, we present the case of a 28-year-old male pulmonary TB patient diagnosed with MDR-TB who is a resident of the Oromia Region of North Shewa, Mulona Sululta Woreda, Ethiopia. Sputum specimen was collected initially and for treatment monitoring using culture and for phenotypic drug susceptibility testing (DST) to first-line and second-line TB drugs. Initially, the patient was infected with a mycobacterial strain resistant to the first-line anti-TB drugs Rifampicin (RIF), Isoniazid (INH), and Pyrazinamide (PZA). Later, during treatment, he acquired additional drug resistance to ethambutol (EMB), ofloxacin (OFX), levofloxacin (LFX), moxifloxacin (MFX), and BDQ. The patient was tested with MTBDR*plus* and MTBDR*sl* to confirm the presence of resistance-conferring mutation and mutation was detected in *rpoB, katG,* and *gyrA* genes. Finally, the patient was registered as having extensively drug-resistant tuberculosis (XDR-TB) and immediately started an individualized treatment regimen.

Conclusion: This case report data has revealed the evolution of BDQ resistance during treatment with a BDQ-containing regimen in Ethiopia. Therefore, there is a need for DST to new second-line drugs to monitor and prevent the spread of DR-TB.

Introduction

Tuberculosis (TB) remains the primary public health concern globally. In 2022, approximately 10.6 million people fell ill with TB worldwide, including 5.8 million men, 3.5 million women, and 1.3 million children. It is the second-leading cause of death with an estimated 1.13 million deaths among HIV-negative people and 167,000 deaths among people with HIV in 2022 [1].

The emergence of drug-resistant tuberculosis (DR-TB) continues to be a major problem for TB control programs worldwide [2,3]. Globally, in 2022, the estimated proportion of people with TB who had MDR/RR-TB was 3.3 % among new cases and 17 % among those previously treated. Among those tested, 149,511 people with MDR/RR-TB and 27,075 people with pre-XDR-TB or XDR-TB were detected. In Ethiopia, MDR-TB accounts for 1.1 % of new TB cases and 12 % of previously treated TB cases. Of the 357 MDR-TB laboratory-confirmed

Abbreviations: BDQ, Bedaquiline; BPaLM, Bedaquiline pretomanid linezolid and moxifloxacin; CFZ, Clofazimine; DST, drug susceptibility testing; DR-TB, drug-resistant tuberculosis; EMB, Ethambutol; EPHI, Ethiopian Public Health Institute; FQs, fluoroquinolones; INH, Isoniazid; LFX, levofloxacin; LPA, Line probe assays; MFX, moxifloxacin; MDR-TB, Multi-drug -resistant tuberculosis; MUT, Mutation; MTB, Mycobacterium tuberculosis; OFX, ofloxacin; RIF, Rifampicin; RR-TB, rifampicin-resistant tuberculosis; PZA, Pyrazinamide; STR, Short treatment regimen; WHO, World Health Organization; WT, Wild-type; XDR-TB, extensively drug-resistant tuberculosis.

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cases, 8 (2.24 %) were pre-XDR-TB or XDR-TB [1]. Rifampicin-resistant TB is TB caused by *Mycobacterium tuberculosis* (MTB) strains that are resistant to RIF, whereas MDR TB is caused by MTB strains that are resistant to RIF and INH. Both RR-TB and MDR-TB require treatment with second-line anti-TB drugs, which is a fully oral short treatment regimen (STR), composed of BDQ, pretomanid, linezolid and moxifloxacin (BPaLM). Given the introduction of this regimen, the meaning of XDR-TB has been revised to MDR-TB, which is resistant to any fluoroquinolone, plus at least one of the bedaquiline and linezolid [3,4].

In 2022, WHO had indeed been actively evaluating and updating guidelines for the treatment of DR-TB [3]. Bedaquiline is a crucial drug in the management of MDR/RR TB and has been associated with improved outcomes in such patients [5]. However, the emergence of resistance to BDQ underscores the evolving challenge of drug resistance in TB treatment [6]. One significant development was the promotion of all-oral BDQ-containing regimens as the preferred treatment choice [7]. World Health Organization has indeed recommended the use of BDQ for the treatment of DR-TB across all age groups [5]. This recommendation likely reflects the promising results from DR-TB regimens containing BDQ, which have been reported to be shorter, less toxic, and more effective compared to conventional regimens [5]. A new and shorter treatment regimen for MDR/RR-TB treatment recommendation was the use of a 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid (600 mg), and moxifloxacin (BPaLM), and in whom the patient's resistance to fluoroquinolones (pre-XDR-TB). The second recommendation was the use of the 9-month all-oral regimen rather than longer (18-month) regimens in patients with MDR/RR-TB and in whom resistance to fluoroquinolones has been excluded [5]. In this report, we present the case of a 28-year-old male initially diagnosed with MDR-TB but later found resistance to BDQ and FQs based on a drug-susceptibility test (DST). To the authors' knowledge, this is the first case report of acquired BDQ resistance in Ethiopia.

Case report

A 28-year-old male living in the Oromia region of North Shewa, Mulona Sululta Woreda, Ethiopia, was referred from Derba Health Center to Chancho Primary Hospital for a GeneXpert test on December 24, 2022. The initial presentation of clinical characteristics in this case, revealed several key findings: The patient was HIV-negative, BMI 19.3, MUAC 21, no presence of comorbidity, had no history of contacts with known TB or MDR/RR-TB case, and had never been previously diagnosed with TB. The CXR showed coarse infiltrates over the left lower 2/3 of the lung with scattered wheezing. This pattern is consistent with pulmonary tuberculosis and suggests the presence of consolidation or infiltrates in the lung parenchyma (Fig. 1). A chest X-ray was taken after eleven months of treatment, and it showed a few infiltrates (Fig. 2). On history taking it was found that he was having a wet cough, low-grade fever, night sweating, poor appetite, and unspecified weight loss in a few months. In laboratory diagnosis, the patient was diagnosed with Rifampicin-resistant (RR) TB using the Xpert MTB/RIF assay and he was immediately started a short treatment regimen. The patient's weight was 56 kg at baseline and vital signs were stable during the diagnosis of RR-TB.

At baseline, sputum was referred to the Ethiopian Public Health Institute (EPHI) National TB Reference Laboratory for culture, phenotypic drug susceptibility testing (DST), and line probe assay (LPA) using Genotype MTBDR*plus* and MTBDR*sl*. The patient's Genotype MTBDR*plus* showed resistance to RIF and INH, whereas there was no resistance to FQs with MTBDR*sl*. Phenotypic DST was performed at baseline, fourth month, ninth month, and eleventh month. At baseline, at the fourth month, and at the ninth month of treatment follow-up, the phenotypic DST and LPA showed resistance only to RIF, INH, and PZA. The final drug concentrations for INH, RIF, and EMB were 1.0 μg/mL, 0.1 μg/mL, and 5.0 μg/mL, respectively. The patient was continued on a short treatment regimen. For the consecutive 11 months, the MGIT culture was persistently positive. At the eleventh month of treatment, additional resistance was detected to EMB, OFX, LFX, MFX, and BDQ by phenotypic DST. The final critical concentrations for this second-line anti-TB drugs in the MGIT method were 2.0 μg/mL of OFL, 1.0 μg/mL of LEV, 0.25 μg/mL of MFX, and 1.0 μg/mL of BDQ. For the same isolate, resistance to OFX, LFX and MFX was detected in the MTBDR*sl* assay. In the molecular test, we identified first-line drug-gene mutations in MTBDR*plus*, which indicated resistance to INH and RIF. The isolate had a mutation at codon *S531L* and a missing *WT8* band at the *rpoB* mutation gene. Also, had a mutation at codon *S315T1* and a missing *WT* band of the *katG* gene. The mutations associated with RIF and INH were similar at the baseline and at the eleventh month. At the eleventh month, we identified second-line drug resistance gene mutations by MTBDR*sl*; the isolate showed a mutation in the *gyrA* region with a mutation at codon *A90V* and the absence of *WT2*. This showed mutations that conferred drug resistance to FQs (Table 1).

The patient started treatment for MDR-TB following the national guidelines for the management of TB, and DR-TB in Ethiopia. According to the treatment guideline, the patient was treated following the regimen; (4–6 Bdq(6 m)-Lfx-Cfz-Z-E-Hh-Eto/5 Lfx-Cfz-Z-E). The initial phase was 4–6 Bdq(6 m)-Lfx-Cfz-Z-E-Hh-Eto; the continuation phase was 5 Lfx-Cfz-Z-E. After completing the eleventh-month treatment regimen, the patient remained culture-positive, indicating treatment failure. This failure was likely due to the persistence of the bacteria despite the administered treatment, which could have been influenced by factors such as drug resistance or inadequate drug penetration at the

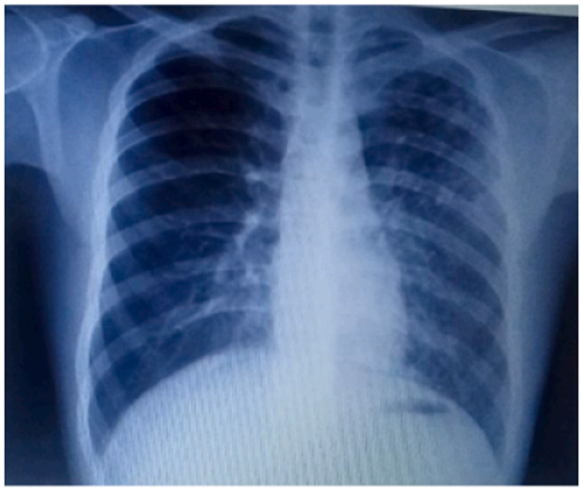

Fig. 1. Chest X-ray on the baseline treatment show infiltrates.

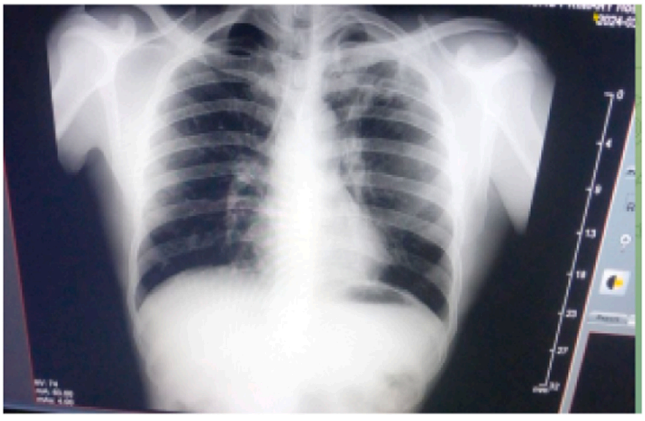

Fig. 2. The chest X-ray after eleven months of treatment completed showed few infiltrates.

Table 1
Gene mutations associated with first and second-line drug resistance.

Drug	Gene	Band	Mutant probe	Results interpretation	Clinical implications
RIF	*rpoB*	*W8*	*530–533*	Resistance to RIF inferred	RIF is not effective
		MUT3	*S531L*	Resistance to RIF inferred	
INH	*katG*	*WT*	*315*	The mutation associated with a high-level increase in MIC was inferred.	INH is unlikely to be effective even at a high dose
		MUT1	*S315T1*	The mutation associated with a high-level increase in MIC was inferred.	
FQs	*gyrA*	*WT2*	*89-93*	Resistance to LFX inferred. Mutation associated with at least a low-level increase in MIC for Mfx inferred.	LFX is not effective. MFX could be used at higher doses. The regimen should be re-evaluated based on phenotypic DST results to MFX at clinical breakpoint
		MUT1	*A90V*	Resistance to LFX inferred. Mutation associated with at least a low-level increase in MIC for MFX inferred.	

DST – Drug susceptibility testing, FQs – Fluoroquinolones, INH – Isoniazid, LFX – Levofloxacin, MFX – Moxifloxacin, MUT – Mutation, RIF – Rifampicin, WT – Wild-type.

site of infection [8]. It's important to reassess the treatment plan, including potential reasons for treatment failure, and consider alternative approaches such as adjusting the drug regimen based on susceptibility testing results. In this case, the patient subsequently developed XDR-TB, indicating the need for a more aggressive and tailored treatment approach.

Discussion

For anti-TB drugs to be effective, early diagnosis, combination therapy, and identification of mutations associated with drug resistance are essential components of TB management, particularly in the context of DR-TB [4]. However, our case report is one of the first to report BDQ resistance acquired over time among patients treated with a BDQ-containing regimen in Ethiopia. In this case, the phenotypic DSTs were consistent with the genotypic DST results, indicating the occurrence of resistance gene to OFX, LFX, and MFX. This indicates that the drug resistance mutations may have gradually accumulated during the treatment follow-up, but the phenotypic DST results were not prompted in time. The treatment scheme was not changed in time, resulting in the gradual accumulation of resistance and treatment failure.

In this case report, we showed the acquired BDQ drug resistance during the treatment follow-up. A similar case report was reported from Indonesia and Uganda [9,10]. In addition, BDQ resistance following effective treatment of MDR-TB was documented in Namibia [6]. In a recent systematic review, 2.2 % phenotypic and 4.4 % genotypic acquired BDQ resistance was reported [7]. The BDQ has demonstrated high efficacy in the treatment of RR/MDR-TB. However, insufficient or incomplete use may lead to the emergence of drug-resistant strains [11]. The emergence of resistance to BDQ is concerning as it results in difficulties in constructing regimens and is commonly associated with unsuccessful treatment outcomes. Future studies should further investigate the mechanisms of BDQ-acquired resistance development, for example, to identify patients at risk.

In this case report, we also observed acquired resistance to FQs during the treatment course. Fluoroquinolones are crucial components of MDR-TB treatment regimens due to their potency against *Mycobacterium tuberculosis* and their ability to improve treatment outcomes. However, the emergence of resistance to FQs poses a significant challenge to effective tuberculosis control efforts. A similar study was observed: a case of acquired FQs resistance during short-course MDR-TB treatment was reported in Rwanda [12]. Furthermore, a recent systematic review and meta-analysis found a high pooled proportion of FQs resistance (27 %) among MDR-TB cases [4]. These findings emphasize the importance of diagnosis and surveillance for drug resistance in tuberculosis treatment programs. Early detection of FQs resistance allows for timely adjustments to treatment regimens, potentially preventing treatment failure and the further spread of drug-resistant strains. Moreover, efforts to optimize treatment adherence and minimize the development of resistance through appropriate drug prescribing practices are essential in combating the growing threat of DR-TB.

The detection of gene mutations in resistance-determining regions in resistant MTB isolates plays a crucial role in the rapid detection of anti-TB drug resistance and could aid strategies to further explore the mechanisms of resistance [13]. Our case report shows that the RIF resistance mutation was at codon *S531L*. Previous studies have shown the mutations in the 81-bp region (codons *507–533*) of the rpoB gene harbor over 95 % of RIF resistance in MTB isolates, and high-level RIF resistance is usually associated with point mutations in *531, 526,* and *516* codons [14]. Also, this mutation was reported as a predominant mutation of the *rpoB* gene causing RIF resistance in various studies previously conducted in Ethiopia, which include reports from the Amhara region (73 %) [15], Jigjiga Somali region, Ethiopia (80 %) [16], systematic review and meta-analysis in Ethiopia (74.2 %) [17], St. Peter's Hospital, Addis Ababa, Ethiopia (81.3 %) [18], Southwest Ethiopia (82.4 %) [14] and Tigray region, Ethiopia (70 %) [19]. Another finding, we observed was that INH-resistant strains had *S315T* mutations in the *katG* region. This mutation in the *S315T* region can be attributed to INH high-level resistance [20]. This mutation is similar to the previous study reported from Ethiopia [19]. Additionally, in this case report, we identified the *gyrA* mutation at codon *A90V*, which was responsible for FQs resistance in MTB isolates. This mutation was also the most common type in the previous studies in Central, and Southeastern Ethiopia and a laboratory-based surveillance study in Ethiopia [21,22]. In this case report, the development of second-line drug gene mutations in a drug-resistant MTB strain may be due to several factors, such as poor adherence to medication, drug malabsorption, incomplete or irregular treatment, inappropriate drug selection, dosing errors, or treatment duration, which can also contribute to the development of drug resistance [23].

We acknowledge certain limitations, notably the absence of whole-genome sequencing (WGS) of an isolate. As the WGS is a powerful tool for identifying all genetic mutations relevant to drug resistance throughout the genome. While the current line probe assays (LPAs) are useful to detect resistance to FLQs, it does not capture the full spectrum of resistance-conferring mutations associated with drugs like BDQ and pretomanid. The lack of WGS in this case underscores the need for advanced molecular techniques to comprehensively understand drug resistance patterns. Despite these limitations, the case report still provides valuable insights into cases of FQs and BDQ resistance in the studied area.

Conclusion

In conclusion, the case report highlights an alarming development of acquired resistance to BDQ in RR/MDR-TB patient treated with all oral treatment regimen, which impacted treatment outcomes. To address this issue, it is essential to emphasize on expanding DST of new drugs to all MDR/RR-TB cases and design individualized treatment regimens tailored to the patient's specific drug susceptibility profile. Additionally, regular clinical and laboratory monitoring should be implemented

throughout the treatment course to detect any signs of treatment failure or control emerging resistance promptly.

Ethical approval

Permission for this case report was obtained from the National Tuberculosis Reference Laboratory of the Ethiopian Public Health Institute and Chancho Primary Hospital. Informed consent was obtained for the publication of this case report.

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Bazezew Yenew: Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation. **Michael Hailu:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Bedo Buta:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Amanuel Wondimu:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Zigba Tefera:** Writing – original draft, Methodology, Formal analysis, Data curation. **Zerihun Ababu:** Writing – review & editing, Visualization, Methodology, Data curation. **Yerosen Ebisa:** Writing – review & editing, Visualization, Methodology, Data curation. **Shewki Moga:** Writing – review & editing, Visualization, Methodology, Investigation, Formal analysis, Data curation. **Gemechu Tadesse:** Writing – review & editing, Validation, Supervision, Resources, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation. **Getu Diriba:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Ayinalem Alemu:** Writing – review & editing, Validation, Supervision, Methodology, Formal analysis, Data curation, Conceptualization. **Betselot Zerihun Ayano:** Writing – review & editing, Methodology, Formal analysis, Data curation.

CRediT authorship contribution statement

GD wrote the original draft manuscript. GD and AA conducted study conceptualization, design, and manuscript drafting. GD, BZ, AW, MH, BB, BY, ZT, SM, and GT conducted laboratory analysis, interpretation, and quality control. AZ and YE were involved in patient diagnosis and management. All authors reviewed the manuscript. The final paper was read, evaluated, and approved by all authors.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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