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Case Report

Situation of multidrug-resistant tuberculosis in the Czech Republic, unusual case study

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ABSTRACT

Multidrug-resistant tuberculosis has been a serious medical and epidemic problem all over the world. Management of patients suffering from multidrug-resistant tuberculosis is complicated and therapy is successful in 60–70% of cases only. Therapeutic strategies recommend the application of standardized or an individual treatment regimen based on the results of susceptibility drug tests for second-line antituberculous drugs. The case study describes treatment for multidrug-resistant tuberculosis with individual drug regimen adjusted according to the results of susceptibility tests. Although smear and culture negativity was reached, course of disease was changed in the seventh year of the individual regimen, the disease progressed and the patient died.

1. Introduction

New cases of tuberculosis (TB) in the world have increased during the last several years. The number of persons is expected to reach about 10 million in this time. TB is the leading cause of death from a curable infectious disease and nearly 2 million patients die yearly.[1] Drug resistance has become a major problem in the treatment of tuberculosis around the globe.[2] For multidrug-resistant TB (MDR TB) is characterised resistance at least to isoniazid and rifampicin which are the main antituberculosis drugs. MDR TB has been a serious problem among some countries of eastern Europe, Asia and Africa. The best way to prevent the acquisition of resistance is well-administered first-line treatment for susceptible TB cases. The Czech Republic with 10 millions inhabitants is situated in the centre of Europe. The incidence of TB is low. The number of reported TB new cases and relapses has continuously declined over the past years, from 1442 (14 per 100 000 population) in 2000 to 867 (9.8 per 100 000 population) in 2007. Incidence of MDR TB is about 2% of all TB cases for several years. The risk factors for resistance include previous treatment, inadequate chemotherapy, not directly observed treatment, shortage of antituberculosis drugs, and interruption of therapy. Drug resistance has developed very often because of the inappropriately or poorly implemented primary programs of tuberculosis control. These mistakes lead to the acquired resistance.[1] Resistance is caused by a genetic mutation. Resistant mutants to any single antibiotic occur readily at random in bacilli undergoing replication and may be selected for by not using the adequate combination of drugs. Ongoing transmission of established drug-resistant strains in a population is a significant source of new drug-resistant cases. Primary resistance occurs when patient is initially infected with a resistant organism. The important factor to stop transmission of MDR TB is quick identification of drug-resistant TB. Next step is early administration of adequate treatment regimen designed for MDR TB. Management of MDR TB is usually complicated and the main principles are arranged into five components. The first one is sustained political commitment with necessary legislation, TB control programme and facilitation to prevent emergence of more MDR TB cases. The second component is a rational case finding strategy with correct and timely diagnosis based on the quality assured culture and drug susceptibility tests. The next point deals with appropriate treatment strategies using second-line drugs in a standardized or an individual regimen. The fourth important component is insurance of uninterrupted supply of quality assured antituberculosis drugs. Recording and reporting system with defined patient categories and treatment outcomes concludes the main management principles.[3]

Treatment outcomes of MDR TB are successful in 60–70% of cases only.[4] Choice of optimal therapeutic strategy may be controversial because there are few directly comparable published protocols.[5] However, several general guidelines for therapy were already published.[6] Generally, the selection of an optimal regimen should be based on the analysis of the patient's drug history and the results of drug susceptibility tests for the first- and second-line drugs. Re-treatment regimens should always include two drugs the patient has not taken before.[7] Therapy is performed

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either on the standardized recommendation for the resistant forms of TB or on the individual treatment regimens. The second-line drugs are represented by aminoglycosides (capreomycin, kanamycin, amikacin), thioamides (ethionamid, prothionamide), fluoroquinolones (ofloxacin, ciprofloxacin), cycloserine, clofazimine, and para-aminosalicylic acid – PAS. The average daily dosage of aminoglycosides is 15 mg/kg. For thioamides it is 10–20 mg/kg. Recommended daily dosage of fluoroquinolones is 7.5–15 mg/kg. Optimal dosage of cycloserine is 10–20 mg/kg, clofazimine 100–200 mg and PAS 10–12 g. The second-line drugs are characterised by the less effect and more adverse reactions. A combination of 5–6 drugs offers the greatest chance of success.[3] Duration of MDR TB therapy is much longer than the treatment of the sensitive form of TB and should be last 18 months after the first negative culture. Surgery is considered for limited number of patients with localised cavity and good lung function.[8]

2. Case study

Patient, a 43-year-old white-male smoker, presented himself with elevated temperature and cough in year 1999. Epilepsy, liver disease, chronic obstructive pulmonary disease (COPD) and no evidence of drug use were mentioned in his anamnesis. A negative result of HIV status was found on testing. A chest X-ray showed infiltration on the left inferior lobe (Fig. 1). Patient was cured 6 months according to the category III as recommended by World Health Organization (WHO) in Guidelines for national programmes in second edition 1997 for new smear-negative pulmonary tuberculosis.[9] Patient received directly observed therapy with a regimen of isoniazid, rifampicin and pyrazinamid in the initial phase. For continuation phase isoniazid and rifampicin were used for 4 months also under direct observation with good patient's compliance. The sputum was smear and culture negative during the whole treatment period.

New pathological findings in the right middle and lower zone and left superior lobe were detected on regular control after 6 months of treatment on 2000. Sputum was culture positive for *Mycobacterium tuberculosis* (M.TB) and therefore the regimen was changed to unapplied drugs with the suspicion on resistant strain.

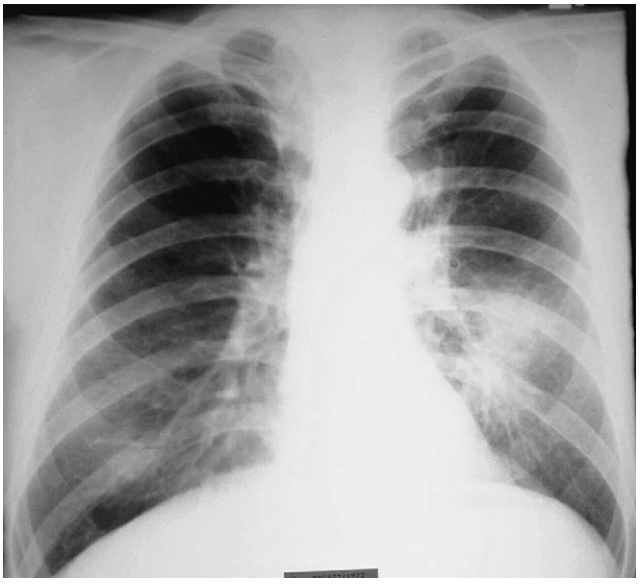

Fig. 1. Posteroanterior chest radiograph with infiltration on the left inferior lobe at the beginning of TB disease in 1999.

Combination of streptomycin, ethambutol, ethionamid and tarofloxacin was applied. Sputum sample was sent to the National Reference Laboratory for drug sensitivity testing. The method of minimal inhibitory concentration proved the presence of multidrug-resistant M.TB with resistance to rifampicin and isoniazid. The regimen was adjusted to combination of amikacin, ethambutol, ofloxacin, ethionamid and pyrazinamid. Amikacin was applied for 3 months without any adverse events and without elevation of creatinine values. The 3 months duration of daily therapy of aminoglycoside was recommended by WHO from year 1997. The patient was in a good clinical status for the following 6 months. Bacteriological investigations of sputum were repeated and positive culture findings were confirmed during second and third year of treatment without any significant changes on the chest X-ray. Because of the unfavourable bacteriological results, susceptibility tests were repeated in 2002 and confirmed resistance to ethambutol.

Therapy was adjusted again and combination of ofloxacin, ethionamid, pyrazinamid, and capreomycin was extended of sensitive drug cycloserine to ensure the favourable course and outcome of the therapy. The combination of all drugs was tolerated very well. Patients suffered from COPD and he was placed on bronchodilators. No interaction with antituberculous drugs was observed. Capreomycin was applied for 3 months only and therapy continued on regimen with remaining four drugs. Although patient was treated by combination of four sensitive drugs, the sputum started to be smear and culture positive intermittently in 2003–2005. Drug susceptibility tests were again repeated in year 2004 with the same resistance result as in 2002. On the chest X-ray bilateral infiltrations proved partial regression. The application of the regimen continued during 2006 and patient remained in the same clinical status. Sputum samples were examined weekly and they started to be smear and culture negative. Despite that the favourable bacteriological findings, the progression of infiltration on the chest X-ray was detected in 2006. During next several months the sputum samples and the clinical status of the patient changed to worse. He was tired, grew slim, suffering from dyspnoe, cough, sweating, and temperature. There were no signs of exacerbation of COPD, malignant disease or other underlying disease. The evidence of prolonged inflammation and progression of malnutrition increased and the chest X-ray proved bilateral worsening of infiltrates and cavities due to MDR TB (Fig. 2). Patient died due to the cardio respiratory failure after seven years of uninterrupted individualized treatment given under direct observation.

3. Discussion

The antimicrobial resistance is the threat for global public health that demands the international attention.[10] The main approaches to the identification of MRD-TB are the establishment of history of previous TB treatment and drug susceptibility tests.[6,11] Susceptibility tests for the first- and second-line drugs should always be performed for patients with possible treatment failure or relapse. This recommendation was followed also in this study case and susceptibility test confirmed multidrug resistance.

The monitoring of treatment efficiency is based on three indicators: 1. clinical response, 2. chest radiographs and 3. repeated sputum microscopy, culture and susceptibility testing.[5] Patient should be evaluated for symptoms and signs of tuberculosis, adherence to treatment and adverse reactions to the medications at least every month, sputum specimens for *Mycobacterium tuberculosis* smear and culture should also be obtained monthly. If cultures remain positive after 2–4 months of treatment, susceptibility tests should be repeated as it was done in this case. To finish the therapy successfully, the regimen should always continue for 18–24 months

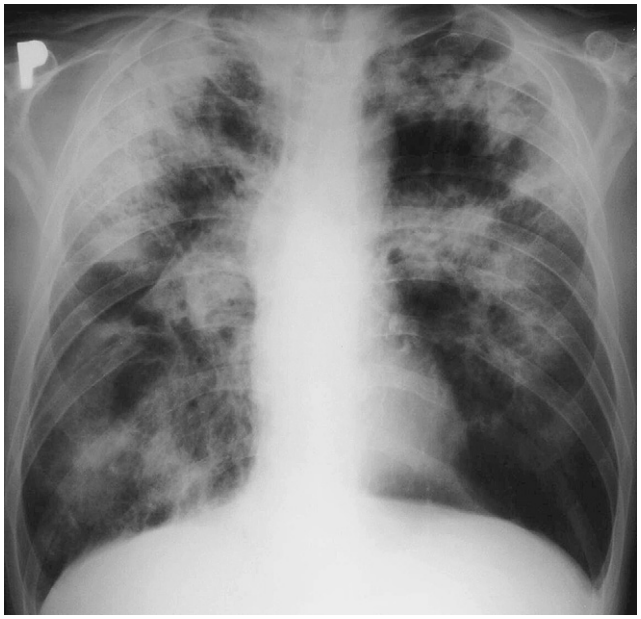

Fig. 2. Posteroanterior chest radiograph obtained two weeks before patient's death shows bilateral extensive infiltrations with cavities due to MDR TB in 2006.

after bacteriological smear and culture sputum conversion.[6,12] This, however, was not the case of the patient studied as the tests turned positive and the clinical status worsens.

Management of MDR TB is quite complicated. General guidelines were presented by Iseman and WHO including five essential components for every national TB control programme with detection and treatment of drug-resistant TB.[3,6] MDR TB is confirmed in patient whose infecting isolates are resistant in vitro to at least isoniazid and rifampicin. Treatment regimen is based on establishment of standardized or suitable individualized drug treatment. The individualized treatment regimen is based on the results of drug susceptibility tests of the specific strain, patient's treatment history and changes of the infecting strain during the treatment period. The therapy should be started in the hospital to permit observation of intolerance and to allow a change of a regimen. The recommended number of not previously used drugs for individual regimens varies in the literature. Three or four drugs are usually recommended.[6,12] The use of the second-line antituberculous drugs, which are more expensive, more toxic and less effective than the first-line drug, is required.[3,11] The therapy is adjusted and switched according to the laboratory results of resistance pattern, clinical deterioration and bacteriological findings of sputum samples.

Drug resistance is strongly associated with previous treatment and can develop in some cases in less than 1 month.[5] The probability of development of resistance to a drug increases with the length of time in has been administered. Evidence of bacteriological treatment failure during a period of regular drug administration is highly suggestive of drug resistance. In this patient the conversion from drug susceptible tuberculosis case to an MDR TB case is supposed. Second-line antibiotics have lower bactericidal activities compared with first-line ones and therefore the selection due to a reduced antibiotic pressure is faster. It could explain the changes of susceptibility patterns, increasing drug resistance and the final unfavourable outcome seen in this patient.

Generally, the results of medical therapy of MDR TB are not satisfactory and about 30% of treatment failure patients have poor prognosis. Favourable bacteriological response to chemotherapy usually occurs within 4 months.[13] In this case study the bacteriological conversion of sputum was found much later. The case study did not fulfil the criteria for surgery approach because of the bilateral pulmonary findings and poor lung function tests' parameters. The surgery was not used in his therapy. Duration of the treatment of MDR TB up to 3 years is quite difficult due to side-effects and often not very successful.[4] However, if the surgery is contraindicated, the drug treatment remains the only possibilities for the patient even the duration of therapy has been longer than 3 years. In this case was quite difficult to finish the therapy after 3 years because the patient was in good clinical condition and there was a hope for favourable outcome.

This study presents extremely prolonged course of MDR TB with 7 years period of directly observed individual treatment regimen. This regimen included use of several drugs that were changed according to the susceptibility tests during the therapy period. Drug susceptibility test was repeated with the aim to confirm the bacteriological resistance. The resistance pattern for isoniazid and rifampicin was once changed and extended of ethambutol. Its repeated version remained unchanged although bacteriological findings were permanent smear and culture positive. Despite that the transient improvement of the bacteriological samples was documented after six years of the therapy, the progression of the chest X-ray, smear and culture positive findings and the worsening of the clinical status were observed during the following months. There was found no other serious or malignant disease contributing to the progression of clinical, laboratory and radiological findings. The study documents that even seven years long uninterrupted individual treatment based on repeated susceptibility tests did not prevent patient from the exitus letalis.

Rapid identification of patients with MDR TB and effective treatment reduces costs and prevents the spread of infection.[14] MDR TB patients respond to treatment slowly and remain sputum smear and culture positive longer than other TB patients and they may infect more contacts. Therefore case finding strategy based on national TB programme with quality assured culture and drug susceptibility test is an excellent method of distinguishing MDR TB cases from others. These patients can be properly isolated and adequately treated.[3] MDR TB is associated with higher rates of failure and death than susceptible TB and is more difficult and expensive to treat. Health care systems should adopt and expand programs of TB control including in addition directly observed treatment, short course strategy of WHO, use of second-line drugs for therapy of MDR TB and reducing of further transmission.[2]

Conflict of interest statement

None of the authors have a conflict of interest to declare in relation to this work.

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