MINISTRY OF HEALTH OF THE REPUBLIC OF BELARUS

Educational Institution “Gomel State Medical University”

Department of Polyclinic Therapy and General Medical Practice, with a Course in Dermatovenereology

S. A. Sokhar, Abdel Malak Walid, V. V. Kozlovskaya

DEEP AND SYSTEMIC MYCOSES

Educational-methodological manual for students of the medical and medical-diagnostic faculties of medical universities, clinical residents, and physician trainees.

Gomel — Gomel State Medical University — 2012

Reviewers: Candidate of Medical Sciences, Associate Professor, Head of the Department of Polyclinic Therapy and General Medical Practice with a Course in Dermatovenereology, Gomel State Medical University, N. F. Bakalets; Deputy Chief Physician for Medical Affairs of the Gomel Regional Clinical Dermatovenereological Dispensary, V. B. Nemanov.

Sokhar, S. A. Deep and Systemic Mycoses: educational-methodological manual for students of the medical and medical-diagnostic faculties of medical universities, clinical residents and physician trainees / S. A. Sokhar, Abdel Malak Walid, V. V. Kozlovskaya. — Gomel: Gomel State Medical University, 2012. — 48 p. ISBN 978-985-506-418-4.

The manual addresses the pathogenesis and clinical manifestations of deep and systemic mycoses. The increasing number of HIV-infected patients makes systemic opportunistic mycoses an important problem. The pathogenesis, clinical features, diagnosis and treatment of tropical deep mycoses are particularly relevant to foreign students from Asia, Latin America and Africa.

The manual was prepared in accordance with the standard educational program of the Ministry of Health of the Republic of Belarus and contains theoretical material as well as examples of tests used during practical classes. It is intended for medical and medical-diagnostic students, clinical residents and physician trainees.

Approved and recommended for publication by the Central Educational Scientific-Methodological Council of Gomel State Medical University on February 13, 2012, Protocol No. 1.

CONTENTS

MOTIVATIONAL CHARACTERISTICS OF THE TOPIC 4

Chapter 1. DEEP MYCOSES 6

1. Sporotrichosis 6

2. Chromomycosis 9

3. Phaeohyphomycosis (subcutaneous phaeomycotic abscess) 11

4. Lobomycosis 13

5. Rhinosporidiosis 15

6. Mycetoma 16

Chapter 2. SYSTEMIC MYCOSES 19

1. Coccidioidomycosis 19

2. Blastomycosis 21

3. Histoplasmosis 24

4. Paracoccidioidomycosis 27

Chapter 3. OPPORTUNISTIC MYCOSES 29

1. Endemic penicillosis 29

2. Cryptococcosis 30

3. Aspergillosis 32

4. Candidiasis 34

4.1 Deep candidiasis 34

4.2 Candidiasis of the gastrointestinal tract 35

4.3 Candidiasis of the respiratory organs 38

4.4 “Chronic” secondary (isolated) disseminated candidiasis 39

4.5 “Acute” primary (generalized) disseminated candidiasis 39

References 43

Examples of tests and problems for knowledge assessment 44

Answers 46

MOTIVATIONAL CHARACTERISTICS OF THE TOPIC

Deep and systemic mycoses are diseases involving the skin, subcutaneous tissue, mucous membranes and internal organs, caused by fungi belonging to various taxonomic groups. Some are classified as particularly dangerous infections because of their severe course and, in some cases, fatal outcome.

In Europe, many deep (systemic) mycoses are traditionally called “exotic.” Most were observed in regions with subtropical and tropical climates — in North and South America, Africa and the countries of the Middle East. At present, however, they are increasingly being registered in countries where they were previously virtually unknown. Population migration and more frequent tourist and business travel from Europe to tropical countries contribute to this.

A large group of systemic mycoses consists of opportunistic mycoses, which occur in people with immunodeficiency, including HIV-infected patients, recipients of internal-organ and bone-marrow transplants, and people receiving immunosuppressive drugs.

Diagnosis of deep and systemic mycoses is difficult because of marked clinical polymorphism, the absence of specific signs, similarity to other diseases, and associations with other conditions such as pyoderma, tuberculosis and tumors. Diagnosis also differs from routine laboratory investigation of dermatophytoses: obtaining a culture of the pathogen is possible only in specialized clinical laboratories. Allergy testing, serologic reactions and animal experiments are unfortunately not readily available.

Undoubtedly, deep and systemic mycoses occur in our regions more often than they are diagnosed; their true nature is sometimes recognized only postmortem.

Aim of the class

To study the etiopathogenesis of deep and systemic mycoses, the clinical manifestations of individual forms, and the principles of diagnosis, differential diagnosis, treatment and prevention.

Tasks of the class

The student should know: 1) the modern classification of deep and systemic mycoses; 2) the biology of their causative agents; 3) pathogenesis; 4) clinical manifestations; 5) laboratory diagnosis; 6) differential diagnosis with clinically similar dermatoses; 7) modern treatment methods; 8) basic preventive measures.

REQUIRED PREVIOUS KNOWLEDGE

For complete mastery of the material, the student should review: 1. From microbiology: the structure and properties of the causative agents of human fungal diseases and methods of bacterioscopic and bacteriological examination. 2. From pharmacology: characteristics of antifungal drugs and rules for prescribing medicines.

CONTROL QUESTIONS

1. Characteristics of the causative agents of deep and systemic mycoses. 2. Classification according to ICD-10. 3. Routes of infection and epidemiology. 4. Clinical manifestations of sporotrichosis, chromomycosis, phaeohyphomycosis, lobomycosis, rhinosporidiosis, mycetoma, coccidioidomycosis, blastomycosis, histoplasmosis, paracoccidioidomycosis, penicillosis, cryptococcosis, aspergillosis and deep candidiasis. 5. Laboratory diagnosis. 6. Differential diagnosis. 7. Principles of treatment and prevention, including the main groups of drugs used.

Duration of the class: 3 hours for third-year students and 7 hours for sixth-year students.

CHAPTER 1. DEEP MYCOSES

1. Sporotrichosis

Synonyms: gardener’s disease; Schenck disease.

Etiology. The causative agent is the dimorphic fungus Sporothrix schenckii.

History of discovery. The causative agent of sporotrichosis was discovered in 1898 by Bernard Schenck, who worked as an agricultural mycologist in the United States.

Epidemiology. Sporothrix schenckii occurs widely in soil. The disease is endemic in warm climates — North and South America, South Africa and Southeast Asia. The natural sources are soil and plants. The fungus is isolated from humus, wilted and decaying plants, hay, straw, moss and wood. The disease therefore has an occupational character, affecting gardeners, florists, horticulturalists, foresters and agricultural workers. Cases have also occurred among miners because the fungus contaminates wooden mine supports. Contamination of soil sold in garden shops, animal bedding and food products is possible. Rats and insects may act as passive carriers.

Sporotrichosis usually occurs sporadically, although outbreaks are possible. Skin trauma is considered an important condition for infection. Penetration through intact skin has been demonstrated experimentally. Sporotrichosis also affects various mammals and may be acquired from animals, particularly domestic cats. A preceding bite or scratch is not always established. Aerogenic infection cannot be excluded.

Pathogenesis. The immune response is mediated by cellular immunity. The causative cells are engulfed and destroyed by neutrophils and macrophages. The immune status of many patients does not demonstrate a significant immunodeficiency. The incubation period from primary trauma to the first skin lesion averages 2–3 weeks. After formation of the primary lesion, lymphatic spread is characteristic, with new lesions developing along lymphatic vessels toward regional lymph nodes. Sometimes only a skin lesion persists for a long time. Deep-organ involvement results from hematogenous dissemination.

Disseminated sporotrichosis usually occurs in the presence of severe predisposing conditions such as AIDS, diabetes mellitus or chronic alcoholism. Its course is severe and may be fatal.

Classification

Three main forms are distinguished: cutaneous-lymphatic, localized cutaneous and disseminated. Primary pulmonary sporotrichosis is considered separately.

ICD-10 classification: B42 Sporotrichosis; B42.0 Pulmonary sporotrichosis — primary pulmonary form; B42.1 Cutaneous-lymphatic sporotrichosis — cutaneous-lymphatic form; B42.7 Disseminated sporotrichosis — all forms of disseminated infection, including dissemination to lungs and skin; B42.8 Other sporotrichosis — localized cutaneous form, sporotrichosis of mucous membranes, etc.; B42.9 Unspecified sporotrichosis.

Clinical picture

Cutaneous-lymphatic form. This form is diagnosed in about 60% of patients. At the site of skin trauma a primary lesion appears, followed by lesions along lymphatic vessels. The primary lesion, or sporotrichotic chancre, is usually on the hand or forearm of the dominant working arm. Less frequent sites are the face in children, legs and trunk. It is usually painless. It begins as a firm erythematous nodule, enlarges into a node, becomes dark red with a bluish tint, and adheres to surrounding tissue. Hyperkeratosis may make the surface verrucous. A bluish-red erythematous halo is characteristic.

The nodule subsequently becomes softer and breaks down, leaving a long-standing ulcer with serous or purulent discharge. The ulcer has irregular, sometimes undermined and elevated edges because of edema. The primary lesion later scars. Several weeks after its appearance, a similar nodule develops elsewhere along a lymphatic vessel. Lymphangitis and regional lymphadenitis occur, usually without ulceration. Secondary lesions undergo the same evolution as the primary lesion and may continue to appear up to the regional lymph node, producing a chain-like arrangement along the lymphatic vessel.

Figure 1 — Primary sporotrichotic chancre and secondary nodules along lymphatic vessels (sporotrichotic arrangement of lesions).

Localized cutaneous form

Occurs in approximately 40% of patients. A primary sporotrichotic chancre may persist without subsequent lesions along lymphatic vessels. Common sites are the face and trunk. Verrucous, plaque, indurated-nodular, acneiform and furuncle-like forms are described.

Disseminated sporotrichosis

Accounts for approximately 5% of all cases. Disseminated cutaneous and systemic forms are distinguished. Cutaneous dissemination probably occurs through autoinoculation. Papules, pustules and nodules appear and may open and ulcerate.

Systemic sporotrichosis affects bones and joints, most commonly the tibia and knee. Internal-organ involvement is rare but pneumonia, meningitis and endophthalmitis may develop.

Diagnosis

1. Microscopy of lesion discharge — rarely identifies the pathogen. 2. Culture — rapid growth of a whitish culture at 25°C; older cultures acquire a brownish color. 3. Skin histopathology — cigar-shaped cells of the pathogen and “asteroid bodies.” 4. Intradermal sporotrichin injection is a rapid test; the result is read after 48 hours, but a positive reaction does not prove active sporotrichosis. 5. PCR.



Treatment

The drug of choice is itraconazole, 100–200 mg/day for 3–12 months. Alternatives include fluconazole and potassium iodide. Amphotericin B is recommended for systemic forms. A solitary lesion may be destroyed or excised. Localized forms may be treated with local hyperthermia at 42°C.

SPOROTRICHOSIS — SUMMARY

Causative agent: Sporothrix schenckii. Route of transmission: contact with soil. Primary site: skin and subcutaneous tissue. Skin lesions: solitary ulcerating nodules with secondary dissemination along lymphatic vessels. Diagnosis: histopathology (round or oval and cigar-shaped cells), culture, and a subcutaneous sporotrichin test. Internal organs: rarely involved. Treatment: potassium iodide, terbinafine, itraconazole, fluconazole and amphotericin B.

2. Chromomycosis

Synonyms: chromoblastomycosis, Pedroso disease, Fonseca disease, chromomycosis, cladosporiosis, verrucous dermatitis, phaeosporotrichosis, black blastomycosis.

Etiology. The causative fungi belong to the genera Fonsecaea, Phialophora and Cladosporium. They grow slowly, producing dark pigmented colonies, and can tolerate temperatures up to 40–42°C.

History. Chromomycosis was discovered in 1911 by Pedroso. Four years later Medlar described a case in the United States. For a long time terminology remained controversial; the disease was called “black blastomycosis” because of its clinical similarity to North American blastomycosis.

Epidemiology. The disease occurs worldwide but is more common in tropical and subtropical regions, including Mexico, Venezuela, Brazil, Kenya and Madagascar. Men are affected much more often (about 9:1); children are rarely affected. The fungi occur in soil and wood. Agricultural workers are predominantly affected. Infection occurs by traumatic implantation.

Chromomycosis — pathogenesis and classification

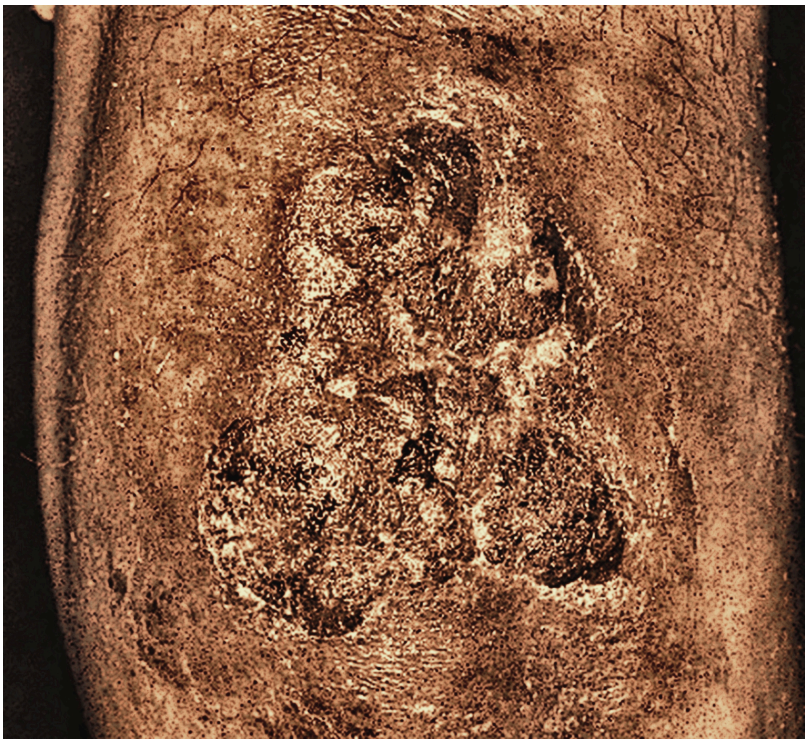
The incubation period is unknown. The pathogenic forms are Medlar bodies. Penetration into the epidermis, dermis and subcutaneous tissue produces a microabscess and a pyogenic and granulomatous inflammatory focus containing fungal cells. Spread occurs per continuitatem by autoinoculation and also by the lymphatic route.

ICD-10: B43 Chromomycosis and phaeomycotic abscess; B43.0 Cutaneous chromomycosis; B43.1 Phaeomycotic brain abscess; B43.2 Subcutaneous phaeomycotic abscess and cyst; B43.8 Other chromomycosis; B43.9 Unspecified chromomycosis.

Clinical picture. Lesions are generally limited to the skin, except in hematogenous spread. At the inoculation site (85% lower extremities; less often upper extremities, trunk or face), an asymmetric papule appears. Slowly enlarging peripheral erythematous-squamous or verrucous lesions develop. Lesions may ulcerate, become crusted and leave scars and depigmentation. Removal of crusts reveals abundant bluish-pink papillomatous growths. The disease is chronic and very prolonged.

Clinical variants include papillomatous-ulcerative, verrucous, plaque or psoriasiform, nodular and cicatricial forms. Pain is usually absent, but lymphostasis may complicate the disease. Rarely, a lesion may undergo carcinomatous transformation.

Figure 2 — Confluent nodules with crusted surfaces in chromomycosis.



Diagnosis

1. Microscopy of ulcer discharge: round pathogens with a double wall — Medlar bodies. 2. Culture: black, gray or dark-blue cultures. 3. Histopathology: identification of Medlar bodies.

Treatment

There is no universally accepted treatment. Surgical treatment is used for solitary nodules. For extensive lesions, itraconazole 200–600 mg/day for at least one year is the drug of choice. Fluconazole or terbinafine may be used as systemic alternatives. In advanced cases, amputation may be required to prevent spread of infection.

CHROMOMYCOSIS — SUMMARY

Causative agents: fungi of the genera Fonsecaea, Phialophora and Cladosporium. Transmission: contact with soil and trauma with penetration of wood particles into the skin. Primary site: skin and subcutaneous tissue. Lesions: verrucous papules and confluent plaques. Diagnosis: histopathology showing Medlar bodies and culture. Internal organs: rarely involved. Treatment: itraconazole, fluconazole, terbinafine and surgery.

3. Phaeohyphomycosis (subcutaneous phaeomycotic abscess)

Causative agents. Common causes of subcutaneous phaeomycotic abscess include Exophiala jeanselmei and Wangiella dermatitidis; more than 100 species capable of causing phaeomycotic abscess have been described. Unlike chromomycosis, the agents of phaeomycotic abscess do not form the characteristic Medlar bodies.

History. The first description of phaeohyphomycosis was made in 1974 by L. Ajello during histopathologic examination of a solitary lesion in a kidney-transplant patient. Epidemiology. The disease is more common in rural areas with warm climates — Central and South America, Southeast Asia and Africa. Infection occurs through contaminated soil or traumatic implantation by wood splinters. There is no person-to-person transmission.

The disease occurs more often in immunosuppressed persons, although cases in immunocompetent patients have been described. Organ transplantation is a risk factor.

Pathogenesis. Once in tissue, the fungi cause a granulomatous inflammatory reaction. The lesion is usually confined to the dermis and part of the subcutaneous tissue. Lymphatic or hematogenous dissemination generally does not occur.

Classification. Subcutaneous phaeohyphomycosis is included under ICD-10 B43.2, “subcutaneous phaeomycotic abscess and cyst,” together with chromomycosis.

Clinical picture. The lesion is usually an abscess on an extremity. It is generally solitary, fluctuant and may reach 7 cm in diameter. The abscess usually does not affect the patient’s general condition. Inhalation of soil-borne fungi may cause pulmonary infection. Less commonly, other organs, including the brain, may be involved with abscess formation.

Figure 3 — Phaeomycotic cyst of the right hand in a kidney-transplant patient.

Diagnosis

1. Culture. 2. Histopathology.

Treatment

For solitary lesions, treatment begins with surgical excision, followed by systemic itraconazole.



PHAEOHYPHOMYCOSIS — SUMMARY

Causative agents: Exophiala jeanselmei and Wangiella dermatitidis. Transmission: contact with soil, trauma with wood particles entering the skin, and inhalation of particles. Primary site: skin and subcutaneous tissue. Lesions: most commonly solitary abscesses on the extremities. Diagnosis: histopathology and culture. Internal organs: rarely involved. Treatment: surgical removal followed by itraconazole.

4. Lobomycosis

Synonyms: Jorge Lobo disease, Jorge Lobo blastomycosis, keloid blastomycosis, Lobo mycosis.

Causative agent. The agent of lobomycosis has never been cultured. Experimental disease has been studied after inoculation into animals. Older sources used names such as Paracoccidioides loboi, Glenosporella loboi, Blastomyces braziliensis, Glenosporopsis amazonica, Loboa loboi and Lobomyces. The currently accepted term is Lacazia loboi.

History. The disease was first described by Jorge Lobo in 1931 in the Amazon region of Brazil. In 1950 Trejos and Ramiro described the first case outside Brazil. Cases have been reported from Peru, Venezuela, Suriname, Bolivia and Ecuador. The disease has also been identified in dolphins; a human case after contact with a dolphin was reported in Spain.

Epidemiology. The disease occurs almost exclusively in Latin America, especially the Amazon Basin. Transmission is not fully understood; it is presumed to occur through contaminated soil and skin microtrauma. A water reservoir may also exist. A case of person-to-person transmission has been reported. Adults, particularly men, are affected more often.

Pathogenesis. The incubation period is unknown and may last several years. Granulomatous inflammation develops at the site of inoculation. Necrosis, purulent inflammation and abscesses have not been observed in the lesion. Spontaneous resolution is not characteristic.

ICD-10 classification: B48.0 — Lobomycosis.

Clinical picture

The primary lesion is a verrucous nodule that later becomes keloid-like. Preferred sites are the skin of the auricles and extremities; less commonly the face, neck and lower back. Nodules are usually pinkish or brownish, with prominent telangiectasia and sometimes scaling. A primary lesion may persist for several years without dissemination. The absence of internal-organ involvement may be explained by the inability of the pathogen to grow at high temperatures.

Figure 4 — Disseminated keloid nodules on the skin of the shoulder and forearm in a patient with lobomycosis.

Laboratory diagnosis

Because a culture method has not been developed, diagnosis is based on microscopy and histopathologic examination of affected tissue.

Treatment

For limited lesions, surgical excision or electrocoagulation is most commonly used. Systemic antifungal drugs are not effective. Clofazimine is used at 300 mg/day for the first month, followed by a reduction to 100 mg; treatment is continued for a prolonged period.

LOBOmycosis — SUMMARY

Causative agent: Lacazia loboi; not cultured. Transmission: unknown, possibly contact with soil, infected dolphins or humans. Primary site: skin and subcutaneous tissue. Lesions: firm keloid-like nodules. Diagnosis: histopathology; the source also lists culture, although the preceding text states that culture is not currently available. Internal organs: not involved. Treatment: surgical removal followed by clofazimine; systemic antifungals are ineffective.



5. Rhinosporidiosis

Causative agent: Rhinosporidium seeberi.

History. The disease was first described by Guillermo Seeber in 1896. It remains uncertain which taxonomic group most appropriately contains the causative organism.

Epidemiology. The disease occurs in tropical countries, especially India and Sri Lanka, where prevalence among children may reach 1.5%. The Amazon region is the second most frequent area. Rhinosporidiosis mainly affects men aged 20–40 years, although conjunctival involvement is reported more often in women. Many cases occur among people working in sand quarries near bodies of water and in rice fields.

Pathogenesis. Transmission occurs when dust reaches the conjunctiva or through inhalation of contaminated dust or water, explaining the primary localization on mucous membranes. The organism has a complex life cycle. Mature forms contain sporangia with sporangiospores. When these enter human tissue, granulomas and abscess-like pseudocysts develop.

ICD-10: B48.1 — Rhinosporidiosis.

Clinical picture. The disease produces painful polyps on the mucosa of the eye and nasal cavity. Small spherical structures corresponding to sporangia may sometimes be seen on the surface. Lesions are usually unilateral. Polyps may also occur on the mucosa of the pharynx, external auditory canal and genital tract.

Figure 5 — Unilateral nasal polyp in a patient with rhinosporidiosis.

Diagnosis is based on histologic examination. Treatment consists of removal of the polyp. After removal, recurrence is common; it may be prevented by local administration of amphotericin B.

RHINOSPORIDIOSIS — SUMMARY

Causative agent: Rhinosporidium seeberi. Transmission: inhalation of dust or deposition on the conjunctiva. Primary site: nasal or ocular mucosa. Lesions: polypoid lesions of the nasal mucosa or conjunctiva. Diagnosis: histopathology. Internal organs: not involved. Treatment: surgical removal and local amphotericin B.

6. Mycetoma

The term “mycetoma” is used differently by different authors. Some use it for deep tissue infection of the foot caused by various organisms: fungi (eumycetotic mycetoma), bacteria (botryomycosis) and actinomycetes (actinomycotic mycetoma). Other authors use mycetoma only for the eumycotic variant. The authors of this manual follow the latter usage.

Synonym: Madura foot.

Causative agents. About 30 species of fungi and actinomycetes can cause mycetoma. Sometimes the agent can be provisionally identified by the color of granules discharged with pus. Black granules may occur with M. mycetomatis, M. grisea, Pyrenochaeta romeroi, Leptosphaeria senegalensis, L. tompkinsii, Exophiala jeanselmei, Phialophora verrucosa and Curvularia lunata. White granules may occur with Pseudoallescheria boydii (Scedosporium apiospermum), Acremonium falciforme, A. recifei, Neotestudina rosatii, Fusarium spp., Aspergillus nidulans and Trichophyton spp.



Epidemiology. Mycetoma occurs worldwide, but most cases are recorded in tropical climates, including India, Sudan, Venezuela, Mexico and African countries. Men aged 25–40 years are most commonly affected. Mycetoma is primarily a rural disease, where people often walk barefoot.

Pathogenesis. The organisms live in soil and enter damaged skin of the foot through microtrauma. Inoculation causes suppurative inflammation with granulomas and abscesses. In human tissue, the organisms form filaments and compact colonies that are discharged from ulcers as granules. Incubation may last from several weeks to several years.

ICD-10: B47 Mycetoma; B47.0 True mycetoma; B47.1 Actinomycetoma; B47.9 Unspecified mycetoma.

Clinical picture

The foot is affected in about 65% of cases, upper extremities in 14%, and trunk in 25%. The characteristic picture is the development of subcutaneous nodules that rapidly ulcerate. Granules of different colors are present in the discharge with pus. Subcutaneous nodules connect through sinuses. Ulcers heal with disfiguring scars. Underlying tissues, including muscles and small bones of the foot, may be involved. Large bones of the leg and thigh are usually spared. Chest lesions may involve pleura and lungs.

Despite foot deformity, the general condition is usually preserved, explaining late presentation to a dermatologist. Secondary bacterial infection can cause a marked deterioration in the patient’s condition.

Figure 5 — Mycetoma.

Diagnosis

1. Aspiration of ulcer contents followed by microscopic examination of granules. 2. Culture of the causative organisms on Sabouraud medium. 3. Histologic examination can identify some causative agents, whereas others may not be visible with routine biopsy stains. 4. Radiographic examination can demonstrate bone involvement.

Treatment

The basis of treatment is surgical excision of the lesion followed by systemic antifungal therapy: itraconazole 200–400 mg/day for 9–12 months and ketoconazole 400 mg/day. Some mycetoma types may respond to dapsone and other sulfone drugs. Actinomycetoma is treated with antibiotics, on average for about 9 months.

MYCETOMA — SUMMARY

Causative agents: numerous organisms producing granules of different colors. Transmission: contact with infected soil and foot microtrauma. Primary site: skin and subcutaneous tissue, usually the lower extremities. Lesions: ulcerating nodules discharging pus with granules of different colors. Diagnosis: aspiration and microscopy, culture and histopathology. Internal organs: not involved. Treatment: surgical removal, systemic antifungals and, for actinomycetoma, antibiotics.



CHAPTER 2. SYSTEMIC MYCOSES

1. Coccidioidomycosis

Causative agent: Coccidioides immitis. In soil, the organism occurs in the mycelial form and forms arthroconidia. When inhaled, arthroconidia enter the human body and form spherules that produce endospores. New spherules develop from the endospores. If spherules from a human return to soil, mycelium develops.

History. The organism was first isolated by A. Posada in Argentina from verrucous facial lesions in a worker. More than 30 years later it was established that coccidioidomycosis causes not only skin lesions but also the fever endemic to the California Valley. This illness has a relatively rapid course, with mild pulmonary intoxication and eruptions resembling erythema nodosum. Cases are now described in HIV-infected patients and organ-transplant recipients. New biological drugs capable of causing immunodeficiency raise concern about increased disease frequency.

Epidemiology. Approximately 100,000 cases occur annually in the United States. Endemic states include Arizona, California and New Mexico. The disease is also widespread in Central and South America. Infection is acquired aerogenically by inhalation. Outbreaks may follow earthquakes. It is occupational in miners, archaeologists and military personnel. Person-to-person transmission does not occur, although transplacental transmission and infection associated with work involving corpses have been described.

Pathogenesis. The lungs are the portal of entry. Infection produces an inflammatory focus with mixed suppurative-granulomatous inflammation. Depending on immunity, infection may be asymptomatic or severe. Hematogenous dissemination from the lungs can affect skin, brain, spleen, liver, kidneys and heart, particularly in HIV infection or other immunosuppression. Previous coccidioidomycosis produces lasting immunity.

ICD-10 classification: B38 Coccidioidomycosis; B38.0 Acute pulmonary coccidioidomycosis; B38.1 Chronic pulmonary coccidioidomycosis; B38.2 Unspecified pulmonary coccidioidomycosis; B38.3 Cutaneous coccidioidomycosis; B38.4+ Coccidioidal meningitis (G02.1); B38.7 Disseminated coccidioidomycosis; B38.8 Other coccidioidomycosis; B38.9 Unspecified coccidioidomycosis.

Clinical picture

About 60% of patients are asymptomatic. In the remaining 40%, cold-like symptoms develop: cough, fever, arthralgia, myalgia and malaise. Symptoms resolve spontaneously within 3–4 weeks. Most patients initially have pulmonary involvement with pneumonia and pulmonary lymphadenopathy. Pneumonia may occasionally be prolonged, with cavities and sclerosis.

Disseminated infection develops in about 1% of patients and is characterized by fever, cough and night sweats. Nonspecific skin symptoms during infection include erythema multiforme, erythema nodosum and Sweet syndrome. Primary cutaneous coccidioidomycosis is rare and occurs more often in agricultural workers after inoculation through the skin.

Disseminated coccidioidomycosis results from spread from the pulmonary focus. Skin lesions may be solitary or multiple and consist of papules, pustules, nodules and plaques that eventually ulcerate. Preferred sites are the face, especially the nose and nasolabial region. Bone and joint involvement (osteomyelitis and arthritis) occurs in 10–15% of disseminated cases. Coccidioidal meningitis occurs in approximately one third of patients with disseminated disease.

Figure 6 — Disseminated coccidioidomycosis.



Diagnosis

1. Serologic studies. 2. Radiographic examination and sputum microscopy. 3. Microscopic examination. 4. Culture. 5. PCR.

Treatment

The preferred drugs are itraconazole 400 mg/day for 2–12 months, fluconazole 400 mg/day for 2–12 months, and amphotericin B. Patients with pulmonary involvement should be examined regularly for 1–2 years.

COCCIDIOIDOMYCOSIS — SUMMARY

Causative agent: Coccidioides immitis. Transmission: inhalation of contaminated soil; primary cutaneous disease may follow skin microtrauma. Primary site: lungs. Lesions: nonspecific hypersensitivity eruptions (erythema multiforme, erythema nodosum, granuloma annulare, Sweet syndrome); disseminated or primary cutaneous disease may produce ulcerating papules and plaques. Diagnosis: radiography, sputum microscopy, serology, culture and histopathology. Treatment: itraconazole, fluconazole and amphotericin B.

2. Blastomycosis

Synonyms: North American blastomycosis; Gilchrist blastomycosis.

History. A detailed description was published in 1939 by Martin and Smith, using earlier work by Gilchrist. They distinguished cutaneous and pulmonary forms. Later, Schwartz and Baum demonstrated that blastomycosis is primarily a pulmonary infection with secondary skin involvement.

Etiology. Blastomyces dermatitidis is a dimorphic fungus. In tissue it appears as round yeast-like cells 8–15 μm in diameter. On Sabouraud medium, white colonies later becoming brownish develop, composed mainly of mycelial threads.

Epidemiology. Soil is the source. Infection occurs by inhalation of Blastomyces dermatitidis conidia. Rarely, infection follows mechanical trauma during laboratory work with cultures or contact with patients with blastomycosis. Epidemic outbreaks have been described among humans and dogs associated with time spent along small rivers in wooded areas. Reliable human-to-human or animal-to-human transmission has not been documented. Agricultural workers are predominantly affected. Reduced immunity is not considered a risk factor in the source text.

The disease has been observed most often in the United States, especially in the Mississippi and Ohio River basins, with sporadic cases in Canada, Australia, India, France, Italy, Hungary and Russia.

Pathogenesis. The lungs are the initial site, followed by skin involvement. Pulmonary blastomycosis is often asymptomatic, so skin manifestations may be the only clinical finding. With generalized infection, organisms spread from the lungs to various organs including skin, bones, liver, spleen and the central nervous system. The source text describes blastomycosis as a T-cell opportunistic infection and notes the role of immunodeficiency in progression. Previous infection produces prolonged, lasting immunity.

ICD-10: B40 Blastomycosis; B40.0 acute pulmonary; B40.1 chronic pulmonary; B40.2 unspecified pulmonary; B40.3 cutaneous; B40.7 disseminated; B40.8 other; B40.9 unspecified.

Clinical picture

Incubation ranges from 1 week to 4 months. Acute pulmonary blastomycosis causes marked fever; in 80–85% of patients temperature exceeds 38°C. Severe cough, chest pain and dry and moist rales occur, often with blood in sputum. Chronic pulmonary disease causes weakness, cough and fever; only about 20% exceed 38°C. Weight loss occurs in about 40%, chest pain and dyspnea are common, and hemoptysis occurs in about 30%. Dry and moist rales may be heard.

Bone and joint involvement occurs in 14–60%. Blastomycotic osteomyelitis may affect the spine, pelvic bones, skull, ribs and long bones. Meningitis and chorioretinitis may occur; in men, prostatitis and orchiepididymitis are possible.

Characteristic skin lesions occur in 30–80%. Typical lesions are sharply demarcated papules and plaques with scaling and peripheral pustules. Lesions may ulcerate. In primary cutaneous (chancriform) blastomycosis, a papule develops at the trauma site within a week and then ulcerates; regional lymphadenitis appears after about two weeks.

Figure 7 — Cutaneous blastomycosis.

Diagnosis

1. Radiography: marked mediastinal lymph-node changes and focal infiltrates; some infiltrates develop cavities with irregular contours. 2. Sputum microscopy: budding yeast-like fungi. 3. Skin histology.

Treatment

Acute pulmonary forms may resolve without antifungal treatment. Chronic pulmonary forms, especially disseminated disease, require prolonged therapy. The source lists amphotericin B 0.3–0.6 mg/day for 2 weeks, itraconazole 200–400 mg/day for 6 months, ketoconazole 400 mg/day for 6 months, and fluconazole 400–800 mg/day.

BLASTOMYCOSIS — SUMMARY

Causative agent: Blastomyces dermatitidis. Transmission: inhalation of contaminated soil; primary cutaneous disease may follow skin microtrauma. Primary site: lungs. Lesions: sharply defined papules or plaques, possibly ulcerating. Diagnosis: radiography, sputum microscopy, culture and histopathology. Treatment: mild cases may require no therapy; severe cases require systemic antifungal therapy.



3. Histoplasmosis

Synonyms: Darling disease, reticuloendotheliosis, reticuloendothelial cytomycosis.

History. Histoplasmosis was formerly considered a life-threatening infection; in 1945 Christie and Peterson demonstrated that infection is asymptomatic in most patients.

Etiology. Histoplasma capsulatum. In Africa, a variant known as Histoplasma capsulatum var. duboisii occurs.

Epidemiology. Histoplasmosis occurs in warm, humid climates and is most common in the southeastern and central United States and, less frequently, Central and West Africa. Birds and bats serve as reservoirs, so caves and sites where birds congregate may be endemic foci. Transmission from an affected person to a healthy person has not been documented.

Pathogenesis. Infection occurs by the airborne route, with the lungs as the primary focus. Immunodeficiency is not essential for infection, but disease is more severe and disseminated when immunodeficiency is present; immunocompetent people may be asymptomatic. Antibodies develop after exposure and can be detected by skin testing. Disseminated histoplasmosis affects reticuloendothelial organs — lymph nodes, liver, bone marrow and spleen. Primary cutaneous histoplasmosis is rare and mainly affects people with direct exposure to the pathogen.

BLASTOMYCOSIS — SUMMARY BOX: The source page also contains a short summary identifying Blastomyces dermatitidis, inhalation of contaminated soil, lungs as the primary focus, ulcerating papules/plaques, radiography/sputum/culture/histopathology, and antifungal treatment.

ICD-10 classification of histoplasmosis: B39 Histoplasmosis; B39.0 acute pulmonary infection due to Histoplasma capsulatum; B39.1 chronic pulmonary infection due to H. capsulatum; B39.2 unspecified pulmonary histoplasmosis; B39.3 disseminated histoplasmosis; B39.5 infection due to Histoplasma duboisii; B39.9 unspecified histoplasmosis.

Clinical picture

Acute pulmonary histoplasmosis may be asymptomatic and may be discovered only by a histoplasmin skin test, positive serology, or calcified lesions in the lungs and hilar lymph nodes. In the mild forms, which predominate, patients remain well and often continue working. Fever is absent or lasts only 3–4 days; the overall illness lasts 2–3 weeks.

Radiography may show increased pulmonary markings and enlarged hilar shadows; some patients have small focal shadows, predominantly in the lower lungs. Fibrotic and calcified foci may develop.

Severe acute pulmonary histoplasmosis begins suddenly, with temperature rapidly rising to 40–41°C. The fever is irregular with a large daily range; chills alternate with profuse sweating. Patients complain of severe headache, weakness, muscle and bone pain, cough and chest pain. Some have nausea, vomiting, diarrhea and abdominal pain. Fever lasts 2–6 weeks. During convalescence, subfebrile temperature, asthenia, marked reduction in work capacity and sweating may persist for up to one year.

Percussion may reveal slight dullness; auscultation may reveal fine moist crackles, predominantly in the lower lungs. Radiography shows large and medium focal shadows resembling “cotton flakes,” which may merge. The source text contains an incomplete sentence after this point because of scan/OCR loss.

Chronic pulmonary histoplasmosis is a prolonged progressive disease with periodic exacerbations. Moderate fever and productive cough occur; radiography may show cavities, fibrosis and multiple calcified foci. Some text fragments on this source page are damaged in the scan.

Acute disseminated histoplasmosis presents with high hectic or irregular fever, recurrent chills and sweating, and severe intoxication symptoms: headache, muscle and joint pain, nausea, vomiting, abdominal pain and increasing weakness. Multiple secondary lesions appear as a result of dissemination: maculopapular, furuncle-like or hemorrhagic eruptions, erythema multiforme or erythema nodosum-like lesions, lymphadenopathy, mesadenitis, hepatosplenomegaly, encephalitis or meningoencephalitis, septic endocarditis, ulcerative colitis and peritonitis. Clinical and radiographic findings may resemble miliary tuberculosis.

Disseminated histoplasmosis may also have an indolent course. Initially the patient’s condition is satisfactory and fever is mild; skin and mucosal involvement is characteristic. Ulcers develop on the tongue and mucous membranes of the pharynx and larynx. Skin lesions are papules or nodules that later ulcerate and become crusted, commonly on the face, chest, forearms and back. Later the condition deteriorates, with septic-type fever, hepatosplenomegaly, generalized lymphadenopathy, gastric and ocular involvement.

Primary cutaneous histoplasmosis: a papule develops at the trauma site, followed by a chancriform ulcer with lymphangitis and lymphadenitis; the lesion may resolve spontaneously without treatment. Histoplasma duboisii more often affects skin, mucous membranes, subcutaneous tissue and bone.

Diagnosis

1. Culture of blood, skin biopsy or discharge. 2. Histopathologic examination of skin. 3. Intradermal test, which the source states may be used only in non-endemic areas. 4. Serology, including complement fixation or immunodiffusion. 5. PCR.

Treatment

Mild histoplasmosis in immunocompetent patients does not require treatment according to the source. Severe forms: amphotericin B 0.5–0.7 mg/day for 10 weeks; itraconazole 200–400 mg/day for 6 months; fluconazole 400 mg/day for 12 months or longer. HIV-infected patients with disseminated histoplasmosis receive itraconazole; the source text is incomplete at the end of this page.

4. Paracoccidioidomycosis

Synonyms: South American blastomycosis, Brazilian blastomycosis, Lutz–Splendore–Almeida disease.

Etiology: Paracoccidioides brasiliensis.

History. The organism was first described by Lutz in 1908 and later assigned by Splendore and Almeida to the genus Paracoccidioides.

Epidemiology. The organism is distributed in Latin American countries, including Brazil, Argentina, Venezuela, Colombia and Ecuador. It has been isolated from soil and from armadillos, monkeys and bats. Disease occurs more often in agricultural workers who inhale organisms present in soil. Primary infection through the skin or mucosa is less common. Young patients of both sexes may be affected; the disease is uncommon in adult women, apparently because of hormonal effects.

Pathogenesis. The lungs are the portal of entry. Nonspecific inflammation develops with a polymorphonuclear infiltrate. An infectious granuloma forms after several days, followed by fibrosis. Disseminated forms are associated with weakened host resistance or immunodeficiency.

ICD-10: B41 Paracoccidioidomycosis; B41.0 pulmonary; B41.7 disseminated; B41.8 other; B41.9 unspecified.

Clinical picture

The incubation period may reach several years, and clinical manifestations may appear after the patient returns from an endemic area. In 96% of cases, the primary foci are the lungs and lymph nodes.

Typical lesions involve the oral mucosa as granulomatous eruptions with pinpoint vascular spots on the surface; lesions tend to ulcerate. The nasal and conjunctival mucosa may then be involved, followed by bilateral lymphadenopathy. Skin lesions arise from dissemination and appear as small papules that slowly enlarge into plaques; ulceration is characteristic. Cutaneous lesions usually occur on the face or extremities. The adrenal glands and skeletal system may also be affected, and the brain less often. Without adequate treatment, death may result from pulmonary failure or CNS involvement.

Figure 8 — Paracoccidioidomycosis: verrucous lesions of the oral mucosa.

Diagnosis

1. Culture. 2. Histopathology. 3. Complement-fixation reaction and ELISA.

Treatment

Sulfone drugs (sulfamethoxypyridazine and sulfadimethoxine) and systemic antifungals: amphotericin B 0.7–1 mg/day for 4–8 weeks; fluconazole 200–400 mg/day for 6 months; itraconazole 100 mg/day for 6 months.

PARACOCCIDIOIDOMYCOSIS — SUMMARY

Causative agent: Paracoccidioides brasiliensis. Transmission: airborne; skin microtrauma. Primary focus: lungs and lymph nodes. Lesions: verrucous oral-mucosal lesions with hemorrhagic spots. Diagnosis: culture and histopathology. Treatment: sulfone drugs and systemic antifungals.



CHAPTER 3. OPPORTUNISTIC MYCOSES

1. Endemic penicillosis

History. The causative agent of penicillosis was first isolated from a bamboo rat living in central Vietnam in 1956 and identified in 1958.

Etiology. The causative agent of endemic penicillosis is Penicillium marneffei, a dimorphic fungus producing mycelial and yeast colonies under different growth conditions. Microscopically, round and oval yeast cells are seen.

Epidemiology. The disease occurs in Asian countries including Thailand, China, Vietnam and Hong Kong. In other countries it is seen mainly in immigrants from Asia. It occurs predominantly in HIV-infected patients and is considered an opportunistic infection.

Pathogenesis. The mechanism by which the organism enters the human body is unknown. It has been isolated only from affected human organs and bamboo rats. Inhalation is suspected, but the organism has not been isolated from soil or bamboo eaten by rats.

ICD-10: B48.4 — Penicillosis.

Clinical picture. In most cases penicillosis begins acutely; less often there are preceding periods of malaise, low-grade fever and weight loss. The lungs may be affected with a bronchopneumonia-like picture. The disease occurs mainly in immunosuppressed patients. Fever is one of the most important symptoms. Leukopenia, thrombocytopenia, splenomegaly, pericarditis and bone involvement are less common. In immunosuppressed patients symptoms are more pronounced, with possible septicemia and mucosal involvement.

Cutaneous manifestations are relatively common and indicate dissemination. In patients without immunosuppression, abscesses are more frequent. In HIV-infected patients lesions vary and may include papules, nodules, vesicles and acneiform eruptions. Lesions occur on the upper trunk, face, scalp and neck and may resemble molluscum contagiosum. Osteomyelitis may occur in children.

Figure 9 — Disseminated penicillosis with lesions resembling molluscum contagiosum.

Diagnosis

1. Microscopy. 2. Culture. 3. Histopathology.

Treatment

Early recognition and treatment are necessary because the disease can be fatal. The source lists amphotericin B 0.6 mg/kg/day for 2 weeks, followed by itraconazole 400 mg/day for 10 weeks.

2. Cryptococcosis

Causative agent: Cryptococcus neoformans.

Epidemiology. The disease occurs in subtropical and tropical climates in Australia, Africa and Southeast Asia. Cryptococcal organisms are inhaled through the upper respiratory tract; pigeons are described as carriers. Infection through damaged skin or mucous membranes is possible.

PENICILLOSIS — SUMMARY

Causative agent: Penicillium marneffei. Transmission: probably inhalational; predominantly affects HIV-infected patients in Asian countries. Primary involvement: septicemia, splenomegaly and skin. Lesions: nonspecific papules, nodules, vesicles, acneiform lesions and lesions resembling molluscum contagiosum. Diagnosis: microscopy, culture and histopathology. Treatment: amphotericin B and itraconazole.



Pathogenesis. After primary pulmonary infection, disease may spread to bone, CNS and skin. Skin involvement usually indicates an unfavorable prognosis; the source reports an 80% mortality. Almost exclusively immunodeficient patients are affected.

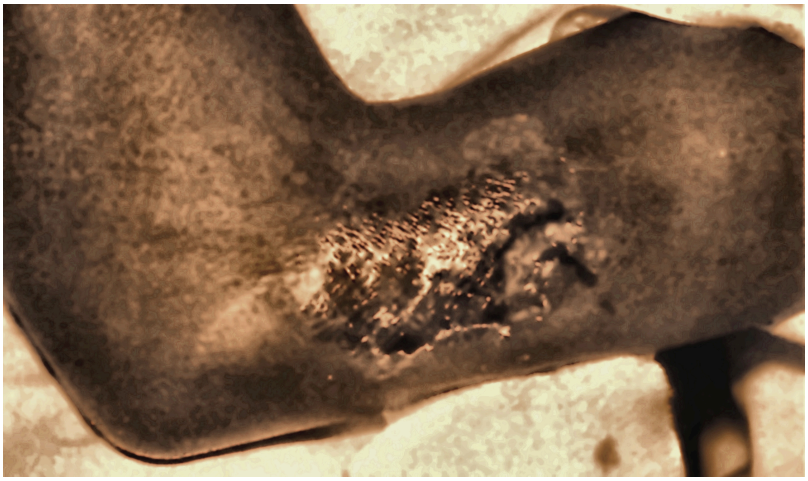
ICD-10: B45 Cryptococcosis; B45.0 pulmonary; B45.1 cerebral; B45.2 cutaneous; B45.3 bone; B45.7 disseminated; B45.8 other; B45.9 unspecified.

Clinical picture

The lungs are primarily affected, producing cryptococcal pneumonia. Cryptococcal meningitis and meningoencephalitis occur in more than two thirds of patients. A cryptococcoma is a rare CNS form. Ocular cryptococcosis may cause optic-nerve paralysis or endophthalmitis. Bone involvement occurs in about 5% of disseminated cases, affecting the pelvis, spine, skull and ribs.

Skin lesions are nonspecific and indicate poor prognosis. They occur mainly on the face, scalp and upper trunk. The primary lesion is usually an erythematous papule or pustule surrounded by erythema, gradually ulcerating. Rapid necrosis is characteristic. Subcutaneous abscesses and cryptococcomas may occur.

Figure 10 — Necrotized nodules in an HIV-infected patient with cryptococcosis.



Diagnosis

1. Microscopy. 2. Culture. 3. PCR. 4. ELISA.

Treatment

Amphotericin B 0.7–1.0 mg/kg/day for 2 weeks, followed by fluconazole 200–400 mg/day for 2–6 months.

CRYPTOCOCCOSIS — SUMMARY

Causative agent: Cryptococcus neoformans. Transmission: inhalational. Primary focus: lungs. Lesions: nonspecific necrotized nodules, lesions resembling molluscum contagiosum and herpes. Diagnosis: microscopy and histopathology. Treatment: amphotericin B and fluconazole.

3. Aspergillosis

Causative agents: Aspergillus fumigatus, A. flavus, A. niger and A. terreus. The principal causative agent of all forms is Aspergillus fumigatus.

Epidemiology. Disease develops after inhalation of the organisms. Spores can always be found in ambient air, household dust and construction dust. Much less commonly, infection follows traumatic implantation, including infection of injection sites and surgical wounds. Nosocomial outbreaks have been described due to Aspergillus contamination of ventilation systems. Immunodeficient persons are predominantly affected; primary cutaneous forms are rare.

Pathogenesis. Aspergillus spores contacting respiratory mucosa do not by themselves destroy tissue. Germination is controlled by macrophages; impaired macrophage function permits mucosal colonization. Contact may cause allergy, including bronchial asthma. Aspergillus hyphae can invade vessel walls, causing thrombosis, hemorrhage and hematogenous dissemination.

ICD-10: B44 Aspergillosis; B44.0 invasive pulmonary aspergillosis; B44.1 other pulmonary aspergillosis; B44.2 tonsillar aspergillosis; B44.7 disseminated aspergillosis; B44.8 other forms; B44.9 unspecified.

Clinical picture

The lungs are usually affected first. Pulmonary aspergilloma is fungal colonization of pre-existing lung cavities, which may result from tuberculosis, sarcoidosis or malignant tumors. Chronic necrotizing aspergillosis causes necrosis of part of the lung. Ulcerative tracheobronchitis can obstruct bronchi and produce a bronchoarterial fistula.

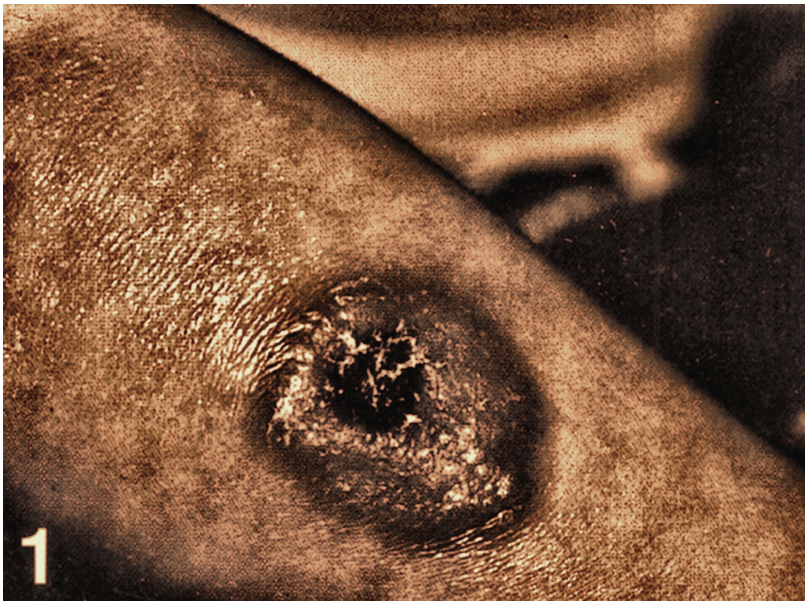
The paranasal sinuses and external auditory canal may be affected by aspergilloma, chronic necrotizing sinusitis, acute invasive aspergillosis and purulent otitis. CNS aspergillosis causes brain abscesses and cerebral infarction. Cardiovascular disease includes endocarditis. Bones and joints are less often affected, producing osteomyelitis.

Skin lesions are nonspecific and occur in disseminated aspergillosis. They consist of papules and plaques that become pustules and ulcerate. Subcutaneous abscesses may occur.

Figure 11 — Necrotized nodule in a patient with cutaneous aspergillosis.

Diagnosis

1. Microscopy. 2. Culture. 3. Histopathology. 4. PCR.



Treatment

Amphotericin B 1.0 mg/kg/day for 2–4 weeks, followed by itraconazole 400 mg/day for 2 weeks to 6 months. Surgical intervention may be required.

ASPERGILLOSIS — SUMMARY

Causative agents: Aspergillus fumigatus, A. flavus, A. niger and A. terreus. Transmission: inhalational. Primary focus: lungs. Lesions: nonspecific necrotized nodules and papules. Diagnosis: microscopy and histopathology. Treatment: amphotericin B, itraconazole and surgery.

4. Candidiasis

4.1 Deep candidiasis

Candidiasis has diverse manifestations. This manual considers only systemic and disseminated forms that represent opportunistic mycoses.

Causative agents. More than 150 Candida species exist and can be classified according to their ability to cause disease. Main pathogens: C. albicans, C. tropicalis, C. parapsilosis, C. glabrata and C. krusei. Less common/rare organisms listed in the source include C. kefyr, C. guilliermondii, C. lusitaniae, C. ciferrii, C. famata, C. lambica, C. lipolytica, C. norvegensis, C. rugosa, C. viswanathii and C. zeylanoides.

The source notes that this section was written jointly with N. A. Sakharuk and V. I. Kozlovsky.

ICD-10 classification: B37 Candidiasis; B37.0 candidal stomatitis; B37.1 pulmonary candidiasis; B37.2 candidiasis of skin and nails; B37.3+ vulvovaginal candidiasis; B37.4+ candidiasis of other genitourinary sites; B37.5+ candidal meningitis; B37.6+ candidal endocarditis; B37.7 candidal septicemia; B37.8 candidiasis of other sites; B37.9 unspecified candidiasis.

Additional codes: B20.4* HIV disease with candidiasis; G02.1* meningitis in mycoses; I39.8* endocarditis, unspecified valve, in diseases classified elsewhere; N77.1* vaginitis, vulvitis and vulvovaginitis in infectious and parasitic diseases classified elsewhere.

Candidiasis of the gastrointestinal tract

The main causative organism of gastrointestinal candidiasis is C. albicans, followed by C. tropicalis, C. kefyr, C. krusei and C. glabrata in decreasing frequency.

Esophageal candidiasis occurs in 1–2% of general medical patients, 5–10% of patients with type 1 diabetes and 15–30% of patients with AIDS. The intestine is described as a source of dissemination to the esophagus.

Predisposing factors for esophageal candidiasis include antibiotics, inhaled or injectable corticosteroids, antacid therapy or hypochlorhydria, diabetes mellitus, alcoholism, intoxication, malnutrition, older age, impaired esophageal motility or obstruction, organ or bone-marrow transplantation, and enteral and especially parenteral nutrition. Immune impairment also predisposes to infection.

General factors include primary and secondary immunodeficiencies, AIDS, malignancy, mucosal dysbiosis, organ and tissue transplantation, endocrine disease, allergic and autoimmune diseases, especially when treated with glucocorticoids. Nutritional disorders due to protein deficiency and low caloric intake impair immune function and predispose to candidiasis.

The source states that reduced gastric acidity is a risk factor and reports pH 7.4 as optimal for Candida growth, with complete inhibition at pH 4.5.

Local factors predisposing to esophageal candidiasis include burns, achalasia, diverticulosis and polyposis of the esophageal mucosa.

Symptoms of candidal esophagitis include pain on swallowing solid and liquid food, leading to impaired nutrition and reduced quality of life; retrosternal burning, dysphagia, regurgitation, nausea and vomiting. Esophageal symptoms may coexist with oral and pharyngeal involvement. Less commonly there is retrosternal pain unrelated to swallowing, heartburn, vomiting with membrane-like pseudomembranes, reduced appetite and weight, and loose stool with mucus. Approximately two thirds of patients with AIDS and esophageal candidiasis have candidal stomatitis. Symptoms are practically absent in 25–30% of patients, particularly immunocompetent people.

Diagnosis is confirmed by radiography and endoscopy with sampling for mycologic and histologic examination. Early radiographic findings are nonspecific. Classical radiographic signs of acute Candida esophagitis include linear or irregular filling defects with clear margins; in severe disease they may cluster in a bunch-of-grapes appearance. The esophagus may appear “shaggy” or “hairy.” A normal radiograph does not exclude esophageal candidiasis.

Endoscopy is the most diagnostically significant method. Characteristic findings include hyperemia, contact fragility of the mucosa, and fibrinous plaques of various sizes and configurations.

Complications are uncommon. Severe disease with erosions and ulcers may cause bleeding, especially with coagulopathy; perforation is possible. Rarely, necrosis with phlegmonous inflammation of the esophagus and mediastinum occurs. Severe specific esophagitis may be complicated by sepsis.

Gastric candidiasis

Gastric candidiasis may occur in oncology patients and after surgery around a gastrostomy. It may complicate peptic ulcer disease, mucosal injury from toxic chemicals or bile reflux. It may be asymptomatic or present like gastritis of another etiology.

Gastroscopy may show edematous mucosa near the gastroesophageal junction, mucosal ulceration and white coating. In other cases, multiple gray-white, round or oval, raised plaque-like lesions surrounded by red halos are seen. They may merge into a continuous coating covering the entire mucosa. In severe disease, necrotic mucosa and submucosa may be shed, leaving deep ulcers with fungal invasion of vessel walls. Bleeding, metastatic candidal lesions and gastric perforation with candidal peritonitis may follow.

Intestinal candidiasis

Patients may complain of anal itching, bloating and abdominal pain, and frequent, paroxysmal, watery stools. Prolonged disease may produce blood and mucus in the stool and intestinal colic. Intestinal lesions may be catarrhal, pseudomembranous or ulcerative, depending on duration and severity, and may coexist.

Colonoscopy may show a white coating. Ulcers are relatively rare and vary in size, shape and number. They are more frequent in the colon and may be superficial defects on the tops of folds or deeper irregular ulcers with undermined edges, merging with each other and reaching the muscular layer. Ulcer surfaces are covered by necrotic material. Very severe intestinal disease may cause atrophy of the lymphoid apparatus.

Candidiasis of the biliary tract

The literature contains limited reports of biliary obstruction associated with Candida, as well as cholangitis and cholecystitis associated with these organisms and responsive to antifungal therapy. Symptoms resemble those caused by other etiologies and include pain, jaundice, hepatomegaly and laboratory evidence of cholestasis. Chronic disseminated candidiasis may involve the liver with cholecystitis and cholangitis.

4.3 Candidiasis of the respiratory organs

The principal respiratory pathogen is C. albicans, followed by C. glabrata, C. tropicalis and C. parapsilosis. Respiratory candidiasis may result from fungi reaching mucosa from outside in inhaled air or from the oral cavity. It more often develops on mucosa previously damaged by inflammation of another etiology.

Candidiasis of the nasal cavity is uncommon; it usually affects the anterior or middle third of the nasal septum and causes mucosal ulceration. The ulcer surface is covered by a gray-white membranous coating. Lesions may be solitary or coexist with oral lesions. The latter is associated in the source with sensitization and dissemination. Predisposing factors include trauma and prolonged antibiotic therapy.

Candidal sinusitis is described, most often involving the maxillary sinus and less often the frontal and sphenoid sinuses. Disease may be superficial or deep, with periosteal and bone involvement of an osteomyelitis type; ethmoidal cells may also be involved.

Candidal pharyngitis usually develops by spread from the oral cavity and esophagus into the airways. A white or yellow-white coating forms, either as islands or, in severe disease, extensive dense plaques. Small erosions are rare. Shedding of necrotic epithelium has been described in patients with hematologic disease and radiation sickness.

Laryngeal candidiasis is dangerous because the vocal cords may be involved. It often accompanies oral and esophageal disease. Discharge appears as whitish membranes and curd-like plaques; less often the lesions are dull white and cover areas of hyperplastic mucosa.

Candida colonization of the bronchi often complicates chronic obstructive pulmonary disease and bronchiectasis. Inhaled corticosteroids can predispose to bronchial candidiasis. It may be asymptomatic, hidden by the underlying disease, or cause whitish sputum containing fungal mycelium.

Prolonged lower-airway colonization may cause an allergic form of bronchopulmonary candidiasis with suffocation, dyspnea and wheezing. In severe cases, bilateral migrating pulmonary infiltrates develop and do not resolve with antibiotics.

Pulmonary candidiasis

Spread may occur by aspiration of fungal elements, by extension from the airways into lung tissue, or hematogenously. Pulmonary candidiasis may accompany severe gastrointestinal candidiasis or occur in isolation. Two varieties are distinguished: primary, which may be bronchial or pneumonic, and secondary, developing from spread from the oral cavity. True invasive disease is characterized by rapid progression, difficult treatment, fever and dyspnea.

Radiographs may show diffuse, lobar or segmental, unilateral or bilateral infiltrates. Massive or miliary infiltration and lymph-node involvement are not characteristic. Histopathology is considered the most reliable diagnostic evidence. If histopathology cannot be performed, invasive respiratory candidiasis is diagnosed in predisposed patients with bronchitis or pneumonia that fails to respond to antibacterial therapy and with yeast cells and/or pseudomycelium in bronchial washings or sputum.

4.4 “Chronic” secondary (isolated) disseminated candidiasis

This form is characterized by involvement of the liver and spleen. Candidemia is confined to the portal venous system, so signs of sepsis are absent. Symptoms include antibiotic-resistant fever, weight loss, abdominal pain, hepatosplenomegaly and leukocytosis. CT shows small lesions, up to 1 cm in diameter, in the liver and spleen.

4.5 “Acute” primary (generalized) disseminated candidiasis

Both superficial and deep candidiasis may allow fungi to enter the bloodstream through penetration of pseudomycelium into vessel walls. The source notes that infection is often exogenous and may be transmitted to patients through the hands of medical personnel.

Candidemia predisposes to candidal sepsis. According to V. L. Kryzhanovsky (2005), the highest rate of candidemia occurs in intensive-care and resuscitation units; two thirds of cases are associated with central venous catheters. Mortality among patients with candidemia is reported as approximately 55%.

Acute candidal septicemia

Acute candidal septicemia is characterized by marked host reactivity with changes in vascular-tissue permeability, fibrinoid changes of vessel walls, allergic vasculitis, hemorrhagic syndrome and absence of purulent metastases. Clinically, acute candidal sepsis presents with fever, sometimes chills, unresponsive to antibiotics. Tachycardia, dyspnea and less often hypotension may occur. Severe cases develop disseminated intravascular coagulation with shock and multiorgan failure, rapidly leading to death.

Renal candidiasis (candidal renal abscesses)

This form has an acute course with multiple small abscesses in the renal cortex and medulla, most around vessels. Yeast-like cells and pseudomycelial filaments occur in the abscesses and inside dilated renal tubules.

Candidiasis of the eyeball (candidal endophthalmitis)

This develops in acute disseminated candidiasis and in patients with asymptomatic candidemia. Causes may be exogenous in immunodeficient patients or associated with ocular surgery. Complaints include impaired vision and eye pain. Fundoscopy shows poorly demarcated white-yellow retinal lesions and diffuse vitreous opacities. The outcome is scarring of the fundus with visual impairment or loss.

Disseminated cutaneous candidiasis

An early manifestation of acute disseminated candidiasis, characterized by sharply demarcated erythematous papules, pustules and nodules tending to central ulceration. Lesions are mainly on the scalp and beard/mustache area. Severe cases produce subcutaneous abscesses and lesions resembling ecthyma gangrenosum.

Candidal thrombophlebitis

Phlebitis usually develops at a catheter site. Peripheral-vein phlebitis causes edema, erythema and induration. Deep-vein thrombosis causes swelling of the limb or another region drained by the affected vein.

Candidal carditis

Candidal endocarditis is a septic infection of heart valves, most often the aortic and mitral valves. It has a prolonged course and two histologic patterns: verrucous and verrucous-ulcerative. Children with congenital heart disease and patients with prosthetic valves are predisposed. There are no specific clinical features; fever, cardiac murmurs, malaise and weight loss occur.

Candidal myocarditis is difficult to diagnose during life because symptoms are nonspecific; autopsy may show abscesses in patients who died from disseminated candidiasis. Candidal pericarditis is very rare and may cause fever, chest pain, a pericardial friction rub and pericardial effusion.

Candidal myositis

A condition characteristic of acute disseminated candidiasis, with pain and weakness in various muscles in the setting of fever and rash.

Candidiasis of the brain

Cases of candidal meningitis and other nervous-system lesions due to dissemination have been described. Meningitis may be acute purulent or productive. Acute purulent meningitis is usually seen in severely debilitated young children; the productive form develops in patients with prolonged candidiasis. Acute cases cause high fever, headache and fever. The course may also be subacute or chronic with few symptoms, normal or low-grade temperature, and scant findings.

Other CNS lesions, such as brain abscess and diffuse metastatic encephalitis, are much less common. Symptoms are scant and neurologic signs may appear at different stages.

Disseminated pulmonary candidiasis

Disseminated pulmonary candidiasis causes cough and dyspnea, sometimes in the setting of yeast-associated sepsis. Radiographs may show diffuse bilateral infiltrates, small- or large-focal dissemination, or no abnormalities.

Candidal osteomyelitis

Most often this is a manifestation of disseminated candidiasis in people who use injectable drugs. It may also be a late complication of candidemia in neutropenic patients receiving parenteral nutrition. Typical sites include the lumbar spine, ribs and sternoclavicular cartilage; joints and bones affected by another disease may also be involved.

Symptoms are scant and usually limited to dull pain in the affected area. Radiography shows localized osteolysis. Differentiation from bacterial disease requires needle aspiration and, less often, open biopsy.

Candidal arthritis

Usually a single large joint is affected, most often the knee or hip. Symptoms include pain, swelling, induration over the joint and limited movement. Examination of synovial fluid is essential for diagnosis; the pathogen may be isolated from synovial fluid and blood.

Diagnosis and treatment

Diagnosis: 1. Culture. 2. PCR. Treatment listed in the source: fluconazole 50–400 mg/day for 1–2 weeks; itraconazole 200 mg/day for 1–3 weeks; amphotericin B 0.5–1 mg/kg for a 6–10-week course.

REFERENCES

1. Sakharuk, N. A. Candidiasis: Etiology, Clinical Features, Diagnosis, Treatment / N. A. Sakharuk, V. V. Kozlovskaya. — VSMU, 2010. — p. 190.

2. Sergeev, A. Yu. Immunity in Candidiasis and Approaches to Immunocorrection / A. Yu. Sergeev, S. A. Burova // Antibiotics and Chemotherapy. — 2000. — No. 12. — pp. 30–31.

3. Sergeev, Yu. V. Candidiasis: Nature of Infection, Mechanisms of Aggression and Protection, Laboratory Diagnosis, Clinical Features and Treatment / Yu. V. Sergeev, A. Yu. Sergeev. — Moscow: Triada-X, 2001. — 472 p.

4. Archer, C. B. Ethnic Dermatology: Clinical Problems and Skin Pigmentation / C. B. Archer. — Informa, 2008. — p. 198.

5. Cutaneous phaeohyphomycosis due to Cladophialophora bantiana / A. Schoeffer et al. // Annales de dermatologie et de venereologie. — 2011. — Vol. 138. — pp. 504–507.

6. Dicaudo, D. J. Coccidioidomycosis: A Review and Update / D. J. Dicaudo // Epidemiology. — 2006. — Vol. 4. — pp. 929–942.

7. Dimino-Emme, L. Cutaneous Manifestations of Disseminated Cryptococcosis / L. Dimino-Emme, W. Gurevitch // Journal of the American Academy of Dermatology. — 1995. — Vol. 32. — pp. 844–850.

8. Lupi, O. Tropical Dermatology: Fungal Tropical Diseases / O. Lupi, S. K. Tyring, M. R. McGinnis // Journal of the American Academy of Dermatology. — 2005. — Vol. 53(6). — pp. 931–951.

9. Primary cutaneous aspergillosis in an immunocompetent child / C. M. Mowad et al. // Journal of the American Academy of Dermatology. — 1995. — Vol. 33(1). — pp. 136–137.

10. Treatment of subcutaneous phaeohyphomycosis and prospective follow-up of 17 kidney transplant recipients / M. M. Ogawa et al. // Journal of the American Academy of Dermatology. — 2009. — Vol. 61(6). — p. 1016.

EXAMPLES OF TESTS AND PROBLEMS FOR KNOWLEDGE ASSESSMENT

Tests

1. Which disease is called “gardener’s disease”? Answer options: a) sporotrichosis; b) chromomycosis; c) actinomycosis; d) mycetoma.

2. What does a “sporotrichosis-like” arrangement of lesions mean? Options: a) along nerve trunks; b) along Blaschko lines; c) along lymphatic vessels; d) in groups.

3. Medlar bodies are found in tissues in: a) sporotrichosis; b) coccidioidomycosis; c) blastomycosis; d) chromomycosis; e) lobomycosis.

4. The most common clinical manifestation of phaeohyphomycosis is: a) brain involvement; b) solitary abscesses of the extremities; c) verrucous papules and plaques; d) keloid-like nodules; e) ulcerating nodules along lymphatic vessels.

5. Keloid-like lesions occur in: a) phaeohyphomycosis; b) lobomycosis; c) chromomycosis; d) sporotrichosis; e) cryptococcosis.

6. Typical localization of mycetoma: a) back; b) upper extremities; c) lower extremities; d) face; e) mucous membranes.

7. Localization on the nasal mucosa is characteristic of: a) sporotrichosis; b) chromomycosis; c) mycetoma; d) rhinosporidiosis; e) cryptococcosis.

8. South American blastomycosis is another name for: a) chromomycosis; b) blastomycosis; c) cryptococcosis; d) paracoccidioidomycosis; e) coccidioidomycosis.

9. The primary focus in paracoccidioidomycosis is: a) bone; b) kidneys; c) adrenal glands; d) lungs and lymph nodes; e) skin and mucous membranes.

Problems

Problem 1. A 45-year-old patient who has lived for a long time in South America and works as a gardener develops solitary nodules on the upper extremities. Later the nodules ulcerate and new lesions appear along lymphatic vessels. The lymphatic vessels are painful and palpable as cords. What is the most likely diagnosis and what should the physician do?

Problem 2. A 12-year-old patient living in India has polypoid growths of the right nasal mucosa. After removal of the polyp and histopathologic examination, fungal cells are identified. What is the diagnosis and what should the physician do?

Problem 3. A 65-year-old agricultural worker originally from India has a foot lesion. The foot is enlarged and deformed; deeply located suppurating nodules are present, discharging pus containing black granules. What is the most likely diagnosis and what should the physician do?

Problem 4. One and a half years after returning from a business trip to Venezuela, a 43-year-old patient develops oral-mucosal disease. Examination shows verrucous growths with vascular spots on the surface. Cervical lymph nodes are enlarged bilaterally. What is the likely diagnosis, what additional investigations are required, and what are the principles of treatment?

Problem 5. A 45-year-old patient complains of headache, nausea, irritability and blurred vision. Facial lesions resemble molluscum contagiosum. The history reveals HIV infection. Chest radiography shows diffuse opacities of the lung fields. What is the likely diagnosis, what additional investigations are required, and what is the physician’s approach?

ANSWERS

1. Tests

Question 1 — a; Question 2 — c; Question 3 — d; Question 4 — b; Question 5 — b; Question 6 — c; Question 7 — d; Question 8 — d; Question 9 — d.

2. Problems

Problem 1 — Sporotrichosis. Problem 2 — Rhinosporidiosis. Problem 3 — Mycetoma. Problem 4 — Paracoccidioidomycosis. Problem 5 — Cryptococcosis.

EDUCATIONAL PUBLICATION

S. A. Sokhar

Abdel Malak Walid

V. V. Kozlovskaya

DEEP AND SYSTEMIC MYCOSES

Educational-methodological manual for students of the medical and medical-diagnostic faculties of medical universities, clinical residents and physician trainees.

Editor: O. V. Kukhareva. Computer layout: S. N. Kozlovich.

Signed for printing 11.06.2012. Format 60×84 1/16. Offset paper 65 g/m². Typeface: Times. Conventional printed sheets: 2.79. Publishing sheets: 3.05. Circulation: 170 copies. Order No. 168.

Publisher and printing: Educational Institution “Gomel State Medical University.” License LI No. 02330/0549419 dated 08.04.2009. Lange Street 5, 246000 Gomel.

PAGE 48

No substantive text is present on the source page. The scanned page contains only a faint MedUniver.com watermark/background.