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Case Report

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Discordant rifampicin-resistance results in a newly treated pulmonary tuberculosis case: a diagnostic challenge from Khyber Pakhtunkhwa

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ABSTRACT

We reveal the situation of a 56-year-old male from Mardan who first presented to the hospital in 2023 with a two-month history of cough with sputum. He was diagnosed using Xpert MTB/RIF (MTB positive, RIF resistance not detected), placed on first-line tuberculosis (TB) treatment, and declared treatment completed after 6 months. Only 2-3 weeks later, he returned with the same symptoms. A repeat Xpert test showed scanty MTB with RIF resistance, and culture identified rifampicin-resistant Mycobacterium tuberculosis (MTB). Subsequent work-up showed Xpert MTB/RIF positive, with RIF resistance not detected. However, Xpert XDR suggested fluoroquinolone resistance. The culture, initially contaminated, later revealed fully drug-sensitive MTB. This case underscores the complexities of interpreting inconsistent molecular and phenotypic results in TB drug-resistance diagnostics. It highlights the limitations of Xpert in low-bacillary-load specimens and the need to combine microbiological, molecular, and clinical findings when handling presumed MDR/XDR-TB cases.

Keywords: Mycobacterium Tuberculosis; Xpert MTB/RIF; Rifampicin Resistance; Drug-Resistant TB; Pakistan

Introduction

The problem of drug-resistant tuberculosis (DR-TB) continues to give the world a hard time. The introduction of the Xpert MTB/RIF assay has facilitated the diagnosis of M. tuberculosis complex (MTB) and rifampicin (RIF) resistance in a very short time and in many places, and has even been used as a surrogate for detecting multidrug-resistant TB (MDR-TB). According to the pooled sensitivity and specificity from meta-analysis data, the detection of RIF resistance by Xpert has about 93% and 98% respectively.[1]

Nonetheless, there are various studies that indicate a discrepancy between the results obtained from molecular assays (e.g., Xpert) and drug-susceptibility tests (DST) or culture performed using the phenotypic method, especially in samples that have a low concentration of bacteria, are from contaminated culture, have mixed infection, or have non-canonical rpoB mutations.[2]

In Pakistan, the burden and risk of DR-TB are both high. Diagnostic dilemmas arising from these issues are a major challenge for treatment and programme management. We want to present an unusual case of drug-sensitive TB. It began as a straightforward case, unexpectedly evolved into rifampicin- and fluoroquinolone-resistant TB, and then reverted to phenotypic sensitivity. This sequence emphasizes the need for careful interpretation of results and management.

Case Report

In the middle of the year 2023, a 56-year-old man who lives in the Mardan district arrived at the PMDT unit in Mardan Medical Complex with a history of a cough that lasted for two months with thick phlegm, and he had never been diagnosed with tuberculosis. There was no trace of contact with drug-resistant TB, and his health was good. He was examined, and his vital signs were stable; crackling sounds were heard in both upper lobes of both lungs, and he did not show any signs of extreme weight loss.

Baseline examinations included sending a sputum sample for the Xpert MTB/RIF test. The result was MTB-positive, with no RIF resistance detected. He was started on first-line anti-tuberculosis treatment (2HRZE + 4HR) according to programme guidelines. The patient tolerated the treatment and completed the 6-month course. He showed no visible adverse events and had improvement in his symptoms.

About 2–3 weeks after treatment ended, the patient returned with a cough, low-grade fever, and weight loss. The latest sputum Xpert MTB/RIF test result was MTB scanty, with RIF resistance claimed. A sputum culture (liquid/solid) was sent and was positive for MTB, showing rifampicin monoresistance. To confirm, a second set of sputum samples was taken. Testing again: Xpert MTB/RIF showed MTB-positive and no RIF resistance, while an Xpert XDR (or equivalent assay) showed fluoroquinolone resistance. However, the repeat sample's culture was positive for MTB, sensitive to all first-line and second-line drugs. An initial culture run was contaminated and excluded from analysis. A comprehensive review of the microbiology and molecular lab logs was conducted.

Clinically, the patient remained stable. There were no signs of disseminated or extensive TB, no prior treatment for DR-TB, and no known exposure to second-line therapy. Following a multidisciplinary review (pulmonology, microbiology, TB programme), it was concluded that the rifampicin resistance detected on the intermediate test was likely a false-positive, possibly due to a low bacillary load (“scanty” result). Similarly, resistance detected on the XDR assay was considered likely to be false resistance or to reflect hetero-resistance/mixed infection. The patient was re-treated with first-line drugs and is under close follow-up for six more months, with repeated sputum studies planned. At the last follow-up (three months), he remains asymptomatic. Sputum results are pending.

Discussion

Our case demonstrates a few critical points in the diagnosis and therapy management of DR-TB. To begin with, the initial diagnosis and management were straightforward: newly diagnosed pulmonary TB with Xpert (MTB positive, RR not detected). The patient completed 6 months of first-line treatment. When the disease recurred within weeks, it raised questions of whether this was a relapse of the initial infection or a new reinfection, particularly since one recurrence was associated with culture-confirmed rifampicin resistance.

Moreover, the discrepancies in this case's results warrant detailed discussion. There was an Xpert that showed "scanty MTB, RIF resistance detected," followed by a repeat Xpert that showed "RIF resistance not detected," and a culture that showed full sensitivity.

Discordance between molecular (genotypic) and phenotypic DST is well documented. For example, a retrospective cohort study reported high rates of false-positive rifampicin resistance results on Xpert in low-bacterial-load specimens.3 Another study found that a "scanty" Xpert result, indicating low bacillary load, was associated with more false Xpert RR detections.4 A meta-analysis of Xpert detection of RIF resistance showed excellent pooled accuracy (sensitivity ~0.93, specificity ~0.98), but emphasized limitations in some settings.[5]

This case highlights the diagnostic challenge of interpreting discordant molecular and phenotypic test results in the context of TB drug resistance. The Xpert MTB/RIF assay has revolutionized rapid diagnosis by simultaneously detecting Mycobacterium tuberculosis

and rifampicin resistance. However, discordant results, such as those seen in our patient, complicate decision-making. Here, the patient initially had a rifampicin-susceptible result, completed six months of first-line therapy, then returned with recurrent symptoms and an unexpected rifampicin-resistant Xpert result, later followed by conflicting repeat tests and cultures.

It is reasonable to consider a low bacillary load as a probable cause of the discrepancy, indicated by the “scanty" Xpert result during relapse. When bacterial concentration is extremely low, DNA amplification in the cartridge can be unstable. This instability can lead to false detection of rifampicin resistance. Also, non-viable bacterial DNA from previously treated bacilli may mislead molecular results if no active resistant organisms remain. Interpretation is further complicated by hetero-resistance: both drug-sensitive and drug-resistant subpopulations of M. tuberculosis may coexist. The molecular assay may indicate resistance or susceptibility at different times, depending on which subpopulation predominates in the specimen.

Not only molecular variability but also culture-related issues may explain these conflicting results. Contamination during specimen collection, handling, or culture processing can obscure actual M. tuberculosis growth. This leads to unreliable phenotypic drug-susceptibility results. In this case, one culture sample was contaminated and discarded, reducing data reliability. Such contamination is common in laboratories with heavy workloads and limited resources, where biosafety and aseptic protocols sometimes suffer.[6]

One other important aspect is mutations outside the canonical rpoB “hot-spot” Xpert MTB/RIF's 81-base-pair target. Some mutations outside this region may cause true rifampicin resistance but remain undetected by Xpert. Conversely, unusual probe binding could suggest resistance even when the drug remains effective. This has appeared in many studies and shows the limits of probe-based resistance testing.

Mixed infection is another possible factor: two separate M. tuberculosis strains, one sensitive and one resistant, may coexist. Such cases are increasingly recognized in high-incidence TB areas. Results can shift depending on which strain dominates a sample. To confirm this phenomenon, advanced molecular methods like next-generation sequencing would be required. However, these methods are rarely used in standard clinical settings.

As a final point, laboratory logistics and procedural errors must be considered as the first step when discordant results arise. Mislabeling of samples, cartridge problems, wrong storage, or writing errors may all affect the final reports. In our resource-limited environment, where the laboratory and quality assurance might not always meet the same standards, these technical issues can heavily influence clinical interpretation and case management.

In the case of Pakistan's TB programme, where the detection and control of DR-TB are very important, this case warns that the results (especially with a low load) should be interpreted with caution. Testing by other methods (repeat Xpert, line-probe assay, culture-DST) is essentially a must, especially before committing to second-line regimens, which are characterized by higher toxicity, cost, and monitoring burden.

This instance, above all, illustrates the necessity of caution in interpreting rapid molecular assays, especially in patients with low bacillary load or incongruent clinical findings. In all cases, molecular results should first be confirmed by retesting, line probe assays, and phenotypic drug-susceptibility testing before changing treatment schedules. The laboratory findings' integration with the clinical assessment is still the best way to prevent unnecessary exposure to second-line anti-tuberculosis drugs that are both expensive and very toxic. Thus, a multidisciplinary approach that includes clinicians, microbiologists, and TB programme staff has been crucial for obtaining the correct diagnosis and proper management of suspected drug-resistant tuberculosis.

In summary, this case illustrates the potential for misleading diagnostics in TB drug resistance and highlights the need for a robust algorithmic approach in resource-limited settings. While rapid molecular tests such as Xpert have transformed TB care, they are not infallible especially in low-bacillary load or complex cases and their results should be complemented by culture, phenotypic DST, and clinical judgement.

Conclusion

In a 56-year-old man with discordant molecular and phenotypic rifampicin-resistance results, we report a case of recurrent pulmonary TB, which emphasizes the difficulties of routine DR-TB diagnosis. Clinicians and TB-programme managers ought to take the limitations of rapid molecular tests into account and wait for confirmatory DST before making any therapeutic changes. Frequent monitoring and thorough analysis remain paramount.

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