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Clinical and Therapeutic Insights into Drug-Resistant Tuberculosis: Experience from Five Clinical Cases

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Abstract

Background: Drug-resistant tuberculosis (DR-TB) poses a major threat to global TB control, with India contributing the highest burden worldwide. Rapid diagnostics and newer drug regimens have improved outcomes, yet clinical management remains complex.

Case presentations: We report five diverse cases of rifampicin-resistant and multidrug-resistant TB among the rural population. Patients presented with symptoms including weight loss, cough, hemoptysis, and dyspnea, with risk factors such as human immunodeficiency virus co-infection, alcoholism, smoking, and treatment default. Diagnosis was confirmed using Truenat/ Cartridge-Based Nucleic Acid Amplification Test (CBNAAT) assays detecting *rpoB* mutations. Treatment strategies were individualized: three patients received shorter bedaquiline-based regimens, one received a longer bedaquiline-based regimen due to prior exposure, and one elderly patient was managed with the BPaLM regimen. All patients demonstrated clinical improvement following therapy initiation.

Discussion: This series documents diverse DR-TB cases, complicated by several risk factors and adverse drug reactions**.** Early molecular diagnosis, treatment for complications and integration of newer anti-tuberculosis agents were crucial for favorable clinical responses.

Conclusion: Individualized, evidence-based regimens guided by rapid diagnostics and supported by holistic patient care remain the cornerstone of DR-TB management. Wider access to novel agents and adherence-focused interventions are essential to advance India's TB elimination target.

Keywords: Bedaquiline regimen, BPaLM regimen, Case Series, Multidrug-resistant tuberculosis, Rifampicin-resistant tuberculosis

Introduction

Even from ancient times, Tuberculosis (TB), caused by Mycobacterium tuberculosis (MTB), remains a leading cause of morbidity and mortality around the world. India continues to bear the highest burden of disease, accounting for nearly 27% of the 10.4 million global TB cases reported by the World Health Organization (WHO) in 2017. (1)

The major challenge in eradicating the growth of TB is the emergence and spread of drug-resistant TB, which constitutes a significant proportion of the global antimicrobial resistance (AMR) burden.

The burden varies as,

1. Mono-resistance of first-line agents such as rifampicin or isoniazid

2. Multi-drug resistant TB (MDR-TB): Resistance to at least rifampicin and isoniazid
3. Extensively drug-resistant TB (XDR-TB): additional resistance to fluoroquinolones and injectable second-line agents.

Drug-resistant TB arises through two major mechanisms: (i) transmission of resistant strains from one individual to another, and (ii) acquired resistance due to inappropriate or incomplete treatment within the host. The clinical outcomes of such cases are highly variable and often depend on host factors, adherence to therapy, comorbidities, and availability of newer drugs. (2)

This case series presents diverse clinical scenarios of drug-resistant TB, highlighting the spectrum of resistance patterns, diagnostic challenges, and therapeutic considerations encountered in routine clinical practice. By documenting these cases, the series aims to emphasize the complexity of management and the importance of individualized, evidence-based treatment approaches in the context of India's national goal of TB elimination.

Case Presentations

Case 1:

A 20-year-old man arrived at the hospital complaining of a chronic 5 kg weight loss, breathing difficulties, a cold, expectorant-associated cough, and chest pain on the right side during coughing during the previous two weeks.
The patient smokes occasionally and has been a chronic drinker for three years.

The results of the liver function test, renal function test, and random blood sugar level were all within normal ranges. The white blood cell count (WBC) was high, 13.5 x 10^3. The weight of the individual was 41kg
For over a month, the patient had been receiving treatment with Anti-tuberculosis therapy (ATT) first-line medications.

Despite this treatment, symptoms persist. Rifampicin resistance was confirmed by the Truenat MTB-Rifampicin Diagnostic (Truenat MTB-Rif Dx) assay, where the rpoB mutation and MTB were detected.

Psychiatric opinion was obtained to start a shorter oral Bedaquiline regimen. When no psychological symptoms were noted, the treatment plan changed to tablet form of isoniazid 600mg, ethambutol 800mg, bedaquiline 400mg, levofloxacin 750mg, clofazimine 100mg, ethionamide 500mg, and pyridoxime 100mg, all once daily in the morning.

The patient was hospitalized for four days and then discharged with resolved symptoms and no new complications. The patient was also appointed for a follow-up after one month.

Case 2:

A 30-year-old female was admitted with progressive weight loss of 7 kg, loss of appetite, exertional dyspnea, productive cough, and chest pain of one month duration. She had a history of microbiologically confirmed pulmonary tuberculosis (PTB) one year earlier, for which she was initiated on ATT. However, she defaulted after 76 days due to persistence of symptoms and lack of follow-up. She presented again after six months of irregular treatment.

On examination, she was underweight (37 kg), conscious, oriented, and afebrile. Laboratory investigations revealed leukocytosis ($14.2 \times 10^3/\mu L$) and mild hyponatremia and hypokalemia. TRUENAT MTB-Rif assay detected *Mycobacterium tuberculosis* with *rpoB* mutation, confirming rifampicin resistance.

The treatment was started with oral regimens including isoniazid 600mg, pyrazinamide 1250 mg, ethambutol 800mg, clofazimine 100mg, levofloxacin 750mg, bedaquiline 400mg, ethionamide 500mg, and pyridoxime 100mg, all in the morning.

The patient was hospitalized for six days and then discharged with resolved symptoms and no new complications. The patient was also appointed for a follow-up after one month.

Case 3:

A 20-year-old male with acquired immunodeficiency syndrome (AIDS), on regular antiretroviral therapy (ART) for six years, was admitted with complaints of breathlessness, intermittent fever, cough, and right-sided chest pain for 15 days. He had a history of chronic alcoholism and tobacco use.

On admission, his weight was 49 kg and his hemoglobin was 8.6 g/dL, indicating anemia. Laboratory tests showed elevated liver enzyme Aspartate Aminotransferase (111U/L), whereas Alanine Aminotransferase remains normal.

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Sputum acid-fast bacilli (AFB) test and CBNAAT assay confirmed pulmonary tuberculosis on day two. Rifampicin resistance was established by TrueNat MTB-Rif Dx, detecting the *rpoB* mutation.

After psychiatric clearance, the patient was initiated on the shorter oral Bedaquiline regimen: isoniazid 900 mg, pyrazinamide 1250 mg, ethambutol 800 mg, levofloxacin 750 mg, bedaquiline 400 mg, clofazimine 100 mg, ethionamide 750 mg and pyridoxine 100 mg, all in the morning.

Due to alcohol use disorder with withdrawal risk, psychiatry recommended IV thiamine 300 mg in 100 ml NS for three days and diazepam 5 mg (2-0-2), later tapered over three days. He remained hospitalized for six days, showed improvement, and was discharged on ART, ATT, oral thiamine 100 mg each morning, and diazepam 5 mg at bedtime for 10 days. The patient was appointed for a follow-up after ten days.

Case 4:

A 40-year-old male, a known case of RR-TB on a longer bedaquiline-containing regimen for 9 weeks, presented with dyspnea, productive cough, hemoptysis for two days, and recent-onset nausea and vomiting.

On examination, he was stable but pale. Laboratory findings demonstrated microcytic hypochromic anemia (Hb 10.0 g/dL, MCV 76.2 fL, MCH 23.4 pg, MCHC 30.7 g/dL) with mild leukocytosis. He weighed 45kg. Endoscopy confirmed gastritis. The temporal association raised suspicion of ATT-induced gastritis, and this condition was treated with,

1. Intravenous ceftriaxone and sulbactam 1.5 g twice a day

2. Intravenous pantoprazole 40mg twice a day

3. Intravenous deriphylline 110mg twice a day.

The condition of anemia was corrected by administering iron sucrose 200mg in 100 mL of normal saline intravenously on alternate days (Day 2, 4, 6)

The patient was diagnosed with multidrug-resistance tuberculosis, and the ATT was altered by,

4. Oral Bedaquiline 200mg in the morning of alternate days

5. Tab. levofloxacin 750mg, linezolid 600mg, clofazimine 100mg, cycloserine 500mg, all once daily in the morning.

The treatment was continued for 7 days of hospitalization. Then, when the symptoms resolved patient was discharged with discharge medication of ATT, ART, Capsule omeprazole 20mg twice a day, before food, tablet vitamin B complex in the morning, syrup Antacid 10ml thrice a day for one week. The patient was appointed for a follow-up after ten days.

Case 5:

A 72-year-old male patient with a history of known rifampicin-resistant tuberculosis is admitted to the thoracic ward with the chief complaints of hemoptysis and cough.

Personally patient has no history of alcoholism or smoking. On examination, the patient was conscious, oriented and afebrile. The complete blood count, liver function test and renal function test were within the normal limits. His weight was calculated as 39kg

The patient was diagnosed with RR-TB.

Considering the age factor of the patient, the RR-TB was treated with (6):

1. Tab. Bedaquiline 400mg in the morning

2. Tab. Pretomanid 200mg in the morning

3. Tab. Linezolid 600mg in the morning

4. Tab. Moxifloxacin 400mg in the morning

5. Tab. Pyridoxime 100mg in the morning

6. Cap. Omeprazole 20mg twice a day before food

The treatment was continued for 5 days of hospitalization. Then, when the symptoms resolved patient was discharged with discharge medication of ATT. The patient was appointed for a follow-up after one month.

Discussion

The WHO Global TB Program continues to face the challenge of DR-TB to date. This barrier potentially can complicate the treatment outcome by increasing the risk of TB relapse, treatment failure, prolonged transmission of bacilli or even death. The Global Tuberculosis Report 2020 shows the existence of about 2,06,030 MDR/RR-TB individuals among approximately 10 million TB-diagnosed individuals.

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The progressive TB with drug resistance has the capacity to convert TB into an incurable disease. (3)

Rifampicin, one of the most potent first-line anti-tubercular drugs, acts by binding to the β-subunit of the DNA-dependent RNA polymerase (encoded by the *rpoB* gene), thereby inhibiting transcription and bacterial replication. Resistance to rifampicin is primarily caused by mutations within an 81-base pair of the *rpoB* gene. These mutations alter the drug-binding site, reducing rifampicin's affinity and resulting in clinical resistance. (4)

Isoniazid resistance most often results from mutations in the *katG* gene or mutations in the *inhA* promoter region. (5)

Risk Factors:

There are several risk factors associated with DR-TB, prior TB treatment, AIDS, low socioeconomic factors, overcrowded living environment, tobacco use, alcoholism, drug abuse and medication non-adherence in TB therapy. (6)

Case 1- Alcoholism, Tobacco use

Case 2- Treatment default, medication non-adherence

Case 3- AIDS, Alcoholism, Tobacco use

Cases 4 and 5 - Prior TB

Diagnostic Procedures:

The diagnostic procedure used here for confirming RR-TB is the Cartridge-Based Nucleic Acid Amplification Test (CBNAAT) and TrueNat. Whereas for MDR-TB we depend on outer sources for,

Xpert MTB/XDR: an expanded assay detecting resistance mutations to isoniazid, fluoroquinolones, second-line injectable medications (amikacin, kanamycin, capreomycin), and ethionamide.

Line Probe Assays (LPA): use PCR and reverse hybridization to detect mutations associated with isoniazid and second-line drug resistance. (5,7)

Symptoms:

Common symptoms of TB are prolonged cough, hemoptysis, chest pain, weakness, fatigue, loss of weight, fever and night sweats. (8)

Case 1- Weight loss, breathing difficulties, a cold, expectorant-associated cough, and chest pain on the right side during coughing.

Case 2- Weight loss of 7 kg, loss of appetite, exertional dyspnea, productive cough, and right-sided chest pain.

Case 3- Breathlessness, intermittent fever, cough, and right-sided chest pain
Case 4- Dyspnea, productive cough, and hemoptysis.

Case 5- Hemoptysis and cough.

Management:

Treatment for DR-TB is altered individually for each participant. The standard methods for treating RR-TB include shorter or longer bedaquiline-based regimens, BPaLM regimen, etc. (9)

Case 1, 2, 3: Shorter Bedaquiline regimen

Case 4: Longer Bedaquiline regimen for a participant previously exposed to bedaquiline for a longer time.

Case 5: Bedaquiline, pretomanid, linezolid, moxifloxacin (BPaLM) regimen for elderly patient

Managing Alcohol Withdrawal And AIDS In Case 3:

The alcoholism was managed therapeutically through intramuscular administration of thiamine 100mg, which was then prescribed as a tablet form of thiamine 100mg during discharge.

AIDS was managed by continuous of anti-retroviral therapy (ART). (10)

Managing ATT-Induced Gastritis In Case 4:

A proton-pump inhibitor, pantoprazole 40mg, is administered intravenously to treat ATT-induced gastritis. Then, a capsule of omeprazole 20mg twice a day is prescribed during discharge. (10)

Managing Anemia In Case 4:

Intravenous administration of iron sucrose 200 mg in 100 mL of normal saline helped in managing microcytic hypochromic anemia. (10)

The presented cases demonstrate that while DR-TB poses diagnostic and therapeutic challenges, appropriate use of rapid molecular diagnostics and individualized regimens, including newer agents like bedaquiline, linezolid, and pretomanid, can achieve favorable outcomes. Strengthening adherence support and addressing comorbidities such as HIV, alcoholism, and malnutrition remain crucial for improving prognosis.

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Conclusion:

The variety of clinical manifestations, risk factors, and therapeutic challenges linked to RR/MDR-TB is highlighted by this case series. To discover resistance early and start successful regimens on time, rapid molecular diagnostics like CBNAAT and Truenat are essential. Even in individuals with advanced disease or comorbidities, the use of newer medications such as pretomanid, linezolid, and bedaquiline has improved treatment results. But effective care also necessitates a patient-centered approach that addresses underlying risk factors, including old age, alcoholism, treatment default, and HIV co-infection.

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