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FREQUENCY OF MYCOSES IN PATIENTS WITH TB-HIV

Abstract. *Currently, one of the pressing problems of phthisiology remains the high incidence of tuberculosis among patients with HIV infection. The high frequency of multiple drug resistance of tuberculosis mycobacteria (resistance to the most effective anti-tuberculosis drugs isoniazid and rifampicin) clearly and directly correlates with the prevalence of HIV infection. The most common causative agents of mycoses are yeast-like fungi of the genus Candida and mycelial, mold fungi of the genera Aspergillus, Penicillium, Mucor, and some others. The fight against it is significantly complicated by the fact that there is a mutually aggravating synergy between tuberculosis and HIV: HIV infection contributes to the progression of tuberculosis infection, and tuberculosis worsens the course of HIV infection. Mycocenoses - associations of pathogens - are of great importance. The more pronounced the immunodeficiency, the more pronounced the manifestations of candidiasis.*

Key words*: tuberculosis, HIV, co-infection, mycoses, diagnosis*

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ЧАСТОТА ВСТРЕЧАЕМОСТИ МИКОЗОВ У БОЛЬНЫХ С ТБ-ВИЧ

Аннотация. *В настоящее время одной из актуальных проблем фтизиатрии остается высокая заболеваемость туберкулезом среди пациентов с ВИЧ-инфекцией. Высокая частота множественной лекарственной устойчивости микобактерий туберкулеза (устойчивость к наиболее эффективным противотуберкулезным препаратам изониазиду и рифампицину) четко и напрямую коррелирует с распространенностью ВИЧ-инфекции. Наиболее распространенными возбудителями микозов являются дрожжеподобные грибы рода Candida и мицелиальные, плесневые грибы родов Aspergillus, Penicillium, Mucor и некоторые другие. Борьба с этим значительно осложняется тем, что между туберкулезом и ВИЧ существует взаимно усугубляющая синергия: ВИЧ-инфекция способствует прогрессированию туберкулезной инфекции, а туберкулез ухудшает течение ВИЧ-инфекции. Микоценозы - ассоциации патогенов - имеют большое значение. Чем более выражен иммунодефицит, тем более выражены проявления кандидоза.*

Ключевые слова*: туберкулез, ВИЧ, ко-инфекция, микозы, диагностика*

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ТУБЕРКУЛЁЗ-ОИВ БИЛАН КАСАЛЛАНГАН БЕМОРЛАРДА МИКОЗЛАРНИНГ УЧРАШ ЧАСТОТАСИ

Аннотация. *Ҳозирги кунда фтизиатриянинг энг долзарб муаммоларидан бири ОИВ инфекцияси билан касалланган беморлар орасида сил касаллигининг юқори даражада учрашидир. Сил микобактерияларининг кўплаб дориларга чидамлилигининг юқори частотаси (силга қарши энг самарали дори воситалари изониазид ва рифампитсинга чидамлилик) ОИВ инфекциясининг тарқалиши билан бевосита ва аниқ боғлиқдир. Микозларнинг энг кўп учрайдиган қўзғатувчилари Candida туркумига мансуб ачитқисимон замбуруғлар ҳамда Aspergillus, Penicillium, Mucor ва бошқа айрим туркумларга оид митселиал ва моғор замбуруғларидир. Бу муаммога қарши курашни сил ва ОИВ ўртасидаги ўзаро кучайтирувчи синергия мавжудлиги сезиларли даражада мураккаблаштиради: ОИВ инфекцияси сил касаллигининг ривожланишини тезлаштирса, сил эса ўз навбатида ОИВ инфекцияси кечишини оғирлаштиради. Микотсенозлар, яъни патогенлар уюшмалари, катта аҳамиятга эга. Иммунитет танқислиги қанчалик кучли бўлса, кандидоз белгилари шунчалик яққол намоён бўлади.*

Калит сўзлар*: сил, ОИВ, ко-инфекция, микозлар, ташҳислаш*

Tuberculosis in patients with HIV infection is a global problem: tuberculosis is the main cause of death in patients with HIV infection. It is known that the same social groups of the population: unemployed, migrants, drug addicts, persons in and out of places of deprivation of liberty are at risk of contracting tuberculosis and can be infected with HIV[3].

The HIV infection epidemic remains largely uncontrolled, despite the intensive efforts of researchers, doctors, and healthcare organizers. Significant progress has been made, including in the field of treatment, however, for every 2 patients receiving antiretroviral therapy (ARVT), there are 5 new HIV infections.[1]

The features of the course, diagnosis, and treatment effectiveness of tuberculosis depend on the stage of HIV infection. In the early stages of HIV infection, the course of tuberculosis does not differ from that of individuals without HIV infection, while in the late stages, tuberculosis acquires atypical clinical, radiological, and morphological features, which causes significant diagnostic difficulties. The incidence of generalized forms of tuberculosis is high in the late stages of HIV infection. Contradictory data on the frequency of bacillus secretion and the presence of other secondary infections in this category of patients require modern comprehensive diagnostics (biopsy, radiation, molecular). Standard short-term treatment regimens for tuberculosis in patients with HIV infection are often ineffective, so the duration of treatment for such patients should be at least 9 months [9] therapy for tuberculosis patients with HIV infection [7].

The growth of AIDS and tuberculosis epidemics, leading to permanent disability and premature death, is a priority problem for the global community. Tuberculosis mortality remains high, while HIV/AIDS mortality continues to rise (V.N.Zimina et al. 2013). Several studies have noted that despite initially good clinical responses to therapy, the prognosis for tuberculosis patients with HIV infection remains unfavorable (S. Swaminathan 2008).

Recently, the number of tuberculosis patients infected with HIV has been increasing: tuberculosis is diagnosed in 5-15% of HIV-infected patients. For Uzbekistan, the problem of tuberculosis in HIV-infected individuals is of particular importance, as the high infection rate of the entire population with tuberculosis mycobacteria and the rapid spread of HIV infection in high-risk groups make the prognosis for this combined pathology unfavorable.

The fight against it is significantly complicated by the fact that there is a mutually aggravating synergy between tuberculosis and HIV: HIV infection contributes to the progression of tuberculosis infection, and tuberculosis worsens the course of HIV infection.

Aim. To study the features of the clinical course and frequency of pulmonary system mycoses in patients with pulmonary tuberculosis diagnosed for the first time with HIV infection.

Research methods. Clinical: collection of complaints and anamnesis, as well as physical examination of the patient; examination of sputum bacterioscopically and by inoculation onto nutrient media.

The emergence of multiple drug-resistant tuberculosis mycobacteria has become a serious threat to the effectiveness of anti-tuberculosis programs in many countries of the world (Harries A., 2004) The spread of HIV infection epidemics is also reflected in drug-resistant tuberculosis situations, which is also related to disorders of anti-tuberculosis immunity. The high frequency of multiple drug resistance of tuberculosis mycobacteria (resistance to the most effective anti-tuberculosis drugs isoniazid and rifampicin) clearly and directly correlates with the prevalence of HIV infection (Panteleev A.M., 2004). Drug resistance of tuberculosis mycobacteria is one of the main factors limiting the effectiveness of anti-tuberculosis therapy.

Resistant forms of tuberculosis mycobacteria in newly diagnosed patients with tuberculosis and HIV infection are higher than in patients with tuberculosis without HIV infection (2% vs. 0.4%).

The recommended treatment regimens for both drug-sensitive and drug-resistant tuberculosis remain the same regardless of the presence or absence of HIV infection in patients. However, treating tuberculosis in HIV-infected individuals is often more difficult, and adverse reactions occur more frequently.

Patients with multi-resistant forms of tuberculosis are epidemiologically more dangerous due to the high virulence of tuberculosis mycobacteria, longer duration of bacterial secretion, high contagiousness, especially for HIV-infected individuals. This category of patients largely determines the level of disability and mortality from tuberculosis.

The most common causative agents of mycoses are yeast-like fungi of the genus Candida and mycelial, mold fungi of the genera Aspergillus, Penicillium, Mucor, and some others. The risk of developing candidiasis in HIV-infected individuals increases with the progression of immunodeficiency.

Almost 20 years before the first case of AIDS was described, it was indicated that Candida albicans could mark the earliest stages of immunodeficiency, which can only be detected through modern laboratory tests. In 1984, when laboratory methods for confirming HIV infection had not yet been developed, Klein R.S. and co-authors indicated that oral candidiasis is an important sign predicting the development of AIDS. Due to the significant increase in HIV infection, fungal infections are becoming increasingly common. At the same time, in HIV-infected individuals, the frequency of candidate carriage in the oral cavity reaches 80%, while in practically healthy individuals it is 46-51%.

Due to the fact that HIV-infected individuals usually had a cellular-functional imbalance of the immune system, they were registered with diseases caused by aspergilli, penicilli, mucor, and other fungi. In recent years, aspergillosis in individuals with various immunodeficiencies has become a pressing issue. In particular, 20% of such patients develop mycoses, and among the latter, more than 70% are aspergillosis. The infection of HIV-infected patients with dust containing aspergillus (airborne dust transmission of infection) is observed.

Patients with candidiasis and tuberculosis against the background of HIV infection usually suffer from profound damage to T-cell immunity, when the number of CD-4 lymphocytes ranges from 50 to 70 per 1 μl. The more pronounced the immunodeficiency, the more pronounced the manifestations of candidiasis.

In our country, a significant increase in the number of diseases caused by yeast-like Candida fungi has been observed over the past 30 years. They affect mucous membranes and lead to severe disseminated forms involving the lungs, gastrointestinal tract, urinary and genital systems in the pathological process, and cases of candidiasis sepsis and meningitis are not uncommon (A.B. Kulko et al. 2003; O.V.Lovacheva et al. 2005).

In recent decades, there has also been a significant increase in fungal diseases, both superficial and severe visceral mycoses associated with HIV infection. This is due to many factors, in particular, the widespread use in medical practice of broad-spectrum antibiotics, immunosuppressants, and other groups of drugs, and the development of pathogen resistance to existing drugs (O.V. Lovacheva et al., 2005; O.F.Rabinovich et al. 2011; Lipnitsky A.V. et al., 2013).

Mycoses are opportunistic diseases caused by parasitic fungi, which mainly occur in patients with local or general immune disorders or immunodeficiency.

M. ubiquitous, i.e., ubiquitous (e.g., actinomycosis, candidiasis, trichophytosis), and endemic, i.e., having distribution areas (e.g., keloid blastomycosis, characteristic of South America), are distinguished.

About 400 species of fungi are pathogenic, affecting humans, domestic and wild animals, birds, insects, amphibians, fish, and plants. In the emergence of M., mycocenoses - associations of pathogens - are becoming increasingly important. Mixed (fungal-fungal) and combined (fungal-bacterial, fungal-parasitic, etc.) mycosinoses are distinguished.

According to G.T. Khaudamova et al. (2005), in 82.0% of cases, candidiasis is detected in patients with HIV and tuberculosis. A peculiarity of the clinical presentation of candidiasis in HIV-infected patients is the high frequency of oral and esophageal lesions, with no skin or nail lesions.

However, currently, insufficient attention is being paid to the early detection and timely treatment of bronchopulmonary mycoses in HIV-infected patients with tuberculosis.

In this regard, studying the frequency of occurrence, clinical manifestations, and treatment of bronchopulmonary system mycoses in patients with HIV/AIDS infection receiving anti-tuberculosis drugs is a pressing task for phthisiology.

According to WHO data, one-fifth of the Earth's population suffers from or has at least once experienced various forms of candidiasis. According to WHO data, by 1995, 20% of the planet's population suffered from mycoses of various localizations, and by the beginning of the 21st century, this figure had doubled. This gives grounds to consider the spread of fungal infections as mass.

In recent years, the opinion has become popular among mycologists that disorders of cellular immunity, including those observed in HIV infection and AIDS, predispose almost exclusively to superficial forms of candidiasis, and damage to internal organs is impossible without a severe disorder of phagocytosis. Analysis of clinical observations gives the right to consider this opinion justified.

It has been proven that the severity of the specific tuberculosis process is more pronounced in animals infected with fungi. A very significant difference in the severity of pathoanatomical changes was found in the lungs: caverns were found in 8.9% of cases with experimental tuberculosis infection, and in the presence of fungi - significantly more often (40%).

In these experiments, the role of Candida fungi, which aggravate the specific, tuberculosis process, has been convincingly demonstrated. Similar observations have been made in patients with tuberculosis.

Even with the availability of modern antifungal agents highly active against Candida spp. in the doctor's arsenal, treatment of visceral forms of candidiasis against the background of severe immunodeficiency and neutropenia is rarely successful, and the patient, as a rule, dies.

The peculiarity of the HIV infection epidemic in Russia to date is the rapid increase in the number of severe patients in the late stages of HIV infection who need antiretroviral therapy, which is associated with a sharp increase in HIV infection cases in 2000-2001. According to V.V. Pokrovsky, by 2008, the situation with HIV infection in Russia had reached a critical level, when, on the one hand, it was quite possible to transition the epidemic to a generalized stage, and on the other hand, the possibility of stabilizing the situation had not yet been missed.

The concept of tuberculosis as a disappearing disease turned out to be wrong. Today, tuberculosis, as many centuries ago, remains one of the main infectious diseases leading to human death. Thus, every year there is an increase in the number of new

cases of this disease. According to WHO data, there were 9.4 million cases of tuberculosis worldwide in 2009. It should be noted that, although in absolute terms, the total number of tuberculosis cases increases as a result of population growth, the number of such cases per capita decreases. The rate of this decline is slow, less than 1% per year. The highest incidence rate was recorded in 2004 and amounted to 142 cases per 100,000 people. In 2009, 1.3 million people with HIV-negative status died from tuberculosis, and another 380,000 deaths occurred among HIV-positive patients who died from tuberculosis.

In Russia, until 1991, the prevalence of tuberculosis decreased and was comparable to the average indicators in most European countries. Due to the deterioration of the socio-economic living standards of the population, during the 1990-2000 period, the incidence and mortality rates from tuberculosis increased more than 2 times, reaching 90.7 and 21.5 per 100,000 population. In recent years, the incidence of the disease has stabilized somewhat at 82.4_83.8 per 100,000 population. In 2009, 117227 new cases of tuberculosis were identified (82.6 per 100,000 population), which is 2.9% less than the same indicator in 2008, however, it is 13-20 times higher than the tuberculosis incidence rates in many developed countries. The mortality rate in 2009 was 16.5 per 100,000 people. According to leading Russian phthisiologists, the slight positive shifts in the dynamics of morbidity in the country since 2003 are due to the adoption of a number of legislative acts and some improvement in the financing of anti-tuberculosis measures. However, the annual significant increase in the prevalence of multidrug-resistant tuberculosis (MDT), the merging of two epidemics, tuberculosis, and HIV infection, as well as social problems in society, do not allow for optimistic forecasts.

The problem of tuberculosis in combination with HIV infection became apparent in the last decade of the 20th century. The similarity of individual pathogenetic links, the involvement of the same risk groups in the epidemiological process, under conditions of high infection of the population with tuberculosis mycobacteria (TBM), led to the extremely unfavorable development of a combined epidemic. Globally, tuberculosis is one of the leading causes of death among AIDS patients. According to WHO data, in 2007, the number of patients with combined infection worldwide was 137,000,000 people, or approximately 13% of all tuberculosis cases. However, the prevalence of tuberculosis as a secondary disease in HIV infection is geographically heterogeneous. Thus, according to medical statistics reports from the USA and Western Europe, tuberculosis at the AIDS stage develops in no more than 5% of patients. In these countries, where antiretroviral therapy is widely used, tuberculosis incidence is declining. At the same time, in the countries of South Africa, Eastern Europe, and Russia, 30_75% of people with the late stages of HIV infection are infected with tuberculosis, while mortality increases to 43_89%. This is because the incidence of tuberculosis in HIV-infected individuals is directly correlated with the overall infection rate of the general population. According to WHO data, 1/3 of the world's population is infected with tuberculosis, and in our country, almost the entire adult population is infected. HIV infection at the stage of severe immunodeficiency is the most potent factor in the progression of latent infection into active tuberculosis. Among all those infected with tuberculosis mycobacteria, the risk of developing tuberculosis is 10% throughout life, and in patients with HIV infection, it increases to 5-10% within one year.

In Russia, until 2003, the epidemics of HIV infection and tuberculosis developed in parallel, without mutually aggravating influence on the epidemiological situation in the country. During this period, the majority of patients had a subclinical stage of HIV infection, and the incidence of tuberculosis in this category of patients was somewhat higher than the general population only due to a significant number of individuals belonging to the social risk groups for tuberculosis. At the beginning of the 2000s, the first publications about the clinical course of tuberculosis against the background of HIV infection began to appear in domestic literature. But already in 2001, O.P. Frolova, based on the analysis of the development of the HIV infection epidemic and the first data on the course and mortality from tuberculosis in patients at the stage of AIDS (1344 people out of 753 developed tuberculosis), determined an extremely unfavorable prognosis regarding the epidemiological situation for the combined pathology for Russia. As early as 2005, there was a persistent trend of two epidemics merging in regions with a greater burden of HIV infection (Saint Petersburg, Moscow, Kaliningrad, Sverdlovsk regions, etc.). By 2008, the epidemiological situation regarding tuberculosis among HIV-infected patients in the Russian Federation continued to develop in accordance with the forecast made at the beginning of the decade. Among the contingent of patients with HIV infection, the number of individuals developing late stages continues to grow. This leads to the fact that an increasing number of HIV-infected patients infected with MTB develop active tuberculosis against the background of immunodeficiency.

Thus, in 2001, the number of people with AIDS was 0.9%, in 2009 - 11.4%, and the number of patients with combined infection in 2001 - 1,298, in 2009 - already 20,755.

Unlike most secondary diseases (including other mycobacterial infections that develop at later stages of HIV infection), tuberculosis can develop at any stage of HIV infection with any number of CD4-lymphocytes, however, acute progressive, generalized, disseminated tuberculosis is characteristic of

patients with severe immunodeficiency. Histomorphological manifestations of tuberculous inflammation in HIV infection reveal a clear correlation with the number of CD4-lymphocytes.

According to Russian scientists, in autopsy studies of deceased individuals from tuberculosis combined with HIV infection, with a CD4-lymphocyte level of less than 200 cells/μl, the microscopic morphological picture has several features: there are no signs of a wave-like course of the process, the monomorphism of specific inflammation foci is noted, the purulent-necrotic nature of inflammation with the absence of a productive component, predominantly perivascular localization of foci, and destructive vasculitis. The loss of features of the specific morphological picture of tuberculous inflammation makes diagnosis difficult, the morphological picture becomes similar to abscessing bacterial pneumonia or mycotic lesions. Upon Ziehl-Neelsen staining in necrotic masses, a large number of acid-resistant mycobacteria are typically found in the cytoplasm of leukocytes. When the number of CD4 lymphocytes exceeds 500 cl/μl, the histological changes in tuberculosis are represented by classical tuberculous granulomas with caseous necrosis in the center, the lesion is limited to the pulmonary component. With moderately pronounced immunodeficiency (the number of CD4 lymphocytes from 400 to 200 cells/μl), the morphological picture of tuberculous inflammation is characterized by the acute progression of tuberculosis with the predominance of alterative-exudative processes, however, a productive reaction in the form of a small number of epithelioid and giant cells is observed around some foci. The clinical manifestations of tuberculosis in patients with HIV infection (as well as the morphological picture) depend on the severity of immunodeficiency. Basic clinical studies have shown that in the "early" stages of HIV infection (IIB_IVA stages according to V.I. Pokrovsky's classification), the clinical manifestations of tuberculosis infection do not differ from the course of tuberculosis in HIV-infected individuals. During this period of HIV infection, tuberculosis usually manifests as an isolated thoracic process with the formation of infiltrative-focal changes, predominantly in the upper lobes of the lungs, often with the formation of decay cavities. The clinical picture is characterized by a mild course initially, then a characteristic intoxication syndrome gradually develops, characterized by fever, predominantly in the evening, weakness, sweating, later accompanied by a cough with a moderate amount of mucopurulent sputum, often hemoptysis or pulmonary hemorrhage. Tuberculin sensitivity is generally preserved and comparable to that of patients without HIV infection. In general, the process proceeds as a secondary tuberculosis.

HIV infection at the stage of its initial manifestations remains a poorly studied problem. Clinical manifestations at this stage occur in 53-93% of cases. During the period of acute HIV infection, when there is a transient decrease in the level of CD4 lymphocytes (stage IIB), tuberculosis can develop as a secondary disease, but due to moderate immunosuppression, in most cases, it is characterized by typical manifestations, and its diagnosis during this period, as a rule, does not cause particular difficulties. Kravchenko A.V. et al. noted the development of various secondary diseases in patients at the stage of primary manifestations in 28.4% of cases, tuberculosis developed only in 3% of observations and was limited to the pulmonary component. As immunodeficiency progresses, when the number of T-lymphocytes, which ensure the effectiveness of acquired natural anti-tuberculosis immunity, decreases, tuberculosis acquires features of a primary one, gradually increasing the degree of suppression of cellular immunity, with a tendency to damage lymphoid tissue, serous membranes, and the development of lymphohematogenous dissemination.

The clinical picture of tuberculosis during this period loses its typical manifestation, the process is characterized by malignancy and a rapidly progressive course. The acuteness and rate of tuberculosis development against the background of immunosuppression resemble the course of a nonspecific bacterial infection, and the rate of development of the developed clinical picture depends on the severity of immunodeficiency. In the structure of clinical forms, tuberculosis of the intrathoracic lymph nodes (60.4-95%), disseminated, miliary processes (62-72%), and damage to the serous membranes (6.7_24%) begin to predominate. A number of authors note that the course of tuberculous pleurisy in such patients is characterized by a sharp progression, a malignant course with prolonged accumulation of exudate.

The deeper the manifestations of HIV-infected immunodeficiency, the more common the generalized forms of tuberculosis. A sufficiently characteristic feature of this period of tuberculosis course is a specific damage to the nervous system, which is the most formidable manifestation of tuberculosis and can occur in the form of meningitis or meningoencephalitis. According to A.M. Panteleev's research, the most common non-thoracic localization of tuberculosis is tuberculosis of the peripheral and mesenteric lymph nodes (69.2% of observations). Their simultaneous involvement with intrathoracic lymph nodes, according to the author, forms a typical triad of generalized tuberculosis in HIV-infected patients.

Skopin M.S. et al. studied the features of abdominal tuberculosis in patients with HIV infection. It was established that among abdominal organs, mesenteric lymph nodes are affected in 39% of observations, liver - in 4%, spleen - in 56%, peritoneum - in 42%, intestines - in 25% of cases. The results of studying the course of tuberculosis against the background of long-term antiretroviral therapy (ARVT) show that with the restoration of immunity in 82% of observations, the specific process again acquires

the characteristics of secondary tuberculosis with a typical clinical and radiological picture.

The radiological picture shows the morphological changes in lung tissue. Numerous studies emphasize that the systolic syndrome complex of pulmonary tuberculosis in the "late" stages of HIV infection is atypical in most observations. Most often (72%), enlargement of the lung roots and upper mediastinum is observed due to damage to intrathoracic lymph nodes, often with radical infiltration. According to some authors, up to 30% of changes in the lungs may not be registered, or there may only be an increase in the pulmonary pattern due to submilliary dissemination.

Information on the detection of the causative agent of tuberculosis in the sputum of patients with HIV infection is contradictory. Some authors believe that bacterial secretion in tuberculosis at the "late" stages of HIV infection is less common and ranges from 17.4% to 36.3%.

According to other studies, bacterial excretion in HIV-infected individuals occurs even more frequently than in HIV-negative individuals (81% vs. 65%). Panteleev A.M. studied the frequency of bacterial secretion depending on the level of CD4_lymphocytes. It was found that with a CD4 lymphocyte level of more than 500 cells/μl, bacterial secretion was recorded in 65% of patients, and with a level of less than 50 cells/μl - in 72.8% of cases. Analysis of clinical data in Africa showed that bacterial secretion in the "late" stages of HIV infection is higher than in the "early" stages.

Conclusions. The clinical manifestations of tuberculosis in patients with HIV infection (as well as the morphological picture) depend on the severity of immunodeficiency. The radiological picture shows the morphological changes in lung tissue. Numerous studies emphasize that the systolic syndrome complex of pulmonary tuberculosis in the "late" stages of HIV infection is atypical in most observations. Mycocenoses - associations of pathogens - are of great importance. The more pronounced the immunodeficiency, the more pronounced the manifestations of candidiasis.

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