

Comparative Characteristic of Cases of Microbacteriosis and Tuberculosis among HIV-Infected Patients

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Abstract

Diagnosis of mycobacteriosis and differential diagnosis of tuberculosis is an urgent problem, which solution will allow starting treatment correctly in time, especially among people with immunodeficiency, incl. HIV/AIDS. From 2007 to 2016, the incidence of HIV infection, tuberculosis and HIV-associated tuberculosis in the Republic of Mari El (RME) was analyzed. The increase in the incidence of HIV infection was revealed (2007: 8.9 per 100,000 population, in 2016: 19.6); there was a decrease in the incidence of tuberculosis in the RME from 76.6 per 100,000 people in 2007 to 48.4 per 100,000 people in 2016. The average annual incidence of tuberculosis is 5.1 times higher than the same indicator for HIV infection in the country. The study uses data from bacteriological studies, statistical and graphoanalytical methods. During the whole period of registration of HIV infection on the territory of the RME, 3 cases of mycobacteriosis, confirmed by laboratory methods, associated with HIV infection were detected, among them 1 case of mixed infection (HIV-associated tuberculosis process and mycobacteriosis). In the period of 2007-2016, there was an increase in reported cases of HIV-associated tuberculosis by 5.7 times (in 2007, tuberculosis was diagnosed in 3.2% of HIV-infected patients, in 2016 - in 18.1%).

Keywords: HIV-Infection, Mycobacteriosis, Tuberculosis

Introduction

Among opportunistic diseases in the Russian Federation (RF) registered among HIV-infected patients, more than 90% are infectious pathologies. More than 60% of cases in the structure of the latter, in turn, are tuberculosis, which causes the death of about 50% of patients with HIV infection. At the same time, among the HIV-infected, there is an increase in the number of diagnosed mycobacteriosis on the background of stage III and IV HIV infection. However, mycobacterial infection can accelerate the progression of AIDS by reducing the number of CD4⁺ lymphocytes [Corbett E. et al., 2003]. HIV-infected patients often suffer from mycobacteriosis caused by *Mycobacterium avium* and

Mycobacterium intracellulare, which tend to form a complex called Mycobacterium avium complex (MAC). Non-tuberculosis mycobacteria (NTMB) are ubiquitous in the environment and are now considered as saprophytes and conditionally pathogenic bacteria capable of causing a disease clinically very similar to tuberculosis. Two ways of human infection of MAC-related NTMB have been proven: airborne (through the respiratory system) and through food and water (through the gastrointestinal tract). One of the objectives of this study is to determine the level of CD4⁺ lymphocytes among HIV-infected patients in the Republic of Mari El (RME), which promoted mycobacteriosis development, since the literature data determine the levels of this clinical and laboratory indicator, in which the incidence of mycobacteriosis among patients with HIV infection increases, as less than 100 cells/μL (N.V. Fomenkova, 2011) or less than 200 cells/μl (N.R. Mikhailova, 2015) [1, 2, 3, 4, 5, 6].

In Western countries, the problem of NTMB has been well studied, since mycobacteriosis is quite often diagnosed in HIV-infected patients at the stage of AIDS. The real picture of the prevalence of mycobacteriosis in the Russian Federation remains unknown. The problem of diagnosing the disease caused by NTMB remains unresolved due to incomplete bacteriological examination of HIV-infected patients for this pathogen because of the lack of standards for diagnosis and treatment of mycobacteriosis. Mycobacteriosis-causing NTMBs cannot be treated with anti-tuberculosis drugs despite their similar clinical and radiologic patterns with tuberculosis, which affects the results of treatment of this, often misdiagnosed, opportunistic disease [7, 8, 9,10, 11].

At the same time, there is a problem of correct interpretation of bacteriological studies on mycobacteriosis. Bacteriological laboratory tests of NTMB culture bear a probability that the received positive result can indicate both its relation to pathological process, and possible contamination of a sample from an environment or an asymptomatic colonization of organs and systems of the patient. This issue requires a comprehensive solution on the part of providing an anti-epidemic regime in

bacteriological laboratories, including during microbiological monitoring of laboratory facilities [12].

The only bacteriological laboratory in the RME involved in the laboratory diagnosis of mycobacteriosis is located on the basis of the Republican tuberculosis dispensary of the RME. The doctors in this bacteriological laboratory have been working in this direction since 1994, which allows correctly prescribing therapy to patients.

Methods

Laboratory bacteriological analysis of biological fluids of patients for *M.tuberculosis* used the method of cultivation on solid nutrient media Levenshtein-Jensen and Finn II and on the liquid medium Middlebrook 7N9 using the VASTES MGIT 960 instrument. A primary identification was performed after growing culture. In the case of NTMB identification, PCR was carried out, followed by hybridization of the amplification products on DNA strips (GenoTypeCM and GenoTypeAS kits, HAIN Lifescience, Germany).

Medical cards of patients with HIV infection of the Republican Center for the Prevention and Control of AIDS and Infectious Diseases of the RME, forms of federal statistical observation (No. 33 "Information on TB patients", No.61 "Information on contingents of patients with HIV infection") were reviewed; statistical and graphoanalytical methods were used.

Results

In the period of 2007-2016, the growth of the incidence of HIV infection was registered on the territory of the RME (2007: 8.9 per 100,000 of people, 2016: 19.6 per 100,000 of people, the equation of approximation is $y=x+75.71$, the reliability of $R^2=0.8894$). During this period, there was a statistically significant decrease in the incidence of tuberculosis in the republic from 76.6 per 100,000 of people in 2007 to 48.4 per 100,000 of people in 2016 (the approximation equation is $y=-3.8618x+87.26$, $R^2=0.8894$). The average annual incidence of tuberculosis is 5.1 times higher than that of HIV infection (Fig.1).

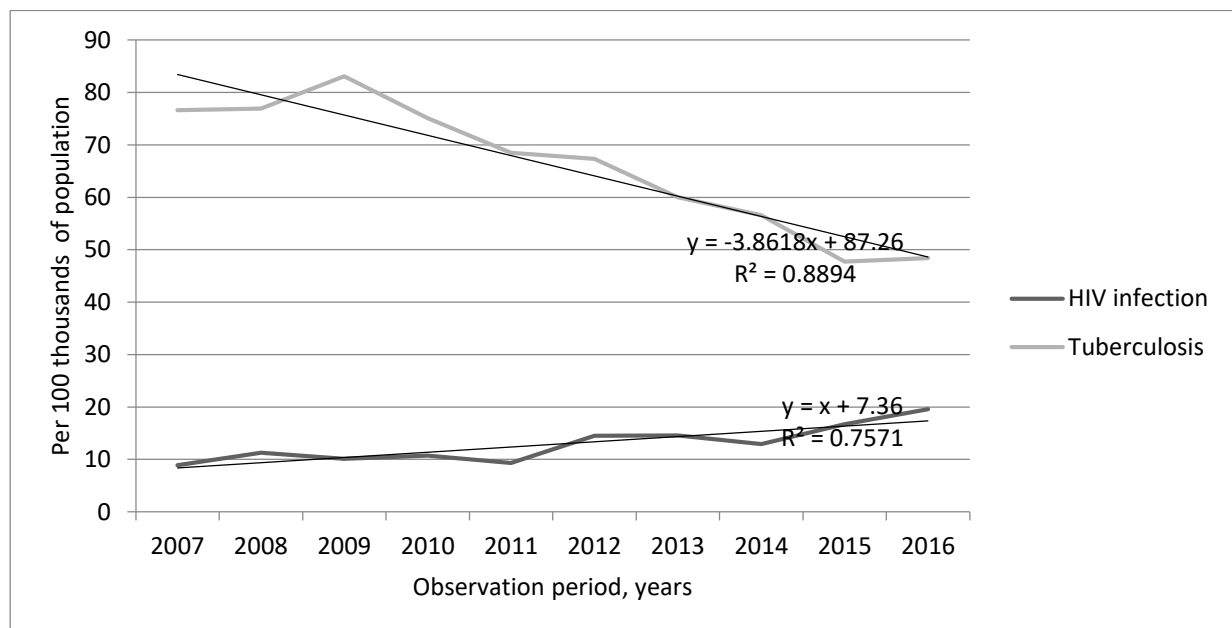


Fig.1. Incidence of HIV Infection and Tuberculosis in the Republic of Mari El for the Period 2007 - 2016

The expediency of prescribing chemoprophylaxis of tuberculosis among patients with HIV infection can be judged subject to such clinico-diagnostic indicator as the level of $CD4^+$ lymphocytes. In the RME, tuberculosis among this cohort is recorded at the level of $CD4^+$ lymphocytes less than 350 cells/ μ l. During the entire period of registration of HIV infection in the territory of the RME (the first cases of HIV infection were registered in the RME since

1990), 3 cases of mycobacteriosis associated with HIV infection were detected. Thus, in order to establish the level of $CD4^+$ lymphocytes, when mycobacteriosis develops in HIV-infected patients, a large sample and number of registered cases, respectively, are required. In the second case, a mixed infection of HIV-associated tuberculosis and mycobacteriosis is observed (Table 1).

Table 1. Data of Levels of CD4 Lymphocytes in the Presence of HIV-Infected a typical mycobacteriosis as an HIV-Infected Disease

Case No., Sex, Age	Level of CD4 lymphocytes in the diagnosis of atypical mycobacteriosis, Cells / μ l	Result
1, Female, 28	30	Died because of AIDS
2, Male, 35	399	4 B stage of HIV infection*
3, Male, 14	1	4V stage of HIV infection*

*Classification of HIV infection is given by V.I. Pokrovskii

In 2007-2016 there is an increase in the registered cases of HIV-associated tuberculosis by 5.7 times. If in 2007, 3.2% of HIV-infected had a tuberculosis process, then in 2016 the same indicator was 18.1%. This situation is characterized as tense and requires the strengthening of chemoprophylaxis of tuberculosis among HIV-infected people.

In 2016, 23 cases of HIV-associated tuberculosis were registered in the territory of the RME. 17 of them are newly diagnosed cases of tuberculosis (including 2 homeless people), 3 - relapsed tuberculosis, and 3 - newcomers to the republic. All newly diagnosed individuals had tuberculosis mycobacteria detected by culture methods; in addition, mycobacteria of tuberculosis were detected microscopically in 15 HIV-infected patients. Among 3 cases of relapses, 2 people did not provide data on primary enrollment in the Republican TB Dispensary of the RME, but 1 person in 1995 was diagnosed with tuberculosis mycobacteria. One

HIV-infected person with a tuberculosis relapse in 2011 was diagnosed with a tuberculosis process without isolation of tuberculosis mycobacteria. In all cases of the relapsed disease, no tuberculosis mycobacteria were isolated by culture methods, however, 1 person was detected to have MBT DNA, found by the real-time PCR method. Among the 3 newcomers, the culture of tuberculosis mycobacteria was found in 1 patient. All HIV-infected bacterioviruses were examined for drug resistance (DR) against the main and reserve anti-tuberculosis drugs (Isoniazid, Rifampicin, Streptomycin, Ethambutol, Kanamycin, Capreomycin, Ofloxacin, Prothionamide, paraaminosalicylic acid, Cycloserine). Multiple drug resistance (MDR) to anti-tuberculosis drugs, as well as DR to Isoniazid and Rifampicin was determined by PCR analysis in 1 case of relapse (Table 2).

Table 2. Clinical Laboratory Indicators of Cases of HIV-Assisted Tuberculosis in 2016 in the Republic of Mari El

	The first cases identified		Relapses		Arrived on the territory of the republic		Total	
	absolute number	%	absolute number	%	absolute number	%	absolute number	%
Tested for mycobacterium tuberculosis Culture method	17		3		3			
Of these, mycobacteria are identified by the culture method	17		0		1		18	
Tested for drug resistance	17	100	0	0	1	100	18	100
Susceptibility to medicines	2	11.8					2	11.1
Monoresistance	2	11.8					2	11.1
Polyresistance	2	11.8					2	11.1
Multiple Drug Resistance (MDR)	6	35.3			1	100	7	38.9
Broad drug resistance	4	23.5					4	22.2

The vast majority of people with HIV-associated tuberculosis are resistant to main anti-tuberculosis drugs.

Summary

Over the past 10 years, the RME has established an increase in the incidence of HIV infection by 2.2 times (2007 - 8.9 per 100,000 of people, 2016 - 19.6),

and a decrease in the incidence of tuberculosis (2007 - 76.6 per 100,000 of people, 2016 - 48.4). The average annual incidence of tuberculosis is 5.1 times higher than the same indicator for HIV infection in the republic. During the whole period of registration of HIV infection on the territory of the RME (since 1990), 3 cases of HIV-associated mycobacteriosis were detected, among them 1 case of mixed infection (HIV-associated tuberculosis process and mycobacteriosis). All patients were found to have *M. avium*. In 2007-2016, there was an increase in reported cases of HIV-associated tuberculosis by 5.7 times (in 2007, tuberculosis was diagnosed in 3.2% of HIV-infected patients, in 2016 - in 18.1%). The epidemiological situation with HIV-associated tuberculosis is characterized as tense and requires adjustment by chemoprophylaxis and work on involvement of HIV-infected patients in antiretroviral and anti-tuberculosis treatment. All 3 cases of atypical mycobacteriosis among HIV-infected people were characterized by different levels of CD4⁺ lymphocytes (1 cell/μl, 30 cells/μl, 399 cells/μl), at which mycobacteriosis was registered, which generally corresponds to literature data (N.V. Fomenkova, 2011; N.R. Mikhailova, 2015), except for the third value of this clinical and laboratory indicator (at CD4⁺ lymphocyte cell count of 399 cells/μl, a case of mixed infection of HIV-associated tuberculosis and atypical mycobacteriosis was established in one HIV-infected patient). In the RME, tuberculosis among HIV-infected patients was recorded at the level of CD4⁺ lymphocytes less than 350 cells/μl.

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