Chapter 18

DEEP FUNGAL SKIN DISEASES

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INTRODUCTION

Fungal infections of humans are divided somewhat arbitrarily into the *superficial* mycoses and the *deep* mycoses. The superficial mycoses, such as the dermatophyte infections, are generally confined to the surface of the skin and hair and are discussed in Chapter 17, Superficial Fungal Skin Diseases. The deep mycoses, discussed here, are fungal infections that regularly involve the dermis and subcutaneous tissues, and often other organ systems. Although deep fungal infections are seen most often in particular geographical locations, the diseases' natural distributions are not necessarily confined there (Exhibit 18-1). Even within an endemic focus, a disease (eg, rhinosporidiosis) may still be uncommon. Other diseases (eg, sporotrichosis) are probably ubiquitous but have hyperendemic foci. Still others (eg, coccidioidomycosis) are acquired only within their specific endemic areas. Our knowledge of the geographical distributions of mycoses depends to some extent on the abilities of local laboratories to detect the pathogens, and on local differences in disease-reporting requirements.

Deep fungal disease is usually acquired via either (*a*) inhalation of fungal spores or (*b*) direct inoculation of the fungus into the skin. Depending on the route of entry, some generalizations can be made on the resulting diseases. Inhalation of pathogenic spores may produce a primary pulmonary infection that resembles a transient, flulike illness. Patients usually recover uneventfully but secondary dissemination to skin is not uncommon. It is from the cutaneous lesions that the diagnosis of a systemic fungal infection is often made (Figure 18-1). Prompt recognition is important because untreated disseminated disease is often fatal. The other common route of acquisition is direct inoculation of the pathogenic fungus via minor, often unnoticed, skin trauma. Again, some generalizations can be made. Some fungi produce granulomatous or verrucous plaques that expand around the initial site of implantation; other fungi produce subcutaneous masses that can spread along lymphatic channels or cause chronic swelling and deformity.

Based on their route of entry, deep fungal diseases can be further divided into the *systemic* mycoses and the *subcutaneous* mycoses. Although this is an artificial classification, it reflects a clinically useful approach to the diagnosis of the deep mycoses. It is important to note that this scheme ignores true taxonomic relationships among the fungi. Indeed, this scheme historically has embraced some bacterial diseases under the rubric of the deep mycoses because of the similarity of their clinical presentations. Because pharmacological therapy of these diseases corresponds more closely with taxonomy than with the clinical syndromes, it is important to recognize the discordance between the clinical and phylogenetic classification systems in medical mycology.

In the wild, the pathogenic fungi usually dwell in the soil or on plants as saprophytes. They are inconspicuous, usually microscopical, and are often undetected in their natural state. Humans are not essential for the life cycle of any deep fungal

EXHIBIT 18-1

PRINCIPAL GEOGRAPHICAL LOCATIONS OF DEEP FUNGAL DISEASES

Systemic Mycoses

Histoplasmosis
- Mississippi and Ohio River valleys
- Panama
- Northern South America

Histoplasmosis duboisii
- Tropical Africa

Coccidioidomycosis
- Southwestern United States
- Northwestern Mexico

Blastomycosis
- South-central United States
- Great Lakes region

Paracoccidioidomycosis
- South America, especially Brazil

Subcutaneous Mycoses

Sporotrichosis
- Oklahoma
- Mexico, Brazil, Japan, South Africa

Chromoblastomycosis
- Pantropical

Mycetoma
- Mexico, India, northeast Africa

Lobomycosis
- Amazon River basin

Rhinosporidiosis
- India, Sri Lanka

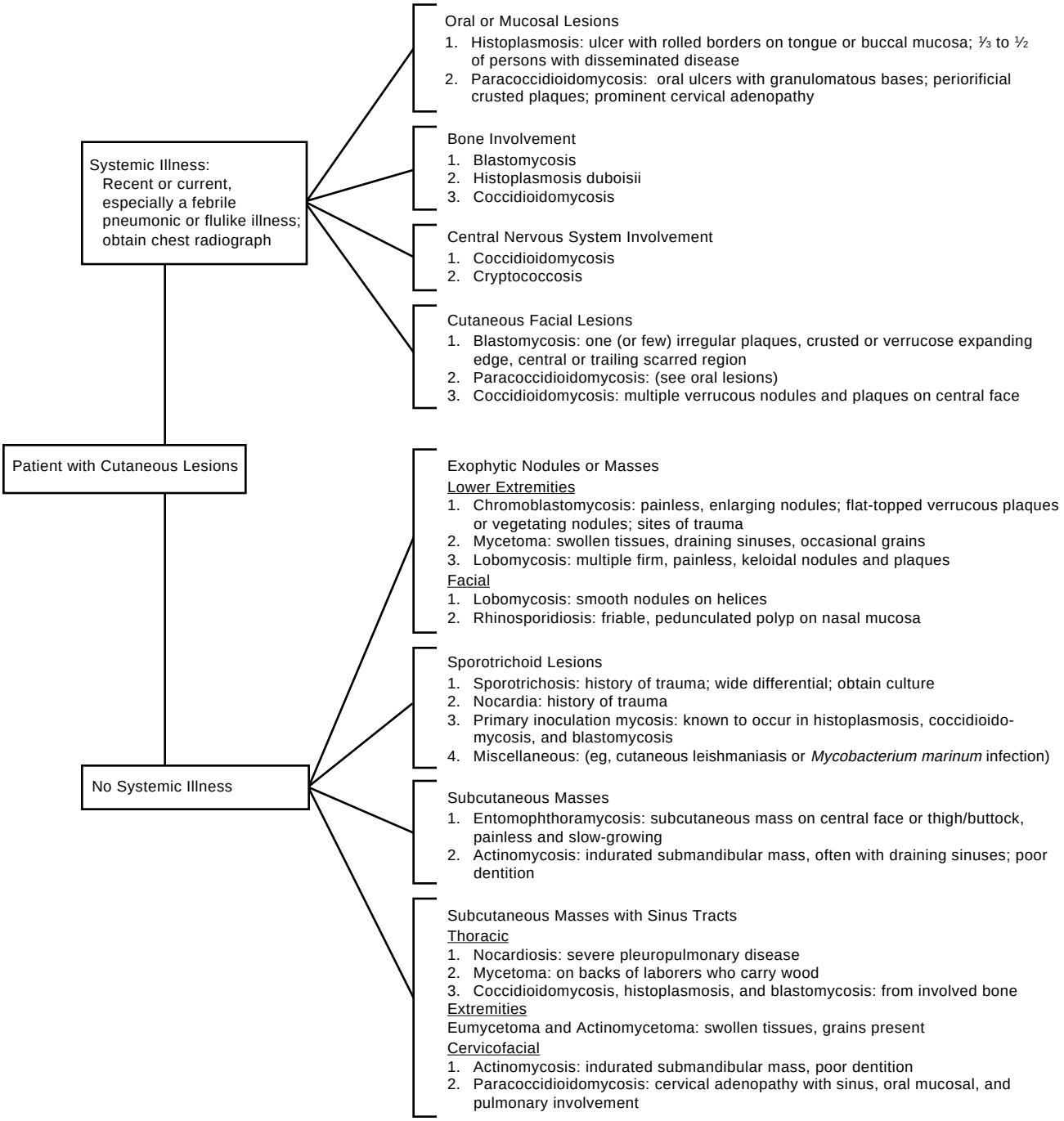

Fig. 18-1. Algorithm for the clinical diagnosis of deep fungal diseases. The clinical presentation of cutaneous lesions and any systemic symptoms can be used to suggest a diagnosis. Deep fungal infections that are typically systemic (eg, histoplasmosis) may occur in a sporotrichoid fashion following an inoculation injury. Conversely, infections that are usually confined to the skin and subcutaneous tissues (eg, sporotrichosis) occasionally occur as serious systemic illnesses. Seemingly isolated cutaneous lesions may be the presenting sign of an otherwise subclinical systemic infection, particularly in blastomycosis. The diagnosis of any suspected deep fungal infection must be confirmed by identification of the pathogen by direct examination of tissue specimen, biopsy, culture, or serologic assay. In patients with disseminated histoplasmosis, cryptococcosis, or sporotrichosis, the physician must consider an underlying immunosuppressive condition (eg, infection with human immunodeficiency virus, chemotherapy, malignancy).

pathogen and become infected only incidentally. Once inside a host, the fungus can undergo a dramatic morphologic transformation to cause the conditions described in this chapter.

Several of the systemic mycoses with epidemic potential have been implicated in occupationally related outbreaks. To date, however, the deep mycoses have not significantly influenced military operations. Nevertheless, outbreaks typically occur in environmentally disturbed areas and therefore armies on the move will continue to encounter some risk from these diseases.

SYSTEMIC MYCOSES

There are four systemic mycoses: histoplasmosis (including histoplasmosis duboisii), coccidioidomycosis, blastomycosis, and paracoccidioidomycosis. Each disease has a distinctive ecological and geographical distribution (see Exhibit 18-1). Infections begin when persons inhale fungal spores into their lungs. There, the spores convert to their thermophilic, pathogenic, yeastlike phase, which causes a primary pulmonary infection. Initial infections are often asymptomatic or may cause a transient, flulike illness. Unrecognized or subclinical infections are very common in endemic areas. Sometimes a severe lung disease develops or the infection may spread to other organs, with a frequent predilection for skin. Indeed, for many years, several systemic mycoses were known only from their cutaneous manifestations.

Histoplasmosis and Histoplasmosis Duboisii

Histoplasmosis is also called Darling's disease, spelunker's disease, cave disease, Ohio Valley disease, and cytomycosis. Histoplasmosis duboisii is also called African histoplasmosis.

Histoplasmosis is probably the most common systemic mycosis in the world. In the United States alone, perhaps 30 to 40 million persons are infected.[1] Most infections are clinically inapparent; however, because of its prevalence, the disease has the greatest morbidity of any systemic mycosis. Infection is acquired by inhaling the spores of *Histoplasma capsulatum* and is established most importantly in the lungs. Cutaneous manifestations arise uncommonly from disseminated infection. *Histoplasma duboisii* is the pathogen in central Africa.

Histoplasma capsulatum is a thermally dimorphic fungus that assumes its mycelial phase in nature and in culture at room temperature. In tissue and in warmer cultures, the yeast form predominates. Yeast, 2 to 4 μm in diameter, are phagocytized but not killed by host macrophages. The apparent capsule seen on histological sections is an artifact and the epithet, *capsulatum*, a misnomer. The fungus has a sexual (ie, perfect) state, an ascomycete, *Emmonsiella capsulata* (synonym *Ajellomyces capsulatus*). *Histoplasma duboisii* (syn *H capsulatum* variety *duboisii*) has larger yeast, about 7 to 15 μm.[2]

History

In December 1905, Samuel Taylor Darling, an American pathologist working for Colonel William Gorgas at Ancon (later Gorgas) Hospital in the Panama Canal Zone, first encountered histoplasmosis. While performing an autopsy on a canal laborer from Martinique, he noted intracellular organisms in many tissues. Darling named the organism *Histoplasma capsulata* [*sic*] because of its location within histiocytes (*Histo-*), its resemblance to plasmodia (*-plasma*), and its encapsulated appearance (*capsulata*).[3] He later masculinized the specific epithet, *capsulatum*, to achieve nomenclatural agreement. Two additional autopsies with similar findings convinced Darling that he had found a new form of visceral leishmaniasis.[4]

Mortality rates among canal workers were extraordinary. Most deaths were caused by pneumonia and the mosquito-borne diseases, yellow fever and malaria.[5] The morbidity of undiagnosed histoplasmosis among the canal workers remains undetermined. Nearly 50 years passed before the next case of histoplasmosis in Panama was reported,[6] although the disease is now known to be common there.[7]

After reviewing Darling's original slides, a Brazilian pathologist, Henrique da Rocha-Lima, determined that *Histoplasma* was more akin to yeasts than to protozoa.[8] Its fungal nature was confirmed by culturing organisms that were recovered from the blood of an infant dying of an unexplained febrile illness.[9] Until a benign form of the infection was recognized during the 1940s, histoplasmosis was considered a uniformly fatal, primarily tropical, disease. During the early 1950s, *H capsulatum* was detected in calcified pulmonary nodules resected from healthy soldiers at Fitzsimons Army Hospital in Colorado.[10] The true geographical range, prevalence, and usual benignity of histoplasmosis

were further clarified by skin testing large groups with histoplasmin and by recovering *H capsulatum* from the soil.

Several outbreaks of acute pulmonary histoplasmosis have occurred in military units training in tropical areas but cutaneous manifestations have not been reported. While training in Panama, 27 of 47 U.S. soldiers (57%), who had cleaned out and then slept in an abandoned bunker, contracted acute pulmonary histoplasmosis. The bunker, inhabited by a colony of bats, had several inches of mixed soil and bat guano (ie, excrement) on the floor. The soldiers' sweeping of the floor had aerosolized the spores of *Histoplasma*, which permitted their inhalation. The severity of the soldiers' illnesses corresponded roughly to the duration of exposure to the aerosolized dust.[11]

During 1977, 8 soldiers in a 35-man engineering unit who were returning from training exercises in Panama suddenly developed fevers. Initial evaluations were unrevealing, leading to a presumptive diagnosis of an arboviral disease, but histoplasmosis was confirmed by complement fixation. The exposure probably occurred while the soldiers cleaned an abandoned Spanish fort that was inhabited by bats.[12]

French and Dutch soldiers serving in colonial French Guiana and Surinam (now Suriname), respectively, occasionally contracted histoplasmosis. Symptomatic illnesses were usually first diagnosed as acute pulmonary tuberculosis. Exposures presumably occurred in bunkers and old huts where bat guano had accumulated.[13,14]

At Chanute Air Force Base, Illinois, there was an outbreak of acute pulmonary histoplasmosis in 10 persons, most of whom had not lived previously in endemic areas. *Histoplasma* had colonized soil in the gardens and orchards around their housing development.[15]

Distribution and Epidemiology

Histoplasmosis occurs worldwide but is hyperendemic along the Mississippi and Ohio River valleys (Figure 18-2). Histoplasmin skin tests and chest radiographs showing calcified granulomata suggest nearly universal infection in residents of these areas. Additional foci occur in Panama and northern South America, Australia, Indonesia, India, South Africa, the Mediterranean, and western Europe.[14] Histoplasmosis duboisii occurs in tropical Africa.

The organism is a saprophyte found in soil laden with excreta of bats or birds. Therefore, habitats with guano accumulations, for example, caves and chicken coops, are consistent sources of infection. Occupations and recreations (eg, chicken farming, spelunking, pigeon breeding) that expose people to these niches predispose for infection. In tropical areas, bats are the usual reservoir of histoplasmosis. They, unlike birds, naturally become ill with infection. The microenvironment in their caves is suitable for the growth of *Histoplasma*, whereas the surrounding environment apparently is not.[16] In temperate regions, outbreaks have occurred in residential areas where excrement from starlings, grackles, blackbirds, pigeons, or other birds accumulates beneath roosting sites.

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Fig. 18-2. Histoplasmosis is hyperendemic in this North American region. The distribution corresponds roughly to the areas drained by the Mississippi and Ohio rivers.

Clinical Manifestations

Histoplasmosis is acquired when a person inhales spores into the lungs, where the spores convert to their yeast forms. In heavily endemic areas, perhaps 95% of the population has been infected, albeit usually with asymptomatic disease or a self-limited, mild, flulike illness. The erythema nodosum and erythema multiforme that sometimes accompany acute disease are probably hypersensitivity reactions.[17] Acute pulmonary infections typically produce inactive, calcified, pulmonary granulomas and transient immunity to further bouts of histoplasmosis. Persons with underlying lung disorders are susceptible to chronic cavitary histoplasmosis. Its clinical and radiographic features resemble pulmonary tuberculosis and may be fatal if untreated.[1]

Hematogenously disseminated histoplasmosis occurs in 1 of 2,000 to 5,000 acute infections and has

a predilection for immunocompromised, elderly, or very young persons.[18] The organisms enter reticuloendothelial organs, such as liver, spleen, lymph nodes, and bone marrow. Infants, in particular, can have a fulminant illness with fungemia characterized by fever, hepatosplenomegaly, and pancytopenia. Their peripheral smears may reveal yeast cells. In adults, disseminated disease has a more protracted course, often localizing in the bone marrow. Subsequent involvement of the meninges, endocardium, or adrenal glands is insidious but potentially lethal.[18] Disseminated histoplasmosis in a person infected with the human immunodeficiency virus (HIV) meets the Centers for Disease Control and Prevention's (CDC's) definition of acquired immunodeficiency syndrome (AIDS).[19]

Oropharyngeal lesions are the most common dermatologic sign, found in one third to one half of disseminated cases (see Figure 18-1). When present, they are often the only clinical manifestation of the disease. Oral papules or nodules typically erode, forming ulcers with prominent rolled borders (Figure 18-3). In order of their frequency, the affected sites are the tongue, buccal mucosa, larynx, lip, and gingiva.[1]

Skin lesions, none distinctive, occur in only 5% of patients with disseminated disease (Figure 18-4). Reported lesions include papules, plaques, ulcers, abscesses and furuncles, panniculitis, purpura, eczema, and erythroderma.[17]

African histoplasmosis differs from classic American histoplasmosis because its pulmonary symptoms are less severe, whereas bony and skin lesions are more common. The most common cutaneous lesions are hypopigmented, dome-shaped papules surrounded by hyperpigmented halos, giving them a targetlike appearance. These heal with scarring. Subcutaneous abscesses and draining sinuses arising from lymph nodes or underlying osteomyelitic foci are less common but still characteristic of the disease.[20,21]

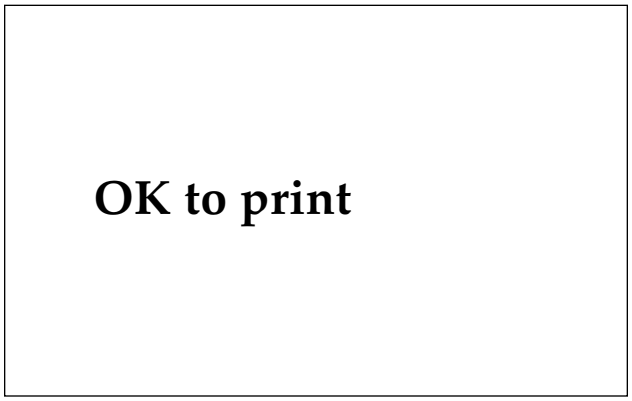

Fig. 18-3. This man has disseminated histoplasmosis. Note the shallow ulcer on his oral mucosa.

Fig. 18-4. Granulomatous plaque of cutaneous histoplasmosis. Cutaneous lesions of disseminated histoplasmosis have varied, nondistinctive morphologies but they can be diagnostic on either culture or histopathology. Photograph: Courtesy of William E. Dismukes, MD, Birmingham, Ala.

Rare cases of primary inoculation cutaneous histoplasmosis have followed laboratory accidents or environmental inoculation.[22] A noduloulcerative lesion arises at the implantation site, followed by lymphangitis and a chain of lymphocutaneous nodules. Except for its spontaneous resolution, the clinical features resemble lymphocutaneous sporotrichosis.

Diagnosis

H capsulatum can be found within parasitized macrophages of involved organs (Figure 18-5). Similarly sized, intracellular parasites also occur in granuloma inguinale, rhinoscleroma, and leishmaniasis. Each may also affect mucocutaneous regions, but only *H capsulatum* picks up fungal stains. Direct examination of Giemsa- or Wright-stained smears of sputum, pus, skin or ulcer scrapings (Tzanck preparation), Buffy-coat smears, or other materials may reveal *Histoplasma*.[17,23,24] Culture has the highest yield with material aspirated from bone marrow but is often positive when performed on skin, blood, and other tissues.[18] Skin testing with histoplasmin is useful mainly as an epidemiological tool, and is often falsely negative in persons with cutaneous or otherwise dissemi-

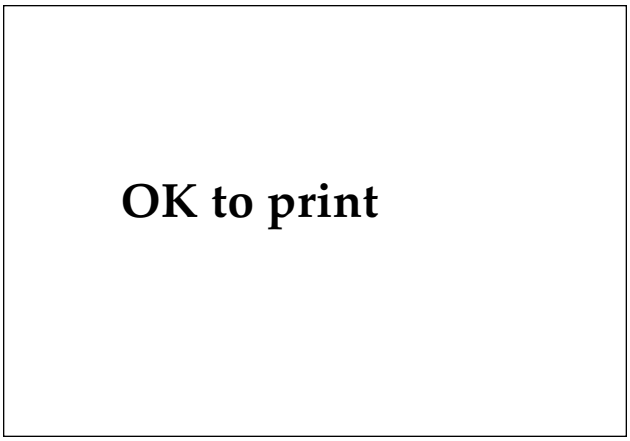

Fig. 18-5. This photomicrograph shows infection of the skin. The yeast forms have been consumed by host macrophages. The unstained rim around the organisms gives the illusion of a capsule, although a true capsule does not exist (hematoxylin-eosin stain, original magnification 430X). Photograph: Courtesy of Colonel James E. Fitzpatrick, Medical Corps, US Army, Aurora, Colo.

nated disease. Investigational radioimmunoassays that detect *Histoplasma* polysaccharide antigen in the urine are rapid and sensitive.[25] Serologic tests are not the subject of this chapter but are reviewed in detail elsewhere.[18]

Treatment

Except in cases of primary inoculation histoplasmosis, cutaneous lesions signify disseminated disease. Accordingly, these patients require aggressive treatment. For severe disease, intravenous amphotericin B should be administered at 25 to 35 mg/d for a total of 2 g over approximately 6 weeks. Immunocompetent patients with mild infections that do not involve the central nervous system may receive the fungistatic agent, ketoconazole, on an outpatient regimen of 400 mg daily, administered orally. Mild, acute, pulmonary infections resolve spontaneously and require no therapy.[18,26,27]

Military Implications

Cutaneous histoplasmosis is unlikely to interfere with military operations. Outbreaks of acute pulmonary disease will continue to occur whenever immunologically naive soldiers enter endemic areas. Caution should be exercised on entering caves and sheltered areas such as old bunkers, especially in the tropics. Care not to disturb dusty soil laden with bat or bird excrement may help prevent outbreaks of histoplasmosis.[24]

Coccidioidomycosis

Coccidioidomycosis has a well-recognized ecological and geographical distribution: it is endemic in certain arid and semiarid regions throughout the Americas, especially in the southwestern United States. Coccidioidomycosis is acquired by inhaling the arthrospores of *Coccidioides immitis* or, rarely, by percutaneous inoculation of the spores. Primary pulmonary infections are usually inapparent or produce a transient, flulike illness. Disseminated disease is uncommon but, when present, frequently has cutaneous lesions.Coccidioidomycosis is also called San Joaquin Valley Fever, Posada's disease, valley fever, coccidioidal granuloma, and desert fever.

C immitis is a dimorphic fungus that exists in nature as a soil saprophyte. The mycelia produce spores (or arthroconidia) that are easily wind-blown and are infectious when inhaled. In tissue, the organisms develop into specialized, thick-walled structures called spherules. Mature spherules are large, (10–) 30 to 60 (–80) µm in diameter, with internal septae separating numerous endospores. When a spherule ruptures, endospores discharge into surrounding tissue. External budding, as seen in other systemic mycoses, does not occur.[2]

History

Coccidioidomycosis was first described in 1892 in an Argentinean cavalryman stationed in the Gran Chaco of northern Argentina. An unexplained sore developed on his cheek and was unresponsive to treatment. The lesion grew more warty so he was transferred to the University Hospital Clinics in Buenos Aires. There, a 21-year-old intern, Alejandro Posadas, evaluated the patient and discovered the characteristic spherules of coccidioidomycosis, describing them as protozoa.[28] A few years later, the organism was isolated from several patients in California with widespread, destructive skin lesions. It was named *Coccidioides* for its superficial resemblance to the avian parasite, *Coccidia*. The epithet, *immitis*, meaning "not mild," reflects the early impression that coccidioidomycosis was nearly always fatal.

Further investigations in the San Joaquin Valley in the 1930s determined that the flulike condition known locally as valley fever was, in fact, benign primary pulmonary coccidioidomycosis.[29] When the U.S. Army Air Corps elected to train aviators there, concerns were raised over bringing nonexposed

individuals into a highly endemic area. Despite the efforts of the military physicians who served as coccidioidomycosis control officers at each airfield, the disease caused significant interruptions in training. Coccidioidomycosis particularly hampered preparations for the World War II North Africa campaign conducted at the U.S. Army's Desert Training Center (west of Twenty-Nine Palms, California, near the Arizona border) and several sites in southern California and Arizona. Prisoner-of-war camps housing Japanese, German, and Italian soldiers in Florence, Arizona, and San Luis Obispo, California, also experienced outbreaks. The foundation of the modern understanding of coccidioidomycosis emerged from the effects of this disease on the U.S. military during World War II and the medical departments' epidemiological and preventive medicine responses.[30]

Military installations in Arizona and California continue to experience high rates of lost man-days due to pulmonary coccidioidomycosis.[31] Active military bases that have reported disease or serologic evidence of infection include Twenty-Nine Palms Marine Corps Base, Lemoore Naval Air Station, Edwards Air Force Base, and Fort Irwin, all in California; Chandler Air Force Base, Davis–Monthan Air Force Base, Luke Air Force Base, and Williams Air Force Base, all in Arizona; and Fort Bliss, Texas.[32–34] In addition, personnel from the Norwegian, Belgian, and German military have acquired coccidioidomycosis during training exercises in the American Southwest.[35–37]

Epidemiology

Approximately 100,000 new cases of coccidioidomycosis occur in the United States each year, most during periods when dry, dusty winds carry the spores aloft. Occupational and recreational activities that expose persons to dusty soils are risk factors for coccidioidomycosis. Agricultural workers, military units, outdoor construction workers, and archeological teams repeatedly have been involved in point (ie, localized, single-occasion) outbreaks.[38,39] California's workmen's compensation laws recognize coccidioidomycosis as an occupational illness.

Risk factors for systemic disease include race, gender, and, possibly, pregnancy.[38,40] The propensity for severe disease is greater in nonwhites than in whites. This disparity is severalfold greater for Mexicans and Native Americans and considerably more so for blacks and Filipinos.[31] The reasons for this are not well understood. Socioeconomic factors (eg, occupational exposures and nutritional status) do not entirely account for the differences. In general, the disease is more often self-limited in females than in males. In contrast, the hormonal milieu and mild immunosuppression associated with pregnancy may permit vigorous growth of the fungus. Infants, the elderly, and persons with blood types B or AB also may be at increased risk for severe disease.[31]

Distribution

C immitis is tolerant of a wide range of environmental conditions but competes poorly with other microorganisms in fertile soils. Therefore, *C immitis* is most abundant in soils too dry and dusty for more fastidious fungi. Also, once lands are under cultivation, other soil fungi displace *C immitis*. In North America, coccidioidomycosis occurs primarily in the Lower Sonoran life zone, which is characterized by semiarid conditions; hot summers; mild winters; and alkaline, sandy soils (Figure 18-6). Plants typically found in this habitat include creosote, yucca,

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Fig. 18-6. *Coccidioides immitis* occurs naturally in the dusty soils of the Lower Sonoran life zone. Ocotillo (the long, wiry-branched shrub) and several types of cacti (saguaro, cholla, and prickly pear) typify this ecosystem, seen here in the Saguaro National Monument near Tucson, Ariz.

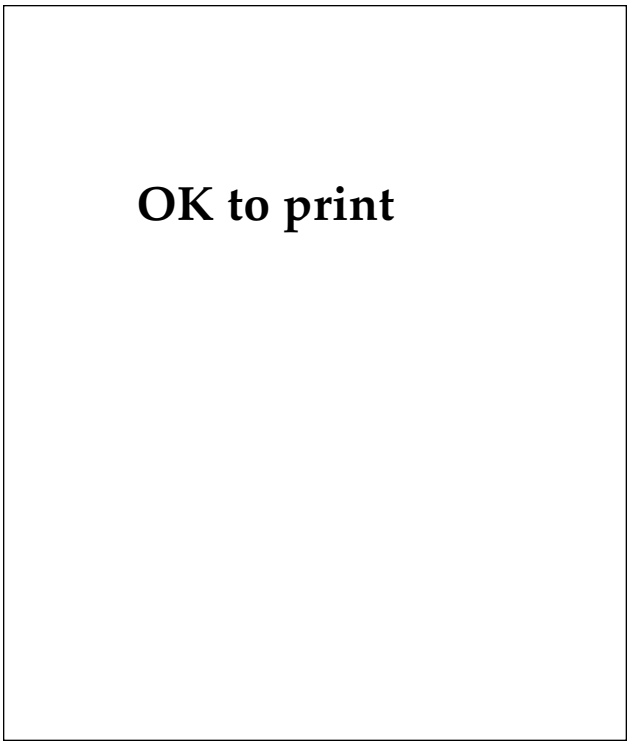


Fig. 18-7. The geographical distribution of coccidioidomycosis. Infection with *Coccidioides immitis* is not known to have occurred naturally outside the Americas.

mesquite, ocotillo, and several types of cacti (saguaro, cholla, prickly pear). Hyperendemic foci are scattered throughout central California's San Joaquin Valley, the southwestern United States, and northwestern Mexico (Figure 18-7). The disease also occurs infrequently in several locations in Central and South America. The disease is not transmissible between humans and there are no reliable reports of coccidioidomycosis acquired outside the Americas. Mammals other than humans are susceptible to infection.[31,38]

Clinical Manifestations

Coccidioidomycosis follows inhalation of dust laden with spores of *C immitis*. After an incubation period of 1 to 4 weeks, a primary pulmonary infection develops. Perhaps 60% of newly acquired cases are asymptomatic.[40] The others experience symptoms ranging from a flulike syndrome with mild fevers to severe pneumonitis with cough, fever, chest pain, dyspnea, chills, and night sweats. Typically, symptomatic illnesses completely resolve.

Several nonspecific cutaneous findings are associated with early coccidioidomycosis. A transient morbilliform or scarlatiniform erythema may accompany the early symptoms in children, adolescents, and 10% of adults. Several weeks later, a syndrome (Valley Fever), more common in women and white people, develops.[29] It affects approximately 25% of infected white women and 10% of infected white men.[38] Erythema nodosum or, less commonly, erythema multiforme may occur, indicating the host's strong immunological response and decreased risk for disseminated disease. Nonmigratory arthralgias (eg, desert rheumatism) occur in one third of patients.[38]

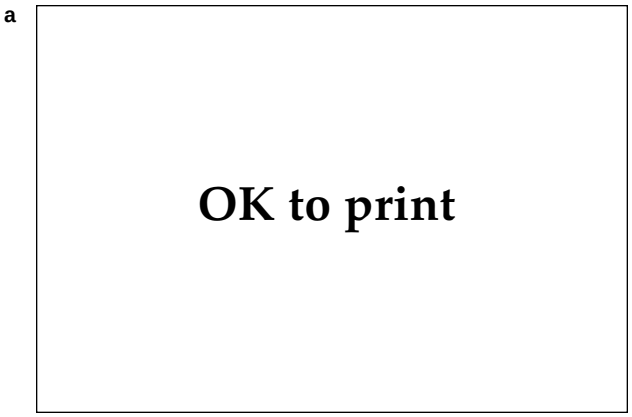
Extrathoracic disease occurs in fewer than 1% of infections, more commonly in the ethnic groups noted above. Target organs for disseminated infection include skin and subcutaneous tissues, bones, and the meninges.[40] Fatalities, approximately 60 per year in the United States,[31] are usually the result of severe involvement of the lungs or central nervous system.

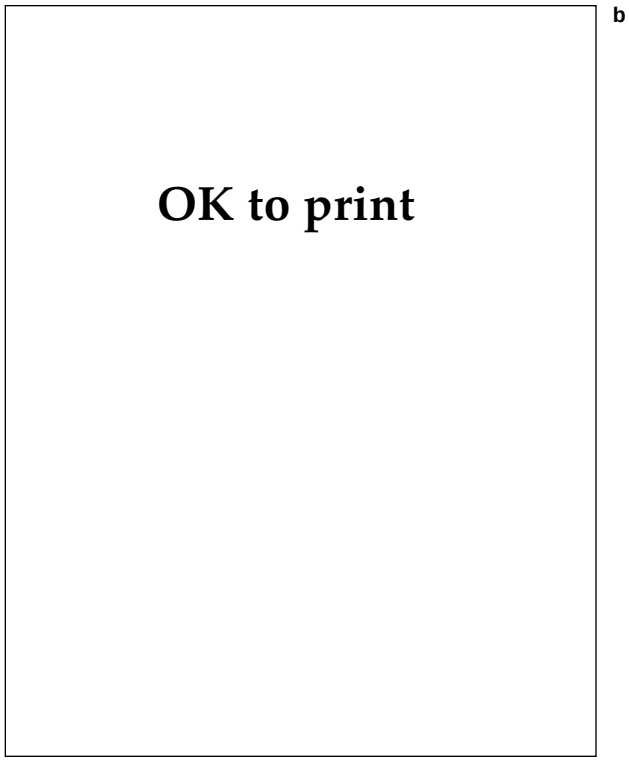
Skin lesions with recoverable coccidioidomycosis organisms occur in 15% to 20% of patients with disseminated disease (Figure 18-8). Papules typically evolve into verrucous nodules or plaques. Plaques frequently occur in the center of the face, particularly along the nasolabial folds (see Figure 18-1). Other lesions have considerable variability, such as subcutaneous cold abscesses or sinuses that arise from involved bones.[41]

Primary inoculation coccidioidomycosis has occurred several times after accidental inoculation during a laboratory or postmortem procedure. Barbed wire and splinter injuries have also led to infections.[42] In immunologically naive patients, ulceration at the site of trauma is typically followed by transient lymphangitis and regional lymphadenitis. One case subsequently disseminated, causing coccidioidal meningitis.[42] Another kind of rare eruption occurs in patients with pulmonary coccidioidomycosis who develop localized skin lesions at sites of trauma unassociated with inoculation.[43]

Diagnosis

The diagnosis of coccidioidomycosis is established quickly by finding spherules in touch preparations of skin lesions or in sputum smears. The spherule's large size, doubly refractile walls, and numerous endospores are pathognomonic. Material taken from a cutaneous pustule, abscess, or ulcer should be cleared with potassium hydroxide and examined by direct microscopy. Lactophenol cotton blue or Papanicolaou stain may give superior results.[44] In histological sections, spherules are





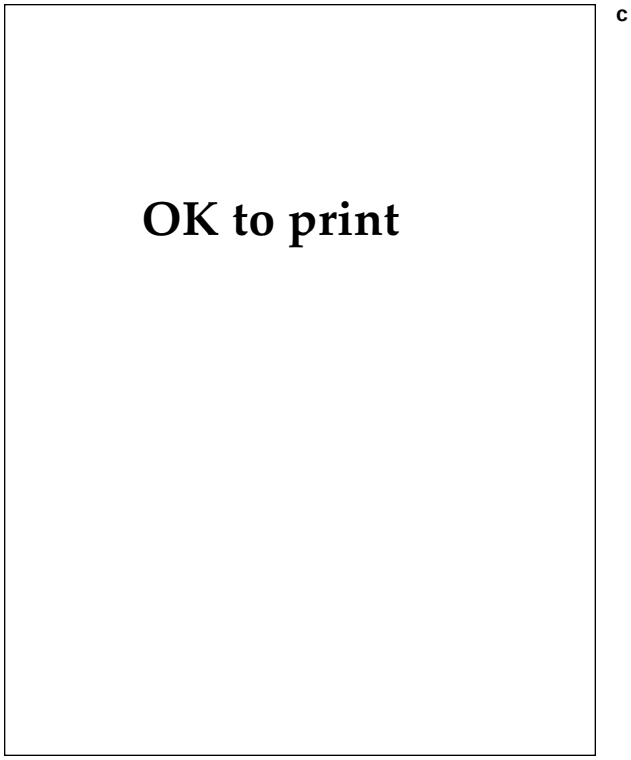


Fig. 18-8. Patients with cutaneous coccidioidomycosis present with varied clinical manifestations. (**a**) This Filipino-American sailor acquired pulmonary coccidioidomycosis after breathing dust that had been stirred up at a cockfight in southern Arizona. The infection subsequently disseminated to his skin and appeared as a cluster of granulomatous papules around his elbow. (**b**) This African-American soldier complained of fever, diplopia, and neck stiffness. He became obtunded and a skin biopsy of this preauricular lesion showed abundant spherules of *Coccidioides immitis*. Despite amphotericin therapy, the patient soon died. A retrospective history revealed that his only geographical exposure had occurred 6 months earlier, when he traveled through southern California. (**c**) Additionally, the skin may become involved when bony lesions produce draining sinuses. This man developed fistulous tracts in his chest wall from rib osteomyelitis caused by *C immitis*. Photographs: (b) Courtesy of Lieutenant Colonel Curt P. Samlaska, Medical Corps, US Army, Honolulu, Hawaii; (c) Courtesy of Captain E. C. Oldfield III, Medical Corps, US Navy, San Diego, Calif.

apparent with hematoxylin-eosin stain but are enhanced by fungal stains (Figure 18-9).

The intradermal skin test is a useful diagnostic and prognostic tool. Spherulin, derived from the pathogenic tissue phase of *C immitis*, is perhaps more sensitive to the arthrospore-derived coccidioidin, which was used previously.[38,45] Skin tests turn positive within 3 weeks after onset of pulmo-

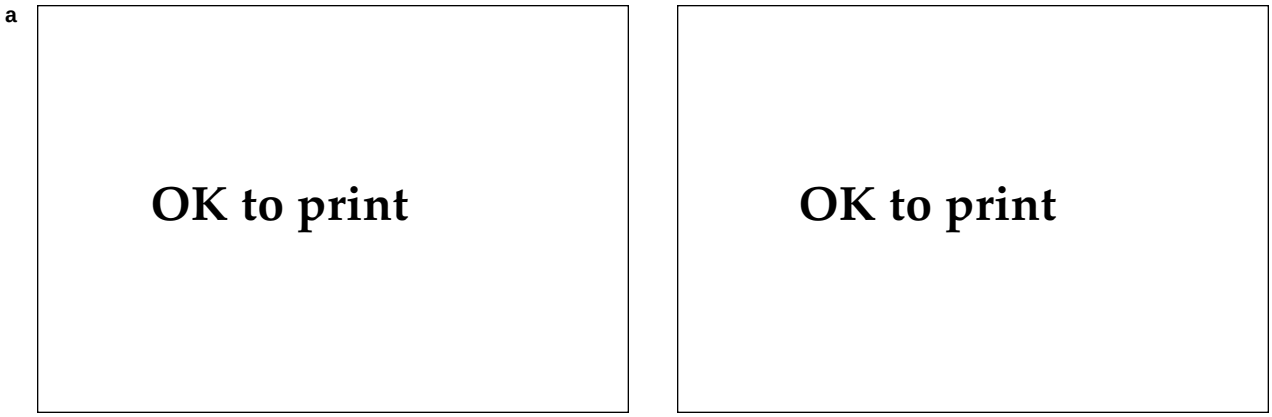


Fig. 18-9. These photomicrographs show cutaneous coccidioidomycosis. (**a**) Exuberant granulomatous skin lesions are characterized histologically by pseudoepitheliomatous hyperplasia of the epidermis. Dermal and intradermal abscess may contain spherules (original magnification 40X). (**b**) A high-powered view shows many endospores within a spherule (hematoxylin-eosin stain, original magnification 430X).

nary symptoms. A positive test confirms infection in previous nonreactors and, presumably, in persons who have never before lived in endemic areas. False positives may indicate previous infection with histoplasmosis, blastomycosis, or paracoccidioidomycosis. False negatives may indicate the host's poor immunological response to infection and signal susceptibility for disseminated disease.[38] Furthermore, persons with persistent negative skin tests during therapy are at increased risk for relapse if therapy is discontinued.

In endemic areas, the most common cause of erythema nodosum in white patients is coccidioidomycosis. It signifies a vigorous immunological response. If skin testing is conducted on these individuals, a dilute strength (1:1000 or 1:10,000) of spherulin should be used to prevent an intense reaction such as local necrosis or erythema multiforme.[41]

Patients with symptomatic primary pulmonary coccidioidomycosis often have chest radiographs showing infiltrates, hilar adenopathy, or pleural effusions. Mild peripheral eosinophilia is frequently present and may reach 80%.

Serologic assays are valuable adjuncts in the diagnosis and management of coccidioidomycosis. Tests that detect immunoglobulin (Ig) M antibodies (eg, tube precipitin, latex particle agglutination, or concentrated immunodiffusion) help confirm acute coccidioidomycosis, whereas complement fixation is more valuable in cases of long-standing or disseminated disease, including cutaneous coccidioidomycosis. A high (> 1:16) or rising complement fixation-titer suggests either dissemination of disease or failure of therapy.[40,41,45] Many medical centers refrain from routine coccidioidal cultures because the mycelia have easily dispersed, highly infectious spores. Hundreds of medical personnel have been infected under seemingly innocuous laboratory conditions.[31] Therefore, if tissue is sent for culture, laboratory personnel must be advised to use appropriate precautions.

Treatment

Most cases of exclusively pulmonary coccidioidomycosis are both unrecognized and untreated. On the other hand, most persons with cutaneous coccidioidomycosis require aggressive therapy for disseminated disease. After determination of the extent of disease, usually by bone scan, gallium scan, and lumbar puncture, a regimen of amphotericin B should be started. Surgical debridement of subcutaneous abscesses and underlying bone infections should be considered.[40] Ketoconazole, fluconazole, and itraconazole are under evaluation for use either in place of, or as a complement to, amphotericin.[46] As azoles, they are fungistatic and probably should not be used alone to treat disease in immunocompromised patients. Members of ethnic groups prone to disseminated disease should be evaluated with extra concern.

Prevention

Most attempts to prevent coccidioidomycosis are impractical because the infectious particles are borne by wind-blown dust. Dust-control measures in-

clude watering down or oiling airstrips, planting lawns or vegetation, encouraging cultivation, and restricting activities downwind of disturbed sites.[32,47] Archaeologists working in the Southwest have tried wearing masks and wetting the ground in their work areas to lessen the dusty conditions. Susceptible persons from nonendemic areas should preferably avoid dusty activities, such as road grading.[48] Efforts to develop an effective vaccine continue.

Blastomycosis

Blastomycosis, caused by *Blastomyces dermatitidis*, is principally a pulmonary infection that involves the skin after rare dissemination. Even more rarely, skin lesions follow percutaneous inoculation of the pathogen. Synonyms include North American blastomycosis, Gilchrist's disease, Chicago disease, Namekagon fever, and blastomycetic dermatitis.

A thermally dimorphic fungus, *B dermatitidis* exists in a mycelial phase in nature and in culture at 25°C. A pathogenic yeast phase grows at body temperature. Yeast cells are spherical, approximately 8 to 15 (–30) μm in diameter, and possess a thick, doubly refractile cell wall. Yeast reproduce by forming single buds attached to the parent cell by a broad base. The sexual stage is *Ajellomyces dermatitidis*.

History

Blastomycosis was identified in 1894 by Thomas Caspar Gilchrist, a dermatologist at The Johns Hopkins Hospital, Baltimore, Maryland, and later president of the American Dermatologic Association. His 1894 report was titled "Protozoan Dermatitis,"[49] despite his recognition that the organism was a hitherto-unknown fungus.[50] The epithet, *dermatitidis*, reflects Gilchrist's appreciation for the organism's affinity for skin. Before self-limited forms of blastomycosis were recognized, the disease was believed nearly always fatal.[51]

Epidemiology

The epidemiology of blastomycosis is poorly defined because clusters of human disease rarely occur. Moreover, it was 1984 before *B dermatitidis* was recovered from a location where human disease had occurred: half of the approximately 100 members of a Wisconsin school group that visited a beaver lodge acquired blastomycosis.[52] The organism was found in the moist, excrement-laden soil surrounding the lodge. Apparently, a microfocus of damp or swampy, nitrogen-rich soil with an acid pH and high organic matter content provides a suitable habitat for the fungus.[53] Persons whose occupational or recreational activities (eg, forestry, hunting, camping) expose them to this ecological niche are at risk for infection. Even so, the disease is unlikely to be contracted more than once in any particular location. One third of foresters in northern Wisconsin and Minnesota have serologic evidence of prior infection.[54]

Sporadic disease affects mostly men, reflecting occupational exposures, but epidemic disease affects the sexes equally.[51] Although the disease is not considered contagious, women have acquired endometrial blastomycosis after sexual contact with partners who had genitourinary disease.[55] In North America, other mammals, most notably dogs, naturally acquire blastomycosis. The geographical range of canine blastomycosis parallels that of human disease,[56] except in Africa where canine disease has not been diagnosed.[57]

Distribution

Blastomycosis is principally a North American disease, endemic in the southeastern United States (particularly Kentucky, Mississippi, and Arkansas), the Great Lakes region, and the drainage basins of the Mississippi and St. Lawrence rivers (Figure 18-10). Many cases of autochthonous infection have occurred in Zimbabwe and South Africa.[57] Fewer cases are reported from other parts of Africa, South

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Fig. 18-10. The North American region where blastomycosis is endemic. Like histoplasmosis, its distribution follows the parts of the Mississippi and Ohio River valleys. Note that the range of blastomycosis extends into the upper Midwest and along the St. Lawrence River.

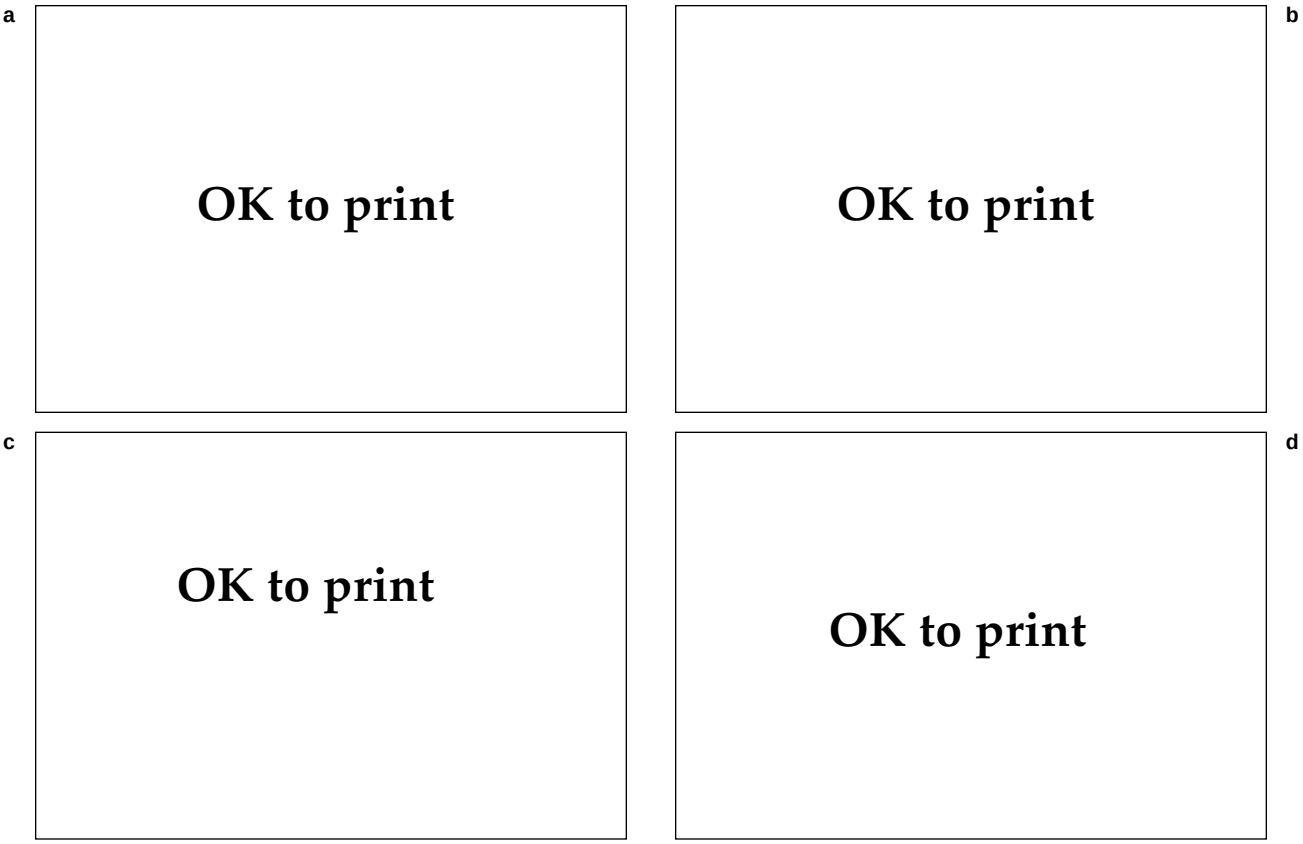

Fig. 18-11. These individuals have cutaneous blastomycosis. The mid-face (**a**, **b**, and **c**) and distal extremities (**d**) are typical locations for cutaneous disease. The appearance of these lesions is quite suggestive of blastomycosis: typical granulomatous plaques with expanding, verrucous borders surmounted by fine, dark puncta.

America, and Asia. Indigenous disease in Europe and the Far East is unknown.

Clinical Manifestations

There are three clinical forms of disease: primary pulmonary blastomycosis, systemic blastomycosis, and primary cutaneous inoculation blastomycosis (see Figure 18-1). The first form is the most common.

Primary Pulmonary Blastomycosis. Primary pulmonary blastomycosis starts with the inhalation of spores. The usual incubation period is 40 to 50 days[53] but may range from 21 to 106 days.[52] Most infections are asymptomatic but patients can present with mild pneumonia; both conditions usually resolve without sequelae. Erythema nodosum may accompany a syndrome of fever, chest pain, and productive cough. Symptomatic conditions also include a fulminant presentation and a chronic, progressive, pulmonary disorder, with or without dissemination.

Systemic Blastomycosis. Hematogenous spread from the lungs produces systemic blastomycosis. The skin is the most commonly affected extrathoracic organ, involved in perhaps 50% of disseminated cases. Bones, the genitourinary system (particularly the prostate), and the central nervous system also are involved frequently.[58] In addition, there is a less aggressive form of systemic blastomycosis in which infection spreads exclusively to skin.[59] About 40% of patients with disseminated blastomycosis have inactive pulmonary disease.[27]

Skin lesions are usually few or solitary and are located on exposed skin, often the face (Figure 18-11). They begin as inflammatory nodules that subsequently break down to form expanding granulomatous ulcers and plaques. Borders are raised and have an annular, arcuate, or serpiginous pattern. Lesions often expand asymmetrically with an exuberant, verrucous, active edge. When the crusted edges are removed, a granulomatous base studded with minute pustules is revealed. Central healing may leave a depigmented, atrophic scar. Oral and

mucocutaneous ulcers also can occur. Bone infections sometimes produce fistulae extending to the skin.[51]

The differential diagnosis of cutaneous blastomycosis includes other deep fungal infections, tuberculosis verrucosa cutis, halodermias, pyoderma gangrenosum, and squamous cell carcinoma.[50]

Primary Cutaneous Inoculation Blastomycosis. Several cases of primary cutaneous inoculation blastomycosis have followed autopsy or laboratory accidents[60] or dog bites.[61] A chancriform syndrome, with regional lymphadenopathy and a chain of subcutaneous nodules, generally resolves on its own within several months.[60]

Diagnosis

Direct examination of a smear of pus or sputum is a simple, quick way to diagnose blastomycosis. Smears are positive in more than half the cases. After the crust has been lifted off an active border, swabbed material from a micropustule should be smeared on a glass slide. A bit of necrotic tissue crushed between two slides is also suitable. After debris is cleared with potassium hydroxide, microscopical examination will show yeast with doubly refractile walls (accentuated by lowering the condenser) and distinctive, single, broad-based buds.

Biopsied skin specimens prepared with fungal stains show pseudoepitheliomatous hyperplasia, microabscesses, giant cells, and the characteristic organisms (Figure 18-12).[51] The organism may be cultured, on Sabouraud's agar at 25°C to 30°C, from pus, skin scrapings, or biopsy specimens.[2,51] Blastomycin skin tests are insensitive, lose reactivity over time, and are often falsely positive in patients with histoplasmosis.[54] Investigational enzyme immunoassay and in vitro lymphocyte stimulation assays show greater reliability than the two more widely available serologic tests, immunodiffusion and complement fixation.[52–54]

Treatment

Because most cases of acute pulmonary blastomycosis probably resolve spontaneously, whether all persons should receive treatment remains unresolved.[58,62] If untreated, pulmonary blastomycosis can reactivate years later. In general, patients with active lung disease or with cutaneous involvement

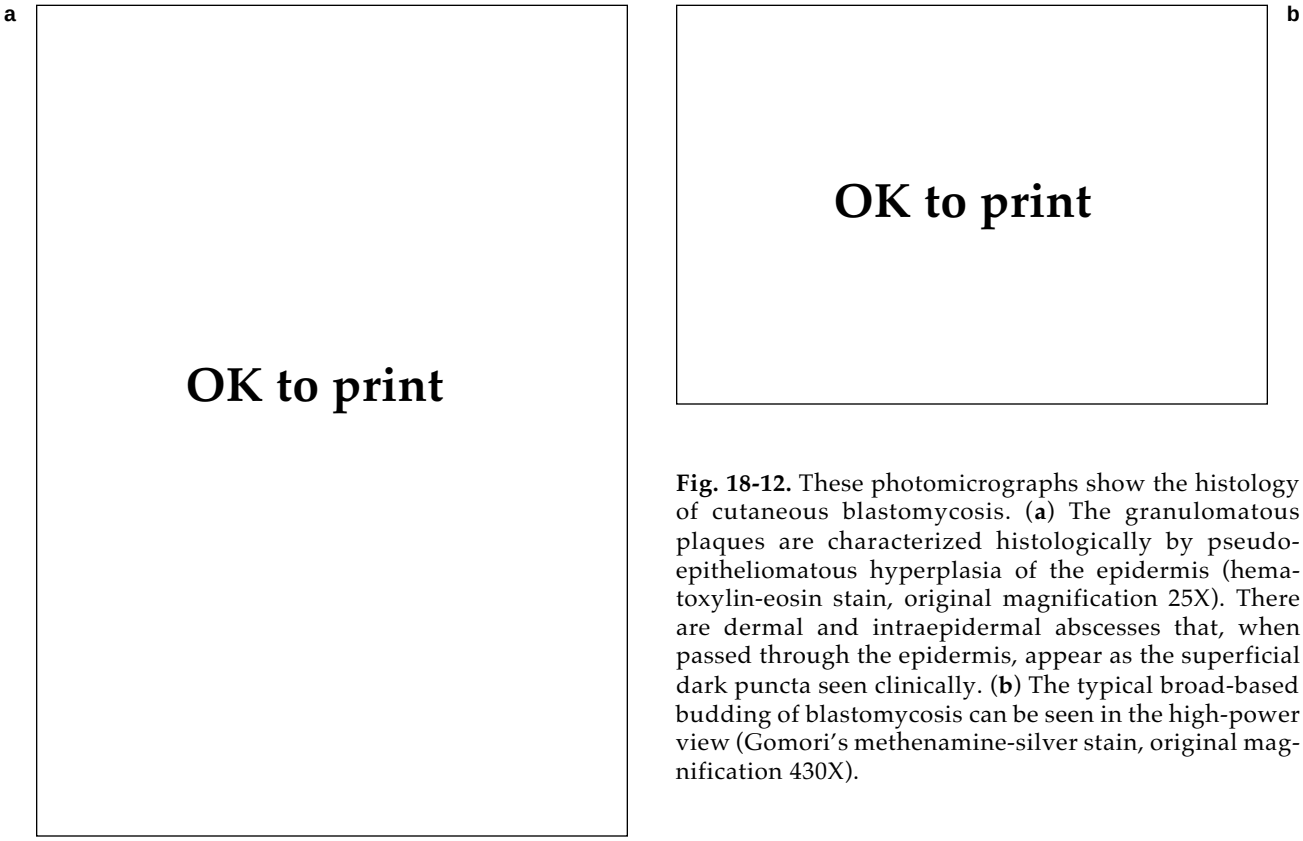

Fig. 18-12. These photomicrographs show the histology of cutaneous blastomycosis. (**a**) The granulomatous plaques are characterized histologically by pseudoepitheliomatous hyperplasia of the epidermis (hematoxylin-eosin stain, original magnification 25X). There are dermal and intraepidermal abscesses that, when passed through the epidermis, appear as the superficial dark puncta seen clinically. (**b**) The typical broad-based budding of blastomycosis can be seen in the high-power view (Gomori's methenamine-silver stain, original magnification 430X).

should receive therapy.[63] An outpatient regimen of ketoconazole (400 mg daily for at least 6 mo) is generally effective.[26,53] If the disease worsens, the dose should be increased to 600 to 800 mg daily. Because ketoconazole is distributed poorly in the central nervous system and is not excreted by the kidneys, it is not recommended for treating meningeal or genitourinary blastomycosis.[27] Intravenous amphotericin B (2-g regimen over 6 wk) is recommended for immunocompromised patients or those with fulminant, refractory, or meningeal disease. The triazole antifungal agent, itraconazole, has shown promise in preliminary investigations.[63]

Military Implications

Few clusters of human blastomycosis have occurred,[52,62] suggesting that the disease has little epidemic potential. Military exercises may expose soldiers to the habitats of *B dermatitidis* but the appearance of skin disease, other than in solitary cases, is unlikely. Because dogs are more susceptible to infection than are humans, close cooperation with veterinary staff may be required.[56]

Paracoccidioidomycosis

Paracoccidioidomycosis (also called South American blastomycosis, Brazilian blastomycosis, Lutz-Splendore-Almeida's disease, and paracoccidioidal granuloma) is a chronic, progressive, potentially fatal, systemic mycosis. It is principally a pulmonary infection but may secondarily involve skin and mucosal surfaces. The causative organism is *Paracoccidioides brasiliensis*. The disease occurs only in South and Central America, where in many areas it is the most prevalent and serious systemic fungal disorder. Paracoccidioidomycosis occurs sporadically and therefore poses little risk to military units.

P brasiliensis is a thermally dimorphic fungus whose pathogenic yeast forms have a diameter of 6 to 40 μm. In tissue, a spherical yeast cell surrounded by narrow-based progeny cells gives the distinctive appearance of a ship's pilot wheel or, if fewer buds are present, a Mickey Mouse head.

History

A mummified woman who died circa AD 290, excavated from northern Chile, was found to have paracoccidioidal pulmonary infection.[64] The first patients described in modern times presented with oral lesions and were reported in 1908 by Adolpho Lutz, director of the São Paulo Bacteriological Institute. Lutz demonstrated the dimorphism and pathogenicity of the fungus, yet its distinction from *Blastomyces* and *Coccidioides* remained in dispute. In the late 1920s, Almeida convincingly differentiated the organisms and provided the name *Paracoccidioides brasiliensis*.[65] Paracoccidioidomycosis is not known to have hampered military operations.

Epidemiology and Distribution

Paracoccidioidomycosis is restricted to the Americas, occurring as far north as Mexico (Figure 18-13). Brazil, in particular the São Paulo region, has the highest incidence of disease.[66] The disease occurs primarily in forested tropical and subtropical regions, although the ecological niche of the fungus remains unknown.[67] Young and middle-aged men who work outdoors are at greatest risk for infection. Women are rarely affected, probably due to the suppressive effects of active estrogens on mycelial-to-yeast transformation.[68] The theory that cleaning one's teeth with contaminated twigs causes gingival inoculation remains unproven.

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Fig. 18-13. This map shows the geographical distribution of paracoccidioidomycosis. The disease is most prevalent in coastal regions of Brazil but can occur throughout South America and Central America.

Clinical Manifestations

The clinical manifestations and natural history of paracoccidioidomycosis are poorly understood. Presumably infectious organisms are inhaled, causing a primary lung infection that is characterized by productive cough, dyspnea, fever, and weight loss.[69] Asymptomatic pulmonary infections, similar to those of histoplasmosis, occur infrequently[70] but may recrudesce after years of dormancy.[71] One half of infected individuals develop oral lesions, often accompanied by nasal and pharyngeal ulcers (see Figure 18-1). Mucosal ulcers have granulomatous, often exuberant, bases. The patient may complain of dysphagia or hoarseness. Periorificial, crusted, granulomatous plaques may encroach onto and destroy facial structures (Figure 18-14). Affected gingivae may lose teeth. Involvement of lymphoid

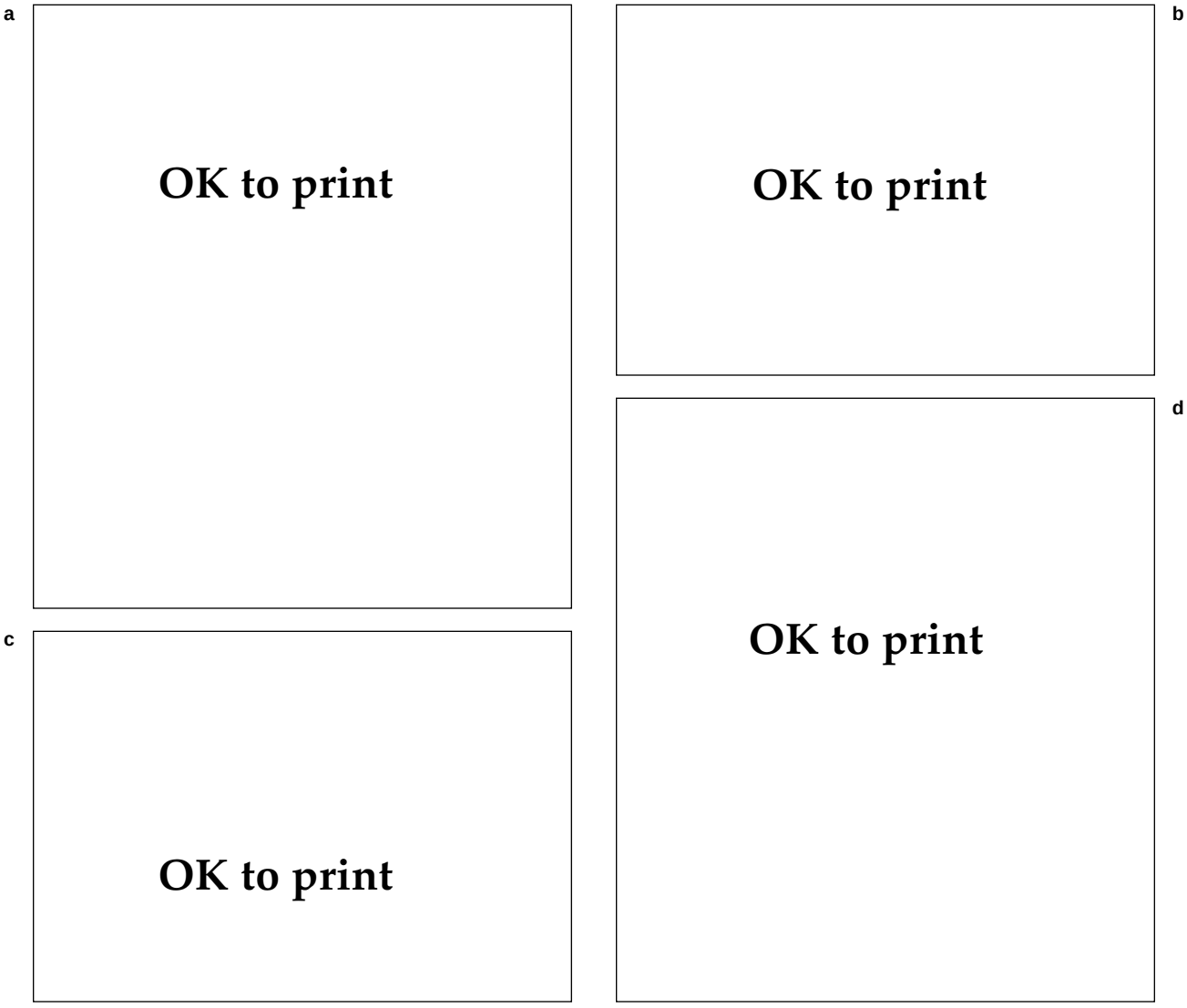


Fig. 18-14. Cutaneous lesions of paracoccidioidomycosis typically appear in or around the mouth. These patients have (**a**) periorificial granulomatous plaques and (**b**) granulomatous infiltration of the tongue and (**c**) labial mucosa. (**d**) Cervical adenopathy resembling tuberculous adenopathy commonly occurs in paracoccidioidomycosis. The lymph nodes may suppurate and form draining sinuses. Photographs: Courtesy of Professor Angela Restrepo-M., Medellin, Colombia.

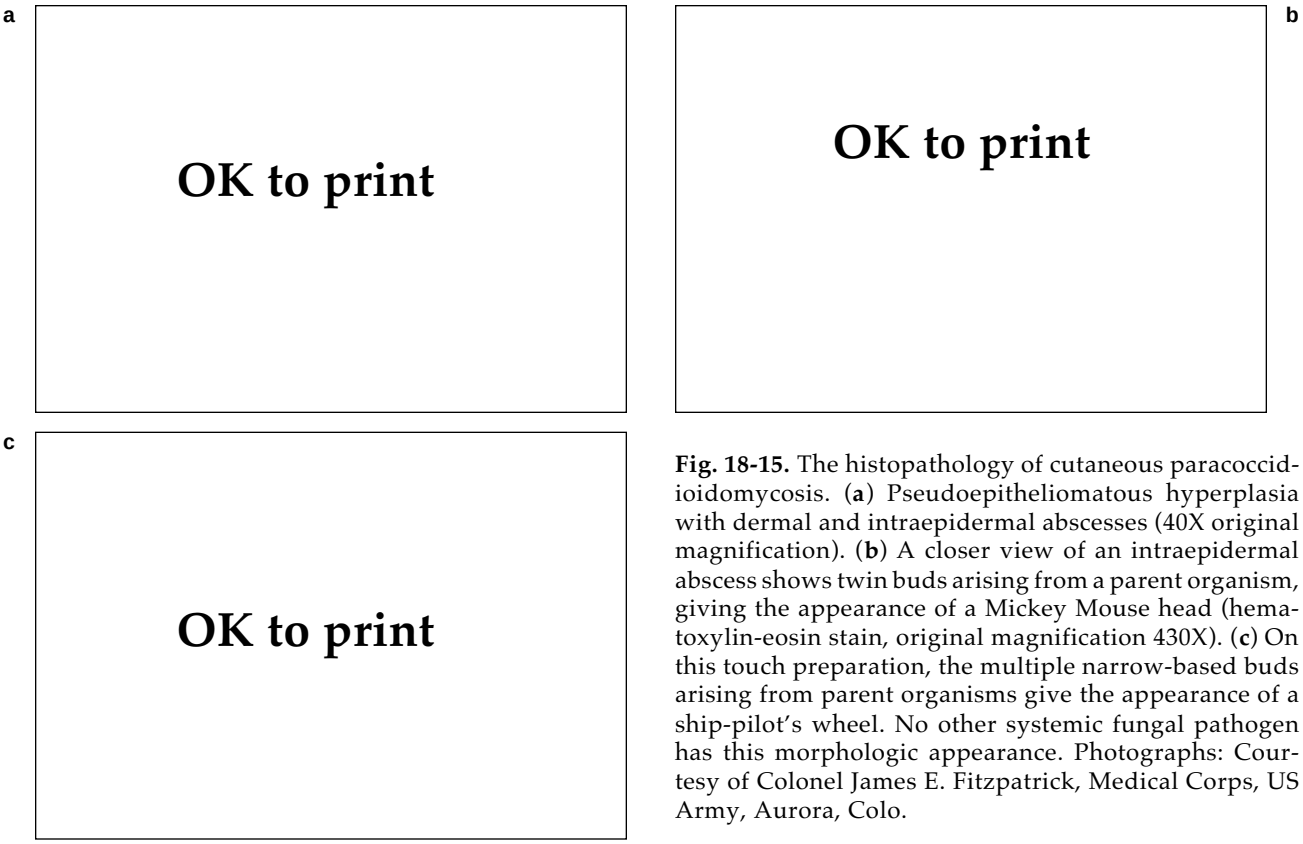


Fig. 18-15. The histopathology of cutaneous paracoccidioidomycosis. (**a**) Pseudoepitheliomatous hyperplasia with dermal and intraepidermal abscesses (40X original magnification). (**b**) A closer view of an intraepidermal abscess shows twin buds arising from a parent organism, giving the appearance of a Mickey Mouse head (hematoxylin-eosin stain, original magnification 430X). (**c**) On this touch preparation, the multiple narrow-based buds arising from parent organisms give the appearance of a ship-pilot's wheel. No other systemic fungal pathogen has this morphologic appearance. Photographs: Courtesy of Colonel James E. Fitzpatrick, Medical Corps, US Army, Aurora, Colo.

tissues is especially common in children. Cervical lymph nodes draining oral lesions may be painful and massive. Invasion of mesenteric lymphoid tissue may cause bowel obstruction and symptoms of an acute abdominal emergency.[71]

Cutaneous lesions do not resolve spontaneously. Untreated paracoccidioidomycosis is often fatal, due mainly to extensive pulmonary fibrosis or adrenal gland invasion. Dormant infections may be reactivated after a 30-year latency.[72]

The differential diagnosis includes mucocutaneous leishmaniasis, fixed cutaneous sporotrichosis, histoplasmosis, lymphoma, and scrofula. Coexisting tuberculosis has been noted often. *Blastomyces* blastomycosis more commonly affects skin instead of mucosa, often heals centrally with atrophic scars, and lacks both gingival involvement and regional lymphadenopathy.

Diagnosis

Evaluation for paracoccidioidomycosis is warranted in patients from endemic regions who have respiratory symptoms and oral lesions. The diagnosis is confirmed by culture or by finding characteristic, multiply budding yeast in tissue (Figure 18-15). Skin biopsies show areas of pseudoepitheliomatous hyperplasia and microabscesses containing the organisms. A potassium hydroxide preparation of lesional scrapings, sputum or lung-lavage fluid, or pus from draining sinuses may reveal the organisms. The thinner cell wall, increased number of buds, and narrow bud stalks distinguish *P brasiliensis* from *B dermatitidis*.

Cultures grow slowly but are diagnostic. Several immunological assays, in particular immunodiffusion, are potentially valuable diagnostic adjuncts and are being evaluated in endemic areas.[73,74] Paracoccidioidin skin tests are unreliable.[67,72]

Treatment

Paracoccidioidomycosis must be treated because it rarely resolves on its own. Therapy with itraconazole for 6 months or more generally is effective for both pulmonary and cutaneous disease.[75,76]

SUBCUTANEOUS MYCOSES

The subcutaneous mycoses comprise sporotrichosis, chromoblastomycosis, mycetoma, lobomycosis, and rhinosporidiosis. They are united by their similar onset after percutaneous inoculation of the pathogen—usually a soil or plant saprophyte. The resulting disease is usually confined to the skin and subcutaneous tissues, and rarely invades deeper or disseminates. The subcutaneous mycoses are most common in tropical or warm temperate regions (see Exhibit 18-1).

Sporotrichosis

Sporotrichosis has a nearly worldwide distribution and is perhaps the deep mycosis that military dermatologists most frequently encounter. Sporotrichosis nearly always results from traumatic implantation of the pathogen *Sporothrix schenckii* into the skin. Infection is generally limited to cutaneous and subcutaneous tissues.

S schenckii, a thermally dimorphic fungus, is the sole member of its genus. It is a common saprophyte, associated with live and decaying vegetation, plant products, and soils. It infects humans and other mammals but simply colonizes the host plants. In nature and in cooler cultures, the mycelial phase predominates. In infected tissues and in culture at 37°C, S schenckii assumes its yeast phase.

Sporotrichosis poses risks to individuals worldwide but has little epidemic potential. There are no reports of sporotrichosis hampering military operations.

History

Sporotrichosis was first described in 1898 by Benjamin Robinson Schenck, then a second-year medical student at The Johns Hopkins University, Baltimore, Maryland.[77,78] Most cases of sporotrichosis are solitary, although clusters of infection have occurred. The largest outbreak was among South African gold miners in the 1940s. Nearly 3,000 Bantu mine workers developed lymphocutaneous sporotrichosis after wounding themselves on the *Sporothrix*-laden timbers that were used to shore the mine tunnels.[79] Such outbreaks can be controlled by discontinuing the use of local timber or treating the wood with antifungals.

Epidemiology and Distribution

Sporotrichosis results from minor, often unnoticed, traumatic implantation of the organism into the skin. Occupations typically at risk for sporotrichosis are those exposed to injuries from plant materials, such as florists, plant nursery and forestry workers, and farmers. Rosebushes, hay, and sphagnum moss have been implicated repeatedly as sources of infection.[80] Hands and fingers are typically involved, except in regions where barefoot farmers get foot infections. Transmission to humans from animals, particularly cats, may cause sporotrichosis even without a clear history of an animal bite or scratch.[81] No clear gender or racial predilections have been identified. Sporotrichosis is not transmitted from person to person.

Sporothrix and sporotrichosis occur in tropical and warm, humid, temperate regions worldwide. Mexico, Brazil, Japan, and Oklahoma have especially high incidences of disease.[80,82,83]

Clinical Manifestations

Sporotrichosis has several clinical forms but rarely causes systemic disease. Classically, inoculation occurs on a distal extremity, and, after an incubation period of several weeks, a violaceous, firm, granulomatous papule or plaque develops. The initial site often remains painless, although it may suppurate, ulcerate, or become verrucous.

Lymphocutaneous sporotrichosis constitutes approximately 75% of cases (Figure 18-16). An ascending chain of painless, subcutaneous nodules develops along lymphatic drainage, causing lymphangitis and regional lymphadenopathy (see Figure 18-1). The nodules may form cold abscesses and ulcerate. Untreated infections have an indolent course and rarely disseminate.

Fixed cutaneous sporotrichosis (approximately 20% of cases) also follows trauma but lacks lymphatic involvement (Figure 18-17). Persistent granulomatous papules or plaques develop at the site of implantation. In particular, children with facial lesions typically present this way. Fixed cutaneous sporotrichosis may resolve spontaneously.

The differential diagnosis for lymphocutaneous sporotrichosis includes other deep fungal infections, atypical mycobacteriosis (eg, from *Mycobacterium marinum*), cutaneous leishmaniasis, tularemia,

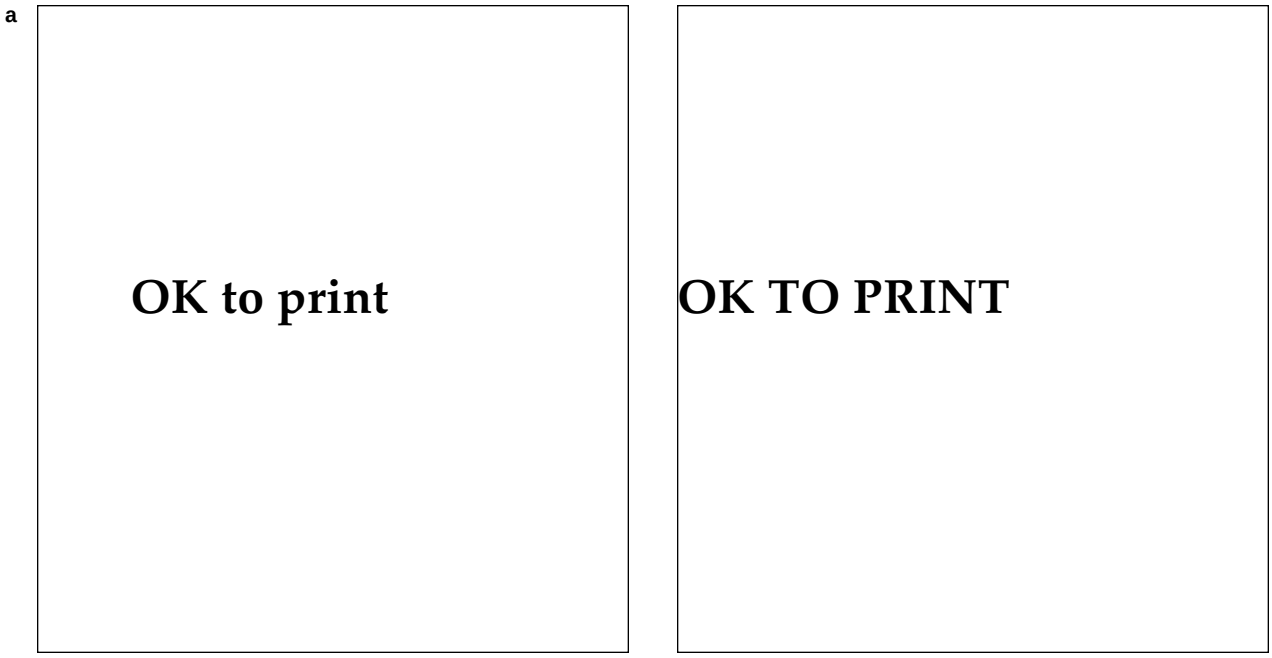


Fig. 18-16. Lymphocutaneous sporotrichosis arises after traumatic inoculation of *Sporothrix schenckii*. (**a**) A veterinary assistant developed dermal nodules on the dorsa of her hands after being scratched by an infected cat. Culture of Sabouraud's medium confirmed the diagnosis 1 week later, and she was successfully treated with a potassium iodide preparation. (**b**) As *Sporothrix* infection spreads along subcutaneous Iymph nodes, the characteristic sporotrichoid appearance develops.

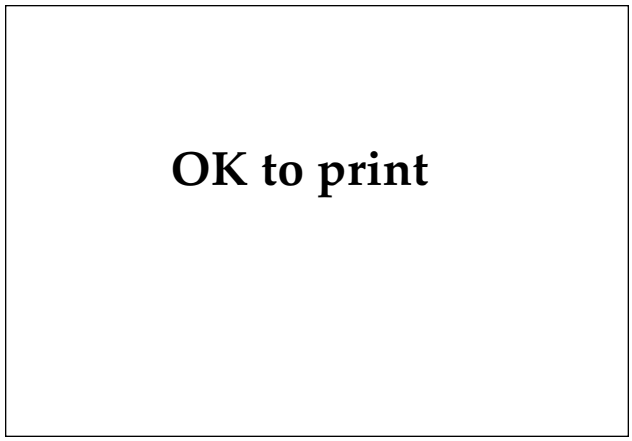


Fig. 18-17. This young girl developed fixed cutaneous sporotrichosis on her face after suffering a cat scratch on her left malar region. Photograph: Courtesy of Colonel M. J. Schleve, Medical Corps, US Army, Aurora, Colo.

cat-scratch disease, anthrax, pyodermas, botryomycosis, and *Nocardia brasiliensis* infection. When evaluating fixed cutaneous sporotrichosis, pyodermas, syphilis, other deep fungal infections, cutaneous tuberculosis, and sarcoidosis should be considered.[80]

Extracutaneous sporotrichosis arising from a primary cutaneous infection is rare. The typical patient with systemic sporotrichosis is immunosuppressed by chronic alcoholism, hematological malignancies, diabetes mellitus, or chronic corticosteroid therapy.[84] Extracutaneous infection commonly involves joints, causing monoarticular or oligoarticular arthritis that often eludes diagnosis for some time.[82] Several patients with chronic *Sporothrix* meningitis had concomitant primary cutaneous lesions. Meningeal disease is uncommon but usually fatal if untreated.[82,84]

Pulmonary sporotrichosis follows inhalation of spores and may range from an inapparent to a tuberculosis-like illness. In some regions, skin tests show a high prevalence of infection, suggesting that asymptomatic pulmonary infection is more common than is ordinarily suspected. Rare hematog-

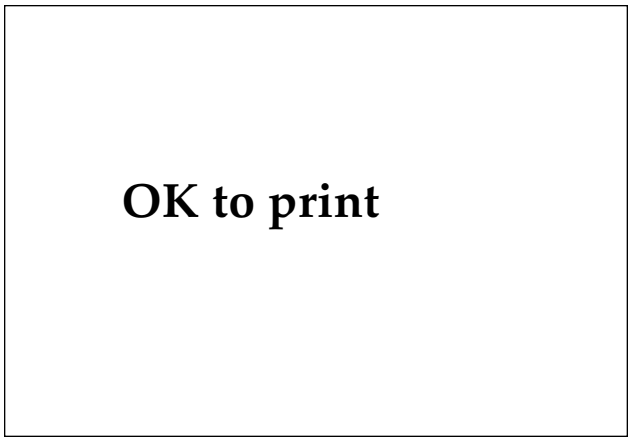


Fig. 18-18. Immunocompromised patients may develop disseminated sporotrichosis. This soldier, debilitated from alcohol abuse, presented with the fever, weight loss, and skin nodules. This picture shows ulceration of dermal and subcutaneous nodules. *Sporothrix schenckii* was cultured from several skin sites. His sporotrichosis may have started as a primary pulmonary infection.

enous dissemination may produce skin lesions (Figure 18-18) or involve joints, tendons, bones, or the brain.[80]

Diagnosis

The clinical picture of an extremity with a painless ulcer and ascending lymphocutaneous nodules is characteristic of sporotrichosis. The diagnosis is strongly supported by (*a*) the history of onset after plant-related trauma and (*b*) the lack of response to presumptive antibacterial therapy. Confirmation requires identification of the organism by culture or microscopy. On histological sections, the organisms appear round to oval and are approximately 4 to 6 μm in diameter (Figure 18-19). Larger, cigar-shaped bodies, 8 μm in length, and asteroid bodies, although characteristic of sporotrichosis, occur infrequently. Rarely, the fungus can be identified on microscopical examination of smears of pus from a lesion, stained with periodic acid–Schiff or Gram's stain. Histological confirmation is often difficult because the organisms are scarce and small.[59]

On the other hand, *Sporothrix* grows rapidly on Sabouraud's agar. Material for culture can be obtained from ulcer scrapings, an aspirated subcutaneous nodule, or macerated biopsy material. After 3 to 7 days at 25°C to 30°C, smooth, moist, cream-colored colonies develop. As aerial hyphae develop, the colonies typically become brown and velvety.

Delayed-hypersensitivity skin tests with sporotrichin are often positive in inhabitants of endemic areas, ranging from 10% in Louisiana and Arizona to more than 90% in parts of Japan. Direct immunofluorescence and serologic tests have varying degrees of sensitivity, specificity, rapidity, and availability.[80,84]

Treatment

Most cases of purely cutaneous disease may be treated simply and inexpensively with supersaturated potassium iodide (SSKI). SSKI (5 drops in juice) is consumed three times daily, increasing the amount by 1 drop per dose per day until a dose of 40 drops three times daily is achieved.[85] Administration is continued until 4 weeks after clinical resolution. SSKI's mechanism of action is uncertain. The untoward side effects of iodides include an acneform

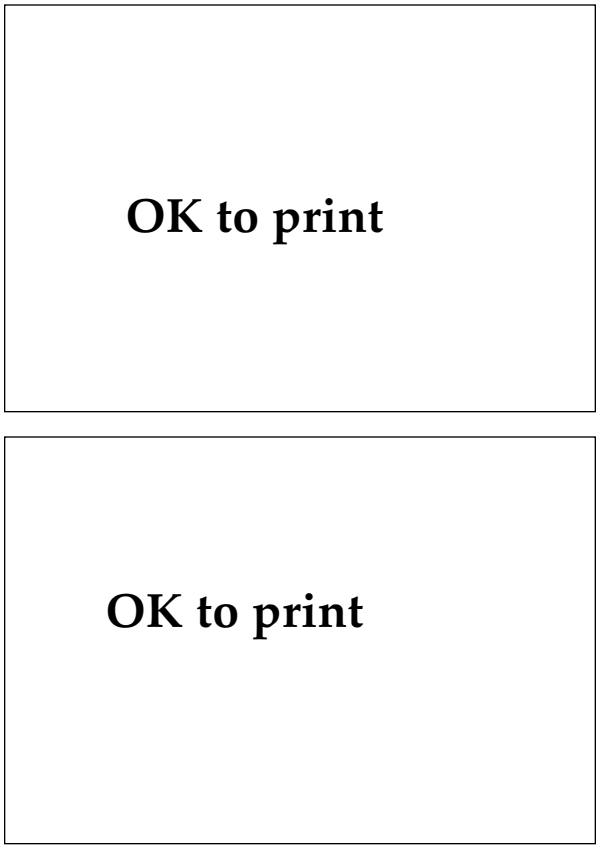


Fig. 18-19. (**a**) Typical skin lesions of sporotrichosis show pseudoepitheliomatous hyperplasia and intraepidermal abscesses (hematoxylin-eosin stain; original magnification 25X). (**b**) A closer view shows the characteristic oval-shaped budding yeast (periodic acid–Schiff stain; original magnification 430X).

eruption, brassy taste, gastrointestinal distress, hypothyroidism, parotid swelling, and increased salivation and lacrimation.[86] Local heat therapy is a useful adjunct because *Sporothrix* is intolerant of temperatures above 38.5°C. Applications of hot (42°C), moist compresses for 30 minutes twice daily will enable the heat to reach subcutaneous infections.[80]

Currently, intravenous amphotericin B is the drug of choice for extracutaneous infections and for refractory, widespread, or debilitating cutaneous disease. Because amphotericin is nephrotoxic and requires intravenous administration, other antifungal agents are being evaluated. Itraconazole, but not ketoconazole, is effective at a daily dosage of 100 to 200 mg, administered orally for 3 to 5 months.[82,87]

Chromoblastomycosis

Chromoblastomycosis designates a group of chronic cutaneous and subcutaneous mycoses caused by several species of dematiaceous fungi. Common pantropically in rural areas, the disease is also called chromomycosis, verrucous dermatitis, Pedroso's disease, Fonseca's disease, and Lane and Pedroso's mycosis.

Chromoblastomycosis occurs sporadically and lacks epidemic potential. In tropical areas, shoes and leg coverings protect individuals from the minor penetrating trauma that inoculates the pathogens.

Several species of dematiaceous (darkly pigmented) fungi cause most cases of chromoblastomycosis. These include *Fonsecaea pedrosoi* (the major pathogen), *Fonsecaea compacta, Phialophora verrucosa, Cladosporium carrionii,* and *Rhinocladiella aquaspersa*.[88] Each species has more than one morphologic strain, compounding the nomenclatural disarray. The related genera produce similar, dark brown, sclerotic bodies in tissue and form pigmented colonies on culture. Because these fungi reproduce by internal septation rather than by budding, some[89] have argued that -blasto- should be deleted from the name of the disease.

History

Early in the 20th century, several workers described patients with chromoblastomycosis and isolated the pathogens.[89] Controversy persists over priority of description, name of the disease, and nomenclature of the causative fungi.[89,90] There are no reports of chromoblastomycosis having hampered military operations.

Epidemiology and Distribution

Although found worldwide, chromoblastomycosis occurs mainly in the humid tropics and subtropics. The causative fungi are saprophytes and are recoverable from soil, rotting wood, and other plant debris. Their spores enter the skin via minor penetrating trauma. Barefooted rural farmers, therefore, have the greatest occupational risk.[91] The disease occurs overwhelmingly in men aged 25 through 50, except in Japan where men and women are affected equally.[92] *Fonsecaea pedrosoi* is the major pathogen, although regional variations exist.

Clinical Manifestations

Chromoblastomycosis starts as painless, skin-colored papules typically on the lower legs or the lateral aspects of the feet (see Figure 18-1). Enlarging lesions develop into nodules or plaques. Their surfaces can be verrucous, papillomatous, scaly, sclerotic, or a combination of these. Flat, rough-surfaced plaques often heal with central atrophy, scarring, or keloid formation (Figure 18-20). Elsewhere, satellite lesions or peripheral expansion along serpiginous borders may develop.[91,93]

After many years, some lesions evolve into cauliflower-like lobulated vegetations (Figure 18-21). Frequently, secondary bacterial infections cause fibrosis of superficial lymphatics and subsequent lymphedema or elephantiasis. The fungi do not invade underlying muscle and bone.

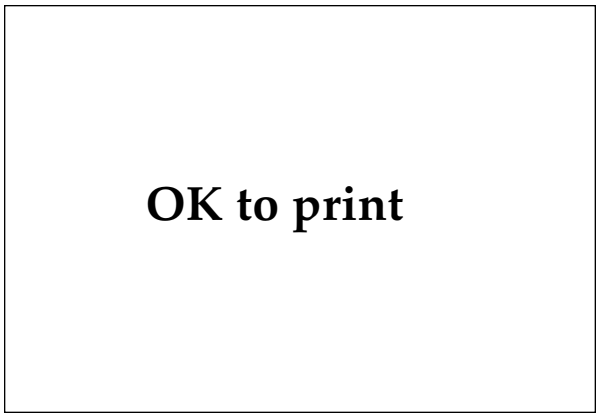
Morbidity in chromoblastomycosis arises from the disfigurement or disability of an affected part, secondary infections, or, rarely, a supervening squamous cell carcinoma. Rare hematogenous spread may lead to cerebral chromoblastomycosis even if cutaneous lesions are absent.[93]

The differential diagnosis includes other deep fungal infections (such as blastomycosis, sporotrichosis, and mycetoma), tuberculosis verrucosa cutis, cutaneous leishmaniasis, and treponemal diseases (eg, yaws and tertiary syphilis).

Diagnosis

Diagnosis of chromoblastomycosis requires both detection of sclerotic bodies from lesional material and a fungal culture. Sclerotic bodies (ie, "copper pennies" or Medlar bodies) are 6- to 12-µm, dark-walled, polyhedral structures (Figure 18-22). Internal cross-walls (ie, septae), produced by intracellular reproduction, give the cells a muriform appearance.[89] They are often seen in potassium

a



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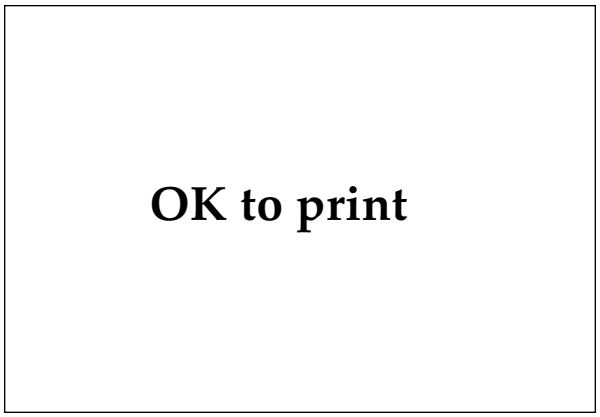

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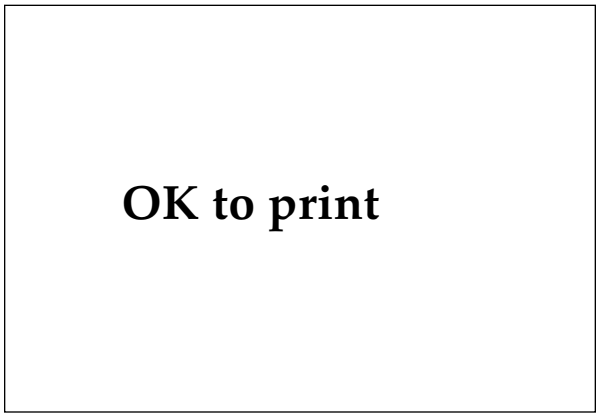


Fig. 18-20. Chromoblastomycosis most commonly appears as granulomatous plaques with serpiginous borders. These photographs (**a** and **b**) show the proximal pretibial surface of a woman from Yap, Federated States of Micronesia. She presumably acquired the infection by kneeling on contaminated wooden planks in her traditional home. (**b**) The scattered dark puncta are found in both blastomycosis and chromoblastomycosis, but the lesion's location on a surface exposed to minor trauma and the tropical setting make the clinical diagnosis straightforward. Chromoblastomycosis can remain indolent for decades. (**c**) This man acquired his infection 50 years earlier during World War II when he was stationed on Manus Island, north of New Guinea. A log fell on his upper back while he was working on a construction project.

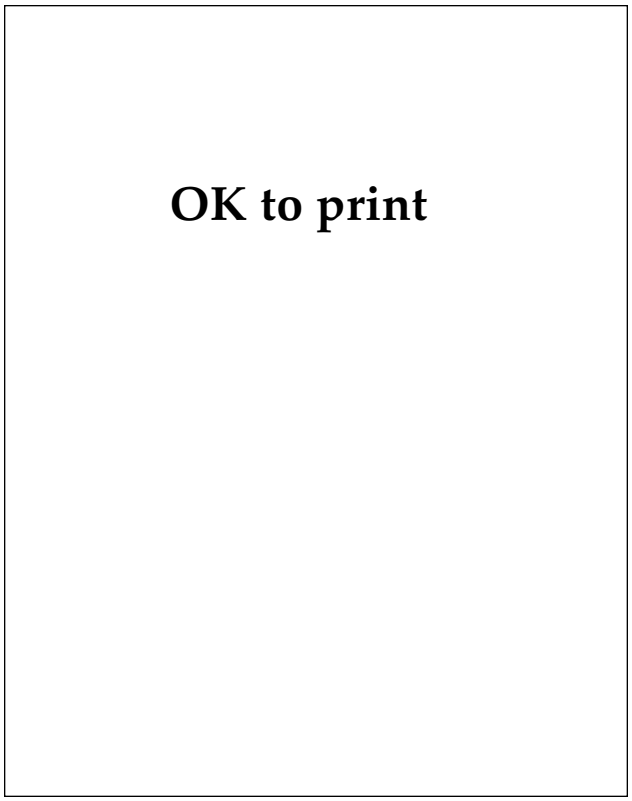


Fig. 18-21. Chromoblastomycosis can also progress into a vegetative form, as seen in this disfiguring vegetative chromoblastomycosis of the leg.

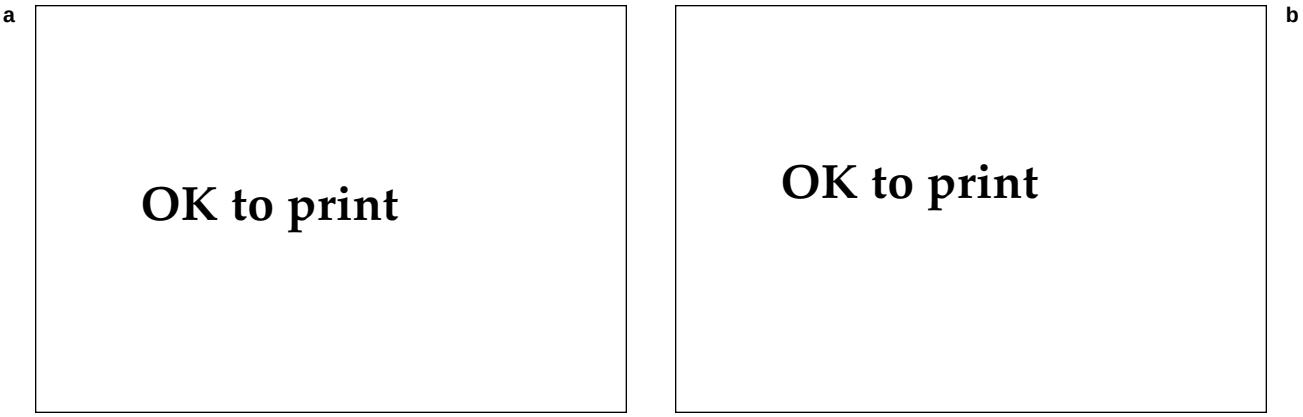


Fig. 18-22. (**a**) A potassium hydroxide preparation of the dark puncta seen in Fig. 18-20 b revealed the diagnostic copper-colored sclerotic bodies of chromoblastomycosis. (**b**) More sclerotic bodies are seen in tissue with a photomicrograph of her skin biopsy (hematoxylin-eosin stain; original magnification 430X). The culture grew *Fonsecaea pedrosoi*.

hydroxide preparations of exudate or surface scrapings. Punctate black dots found on the surface of exuberant lesions are often composed of transepidermally eliminated sclerotic bodies. Skin biopsies show pseudoepitheliomatous hyperplasia, multinucleated giant cells, microabscesses, and sclerotic bodies. Sclerotic bodies, easily seen with hematoxylin-eosin staining, appear singly or in clusters, and are most numerous in vegetative growths.[94] Material grown on Sabouraud's agar forms gray-green or black colonies. Species identification is based on sporulation patterns.

Treatment

Treatment regimens for chromoblastomycosis have been disappointing. Physical measures include wide surgical excision, Mohs' surgery, carbon dioxide laser, radiation, local heat, and cryotherapy. Curettage and electrodesiccation may promote lymphatic spread and should be avoided. Chemotherapeutic approaches include potassium iodide, intralesional amphotericin, ketoconazole, itraconazole, thiabendazole, and 5-fluorocytosine.[91,95] Small, early lesions may be excised successfully. More extensive disease requires long-term treatment with itraconazole alone or with a regimen combining 5-fluorocytosine and amphotericin.[96,97] Limbs disabled or deformed from refractory infections may require amputation.

Mycetoma

Mycetoma is also called maduramycosis, Madura foot, eumycetoma, eumycotic mycetoma, actinomycetoma, and actinomycotic mycetoma. The word mycetoma means "fungal tumor" but most cases are caused by bacteria. Perhaps 20 different pathogens cause mycetoma, the main ones being *Pseudallescheria* (syn *Allescheria, Petriellidium, Monosporium, Scedosporium*) *boydii* in the United States, *Nocardia brasiliensis* in Mexico, and *Madurella mycetomatis* in India and Africa (Table 18-1). The organisms are saprophytes, recoverable from soil and plant debris. Ecological conditions influence their distribution and medical importance so that, for example, in Central and South America the overwhelming majority of cases are due to *Nocardia brasiliensis*, a less important pathogen elsewhere.[98]

Mycetoma is a chronic, progressive infection of skin and subcutaneous tissues and is found mostly in the tropics. Infection follows traumatic implantation of pathogenic true fungi (eumycetoma) or filamentous bacteria (actinomycetoma). The two forms are similar clinically. Mycetomas frequently affect the lower extremities and may invade deeper structures. Infection is characterized by swollen tissues and destructive sinuses from which drains pus containing characteristic granules.

In hyperendemic tropical regions, soldiers should protect themselves from minor trauma by wearing footgear and uniforms. Activities during which implantation could occur, such as carrying locally obtained wood on bare shoulders or backs, should be avoided.

History

Royal Army physicians stationed in the Madura region of India first described mycetomas in the

TABLE 18-1

MAJOR PATHOGENS IN MYCETOMA: THEIR DISTRIBUTION AND GRANULE COLOR

Pathogen	Location						
	Eur	USA	Mex	SAm	WAf	EAf	Ind
Eumycetoma (Ascomycetes and deuteromycetes)							
Pseudallescheria boydii	Y-W	Y-W					
Madurella grisea				B			
Madurella mycetomatis					B	B	B
Leptosphaeria senegalensis					B		B
Actinomycetoma (Actinomycetes and streptomycetes)							
Streptomyces somaliensis						Y	Y
Streptomyces (Acremonium) pelletieri					R	R	
Actinomadura (Nocardia) madurae							W
Nocardia brasiliensis			C-W	C-W			C-W

Eur: Europe, USA: United States; Mex: Mexico; SAm: South America; WAf: West Africa; EAf: East Africa; Ind: India; Y: yellow; W: white; B: black; R: red; Y-W: yellow-to-white; C: colorless; C-W: colorless-to-white
Data sources: (1) Magaña M. Mycetoma. *Int J Dermatol*. 1984;4:221–236. (2) Gumaa SA, Mahgoub ES, El Sid MA. Mycetoma of the head and neck. *Am J Trop Med Hyg*. 1986;35:594–600. (3) Develoux M, Audoin J, Tregeur J, Vetter JM, Warter A, Cenac A. Mycetoma in the Republic of Niger: Clinical features and epidemiology. *Am J Trop Med Hyg*. 1988;38: 86–90. (4) McGinnis MR, Fader RC. Mycetoma: A contemporary concept. *Infect Dis Clin North Am*. 1988;2:939–954. (5) Zaias N, Taplin D, Rebell G. Mycetoma. *Arch Dermatol*. 1969;99:215–225.

local population in the 1840s. Vandyke Carter, surgeon in the British India Army in Bombay, recognized the fungal etiology and coined the name "mycetoma."[99] Military health reports from India did not include mycetoma as a significant problem for British forces there.

Epidemiology and Distribution

Although it is a cosmopolitan disorder, mycetoma is important only in the tropics and subtropics. Adult males engaged in outdoor work are at greatest risk. The site of infection corresponds to the body parts exposed to trauma: barefoot laborers have foot and leg infections, whereas persons who carry contaminated wood and other plant products on their heads, upper backs, and shoulders develop mycetomas there. The infections are not contagious.

Infections occur more often in moist regions, although some organisms, notably *Nocardia brasiliensis* and *Streptomyces pelletieri*, are common in dry areas. Incidence is highest in Mexico, India, and parts of Africa (Sudan, Somalia, Senegal).[98,100,101]

Clinical Manifestations

Mycetoma is characterized by the clinical triad of swollen tissues, draining sinuses, and extrusion of grains.[102] Mycetomas principally occur on the foot, ankle, leg, hand, and upper trunk, although any exposed area is susceptible (see Figure 18-1). After the pathogen is implanted, there is a several-month incubation period. Early lesions are painless, indurated, subcutaneous nodules that grow slowly, coalescing into large plaques or tumors (Figure 18-23). These subsequently form necrotic abscesses and draining sinuses. Grains, usually 0.5 to 2.0 mm in diameter, which are actually colonies of organisms, can be recovered in the seropurulent drainage. Invasion into subcutaneous tissues causes more swelling and induration, often destroying fascia and muscle, and producing chronically draining fistulae. Further extension occurs by direct invasion along fascial planes or by coalescence of abscesses and sinus tracts. Bone involvement leads to periostitis, chronic osteomyelitis, and osteolysis. Mycetomas do not self-heal. Infections progress relentlessly, ultimately leading to deformity and disability. Encroachment into the central nervous system has been reported, although mortality is generally low.[98,100,103–105]

The differential diagnosis for mycetoma includes other deep fungal infections, tuberculous and bacterial osteomyelitis, actinomycosis, botryomycosis,

Fig. 18-23. The swollen tissues and draining sinuses of a mycetoma are apparent in this photograph. The feet and lower legs are the most common sites for mycetomas because those sites suffer the most minor trauma, especially in individuals who go barefoot.

Kaposi's sarcoma, tertiary syphilis, yaws, leprosy, and cutaneous leishmaniasis.[106]

Laboratory Diagnosis

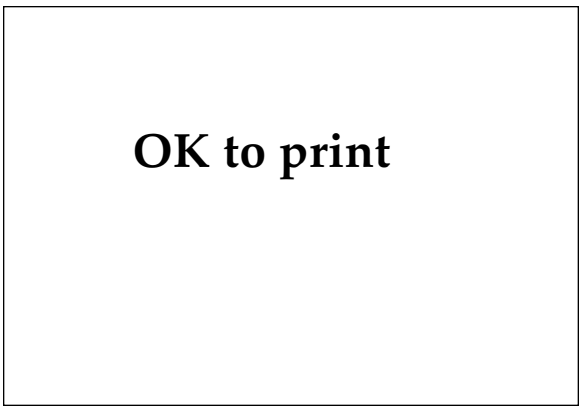
It is essential to determine whether a fungus or an actinomycete causes a mycetoma so that appropriate therapy can be started. Preliminary identification can be made from clinical assessment, the patient's travel history, and, most importantly, examination of the grains (see Table 18-1). Grains, particularly dark ones, are often visible to the naked eye but may be found by diluting purulent exudate with sterile saline. Grains should be examined grossly for color and texture and microscopically for hyphae or filaments. Black grains (Figure 18-24) are produced exclusively by eumycetomas. Pale (colorless, white, or yellow) granules are produced by most actinomycetes but only by one eumycete, *Pseudallescheria boydii*. Red granules are formed by *Streptomyces pelletieri*. A hard, brittle texture characterizes *Madurella* species' grains. Extensive details on mycetoma grains can be found elsewhere.[98,106]

Crushed granules should be examined with Gram's stain and potassium hydroxide preparations. Eumycotic grains will reveal Gram-negative septate hyphae. Actinomycotic grains have Gram-negative centers with Gram-positive, fine, radiating fringes. Also, preparations with potassium hydroxide or lactophenol cotton blue demonstrate the delicate (1 μm thick), branching filaments of

a

Fig. 18-24. Histopathology of eumycetoma. (**a**) This skin biopsy of a eumycetoma shows fibrosis, deep abscess, and two dark granules (hematoxylin-eosin stain, original magnification 10X). (**b**) A closer view of the same biopsy tissue (hematoxylin-eosin stain, original magnification 40X).

b



actinomycetes and the larger (4-5 μm) septate hyphae of eumycetes.[103,107]

Skin biopsies show dermal inflammation and microabscesses surrounded by a polymorphous infiltrate. The grains of botryomycosis and actinomycosis resemble those of mycetoma. Often the organism can be identified by histopathological examination alone. True fungi are enhanced with periodic acid–Schiff or Gomori's methenamine-silver stains, whereas *Nocardia* is partly acid-fast.

Culture of the pathogen permits a determination of drug sensitivities. Grains should be either washed in sterile saline to remove contaminants or obtained from deep sites.[103] They should be minced into a suspension for plating onto an appropriate agar (eg, Sabouraud's with and without antibiotics). Growth requirements for the various organisms are discussed elsewhere.[107,108]

Serologic tests and immunoassays are under investigation but are not widely available. Radiographs of affected parts will help assess extent of bony destruction.[105]

Treatment

Therapy for mycetoma depends on the organism, the site of the infection, and the degree of invasion. The prognosis for actinomycetoma is better than for eumycetoma but therapies for both are often disappointing. Actinomycetoma may be treated with long-term combinations of oral antibiotics, such as streptomycin with either dapsone or co-trimoxazole. Eumycetomas are resistant to amphotericin and griseofulvin but on occasion respond to imidazoles. Small, solitary nodules can be excised but that must be followed by chemotherapy to prevent relapses. Larger nodules can be debrided and abscesses drained. Advanced disease should receive combined surgical and chemotherapeutic measures. Limbs with refractory, destructive disease may require amputation, although stump recurrences are common.[98,103,105]

Lobomycosis

Lobomycosis is a chronic, cutaneous mycosis of the New World tropics. It typically appears as multiple, smooth, firm nodules of skin only, sparing mucosa and viscera. The disease is also called Jorge Lobo's disease and keloidal blastomycosis.

Jorge Lobo first described the cutaneous lesions of lobomycosis in 1931 in a patient from the Amazon basin.[109] The fungus is recoverable only from cutaneous lesions. It has neither been isolated from nature nor grown satisfactorily in culture. Taxonomists have never been sure of the proper affinities of this fungus, and in the early literature, it was included at times in several genera, such as *Paracoccidioides, Blastomyces, Glenospora, Glenosporella*, and *Lobomyces*. Until its taxonomic affinities are better determined, the organism, *Loboa loboi*, is best regarded as the sole member of its genus.[110]

Lobomycosis is rare even in endemic areas and poses little risk to military units. Individuals may become infected in the dense lowland forests of Central and South America, but, owing to the lengthy incubation period, clinical manifestations will be inapparent for months. No military activities are known to have been hampered by this disease. Several Atlantic bottle-nosed dolphins on duty with the U.S. Navy have been afflicted with lobomycosis.

Distribution and Epidemiology

Lobomycosis occurs only in South and Central America, where it is, nevertheless, rare (Figure 18-25). It occurs mostly in densely forested humid areas,

OK to print

Fig. 18-25. The distribution of human lobomycosis, which occurs principally in the Amazon River basin. Dolphin lobomycosis is found more northward, along the Caribbean coast of South America and the coast of southern Florida.

such as the Amazon basin of Brazil, and less often in contiguous countries from French Guiana to Costa Rica. Farmers, miners, workers on rubber plantations, and Brazil's Cayabi Indians are most frequently affected.[111,112] Presumably, the fungus enters the skin by minor trauma or via arthropod bites.[112] Another enigma is that lobomycosis naturally occurs in dolphins found along the coasts of Florida (Atlantic bottle-nosed dolphin, *Tursiops truncatus*) and an estuary in Suriname (Guyana River dolphin, *Sotalia guianensis*).[109]

Clinical Manifestations

The incubation period of lobomycosis is probably months to years. Skin lesions begin as multiple, painless, firm, violaceous nodules that coalesce into variably sized keloidal plaques (Figure 18-26). Although their surfaces are usually smooth and shiny, they may instead show epidermal atrophy or warty changes. Lobomycosis principally involves the face and ears, distal extremities, and buttocks (see Figure 18-1). This distribution and the relative sparing of the back support the idea that the disease is acquired initially by minor trauma and spread subsequently by autoinoculation. Lesions also may spread locally by direct extension or via the superficial lymphatics. Sequelae include ulcers, fistulae, and, rarely, squamous cell carcinoma.[111]

Helical lesions must be distinguished from lepromatous leprosy, sarcoidosis, cutaneous leishmaniasis, and true keloids. Verrucous plaques of the legs may resemble other deep mycoses, such as chromoblastomycosis.[112]

The disease is chronic and spreads slowly, though the patient remains generally well. Morbidity is a consequence of disability or disfigurement.

Diagnosis

The diagnosis of lobomycosis must be confirmed histopathologically.[110] The dermis is nearly replaced by an infiltrate of macrophages and multinucleate giant cells. Abundant fungal spores, averaging 8 to 10 μm in diameter, appear within and freely between the giant cells. The organisms stain poorly with hematoxylin-eosin, producing a characteristic sievelike pattern (Figure 18-27).[59] Fungal stains, such as periodic acid–Schiff, reveal chains of thick-walled organisms with tubular interconnections. Single buds are seen occasionally. Skin tests, serologic tests, and attempts to culture the pathogen are not useful in the evaluation of lobomycosis.

Treatment

Lobomycosis does not resolve spontaneously nor is there any satisfactory treatment. Medical intervention, even with amphotericin and ketoconazole, has been uniformly unsuccessful. Small lesions may be excised but recurrences are common.[112]

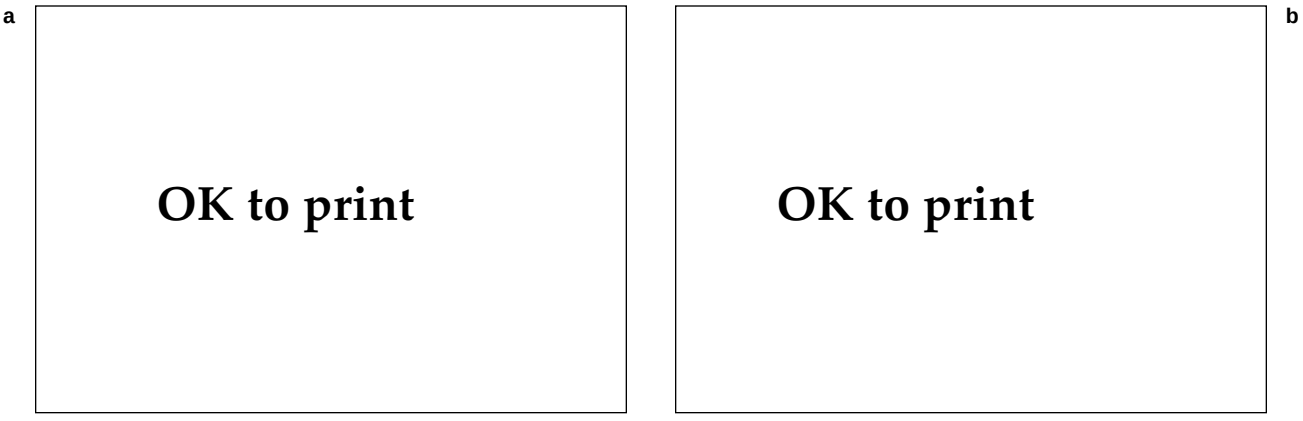


Fig. 18-26. (**a**) Human and (**b**) dolphin lobomycosis. The smooth, whitish, warty excrescences of lobomycosis are similar in both species. This Atlantic bottle-nosed dolphin was captured in an estuary in central Florida. For over a decade, the dolphin has been an active member of the US Naval Command Control Ocean Surveillance Center research facility, formerly at Kaneohe Marine Corps Air Station, Hawaii. The lesions are unresponsive to imidazole therapy but they do not seem to hamper the dolphin's life or performance of its duty. Photograph (a): Courtesy of Professor Angela Restrepo-M., Medellin, Colombia.

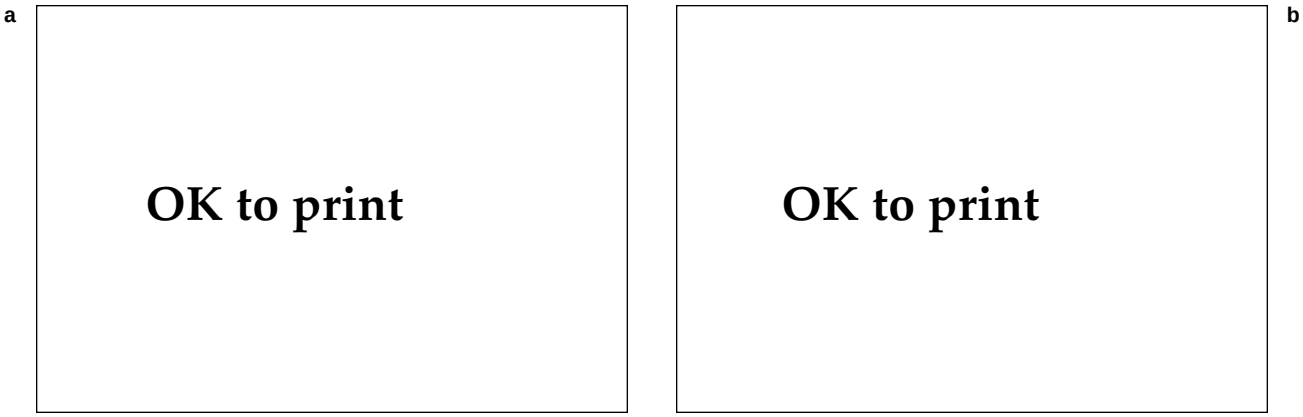


Fig. 18-27. The characteristic histology of *Loboa loboi* infection in a human. (**a**) The low-power view shows dermal fibrosis and a sievelike pattern created by numerous organisms. (**b**) Chains of *L loboi* are seen on closer view (hematoxylin-eosin stain, original magnification 430X).

Rhinosporidiosis

Rhinosporidiosis is a chronic, painless, mucosal infection caused by *Rhinosporidium seeberi*. Typically, an intranasal papule evolves into a hyperplastic polyp. Lesions may obstruct the nares and impair breathing, cause nasal bleeding, or, if the oral mucosa is involved, compromise speech and digestion.

In infected tissues, *R seeberi* appear as abundant spores and sporangia. Immature spores (7–10 μm) enlarge and undergo repeated mitotic divisions, forming thick-walled sporangia (100–350 μm).[113–115]

Solitary cases of rhinosporidiosis may occur after individuals are exposed to fresh water in India and adjacent countries. No cases were reported among U.S. soldiers in Vietnam. The disease lacks epidemic potential.

History

Rhinosporidiosis was first described in 1896 in Argentina, where few cases have been reported since. Guillermo Seeber, a medical student in Buenos Aires, described a 19-year-old farm worker whose breathing was impaired by a nasal mass. The pathogen was considered a coccidia-like protozoan, but in 1923, Ashworth determined it was a fungus and established the current name.[116]

Epidemiology and Distribution

Nearly 90% of cases of rhinosporidiosis are from India and Sri Lanka. The disease has been reported worldwide except in parts of Europe and Oceania. Details of transmission remain largely speculative, but infection seems to follow exposure to contaminated water. Paddy cultivators and persons who bathe in waters frequented by large farm animals are at increased risk. Young men are most often affected, but this may reflect occupational exposure. The disease also occurs in horses, mules, cattle, goats, dogs, and birds.[116,117]

Clinical Manifestations

In 70% of cases, patients with rhinosporidiosis present with a friable, usually pedunculated, polyp

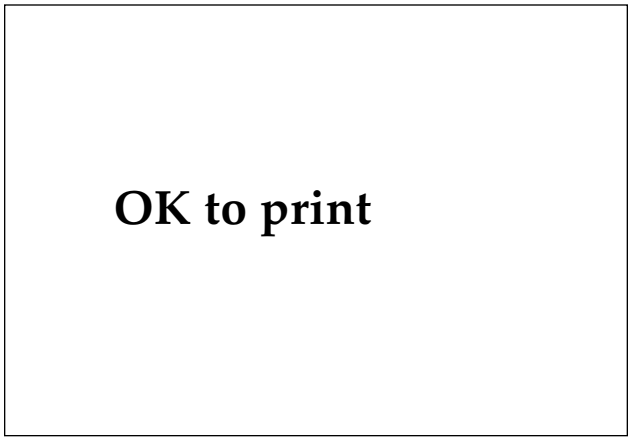


Fig. 18-28. Although most patients with rhinosporidiosis present with nasal lesions, other mucosal sites such as the conjunctiva may also be affected. The glistening, red, pedunculated lesion may have the appearance of a pyogenic granuloma. Photograph: Courtesy of Colonel William D. James, Medical Corps, US Army, Washington, DC.

emerging from the nasal mucosa (see Figure 18-1). The surface of lesions appears vascular and has sharply defined white dots corresponding to visible sporangia. Usually only one nostril is involved, though both may be. Mucosal sites involved less frequently include the palpebral conjunctiva (Figure 18-28), oropharynx and nasopharynx, external ear canal, and genitalia. Visceral dissemination has been reported several times.[113,114,116–118]

Diagnosis

Histopathological demonstration of the characteristic thick-walled, giant sporangia is diagnostic. The organisms are abundant and appear in various sizes and stages of development.[118] Recently, *R seeberi* has been cultivated successfully in vitro in a human epithelial cell culture.[119] The technique is not suitable for routine diagnostic work.

Treatment

Medical management is inadequate. Excision of the polyps is necessary, although recurrences are common.[117]

OPPORTUNISTIC MYCOSES AND MISCELLANEOUS INFECTIONS

In addition to the systemic and subcutaneous mycoses, deep fungal skin diseases also include the opportunistic mycoses and miscellaneous infections. Cryptococcosis was formerly an uncommon opportunistic infection, but it is seen frequently now in HIV-infected persons. Entomophthoramycosis is a rare, tropical fungal infection of deep subcutaneous tissues of immunocompetent hosts. Actinomycosis and nocardiosis are traditionally placed with the deep fungal infections although they are caused by related, true bacteria.

Cryptococcosis

Cryptococcosis, also called Busse-Buschke's disease, torulosis, and European blastomycosis, is an opportunistic infection that has its most severe effects on the central nervous system. Cutaneous cryptococcosis occurs in approximately 15% of patients with disseminated disease.

The disease is caused by *Cryptococcus neoformans*, the only basidiomycete known to cause deep fungal infections. The organism has a perfect state (*Filobasidiella neoformans*) but lacks thermal dimorphism. The pathogenic form is a unicellular, round-to-oval, thin-walled yeast that reproduces by budding. In tissue, *C neoformans* often acquires a thick, mucoid, polysaccharide capsule, assuming a size of 4 to 12 μm. Differences in capsular antigenicity produce four serotypes (A, B, C, and D), of which types A and D are most common in the United States.[120,121] Capsular features influence virulence, although the patient's immune status determines the course of the disease. Two varieties, *C neoformans* var *neoformans* and *C neoformans* var *gattii*, but rarely other cryptococcal species, cause disease.[120]

Epidemiology and Distribution

Cryptococcosis, a cosmopolitan disease, is reported most frequently from temperate regions. *C neoformans* is ecologically associated with birds, especially pigeons, because it thrives in their excreta. The organism passes harmlessly through the bird's gut. Pigeon fanciers often have antibodies, indicating frequent exposure, but do not have an increased rate of infection. *C neoformans* is easily recovered from pigeon excrement but is rapidly cleared from soil by *Acanthamoeba* organisms.

In Australia, *Cryptococcus neoformans* var *gattii* is closely associated with *Eucalyptus camaldulensis*, one of the few trees on which koalas feed. Koalas pass the yeast fecally (in the same ecological role served by pigeons elsewhere) but also contract cryptococcosis occasionally.[122] Serious infections caused by *Cryptococcus neoformans* var *gattii* have been found not only in immunocompromised but also in immunocompetent patients.[123]

Persons at increased risk for infection are those with impaired cell-mediated immunity from, for example, chronic corticosteroid therapy, lupus erythematosus, sarcoidosis, or iatrogenic immunosuppression associated with organ transplantation.[121] Cryptococcal infection in an HIV-infected person meets the CDC definition for AIDS. Indeed, the unexpected diagnosis of cutaneous cryptococcosis requires prompt evaluation for other involved organs and for underlying immunodeficiency.

Clinical Manifestations

The primary infection in cryptococcosis is pulmonary, but involvement of the central nervous

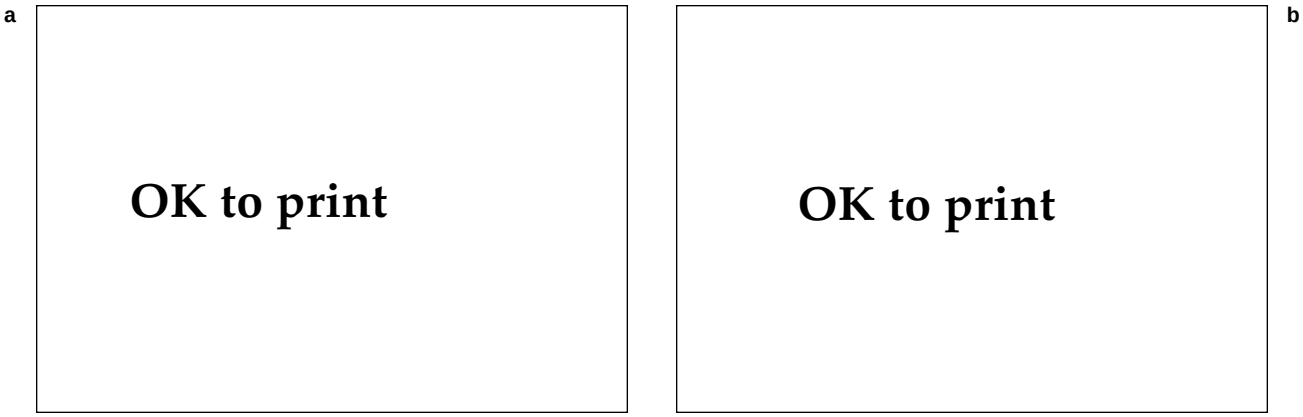


Fig. 18-29. Disseminated cryptococcal infection usually occurs in immunocompromised individuals. (**a**) Most lesions of cutaneous cryptococcosis are not distinctive. (**b**) However, in an individual infected with the human immunodeficiency virus, the lesions may resemble those seen in patients with molluscum contagiosum. Photograph (b): Courtesy of Colonel Richard Gentry, Medical Corps, US Army, Aurora, Colo.

system is the most common and serious complication. Cutaneous manifestations appear in approximately 15% of persons with disseminated disease, occasionally before the start of life-threatening meningeal involvement (see Figure 18-1).[124] The clinical diagnosis of cutaneous cryptococcosis is difficult because the manifestations are diverse and nonspecific (Figure 18-29). Most often, painless papules arise on the head or neck and then evolve into nodules, pustules, abscesses, grouped vesicles, purpura, vasculitis, plaques, or ulcers.[125–127] Two uncommon but well-described cutaneous presentations are cryptococcal cellulitis in prednisone-treated patients who have had renal transplants[125,128] and molluscum-like facial papules in patients with AIDS.[124] More rarely, the lesions resemble pyoderma gangrenosum or Kaposi's sarcoma. Primary inoculation cryptococcosis is extremely rare[129–131] and it is best to consider a cutaneous lesion evidence of disseminated cryptococcosis until proven otherwise.[126]

Diagnosis

The clinical diagnosis may be difficult but the histological diagnosis is not. Two patterns—gelatinous and granulomatous—are seen in biopsy specimens. The gelatinous pattern demonstrates many organisms with minimal host response. The thick, mucopolysaccharide capsules do not stain with hematoxylin-eosin, producing a sievelike appearance (Figure 18-30). The granulomatous pattern has fewer organisms, which measure 2 to 4 μm in size, with inconspicuous capsules. In this type, the host response is vigorous and organisms are seen within macrophages and giant cells.[59] Mucopolysaccharide capsules are enhanced with Meyer mucicarmine stain but the organisms within are better seen with periodic acid–Schiff stain. Gram's stain, India ink, and Tzanck preparations on aspirated or biopsied material also may reveal the organisms.[125] Culture of skin, sputum, and cerebrospinal fluid should be set up on Sabouraud's agar.[121]

Cryptococcal infections of the meninges are traditionally diagnosed by examining a cerebrospinal fluid–India ink preparation, which has only 50% sensitivity. Latex agglutination tests for cryptococcal antigens are more sensitive. Serologic tests may demonstrate antibodies.

Treatment

Disseminated cryptococcosis is usually fatal if untreated. Combination therapy with flucytosine and amphotericin is the treatment of choice for cryptococcal meningitis.[121,132] Fluconazole is proving increasingly valuable in managing cryptococcosis in patients with AIDS.

Entomophthoramycosis

Entomophthoramycosis (also called entomophthoromycosis, subcutaneous zygomycosis or phycomycosis, rhinophycomycosis, and rhinoentomophthoromycosis) comprises two rare infections, conidiobolomycosis and basidiobolomycosis, that are caused by the related zygomycetes *Conidiobolus coronatus* and *Basidiobolus ranarum*, respectively. Both diseases occur mainly in forested

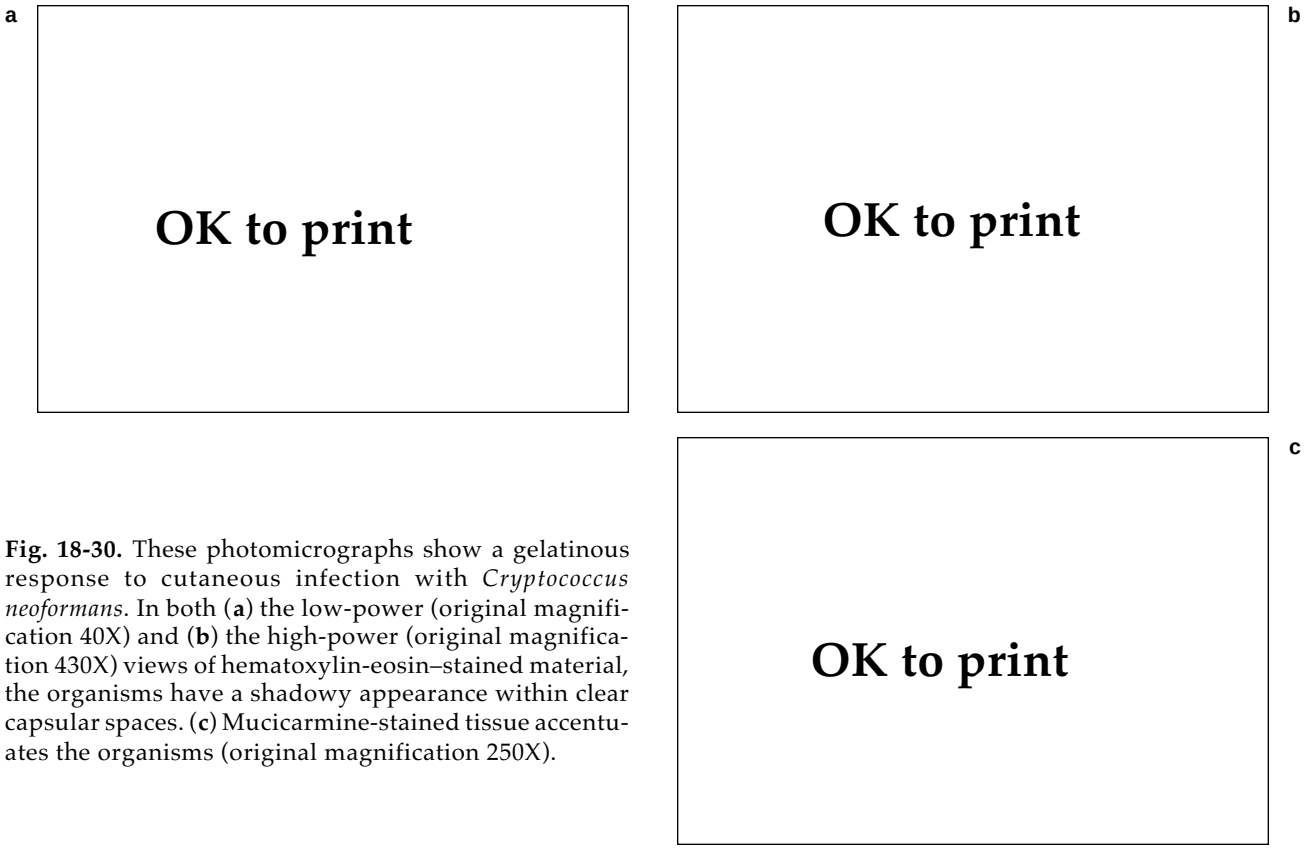


Fig. 18-30. These photomicrographs show a gelatinous response to cutaneous infection with *Cryptococcus neoformans*. In both (**a**) the low-power (original magnification 40X) and (**b**) the high-power (original magnification 430X) views of hematoxylin-eosin–stained material, the organisms have a shadowy appearance within clear capsular spaces. (**c**) Mucicarmine-stained tissue accentuates the organisms (original magnification 250X).

tropical regions even though the causative fungi are ubiquitous. *Conidiobolus coronatus* naturally occurs both as a plant saprophyte and as a pathogen of several arthropods. *Basidiobolus ranarum* is frequently recovered from the digestive tracts of reptiles and amphibians.[133] Their portal of entry and incubation period in humans is unknown. Neither organism is opportunistic. Some generalizations regarding each infection can be made (see Figure 18-1).

Conidiobolomycosis is usually confined to subcutaneous tissues of and surrounding the nose. The disease usually occurs in adult males, starting as a swelling of the inferior nasal turbinates with subsequent bilateral invasion of perinasal structures (such as the sinuses and upper lip). The resulting masses are firm, mobile, nontender, and profoundly disfiguring but rarely lethal.[133–135] The patient generally remains otherwise healthy, a feature that clinically distinguishes this condition from rhinocerebral mucormycosis. Basidiobolomycosis occurs as large, indurated, subcutaneous masses on the proximal extremities, buttocks, or trunk of healthy children. Biopsy specimens of both organisms show broad hyphae with infrequent septae and no vascular invasion. The hyphae are surrounded by eosinophilic debris (the Splendore-Hoeppli phenomenon).

Treatment consists of oral potassium iodide.[135] Amphotericin alone is ineffective but ketoconazole has shown some promise.[136]

Actinomycosis

Infections caused by actinomycetes (also called ray fungi) are traditionally placed with fungal disorders despite their proper position among true bacterial diseases. Synonyms include lumpy jaw, leptothricosis, and streptothricosis. The source of infection is the normal oral flora harboring *Actinomyces israelii*. Several clinical forms of actinomycosis are recognized: cervicofacial (the most common), thoracic, and abdominal. Another form, pelvic, was linked with endometritis associated with intrauterine devices.[137]

Years ago, actinomycosis was commonly diagnosed but it is rare in the United States now because of improved oral hygiene.[137] During World War II, there were approximately 230 cases of actinomycosis in U.S. troops. Of these, four died of complications of their infections.[138]

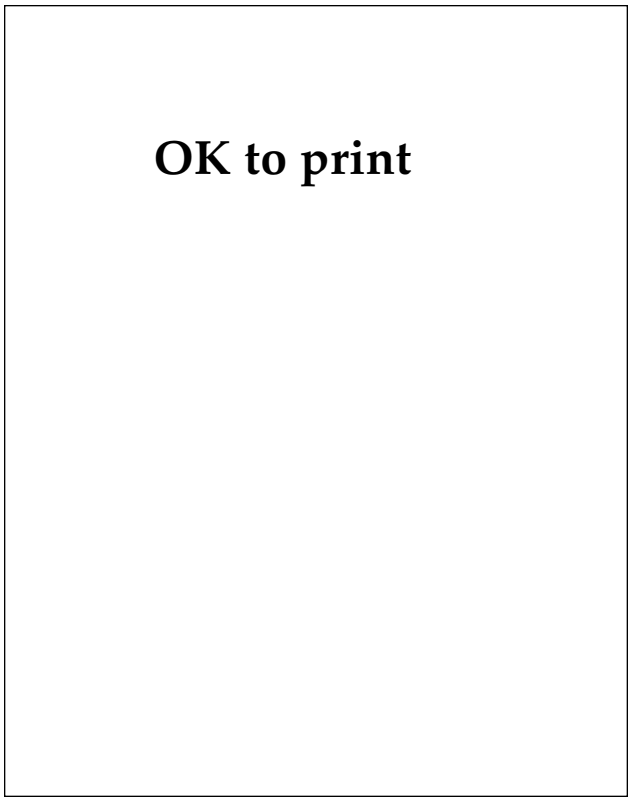


Fig. 18-31. This Fijian soldier developed cervicofacial actinomycosis after repeated dental procedures on an abscessed tooth. On palpation, the mass was woody and adherent to the mandible. Exploratory surgery showed five yellow-green sulfur granules, each approximately 2 mm in diameter.

Actinomyces israelii is the most common cause of human actinomycosis. Several congeners and members of related genera (*Arachnia, Bifidobacterium*) have also been implicated. They are anaerobic, Gram-positive, filamentous bacteria that grow best under anaerobic conditions. *Actinomyces bovis* causes actinomycosis of cattle, commonly presenting as woody tongue disease.[139]

The clinical forms of actinomycosis are characterized by chronic suppuration. Predisposing factors to cervicofacial infection include accidental trauma to the area, dental extraction, caries, or other evidence of poor oral hygiene. Patients with cervicofacial actinomycosis typically present with a painless, indurated mass growing insidiously along the jawline (Figure 18-31). The masses consist of deep nodules that coalesce and form sinuses draining to the exterior (see Figure 18-1). The discharge often contains minute, yellow spherules (1–5 mm in diameter) called sulfur granules. They contain no sulfur but are colonies of organisms that form dense aggregates of mycelia.[140] The swellings are characteristically woody in their firmness. Mandibular periostitis and osteomyelitis may ensue. Abdominal and thoracic infections follow aspiration or ingestion of oral material. Their cutaneous manifestations also appear as sinuses draining to the exterior.[137,139,140]

The diagnosis is confirmed by detecting organisms by culture, biopsy, or tissue examination. Gram's stain of a crushed granule shows thin (approximately 1 μm), Gram-positive filaments radiating and intertwining along the periphery.[139] Biopsy specimens stained with hematoxylin-eosin show that the centers of grains are basophilic and the fringes are eosinophilic (Figure 18-32). *Actinomyces* may be distinguished from *Nocardia* by their lack of acid-fastness and by specific fluorescent antibody stains. Culture has special requirements so prior consultation with a laboratory officer is necessary.[140]

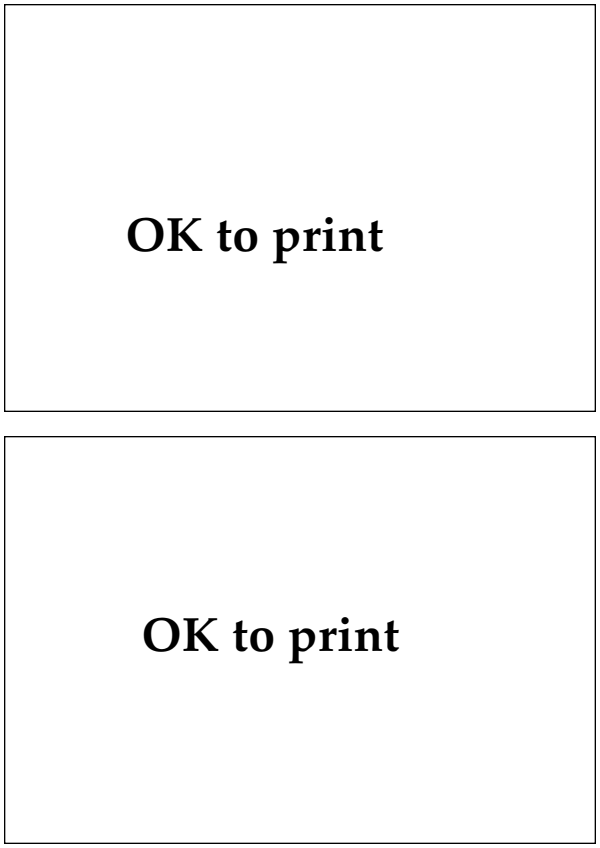


Fig. 18-32. Histology of actinomycotic granule. (**a**) Basophilic center and eosinophilic periphery (hematoxylin-eosin stain, original magnification 100X). (**b**) Radiating fringe of filamentous organisms from the same tissue (hematoxylin-eosin stain, original magnification 250X).

Cervicofacial infection requires long-term antibiotic therapy, usually 6 months or more, often coupled with surgical debridement of indurated masses. Penicillin is the drug of choice and should be given parenterally during the initial weeks of therapy.[140]

Nocardiosis

Several forms of nocardiosis involve the skin. The most common and serious form mostly affects debilitated hosts and is caused by *Nocardia asteroides*. It usually causes a pleuropulmonary disease resembling tuberculosis. Secondary involvement of the skin is due to hematogenous spread or the formation of thoracic sinuses. Its most serious complication is metastatic cerebral infection.[141] Primary cutaneous nocardiosis is caused by *Nocardia brasiliensis*, the organism also responsible for most New World actinomycetomas. This form typically follows plant-associated percutaneous injuries to the hands, followed by a chain of nodules ascending along lymphatic channels (see Figure 18-1). By history and examination, primary cutaneous nocardiosis may be clinically indistinguishable from lymphocutaneous sporotrichosis.[142] Diagnosis requires identification of the organism because there are no pathognomonic clinical features.[143] *Nocardia* grows slowly on a wide range of culture media. Gram's stain of purulent material shows Gram-positive filaments that also are partially acid-fast. Granules, as seen in nocardial actinomycetoma, are absent. Initial therapy should be with cotrimoxazole or other sulfa derivatives. Because long-term treatment is necessary, antibiotic sensitivity studies should be conducted. Other unrelated agents, such as minocycline and amikacin, are often effective.[141,142] Incision and drainage or excision of lymphocutaneous abscesses also may be indicated.[143]

SUMMARY

Deep fungal infections can involve a number of organ systems, and patients can present with a broad range of clinical signs and symptoms. Often, it is the cutaneous aspects of an illness that allow clinicians to make a diagnosis, whether by physical examination, biopsy, or culture.

Many pathogenic fungi have distinctive environmental or geographical predilections. Consequently, the diseases they cause also have environmental or geographical distributions. Our knowledge of coccidioidomycosis, for example, comes largely from the problems the disease posed during World War II exercises in Arizona and California. Military physicians continue to see patients with systemic coccidioidomycosis acquired during duty in the southwestern United States.

Several of the deep mycoses are uncommon or unreported in the U.S. armed forces or, for that matter, in personnel of any military. The endemic foci of several diseases are in areas where armies have rarely deployed. As the missions of the U.S. military evolve and as populations migrate, however, it behooves medical officers to know the epidemiology and clinical manifestations of even the uncommon deep mycoses.

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