Case report

New strain multidrug resistant tuberculosis G24767 in Puerto Rico: Old disease a continuous threat

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ABSTRACT

Multidrug resistant tuberculosis (MDR-TB) is defined as a *Mycobacterium tuberculosis* strain resistant to two or more first-line anti-tuberculous drugs. Tuberculosis (TB) is a global threat to society despite improvement in therapy as it continues to be an economic burden especially in underdeveloped countries. The downfall of global economics and growing travel destinations in developing countries has escalade the exposure of organism not previously encountered in industrialized nations. Most cases of MDR-TB are reported on immunosuppressed patients with risk factors and from endemic areas. Nevertheless new strains with higher transmission degree are emerging as a threat in patients who have low risk factors for the development of MDR-TB.

1. Introduction

Multidrug resistance is defined as resistance of *Mycobacterium tuberculosis* of two or more first-line anti-tuberculous drugs that include isoniazid and rifampicin [1]. The most recent estimates suggest that globally there were about 489,000 case of multidrug-resistant TB [2]. Multidrug-resistance can be classified as primary or acquired [3]. Primary is defined as resistance in patients never been exposed to anti-tuberculous drugs treatment, whereas acquired resistance occurs in patients with prior exposure to anti-tuberculous drugs for at least one month and in those with treatment failures and relapses [3]. Before the early 1990s multidrug-resistant tuberculosis was not a mayor public health problem [4]. Interestingly, multi-drug resistance started appearing in patients with *M. tuberculosis* infection soon after the introduction of effective anti-tuberculous drugs [5].

Factors that predispose a patient to the development of multidrug-resistant tuberculosis include incomplete or inadequate treatment, failure to identify pre-existing resistance and failure to identify an appropriate adherence to treatment. Factors favoring the spread of tuberculosis, include increasing high-risk groups, the elderly, prisoners, immigrants and drug addicts [1]. Certain host genetic factors and coexistent HIV infection may also predispose to the development of multidrug-resistant tuberculosis [1].

The patient presented in this case was diagnosed at first with susceptible TB and was treated with first line anti-tuberculous drugs with good clinical response. Unexpectedly, during the course of treatment was found positive for MDR-TB. The initial culture of *Mycobacterium tuberculosis* did not exhibit any resistance to anti-tuberculous drugs, the patient is an immunocompetent host and treatment fulfilled the standards of care including proper adherence. Moreover, the patient had three negative sputum samples for acid-fast bacilli (AFB) and cultures during initial treatment. Patient was retested due to recurrence of symptoms and positive sputum for AFB smear and cultures lead to the genomic study of the organism. Results were consistent with a new strain MDR-TB not reported in the United States of America or the Caribbean. In 2014, the World Health Organization (WHO) reported 40 cases tested for suspected MDR-TB in Puerto Rico and only our case was confirmed to be MDR-TB [6].

2. Case presentation

We present the case of a 59-year-old male patient with past medical history of Diabetes Mellitus type 2 who developed

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progressive fatigue, shortness of breath and dry cough by the end of 2012. Within the next 7 months patient had worsening of symptoms with rapid weight loss of 55kg (121bs) associated fever, chills, night sweat, loss of appetite and relentless weakness. Patient had traveled only to Ecuador for vacation with his family in 2010. During this travel he denied exposure to sick contacts or crowded household conditions. A chest x-ray and PPD skin test was performed by his primary care physician for the initial evaluation of symptoms. The PPD revealed no skin induration. Chest x-ray showed multiple pulmonary nodules with no obvious cavitary lesion. Patient was referred to a pulmonary specialist for further evaluation. He underwent bronchoscopy that resulted inconclusive and the patient has lost to follow-up.

In mid-2013, because of worsening of his symptoms as described above he returned to the pulmonary disease specialist who repeated the bronchoscopy due to suspected malignancy vs. infectious process. Samples from the bronchoalveolar lavage had positive AFB smear, with positive culture growth for *M. tuberculosis*. Initial culture resulted pansensitive for TB. Other studies were remarkable for an indeterminate Quantiferon-TB Gold test (see Table 1), chest x-ray with right upper lung opacity and chest CT scan showing right upper lobe consolidate with central cavitation (see Figs. 1 and 2). He was placed on airborne isolation and started in 4 anti-tuberculous drugs regimen including isoniazid, pyrazinamide, ethambutol, and rifampin. After 36 days of treatment and 3 negative sputum samples for AFB smear the patient was removed from negative pressure room, airborne precaution and discharged home.

The patient was followed by the Department of Health (TB office) as outpatient with Direct Observed Therapy (DOT). Two months after been discharged form hospital and while still on TB treatment symptoms reappeared. For this reason patient was readmitted and repeated sputum cultures for *M. tuberculosis* were done on January 2014. Samples sent to the Centers of Disease Control (CDC) found to have multidrug resistant tuberculosis with resistance to isoniazid, rifampin, ethambutol and streptomycin. Genotype G24767 revealed the first of its kind genomic sequence not classified in the known cluster of Puerto Rico nor in the United States Population. The patient was hospitalized and started on second line anti-tuberculous drugs which included linezolid, levofloxacin, amikacin and cycloserine. The patient remained in hospital isolated for 46 days until 3 negative sputum for AFB smear were reported, but had to continue on at least three effective drugs and one injectable after culture conversion. The patient has at this point completed the 18 months after culture conversion, is symptom free and has gained all his lost weight.

3. Discussion

Multidrug-resistant tuberculosis is defined as disease caused by

Table 1
Laboratories.

Absolute CD4 helper	500
% CD 4	55.5
Absolute CD8	95
% CD 8	10.5
CD4/CD8	5.29
HIV	Non-reactive
IgA	881
IgM	104
IgG	2069
Quant TB Ag	0.87
Quant Nil	0.14
Quant TB Gold	Indeterminate

Fig. 1. Chest x-ray posterior-anterior view shows right upper lung opacity.
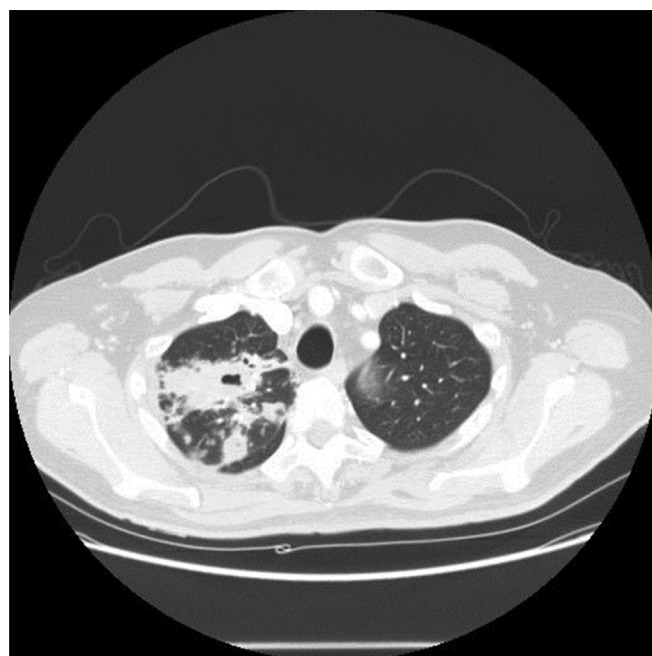

Fig. 2. Chest CT scan shows right upper lobe consolidate with central cavitation.

strains of *Mycobacterium tuberculosis* that are resistant to both first line anti-tuberculous drugs isoniazid and rifampicin. MDR-TB are serious threats to the progress that has been made in the control of tuberculosis worldwide over the past decade [7]. Statistical data has shown more than 400,000 cases of MDR-TB worldwide with a mortality ratio of 30 per 100 affected individuals. This means that every day there are about 400 deaths related to MDR-TB [8,9]. Globally, in 2014 the WHO reported an estimate of 190,000 death related to MDR-TB [10]. The highest proportions of MDR-TB cases, and the most severe drug-resistance patterns, appear in the countries of the former Soviet Union [7]. High prevalence among new cases were found in China, and Israel as well [1]. This alarming prevalence of resistance could be attributed to poor TB control by deficient use of national guidelines, immigration of patients from areas of high resistance and outbreak of resistant disease [1].

There are many potential mechanisms for the development of drug resistance attributed to *M. tuberculosis*. The term 'primary' is resistance in a new patient that has never been exposed to anti-tuberculous drugs and 'acquired' is resistance in a previously treated patient [11]. The main causes of acquired resistance are poor patient management, non-adherence to the prescribed regimen, inadequate national program or some combination of these three [11]. The most powerful predictor for MDR-TB is a history of previous treatment for TB [1,11]. However, another less common factors for primary resistance is host predisposition as seen in HIV-positive patients, particularly to rifampin [12].

The diagnosis of MDR-TB is made by sensitivity tests showing resistance to isoniazid and rifampicin. Three conventional methods are available for sensitivity; the absolute concentration method, resistance ratio method, and the proportion method [1]. These conventional methods requires up to 6–8 week for sensitivity results to be available. Newer molecular methods are currently available with faster sensitivity results ranging from 48hr (gene assay system) and 10 days (radiometric methods). These newer methods are not readily available in all laboratories [1].

In terms of management, it is important to recognize that MDR-TB curable rates are low and may be fatal. The management involves a complicated treatment regimen that requires trained and experienced persons because inappropriate management can have life-threatening results [13]. When suspected MDR-TB either by epidemiologic or history information, sputum samples must be send for culture and sensitivity testing [1]. Empirical regimens employing second line reserve drugs must be initiated pending sputum culture report as recommended by the American Thoracic Society (ATS), CDC, Infectious Diseases Society of America (IDSA) or WHO treatment regimen [14]. Further MDR-TB therapy will depend on sensitivity report. The national guidelines also states that a single drug should never be added to a failing regimen. Furthermore, when initiating, at least three previously unused drugs must be employed to which there is in vitro susceptibility [14]. MDR-TB treatment is based in the use of second line drugs. DOT plays also an important role in the control of MDR-TB. This practice not only aims to cure the patient but also to reduce the risk of further spreading and resistance ensuring treatment compliance by supervised administration of drugs [11]. Patients receiving therapy for MDR-TB must be closely followed up. Response to treatment should be assess by clinical, radiological and microbiological parameters. Likewise, attention must be focused on periodic monitoring for adverse drug reactions [1].

We have presented an interesting but at the same time alarming case of a new strain MDR-TB G24767 genomic pattern resistant to first line drugs (isoniazid, rifampin and ethambutol) and borderline secondary drugs (streptomycin) in a patient who was otherwise healthy. The only risk factor in our patient for MDR-TB was current use of anti-tuberculosis drugs. The patient received first line treatment according to the national guidelines for susceptible TB and still became infected with a new strain MDR-TB while completing therapy. Then, is there a genetic factor involved with new adaptive capacity for such fast mutation in *M. tuberculosis* even with the appropriate treatment regimen or it is just a new era of MDR-TB? Whichever the reason is, this raise a concern for a serious threat. TB is an old disease known to be a major public health issue for decades. For this reason we must create awareness among health care professionals of this existing fact, this way all new cases of MDR-TB can be notified for genomic sequence and immunogenicity studies to understand virulence and drug resistance. Similarly, all cases must be managed appropriately to reduce spreading, mortality rates, and more resistance.

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