ISSN 0975-2366
DOI: https://doi.org/10.31838/ijpr/2021.13.02.133

Research Article

Epidemiology, Etiopathogenesis, Diagnosis and Treatment of Visceral Mycosis in Patients with Tuberculosis/HIV Infection Co-Infection

MUHABBAT DZHURABAEVA[1-2*], EKATERINA ANVAROVA[1-2], SANJAR SULTANOV[1-2], SHERALI MASSAVIROV[1-2], KOZIM MUKHAMEDOV[2], MALIK UTESHEV[2], KHILOLA BABAMATOVA[1-2], AKBAR SOBIROV[1], JAVOKHIR RAJABOV[1]

[1]Department of Phthisiology and Pulmonology, Tashkent Medical Academy, Tashkent Uzbekistan.
[2]National Specialized Medical Science Center for Phthisiology and Pulmonology, Tashkent, Uzbekistan.
*Corresponding Author
Email ID: marufjonsalokhiddinov@gmail.com
Received: 01.11.20, Revised: 08.12.20, Accepted: 20.01.21

ABSTRACT
The World Health Organization (WHO) estimates that among 10.4 million tuberculosis patients worldwide, 1.2 million are people with HIV infection in 2015. To the 1.4 million deaths from tuberculosis worldwide that same year, WHO estimates that 400,000 deaths from tuberculosis-related HIV infection are added. According to WHO, HIV infection and tuberculosis are considered the most dangerous infectious diseases. Due to severe immunodeficiency, tuberculosis patients with HIV infection and AIDS are likely to develop severe systemic and disseminated forms of secondary fungal infection caused by Candida, Cryptococcus and other pathogens. Candidiasis - anthroponosis with contact mechanism of pathogen transmission, characterized by lesions of skin, mucous membranes and internal organs.

Keywords: tuberculosis, HIV-infection, HIV/TB co-infection, visceral mycosis, mycotic complications

INTRODUCTION

Epidemiological data on tuberculosis and HIV infection

The World Health Organization (WHO) estimates that among 10.4 million tuberculosis patients worldwide, 1.2 million are people with HIV infection in 2015. To the 1.4 million deaths from tuberculosis worldwide that same year, WHO estimates that 400,000 deaths from tuberculosis-related HIV infection are added [12-17]. The developing HIV epidemic is beginning to have a negative impact on the development of the epidemiological process for tuberculosis. The "prevalence of tuberculosis" decreases not so much due to the cure of tuberculosis as due to the death of patients with tuberculosis from various causes, primarily HIV infection []. In 2015, for the first time, HIV mortality exceeded TB mortality []. By 2020. 25% or more of new identified tuberculosis patients will be infected with HIV; up to 60% of HIV-related deaths will be due to tuberculosis; deaths from HIV will be 1.5 times more likely to be registered than deaths from tuberculosis among deceased TB patients []. According to WHO, HIV infection and tuberculosis are considered the most dangerous infectious diseases. These two infections are interconnected with each other. Tuberculosis, which has been the leading cause of death for humanity for a millennium, has been driven by the HIV epidemic, and globally, tuberculosis is one of the leading causes of death among HIV-infected people and HIV/AIDS patients. According to WHO estimates, at the beginning of the 21st century about 9 million new cases of tuberculosis develop annually in the world, and almost 10% of them are HIV-positive [].

Tuberculosis also has an impact on HIV infection: WHO estimates that 13% of deaths among HIV-infected people worldwide are due to tuberculosis [7.12]. The HIV pandemic, and advances in the treatment of bacterial infections have led to an increased population of immunocompromised patients at high risk of invasive (deep) mycosis []. The number of invasive mycoses in HIV/TB patients is progressively increasing, and these diseases are characterized by severe clinical manifestations and very high mortality rates. [6,18]. One of the reasons for the worsening epidemiological situation with regard to tuberculosis is the rapid increase in the HIV pandemic [4]. Every 15th TB case in the world is linked to HIV infection, with 9% of all new annual TB cases being registered with HIV-infected people [3,18]. The risk of tuberculosis development in HIV-infected people is significantly higher than in other population

groups. The problem is particularly acute in developing countries [1,5,7,13].

Since 1990 in the world there has been an increase of tuberculosis morbidity, the disease has returned to developed countries, while the prevalence in developing countries remains high. [10,12].

According to official statistics, as 2014 was 28.250 people with HIV infection are registered in the Republic of Uzbekistan. The share of parenteral route of transmission was 40.6%, the share of sexual route was 41.8%, and the share of vertical route was 3.4%. Cases of HIV were registered in all administrative territories of the Republic. During the reporting period, a total of 25,644,463 people was tested for HIV in the Republic, including 4,247 newly registered cases of HIV infection (14.1 intensive cases per 100,000 of the population) []. The proportion of women in the total number of PLHIV remains consistently high. In 2013, 46.3% of PLHIV were women and 53.6% of newly registered cases were men. In 2013 65.2% of newly registered cases of HIV infection are among the population aged 25-49 years. By geographical distribution, HIV prevalence is higher in large cities of the republic and in regions with higher population density. Thus, 40% of registered cases are related to Tashkent city and Tashkent region (the capital city and surrounding region) [3].

Etiological prerequisites for developing mycotic complications in tuberculosis patients with HIV infection

In recent decades, HIV infection has had a significant impact on the spread of tuberculosis worldwide. The morbidity, mortality, and efficacy of tuberculosis treatment are largely related to HIV prevalence in both the general population and tuberculosis patients [].

During the last decade opportunistic mycoses have become an important health problem both in our country and in many countries of the world. The increasing number of HIV cases, the widespread use of immunosuppressants, cytostatic, corticosteroids, broad-spectrum antibiotics, and invasive diagnostic and treatment procedures are only some of the reasons why the number of fungal infections is increasing significantly [11]. Risk factors for invasive mycosis in HIV-infected patients include high immune deficiency (CD4 below 200 cells/μL), lack of antiretroviral therapy, and presence of surface candidiasis foci [10].

Invasive fungal lesions (mycoses) are among the most commonly reported diseases, both in the early and late stages in people with HIV infection. In the early stages of the HIV epidemic, they were even fatal. In 64% of cases, fungal diseases in HIV-infected people are represented by C. albicans monoculture with other types of fungi - 33% [2].

Respiratory tuberculosis is one such background for development of mycoses of chronic infectious diseases. Mycotic infection can complicate lung tuberculosis in any form and phase. Mycosis can be considered a pathogenetic and environmental satellite of tuberculosis. Like tuberculosis, mycosis occurs against the background of immunodeficiency; it is facilitated by further medication suppression of immunity in a patient [6,9].

In the process of examination of patients with lung tuberculosis it was found out that yeast like fungi from sputum or washing water of bronchi are detected by sowing in 48,7% of cases. Weighting of the course of tuberculosis in combination with candidiasis is caused by aggravation of immunodeficiency state and negative influence of the emerging association of microorganisms on the patient's organism. Symbiotic existence of mycobacteria and fungal colonies creates significant barriers to the penetration of TB specific drugs into the infectious focus. Fungal colonies create both mechanical barriers and enzymatic activity to inactivate the action of antituberculosis drugs [5].

The clinical and epidemiological data accumulated so far allow us to speak about the ability of fungi taking different taxonomic positions to form combined forms of infection with the causative agents of many infectious and parasitic diseases. The phenomenon of combination is especially important in cases of HIV infection and AIDS [1,7].

Due to severe immunodeficiency, tuberculosis patients with HIV infection and AIDS are likely to develop severe systemic and disseminated forms of secondary fungal infection caused by Candida, Cryptococcus and other pathogens. [1,4,8,13]

The complexity and importance of tuberculosis in HIV-positive patients is important for physicians treating mycoses, as mycosis in patients with this combined pathology is becoming more and more common [5,14].

In recent decades, mycoses, i.e. diseases caused by microscopic fungi, have become an important clinical problem.

According to O.P. Frolova 2016 mycoses were registered in Russia in 2014 in more than a third of patients with HIV-infected tuberculosis.

Opportunistic deep mycosis is a group of infections caused by opportunistic fungi, usually in the background of immunodeficiency. Widespread opportunistic fungi live in the external environment, decomposing dead organic substrate or parasitizing on plants. Opportunistic

mushrooms are also able to persist in tissues in the human body and under certain conditions to show pathogenic properties, causing different localization and clinical forms of mycosis.

The development of an infection process caused by a opportunistic fungus is usually preceded by a primary illness or a decrease in immune status. In general, secondary opportunistic mycoses develop in the initially weakened human body, being frequent complications of a number of serious chronic diseases: AIDS, malignant tumors, diseases of the blood system, tuberculosis. Disposition to the development of pathological process is determined not by virulence of this or that type of opportunistic fungus, but by individual susceptibility of human organism [1].

A significant part of different types of fungi is able to inhabit lung and pleural cavities formed earlier in TB patients. Thus, not only aspergillosis agents were found in the contents of destructive cavities (caverns, tuberculems, cysts, aspergilles) (6 species were identified), but also fungi of Candida (4 species), Penicillium (2 species), as well as Alternaria alternata, Aureobasidium pululans, Cladosporium cladosporioides, Cryptococcus neoformans, Fusarium oxysporum, Geotrichum candidum, Paecilomyces variotii, Rhizopus oryzae [17].

Candidosis - anthroponosis with contact mechanism of pathogen transmission, characterized by lesions of skin, mucous membranes and internal organs. Of the conditionally pathogenic asporogenic fungi Candida spp. predominate in human pathology are Candida albicans, less often Candida tropicalis, S. krusei, S. pseudotropicalis, S. stellatoidea and some other species. Candida are aerobes; they are often saprophytes of the mucous membranes of the mouth, intestines, vagina and skin [11,15].

Candidiasis is often a secondary superinfection for a number of infections (most commonly HIV), as well as a combined pathology with multiple opportunistic microflora representatives.

Endogenous infection is connected with the activation of yeast-like fungi already present in the microbial associations of the organism, so in severe diseases (tuberculosis, HIV infection, pneumonia, malignant neoplasms, etc.) candidiasis can occur as a concomitant disease. In case of candidiasis of the mucous membranes of the oral cavity and pharynx, surface easily detachable whitish-yellowish films are found.

Microscopically, they consist of pseudo-mycelium of the fungus, sloughing epithelium and a small number of segmented leukocytes. In more severe forms of lesions, the fungus penetrates between the epithelium layers and parasitizes the cells. Their dystrophy and edema, perivascular inflammatory infiltrates in derma are observed. Visceral candidiasis can be isolated (gastrointestinal tract, respiratory organs, urogenital system) and generalized with single or multiple metastases in internal organs, nervous system, muscles, bones.

Candidiasis esophagitis is more often a consequence of spread of the process from the mucosa of the oral cavity and pharynx; three types of lesions are distinguished: 1) individual whitish plaques consisting of sloughed epithelial cells, leukocytes, and filaments of fungus, which invade between the cells of the multilayer squamous epithelium; 2) formation of confluent dense deposits and invasion of the fungus into the submucosal layer; 3) pseudomembranous deposits developed on ulcerated mucosa; threads of fungus not only penetrate necrotic masses, but also penetrate deeply into muscular esophagus and grow into vessels [2].

The risk of developing secondary (opportunistic) bronchial and pulmonary aspergillosis in patients with respiratory tuberculosis is determined both by the course of the primary lung disease caused by Mycobacterium tuberculosis and by the presence of a number of predisposing factors. Risk factors should include: the presence of cavitary changes and bronchiectasis in the lungs, various immunosuppressive conditions, long-term use of broad-spectrum antibiotics, invasive procedures, as well as colonization of the mucous membranes of the respiratory tract with fungi of the genus Aspergillus [6,13]

To date, about 50 species of fungi of the genus Aspergillus are already known and have been described as etiological agents of human bronchial and lung lesions [16].

Aspergillosis pathogens are not transmitted from person to person, and infection usually occurs through inhalation of air containing conidia of fungi of the genus Aspergillus. Most Aspergillus spp. species, including all major aspergillosis pathogens (Aspergillus fumigatus, A. flavus, A. niger and A. terreus), are widely distributed and present in ambient air and inside various premises, including medical hospitals [3,6,9].

Conidia of the pathogenic fungi Aspergillus spp. (2 to 5 μm in diameter) can penetrate into the respiratory tract and reach the alveoli, causing various clinical forms of bronchopulmonary aspergillosis in susceptible individuals [3,4].

Thus, respiratory tract fungi colonization among newly diagnosed pulmonary tuberculosis patients is high and reaches 66.7%, mainly fungi of the genus Candida at a titer of more than 1 × 103KOE/ml, but in 14.3% of them there is a

combination with other fungi, including the genus Aspergillus [10].

Diagnostic features of mycosis detection in patients with tuberculosis combined with HIV infection.

Due to severe immunodeficiency, TB patients with HIV infection and AIDS are highly likely to develop secondary fungal infections caused by Candida, Cryptococcus and other pathogenic fungi [2,6].

Fungal colonies are an ideal biocenosis for Mycobacterium tuberculosis. Mycobacteria enter into unified microecosystems with fungal colonies in the lungs and settle within the colonies, which makes it difficult for the microorganism's immune system and anti-tuberculosis drugs to affect them. The surrounding colony of fungi completely isolates mycobacteria from damaging factors and allows them to multiply under favorable conditions [11].

HIV-associated visceral mycoses are the most common opportunistic infection, joining as CD4 immunocompetent cells decline, which also contributes to the progression of HIV infection []. The significance of the role of mycoses in human pathology is determined by their worldwide prevalence, their extraordinary frequency (higher than that of all other infectious diseases), etiological and nosological heterogeneity (pathological changes ranging from superficial and harmless to severe and life-threatening).

Therapeutic resistance (in particular, due to the fact that mycoses in most cases develop secondary, on the pathological basis of the underlying disease), the tendency to relapse, as their ubiquity is due to the presence of a more or less constant risk of infection. The danger of mycoses is not limited to skin and mucosa lesions. Lethality in visceral deep mycoses reaches 86%. In the 70s, the mortality rate in septicemia caused by fungi of the genus Candida, during the first month of life of newborns was 70-80%, in recent years this figure has decreased, but remains high, amounting to about 40% at the present time. Out of 69 thousand described and studied species of fungi causing human diseases, 400 fungal infectants are recognized.

The morbidity of visceral mycoses is increasing worldwide, often due to the widespread use of antibacterial drugs, hormones, including oral contraceptives, cytostatic. In addition, the spectrum of diseases has increased, creating a favorable background for their development: diseases of the hematopoietic organs, disharmonies, disorders of the digestive system, radiation lesions, malignant tumors, HIV infections, immunodeficiency states, etc. Certain physiological conditions (pregnancy) and such biological factors as age contribute to the development of mycoses.

Opportunistic mycoses have a much lower degree of invasiveness than opportunistic bacteria, and for the development of infection a violation of the organism's defenses is essential, especially for the state of cellular immunity, since the antibodies formed are not able to penetrate to the sites of usual localization of fungal infection.

Among the most frequent visceral mycoses in patients with HIV infection is pneumocystis pneumonia (PCP) caused by Pnevmocistis jiroverci, one of the most severe diseases, which, if not treated in time, inevitably leads to the death of the patient.

Diagnosis of PCP is very difficult due to the lack of pathognomonic clinical symptoms, clear criteria and effective laboratory methods. The problem of the increasing number of diseases caused by mycoses of the genus Candida is becoming increasingly important. Candida lesions are more common in HIV-infected individuals than any other mycosis infection.

Clinical manifestations of Cryptococcus neoformans can range from asymptomatic infiltrates to severe acute respiratory dysfunction. Diagnosis of Cryptococcus neoformans by clinical methods alone is not possible due to the fact that its clinical manifestations and signs have no absolute specificity.

We can add to the above that the diagnosis of mycotic diseases cannot be based solely on laboratory data, since many pathogens can be found in healthy individuals. Therefore, in visceral mycoses, to make a diagnosis, a complex clinical and laboratory examination of the patient is used, including:

1. Anamnesis (use of antibiotics, immunodeficiency states).
2. Clinical manifestations of mycotic infection.
3. Isolation of a pathogen with its confirmed involvement in a given infectious process:

а) microscopic examination in native or stained smears;

б) isolation of the pathogen on nutrient media;

в) serological methods;

The comparative rarity of widespread deep mycosis lesions, the lack of objective clinical and laboratory data allowing timely suspicion and confirmation of disseminated mycosis, also lead to errors in the diagnosis and treatment of this pathology.

Analysis of world data on the provision of therapeutic and preventive care to HIV-infected patients with clinical manifestations of visceral mycoses shows the feasibility of implementing

and conducting scientific research, taking into account the specifics of the region.

In addition, it is advisable to pay attention to the effectiveness of fungicide therapy, its combination with antiretroviral drugs and the possibility of resistance formation, which is currently important for Uzbekistan.

Cryptococcosis is the most common life-threatening mycosis to which people with insufficient cellular immunity, in particular HIV-infected people, are prone. The disease is usually generalized, affecting the central nervous system.

Cryptococcosis (Blastomycosis Busse-Buschke, Saccharomycosis, Torulosis) is a disease caused by a yeast-like fungus of the genus Cryptoccocus, which belongs to the opportunistic infections. In immunocompetent people pathogen is localized in lungs, with immunodeficient states there is generalization of the process with involvement of brain membranes, kidneys, skin, bone apparatus. Cryptococcosis refers to AIDS-marker diseases.

The causative agent is Cryptococcus neoformans. In pathological material, it looks like yeast cells of round shape, 3-10 microns in diameter, surrounded by a transparent gelatinous capsule up to 50 microns wide. It is resistant in the external environment.

Cryptococcus is widespread in nature, it is found in the droppings of pigeons, sparrows and other birds, while the birds themselves are not sick. In a dried state, Cryptococcus can persist for many months. Cryptococcus has been found on the mucous membranes of healthy humans as a saprophyte. Infection of humans occurs by airborne dust. There are two varieties of C. neoformans. In Europe and North America, C. neoformans var. neoformans is common, and in tropical and subtropical areas, C. neoformans var. gatti. Both variants are pathogenic to humans. C. neoformans var. neoformans prevails in patients with AIDS (even in tropical areas, where previously only C. neoformans var. gatti was common, C. neoformans var. neoformans is now predominantly found in HIV-infected people).

The respiratory tract is the gateway for infection. An aerosol containing the pathogen (dust, mucosal secretions from a patient or carrier) entering the respiratory tract leads to the formation of a primary focus in the lungs, which in immunosuppressed individuals may be a source of further hematogenous dissemination to organs and tissues. It is believed that infecting are small, capsule-free, yeast-like cells with a diameter less than 2 microns, capable of reaching the alveoli with air flow. It is assumed that basidiospores due to their small size can also be considered pathogenic [].

Cryptococci can also enter the human body through damaged skin, mucous membranes, and the gastrointestinal tract. In immunocompetent individuals, the disease occurs sparingly, locally and ends spontaneously with sanitation of the body [].

Factor contributing to the development of cryptococcal infection is congenital or acquired immunodeficiency, mainly its cellular component. In people with preserved immune status cryptococcal pathogen, getting into the lungs, persists there for months or years and only under changed conditions (immunosuppression) begins to multiply and disseminate in the body, affecting different tissues and organs. Indirect evidence of this position is the high incidence of cryptococcosis in AIDS patients.

Diagnostic methods for mycoses

However, the diagnosis of invasive mycoses is not easy. This is due not only to the difficulties in obtaining fungal culture, but also in the interpretation of the results of the study, since fungi, both yeast and mycelial, can colonize mucous membranes, contamination of the samples under study. In this regard, the diagnosis of invasive mycoses is based on a comprehensive approach, including not only the results of mycological (cultural) and serological (determination of fungal antigen) studies, but also clinical symptoms of fungal infection, data of auxiliary research methods (computer or magnetic resonance imaging, ultrasound) [17].

The European-American Cooperative Group for the Study of Invasive Mycoses in Immunocompromised Patients has developed diagnostic criteria for invasive mycoses. The criteria of proven, probable and possible invasive mycosis are defined and recommended for use in clinical and epidemiological studies [].

Proven invasive mycosis caused by yeast fungi: detection of yeast cells (fungi of the genus Candida can form pseudomycelium or true mycelium) in biopsy or aspirates, except mucosal samples, or culture isolation from samples obtained under aseptic conditions from a normally sterile focus, that is clinically and radiologically linked to the infection, except for urine, sinus and mucosa specimens, or the detection of yeast cells or positive Cryptococcus spp. antigen on microscopy and specific staining (ink drop, mucicarmine staining). in cerebrospinal fluid [17].

For the species identification of yeast strains, a set of common techniques is most commonly used: CandiSelect 4, Bio-Rad and Brilliance Candida Agar chromogenic media, OXOID, Saburo Agar with glucose and chloramphenicol, Nickerson medium, Chapik-Dox agar, High-Chromium

selective agar; Auxacolor 2, Bio-Rad and ELIchrom FUNGI, ELITech MICROBIO test systems for biochemical studies; macro- and micromorphological signs (microscopy of unstained and ink-stained preparations) on agarized nutrient media; temperature limits of growth [8,14,15].

Identification of fungi, especially those derived from sterile loci, is necessary primarily for the choice of antimycotic and adequate antifungal therapy. For example, Candida krusei is resistant to fluconazole and less sensitive than yeast fungi of other species to amphotericin B; Aspergillus terreus, Scedosporium apiospermum (Pseudallescheria boydii), Trichosporon beigelii, Scopulariopsis spp. are resistant to amphotericin B; Mucorales are resistant to itraconazole, voriconazole, Candida glabrata shows dose-dependent sensitivity to fluconazole, and if this fungus, even sensitive strains are isolated, the fluconazole dose should be increased (adults are given 800 mg instead of 400 mg); Candida lusitaniae is resistant to amphotericin B [17]. ??????

Determination of sensitivity to antimycotics is carried out by microdilution in broth with RPMI 1640 medium with determination of minimum suppressive concentrations (MSC) in μg/ml [Sensititre system (colorimetric test "YeastOne"), TREK Diagnostics Systems) [9,16].

Thus, it is necessary to study the species composition and sensitivity levels to antifungal drugs of yeast strains isolated during the diagnosis of mycoses of various localizations in HIV-infected patients with tuberculosis in order to improve the effectiveness of anti-tuberculosis therapy.

DISCUSSION

As can be seen from the above data, opportunistic (secondary) infectious diseases of the bronchi and lungs of a mycotic nature (Pneumomycosis: Aspergillosis, Candidiasis, Cryptococcosis, Mucormycosis, fusarium and other Hyalogyphomycosis, Pheogyphomycosis) and disseminated mycoses with a number of chronic lung complications are becoming more and more frequent diseases: malignant neoplasms, diseases of the blood system, diseases caused by the human immunodeficiency virus (HIV), tuberculosis, etc. The most susceptible to these diseases are patients with immunodeficiency conditions, often caused by modern immunosuppressive therapy. With an increase in the number of patients with immunodeficiency and patients predisposed to the development of deep mycoses, opportunistic fungi have become one of the main and dangerous pathogens of nosocomial infections.

The list of potential causative agents of human mycoses is constantly increasing due to the description of new yeast and mycelial (mold) opportunistic fungi - Micromycetes, common in the external environment, which are able to persist in the human body and, under certain conditions (decrease in the host's antimicrobial defense, massive infection), exhibit pathogenic properties ; the composition of yeast fungi is expanding, as well as light-colored (Hyalogyphomycetes) and dark-colored (Pheogyphomycetes) mold fungi - causative agents of deep infections that are difficult to diagnose and amenable to treatment. At the moment, the group of pathogenic fungi already includes more than 500 primary pathogenic and opportunistic species from the Zygomycota, Ascomycota, Basidiomycota divisions.

Micromycete lesions of the bronchi, lungs and pleura are likely infectious complications of tuberculosis, which is due to the presence of a severe primary lung disease (its course and progression) and a number of predisposing factors: the formation of cavitary changes and bronchiectasis in the lungs; various immunosuppressive conditions, including cases of tuberculosis combined with HIV infection; long-term use of several broad-spectrum antibacterial drugs; the presence of widespread colonization of the lower respiratory tract by opportunistic fungi; carrying out invasive procedures and other risk factors associated with staying in a phthisiatric hospital. The settlement and subsequent colonization of the lower respiratory tract by fungi of the genera Aspergillus or Candida can lead to the development of allergic forms of diseases that can complicate the course of the tuberculous process. A significant number of patients have two or more factors that predispose to the development of mycosis; their combination with the presence of spores of Aspergillus spp. is especially dangerous. and other filamentous fungi in the air of a hospital.

Diagnosis of mycoses of the respiratory system in phthisiatric practice is one of the difficult clinical and laboratory tasks, since the clinical and radiological signs of pneumomycosis are nonspecific and not always expressed, and mycosis can proceed under the guise of tuberculosis, abscess and other lung diseases. Of decisive importance in the diagnosis of mycoses of the bronchi and lungs are the data of microbiological and immunological laboratory studies, which make it possible to establish and prove the etiology of the lesion and give informed recommendations for the development of

adequate drug therapy based on the properties of the isolated pathogen.

In recent years, ideas about the etiology and clinical forms of deep opportunistic mycoses have changed, the composition of potential pathogens has expanded, some of which are primarily resistant to antifungal drugs widely used in the clinic; laboratory methods for the diagnosis of invasive mycoses and chronic forms of pulmonary aspergillosis have been standardized and improved and their reliability has been increased; new drugs with different spectrum of action have been developed and are being developed. Obviously, the laboratory mycological service in a modern phthisiatric clinic should be ready to solve the increasingly complicated problems of diagnosing secondary bronchopulmonary mycoses and selecting drugs for their treatment. Considering the above, the urgency of the problem of introducing into the work of anti-tuberculosis institutions of adequate laboratory diagnosis of pneumomycosis on the basis of methodological approaches developed by specialized research centers, using standardized methods adapted for practical research, is obvious.

ACKNOWLEDGMENTS

The authors thank National Tuberculosis Program of Uzbekistan, The Republican Specialized Scientific-Practical Medical Center of Phthisiology and Pulmonology and Tashkent Medical Academy - ambulatories for administrative support and collaboration during the study period and providing access to the data.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Amiri MRJ, Siami R, Khaledi A. Tuberculosis Status and Coinfection of Pulmonary Fungal Infections in Patients Referred to Reference Laboratory of Health Centers Ghaemshahr City during 2007-2017. *Ethiop J Health Sci*. 2018;28(6):683-690. doi:10.4314/ejhs.v28i6.2
2. Amiri MRJ, SiamiR, KhalediA. Состояние туберкулеза и ко-инфекция легочных грибковых инфекций у пациентов, направленных в референс-лабораторию медицинских центров города Гемшахр в течение 2007-2017 гг. Ethiop J Health Sci. 2018; 28 (6): 683-690. DOI: 10,4314 / ejhs.v28i6.2
3. Bansod S, Rai M. Emerging of Mycotic Infection in Patients Infected with Mycobacterium tuberculosis. *World J Med Sci*. 2008;3(2):74-80. https://pdfs.semanticscholar.org/6857/5341de2343b79d75295800aeb2168efc01b4.pdf. Accessed October 3, 2019.
4. Bruchfeld J, Correia-Neves M, Källenius G. Tuberculosis and HIV Coinfection. *Cold Spring Harb Perspect Med*. 2015;5(7):a017871. doi:10.1101/cshperspect.a017871
5. Clinical and Laboratory Standards Institute (CLSI). Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts; Third Informational Supplement. CLSI document M27-S3. CLSI: Wayne, PA., 2008.
6. Clinical and Laboratory Standards Institute (CLSI). Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts; Fourth Informational Supplement. CLSI document M27-S4. CLSI: Wayne, PA., 2012: 30 p.
7. Getahun H, Gunneberg C, Granich R, Nunn P. HIV Infection–Associated Tuberculosis: The Epidemiology and the Response. *Clin Infect Dis*. 2010;50(s3):S201-S207. doi:10.1086/651492
8. Global tuberculosis report, 2016, WHO/HTM/TB/2016.13.
9. Hoog de G. S., Guarro J., Gene J., Figueras M .J. Atlas of clinical fungi. Electronic Version 3.1 – CBS: Reus, 2011. The Aspergillus Website http://www.aspergillus.org.uk/
10. Kulko A., Dreval P. Yeasts and mycelial fungi in lung cavities of tuberculosis patients. 20 th European Congress of Clinical Microbiology and Infectious Diseases Vienna, Austria. 10−13 April 2010. Abstracts on CD-ROM. Clinical Microbiology and Infection, 2010; v. 16 (2).
11. National Progress Report on Commitment to Combat HIV/AIDS.; 2014.
12. Perfect J.R., Dismukes W.E., Dromer F. Clinical Practice Guidelines for the Management of Cryptococcal Disease: 2010 Update by the Infectious Diseases Society of America. Clinical Infectious Diseases 2010; 50: 291–322.
13. Talle M, Hamidu I, Nasir I-A и др. Распространенность и профиль патогенных микроорганизмов в легких среди ВИЧ-инфицированных пациентов, посещающих Университетскую больницу Майдугури, Нигерия. Египет JInternMed. 2017; 29 (1): 11. DOI: 10,4103 / ejim.ejim_5_17
14. Talle M, Hamidu I, Nasir I-A, et al. Prevalence and profile of pulmonary fungal pathogens among HIV-infected patients attending University of Maiduguri Teaching Hospital, Nigeria. *Egypt J Intern Med*. 2017;29(1):11. doi:10.4103/ejim.ejim_5_17
15. TB Country Profile, Uzbekistan.; 2017. https://extranet.who.int/sree/Reports?op=Replet&name=%2FWHO_HQ_Reports%2FG2%2FPROD%2FEXT%2FTBCountryProfile&ISO2=UZ&outtype=pdf. Accessed October 3, 2019.
16. WHO | Global Tuberculosis Report 2018.; 2018.

17. WHO's global TB database http://www.who.int/tb/country/data/download/en/
18. World Health Organization (WHO/HTM/TB/2009.411). 2009. Geneva,
19. Алексеева Л.П. Особенности выявления, клинического течения и лечения больных туберкулезом и ВИЧинфекцией: Автореф. дис…. канд. мед. наук. М., 2008
20. Атлас грибковых заболеваний. Под ред. К.А. Кауфман, Д.Л. Манделла (Kauffmann C.A., Mandell G.L.). Пер. с англ. под ред. Ю.В. Сергеева. – М.: ГЭОТАР-Медиа. 2010: 240 с.
21. Бансод С., Рай М. Появление микотической инфекции у пациентов, инфицированных микобактериями туберкулеза. WorldJMedSci. 2008; 3 (2): 74-80. https://pdfs.semanticscholar.org/6857/5341de2343b79d75295800aeb2168efc01b4.pdf. Доступ 3 октября 2019 года.
22. Большая медицинская энциклопедия. Кандидоз. http://xn--90aw5c.xn--c1avg/index.php/
23. Брухфельд Дж., Коррейя-Невес М., Келлениус Г. Туберкулез и ко-инфекция ВИЧ. Холодная весна HarbPerspectMed. 2015; 5 (7): a017871. DOI: 10,1101 / cshperspect.a017871
24. Владимиров С.К. Статистическая связь выявляемости ВИЧ инфекции с заболеваемостью туберкулезом и учетом больных туберкулезом в России. Соц. Аспекты здоровья населения. 2008; 3
25. ВОЗ | Глобальный отчет по туберкулезу 2018 г .; 2018.
26. Гашенко А.В. Совершенствование организации раннего выявления, диспансерного наблюдения и мониторинга туберкулеза, сочетанного с ВИЧинфекцией: Автореф. дис…. канд. мед. наук. М., 2010.
27. Гетахун Х., Ганнеберг С., Гранич Р., Нанн П. Туберкулез, связанный с ВИЧ-инфекцией: эпидемиология и ответ. ClinInfectDis. 2010; 50 (s3): S201-S207. DOI: 10,1086 / 651492
28. Гролл А. Х., Уолш Т. Д. Аспергиллез // Атлас грибковых заболеваний / Под ред. К. А. Кауфман, Д. Л. Манделла. – М.: ГЭОТАР-Медиа, 2010. С. 133-159.
29. Диагностика и лечение микозов. Под ред. Д. Р. Хоспентала, М. Дж. Риналди (D.R. Hospenthal, M.G. Rinaldi). Пер. с англ. под ред. Ю.В.Сергеева. – М.: ГЭОТАР-Медиа. 2013: 448 с.
30. Диагностика и лечение микозов. Под ред. Д. Р. Хоспентала, М. Дж. Риналди (D.R. Hospenthal, M.G. Rinaldi). Пер. с англ. под ред. Ю.В.Сергеева. – М.: ГЭОТАР-Медиа. 2013: 448 с.
31. Ермак Т. Н. Пневмоцистная пневмония, туберкулез легких и их сочетание у больных ВИЧ-инфекцией. Эпидемиология и инфекционные болезни 2008; (3): 34-38.
32. Залескис Р. Принципы контроля ВИЧ-ассоциированного туберкулеза в Европейском регионе. Туберкулез и болезни легких. 2014; 6: 69-70.
33. Источник: https://meduniver.com/Medical/gematologia/diagnostika_mikozov.html MedUniver
34. Климко Н.Н. Микозы: диагностика и лечение. Руководство для врачей. 2е изд., перераб. и доп. — М., Ви Джи Групп, 2008. — 336 с.
35. Кожушко М. Ю. Клинические особенности туберкулеза у ВИЧ-инфицированных: лекция / М. Ю. Кожушко, И. В. Евстигнеев // Therapia. – 2010. – № 9 – С. 12–17.
36. Конончук О.Н. Оптимизация выявления туберкулеза у больных ВИЧ-инфекцией и прогнозирование распространенности сочетанной патологии на примере Кемеровской области: Автореф. дис…. канд. мед. Наук. Новосибирск, 2010
37. Кулько А.Б. Туберкулёз и болезни лёгких. Изучение чувствительности к противогрибковым препаратам грибов рода aspergillus– возбудителей бронхолегочных инфекций у больных туберкулезом том 95, № 7, 2017 с.54-60.
38. Кулько А.Б. Успехи медицинской микологии. Микозы у ВИЧ-инфицированных больных туберкулезом: видовой состав дрожжевых грибов и чувствительность к противогрибковым препаратам 2015 С.135-138.
39. Кулько А.Б. Чувствительность к противогрибковым препаратам клинических штаммов грибов рода Candida, выделенных от больных туберкулезом легких. Туберкулез и социально значимые заболев. 2013. № 2: 35-8.
40. Ловачева О. В., Корниенко И. И., Кулько А. Б., Слогоцкая Л. В., Литвинов В. И. Лечение итраконазолом в суспензии патологической колонизации грибами дыхательных путей у больных туберкулезом легких // Пробл. туберкулеза и болезней легких. – 2008. – № 1. – С. 42-46.
41. Макарова Н. Ю., Кравченко А. В., Юрин О. Г. и др. Особенности этиологии грибковых инфекций у больных ВИЧ-инфекцией и лекарственная устойчивость выявленных грибковых патогенов к флюконазолу. Эпидемиология и инфекционные болезни 2003; (2): 33-35.

42. Национальный доклад о ходе выполнения декларации о приверженности делу борьбы с ВИЧ/СПИД специальной сессии генеральной ассамблеи ООН. Дата представления: 31 март 2014 года С.29.
43. Национальный отчет о прогрессе в борьбе с ВИЧ / СПИДом. 2014.
44. Нечаева О. Б Эпидемическая ситуация по туберкулезу среди лиц с ВИЧ-инфекцией в России. Tuberculosis and Lung Diseases, Vol. 95, No. 3, 2017 С.13-19.
45. Парпиева Н.Н., Мухамедов К.С. ,Якуббеков Т.Ю., Джурабаева М.Х., Массавиров Ш.Ш Диагностика и лечение висцеральных микозов у больных туберкулезом сочетанных с ВИЧ-инфекцией» Учебно-методическое пособие для резидентов магистратуры медицинских ВУЗов, врачей-фтизиатров и инфекционистов. Ташкент 2010г..
46. Профиль страны по туберкулезу, Узбекистан .; 2017. https://extranet.who.int/sree/Reports?op=Replet&name=%2FWHO_HQ_Reports%2FG2%2FPROD%2FEXT%2FTBCountryProfile&ISO2=UZ&outtype=pdf. Доступ 3 октября 2019 года.
47. Разработка и реализация стратегии противодействия туберкулезу в России (Ресурсный центр по изучению политики в сфере ВИЧ/СПИДа). Институт демографии Гос. университета Высш. шк. экономики. Демоскоп Weekly. Население и общество (эл. версия). 2008; 327–328. http://www.demoscope.ru/weekly/2008/0327/analit05.php
48. Сарсенбаева М. З. Этиологическая роль различных видов дрожжеподобных грибков рода Candida в развитии кандидоза у больных туберкулезом и особенности микробного синергизма при сочетанных инфекциях: Автореф. дис. канд. мед. наук. – Алматы, 2006. 24 с.
49. Сергеев А.Ю., Сергеев Ю.В. Грибковые инфекции. Рук. для врачей. – М.: Изд-во Бином. 2008: 480 с.
50. Стойчакова В. Б. Медицинская микология: руководство для врачей. М: ГЭОТАР-медиа 2008.
51. Узбекистан ЮНЭЙДС. https://www.unaids.org/en/regionscountries/countries/uzbekistan.
52. Фролова О.П., Белякова Е.Ф., Шаркова Т.И., Казенный А.Б. Микозы у больных ВИЧ-инфекцией в сочетании с туберкулезом, подходы к их выявлению. Успехи медицинской микологии. 2016 С. 17-20.
53. Фролова О.П., Шинкарева И.Г., Казенный А.Б., Новоселова О.А. Мониторинг туберкулеза, сочетанного с ВИЧ инфекцией. Пробл. туб. у больных ВИЧ инфекцией 2009; 9: 12–21.
54. Хауадамова Г. Т. Выявление системных кандидозов у больных туберкулезом//I конгресс фтизиатров Казахстана. – 2004. – 209 с.
55. Чарушина И. П. Оппортунистические инвазивные микозы у ВИЧ-инфицированных пациентов. Пермский медицинский журнал. 2015 том XXXII № 1 с.71-77