Journal of Clinical Case Reports

Case Report Open Access

Risk Factors in Multidrug-Resistant TB: A Case Report and Review of the Literature

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Abstract

Tuberculosis (TB), as a kind of chronic infectious disease by Mycobacterium Tuberculosis (Mtb), is one of the most common causes of death worldwide. The strategy of anti-TB therapy has improved during the last decades following the development of agents against TB and advanced exploration of TB. However, accompanied with the medical progression, Multidrug-Resistant TB (MDR-TB) has also emerged which causes higher mortality and morbidity due to multiply factors from clinical treatment, epidemiology and compliance of patients including drug abusing, irregular schedules and gene mutations. Therefore, we present a case of TB with rifampin-resistance in this article to explore risk factors of drug-resistance.

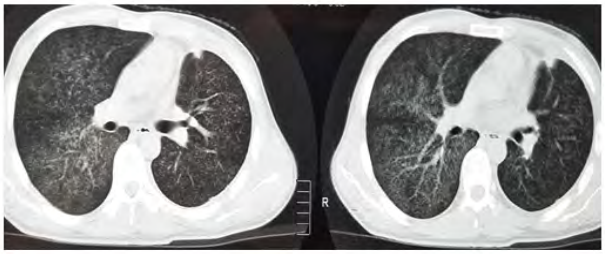
Keywords: Mycobacterium tuberculosis; Multidrug-resistance TB; Epidemiology; Prevention; Treatment; Risk factors

Introduction

It has been reported that the number of patients with tuberculosis in 2015 was 10.4 million and the death rate was 1.4 million [1]. Recently, both prevention and treatment of TB are more difficult and tough due to MDR-TB, which resists at least two first-line drugs of anti-tuberculosis including rifampicin and isoniazid. Based on data of 2015, the number of newly diagnosed patients with MDR-TB was 480000 and 45% were from India, China and Russia [1]. Hence, as the one of three countries which predominates the prevalence of MDR-TB around the world, it is urgent to establish medical system of anti-TB including prevention, treatment and follow-up in China. Currently, there are two types of MDR-TB, primary MDR-TB and acquired MDR-TB. Biologically, both efflux pump and permeability of cell wall are associated with drug-resistance [2]. Meanwhile, the associated gene sites for both rifampicin and isoniazid are mainly explored. Theoretically, it is rarely to find the mutated strains of MDR-TB under natural environment. Herein, we present a case of TB with rifampin-resistance aiming to optimize the prevention and treatment of anti-TB with drug-resistance.

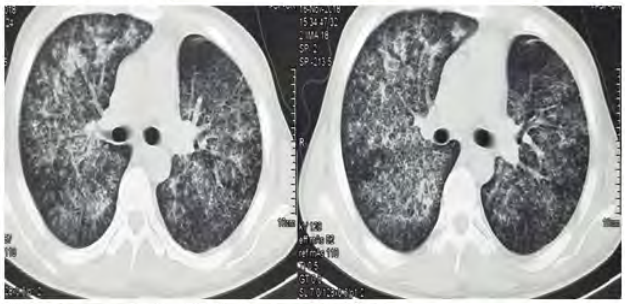
Case Presentation

A 29-year-old male patient admitted to hospital with complaining of progressive fever for 10 days on Oct. 26. 2018. Previously, the patient had been diagnosed with hematogenous disseminated pulmonary tuberculosis. Although local treatment initiated (exact strategy not provided), however, fever had not been controlled completely. No positive signs were found in physical examination. No other complications or chronic exhaustive diseases were found. A brother with TB died two years ago. Previously, both sputum DNA of Mtb and T-SPOT were positive, whereas, sputum smear was negative. It was shown from CT scan, disseminated miliary lesions within bilateral lungs (Figure 1). After admitting, TB-RNA was positive and sputum smear was also positive (3+). Based on CT scan in our hospital, disseminated miliary lesions within bilateral lungs were found. Besides, local thickened pleura adhesion and swollen nodes within mediastinum were also found (Figure 2). Significant lab results of cerebrospinal fluid by lumbar puncture were shown as glucose of 2.06 mmol/L and TP-csf of 0.62 g/L. Finally, the patient was diagnosed as acute hematogenous disseminated pulmonary tuberculosis, lung infection and suspected tuberculous meningitis. Subsequently, the strategy of anti-TB therapy for the patient was made as H-R-Z (H: Isoniazid, 300 mg/d; R: Rifampin, 600 mg/d; Z: Pyrazinamide, 1.5 g/d) combined with prednisone (20 mg/d) and antibiotics. During the initial stage of treatment, temperature had been tested intermittently. Fever was controlled after Nov.18 and the patient discharged on Nov.22 due to poor financial support with the follow-



Disseminated miliary lesions within bilateral lungs

Figure 1: Previous CT scan before admitting.



Disseminated miliary lesions within bilateral lungs; Local thickened pleura adhesion and swollen nodes within mediastinum

Figure 2: CT scan after admitting.

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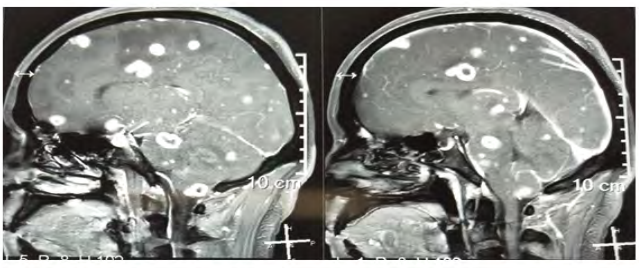
Received January 27, 2020; **Accepted** February 18, 2020; **Published** February 25, 2020

Citation: Yao C, Zhang X, Hong Q, Lin W (2020) Risk Factors in Multidrug-Resistant TB: A Case Report and Review of the Literature. J Clin Case Rep 10: 1317

up oral strategy of R-E-Z-MFX-prednisone (R: Rifampin, 600 mg/d; E: Ethambutol, 750 mg/d; Z: Pyrazinamide, 1.5 g/d; MFX: Moxifloxacin, 400 mg/d; Prednisone, 20 mg/d).

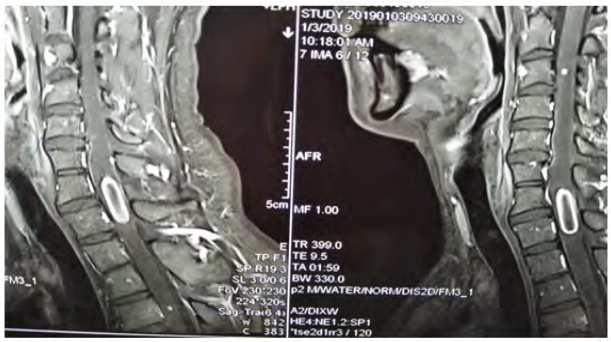
One week later, the patient readmitted with complaining of mild fatigue and weakness of bilateral lower limbs for 7 days. The strategy of R-E-Z-MFX-prednisone (R: Rifampin, 600 mg/d; E: Ethambutol, 750 mg/d; Z: Pyrazinamide, 1.5 g/d; MFX: Moxifloxacin, 400 mg/d) was performed strictly. Renal disfunction was found at the admitting with Creatinine (CREA) of 168.7 umol/L. Original treatment continued and both piperazine ferulate and alprostadil were added to improve renal function. Acid fast staining of urine was shown as positive (3+). Therefore, the patient was diagnosed with urinary tuberculosis. It was shown by ultrasound that crystals within bilateral renals were found. Midstream urine culture was negative. For both red cells and white cells, in urine routine test, were 7 u/L, meanwhile, both occult blood and protein were also 1+. After consultant with urology, any drugs may induce nephrotoxicity were avoided or cautioned. Patient discharged on Dec.18 following the same strategy of R-E-Z-MFX-prednisone (R: Rifampin, 600 mg/d; E: Ethambutol, 750 mg/d; Z: Pyrazinamide, 1.5 g/d; MFX: Moxifloxacin, 400 mg/d; Prednisone, 30 mg/d) combined with drugs of renal protection. The patient was diagnosed with acute hematogenous disseminated pulmonary tuberculosis, urinary tuberculosis and suspected tuberculous meningitis. During hospitalization, the patient was temporarily catheterized due to acute urine retention. The potassium of 2.7 mmol/L was the possible explanation. However, 3 days after discharging, acute urine retention and progressive fatigue of lower limbers recurred, and the potassium was normal. Hence, suspected spinal tuberculosis leading to nerve compression was considered. It was demonstrated from MRI that multiply tuberculoma of brain were detected and complicated with lesion within spinal cord from C7 to T1 (Figures 3 and 4).

The acid-fast staining stool was positive and gene assay of urine was shown as rifampin-resistance. Pathologically, spinal tuberculosis was confirmed after surgical removal of spinal lesion. The patient was diagnosed with acute hematogenous disseminated pulmonary tuberculosis (rifampin-resistance), multiply tuberculoma, spinal tuberculosis, urinary tuberculosis and intestinal tuberculosis. The recommended strategy was E-Z-MFX-Pto-Cs-LZD-Vitb6 (E: Ethambutol, 750 mg/d; Z: Pyrazinamide, 1.5 g/d; MFX: Moxifloxacin, 400 mg/d; Pto: Protionamide, 200 mg triple/d; Cs: Cycloserine, 250 mg twice/d; LZD: Linezolid, 600 mg/d; Vitb6: Vitamin b6, 300 mg/d). At 6 months after recommended strategy initiated, the lesions of tuberculosis including lungs, brain and spine have been improved significantly (Figures 5-7).



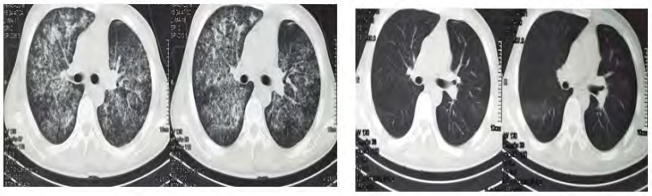
Multiply tuberculoma of brain

Figure 3: Detected lesions within brain of MRI.



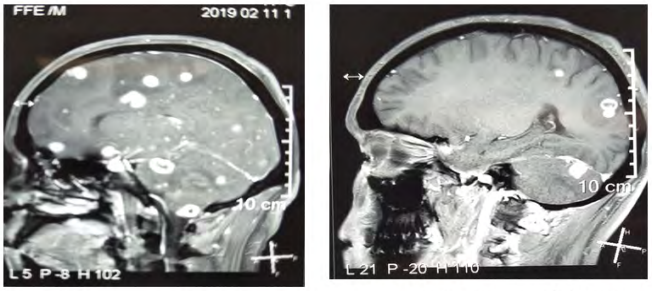
Lesion within spinal cord from C7 to T1

Figure 4: Detected lesion within spinal cord of MRI.



Before recommended strategy *After recommended strategy*

Figure 5: Comparison of lesions within lungs.



Before recommended strategy *After recommended strategy*

Figure 6: Comparison of lesions within brain.

Before recommended strategy *After recommended strategy*

Figure 7: Comparison of lesion within spine cord.

Discussion

For this case, the patient had received consecutive anti-TB treatment, however, during the initial stage; the outcome was not

optimistic or even worse. Based on the final diagnosis, drug-resistance (rifampin-resistance) was considered as main cause leading to difficulty of anti-TB strategy, although many attempts were tired. Clinically, it is challengeable for both physicians and tuberculosis specialists to handle drug-resistance. Besides rifampin-resistance shown in this patient, MDR-TB has been the major threat of public health. Although fast development and considerable improvement in both economy and life quality during last decades, however, China is still the one of countries influenced by Mtb mostly and seriously. In this case, pretreatment of anti-TB, inadequate treatment of anti-TB as well as the multiply TB lesions have been associated with drug-resistance.

Based on the information of case study, positive family history of TB is indicative. Further, the medical history of previous treatment of anti-TB is clear and critical, though exact strategy of anti-TB not provided. Liang et al. [3] investigated the prevalence of MDR-TB in 30 counties in Heilongjiang province including 1995 patients. It was found that compared with new patients (7.2%), the prevalence of MDR-TB of patients with previous treatment was higher significantly (30.4%). Liu et al. [4] showed that the rate of MDR-TB for newly diagnosed TB patients was 23.4% rather than 59.7% for patients with previous treatment of anti-TB, among whom, resistances for both isoniazid and rifampicin were majority in a study with the aim of testing drug susceptibility of Mtb including 1012 positive TB patients in Lianyungang. Similarly, in a case control study of Henan province, compared with the control, the number of cases with previous treatment of anti-TB increased significantly (214, 74.4% vs 127, 43.8%), which indicated that history of anti-TB treatment was an identified risk factor of MDR-TB [5]. Meanwhile, drug resistance is positively correlated with treatment duration and frequency. It has been demonstrated that the rate of MDR-TB for patients with previous treatment duration of isoniazid and rifampicin for more than 3 months was 4.8 times more than patients whose duration for less than 3 months [3]. Besides, treatment frequency is also an important factor of MDR-TB. Zhao et al. [6] have conducted a national survey of drug resistance tuberculosis focusing on epidemiology and estimating the rate of MDR-TB. It was shown that the OR of MDR-TB for patients with higher frequency ≥ 2 times of previous treatment was 13.3 (95% CI: 3.9-46.0).

Due to poor financial support, the treatment of this patient in hospital is not smooth and persistent. Alternatively, oral anti-TB strategy was selected and performed. Lack of supervision and management of administration, the effect of anti-TB was inadequate, and the outcome was limited. Discontinuation of anti-TB, absence of supervision and adverse events are risk factors of MDR-TB with ORs of 13.1 (95% CI: 3.0-56.6), 11.7 (95% CI: 4.0-34.3) and 4.5 (95% CI: 1.9-10.5), respectively [7]. It has been supposed that inadequate treatment of anti-tuberculosis is another critical cause for drug resistance. Among patients with previous treatment, 43.8% had failed their last treatment [6]. In a case-control study, 61 patients with MDR-TB and 50 patients with non-MDR-TB were selected to assess associated factors of MDR-TB [8]. It has been suggested that lack of initial fixed dose combinations (FDCs) and adverse events were independent risk factors of MDR-TB with the ORs of 4.0 (95% CI: 1.5-11.1) and 3.6 (95% CI: 1.4-9.0), respectively. Also, gene mutations of Mtb may be detected under the condition of discontinuation or irregular treatment of anti-tuberculosis, which evolve drug resistance of TB [9]. Otherwise, delay of treatment should not be ignored. Compared with patients with delay ≤ 60 days, the rate of MDR-TB for patients with delay >60 days increase by 2.6 times and for patients with retreatment, delay is more significant [3]. However, oppositely, it was found that there was no significant association between treatment delay and the rate of MDR-TB in a cohort study in Switzerland [10]. In this study, 46 out of 51 patients were from foreign origin; only 5 patients were from Swiss origin, which may explain the difference between two studies.

After admitting, the initial sputum smear of this patient was negative. The association between positive sputum smear and MDR-TB is still controversy. El-Mahalli et al. [11] demonstrated that positive Acid-Fast Bacilli (AFB) smear is shown as the critical trend for development of MDR-TB, especially on admission (OR=40.1; 95% CI: 9.0-178.9). Compared with negative smear, positive smear is a more significant risk factor of recent transmission due to larger load of Mtb and more infectious strains [12,13]. A retrospective study was conducted in Armenia and a total of 992 TB patients were enrolled for identification of association between smoking and MDR-TB. Besides smoking, other independent factors were also found including positive sputum smear (P=0.001) [14]. However, Shen et al. [15] estimated the rate, trend and risk factors of MDR-TB in Shanghai through another retrospective study including 8419 TB patients. Nevertheless, rather than age and previous treatment of TB, it was demonstrated that there was no association between positive sputum smear and MDR-TB (P=0.17). Huang et al. [16] prospectively assessed the risk factors of MDR-TB through drug susceptibility test, Genotype and DNA sequencing for a total of 298 sputum smear positive TB patients. Sequentially, positive smear at the end of intensive treatment was shown as the risk factor of MDR-TB.

From MRI scan, multiply TB lesions are found and the compression from spinal lesion leads to serious symptom. The number of TB lesions also plays a critical role on the rate of MDR-TB. Compared with ≤ 3 TB lesions, the rate of MDR-TB for >3 TB lesions is higher significantly (OR=2.0; 95% CI: 1.5-3.3) [5]. Other special pathological change, such as TB with cavity is also associated with MDR-TB due to less penetration of anti-tuberculosis to cavity wall, therefore, surgical attempts should be performed if necessary [16]. Furthermore, for newly diagnosed TB patients with cavitation, the rate of MDR-TB is more significant [17]. Similarly, Zhang et al. [18] investigated the potential risk factors associated with cavitary TB. Multidrug resistance has been confirmed as independent factor associated with cavitation.

For this case, the possibility of acquired drug-resistance is considered strongly. Acquired-drug resistance is emergent following the high rate of primary drug resistance even though standardized treatment has been used before. A retrospective study was conducted in Thailand to estimate acquired drug resistance [19]. It was supposed that the number of patients with acquiring MDR-TB after regimen of 2HRZE/HR. Hence, alternative or intensive regimens must be proposed to avoid acquired drug resistance. Recommended Directly Observed Treatment Short course (DOTS) is not the only treatment of anti-TB due to acquired drug resistance in areas in which high rates of initial drug resistance and drug susceptibility test is necessary [20]. In an observational prospective analysis, a total of 1671 patients with standard treatment were assessed to explore the emergency of acquired drug resistance [21]. It has been found that compared with earlier emergence of acquired drug resistance within 2 months after treatment, late emergency around 3-5 months of treatment was more associated with MDR-TB (OR=25.7; 95% CI: 4.3-153.4). As a new finding shown in a retrospective study with the aim of estimating risk factors of acquired resistance, persistent positive AFB at 4 and 6 months was also the predictor which was more practical and available for clinicians rather than culture [22]. Both administration and dosing should be considered to improve acquired drug resistance, because even if under the guide of strict standard treatment regimen, the resistance is also still checked.

Conclusion

In conclusion, clinically, history of previous treatment of TB, inadequate treatment as well as the number of lesions, to some extent, are potentially associated with MDR-TB and how to eliminate MDR-TB is still urgent to global medical system. Therefore, TB treatment should be performed strictly and monitored intensively. Local medical facilities are advised to make appropriate tactics of prevention and control based on local epidemiology of TB or MDR-TB. However, some limitations in this brief review, we do not discuss the influences imposed by patients and social environment which maybe also significant factors on transmission of MDR-TB. Further studies for more details focusing on the MDR-TB are expected.

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