A CASE OF AN HIV-POSITIVE PATIENT CO-INFECTED WITH MULTIDRUG-RESISTANT TUBERCULOSIS

Nina Yancheva-Petrova[1], Vladimir Milanov[2], Dimitar Strashimirov[1], Dimitar Kostadinov[2]

[1]Department of Infectious Diseases, Parasitology and Tropical Medicine, Medical University – Sofia, Department of AIDS, Specialised Hospital for Active Treatment of Infectious and Parasitic Diseases „Prof. Iv. Kirov“, Sofia, Bulgaria
[2]Department of Pulmonary Diseases, Medical University – Sofia, Hospital for Pulmonary Diseases „St. Sophia“, Sofia, Bulgaria

ABSTRACT

Tuberculosis has a greater impact on morbidity and mortality in HIV-1-infected individuals than the rest of the opportunistic infections. We report a case of 57-year-old HIV-infected patient co-infected with multidrug- resistant tuberculosis (MDR-TB).

The patient`s leading clinical syndromes were fever, diarrhoea and weight loss. The meticulously performed laboratory investigations revealed severe immune suppression and high HIV viral load. Microbiological and parasitological tests confirmed the presence of two AIDS-defining conditions: disseminated candidiasis and cryptosporidiosis. Sputum smear microscopy for acid-fast bacilli was negative but sputum culture showed positive result for *Mycobacterium tuberculosis*. Drug susceptibility testing determined resistance to isoniazid and rifampicin (MDR-TB). The diagnosis was confirmed with Xpert-MTB/RIF PCR test. Treatment continued with second-line anti-TB drugs, together with antiretroviral therapy. Culture conversion was recorded in the first month. The outcome was reported as „cured“ after 16 months` therapy.

This case shows yet again that the clinical manifestation of tuberculosis in HIV-infected patients is very atypical. Multidrug-resistant tuberculosis requires prolonged treatment and represents therapeutic challenge because of the possibility of adverse drug reactions.

KEYWORDS:

HIV, tuberculosis (TB), multidrug-resistant TB (MDR-TB), atypical presentation, therapeutic challenge

ADDRESS FOR CORRESPONDENCE:

Nina Yancheva-Petrova, MD, PhD
17 Akademik Ivan Geshov Blvd.
Sofia, Bulgaria 1303
Phone: 00359878750904
Email: dr.yancheva@abv.bg

INTRODUCTION

One of the major risk factors for developing both drug-susceptible and drug-resistant tuberculosis (TB) is infection with the human immunodeficiency virus (HIV) (1, 2). It has been estimated that people living with HIV are 16-27 times more likely to develop TB than the general population (1, 2). Approximately 10 million people infected with HIV-1 worldwide are co-infected with *Mycobacterium tuberculosis*. In 2017, an estimated 920,000 people living with HIV worldwide fell ill with TB (1, 2). TB is the primary mortality cause in HIV-positive individuals, and that same year 390,000 deaths from HIV-associated TB were reported (1, 2). Recently, co-infection with the two pathogens has become more noticeable in Eastern Europe, including in Bulgaria (3, 4). There is a growing concern that HIV-1 enhances the spread of multidrug-resistant tuberculosis (MDR-TB) in these regions (3, 4). MDR-TB is 10 times more frequent in Eastern Europe than in Africa (4). Not only does HIV infection increase TB prevalence in general, but it may also be held accountable for the rise in the number of MDR-TB cases. These conditions require regular examination of HIV patients for *Mycobacterium tuberculosis* and monitoring of the patients with latent tuberculosis (5). Since drug-resistant TB is frequently linked to higher mortality rates in people living with HIV, the treatment of patients requires better integration of HIV and TB services in settings with a wide spread of HIV, and in all settings with a high prevalence of the HIV-TB co-infection. (6). The management of drug-resistant TB in

HIV-positive patients requires early diagnosis of the drug-resistant TB and HIV infections, timely commencement of relevant second-line anti-TB medications and antiretroviral treatment (ART), unwavering patient support and strict measures for infection control (6).

CASE PRESENTATION

We present a 57-year-old male who was diagnosed as HIV-positive in March 2017. The patient was hospitalised in the Department of Infectious Diseases at the Multiprofile Hospital for Active Treatment in the city of Burgas with the following complaints and symptoms: watery diarrhoea, fever, night sweats and weight loss. Laboratory investigations revealed anaemia and leucopenia. Microbiological examination of faeces found no bacterial agent. The patient was tested for HIV and the result was positive. He was transferred to the Department of AIDS at the Specialised Hospital for Active Treatment of Infectious and Parasitic Diseases in Sofia. Meticulously performed laboratory tests revealed severe immune suppression (CD4 count of 16 cells/μl; CD8 count of 90 cells/μl; CD4/CD8 ratio of 0.18) and a high HIV viral load of 237,986 copies/μl. Confirmation of HIV diagnosis and quantitative PCR for viral load were performed in the National Reference Laboratory of HIV at the National Centre of Infectious and Parasitic Diseases (NCIPD), Sofia. The immune status study was performed in the National Reference Laboratory of Immunology at the NCIPD. Microbiological and parasitological examination of stool samples found *Candida albicans* and *Cryptosporidium* spp. Sputum smear microscopy for acid-fast bacilli was negative. Chest X-ray showed evidence of interstitial infiltrates in the right lung (Fig. 1).

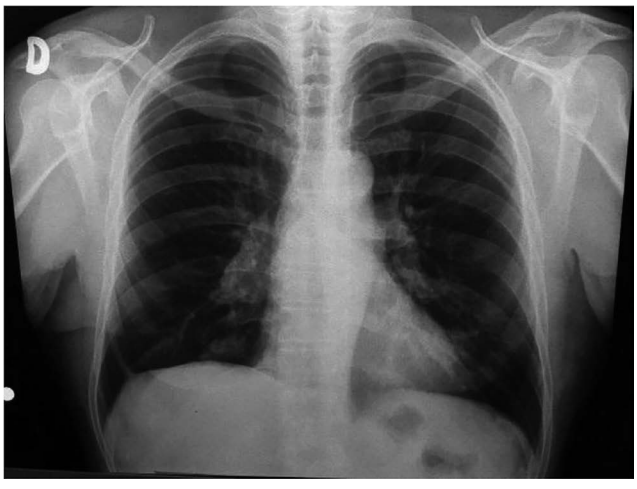

Figure 1. Chest X-ray of the patient on the day of hospitalisation in the Department of AIDS.

The patient was treated effectively for cryptosporidiosis (with azithromycin) and candidiasis (with fluconazole) together with initiation of combined antiretroviral therapy (emtricitabine/tenofovir disoproxil fumarate 445 mg + darunavir/ritonavir 900 mg). However, sputum culture on liquid media (MGIT, Mycobacterial Growth Indicator Tube) showed positive result for *Mycobacterium tuberculosis* after 4 weeks` cultivation.

Standard anti-tuberculosis therapy comprising rifampicin, isoniazid, pyrazinamide and ethambutol was assigned to the patient in the beginning of July 2017, but 2 weeks later phenotypic drug susceptibility testing (DST) by BACTEC MGIT 960 revealed MDR-TB with resistance to both rifampicin and isoniazid, combined with resistance to streptomycin and sensitivity to ethambutol. DST to second-line anti-TB drugs found sensitivity to amikacin (Am), kanamycin (Km), capreomycin (Cm), ofloxacin (Ofx), moxifloxacin (Mfx) and linezolid (Lzd). All DSTs were conducted in the National TB Reference Laboratory (NRL-TB) at the NCIPD. The diagnosis was confirmed by Xpert MTB/RIF (MTB detected, RIF resistance detected).

After receiving the results confirming the presence of MDR-TB, the patient was immediately referred

for hospitalisation in the Hospital for Pulmonary Diseases – Gabrovo, where all confirmed MDR-TB patients are treated and MDR-TB consilium is commenced as inpatient treatment during the intensive phase.

On 14 July 2017 together with ART was started treatment regimen containing second-line anti-TB drugs, including kanamycin (Km) 750 mg, levofloxacin (Lfx) 500 mg, prothionamide (Pto) 500 mg, pyrazinamide (Z) 1500 mg and ethambutol (E) 750 mg, based on body weight (65 kg at the beginning of treatment) and DST results. The baseline audiometry was normal.

Elevated levels of total and conjugated bilirubin, AST and ALT in the blood were registered 24 days after the initiation of treatment, which caused a temporary exclusion of Z, Lfx and Pto, and inclusion of cycloserine (Cs) 500 mg and hepatoprotective therapy. Administration of Lfx was resumed after 10 days with a daily dose increased to 750 mg due to weight gain. On 11 October 2017 bedaquiline (Sirturo) was added in the following dosages: 400 mg daily dose for 14 days and 200 mg 3 times a week for 22 weeks.

After initial presentation of hepatotoxicity, there were no other adverse drug reactions. The drugs were well-tolerated and the patient exhibited good adherence throughout the duration of treatment. All doses received at the hospital were administered under direct observation of therapy (DOT). Clinical assessment was performed daily; sputum smear microscopy and culture, measuring the level of blood cells, total and conjugated bilirubin, AST and ALT, creatinine, sodium, potassium, uric acid, and weight was conducted on a monthly basis at the hospital in Gabrovo to monitor the response to the treatment during the intensive phase. Sputum smear microscopy was negative during the whole treatment course, culture conversion was recorded in the first month and continued to be negative until the end of treatment.

Kanamycin was excluded from the drug regimen on 8 December 2017, 148 days (5 months) after beginning of treatment, with weight gain from 65 to 78 kg.

The patient was discharged from the hospital and referred to continue the treatment in ambulatory settings under monitoring conducted by the regional Hospital for Pulmonary Diseases – Burgas. Drug regimen included levofloxacin 750 mg, prothionamide 750 mg, cycloserine 500 mg and ethambutol 750 mg daily doses. During the continuation phase, DOT was organised by the Regional TB manager and patronage nurses in the hospital in Burgas. In order to encourage adherence to the treatment, food vouchers were handed to the patient throughout the whole therapy course. Drug dosages were modified according to body weight. All drugs for the treatment of MDR-TB and for the management of adverse effects were free of charge. During the ambulatory phase sputum monitoring by smear microscopy and culture was done monthly in the Microbiological laboratory at the Hospital for Pulmonary Diseases – Burgas.

Treatment outcome was reported as “cured” on 14 November 2018, 16 months after the start of MDR-TB therapeutic regimen, with 14 consecutive negative culture results and remarkable clinical progress with improved weight gain, adequate blood levels of total and conjugated bilirubin, AST and ALT. In the case with this patient was achieved optimal viral suppression (undetectable HIV viral load, < 40 copies/μl) and good immunological response (CD4 T cells of 200/μl, CD8 of 652/μl, and CD4/CD8 ratio of 0.30).

DISCUSSION

The diagnosis of tuberculosis in HIV-infected patients with advanced immune deficiency is difficult. In most cases, X-ray findings are not specific and sputum smear microscopy is negative. The leading complaints in our patient were diarrhoea, weight loss and night sweats. The confirmation of two pathogens (*Candida* and *Cryptosporidium*) which can explain the symptoms initially put these agents at the forefront of differential diagnosis. Despite the fact that we did not consider tuberculosis as a possible co-infection, we are providing routine TB testing for all HIV-positive patients. Culture is the golden diagnostic standard but requires a long time to obtain the results – from 4 to 6 weeks. That was the reason for

the delay in diagnosis of tuberculosis in our case. Xpert MTB/RIF is rapid molecular test, which is important especially in cases with drug-resistant TB. Treatment of MDR-TB is prolonged and quite expensive, but timely diagnosis is essential for the patient`s survival and the evolution of the HIV infection.

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