ENGLISH VERSION: CLINICAL FEATURES OF SKIN LESION IN DEEP MYCOSES AGAINST THE BACKGROUND OF HIV/AIDS*

Daschuk A.M., Kutsevliak L.O.

Kharkiv National Medical University, Kharkiv

Introduction. The incidence of HIV/AIDS infection in Ukraine has reached a considerable scale. One of the earliest markers of HIV/AIDS infection is the skin lesion caused by fungi. Deep mycoses develop in the spread of infection from the skin to the underlying tissues, or as a result of hematogenous dissemination. Due to the fact that HIV/AIDS infection has gone beyond the vulnerable groups (commercial sex workers, injecting drug users, etc.), knowledge and alertness of doctors about the unusual clinical manifestations of dermatoses may be a factor in early diagnosis of HIV/AIDS. Timely diagnosis, treatment and conduction of anti-epidemic measures will reduce the incidence of HIV/AIDS infection in Ukraine. Treatment of concomitant HIV-related fungal skin lesions can improve the effectiveness of antiretroviral therapy. The aim of the research was to study the clinical picture, diagnostics and treatment of deep mycoses in HIV/ AIDS infected patients. Methods. The analysis of the scientific literature on the etiology, pathogenesis, clinical picture, diagnosis and treatment of deep mycoses in patients with HIV/AIDS infection has been conducted. Conclusions. The treatment of deep mycoses in HIV/AIDS infection is quite difficult and requires continuous use of antifungal agents.

Key words: HIV/AIDS infection, deep mycoses, diagnosis and treatment.

Pandemic of infection caused by the human immunodeficiency virus is the high-profile event in the twentieth century and in the history of mankind. It unfolds against the backdrop of increasing number of people who are promiscuous with frequent partner change [1,2,3]. These are mainly young persons of reproductive and working age. One of the earliest markers of HIV/AIDS infection is the skin lesion caused by fungi. Deep mycoses develop in the spread of infection from the skin to the underlying tissues, or as a result of hematogenous dissemination.

COCCIDIOIDOMYCOSIS

Coccidioidomycosis is a deep mycosis which elapses with the primary lung damage. In many cases, the disease subsides on its own, but in some patients the infection spreads hematogenously in the skin, bones, meninges, lungs. Thus, there are multiple foci of chronic granulomatous inflammation. Occasionally, the pathogen (Coccidioides immitis) enters the body through the damaged skin. It is widespread in the arid zones of the western hemisphere [5].

According to the classification, one can distinguish between the following forms of coccidioidomycosis [4]:

- Asymptomatic infection
- Acute pulmonary coccidioidomycosis (valley fever)
- Disseminated coccidioidomycosis (skin, bones and joints, meningitis)

In acute pulmonary coccidioidomycosis on the skin, one can observe widespread erythema, morbilliform rash. Urticaria, erythema nodosum, polymorphic erythema may be present.

Disseminated coccidioidomycosis is characterized by papules, pustules, plaques, nodes, abscesses, cellulitis, multiple fistulas, ulcers, warty growths, granulomas, scarring. As a rule, it develops when the level of CD4 cell count is below 200 mcl^{-1}.

The primary skin lesion is extremely rare. In the site of pathogen permeation, there is a node which subsequently ulcerates. Sometimes lymphangitis and regional lymphadenitis develop.

Skin rash is usually localized in the central part of the face, especially in the area of nasolabial folds, limbs. In acute pulmonary coccidioidomycosis, mucous membranes are usually affected.

The differential diagnosis is carried out with the presence of limited neurodermatitis, nodular prurigo, keratoacanthoma, cryptococcosis, skin tuberculosis, tertiary syphilis, and pyoderma.

Additional research methods are pathomorphological study of the skin, as well as bacterial inoculation.

In pathomorphological examination of the skin biopsy samples, granulomatous inflammation is determined. Spherules − large round fungal sporangia filled with spores − are found in the tissues.

For inoculation of Sabouraud's medium, pus or biopsy material is used. Diagnosis is confirmed by detection of spherules in sputum or pus; identification of Coccidioides immitis colonies in the culture; results of skin biopsy.

Treatment is carried out by antifungal agents: fluconazole (200-400 mg/day per os) or itraconazole. In life-threatening conditions, Amphotericin B is prescribed intravenously [4].

In HIV, lifelong prophylactic treatment with antifungal drugs is needed.

HISTOPLASMOSIS

Histoplasmosis is a deep mycosis which begins with lung disease. Disseminated histoplasmosis is uncommon, and the causative agent hematogenously enters the mucous membranes, skin, liver, spleen and bone marrow.

Histoplasmosis is the endemic disease with clearly limited geographical distribution. The peculiarity of histoplasmosis in AIDS is the possibility of its development, both in endemic and non-endemic areas. The pathogen is Histoplasma capsulatum.

The disease is common among HIV-infected. Histoplasmosis in AIDS takes the form of generalized infection with lesions of many organs, including the skin.

Classification of histoplasmosis [4]:

1. Pulmonary histoplasmosis

a) Acute pulmonary histoplasmosis (often asymptomatic)

b) Chronic cavernous pulmonary histoplasmosis

c) Other forms of pulmonary histoplasmosis

* *To cite this English version: A.M. Daschuk, L.O. Kutsevliak Clinical features of skin lesion in deep mycoses against the background of hiv/aids // Problemy ekologii ta medytsyny. - 2016. - Vol 20, № 1-2. - P. 33–36.*

2. Disseminated histoplasmosis

a) Acute disseminated histoplasmosis

b) Chronic disseminated histoplasmosis

In HIV-infected patients, disseminated histoplasmosis occurs in the significant reduction CD4-lymphocytes number. In acute pulmonary and disseminated histoplasmosis, eruptions on the skin can be observed. Cutaneous manifestations are nonspecific.

In acute pulmonary histoplasmosis, skin rash is the result of an allergic reaction to antigens of the pathogen. The rash usually resembles knobby and polymorphic exudative erythema.

In disseminated histoplasmosis, rash is the result of skin damage by the pathogen. It is usually observed in 10% of HIV-infected patients. These may be erythematous patches, red papules and nodes stratum or necrotizing pustules, plaques, covered with vegetations; erythroderma, cellulitis. Most often, these are multiple red scaly papules on the trunk and arms, resembling parapsoriasis guttata. In adrenal glands damage, diffuse hyperpigmentation develops due to adrenal failure.

Regardless of the form of histoplasmosis, lesions are usually located on the face, trunk, extremities. Very often, the mucous membranes of the mouth, epiglottis, vestibule of nose are involved in the process.

Differential diagnosis is usually carried out with leishmaniasis, coccidioidomycosis, cryptococcosis, lymphomas.

To diagnose histoplasmosis, the following additional studies are performed: skin pathology; Gomory-Grohottu sections staining enables to reveal Histoplasma capsulatum and distinguish them from Coccidioides immitis, Blastomyces dermatitidis, Leishmania donovani, Toxoplasma gondii.

Microscopy. The pathogen can be detected in Giemsa stained smears from biopsy material, in sputum and bone marrow smears.

Inoculation. For inoculation, blood, urine, bone marrow, biopsy material from skin, mucosa, liver, lymph nodes, and lungs are used.

Defining Histoplasma capsulatum antigens. Determination of titer of Histoplasma capsulatum polysaccharide antigen in the serum of patients is used for diagnosis, evaluation of treatment outcomes and recurrence prediction.

Determination of antibodies to Histoplasma capsulatum. For detection of antibodies to Histoplasma capsulatum in the serum of patients, the method of immunodiffusion and complement fixation are used. The result is considered positive if in immunodiffusion precipitation lines with M and N antigens are formed and in complement fixation the antigens titer is more than 1:32.

For treatment, itraconazole 200 mg 2 times a day per os or fluconazole 800 mg/day per os for 2 weeks are used.

Secondary prophylaxis of histoplasmosis in HIV-infected patients is conducted by lifelong prescription of itraconazole (200 mg/day per os) or fluconazole (400 mg/day per os).

CRYPTOCOCCOSIS

Cryptococcosis is a disseminated fungal infection that starts with lung damage. From there, the causative agent hematogenously enters the meninges, and in some patients − the skin and mucous membranes. According to the scientific literature, in 10-15% of HIV-infected patients with cryptococcosis, skin lesions are observed [5].

Eruptions are polymorphic in nature; most often the face and scalp are affected. In less than 5% of patients, the oral mucosa in involved in the process.

Papules and nodes surrounded by erythema appear on the skin. Sometimes they burst with liquid mucus effusion. Eruptions in HIV-infected patients resemble molluscum contagiosum, acneiform, herpetiform rash in the form of panniculitis, vasculitis, subcutaneous abscess, folliculitis, papula vegetans, ulcers. On the buttocks, hips, lower limbs, nodes in subcutaneous adipose tissue appear and gradually increase in size. They merge to form extensive conglomerates of tightly-elastic consistency with clear boundaries. Occasionally, tissue softening develops and fistulous passages with the slim seropurulent discharge appear. In deeper tissue destruction, there are lethargic ulcers with granulation, purulent crusts that are easy bleeding when touched. The edges of ulcers are infiltrated and underlined.

Patients with HIV infection are usually characterized by disseminated cryptococcosis with fungemia, damage of the meninges, lungs, bone marrow, skin, mucous membranes of the urinary tract and genital organs, including the prostate gland. There are hepato- and splenomegaly [4].

The differential diagnosis is carried out with pyoderma, molluscum contagiosum, blastomycosis, histoplasmosis.

The clinical picture of cryptococcosis is confirmed by skin biopsy and culture. In smears from biopsies or scrapings from the lesions, treated with potassium hydroxide, Cryptococcus neoformans can be observed.

For inoculation, biopsy materials from skin or CSF are usually taken. If the pathogen is isolated from skin biopsy to evaluate the disease severity, it is necessary to investigate CSF, bone marrow, sputum, urine, prostate secretion. In HIV-positive patients, pathogen is cultured from the blood, sputum, bone marrow, urine.

As a result of pathomorphological studies of the skin, there may be two distinct histological patterns. In the first case, large concentrations of pathogens, surrounded by mucous, gelatinous capsule are observed. The inflammatory response is insignificant. In the second case, granulomatous inflammation is revealed: histiocytes, giant and lymphoid cells, fibroblasts, and sometimes necrosis. The number of agents in the focus of inflammation is much smaller. Mucicarmine binds to glycosaminoglycans and stains the fungal capsule in red that enables to distinguish Cryptococcus neoformans from Blastomyces dermatidis.

Treatment of skin lesions in cryptococcosis is carried out with fluconazole 200-400 mg/day per os and itraconazole 400 mg/day per os. Secondary prevention of cryptococcosis in HIV infection is limited to lifelong prescription of fluconazole (200-400 mg/day per os) or itraconazole (200-400 mg/day per os).

SPOROTRICHOSIS (synonym − Schenck's disease)

The causative agent of the disease is a dimorphic fungus Sporothrix schenkii that lives in the soil, on plant leaves and organic waste. In the tissues it is found in the form of oval or cigar-shaped yeast cells, which are called shuttles [1,4].

Men get sick more often, especially with disseminated sporotrichosis. Most commonly, infection occurs when the skin is damaged by spines, thorns, splinters − deep enough for the pathogen to enter the subcutaneous tissue. Getting into the subcutaneous tissue, Sporothrix schenkii multiplies and spreads gradually through the

draining lymph vessel. Along this vessel, there are secondary lesions. More rare infection mechanisms are inhalation, ingestion and aspiration of infected material, leading to visceral sporotrichosis. Hematogenous dissemination of the pathogen from the skin or pulmonary lesions is possible.

The incubation period is an average of three weeks after injury, but may be from 3 days to 12 weeks. Skin lesions are characteristic for the disease. In the place of pathogen permeation, an ulcerated node appears, subsequently accompanied by lymphangitis and regional lymphadenitis. In patients with AIDS, the infection spreads hematogenously from the primary lesion (cutaneous or pulmonary), and disseminated sporotrichosis occurs. Cutaneous manifestations of sporotrichosis may have further symptoms [3].

In 40% of cases, after a few weeks there is a pustule or a node in the site of injury which is soldered to surrounding tissues and ulcerates. The surrounding skin becomes pink or purple. Sporotrichosis chancre is formed, which is a painless ulcer on a dense base with jagged and underlined edges. Most often, sporotrichosis chancre is localized on the dorsum of the hand or finger. In 60% of cases, the spread of infection occurs from the primary tumor (chancre) in the lymphatic vessels. Lymphangitis develops: a dense thick fibrotic fold with multiple nodes along the draining lymphatic vessels (lymphatic sporotrichosis). Regional lymph nodes are enlarged and inflamed.

In cutaneous sporotrichosis, in children usually on the face, and in adults on the hands, sores covered with crusts develop; plaques with warty surface erupt; foci resembling ecthyma and pyoderma gangrenosum appear; papules and plaques on infiltrated base are observed. In disseminated sporotrichosis, generalized rash develops, with the exception of the palms and soles.

Among other organs, the lungs and joints are most commonly affected. Wrist, elbow, ankle, knee joints increase in volume and become painful, often even before the appearance of rash.

The differential diagnosis of sporotrichosis chancre is carried out with skin tuberculosis, infections caused by atypical mycobacteria, tularemia, primary syphilis.

Cutaneous sporotrichosis should be differentiated from pyoderma, foreign body granuloma, dermatophytes, North American blastomycosis, chromomycosis, leishmaniasis.

For diagnosis, microscopic, cultural and histological studies are used. An additional study method is taking smears. After node biopsy (ulcer), the glass slide is applied to the inside of the surface of the biopsy material. The preparation is then treated with potassium hydroxide. Material for smear is taken from crusted lesions. Then smear is stained by Gram. In disseminated sporotrichosis in AIDS patients, cigar-shaped cells are observed in the smear.

The histological study of biopsy materials is determined by granulomatous inflammation, Langhans giant cells, microabscesses. As a rule, one can identify the pathogen (cigar-shaped cell with a diameter of 1-3 mm and a length of 3-10 microns) only in immunocompromised patients.

Biopsy material is also used for inoculation. Growth of the fungus colonies begins within a few days.

Serological tests are usually uninformative.

Thus, the diagnosis of sporotrichosis is confirmed by clinical and inoculation data.

Treatment.

Self-healing of sporotrichosis is uncharacteristic. Itraconazole at 200-600 mg/day is prescribed. The medication is especially effective in lesions of the skin and lymph vessels. It is less effective in the damage of the bones, joints and lungs. Reserve medications are fluconazole 200-400 mg/day, ketoconazole 400-800 mg/day. In disseminated sporotrichosis, with the damage of the lungs, intravenous amphotericin is used.

After completing the course of treatment, relapses often occur. Disseminated sporotrichosis in HIV-infected patients defies treatment and therefore requires lifelong prescription of medications.

NORTH AMERICAN BLASTOMYCOSIS.

North American blastomycosis is a deep mycosis that begins with lung disease. Hematogenous dissemination of infection leads to skin lesions and damage to other organs.

Causative agent is Blastomyces dermatitidis.

Infection usually occurs through airborne droplets, occasional contact, when the skin is damaged. Risk factor is HIV infection at the CD4 cell count below 200 mcl.

Primary pulmonary infection is usually asymptomatic; it rarely resembles flu or pneumonia. It manifests itself on the skin in the form of polymorphic exudative erythema nodosum, as a result of an allergic reaction to the permeation of Blastomyces dermatitidis. Most often, the penetration of the pathogen into the body through the lungs in a short time leads to the generalization of mycosis. In generalized form, skin rash that occurs simultaneously with the damage to visceral organs and deep tissues is often observed. In disseminated form, the disease is presented by nodes occurring in the skin depth. Depending on the evolutionary changes of these nodes, the disease may resemble lupus (pseudolupus) or, less often, with neoplasms (pseudoepithelioma). In similarity with the latter, painful ulcers on the skin appear that are formed at the burst of the inflamed sites. The edges of the sores are edematous, erythematous and dense [1,4,5].

The form which resembles lupus is characterized by the formation of subcutaneous nodules, over which there are many small pustules. Subsequently, there are plaques with a warty surface, encrusted with clear winding boundaries. If the crust is slightly raised, fine drops of pus appear from under it, in the area of marked vegetation at the focus periphery. Peripheral growth in one direction leads to the fact that the center resembles a half or three-quarters moon. Healing starts from the center. The result is an atrophic scar, resembling a map. The form of the rash is irregular. Localization is usually symmetrical on trunk, rarely − on the face, hands, forearms. In half of patients, there are multiple foci.

Infection with blastomycosis is also possible directly through the skin. In the contact infection, the focus is localized at the site of the pathogen permeation. Primary cutaneous form usually occurs on exposed skin of the face, arms, legs. The disease begins with the appearance of small, somewhat pointed red papules, painless and slightly itchy. During the first days, a papule turns into a pustule. Subsequently, the skin develops rash, similar to the eruptions in disseminated infection. Due to autoinoculation around the main focus in the area of scratching, new rash often arises in the form of areola of reddish-purple vegetation. In 25% of patients, mucosa of the mouth and nose is affected. The damage to the larynx is possible.

Only primary skin infection is characterized by the increase in regional lymph nodes.

The differential diagnosis is carried out with mycosis fungoides (tumoral stage), warty skin tuberculosis, actinomycosis, nocardiosis, mycetoma, tertiary syphilis, leprosy [4].

For confirmation of the diagnosis, preparations microscopy, the culture and pathological examination are performed. The materials for laboratory research are pus, mucus, scrapings from under the edge of ulcers, punctuate of softened lymph nodes. The staining of smears is conducted via Romanovsky-Giemsa method. For diagnosis, revealing the large yeast cells with a diameter from 10-30 to 60 microns with multiple budding, very characteristic of the pathogen, is of particular importance.

For cultures, wort agar and Sabouraud's medium are used. The features of pathological studies in deep abscessed nodes gain diagnostic value, because it is most often possible to detect in them specific tissue forms of the pathogen, to receive the culture of the content from nonopened foci. Diffuse infiltrate is composed of mononuclear cells, plasma cells, mast cells, polynuclear neutrophils and eosinophils, forming abscesses, clusters of epithelioid and giant cells resembling tubercular follicles, but without signs of necrosis. In microabscesses of dermis, with the help of silvering or PAS reaction, multiplying cells with thick walls are revealed, connected by a wide cross-connection. Mucicarmine staining of sections enables to distinguish Blastomyces dermatitidis from Cryptococcus neoformans.

In the blood, Blastomyces dermatitidis antigens are present, but serological diagnosis is not always reliable. Skin tests have not yet been developed.

For treatment, antifungals are used: itraconazole from 200 to 400 mg/day for at least 2 months.

Reserve medication is ketoconazole at a dose of 800 mg/day.

Treatment of deep mucoses in HIV/AIDS infection is quite difficult and requires the continuous lifelong use of antifungal medications.

References

1. Dashchuk A.M. VICH/SPID-infektsiya/A.M. Dashchuk, L.I. Chernikova. − KH.: «S.A.M.». – 2015. − 246 s.
2. Dashchuk A.M. Klinicheskaya dermatovenerologiya / A.M. Dashchuk, L.O. Kutsevliak, O.M. Karaban. – KH.: «S.A.M.». – 2015. – 769 s.
3. Dermatologiya i venerologiya/Pod red. prof. V.I. Stepanenko. – Kiyev: KIM, 2012. – 904 s.
4. Dermatologiya po T.Fitspatriku. Atlas-spravochnik/Vul'f K., Dzhonson R. Syurmond D. // Vtoroye russkoye izdaniye. Per. s angl. − M.: Praktika, 2007 − S. 1248.
5. Kozhnyye bolezni. Diagnostika i lecheniye/P. Khebif. − M., 2007. – 672 s.

Матеріал надійшов до редакції 03.10.2016