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Extensively Drug-Resistant Tuberculosis: Report and Literature Review on Two Cases Requiring Prolonged Treatment

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Case series
Patient: Female, 28 • Male, 20
Final Diagnosis: Extensively drug-resistant tuberculosis
Symptoms: Cough productive • dyspnea • hemoptysis • respiratory failure • weight loss
Medication: —
Clinical Procedure: —
Specialty: Pulmonology

Objective: Unusual clinical course
Background: Extensively drug-resistant tuberculosis (XDR-TB) is a global problem due to the high morbidity and mortality it causes. Peru is one of the countries with the highest numbers of cases of XDR-TB, which increase every year.
Case Report: We present the case of two siblings who developed XDR-TB, underwent surgery twice, and were in individualized treatment for more than 6 years. Finally they achieved remission of symptoms, despite not having standardized treatment schemes during their diagnosis period.
Conclusions: Extensively drug-resistant tuberculosis can be cured with a treatment that involves both medical care and patient actions to achieve remission of the disease.

MeSH Keywords: Extensively Drug-Resistant Tuberculosis • Mycobacterium tuberculosis • Tuberculosis, Multidrug-Resistant

Full-text PDF: http://www.amjcaserep.com/abstract/index/idArt/900001

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Background

Tuberculosis (TB) is an infectious, contagious disease that is considered to be a major public health issue worldwide. In 2014, there were 9.6 million cases of people with TB, and 1.5 million people died because of it; 0.4 million of these people were HIV positive. TB is globally spread; nevertheless, the incidence of the disease has decreased in all six World Health Organization (WHO) regions, and the related Millennium Development Goal has been achieved in 16 of the 22 high-burden countries. According to the WHO, in 2014 Peru reported an incidence and mortality of 120 and 8 per 100,000 people, respectively [1].

Nowadays, the biggest concern, locally and internationally, is the rise of the multidrug-resistant tuberculosis (MDR-TB) and the extensively drug-resistant tuberculosis (XDR-TB) cases. The first type can be defined as a strain resistant to isoniazid (H) and rifampicin (R), while the second type has the criteria of MDR plus resistance to any fluoroquinolone and at least one intravenous drug of the second line: amikacin (Amk), kanamycin (Km), or capreomycin (Cm). XDR-TB has been reported in 105 different countries and is estimated that 10% of these are MDR-TB [1,2]. Peru reported one of the first cases of XDR-TB in 1999 [3], and from 1999 to 2013, 557 cases have been reported, with 79% corresponding to Lima [4].(3, 4) Additionally, coinfection with XDR-TB and HIV worsens the prognosis of the patients with this condition, increasing the mortality [5].

On the other hand, individualized treatment (IT) is an efficient approach to cure the disease, with the use of sensitivity tests and 5 different groups of drugs based on efficiency and clinical experience [6,7]. Additionally, surgical treatment of patients with resistant strains has an important role as a complementary treatment, showing high rates of success [8]. We present two patients with MDR-TB that evolved to XDR-TB who received individualized treatment for 6 years and underwent surgery 2 times as a complementary treatment.

Case Report

We present the case of two siblings, both diagnosed with XDR-TB, from Villa El Salvador, Lima, with an overcrowded home, MDR-TB contacts, and a poverty background.

Case 1

The first case is a female patient diagnosed with TB at 28-years-old with 2 MDR-TB contacts in her home. She presented with cough with expectoration, hemoptysis, consistent weight loss, and a body mass index (BMI) of 25.8 kg/m^2 as initial symptoms. The pulmonary examination evidenced forced breathing and crackles in the base of the left lung. The direct sputum bacilloscopy (SB) and microbiological cultures evidenced positive results (+++). Hence, scheme 1 was started, which was composed of H, R, pyrazinamide (Z), and ethambutol (E), until the fifth month of treatment, when the drug-susceptibility test (DST) showed a resistance to all drugs in scheme 1. At this point she was diagnosed with MDR-TB. Therefore, after having prescribed the standardized treatment for four months, failure was declared (Table 1).

The standardized treatment was suspended and she received only isoniazid for 5 months, until the response for the approbation of individualized treatment (IT) from the Reassessment of Intermediate Treatment Committee (RITC) was received (Figure 1). After that, she was diagnosed with XDR-TB and IT was started with capreomycin, ciprofloxacin, para-aminosalicylic acid, cycloserine, ethionamide, clofazimine, and amoxicillin/clavulanate. All of these drugs were administered until the 87th month after TB diagnosis, with the exception of clofazimine due to presence of an adverse anti-TB drug reaction (AADR). Later in the treatment moxifloxacin was added (Figure 1). In addition, a pulmonary radiography taken one month prior to IT showed the presence of caves, fibrous tracts, and alveolar infiltrates. After 14 months of the diagnosis, IT was started, and after two months she presented with nausea, vomiting, earache, diarrhea, hyporexia, gastritis, and enterocolitis as moderate AADRs.

After 42 months of diagnosis, she underwent cuneiform lung resection where chronic necrotizing pneumonitis and scar areas with fibrous pulmonary hemorrhage calcifications were found. A spirometry prior to surgery indicated a moderate restrictive pattern, but all the former tests showed a severe degree. Subsequently, a left upper lobectomy was performed 26 months after the first surgery, where pleural fibrosis was added to the previous diagnosis (Table 1).

At 52 months of IT, she had a negative SB and microbiological culture. The patient was declared cured in the 70th month of IT and 84 months after the initial diagnosis, but received IT for 73 months. Evaluations by other specialists mentioned that she had a persevering-stubborn personality and a dominant-reflective temperament. Because of those traits, she continually persisted in receiving her treatment until the resolution of the disease (Figure 2).

Case 2

The second case is a male patient diagnosed with TB at 20-years-old; he was a student with moderate gastritis and a history of 3 contacts with MDR-TB at home. The initial symptoms were cough with expectoration, hemoptysis, respiratory failure, hyporexia, dyspnea, and weight loss, with a BMI of

Table 1. Demographic and treatment data for two patients with XDR-TB treated with individualized therapy.

	Patient 1	Patient 2
Age in years at diagnosis/sex	29/female	20/male
Regimens received (time)	Category 1 anti-TB regimen (5 m) H, R, E, Z Category 3 anti-MDR-TB regimen (4 m) E, Z, K, Cipx, Eth, Cs, PAS Individualized regimen (74 m) Cp, Cipx, Mx, PAS, Cs, Eth, Clf, Amc	Category 1 anti-TB regimen (21 d) H, R, E, Z Empiric/individualized regimen (77 m) Amk, Cipx, Ofx, Cs, PAS, Clf, Amc
Drugs used for XDR- TB	After 14 months of TB diagnosis Cp, Cipx, Mx, PAS, Cs, Eth, Clf, Amc	After 2 months of TB diagnosis H, Amk, Cp, Cipx, Mx, Ofx, PAS, Cs, Clf, Amc, Clr
Drug resistance	After 9 months of TB diagnosis H, R, E, Z, Km, S	After 2 months of TB diagnosis H, R, Z, E, Km, Amk, Eth, Clr After 7 months of TB diagnosis H, R, Z, E, Km, Amk, Eth, Cipx, Clr
Surgeries (months after TB diagnosis/ technique)	42/Segment 2 wedge resection of the left upper lobe 68/Left upper lobectomy	37/Right upper lobectomy 61/Wedge resection of the lung
Spirometry/months after TB diagnosis	Severe restrictive pattern/64	Severe restrictive pattern/14 Moderate restrictive pattern/59

H – isoniazid; R – rifampicin; Z – pyrazinamide; E – ethambutol; S – streptomycin; Km – kanamycin; Amk – amikacin; Cp – capreomycin; Cipx – ciprofloxacin; Mx – moxifloxacin; Ofx – ofloxacin; PAS – para-aminosalicylic acid; Cs – cycloserine; Eth – ethionamide; Clf – clofazimine; Amc – amoxicillin/clavulanate; Clr – clarithromycin.

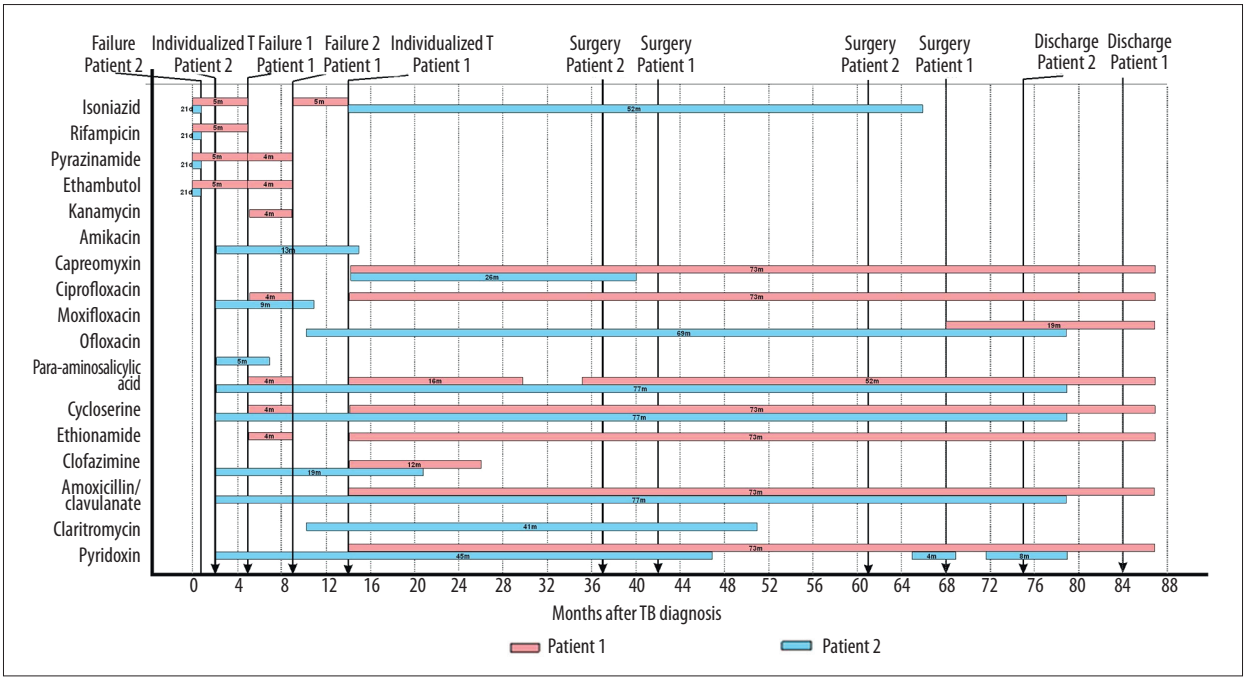

Figure 1. Time of administration of drugs during the evolution of the patients' disease.

23 kg/m^2. Pulmonary examination showed wheezing and crackles in both lungs, with right predominance. SB and microbiological culture were performed with positive results (+++). Treatment was started with scheme 1, but after 21 days, failure was declared and a MDR-TB diagnosis was established. He went one month without treatment, until the response

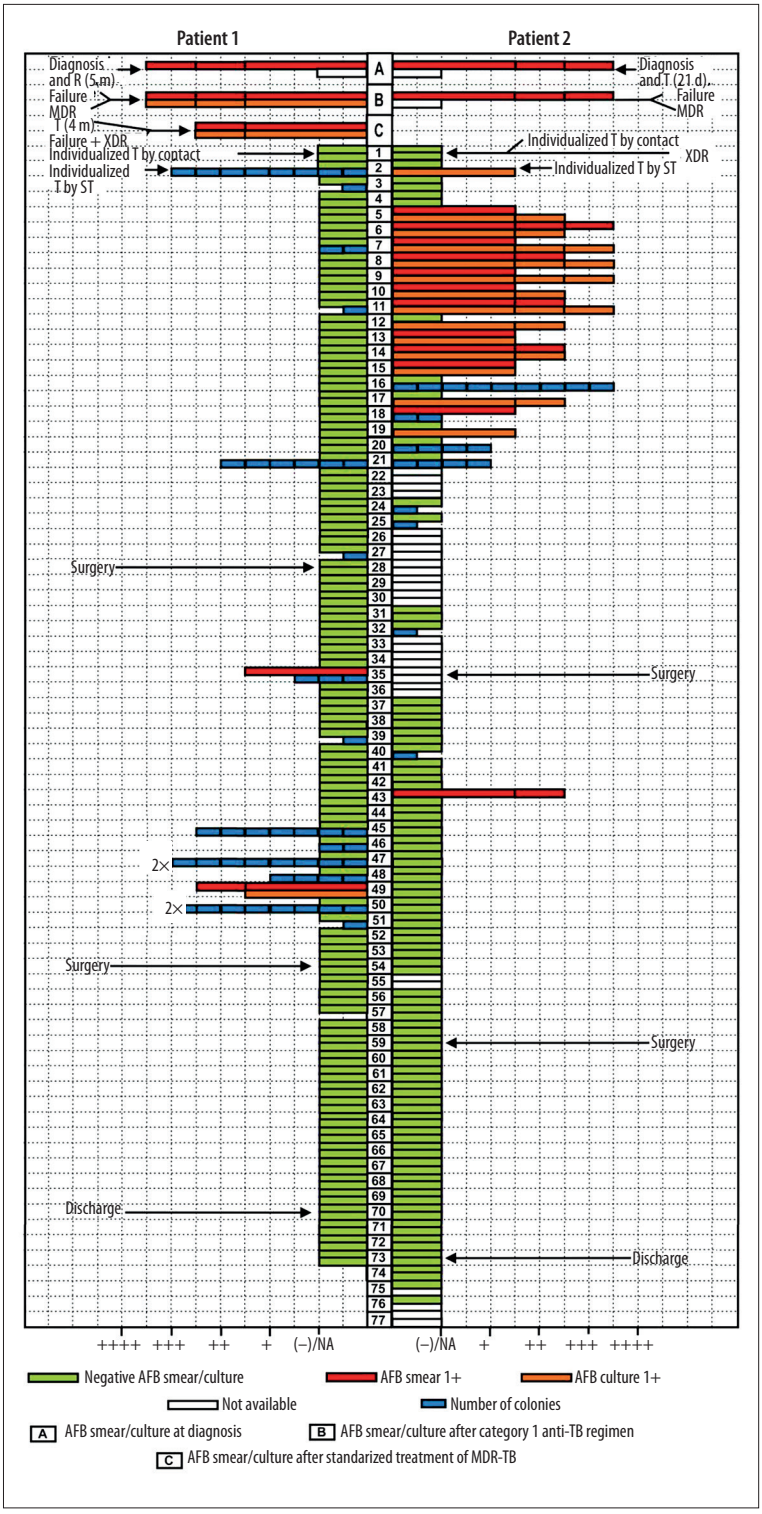

Figure 2. Results of acid-fast bacilli (AFB) smears and cultures from the patients according to month of individualized treatment.

from the RITC. Two months after diagnosis, IT was started due to the MDR-TB contact he had with the following drugs, amikacin, ciprofloxacin, ofloxacin, para-aminosalicylic acid, cycloserine, clofazimine, and amoxicillin/clavulanate. When the DST arrived, he was catalogued as a XDR-TB patient and continued with the same scheme. However, of the drugs previously mentioned, only the para-aminosalicylic acid, cycloserine, and amoxicillin/clavulanate remained until the end of the treatment, with the addition of moxifloxacin. It is worth mentioning that no AADRs developed (Table 1 and Figure 1).

After 21 months of IT, surgery was denied because of the bilateral commitment, and 3 months later his condition was declared hopeless and the medication was removed. But after the insistence of the patient and his family, and the absence of AADRs, the treatment was restarted. At 35 months of IT, a right superior lobectomy was performed. Adhesions, fibrosis on the right upper lobe, and bullae in segment 6 were found. Then, in the 59th month of IT, a second surgery on the left inferior lobe was performed due to a cavitation in this lobe. Chronic necrotizing pneumonitis complicated with cavitation was found. The SB and microbiological cultures became negative in the 53th month, so he was discharged at month 73 of IT or month 75 after initial diagnosis. He received IT for 77 months. Psychologically he had low self-esteem, feelings of inferiority, anxiety, and impulsivity traits, and was referred to psychiatry for insomnia and anxiety. In spite of this, the social support he received gave him the opportunity to continue the treatment until remission of the disease, which was a cornerstone for his maintenance of the therapy (Figure 2).

Both patients lived in the same home, shared bedrooms, and spent a great amount of their time together, as well as with their other relatives in the home. In relation to the disease, they underwent surgery two times and received IT for more than 6 years. In case 2, the patient and the family demanded to continue treatment, despite his condition having been declared hopeless. In the end, the patients recovered from the disease and their clinical condition normalized.

Discussion

Socio-demographic and clinical data

The treatment and management of XDR-TB are worldwide concerns [3]. Peru reports more cases of XDR-TB each year. For example, in 2013 there were 77 cases, 90% of them being from Lima and Callao [4]. In response, The WHO Global Task Force on XDR-TB recommends measures of control and prevention for its management [1]. In the cases presented in this article, the female patient got infected in her home and 6 months after her diagnosis, she infected her brother. This shows that the isolation and intradomicilliary quarantine alone cannot stop its spread [9–11]. A more rigorous and controlled isolation is necessary in order to stop the spread of these highly resistant strains, accompanied with more surveillance and support of the health care system.

There are several risk factors for TB infection, such as a suppressed immune system, the lifestyle in Latin America, poverty, substance abuse, and occupational exposure to TB [12]. Additionally, a study states that one important risk factor for acquiring MDR-TB is a history of previous TB treatment [13]. In contrast, for XDR-TB, the risk factors are family history of TB, socioeconomic status, co-morbidities, and previous intake of second-line injectable drugs [14]; while the risk factors for mortality from drug-resistant tuberculosis are previous TB episodes, diabetes history, education level, and HIV infection [15]. Both patients had a positive family history of MDR-TB contacts living in the same house. This was the only risk factor identified and necessary to develop a more highly resistant strain. Hence, we highlight its importance in the presence of XDR-TB.

On the other hand, in 2014, 12% of patients with TB were HIV positive. The association of XDR-TB with HIV is conducive to high mortality, since 98% of these patients die with an average survival of 16 days [1,6]. However, neither of the two patients described in this report was HIV positive, favoring the prognosis and evolution of the disease. On the other hand, the bacillus Calmette-Guérin (BCG) vaccine produces immunity for up to 2 years, and both the innate and acquired immunity decrease over a few years; this vaccine also protects against severe forms of TB such as meningeal and miliary from 75% to 86% [16,17]. Both patients were vaccinated; they developed the disease, but not severe forms of TB.

Treatment and monitoring

In the year 2002 the detection of MDR/XDR-TB was difficult and the availability of second-line drugs was limited; hence, groups of drugs with higher profiles of toxicity were used for a long time. This caused an increased percentage of adverse effects, especially in patients with good adherence [18]. Nowadays, the most common AADRs among MDR-TB patients are liver and kidney function damage, leucopenia, rash, decreased hearing, and psychosis, which are present in approximately 35% of the patients [19,20]. In addition, a systematic review of 1389 articles mentioned that the risk factors for the AADRs were age greater than 60 years, alcoholism, anemia, and sodium, iron, and albumin deficiency [21]. Interestingly, only the female patient evidenced AADRs, and they were not the most frequent ones, according to the international evidence. Also, she presented with a darkening of the skin during the treatment, which is a known consequence of clofazimine [22–24]. Moreover, AADR events are more frequent in the female population, as was shown in the first case [18]. The patient received three different treatment schemes, which led to a greater exposure to the drugs, in comparison to the second case.

According to the current national guideline of Peru, the therapy schemes should be developed by the treating physician of the Specialized Unit in Tuberculosis and be reviewed by the National Committee of Evaluations of Retreat to start treatment immediately based on a DST, without the use of other previous treatment schemes. Thus in the reported cases, due to the lack of information and the difficulty accessing the

DST, proper management could not be given. This guideline states that XDR-TB patients should start treatment within the mentioned Unit, at least for 2 months, and receive parenteral drugs by subcutaneous catheters for a long-term period [25]. However, both patients were not hospitalized; they stayed at home without the correct care measures, with lack of supplies and late onset of IT. These conditions prolonged the onset of treatment and increased the risk of infection among the family members.

Both patients started therapy with the first-line agents, but after the treatment failure and the detection of the drug-resistant strains, these were discontinued and the second-line agents were given. One of these agents is injectable fluoroquinolones. A meta-analysis states that this drug increases 3-fold the probability of cure from XDR-TB [26]. Also, a meta-analysis provided evidence that treatment success was associated with at least six drugs being used in the therapy [27]. Both patients were treated with the injectable fluoroquinolones and were given more than six drugs; thus, these combinations contributed to the remission of the disease. In addition, the case patients received a third-line agent, clofazimine. A retrospective cohort study mentioned that this drug is effective in culture conversion [28]. Both case subjects received it, but it was discontinued due to onset of AADRs. Therefore, its contribution to the remission of the disease was limited. After the sputum conversion, the patients received their own IT with any intercurrence, even after the discharge of the patients, which means a positive effect of the medical therapy.

Wang et al. published a prospective study where the importance of the different drug-resistant strains was addressed. Therefore, a different pattern of resistance to specific drugs, depending of the strain, was identified [2]. In our experience, the specific type of mycobacterium-resistant strain could not be identified, and a classification could not be made. Nevertheless, both patients shared common drugs as medical therapy; hence, the infectious bacteria strain could have been the same in both of them, facilitating the treatment. In order to corroborate this, there is a need for more research in this field.

The emergence and global spread of XDR-TB have led to the reexamination of surgery as a possible adjuvant therapy [8]. There are several studies that point out that surgical resection has an important role in therapeutic success [8,29,30]. According to a recent review, there are two main indications for these types of procedures: the first one is the persistence of the disease after completing the medical treatment, and the second is the patient who has a negative culture after completing the treatment, but who has localized cavitary disease or bronchiectasis [31]. Also, when surgical treatment is combined with direct observation therapy (DOT) for MDR-TB, it can enable favorable evolution of the disease compared to only drug therapy when applied to patients with resectable pulmonary disease, with an overall rate of favorable results from 18% to 75% with a median of 66% [32]. Both patients were operated on twice while they were receiving IT, and they managed to go through the therapy without any adverse outcome, which demonstrates the efficacy of this adjuvant treatment.

Results

The cure rate of XDR-TB not associated with HIV is 60% [33]. Of the 500,000 annual cases of MDR-TB registered worldwide, it is estimated that approximately 10% are XDR-TB. Both patients were diagnosed with MDR-TB in the year 2003, when the definition of XDR-TB did not exist, because it only came out in the year 2006 [34,35]. Therefore, the time they spent with the characteristics of XDR-TB was much longer. In spite of this, the treatment did not vary greatly, because they were already in IT. Moreover, the treatment for XDR-TB takes longer and has worse outcomes than the treatment for MDR-TB, requiring at least 24 months of IT. The extension of this period must be authorized by the Regional Committee of Retreatment Evaluation (RCRE) [25,26]. Our patients, who both had resistant strains of tuberculosis mycobacteria, received IT for 73 to 77 months, respectively, and were always evaluated by the RCRE, since they needed an extension of treatment until they managed to heal.

According to the national guideline, a patient is considered cured when, after completing the treatment, there is an absence of three or more positive cultures each month after the intensive phase, and when there is no evidence of failure. This last term is defined as the persistence of symptoms and positive laboratory results at the end of treatment or a permanent shift of at least two drugs due to failure of conversion at the end of the intensive phase, bacteriological reversal in the continuation phase once the results came out negative, evidence of further acquired resistance to quinolones or second-line therapy drugs, and AADRs [35]. Both patients showed several positive cultures, even after presenting negative serial cultures, which were evaluated by the RCRE to develop another treatment scheme.

One important feature of the treatment success was the family and social support the patients had. This key component has been identified as a way to improve the therapy in TB patients [36,37]. Moreover, a study showed that a higher percentage of the gross domestic product spent on social protection was inversely associated with tuberculosis prevalence, incidence, and mortality [38]. Since our patients had an important source of social support, this condition prevented a relapse. Thus, this strategy should also be implemented in the treatment of patients with drug-resistant strains.

Conclusions

In summary, this report presents the case of two siblings from Lima, Peru, diagnosed with XDR-TB, who required complex and prolonged treatment due to deficient management and a lack of information about this type of TB during the early years of treatment. Both case patients lived in the same house and had the support of each other and their relatives. Hence, we highlight the importance of social support, medical therapy, and adjuvant surgery in order to cure the disease. On the other hand, despite strictly following the specialist recommendations, the patients did not achieve favorable results; however, the perseverance, determination, and insistence of both siblings were the key to the successful resolution of the disease. In accordance with this, we suggest that with the current technological advances, a comprehensive assessment of each case of XDR-TB should be conducted, because some patients can achieve cure, even if few encouraging results are seen for a long period of time, as happened with the patients in this report. Thus, 7 years after having completed treatment, both patients are now in remission.

Statement

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