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Case Report

A Unique Case of Pretonamid Resistance on MDR TB Patient: A Case Report

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Abstract

Background: Pretomanid is a novel medication that belongs to the class of nitroimid-azooxazines. The development of resistance to this novel agent not only complicates clinical management but also poses a threat to public health efforts aimed at controlling TB. This case report highlights the clinical presentation, laboratory findings, and therapeutic implications associated with a patient exhibiting pretonamid resistance. Through this examination, we aim to enhance understanding of resistance mechanisms, underscore the importance of ongoing surveillance, and advocate for refined treatment strategies in the context of MDR-TB management understanding the mechanism of this resistance is crucial for developing effective treatment strategy and improving patient outcome. *Case presentation*: a sixteen-year-old male patient diagnosed with rifampicin-resistant PTB (RR-PTB) after he presented with a cough of two weeks duration and he is on treatment for RR-PTB, and he is on BpaLM regimen. The third-month second-line phenotypic DST result revealed pretomanid (Pa) resistance. [Stm, INH, RIF, EMB, Pa are resistant, and Bdq, Clf, Dlm, Lfx, Lzd, and Mfx are sensitive]. *Clinical Discussion*: Following the hospital's clinical panel team and national TB program expert's discussion we changed the regimen to individualized (Lfx, Cs, Bdq, Dlm, Cfz and Lzd). *Conclusion*: Pretomanid resistance in humans reveals a low prevalence but highlight the need for vigilance. And since it's the incorporated in BPaL regimine and its among the backbone of the regimen we should have to follow the resistance pattern. While facing Pretomanid resistance Consult experts, engage a physician experienced in drug-resistant TB for treatment planning and management, monitor adverse effects closely observe patients for signs of myelosuppression, peripheral neuropathy, and hepatotoxicity during treatment with the BPaL regimen. And also ensure timely susceptibility testing for all components of the BPaL regimen to guide effective treatment adjustments then go for alternative regimen.

Keywords

Pretomanid, Ethiopia, Addis Ababa, Tuberculosis, Multidrug Resistance

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1. Introduction

The World Health Organization claims that molecular evidence for tuberculosis (TB) dates back more than 17,000 years, making it one of the oldest diseases in human history. TB is one of the top 10 infectious diseases that kill people globally, second only to HIV, and despite improved diagnostic and treatment methods, people are still suffering. TB affects people of all ages and in all nations though it is preventable and cured. TB claimed the lives of 1.3 million people, including 167 000 HIV-positive individuals. After COVID-19, TB is the second most common infectious disease that kills people worldwide, surpassing HIV and AIDS, in 2022. An anticipated 10.6 million persons worldwide contracted tuberculosis (TB) in 2022, comprising 1.3 million children, 3.5 million women, and 5.8 million men. [1, 2]

MDR-TB is still a threat to health security and a public health concern. In 2022, only over two out of five patients with drug-resistant TB sought treatment. Since 2000, an estimated 75 million lives have been saved due to global efforts to combat tuberculosis. For TB prevention, diagnosis, treatment, and care, US$13 billion is required each year in order to attain the global target set at the 2018 UN high-level summit on TB. [2]

A particular kind of bacteria known as mycobacterium tuberculosis (and some similar strains like mycobacterium bovis) is the cause of tuberculosis (TB), an infectious disease that primarily affects the lungs. When infected persons cough, sneeze, or spit, it spreads via the air. It is believed that approximately 25% of the world's population has contracted tuberculosis. Approximately 5–10% of TB patients will eventually have symptoms and acquire TB disease. [2, 3] Those who are infected but not (yet) ill cannot spread the disease. The most common treatment for tuberculosis (TB), which can be fatal if neglected, is antibiotics. In certain countries, newborns and young children receive the Bacille Calmette-Guérin (BCG) vaccine to prevent tuberculosis. The vaccination prevents tuberculosis outside the lungs but not in the lungs [2, 3].

Symptoms: Latent tuberculosis infections do not cause illness and do not spread easily. Only a small percentage of TB infections result in TBdisease and symptoms. Children and babies are more vulnerable. A person will have symptoms when they contract tuberculosis. These can be moderate for several months, making it simple to unknowingly infect others with tuberculosis. Common signs of tuberculosis include fever, night sweats, weakness, exhaustion, weariness, and a persistent cough, occasionally accompanied by blood [2, 4] Diagnosis: Rapid molecular diagnostic tests should be used as the first diagnostic test for anyone exhibiting TB symptoms, according to WHO guidelines. The WHO recommends the Xpert MTB/RIF Ultra and Truenat assays as rapid diagnostic tests. These tests will significantly enhance the early diagnosis of tuberculosis and drug-resistant tuberculosis due to their high diagnostic accuracy [2, 3].

The TB Alliance developed Pretomanid, a tablet used in conjunction with other anti-TB medications to treat tuberculosis (TB). Pretomanid is a novel medication that belongs to the class of nitroimid-azooxazines. Due to the growing prevalence of drug and drug class resistance, novel chemicals are crucial in the search for new TB treatments. [5-7]

In its early stages of development, pretomanid was known as PA-824. The safety and effectiveness of Pretomanid have been assessed in 19 clinical trials involving over 1,100 participants. In 14 countries, pretomanid has been the subject of clinical studies. Currently, over 40 nations have acquired over 4,000 pretomanid treatment courses. [3, 8, 9]

The U.S. Food and Drug Administration (FDA) originally approved pretomanid in August 2019 as a component of a therapy regimen known as BPaL (bee-pal), which combines bedaquiline and linezolid. For the treatment of individuals with drug-resistant tuberculosis, the regimen was approved. [8, 10] For the first time, nearly all DR-TB patients can get treatment with an all-oral regimen in six months. The new guidelines from the World Health Organization (WHO) are based on clinical evidence and permit the programmatic use of either BPaLM (a combination of Bedaquiline, Pretonamid, linezolid, and Moxifloxacin) or BPaL (Bedaquiline, Pretonamid, and linezolid) to treat nearly all types of drug-resistant tuberculosis (DR-TB). [1, 11, 12]. "WHO suggests the use of a 6-month treatment regimen composed of Bedaquiline, Pretomanid, linezolid (600 mg), and Moxifloxacin (BPaLM) rather than the 9-month or longer (18-month) regimens in MDR/RR-TB patients," according to the updated guidelines, which permit the implementation of BPaLM and BPaL regimens under programmatic conditions. [1, 12]

According to the guidelines, "each comparison that resulted in the conclusions and final recommendation on the use of the BPaLM/BPaL regimen used data from patients in relevant arms of [the TB-PRACTECAL and ZeNix trials]. [1, 6]

Pretonamid resistance is often linked to mutations in a specific genes which can compromise drug efficacy and exacerbate disease progression. Protinamid resistance has emerged a significant challenge in treatment of MDR-TB As an essential component of current therapeutic regimens, pretonamid plays a critical role in improving treatment outcomes for patients with limited options. However, the development of resistance to this novel agent not only complicates clinical management but also poses a threat to public health efforts aimed at controlling TB.

Recent findings on Pretomanid resistance in humans reveal a low prevalence but highlight the need for vigilance. In a study involving over 1,000 TB patients, baseline resistance to pretomanid was rare, with rates around 0–2.1% across different drug resistance types [13]. However, a separate analysis indicated a pre-existing resistance rate of approximately 3% among 475 isolates in China, suggesting potential undiscovered resistance mechanisms [14]. Mutations in specific genes

(e.g., fbiA, ddn) are associated with resistance, but clinical data on their impact remain limited [15]. Ongoing monitoring and research are essential to address these challenges effectively.

This case report highlights the clinical presentation, laboratory findings, and therapeutic implications associated with a patient exhibiting pretonamid resistance. [6, 8, 11] Through this examination, we aim to enhance understanding of resistance mechanisms, underscore the importance of ongoing surveillance, and advocate for refined treatment strategies in the context of MDR-TB management understanding the mechanism of this resistance is crucial for developing effective treatment strategy and improving patient outcome [4, 6, 8, 11, 12].

2. Case Presentation

He is a sixteen-year-old male patient who was referred from a nearby health center to our hospital MDR center and diagnosed with Multi Drug Resistant PTB (MDR-PTB) after he presented with a cough of two weeks duration. Associated with he has appetite loss. Otherwise, he has no history of weight loss or previous treatment history for TB. He has a close contact history with his father and is on treatment for Rifampicin resistance PTB (RR-PTB), and he is on BpaLM regimen. During his visit to our OPD, his vital signs are in the normal range; his BMI was 23.5 kg/m ², and the only pertinent finding is a decrease in air entry over the right upper lung field area posteriorly and bilaterally. A baseline investigation was done, and the results are as follows: AFB was +2. Following the Gene Xpert result, Xpert Ulta was sent and revealed only RR-resistant. An x-ray of the chest showed atelectasis and consolidation of the right upper lobe. The top differential was PTB. CBC, RFT, and LFT are in the normal range. Clinical tests like visual acuity, the Ishara test, and ECG revealed normal. PICT was done, and it was negative.

Following the investigation results, the BPaLM regimen was initiated as an outpatient and linked to a health center for direct observed therapy (DOT) and has monthly follow-up at our hospital with monthly CBC, LFT, RFT, ECG, and Isharaa tests. And also AFB and sputum culture. All were normal till the third-month second-line phenotypic DST result revealed pretomanid (Pa) resistance. [Stm, INH, RIF, EMB, Pa are resistant, and Bdq, Clf, Dlm, Lfx, Lzd, and Mfx are sessile.] Follow the hospital's clinical panel team and national TB program experts discussion we changed the regimen to individualized (Lfx, Cs, Bdq, Dlm, Cfz and Lzd).

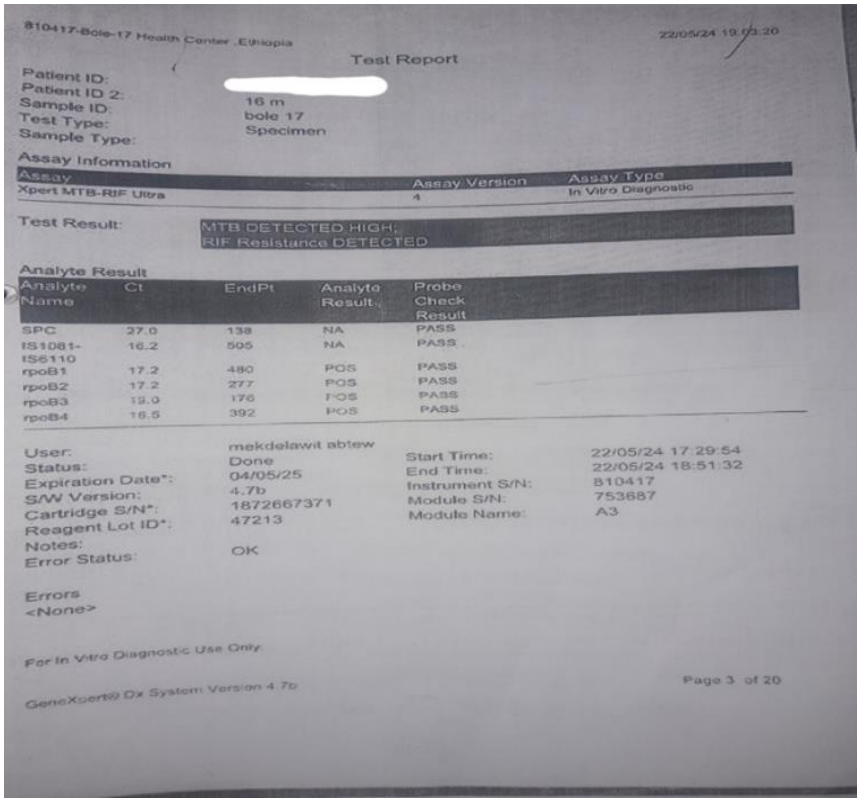

Figure 1. *Pretonamid resistance in extensively Drug Resistance TB Xpert MTB Rif Ultra.*

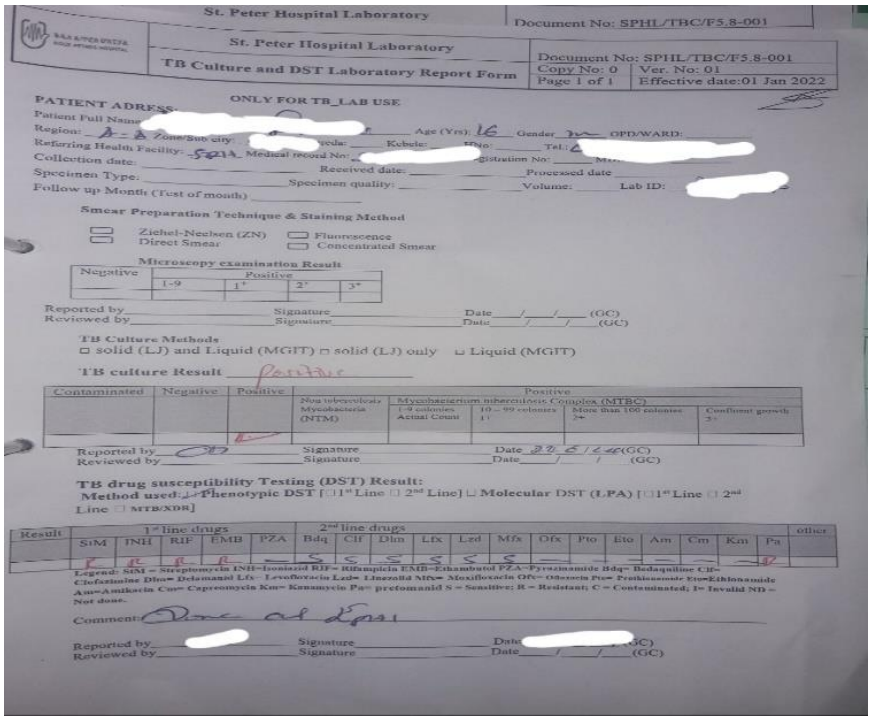

Figure 2. *Pretonamid resistance in extensively Drug resistance TB Culture Result.*

Table 1. *Review of literature on case of Pretonamide resistance on MDR.*

no	Title	Author	Years of publication
1	Pretomanid for tuberculosis: a systematic review. *Clinical Microbiology and Infection* *	Gils, T., Lynen, L., et al	2022
2	Pretomanid-resistant tuberculosis.	Koehler, N., Andres, et al 2	2023
3	Bedaquiline, pretomanid and linezolid in multidrug-resistant and pre-extensively drug-resistant tuberculosis in refugees from Ukraine and Somalia in Germany	Trauth, J., Kantelhardt, V., et al	2024
4	Baseline and acquired resistance to bedaquiline, linezolid and pretomanid, and impact on treatment outcomes in four tuberculosis clinical trials containing pretomanid.	Timm, J., Bateson, A., Solanki, et al	2023
5	Prevalence and genetic basis of Mycobacterium tuberculosis resistance to pretomanid in China.	Zhao, B., Zheng, H., Timm, J. et al	2024

3. Results

Case presentation: a sixteen-year-old male patient diagnosed with rifampicin-resistant PTB (RR-PTB) after he presented with a cough of two weeks duration and he is on treatment for RR-PTB, and he is on BpaLM regimen. The third-month second-line phenotypic DST result revealed pretomanid (Pa) resistance. [Stm, INH, RIF, EMB, Pa are resistant, and Bdq, Clf, Dlm, Lfx, Lzd, and Mfx are sensitive].

Clinical Discussion: Following the hospital's clinical panel team and national TB program expert's discussion we changed the regimen to individualized (Lfx, Cs, Bdq, Dlm, Cfz and Lzd).

4. Discussion

In the third-month second-line phenotypic DST result revealed pretomanid (Pa) resistance. [Stm, INH, RIF, EMB, Pa are resistant, and Bdq, Clf, Dlm, Lfx, Lzd, and Mfx are sensitive. This is the first case report on our country set up. Following the hospital's clinical panel team and national TB program expert's discussion we changed the regimen to individualized (Lfx, Cs, Bdq, Dlm, Cfz and Lzd). Recent find-

ings on Pretomanid resistance in humans reveal a low prevalence but highlight the need for vigilance. In a study involving over 1,000 TB patients, baseline resistance to pretomanid was rare, with rates around 0–2.1% across different drug resistance types [13] However, a separate analysis indicated a pre-existing resistance rate of approximately 3% among 475 isolates in China, suggesting potential undiscovered resistance mechanisms [14]. Mutations in specific genes (e.g., fbiA, ddn) are associated with resistance, but clinical data on their impact remain limited [15]. Ongoing monitoring and research are essential to address these challenges effectively.

5. Conclusions

Pretomanid resistance in humans reveals a low prevalence but highlight the need for vigilance. And since it's the incorporated in BPaL regimen.

Abbreviations

AFB	Acid Fast Bacillus
INH	Isoniazid
MDR	Multidrug Resistance
OPD	Out Patient Department
PI	Principal Investigator
QOF	Quality of Life
RIF	Resistance to Rifampicin
SPSS	Statistical Package for Social Science Studies
SPSH	Saint Peter Specialized Hospital
TB	Tuberculosis
USA	United States of America

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Author Contributions

Mustofa Hassen Yesuf, MD - Primary physician on MDR-TB writing the paper and literature review.

Getachew Mekete Diress - editing of the paper and patient management, acquisition of data, and critical review of the paper.

Abdurehman seid Mohammed - editing of the paper and patient management, acquisition of data, and critical review of the paper.

Abraham Eshetu Mamo, MD - editing of the paper and critical review of the paper investigation.

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Data Availability Statement

The data that support the findings of this study can be found at with corresponding Author (The data is available from the corresponding author upon reasonable request).

The data supporting the outcome of this research work has been reported in this manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

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