CASE REPORT

Cycloserine- and Fluoroquinolone-Induced Seizure in Multidrug-Resistant Tuberculosis (MDR-TB) Patient: A Case Report

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ABSTRACT

Introduction: Multidrug-resistant tuberculosis (MDR-TB) is a type of tuberculosis (TB) that is resistant to at least two of the most effective first-line anti-TB drugs, isoniazid (H) and rifampicin (R). Cycloserine (Cs) and levofloxacin (Lfx) are second-line anti-TB drugs used in MDR-TB therapy. Even though they are considered to have high effectiveness, both drugs have the potential to cause side effects. One important side effect is neurotoxicity. Seizures have been reported as a common complication of some drugs.
Case: A 39-year-old man was diagnosed with MDR-TB and was treated with individual regimens consisting of Lfx, bedaquiline (Bdq), linezolid (Lzd), clofazimine (Cfz), and Cs. After consuming anti-TB drugs for 27 days, the patient had seizures several times. The patient experienced full-body seizures and loss of consciousness during the seizures. Cs and Lfx were discontinued and replaced by other regimens. Serial electroencephalogram (EEG) showed normal results. After Cs and Lfx were discontinued, the patient never had another seizure.
Conclusion: Management of MDR-TB is sometimes complicated because of severe drug side effects. Patients taking Cs and fluoroquinolones (FQs) should be advised to report any sign of seizure or changes in mental status to their healthcare provider.

INTRODUCTION

Multidrug-resistant tuberculosis (MDR-TB) is TB that is resistant to at least rifampicin (R) and isoniazid (H), the two most potent drugs.[1] In 2013, the World Health Organization (WHO) estimated that there would be 6,800 new cases of MDR-TB annually in Indonesia. The predicted number is 2% for new TB cases and 12% for MDR-TB cases.[2] Based on WHO, in 2021, there were 450,000 cases of MDR-TB in the world, an increase of 3% compared to 2020. In Indonesia, 8,268 cases of DR-TB were reported, with 5,234 people having already started the treatment.[3]

The diagnosis of MDR-TB is confirmed based on the results of a sensitivity test which aims to determine whether *Mycobacterium tuberculosis* (M. tb) has or has not been resistant to anti-TB drugs. MDR-TB treatment uses at least five drugs and lasts for 18 to 24 months. Most of the patients can complete the treatment without experiencing significant side effects. However, a small percentage of patients may experience significant side effects that interfere with their daily

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work.[4] The unwanted effects of anti-TB drugs can be classified into severe and mild effects. Patients who experience mild side effects should continue treatment and be given symptomatic therapy. For patients with severe side effects, the anti-TB drug combination or causative anti-TB drugs should be discontinued.[5]

Cycloserine (Cs) and fluoroquinolones (FQs) are known to have the potential to cause seizures as a side effect. Cs is a medication used to treat TB, and FQs are frequently prescribed antibiotics for various infections. Although seizures are rare with both medications, they should be used cautiously in patients with known seizure disorders or risk factors for seizures, such as brain injury.

The exact mechanism behind these medications causing seizures is not well understood, but it is hypothesized to be due to their effects on the central nervous system (CNS). Cs and FQs may reduce inhibitory neurotransmitters, such as gamma-aminobutyric acid, or increase excitatory neurotransmitters, such as glutamate, leading to hyperexcitability of the brain and potential seizures.[6–8] Patients taking Cs or FQs should be advised to report any signs of seizures or changes in mental status to their healthcare provider immediately. If seizures occur, the medication may need to be discontinued, and alternative treatment options should be considered.

CASE

A 39-year-old man came to the hospital with seizures. The seizures started one day before hospitalization. The patient experienced a whole-body seizure with a duration of one minute. A history of previous seizures was denied. The patient experienced seizures after 27 days of taking anti-TB drugs. The symptoms included loss of consciousness. There was no history of fever in the patient. The patient also complained of a dry cough for the previous two months without coughing up blood. The patient felt right chest pain when coughing. Moreover, the patient experienced weight loss and decreased appetite. There were no symptoms of nausea and vomiting. The patient works as a private employee. The patient came to the hospital in August 2022 with a diagnosis of drug-resistant (DR) TB and received an individual regimen consisting of levofloxacin (Lfx), bedaquiline (Bdq), linezolid (Lzd), clofazimine (Cfz), and Cs. After 27 days of taking anti-TB drugs, the patient had a seizure.

The initial physical examination found additional breath sounds in both lung fields. A chest X-ray was performed at the hospital on 23 July 2022 and found fibroinfiltrates in the upper part of the right and left lung, referred to as moderate lung lesions (Figure 1). The rapid molecular test (TCM) examination results at the hospital on 28 July 2022 and 22 August 2022 showed M. tb detected (medium) Rif. resistance detected. TCM was examined twice because the patient was a primary or new case of MDR-TB.

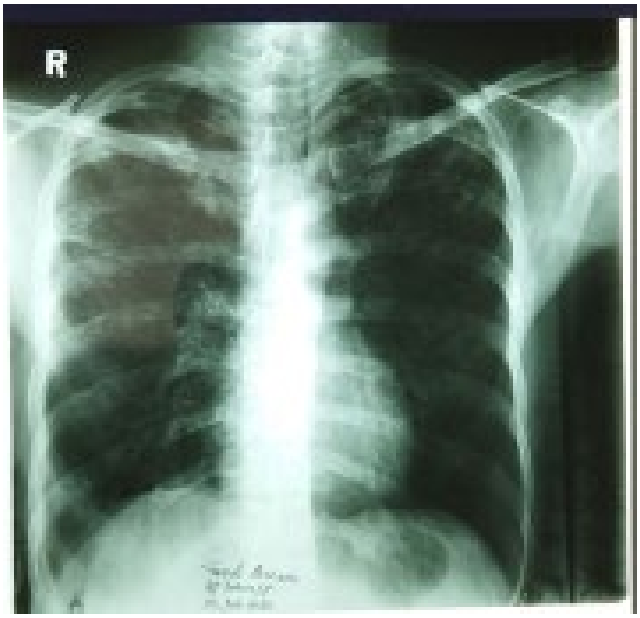


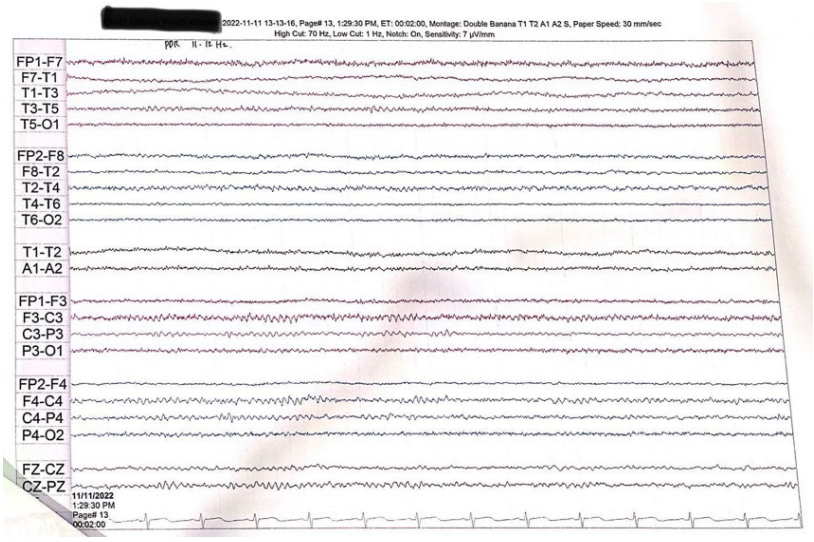
Figure 1. Chest X-ray before starting treatment of DR-TB (23 July 2022)

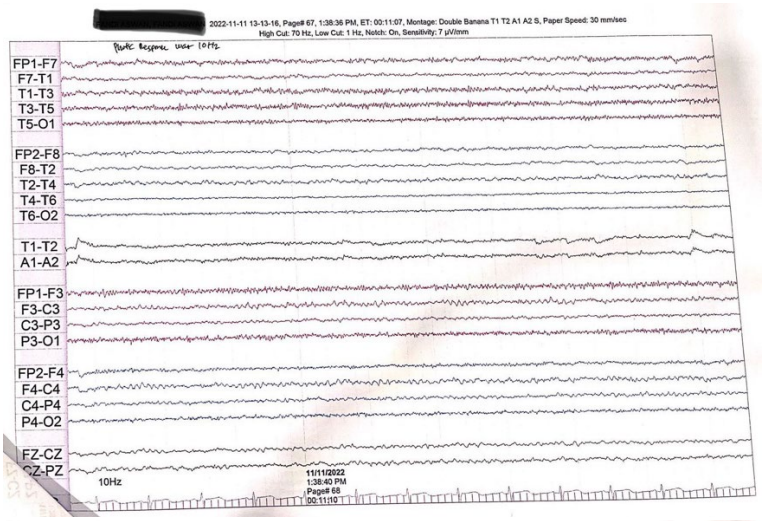
Before starting treatment, the patient had performed basic examinations, such as complete blood tests and consultations with the Department of Cardiology, the Department of Psychiatry, and the Department of Ophthalmology, to get approval for the therapeutic regimen. Second-line line probe assay

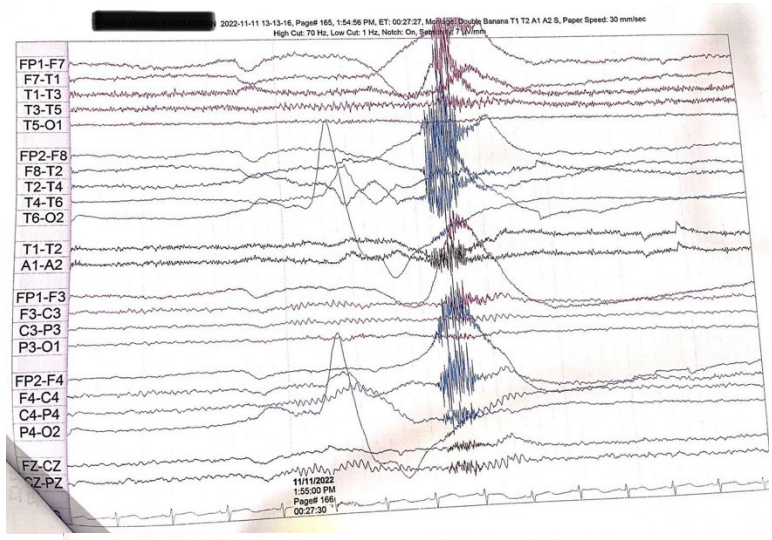
(LPA) test on 26 August 2022 showed results M. tb detected, Lfx (S), Mfx (S), Mfx^{dt} (S), Km (S), Am (S), Cm (S). Drug sensitivity test results on 30 August 2022 showed results H^{dt} (S), H (R), Lfx (S), Mfx^{dt} (S), Bdq (S), Cfz (S), Lzd (S), Z (S). After summarizing all results of the baseline examination, we started to give individual (long-term) regimens consisting of five effective drugs, Lfx, Bdq, Lzd, Cfz, and Cs, from 7 September 2022. The patient had been educated about how to consume the drugs and the possible side effects. Due to the patient's house being far from the hospital, the patient only came to the hospital once a month. After 27 days of medication, the patient experienced a seizure. The patient was hospitalized, and anti-TB drugs (Lfx and Cs) were temporarily discontinued. The patient also consulted a neurologist with diagnosis observation of general seizures. The neurologist recommended an electroencephalogram (EEG) and administration of antiepileptic medication such as diazepam and citicoline injection.

Laboratory examination results while being hospitalized on 4 October 2022 found a decrease in hemoglobin (Hb) levels of 9.8 (normal 14-17 g/dL), serum glutamic oxaloacetic transaminase (SGOT) 23 (normal <35 U/L), serum glutamic pyruvic transaminase (SGPT) 3.0 (normal <45 U/L), total bilirubin 0.3 (normal 0.3-1.2 mg/dL), ureum 18 (normal 13-43), creatinine 0.9 (normal 0.51-0.95), sodium 143 (normal 132- 146), potassium 4.8 (normal 3.7-5.4), and chloride 114 (normal 98-106). After the patient's condition improved, we continued the individual anti-TB drugs regimen with adjustments or changes to some drugs that could potentially have a side effect of seizures. Lfx and Cs, which had convulsion side effects, were discontinued and replaced with ethambutol (E) and delamanid (Dlm). On 7 October 2022, the patient started treatment with the individual regimen group 2A+1B+2C, which consisted of Bdq (200 mg), Lzd (600 mg), Cfz (100 mg), E (800 mg), and Dlm (200 mg).

Routine follow-ups were performed (clinical, blood laboratory, and electrocardiogram/EKG) once a month while the patient was in control on 7 November 2022. The patient underwent an EEG examination at the neurologist's polyclinic on 11 November 2022 with normal awake and sleep EEG results after the patient discontinued Lfx and Cs (Figure 2). The patient is currently receiving five types of TB drugs, an individual regimen consisting of Bdq (200 mg), Lzd (600 mg), Cfz (100 mg), E (800 mg), Dlm (200 mg), and supplements.







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RSUZA

LAPORAN HASIL ELEKTROENSEFALOGRAFI (EEG)

A. Introduksi :
Nama : [redacted]
Umur
Tanggal Rekaman : 11/11/2022

Nomor EEG : 1-01-45-28
Kiriman dari : dr. Elsa Susanti Sp S (K)
Klinis : Riwayat kejang sejak 2 bukan sebelum perekaman. Kejang kaku kelojotan seluruh tubuh, wajah tertarik ke kanan. Pasien dengan TB paru on OAT.

Rekam Medis : [redacted]

Physician:	dr. Sri Hastuti, Sp.N, Subsp.Ped(K)	**Technician:**	Ny Emifarianti
Ref. Physician:	dr. Elsa Susanti Sp S (K)		
		Time:	1:27:30 PM
Recording Date:	11/11/2022	**Report Date:**	11/12/2022
Duration (min):	30		

This is 30 minute eeg was done on 39 years old man who has got history of seizure

During wakefullness, eeg background showed PDR in Alpha at range 11-12 hz which attenuation upon eyes opening and central rhythm was also seen in Alpha at range 11-12 hz. His PDR is well modulated.

During sleep, sleep architectures is normal including vertex, symmetrical sleep spindles and synchronous K Complexes.

During photic stimulation, good photic response at 10Hz.

During Hyperventilation, It couldn't comply

During eeg recording, seizure can't capture.

Conclusion:

Normal awake and sleep EEG

Best regard

dr. Sri Hastuti, Sp.N, Subsp.Ped(K)

Figure 2. Normal awake and sleep EEG results after Lfx and Cs were discontinued

DISCUSSION

The management of MDR-TB can sometimes be complicated. Treatment of sensitive TB only uses four drugs and takes six months, whereas treatment of MDR-TB with an individual regimen uses at least five drugs and lasts 18 to 24 months.[9] The use of many drugs for a long time will undoubtedly cause more risks of side effects, ranging from mild to severe side effects. Drug side effects that occur have the potential to result in reduced patient adherence to treatment, which has an impact on decreasing treatment success, treatment failure, and even death.[10,11]

In Indonesia, there is a guideline from the Ministry of Health for MDR-TB treatment that categorized short-term without injection drugs and long-term regimens. The short-term regimen without injection consists of seven drugs for the early phase and four drugs for the advanced phase with a duration of 9-11 months with the regimen 4-6 BDQ (6 months) – Lfx-Cfz-H^{dt}-Z-E-Eto / 5 Lfx-Cfz-Z-E.[12] The long-term regimen, also known as an individual regimen, is given to patients who cannot be on the short-term regimen. The long-term regimen for MDR-TB treatment can be modified according to the patient's condition (individualized) in order to increase the effectiveness and safety of this guideline in treating MDR-TB patients. The drugs of choice are divided into three groups A, B and C. Group A consists of Lfx or moxifloxacin (Mfx), Bdq, and Lzd, group B consists of Cfz and Cs, and group C consists of E, Dlm, pyrazinamide (Z), amikacin (Am) or streptomycin (S), ethionamide (Eto) or prothionamide (Pto), and *p*-aminosalicylic acid (PAS). The treatment starts with five anti-TB drugs that may be effective, and there are at least three drugs after Bdq was discontinued.[12]

One of the side effects of second-line anti-TB drugs that must be considered is neurotoxicity, with symptoms such as peripheral neuropathy and seizures.[13] Most drug-induced seizures are self-limited and do not cause permanent sequelae. Even so, repeated or prolonged seizure activity can lead to irreversible neurologic injury. In addition, other life-threatening complications like hypoxia, hypotension, pulmonary aspiration, hyperthermia, and metabolic acidosis might also occur.[14]

A seizure indicates the abnormal electrical activity of the brain and can change the level of consciousness, memory, behavior, or feelings of someone who experienced it. There is a concept of a seizure threshold that refers to everyone tending to have seizures if there is a disturbance with the threshold. There are many factors contributing to that susceptibility, such as medications, genetic factors, electrolyte abnormalities, sleep state, infections, brain inflammation, or injury from many causes. On a cellular level, seizures start with the excitation of cerebral neurons, leading to synchronous discharges of larger groups of connected neurons. Neurotransmitters like glutamate are the most common excitatory neurotransmitters, and gamma-aminobutyric acid (GABA) is an inhibitory neurotransmitter involved in the mechanism of seizures. An imbalance of this neurotransmitter starts off abnormal electrical activity. It means increased activation or decreased inhibition of neurotransmitters could result in seizures.[15]

Some anti-TB drugs that can cause seizures are H, Cs, and FQs. This is supported by a study of adverse drug reactions (ADR) by Ausi, *et al*. (2021), who stated that one of the anti-TB drugs ADR was seizures found in the anti-TB regimen that has Cs or H or FQs in it.[16] The incidence of neurotoxicity due to Cs in DR-TB patients was recorded to be around 1-3%.[17]

Cs can be bactericidal or bacteriostatic. The use of Cs often causes side effects on the CNS. Many patients complain of experiencing an inability to concentrate or lethargy after taking Cs. These complaints appear even though the drug levels in plasma concentrations are very low. Cs is often contraindicated in patients with epilepsy because it can induce seizures and may be dangerous in people who are depressed.[18] Cs is actually a drug that has been used as a TB therapy since 1950 and is currently being used as one of the MDR-TB drugs. This drug was included in group B as a second-line anti-TB drug based on meta-analysis data showing that Cs were more effective than kanamycin (Km) and Eto.[19] Cs acts as a D-alanine analogue and inhibits the formation of the M. tb bacterial cell wall with alanine racemase and D-alanine ligase as targets.[20,21] According to the history of use, Cs is one of the anti-TB drugs associated with toxicity in the CNS.[8] This drug is well absorbed in the cerebrospinal fluid and reaches full concentrations in the blood. There is evidence to suggest that 20-33% of neurological and psychiatric manifestations are associated with Cs use. Because of the neuropsychiatric side effects it causes, Cs is nicknamed “psych-serine”.[8] Moreover, Cs is also called treating as well as killing.

Court, *et al*. (2021) showed that the mechanism for the occurrence of neuropsychiatric side effects, including seizures by Cs, was due to the accumulation and long-term usage of these drugs.[8] This indicates that the side effects are related to the dose, but the duration of treatment is also a significant risk factor for drug side effects.[8] Symptoms of a seizure may include loss of consciousness, muscle twitching, and convulsions. If a seizure occurs, treatment includes supportive care and administration of antiepileptic medications, such as benzodiazepines or phenytoin. Yadav and Rawal (2019) also reported cases of CNS side effects due to Cs in

MDR-TB patients.[22] They reported three cases with different manifestations, such as convulsions, tremors, dizziness, changes in behaviour and suicidal thoughts, although the cases we presented did not have these clinical signs.[22] However, the three cases reported by Yadav and Rawal (2019) were of the same age and sex as the cases we presented.[22] Although the pathogenesis of this side effect is not known with certainty due to limited published data, it may be due to the reduced production of GABA by the CNS as a result of glutamic decarboxylase inhibition.[21,22]

The risk of seizures due to Cs can be increased due to interactions with other drugs that also have effects on the CNS and other drugs that can induce clinical psychiatric disease, such as interactions with FQs.[23] Neurotoxicity side effects due to Cs are usually temporary and disappear when the drug is discontinued. Due to its long half-life, it usually takes several days to weeks for patients to return to normal conditions.[24] Based on this, in this case, we chose to replace Cs in the combined therapy to prevent the ineffectiveness of the therapy that had been given.

FQs have activity against M. tb and have good penetration in macrophages. This is important considering the ability of M. tb to live and survive in macrophages. Newer generations of FQs like Lfx and Mfx have greater activity against M. tb than ciprofloxacin (CIP) and ofloxacin (Ofx).[25] Currently, WHO guidelines include FQs as drugs in group A and are recommended for all MDR-TB therapy regimens if there are no contraindications. FQs are the backbone of MDR-TB therapy. This is based on meta-analysis data stating that using Lfx or Mfx provides successful MDR-TB therapy.[10]

FQs work as a bactericide by inhibiting mycobacterial deoxyribonucleic acid (DNA) gyrase, which in turn inhibits bacterial replication.[26,27] The side effects of FQs are usually associated with musculoskeletal disorders and prolongation of the QT interval. However, side effects that must be considered are disturbances to the CNS, especially in patients who already have problems with that system.[28]

CNS manifestations of FQs are well-recognized, including insomnia, headaches, seizures, confusion, delirium, psychosis, myoclonus, and muscle jerks. Mfx shows the least CNS toxicity. In addition, in a study by Kang, *et al*. (2016), patients with Lfx had more side effects than those with Mfx (79.2 vs. 63.5%, p = 0.03).[29] Seizures are more likely to occur in patients with renal impairment, a prior seizure history, electrolyte imbalances, or adverse drug interactions that lower the seizure threshold. The mechanism of seizures due to FQs is not fully understood. It is suspected to be related to the ability of these antimicrobials to either antagonize the inhibitory effect of GABA or the capacity to activate the N-methyl-D-aspartate (NMDA) receptors. Most likely, seizures arise from a combination of both mechanisms. Previous reports of FQ-induced seizure activity have suggested that the elderly and patients with decreased renal function are at a higher risk. In this case, these factors did not apply. The patient was not elderly and had an estimated creatinine clearance within the normal limit. Consequently, the dose of Lfx used was within the range recommended by the current guidelines. In this case, the origin of seizures was likely Lfx epileptogenic properties added with other drug interactions (Cs), which further increased the risk of seizures.[30]

This is similar to the study conducted by Ngoc, *et al*. (2021) that showed out of 659 patients assessed, there were 71.3% of patients experienced at least one side effect, and 17.5% of patients suffered at least one serious side effect.[31] It reported that 33.7% of patients in the study developed psychiatric disorders, and 30.0% of patients developed CNS disorders.[31] Most of the patients had Cs and Lfx in their regimens, which might be possible reasons for the side effects that occurred. Reported CNS disorders are found in 0.9–11% of adults treated with FQs, and psychiatric disorders are found in 20-30% of patients treated with Cs.[31] The study by Lan, *et al*. (2020) strengthened the result that of the 8,622 patients included in the analysis, 23.5% had at least one drug permanently discontinued because of the side effects, and the mean number of side effects leading to permanent drug discontinuation per patient was 1.4 (SD 0.8).[32] The percentage of patients who permanently discontinued at least one drug because of side effects varied in different studies, with a median of 29.1% (IQR 16.1–53.3). The incidence of Lfx side effects leading to permanent drug discontinuation was 1.3% [95% CI 0·3–5·0]. It has also been reported that Cs and terizidone (Tr d), Eto and Pto, PAS, second-line injectable drugs, and Lzd had the highest incidence of side effects leading to permanent drug discontinuation.[32]

The patient underwent an EEG because the patient had a seizure. EEG is an excellent examination to assess and predict the occurrence of seizures because it observes the recording of the electrical activity of the brain and is a non-invasive method.[33,34] In this case, the results of the EEG examination showed normal results. It proved that the patient had no organic disorders that could trigger seizures.

Some action needs to be considered if seizures occur. First, we can temporarily or entirely discontinue the causative drugs, otherwise disrupting the balance of the regimen. If the causative drug is discontinued temporarily, consider restarting or reintroducing the drug when the patient's condition is stable. Second, we can initiate anticonvulsant therapy, like phenytoin, carbamazepine, and valproic acid, after consulting with

the neurologist. Valproic acid is favored in patients taking Bdq. Anticonvulsants are generally continued until DR-TB treatment is completed or the causative drugs are discontinued. Patients with a history of seizures may have a higher risk for developing seizures during DR-TB treatment. Nevertheless, it is not contraindicated if the seizures are well controlled and/or the patient is receiving anticonvulsants. Lastly, we can raise the pyridoxine supplement to a maximum daily dose (200 mg per day). We need to monitor the condition every month and the dosing of drugs using creatinine clearance.[13]

The usage of several types of drugs in MDR-TB therapy might cause several problems in terms of tolerance to these drugs. The response of each individual is different, and the treatment should not be discontinued immediately because we are afraid of the effects that may arise.

CONCLUSION

The management of MDR-TB cases is often associated with side effects of medication ranging from mild to severe. Seizures are a side effect of drugs that should be a concern even though they often do not show sequelae. Although the cases are rare, they are often associated with the use of Cs and Lfx. It should be administered with caution, and the patients should be regularly monitored and followed up to see drug side effects that can occur to prevent patient non-adherence to therapy.

Consent

Written informed consent was obtained from the patient.

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Conflict of Interest

The authors declared there is no conflict of interest.

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Authors' Contributions

Conception: DBY, YA. Data collection and manuscript writing: WAU, YA. Review and revision: DBY, YA, WAU, WW. All authors contributed and approved the final version of the manuscript.

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