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ORIGINAL ARTICLE

PATIENTS WITH HIV AND TUBERCULOSIS COINFECTION, TREATED IN THE SPECIALIZED HOSPITAL FOR INFECTIOUS AND PARASITIC DISEASES IN SOFIA, BULGARIA, FOR THE PERIOD 2017-2019

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Abstract. Background. *Infection with human immunodeficiency virus (HIV) is the most powerful risk factor known to predispose to Mycobacterium tuberculosis infection and further progression to active disease, which increases the risk of latent TB reactivation. TB is one of the most common opportunistic infections worldwide.* ***Aim.*** *The objective of the study was to describe the main clinical characteristics of the HIV – positive patients, examined for TB for 2 years (January 2017-January 2019), as well as to delineate the clinical characteristics and treatment of patients with bacteriologically confirmed TB who were treated for it, analyze characteristics of the results from the microbiological tests performed and, further, describe the patients with multidrug – resistant tuberculosis.* ***Study design.*** *This was a prospective cohort study.* ***Methods.*** *Diagnosis was based on clinical, radiological, and microbiological data, such as smear microscopy, culture, and rapid molecular methods (Xpert MTB/RIF).* ***Results.*** *The baseline CD4+ count of the patients was significantly lower compared with the other patients without coinfection (86 ±138 cells/µcl). Acute inflammatory response syndrome was observed in 9 patients (30%). Multidrug-resistant (MDR) M. tuberculosis was presented in three patients (20%). The predominant localization was pulmonary tuberculosis in 12 patients (80%). Six of them (50%) tested positive for MTB. The extrapulmonary involvement engaged lymph nodes in two patients and the CNS – in one.* ***Conclusion.*** *TB is a disease of advanced immune suppression. Factors predicting the development of IRIS syndrome included low CD4 count, delay of diagnosis, HIV/HCV coinfections, infection with MDR Mycobacterium tuberculosis. The principal location was pulmonary; MTB was isolated in 50% of those cases. TB meningitis should be suspected in patients with advanced immune deficiency presented with progressive neurologic deficiency, changes of consciousness, and meningeal irritation.*

Key words: *MTB, MDR-TB, HIV, Xpret MTB*

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Abbreviations: TB – tuberculosis, MTB – Mycobacterium tuberculosis, FTC/TDF – Emtricitabine/Tenofovir disoproxile fumarate, DRV/c – Darunavir boostered with cobicistate, IRIS – immune reconstitution inflammatory syndrome, CNS – central nervous system, FLDs – first line drugs, SLDs – second line drugs, ABC/3TC/EFV – Abacavir/Lamivudine/Efavirenz, CSF – cerebrospinal fluid

INTRODUCTION

Tuberculosis (TB) and human immunodeficiency virus (HIV) co-infections place an immense burden on health care systems and pose particular diagnostic and therapeutic challenge. Infection with HIV is the most powerful risk factor known to predispose to a *Mycobacterium tuberculosis* (MTB) infection and further progression to active disease, which increases the risk of latent TB reactivation 20-fold. TB is also the most common cause of AIDS-related death. Thus, MTB and HIV act in synergy, accelerating the decline of immunological functions and leading to subsequent death, if untreated. HIV/TB co-infection is a global problem: it accounts for 12% of all cases with HIV infection. This is due to interference between the two infections.

With the introduction of combined antiretroviral therapy (cART) the incidence of HIV/TB co-infection decreased significantly, but there is still a risk, regardless of the CD4+ count. TB and HIV/acquired immune deficiency syndrome (AIDS) constitute the main burden of infectious diseases in resource-limited countries. Estimates by the World Health Organization (WHO) indicate that in 2017, there are more than 10 million new active cases of TB and close to 1.3 million deaths per year, and that 2.6 million new cases of HIV infection and 1.8 million AIDS-related deaths occur on an annual basis. MTB/HIV co-infections pose particular diagnostic and therapeutic challenge and exert immense pressure on health care systems in African and Asian countries with large populations of co-infected individuals. The transition from active to latent TB infection, so-called *reactivation*, is induced by multiple factors, but the drop in CD4+ counts plays a special role [20].

The immunopathogenesis of TB infection in the presence of HIV is very complex. In fact, the entire immunological cascade, all known mediator systems (pro-inflammatory, anti-inflammatory) interfere with the immunopathogenesis at some stage. Cell-mediated immunity is essential for the control of MTB infection; activation of both CD4+ and CD8+ T cells has been witnessed in active TB in humans, as well as in mice after experimental infection. CD4+ T lymphocytes of the T helper cell type 1 (Th1) are thought to be most critical. Also, there is experimental evidence that CD8+ T cells, as well as unconventional T cells, such as CD1-restricted cells recognizing the mycobacterial lipids, contribute to the optimal control of the disease. T cells recruited to the infected lung are thought to control infection by producing interferon gamma (IFN-γ) in response to mycobacterial antigens presented by macrophages. In turn, IFN-γ activates macrophages to kill the intracellular bacteria through reactive nitrogen and oxygen intermediates, and by inducing phagolysosome formation. However, these mechanisms might even be present in susceptible hosts, in which the infection progresses to disease. The full knowledge of the constituents of an effective protective immune response to TB is still incomplete. In the MTB – infected host there is also a robust humoral response, with a wide spectrum of antibodies (Abs) of different specificities and isotypes; although secondary to the cellular immune responses in terms of protection, B cells as well as certain Ab responses, have been shown to be capable of playing an important role in the protective immunity to TB [1, 11].

Timely diagnosis is also a challenge: there is low percentage (< 50%) of isolation of the causative agent, especially from patients with a low CD4+ count, (< 100/mm^3); that is the reason why sometimes diagnosis is made by means of observation of the patients during the course of treatment.

Even with the most accurate diagnostic methods, if there is a clinical suspicion, multiple sputum samples should be obtained, and molecular-genetic methods should be involved as well.

So our aim was to make a description of the main characteristics of the HIV – positive patients, examined for TB for 2 years (January 2017-January 2019), as well as to delineate the clinical characteristics and treatment of patients with bacteriologically confirmed TB who were treated for it, analyze characteristics of the results from the microbiological tests performed and, further, describe the patients with multidrug – resistant tuberculosis.

MATERIALS AND METHODS

Due to clinical suspicion, 30 patients were examined for TB in the Department for Acquired Immunodeficiency at the Specialized Hospital for Infectious and Parasitic Diseases in Sofia over the period January 2017–January 2019. Their mean age was 41 years (range, 22-57 years), and there were 27 men (90%) and 3 women (10%). Fifteen of them (50%) were diagnosed with TB and received anti-TB treatment. Diagnosis was based on clinical, radiological, and microbiological data, such as sputum smear microscopy, culture, and rapid molecular DNA amplification methods (Xpert MTB/RIF). Statistics was performed by SPSS v. 21; the level for rejection of null hypothesis was set at $p < 0.05$.

RESULTS

The baseline characteristics of the patients are presented in Table 1.

Table 1. Baseline characteristics of the presented HIV/TB patients (n = 30)

Average CD4+ count upon detection (cells/µcl)	86 ± 138
CD4+ at presentation (cells/µcl)	364 ± 300
VL upon detection (copies/ml)	564,644 ± 1,039,188
Time until VL dropped to undetectable levels (weeks)	36 ± 16
Newly registered patients	12
Average hospital stay (days)	62 (p = 0.0001)*
Patients with observed IRIS	9

The baseline CD4+ count of the patients was low: 86 ± 138 cells/µcl, which was significantly lower compared with the other patients, while the viral load (VL) levels were high: 564,644 ± 1,039,188 copies/ml. The time needed for VL to drop to undetectable levels exceeded months. The average hospital stay was significantly longer compared with other patients. Immune reconstitution inflammatory syndrome was observed in 9 patients (30%). Three of them died.

The IRIS syndrome was observed on average 6 to 12 days after the onset of anti- TB treatment. Comparing with the other patients without IRIS the patients had significantly lower CD4+ T cells counts, varying from 5 to 284 (65 ± 76) cells/µcl (p = 0.001).

The main characteristics of the patients developing IRIS are included in Table 2.

All patients were febrile. Six of them had progressive pulmonary failure with tachypnea, dyspnea, hypoxemia, and hypercapnia. In four patients, progression to multiple organ failure, liver and renal failure was observed. Liver involvement included elevated ALT and GGT levels for 2-4 weeks. These patients presented terminal immune deficiency with concomitant wasting syndrome and candidiasis. Six of the patients had an underlying liver disease (HCV in 4, and HBV in 2, respectively). Treatment was complex and included anti- TB drugs, methylprednisolone for appropriate duration, fluconazole, supportive care, and an oxygen therapy. cART was initiated 2 weeks after the commencement of anti-tuberculosis treatment. The cART regimen was compliant to the administered anti – TB drugs, the underlying diseases, the result of the HLA B*5701 test (since the carriers of this allele could develop hypersensitivity to Abacavir), the presence or absence of hepatitis infection, the methadone substitution therapy, and the test of resistance to antiviral drugs.

Table 2. Symptoms in patients with observed IRIS (n = 9)

Symptoms (per number of patients)	Duration (days)
Fever (9/9)	12 ± 3
Respiratory failure (6/9)	10 ± 3
X-ray changes (8/9)	12 ± 3
Liver involvement (4/9)	25 ± 4
Multiple organ failure (4/9)	5 ± 3
Corticosteroid administration (9/9)	12 ± 4
Predisposing diseases, IVDU (5/9)	
HCV (+) (4/9)	
HBV (+) (2/9)	
HIV wasting syndrome (9/9)	
HIV-connected dementia (3/9)	
Candidiasis (9/9)	16 ± 4

Laboratory confirmation of TB was achieved in nine of the followed-up patients (33.3%). Multidrug-resistant TB (MDR-TB) – TB with resistance to, at least, both rifampicin and isoniazid, was present in three patients.

TB localization on X-ray of the patients is presented in Figure 1.

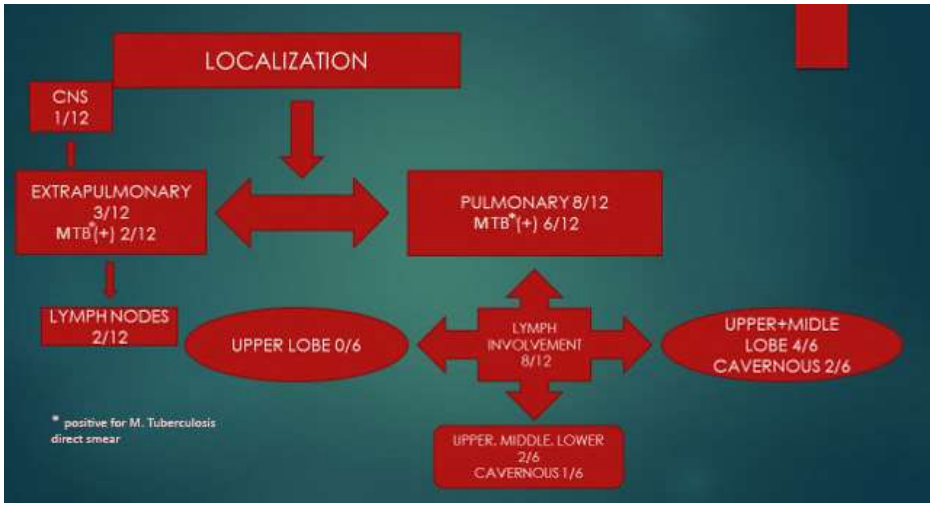

Fig. 1. TB localization based on chest X-rays of the presented HIV/TB patients (n = 30)

The predominant localization was pulmonary, in 12 out of 15 patients (80%). Six of them (50%) were tested positive for MTB. The X-ray findings showed involvement of the mediastinal lymph nodes in eight patients (53,8%). None of the patients revealed involvement only of the upper lobe. In four of the patients, the TB infection engaged the upper and the middle lobes, whereas in two of them it engaged the upper, the middle and the lower lobes. In three patients, one with upper, middle and lower involvement and two with upper and middle involvement, cavities were observed. The patients with cavities were with microbiological confirmation: sputum smear and/or culture positivity.

The extra-pulmonary involvement included lymph nodes enlargement in two patients and the CNS engagement in one patient. One patient with lymph node involvement and the patient with CNS involvement were tested using Xpert MTB/RIF and proved positive for MTB.

The patients' underlying diseases were as follows: 5 of the 12 patients with pulmonary tuberculosis (42%) were intravenous drug users (IVDU); chronic hepatitis B – HBV (+) was concomitant disease in 3 of the 12 patients (25%); 2 of 12 patients (17%) had liver cirrhosis; 2 of 12 (17%) had chronic gastritis; one patient (8%) had nephrolithiasis and one had exacerbated chronic sialadenitis (8%).

In 5 patients there was an evidence of intravenous drug use, 3 of them were HCV (+) positive.

Three patients, were of peculiar interest to our practice, since they were proven with MDR – TB. Two of them of the age 64 and 47 years, respectively, had pulmonary localization and one – a 34-year-old patient had extrapulmonary localization in the CNS. Hereby, we will make a more detailed presentation of these three cases.

Case 1. This was a 64-year-old male, who was diagnosed with HIV in 2017. He was hospitalized for the period March 31, 2017 – July 7, 2017. He had a baseline CD4+ count upon registration of 16 cells/µcl, and a VL of 237,986 copies/ml. At present, his CD4+ count is 278 cells/µcl, and VL is < 50 copies/ml, i.e. undetectable. Concomitant diseases included: oropharyngeal candidiasis with subsequent cryptosporidiosis. The patient had a HIV/HBV coinfection. The chest X-ray showed infiltrates in the middle and lower pulmonary lobes of the right lung, and mediastinal lymphadenopathy (Figure 2). The cART regimen included FTC/TDF/DRV/r.

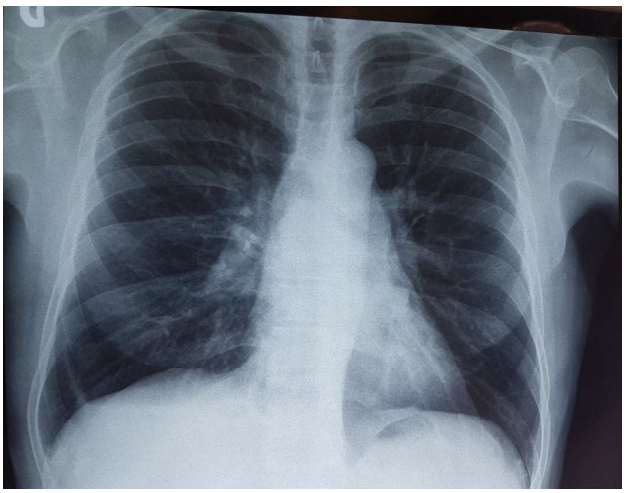

Fig. 2. Chest X-ray of the 64-year-old patient presented with MDR-TB

Microbiological investigations by liquid cultures (MGIT – Mycobacteria Growth Indicator Tube) of three consecutive sputum samples at the beginning were positive for MTB. An MDR strain of MTB was found resistant to rifampicin, isoniazid and ethambutol. IRIS was developed nearly 15 days after the onset of anti-TB treatment. Initial treatment included rifampicin, izoniazid, ethambutol, pyrazinamide, amikacin and levofloxacin. After obtaining the results by the drug-susceptibility testing (DST) to first- and second-line anti-TB drugs (FLDs and SLDs), the treatment regimen was changed and consisted of high-dose isoniazid, pyrazinamide, amikacin, levofloxacin, and prothionamide, included during the intensive phase.

Continuation phase of MDR-TB treatment further included: Kanamycin vial 1.0 – 0,750 s.c. daily – 148 days; Pyrazinamide tab. 0,500 – 3 x 1 tab. daily – 24 days; Ethambutol tab. 0,250 – 2 x 2 tab. daily – 265 days; Cycloserine caps. 0,250 – 2 x 1 caps. daily – 236 days; followed by 6 months of treatment with: Ethambutol 0,750 daily, Levofloxacin 0,750 daily, Protionamide 0,750 daily, and Cycloserine 0,500 daily.

After 180 days of MDR-TB treatment, MGIT sputum culture was negative, i.e. the patient was reported as "Cured".

Case 2. This was a 47-year-old male patient, hospitalized for 75 days in the clinic from April 20, 2017 till July 3, 2017. He was with positive sputum cultures using MGIT, and confirmed as *non*-tuberculous mycobacterial (NTM) infection. Concomitant conditions included oropharyngeal and intestinal candidiasis. The patient developed IRIS within 12 days, which lasted for another 12 days. The baseline CD4+ count upon HIV diagnosis was 49 cells/µcl, and the VL was 413,653 copies/ml. At present, the CD4+ count is 280

/mm^3, and the VL is below 50 copies/ml, i.e. undetectable. The cART regimen included FTC/TDF/DRV/r.

Microbological investigations by liquid cultures (MGIT) in two out of three consecutive sputum samples at the beginning were positive for NTM, and confirmed as M. avium by molecular-genetic tests.

The treatment regimen included the following drugs: Kanamycin vial 1.0 – 0,750 s.c. daily – 180 days; Bedaquiline tab. 100 mg – 3 times weekly x 2 tab. – 112 days; Amoxicillin/Clavulanic acid tab. 875/125 mg – 2 x 1 tab. daily – 9 days; Levofloxacin tab. 0,250 – 3 x 1 tab. daily – 273 days; Cycloserine caps. 0,250 – 3 x 1caps. daily – 273 days; Clarithromycin tab. 0,500 – 2 x 1 tab. daily – 262 days; Prothionamide tab. 0,250 – 3 x 1 tab. daily – 187 days; Para-aminosalycillic acid (PAS) sachet 4,0 – 2 x 1 sachet daily – 118 days.

The treatment regimen during the continuation phase included: Clarithromycin 1000 mg/daily, Pyrazinamide 1500 mg/daily, Protionamide 0,750 mg/daily, Levofloxacin 750 mg/daily, Cycloserine 750 mg/daily,and PAS 800 mg/daily for 6 months. Sputum cultures (MGIT) at 6th and 12th month were negative.

Case 3. The third patient was a 34-year-old male diagnosed with HIV in 2011 and cART was initiated in 2011 with the following regimen: ABC/3TC/EFV (Abacavir/Lamivudine/Efavirenz), but with poor adherence. Patient's first hospitalization in the clinic was from October 25, 2017, till November 30, 2017. He was with oropharyngeal candidiasis (OPC) and HIV-related cachexia. The patient was confirmed with MTB-positive pulmonary TB. On March 1, 2018, the patient was presented with the following symptoms: fatigue, leg pain, loss of appetite, and since the morning of March 6, 2018, he became unresponsive. General condition included: pronounced *meningitis*-retention syndrome (MRS), weakened reflexes, positive Babinski's sign bilaterally.

Other results were as following: CD4+ count of 10 cells/µcl, and VL of 3,724,206 copies/ml. Cerebrospinal fluid (CSF) investigation included: CSF cells 188/µcl, glucose levels 1.03 mmol/l, protein levels 1.66 g/l (on March 7, 2018). Next CSF examination from March 29, 2018, included: CSF cells – 82/µcl, CSF glucose levels – 2.05 mmol/l, CSF protein levels – 1.11 g/l. CSF was tested positive for MTB using Xpert MTB/RIF. Treatment included: Mannitol, Ceftriaxone, Amikacin, Levofloxacin, Fluconazole, *Vitamin B complex*. The cART regimen included: ABC/3TC/Efavirenz. DST to FLDs using MGIT confirmed polyresitant MTB both to streptomycin and isoniazid. Lethal outcome occurred 30 days after discharge.

DISCUSSION

Fifty percent out of 30 HIV-positive patients presented in our study and tested for TB due to clinical suspicion, were diagnosed with MTB infection. They received the appropriate treatment. An etiological agent was proven in 60% of these 15 patients. In the remaining number, the diagnosis was made ex juvantibus during the treatment course. According to data from the literature, clinical manifestations are varying from classic symptoms of prolonged fever, hemoptysis, productive cough, weight loss, or night sweat, to minimal or nonspecific symptoms [3, 14, 20].

TB is a disease of advanced immune suppression, which was observed in 21 of the patients [6, 11]. The CD4+ counts were significantly lower than those of other HIV patients ($p = 0.0001$), and, accordingly, the VL levels were significantly higher.

Factors predicting the development of IRIS included: low CD4 count, delay of diagnosis, presence of underlying diseases, especially HIV/HCV co-infections, and infection with MDR-TB [2, 4]. The pathogenesis and epidemiology are not completely described. In co-infected HIV/TB patients, IRIS usually occurs during or after completion of anti – TB therapy [7], while in the cases presented in this study, IRIS occurred after initiation of anti – TB therapy. The manifestation of IRIS includes aggravation of the initial clinical picture, with onset of fever and respiratory failure.

HIV/HCV co-infections pose additional impact on the immune deficiency progression and the clinical course of TB infection, especially in cases of acquisition of MDR-TB. Further investigations are needed for specific high risk groups: congregate settings, miners, injecting drug users [16].

The TB main localization was pulmonary, and MTB was isolated in 50% of the presented cases. The predilection sites are atypical, including right middle lobe and lower pulmonary segments, and the lymph nodes. No single upper lobe engagement was found. However, according to the literature, usual place of TB lung engagement in HIV patients with CD4+ counts of 200/mm^3, is upper lobe involvement. Disease progression can be followed by dissemination [13]. According to literature data, TB patients with CD4 cell counts less than 200 cells/µcl are likely to have hilar or mediastinal adenopathy on chest X-rays, but less likely to have cavitary lesion [12]. Especially in MDR-TB cases, diagnosis and treatment represent a challenge [4]. Patients with impaired immunity are at higher risk for acquisition of rifampicin-resistant TB (RR-TB), which treatment is prolonged [17, 18, 21]. Multiple sputum samples have to be taken. Xpert

MTB/RIF is useful for rapid detection and identification of RR-TB [2, 15].

Treatment of TB infection is another challenge in co-infected patients. Drug susceptible TB usually is treated with the FLDs: rifampicin, isoniazid, pyrazinamide, and ethambutol. Izoniazid and especially rifampicin are the most potent FLDs [5]. Based on WHO recommendations and international standards, if the patient is a re-treatment TB case, an injectable aminoglycoside should be added to the drug regimen. All existing methods should be used for diagnosis of possible TB drug resistance, as in Case 1 presented in our study. cART should be initiated irrespectively of the CD4+ levels during the first 8 weeks after TB treatment and within the first 2 weeks for patients with CD4+ levels below 50 cells/μcl [5, 18]. The cross reactions between the anti-tuberculosis drugs and the antiretroviral agents should be considered [9].

TB meningitis is a life-threatening complication. It should be suspected in patients with advanced immune deficiency, which are presented with progressive neurologic deficiency, changes of consciousness, and meningeal irritation. It is a disease of advanced immune deficiency [1, 8]. Basal localisation, behaviour changes such as confusion, and cranial nerve involvement are the cornerstones for suspicion. Diagnosis and treatment are difficult, and cultures should be obtained systematically [1]. However, growing of the mycobacteria takes a considerable period of time (over 1 month). Administration of the cART therapy is another obstacle due to patients' compromised ability to swallow. Full recovery without neurologic sequelae is almost impossible, and prognosis is poor.

Disclosure Summary: *The authors have nothing to disclose.*

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