



Case Report

Multiple Adverse Drug Reactions in a Patient with Disseminated MDR-TB: A Case Report

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ABSTRACT

Disseminated multidrug-resistant tuberculosis is a serious form of tuberculosis that requires prolonged treatment with multiple second-line antitubercular drugs, which are frequently associated with adverse drug reactions that may complicate the treatment. Here we report the case of a 57-year-old man with disseminated multidrug-resistant tuberculosis involving the lungs, bilateral pleura and peritoneum who developed multiple adverse drug reactions during treatment with a longer all oral multidrug-resistant tuberculosis regimen. During the course of treatment, patient developed anaemia, QTc prolongation and recurrent hypoglycaemia requiring withdrawal and modification of suspected drugs along with appropriate supportive management. Patient's condition gradually improved with timely intervention and close monitoring. The suspected adverse drug reactions were reported to the Pharmacovigilance Programme of India. This case highlights the importance of early detections of adverse drug reactions, regular monitoring, prompt modification of treatment and pharmacovigilance reporting to improve patient safety and treatment outcomes in multidrug-resistant tuberculosis.

Keywords: Disseminated multidrug-resistant tuberculosis, Adverse drug reactions, Linezolid-induced anaemia, QTc prolongation, Hypoglycaemia.

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INTRODUCTION

Tuberculosis (TB) is a highly contagious chronic granulomatous disease caused by *Mycobacterium Tuberculosis* and is primarily transmitted through airborne droplet nuclei expelled by individuals with active TB. Common manifestation includes persistent cough lasting for more than two weeks, fever, night sweats, weight loss, anorexia, fatigue and haemoptysis. ^[1,2]

Disseminated TB is a severe form of tuberculosis resulting from hematogenous spread of *M. tuberculosis* to two or more non-contiguous sites. It commonly involves lungs and then spreads to extrapulmonary sites such as pleura, peritoneum, lymph nodes, bone marrow or brain. It is associated with significant morbidity and mortality owing to its varied clinical manifestations, extensive organ involvement and diagnostic and therapeutic challenges. ^[3]

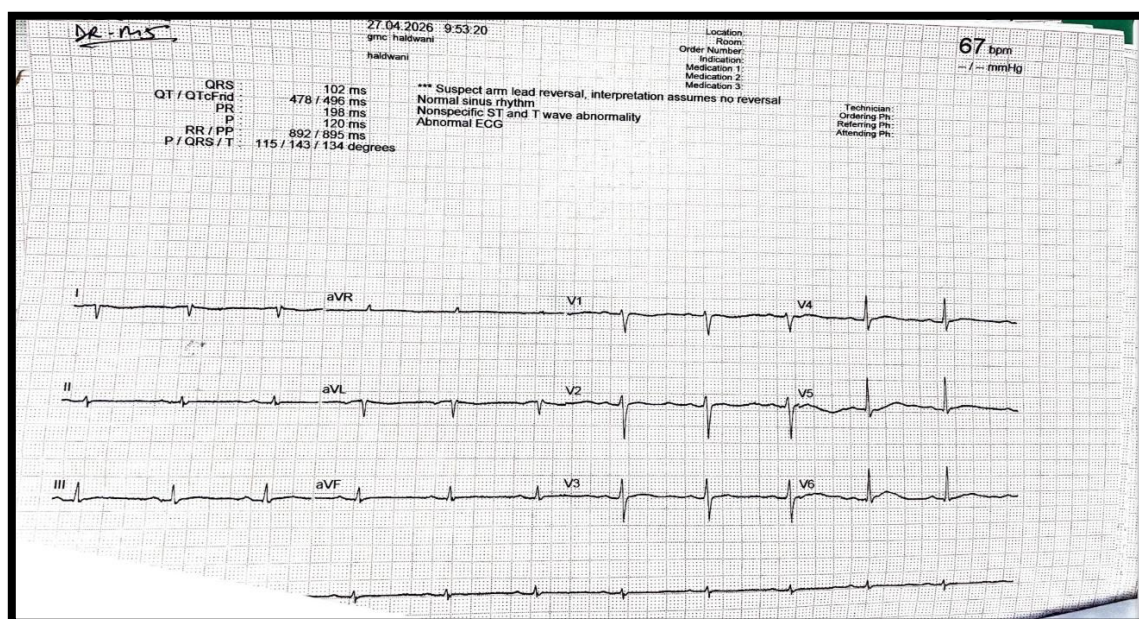
Despite the availability of effective anti-tubercular therapy, the emergence of drug-resistant tuberculosis (DR-TB) has become a major global health problem. *Multidrug-resistant tuberculosis (MDR-TB)* is defined as resistance to at least both Isoniazid and Rifampicin with or without resistance to other first line anti-TB drugs ^[5]. The development of MDR-TB has been attributed to several factors, including genetic mutations in *M. tuberculosis*, poor compliance to first line therapy, treatment failure or relapse of previous infection, transmission of resistant strains and other immune-compromised states. ^[4] Globally approximately 3,90,000 individuals developed MDR-TB/RR TB in 2024 of whom India accounts for more than 32% of cases as per WHO global Tuberculosis report 2025. ^[5]

According to the NTEP guidelines, management of MDR-TB involves the use of second-line anti-tubercular drugs selected on drug susceptibility patterns and patient eligibility for specific regimens. Longer all-oral regimens (18-20months) commonly include bedaquiline, fluoroquinolones, linezolid, clofazimine and cycloserine. Although these regimens have improved the management of MDR-TB, their prolonged duration and use of multiple drugs increase the risk of adverse drug reaction, requiring close monitoring during treatment.^[6]

CASE REPORT:

The patient had no history of diabetes mellitus, hypertension or thyroid disorder. He had previously undergone hemimandibulectomy for carcinoma of the oral cavity. He reported regular adherence to anti-tubercular therapy.

Patient was admitted for further evaluation and management. All relevant investigations were sent including CBC, S. electrolytes, LFT, KFT, CXR-PA, ECG, Sputum gram /Giemsa / ZN / CS / Fungal KOH, Urine R/M and viral markers (HIV, HBsAg, HCV). On Day 1 of admission laboratory investigation revealed hemoglobin of 7.92g/dL, serum sodium of 128mEq/L, serum creatinine of 2.37mg/dL and random blood glucose of 68mg/dL. ECG demonstrated QTc prolongation [QT/ QTcF – 478/496ms] Other investigations were unremarkable.



as per hospital protocol with appropriate supportive measures and serial monitoring of serum electrolytes, blood glucose levels and ECG was done.

Following withdrawal of linezolid due to severe anemia, delamanid was subsequently introduced as a substitute agent as part of the modified MDR-TB regimen. Due to raised creatinine levels levofloxacin was replaced with moxifloxacin. On Day 12 of admission, patient experienced multiple episodes of hypoglycemia. Blood glucose levels remained persistently low despite administration of dextrose-containing intravenous fluids. Considering a possible drug related adverse event, moxifloxacin was withheld for several days, following which blood glucose levels improved. Despite withdrawal of bedaquiline, QTc prolongation [8/5/26: QT/ QTcF– 462/486 ms, 9/5/26: QT/ QTcF– 464 / 488 ms] persisted after initiation of delamanid, necessitating discontinuation of delamanid as well.

Following withdrawal of the suspected drugs, supportive management and close monitoring of hematological, biochemical and electrocardiographic parameters were done, patient's clinical condition gradually improved. On Day 30 of admission, MDR-TB regimen was resumed with appropriate modifications and continued under close supervision.

Suspected adverse drug reactions were reported to the Pharmacovigilance Programme of India (PvPI) via Adverse Drug Monitoring Centre of the Department of Pharmacology. Assessment of causality was done using the WHO-UMC causality assessment system. The reactions were categorized as probable for linezolid induced anaemia, probable for bedaquiline and delamanid associated QTc prolongation and probable for moxifloxacin / linezolid associated hypoglycaemia.

DISCUSSION:

In recent years, occurrence of multiple adverse drug reactions in a single patient has been infrequently reported in literature making such cases clinically significant and important worthy of attention. This case highlights the importance of drug related adverse events and vigilant monitoring, detection and reporting of multiple ADRs occurring concurrently in an individual patient.

Linezolid, an oxazolidinone antibiotic included in MDR-TB regimen as it causes disruption of protein synthesis, binding to 50s ribosome. [7] It helps in clearing mycobacterium relatively, rapidly when included in treatment of complex case of drug-resistant TB. Long term repeated use of linezolid can lead to adverse drug reaction such as pancytopenia, hypoglycaemia, myelosuppression and lactic acidosis. [7,8]

Our patient developed anaemia and linezolid induced anaemia is attributed to the inhibition of mitochondrial protein synthesis, leading to mitochondrial dysfunction and abnormal iron metabolism in erythroid precursor. Dai Ying et.al. reported that patients receiving a high initial dose of linezolid, particularly those with moderate to severe renal insufficiency, are at an increased risk of developing anemia. [9]

In this patient, the development of severe anaemia (Hb 7.92 g/dL) prompted the immediate withdrawal of linezolid and supportive blood transfusion. This aligns with the National Tuberculosis Elimination Programme (NTEP) guidelines, which mandate the cessation of the offending drugs and aggressive supportive care in the event of grade 3 or 4 haematological toxicities. [6]

The sequential development of QTc prolongation further complicated the therapeutic approach. Both bedaquiline, a diarylquinoline, and delamanid, a nitro-dihydro-imidazooxazole, are potent anti-tubercular agents known to prolong the cardiac repolarization phase by blocking the human ether-à-go-go-related gene (hERG) potassium channel. [10] Our patient exhibited marked QTc prolongation (QTcF 496 ms) during bedaquiline therapy, requiring its discontinuation. Despite discontinuation of bedaquiline, the QTc interval remained persistently prolonged. This phenomenon is likely attributable to the exceptionally long terminal half-life of bedaquiline (up to 5.5 months), meaning that its arrhythmogenic potential persists long after the drug has been stopped. [10,11] The subsequent addition of delamanid likely contributed additional QT-prolonging effects in the presence of residual bedaquiline concentrations underscoring the necessity of continuous electrocardiographic monitoring when these agents are used sequentially or concurrently. [6,12]

Following the substitution of levofloxacin with moxifloxacin, the patient developed profound and recurrent hypoglycaemia. [13] The proposed mechanism of fluoroquinolone-induced hypoglycaemia involves the blockade of ATP-sensitive potassium channels in pancreatic beta cells, which stimulates unregulated insulin exocytosis, leading to profound hypoglycaemia. Among the fluoroquinolones, gatifloxacin (now withdrawn) has been most strongly associated with hypoglycaemia, while cases of moxifloxacin-induced hypoglycaemia have also been reported. [14,15]

However, some studies have suggested linezolid associated hypoglycaemia, although the exact mechanism is not clear and linezolid is weak monoamine oxidase inhibitor (MAOI). MAOI may enhance insulin secretion and improve insulin sensitivity. Therefore, the occurrence of hypoglycaemia could also be side-effect of linezolid therapy. [16,17] The resolution of the patient's hypoglycaemia following the withdrawal of moxifloxacin and linezolid provides strong clinical evidence for this causality.

CONCLUSION:

The treatment regimen recommended for disseminated MDR-TB consist of various drugs and these drugs are prescribed for longer duration. Such a long duration of therapy and high dose of antibiotic result in adverse drug reaction, therefore clinician should pay attention to such adverse drug reaction such as linezolid induced anemia, hypoglycemia with moxifloxacin and linezolid, QTc prolongation with bedaquiline and delamanid. These adverse drug reactions can complicate therapeutic approach and can lead to non-compliance, replacement of therapy and therapy withdrawal. Early recognition and prompt discontinuation of the drugs are crucial for optimal patient outcomes. Further research is needed to strengthen the strategies for early detection and prevention of adverse drug reaction and safety profile in patients receiving MDR-TB treatment.

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