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Cycloserine-Induced Fever in a Patient with Multidrug-Resistant Tuberculosis and its Successful Desensitization: A Case Report

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Abstract

Cycloserine is one of the second-line anti-tuberculosis drugs used for treating multidrug-resistant tuberculosis (MDR-TB). Psychiatric and neurologic adverse reactions of cycloserine are commonly observed; however, fever as its only adverse reaction was rare. Here we report a case of cycloserine-induced fever in a 23-year-old female patient with MDR-TB and its successful management. After desensitization, the patient was able to continue the treatment regimen for MDR-TB and her symptoms were improved significantly. Our case indicates that fever could be the only adverse reaction of cycloserine in a patient who uses cycloserine as part of a treatment regimen for MDR-TB and the fever is manageable.

Keywords: Multidrug-resistant tuberculosis; Cycloserine-induced fever; Desensitization

Introduction

Drug-resistant tuberculosis (TB) is a difficult obstacle to overcome for the effective control and prevention of TB in the world. The continued spread of multidrug-resistant TB (MDR-TB) is associated with improper treatment of TB patients, poor management of supply and quality of drugs, and human-to-human transmission of *Mycobacterium tuberculosis* in public places [1]. Globally, there were an estimated 480,000 new cases of MDR-TB and an additional 100,000 cases of rifampicin-resistant TB in 2015 [1].

The clinical management of TB, especially MDR-TB, is a major challenge in resource-limited regions such as rural areas of Guizhou Province, China. Cycloserine (CS) is one of the oral bacteriostatic second-line anti-tuberculosis drugs used for the treatment of MDR-TB [2]. Common adverse reactions of cycloserine include dizziness, headache, seizure, depression, insomnia, fear, palpitation, tachycardia, psychosis and suicidal ideation, peripheral neuropathy and skin changes [3-6], but fever as the only adverse reaction was rarely reported [7]. Additionally, there was no standard protocol available for desensitization of cycloserine-induced fever in patients with MDR-TB. In this report, we describe an unusual case of cycloserine-induced fever in a patient with MDR-TB and its successful desensitization.

Case Report

A 23-year-old Chinese woman with a two-year history of pulmonary TB presented to our hospital with symptoms of cough and sputum. She was previously treated with first-line anti-tuberculosis drugs isoniazid, rifampicin, ethambutol, and pyrazinamide. However, her symptoms were not significantly improved because the patient did not follow a prescribed course of treatment. Her two sputum samples revealed the presence of acid-fast bacilli graded as 4+ and her sputum culture was confirmed to contain multidrug-resistant *Mycobacterium tuberculosis*. Results of drug susceptibility testing (DST) showed that the collected clinical isolate was resistant to isoniazid, rifampicin, ethambutol, streptomycin, kanamycin, capreomycin, amikacin, and ofloxacin, but susceptible to levofloxacin, moxifloxacin, prothionamide amines, and *para*-aminosalicylic acid. The patient was admitted to our hospital for further treatment after a diagnosis of previously treated MDR-TB.

The patient's vital signs, routine blood, urine and stool tests, liver and kidney functions, and heart and abdomen were normal at the admission. In addition, there was no abnormal breath sounds in both lungs, but the breath sound was reduced in the left lung. Her chest computed tomography (CT) scan showed the presence of bilateral tuberculosis, multiple cavities and bronchiectasis in the left lung, bronchial stenosis in the main bronchus, upper and lower lobes of the left lung, multiple enlarged mediastinal and bilateral hilar lymph nodes, as well as left sided pleural thickening with a small amount of fluid.

Treatment with five second-line anti-tuberculosis drugs was initiated for the patient two days after her admission to the hospital, which included levofloxacin (0.5 g intravenous infusion once daily), cycloserine (500 mg once daily), prothionamide (600 mg once daily), pyrazinamide (1.5 g once daily), and amikacin (0.5 g intravenous infusion once daily). Even though DST results showed that the clinical isolate from the patient was resistant to amikacin, amikacin was included for the treatment because the patient never used it previously. Vitamin B6 (100 mg twice daily) was also included to prevent potential side effects of cycloserine.

Three days after the initiation of treatment, the patient had persistent fever with temperature fluctuations above 39°C and up to 40.2°C, and felt chilly every night (Figure 1). She was given ibuprofen to reduce her temperature to about 38°C. Bacterial pneumonia was initially considered as the cause of fever, and flucloxacillin (1.5 g intravenous infusion three times a day) was given to the patient. On day 7, flucloxacillin was replaced by ceftazidime (2 g intravenous infusion twice daily) to treat potential bacterial infections; however, the patient still had fever. On day 9, a Chinese antiviral medicine, Xiyanping, was

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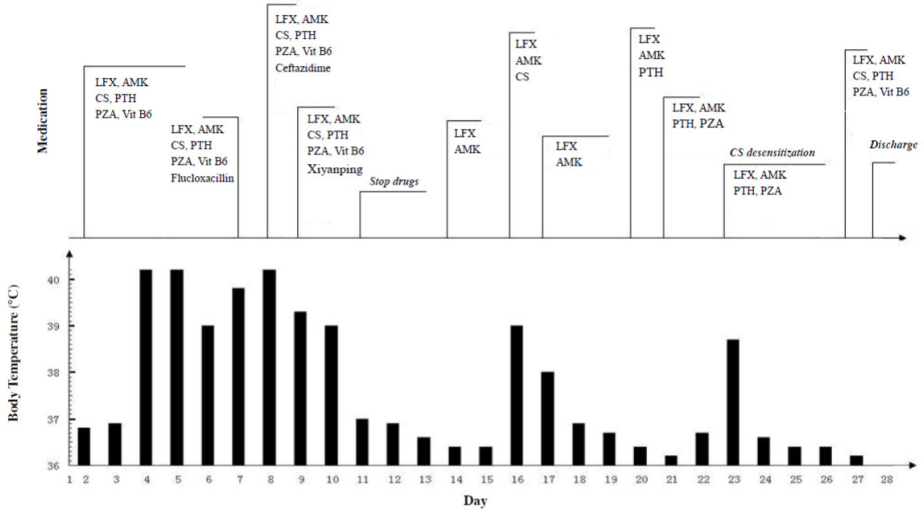

Figure 1: Medication and body temperature changes in a patient with MDR-TB during her 28-day stay in the hospital. LFX: Levofloxacin; AMK: Amikacin; CS: Cycloserine; PTH: Prothionamide; PZA: Pyrazinamide; and Vit B6: Vitamin B6.

Day	Time	Cycloserine (mg)
Day 1	12:00	0.1
	12:45	0.5
	13:30	1
	14:15	2
	15:00	4
	15:45	8
	16:30	16
	17:15	32
	18:00	50
	18:45	100
	19:30	150
	23:00	250
Day 2	08:00	500
Day 3	08:00	500
Day 4	08:00	500

Table 1: Desensitization by challenging the MDR-TB patient at different time points with incremental dosing of cycloserine.

used for treating potential viral infections (250 mg intravenous infusion once daily); nevertheless, the patient had fever consistently at night (Figure 1). Because the patient had no symptoms related to respiratory tract infections such as sputum aggravation, headache, runny nose, and sneezing other than fever, we suspected that one of the five second-line anti-tuberculosis drugs might have caused the fever. Therefore, all drugs were suspended on day 11, and the patient's fever disappeared on the same day and during the following three days (Figure 1).

To determine which anti-tuberculosis drug caused the fever, we started to give five second-line anti-tuberculosis drugs back to the patient one by one. When amikacin and levofloxacin were given to the patient, she had no fever and any discomfort. However, she had fever (up to 38.9°C) with chills again at night on the same day (day 16) when cycloserine was added. After taking ibuprofen, her temperature went gradually back to normal (Figure 1). Knowing fever could be one of cycloserine's side effects, we stopped giving it to the patient for three more days and her temperature was normal. Prothionamide and pyrazinamide were then given to the patient one by one and she had no fever. Our testing results confirmed that cycloserine caused fever in this patient.

After obtaining informed consent from the patient, we started our own protocol for desensitization of cycloserine-induced fever on day 23 with four second-line anti-tuberculosis drugs (levofloxacin, amikacin, prothionamide and pyrazinamide) and incremental dosing of cycloserine at different time points shown in Table 1. The patient had fever up to 38.8°C at night but without chills and other symptoms which last about half an hour (Figure 1). We continued the cycloserine desensitization on the following three days with the same dose of 500 mg given at 08:00 daily and the patient had no fever. The patient was stable for two days and discharged after 28-day stay at the hospital (Figure 1). The patient continued the prescribed course of treatment including cycloserine, levofloxacin, amikacin, prothionamide, pyrazinamide and vitamin B6 after discharge from the hospital, and there were no fever, rash, depression and other adverse reactions. Follow-up chest CT scans performed at two months 18 days, five months 25 days, and seven months 19 days after the treatment showed that the lung lesions of the patient were reduced gradually, and her symptoms were improved significantly (data not shown). In addition, her sputum smears for acid-fast bacilli were negative after three-month treatment.

Discussion

Treatment options for MDR-TB patients are limited and expensive in some low- and middle-income countries, and some patients may experience many adverse effects from second-line anti-tuberculosis drugs [2]. Cycloserine is often used for the treatment of MDR-TB and has different adverse reactions such as headache, seizure, depression, peripheral neuropathy and skin changes [3-6]. However, fever as the only adverse reaction of cycloserine was uncommon, and the standard protocol was not available for desensitization of cycloserine-induced fever in patients with MDR-TB. In one recent report, hypersensitivity reactions to second-line anti-tuberculosis drugs in a MDR-TB patient co-infected with human immunodeficiency virus (HIV) were successfully managed by challenging the patient with incremental dosing of cycloserine in seven days [8].

In this case report, the treatment regimen containing cycloserine and other four second-line anti-tuberculosis drugs was initiated for the patient with MDR-TB two days after her admission to the hospital. Three days later, the patient had persistent fever and felt chilly every night for several days. However, the patient's fever disappeared on the

same day when all drugs were suspended and during the following three days. By giving the five second-line anti-tuberculosis drugs back to the patient one by one, we found out that cycloserine caused fever in this patient. To increase the chance of curing MDR-TB, we wanted to include cycloserine as one of the five second-line anti-tuberculosis drugs for this patient, but would have to overcome one of its side effects, cycloserine-induced fever. Therefore, we used our own protocol for desensitization with four second-line anti-tuberculosis drugs and incremental dosing of cycloserine.

Conclusion

In summary, we present here an unusual case of cycloserine-induced fever in a patient with MDR-TB and its successful desensitization by challenging the patient with incremental dosing of cycloserine, which enabled the patient to continue the cycloserine-containing treatment regimen and her symptoms were improved significantly. We believe that this case report is unique and presents a novel solution to clinically relevant issues which will help physicians around the world to treat MDR-TB patients with cycloserine-induced fever.

Results from this case report indicate that fever could be the only adverse reaction of cycloserine in a patient who uses cycloserine as part of a treatment regimen for MDR-TB and the fever is manageable which made it possible for the patient to safely continue the cycloserine-containing treatment regimen for MDR-TB.

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