Case Report/Relato de Caso

Primary multidrug-resistant tuberculosis and its control implications in the State of Amazonas, Brazil: report of 3 cases

Multirresistência primária da tuberculose e implicações no controle no Estado do Amazonas, Brasil: relato de três casos

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ABSTRACT

The occurrence of tuberculosis with first-line multidrug resistance leads to the use of alternative medications, often at higher costs, longer treatment periods, and greater clinical complexity. Here, we report 3 patients with multidrug-resistant tuberculosis. One patient with human immunodeficiency virus died before the sensitivity test was performed. The early diagnosis of multidrug-resistant tuberculosis and appropriate treatment should be priorities of the National Tuberculosis Control Program in order to break the chain of transmission. In addition, the possibility of substituting the proportion method with more modern and faster techniques should be urgently evaluated.

Keywords: Tuberculosis. Primary drug resistance. Multidrug-resistant tuberculosis.

RESUMO

O surgimento de resistência múltipla às drogas de primeira linha implica na utilização de fármacos de maior custo, com duração mais longa, maior complexidade e mais efeitos colaterais. Relatamos os casos de três pacientes com multirresistência primária aos tuberculostáticos. O portador de HIV evoluiu para óbito antes do resultado do teste de sensibilidade. Portanto, o diagnóstico precoce de tuberculose multirresistente e o tratamento adequado devem ser prioridades do Programa Nacional do Controle da Tuberculose, visando interromper a cadeia de transmissão. Além disto, é urgente que seja avaliada a substituição do método das proporções por técnicas mais modernas e mais rápidas.

Palavras-chaves: Tuberculose. Resistência primária às drogas. Tuberculose multirresistente.

INTRODUCTION

The prevalence of multidrug-resistant tuberculosis (MDR-TB) constitutes a global problem. According to the World Health Organization, MDR-TB is defined as the resistance of *Mycobacterium tuberculosis* to at least rifampicin (R) and isoniazid (H)[1], the 2 most important drugs in treating this disease. While repeated inadequate tuberculosis (TB) treatment courses represent the most important risk factor for developing MDR-TB, new patients may also be diagnosed with MDR-TB as a result of the transmission of resistant strains[2]. Late diagnosis, as a consequence of limited access to diagnostic services, and the poor socioeconomic conditions of many patients are factors that contribute to the development of resistant strains[3].

In the State of Amazonas, Brazil, a proper investigation of MDR-TB cases, even among retreatment cases (i.e., relapse and re-registration after default), is only undertaken in ~50% of cases (Amazonas TB Control Program: data not published). This is another factor that may contribute to the transmission of resistant strains of TB.

In the transmission of resistant strains, the greatest individual risk factor is sharing living quarters with individuals who have defaulted on their TB treatment or are relapse cases[4,5]. The appearance of patients with first-line MDR-TB leads to the use of alternative medications, often at higher costs, longer treatment periods, and greater clinical complexity due to the fact that these drugs are injectable and tend to lead to more side effects[6,7].

In Manaus, State of Amazonas, the last decade has seen a TB incidence rate of >92 cases/100,000 inhabitants. The cases identified in the registry as defaulters correspond, on average, to 12% of cases per year, and new entries due to relapse represent 5% of all notified cases. From 2000-2010, 60 cases of MDR-TB were registered in State of Amazonas; 95% (57/60) of these patients resided in Manaus. Of these, 94.7% (54/57) were cases of acquired MDR-TB and 5.3% (3/57) were primary cases of MDR-TB detected following the failure of the initial course of treatment (Helio Fraga Reference Center/System TBMR: data not published).

During the first study on primary resistance to anti-TB drugs, which was carried out in Manaus from November 2009 to October 2010 (Garrido: submitted for publication), 3 cases of primary MDR-TB were identified.

CASE REPORT

Case report 1

The patient was a 26-year-old single man who was born in and lived in Manaus and worked as an industrial production assistant. He lived with 3 family members in precarious housing conditions. On April 6, 2010, he was treated at the Cardoso Fontes Referral Center, for the complaint of productive cough of ~1 month-duration, along with dyspnea and weight loss of 5kg. He stated that he did not regularly smoke, drink alcohol, or use illicit drugs. He was the third case of TB in the family, as confirmed through a subsequent review of patient charts. The first case of TB in the family was his father, who had pulmonary TB in 1979 and 2002, with a history of irregular adherence to treatment, alcohol use, and eventual default. His brother was the second case, with positive pulmonary TB (++) in 1998, at 12 years of age, initially defaulting treatment, but subsequently completing a 12-month course and was released from treatment as a cured case.

The patient had positive results for direct sputum bacilloscopy (+), negative results for human immunodeficiency virus (HIV), using the Bio-Manguinhos Rapid Test (FIOCRUZ-Bio-Manguinhos, Rio de Janeiro, Brazil) and normal results for the chest X-ray. Treatment was initiated on April 8, 2010, with rifampicin, isoniazid, pyrazinamide, and ethambutol (the basic course for TB). On May 11, 2010, a sputum culture was positive for *M. tuberculosis* by using the Ogawa-Kudoh method and was forwarded for sensitivity testing at the State Referral Laboratory. Due to technical problems, the test was not concluded before the end of the treatment period. The patient was released from treatment after 6 months, after showing a negative smear result. On November 10, 2010, the sensitivity test was completed and showed resistance to rifampicin and isoniazid. Another sputum bacilloscopy produced a negative result with a positive culture using Petroff's method. A new chest X-ray showed a non-cavitary, unilateral lesion. The patient complained of a sporadic, productive morning cough, without other symptoms. He began treatment with streptomycin, ethambutol, levofloxacin, pyrazinamide, and terizidone on May 11, 2011, and has shown a favorable clinical course.

Case report 2

The patient was a 42-year-old single man who was born in and resided in Manaus; he lived alone and worked as a plaster construction worker. On April 12, 2010, he presented with a dry cough of more than 1 month duration, together with fever, dyspnea, chest pain, and weight loss of 12 kg. He did not know of prior cases of TB in his family, although he had contact with 2 neighbors who died from TB. He described himself as a smoker, but did not drink alcohol frequently or use illicit drugs. Direct sputum bacilloscopy and culture in Ogawa-Kudoh medium were both positive. An HIV test was negative and a chest X-ray showed volume reduction in the lungs, most notably in the left lung. There were bilateral pleurodiaphragmatic adhesions and fibroatelectatic opacity, with bronchiectasis in the upper parts of the lungs, in contact with the mediastinal and hilar structures. He began treatment with the standardized course of anti-TB drugs. The control smear was negative in the second month of treatment; however, it was positive once again in the fifth month and stayed that way until the eighth month. The sensitivity test showed resistance

to rifampicin, isoniazid, and streptomycin. He began MDR-TB treatment (terizidone, levofloxacin, pyrazinamide, ethambutol, and amikacin), showing a favorable clinical evolution.

Case report 3

The patient was a 23-year-old single male who worked as a metallurgist; he was born in and lived in Manaus. He lived with 2 family members in a single-room brick house. He presented with a dry cough of 2-month duration, along with dyspnea, fever, chest pain, night sweats, and weight loss of 13kg. There had been no reports of TB in the family; he reported a history of contact with TB patients during a hospital stay less than 2 years before. He was a smoker who did not drink alcohol or use illicit drugs. He had gastritis and acquired immunodeficiency syndrome (AIDS), as associated illnesses.

Direct sputum bacilloscopy and culture in Ogawa-Kudoh medium were both positive (+++) for *M. tuberculosis*. He had a positive HIV test and a chest X-ray suggestive of TB. He began treatment with the standardized course of anti-TB drugs. The sensitivity test showed resistance to rifampicin, isoniazid, streptomycin, and ethambutol. The patient died before he could begin treatment for MDR-TB.

DISCUSSION

The 3 patients with MDR-TB in this study were young, single, male adults between the ages of 23 and 42 years; they were born in and currently living in Manaus, with no history of prior treatment for TB. All reported having been exposed to *M. tuberculosis*, albeit in different ways, i.e., household, neighborhood, and hospital contact. All had low family income with precarious housing and living conditions.

The 2 patients with negative HIV serologic test results are undergoing treatment and have a favorable prognosis. The patient who had HIV died before the sensitivity test was performed, thereby showing the need for the implementation of faster drug susceptibility testing methods than the proportion method performed on Lowenstein-Jensen medium, which is the standard test used by state referral laboratories in Brazil[8].

These cases came from different sanitary districts in Manaus (east, south, and west), suggesting that the occurrence of MDR-TB cases is distributed uniformly. This is in agreement with the findings of a study on primary drug resistance for first-line TB treatment in Manaus that showed no difference in the distribution of cases sensitive to anti-TB drugs and those resistant to any of the drugs tested (i.e., rifampicin, streptomycin, isoniazid, and ethambutol) (Garrido: submitted for publication).

Knowledge of the epidemiological impact of HIV on the epidemic of resistant TB cases is limited, especially due to the high incidence of negative smear tests among patients co-infected with TB/HIV/AIDS. This aspect tends to preclude drug sensitivity testing, resulting in the late diagnosis of MDR-TB and higher mortality rates. Negative bacilloscopy in a fatal case suggests a lower rate of transmission. However, persons living with HIV can degenerate more quickly from the disease, and in locations with a high risk of exposure, such as hospitals, may transmit MDR-TB to other patients, thereby leading to further outbreaks[7].

Of the 3 MDR-TB patients mentioned in this study, only 1 was investigated for MDR-TB by the health center treating him. This was

due to the persistence of positive smear tests into the fifth month of treatment. In this center, there is a project funded by the United States Agency for the International Development/Pan American Health Organization for the implementation of the Stop TB Strategy[9], demonstrating the importance of the presence of committed and well-trained professionals. This patient presented with HIV/MDR-TB co-infection with resistance to the 4 main drugs used for TB treatment. The first case was apparently cured after 6 months of treatment and he was released from treatment because of a negative sputum smear. Given the discrepancy between this result and the sensitivity test done as part of this study, a re-evaluation was made. The culture confirmed the presence of *M. tuberculosis* and the chest X-ray showed a small, inflammatory lesion. Without the culture, this discreet clinical condition would have gone undetected and been a source of MDR-TB transmission during the months or even years before being diagnosed.

Recent research[4,5] (Garrido: submitted for publication) shows that contact with TB patients (in the same household, neighborhood, workplace, or hospital) is an important risk factor that requires investigation for MDR-TB at the beginning of treatment. Therefore, sputum culture, strain identification, and sensitivity testing should all be included in the list of priorities of the National Tuberculosis Control Program in order to break the chain of transmission[10]. In addition, the possibility of substituting the proportion method on Lowenstein-Jensen medium with more modern and faster techniques such as microscopic observation drug susceptibility should be urgently evaluated[11].

The cases presented in this study show the difficulties in investigating MDR-TB in basic health centers where this type of screening among new TB cases is not yet a standard procedure. This constitutes an emerging and serious public health problem. In addition, the tools commonly used for investigation require a long wait for the results. Faster, low-cost methods that make possible the adequate treatment of patients and avoid the propagation of resistant strains of *M. tuberculosis* are needed.

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