at the maximal tolerated doses of 1 to 1.5 mg/kg/day.[189] Unfortunately, high doses of conventional amphotericin B are usually not tolerated for more than several days before renal function deteriorates, especially in patients with diabetes or receiving concomitant nephrotoxic therapies.

Lipid Amphotericin B Formulations

Lipid formulations of amphotericin B are safer than ABD for long-term administration and, in our opinion, are the preferred first-line treatment for severe mucormycosis.[187,190] Most experience in the treatment of mucormycosis has been with either liposomal amphotericin B (L-AMB) or amphotericin B lipid complex (ABLC). Although no comparative studies have been performed, outcomes with the use of the two lipid amphotericin B formulations are similar to those historically reported for conventional ABD, albeit with lower rates of nephrotoxicity.[189]

In one of the few published case series, 24 patients with mucormycosis and diabetes as the predominant underlying risk factors were treated with ABLC after failure or intolerance of the conventional ABD formulation.[190,191] The overall response rate (improvement or cure of infection) was 71% (17/24 patients), with few reported toxic effects, even in patients with preexisting renal dysfunction. Several case series have reported the successful treatment of mucormycosis with the liposomal formulation of amphotericin B, sometimes administered at high doses (i.e., 10 mg/kg/day) for prolonged treatment courses.[192,193]

The optimal dosing approach for L-AMB in patients with mucormycosis is frequently debated. Preclinical pharmacokinetics/pharmacodynamics studies in murine models of pulmonary mucormycosis that simulated human dosing have suggested that ABLC at 5 mg/kg/day or L-AMB at 10 mg/kg/day results in rapid antifungal accumulation in the lung, reduced fungal burden, and improved survival.[194] However, these animal models focus on short treatment periods and do not routinely assess nephrotoxicity of higher-dose L-AMB regimens. Both clinical and observational studies have suggested an early "window" of 10 to 14 days when nephrotoxicity risk is lowest with L-AMB, which may be shortened in patients receiving concomitant nephrotoxic agents or aggressive diuresis.[195–197]

In one of the few randomized trials that compared standard doses of L-AMB (3 mg/kg/day) to a higher dose-regimen (10 mg/kg/day for 14 days, then 3 mg/kg/day) for invasive aspergillosis, patients randomized to the higher-dosed L-AMB regimen failed to achieve higher response rates but experienced significantly higher rates of nephrotoxicity and severe hypokalemia.[198]

The feasibility of high-dose (10 mg/kg/day) L-AMB treatment for the initial treatment of mucormycosis was explored in a multicentric prospective French study of 40 patients with invasive mucormycosis.[199] The planned treatment of 10 mg/kg/day was administered as an infusion of at least 2 hours for 4 weeks. In patients in whom there was doubling of serum creatinine levels, compared with baseline, it was recommended that the L-AMB dose be reduced to 7.5 mg/kg/day. If creatinine values did not improve within 3 days, L-AMB dosing was further reduced to 5 mg/kg/day. Among the 33 patients who could be analyzed at 4 weeks after starting therapy or end of therapy, a favorable response was documented in 12 of 33 (36%) at week 4 and 14 of 31 (45%) by week 12. Most patients (24/31, 71%) underwent at least one surgical procedure. Of importance, although 4 weeks of high-dose L-AMB was planned, the average treatment duration at this dose was 13.5 days (range, 0–28), with 40% of patients experiencing a doubling in the baseline serum creatinine and severe hypokalemia (serum potassium <3 mmol/L). Therefore considerations for using doses of L-AMB higher than 5 mg/kg/day should take into account that a sizable proportion of patients will develop renal injury requiring dosage reduction or possibly a switch to triazole therapy after the first 1 to 2 weeks of therapy. Daily infusions of a liter of saline are used in some centers to reduce L-AMB nephrotoxicity in adults who can tolerate an increased sodium load.

Triazoles

The prospects for using posaconazole in the treatment of mucormycosis has improved with the introduction of an extended-release tablet formulation with improved bioavailability compared with the older suspension, and an IV formulation solubilized in sulfobutyl ether β-cyclodextrin. These newer formulations are dosed differently than the oral suspension, which has to be administered two to four times daily in smaller doses to maximize absorption. The extended-release tablet and IV formulation of posaconazole are the preferred formulations of posaconazole for most patients due to their more reliable pharmacokinetics properties.[200]

Most of the published clinical experience concerning mucormycosis treatment with posaconazole has used the older suspension formulation administered at 800 mg/day in divided doses. In an open-label study evaluating posaconazole as salvage therapy (not initial therapy), the overall success rate of posaconazole (800 mg/day) was 70% in 24 patients, and it was well tolerated with only minimal GI side effects.[201,202] Similarly, a retrospective survey of posaconazole-based salvage therapy in 91 patients with refractory mucormycosis indicated an overall success rate of 61%, including 65% in patients with pulmonary mucormycosis.[203] Among patients who were not categorized as treatment successes, 21% had evidence of stable disease after 12 weeks of treatment. At present the US Food and Drug Administration (FDA) has not approved posaconazole for primary or salvage therapy of mucormycosis, indicating the need for further studies.

The extended-release tablet formulation of posaconazole is administered at a dose of 300 mg (three 100-mg delayed-release tablets) twice a day on the first day, then 300 mg daily. Although the absorption of the tablets is improved with food, the tablets have adequate bioavailability even in patients with poor dietary intake or receiving acid-suppression therapy, such as a proton pump inhibitor.[204] The IV formulation of posaconazole is dosed at 300 mg IV twice daily on day 1, followed by 300 mg daily thereafter, and rapidly achieves plasma concentration exposures of greater than 500 ng/mL in 95% of patients, which often took more than a week in patients receiving posaconazole suspension.[205] Although therapeutic drug monitoring has been recommended for posaconazole in *Aspergillus* treatment guidelines to ensure serum trough levels greater than 1.5 mg/L during the treatment of infection,[206,207] a similar relationship between serum trough levels of posaconazole and outcome of mucormycosis has not been reported.

In 2015 the FDA approved isavuconazole for treatment of invasive mucormycosis based on an open observational report by the manufacturer[208] of 21 patients who received isavuconazole as primary therapy for proven or probable disease; 7 had the drug discontinued, 2 were still on therapy when reported, 6 died during isavuconazole treatment, and 6 were alive when isavuconazole treatment was considered completed. Results with salvage therapy in 16 patients were also considered favorable. The small numbers and diverse results make comparisons with amphotericin B and posaconazole difficult.[209] Isavuconazole may be a possible alternative to posaconazole or L-AMB, particularly for longer-term therapy. An advantage of isavuconazole is that it is administered as a prodrug formulation (isavuconazonium) in either an IV and oral formulation with excellent bioavailability that is not affected by dietary intake or acid-suppression therapy. Isavuconazole is dosed with a 372-mg loading dose administered every 8 hours for 6 doses (48 hours), then a 372-mg maintenance dose daily. Isavuconazole is generally well tolerated, making it a possible alternative for patients who are clinically stable and have limiting drug interactions with posaconazole or cannot tolerate the nephrotoxic effects of L-AMB. However, some species, such as *M. circinelloides,* exhibit MICs greater than achievable serum levels of patients with currently recommended isavuconazole dosing.[172] We have also observed cases of breakthrough mucormycosis during isavuconazole treatment in patients with prolonged neutropenia and relapsed hematologic malignancies.

Combination Therapy

Successful treatment of mucormycosis with combinations of amphotericin B, terbinafine, rifampicin, L-AMB, posaconazole, and echinocandins has also been described in small case series and case reports.[183,210] Interpretation of these studies is confounded by small numbers, retrospective nature, and confounding factors such as neutrophil recovery and surgery.[210,211] One of the largest case-control studies evaluating the possible benefits of combination therapy for invasive mucormycosis was performed at MD Anderson Cancer Center,[212] which identified 47 patients who received early L-AMB monotherapy and 59 patients who received combination treatment. The most common combination regimens were L-AMB plus an echinocandin (46%), L-AMB plus

posaconazole (27%), or triple combination therapy (27%). A propensity score analysis for combination therapy was used to attempt to adjust for confounding variables associated with prescription of combination therapy. The investigators could not identify any survival benefit for combination therapy over timely administration of L-AMB, even after propensity score adjustment (odds ratio, 0.8; 95% confidence interval, 0.3 to 2.4; $P = .69$) or if patients were stratified into groups for low versus high risk for mortality.[212]

Treatment Duration

The duration of treatment required for mucormycosis is highly individualized to the patient. Near normalization of radiographic imaging, negative biopsy specimens, and cultures from the affected site and recovery from immunosuppression are indicators that a patient is a candidate for stopping antifungal therapy. Late relapses of mucormycosis after successful treatment have been reported several years after discontinuation of secondary posaconazole prophylaxis or onset of new immunosuppression.[213] In one case relapsing disease was accompanied by increased ^{18}F-fluorodeoxyglucose uptake in lesions detected by positron emission tomography–CT.[213] Therefore continued follow-up of patients is critical in any patient who discontinues treatment for mucormycosis.

Prophylaxis

Because mucormycosis is a relatively rare infection, primary prophylaxis is generally not recommended. Secondary prophylaxis is often desired in patients requiring further immunosuppression after treatment for mucormycosis. Posaconazole, and possibly isavuconazole, appears to be a safe option for patients who require continuous, oral long-term antifungal therapy because they remain at high risk for relapsing infection.[213]

Surgical Management

In rhinosinusitis surgical débridement of infected tissue is a crucial component of therapy and should be urgently performed to limit the aggressive spread of infection to contiguous structures. Repeated removal of necrotic tissue or radical surgical resection (e.g., exenteration of the orbit) with subsequent reconstructive surgeries may be required for lifesaving control of rapidly evolving infection.[118] However, rhinosinusitis has been treated successfully in select patients without radical resection, particularly when multimodality treatment options are used with careful follow-up.[214] Extension to the brain usually portends a fatal outcome. Decisions regarding the extent of surgical débridement are highly individualized to the patient. Intraoperative frozen sections and MRI can help determine the extent of involved tissue and tissue margins. Conditions such as low platelet counts and other bleeding problems must be corrected with sufficient transfusions before surgical intervention. Unfortunately, bleeding risks may limit surgical options in some patients with profound thrombocytopenia.

In patients with pulmonary mucormycosis, surgical treatment in conjunction with systemic antifungal therapy has been shown to significantly improve survival compared with antifungal therapy alone.[118,215] One large case series reported a mortality rate of 55% in patients who received systemic antifungal therapy alone compared with 27% in patients who received antifungal therapy plus surgical intervention.[110] Although the reported outcomes may reflect a selection bias in offering surgery to less severely ill patients with unifocal disease, removal of infected or devitalized tissue early, when the infection is localized, provides the greatest benefit. Cavitation of lesions near the hilum has been followed by fatal hemoptysis, providing an incentive for resection in selected patients. Repeated surgeries are also necessary in some cases. The benefit of pulmonary resection of a dominant lung lesion (debulking) is unknown in patients with multifocal or disseminated mucormycosis.

Adjunctive Therapies

Patients with profound neutropenia and progressive mucormycosis despite optimal therapy may be candidates for neutrophil transfusion. With currently available techniques, more than 10^{10} granulocytes can be infused, resulting in an immediate postinfusion absolute neutrophil count usually exceeding 1000/μL. Repeated infusions are needed every few days and can lead to diminishing response in the patient's neutrophil count due to allosensitization. Success of this bridging procedure in treating mucormycosis is still uncertain but likely depends ultimately on the patient's marrow recovery.

Several other adjunctive measures have been explored for improving tissue viability, impeding fungal proliferation, and improving host immunity. Hyperbaric oxygen therapy was reported to be a beneficial adjunct to standard surgical and antifungal therapy for mucormycosis, particularly for diabetic patients with rhinocerebral disease.[216–218] Although this is not one of the approved uses of hyperbaric oxygen (see Chapter 50), the increased oxygen pressure achieved with hyperbaric oxygen may improve neutrophil activity and the putative oxidative killing effects of polyene antifungals.[219] High oxygen concentrations have also been reported to inhibit growth of Mucorales in vitro and to improve the rate of wound healing by increasing the release of tissue growth factors.[220] Lack of convincing clinical evidence supporting the benefit of hyperbaric oxygen therapy, however, limits its recommendation for routine clinical use for this expensive, controversial, and logistically difficult intervention for mucormycosis.[71]

Multiple immune-augmentation strategies have been proposed for mucormycosis, including administration of cytokines that enhance phagocytic activity, such as granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor, or IFN-γ alone or in combination with granulocyte transfusions. Various combinations of these approaches have been reported with some favorable outcomes in case reports.[219,221] However, many of these immune-augmentation strategies carry some risk for enhancing inflammatory lung injury[222,223]; therefore the relative benefits of such adjunctive strategies must be balanced against the risk for increased harm to the patient.

Prognosis

The site of infection and underlying host factors are the key prognostic determinants of mucormycosis outcome. Active hematologic malignancy, allogeneic HSCT, and disseminated infection are associated with poor outcome.[166] In our experience, most patients with hematologic cancer who develop mucormycosis die within 12 weeks of diagnosis.[121,212,224] However, earlier diagnosis of the disease and aggressive treatment have been associated with improved survival rates in recent series.[166,212] Correction of underlying immune impairment (e.g., rapid tapering of glucocorticoids), combined with aggressive multimodality treatment approaches, offer the best chance for patient survival.

ENTOMOPHTHORAMYCOSIS

Infections caused by fungi in the subphylum Entomophthoramycotina, called *entomophthoramycosis,* include both conidiobolomycosis and basidiobolomycosis. These are rare infections of the paranasal sinus and subcutaneous tissues, principally encountered in the tropics, that rarely affect other tissues.[225] In contrast to mucormycosis, entomophthoramycosis is usually a chronic, nonangioinvasive infection in relatively immunocompetent individuals.[226,227] Although rare, case clusters of invasive disease have been reported in both immunocompromised and immunocompetent patients.[228,229] Conidiobolomycosis affects primarily the head and face, whereas basidiobolomycosis is often localized to the subcutaneous tissues of the trunk and arms or the GI tract.[226,227] The infections are characterized by slow-growing, tumor-like masses in infected tissues that can remain indolent for years. Both fungi are common inhabitants of the soil throughout the world, including the United States. However, most cases of conidiobolomycosis are found in tropical Africa, South America, Central America, and Asia.[226] Similarly, reports of cutaneous basidiobolomycosis are primarily concentrated in tropical areas of Africa and Southeast Asia and in the tropical and subtropical regions of Asia, Australia, and South America.[227] Entomophthoramycosis also demonstrates some age specificity: conidiobolomycosis is uncommon in children, but 88% of basidiobolomycosis cases occur in patients younger than 20 years.[230]

Conidiobolomycosis

Subcutaneous rhinofacial conidiobolomycosis is the most common manifestation of infection caused by *Conidiobolus coronatus.* Symptoms typically begin with nasal discharge, epistaxis, unilateral nasal obstruction,

sinus tenderness, and extensive and persistent facial swelling that may result in disfiguration. The infection slowly progresses with granulomatous inflammation in the subcutaneous tissue without bone involvement or ulceration of the skin.[231] Systemic symptoms are rare, but disseminated conidiobolomycosis has been observed.[226] Infections with *Conidiobolus incongruus* are extremely rare but often more aggressive.[159]

Basidiobolomycosis

Infections caused by *Basidiobolus ranarum* often begin as a nodular subcutaneous lesion on the trunk, arms, or buttocks. The mode of transmission for *B. ranarum* is assumed to be through minor trauma and insect bites. Fungal spores are found in the bristles of mites and are probably carried by other insects. *B. ranarum* has been theorized to be present on "toilet leaves" used for skin cleaning after a bowel movement, resulting in direct inoculation of the perineum.[232] The predominance of lesions in the buttocks, thighs, and perineum would appear to support this theory. The subcutaneous lesions elicited by *B. ranarum* are typically firm but not painful, with edema around the involved sites. Deeper invasion of muscle underlying the subcutaneous tissue has been reported.[227] Several cases have been reported of otherwise healthy persons with GI tract basidiobolomycosis, most often in the colon,[233] that may present as obstruction or mimic the presentation of Crohn disease.[232,234,235] Clinical features of GI basidiobolomycosis include abdominal pain, nausea, vomiting, diarrhea, or abdominal mass.[235] Peripheral blood eosinophilia and high serum immunoglobulin E concentrations are usual. Most cases are slowly progressive locally and may be mistaken for Crohn disease or form large abdominal masses mimicking malignancy. Chronic fibrotic-appearing lesions, including angioinvasive disease reminiscent of mucormycosis seen in diabetic and immunocompromised patients, have also been described.[229]

Diagnosis

In areas where entomophthoramycosis is common the diagnosis is often suspected from the clinical appearance of the patient and characteristic lesions or swelling.[232,235] Definitive diagnosis requires biopsy of the involved site, with characteristic findings of broad, sparsely septated hyphae surrounded by eosinophilic granular material (Splendore-Hoeppli phenomena).[232,236,237] Tissue eosinophilia and granulomatous inflammation are usual. Peripheral eosinophilia may also be present, but cultures from the infected site are often negative. PCR assay of DNA extracted from tissue or from the isolated fungus, followed by sequencing, may be the most useful confirmatory diagnostic test.[13,233]

Differential Diagnosis

Eumycetomas have some clinical similarities to entomophthoramycosis, presenting as a chronic granulomatous fungal disease that affects the limbs, most commonly the feet (mycetoma pedis or Madura foot), and on occasion the abdomen, chest, and head, typically with draining sinuses. Eumycetomas can be differentiated by the presence of grains surrounded by neutrophils on biopsy and by culture. Pythiosis is usually a disease of horses, cattle, dogs, and cats but is a rare cause of subcutaneous disease in humans that can resemble entomophthoramycosis or can cause GI or disseminated infection resembling mucormycosis. Although the histologic appearance of the hyphae is similar, presence of vascular invasion and the appearance of motile zoospores on water culture of the causative organism, *Pythium insidiosum,* can distinguish the entities.[13]

Therapy and Prevention

Conidiobolus spp. are generally more resistant to systemic antifungals than *Basidiobolus* spp.[238] In the older literature agents used to treat entomophthoramycosis included potassium iodide, trimethoprim-sulfamethoxazole, ketoconazole, itraconazole, and amphotericin B with varying success and clinical outcome.[226,227,239–241] At present the preferred drugs for rhinofacial conidiobolomycosis appear to be a combination of a saturated solution of potassium iodide and itraconazole.[241] Surgical removal and reconstructive surgery for grossly swollen or disfigured tissues, combined with medical therapy, often provides the best chance for complete recovery. Subcutaneous basidiobolomycosis has been reported to respond to itraconazole.[242] Response of GI basidiobolomycosis to mold-active azoles has generally been favorable in small numbers of cases, including itraconazole, posaconazole, or voriconazole.[241,243–245]

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The complete reference list is available online at Expert Consult.

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259 *Sporothrix schenckii*

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SHORT VIEW SUMMARY

Microbiology and Epidemiology

- *Sporothrix schenckii* sensu lato, a group of closely related species, are dimorphic fungi that cause sporotrichosis with budding yeast in tissue and a mold in culture. Fungal cells in tissue may be oval, spherical, or elongate (cigar-shaped), with variable size in the same lesion.
- Worldwide distribution, especially in tropical and subtropical regions.
- Acquisition is associated with exposure to soil, plants, plant products (hay, straw, sphagnum moss), and a variety of animals (especially cats).
- Grows slowly on fungal culture from involved tissues.

Diagnosis

- Lymphocutaneous disease: presentation with an indolent papulonodular lesion, sometimes ulcerating, should suggest the diagnosis. Secondary lesions along lymphangitic channels are characteristic. Biopsy will show pseudoepitheliomatous hyperplasia with pyogranulomas and microabscesses in the dermis. Yeastlike cells can be seen with Gomori methenamine silver stain in one-third of cases but are not seen with hematoxylin and eosin stain. Culture will be positive.
- The most common extracutaneous form is osteoarticular. Pulmonary disease (usually cavitary) and meningeal disease are also well described. All are diagnosed by culture. Organisms can be seen in tissue with Gomori methenamine silver stain but may not be sufficiently distinctive to permit diagnosis of sporotrichosis.
- Multifocal dissemination may also occur, in immunocompromised subjects: cultures of skin lesions and joints are usually positive, whereas blood, spinal fluid, and bone marrow cultures are only occasionally positive.

Therapy

- Itraconazole at 100 to 200 mg/day (or 65 mg to 130 mg/day if using the enhanced bioavailability SUBA-itraconazole formulation; see Chapter 40B) orally is the treatment of choice for lymphocutaneous disease, with 3 to 6 months of therapy typically needed for complete resolution. Terbinafine 250 mg daily has also been successful in some cases of cutaneous disease.
- Therapy with a saturated solution of potassium iodide is also effective for lymphocutaneous disease, although it is associated with many side effects.
- Itraconazole is also active in extracutaneous disease, but extended therapy may be required. In difficult settings, amphotericin B is also employed. Success has also been reported in a few cases with terbinafine. Improvement of immune status (e.g., introduction of antiretroviral therapy in subjects with human immunodeficiency virus coinfection, reduction of immunosuppressive agents) is useful.

MYCOLOGY

Sporothrix schenckii sensu lato (meaning in the broadest sense) is a dimorphic fungus that exists in a hyphal form in vitro at temperatures less than 37°C. Colonies are initially white but gradually become brown to black due to the production of pigmented conidia. In vivo or at 37°C on rich media such as brain heart infusion agar, the organism converts to an oval- or cigar-shaped budding yeast. Along with the characteristic morphology of the sporulating mold, identification is based on demonstration of this conversion to a yeast form. DNA sequencing has shown that *S. schenckii* sensu stricto (meaning in a narrow sense) is a cluster of several closely related species.[1–5] Identification to the species level is currently done by partial sequencing of the calmodulin gene. Identification of species by matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry appears promising.[6] There are small morphologic and biochemical differences between some species, but these are not sufficient for identification. As an exception, *Sporothrix luriei* has been rarely isolated from humans and differs by producing a variety of unusual shapes in vivo.[7] The most common species is *S. schenckii* sensu stricto, which is found in America, Asia, and Africa. *Sporothrix brasiliensis* has so far been found only in Brazil, where it has often caused disseminated infection. Erythema nodosum or erythema multiforme has accompanied skin lesions in some of the cutaneous *S. brasiliensis* cases.[8] *Sporothrix mexicana* has been isolated from a few environmental sources and infections in Mexico, Brazil, Italy, and Portugal. *Sporothrix pallida,* which may be nonpathogenic, and *Sporothrix globosa* have been more broadly distributed geographically.[5] Because most of the information about sporotrichosis has not distinguished the cryptic species within the *Sporothrix schenckii* complex, the term *S. schenckii* is understood for the remainder of this chapter to include these closely related cryptic species.[4]

EPIDEMIOLOGY

Sporotrichosis has been reported from locations around the globe, but most case reports come from the tropical and subtropical regions of the Americas.[2,9] Most of the cases in the United States so far have been identified as *S. schenckii.*[10] Regions of hyperendemicity are known.[9,11] *Sporothrix schenckii* is most often isolated from soil, plants, or plant products such as straw, wood, sphagnum moss, and thorny plants, though the fungus is not a plant pathogen. Scratches on exposed skin of florists, rose gardeners, horticulturalists, farmers, miners, and armadillo hunters have increased risk of infection.[2,12,13] Because most cases appear to be due to occupational or avocational exposure to these materials, typically in the form of gardening or farming, patients with suggestive syndromes should be asked about these activities. Cases of animal-to-human transmission involving squirrels, horses, dogs, cats, pigs, mules, insects, and birds have been described.[14,15] An ongoing epidemic of sporotrichosis in Brazil has its origin in thousands of urban cats infected with *Sporothrix brasiliensis,* transmitting infection to thousands of humans and dogs.[11,16] Finally, sporotrichosis was apparently transmitted from the infected cheek of a mother to her infant[17] and to a lung transplant recipient via the transplanted lung.[18]

CLINICAL SYNDROMES

Infections due to *S. schenckii* can be divided into several syndromes. The lymphocutaneous forms are the most common.

Lymphocutaneous Sporotrichosis

Cutaneous disease arises at sites of minor trauma and inoculation of the fungus into the skin. The initial lesion is most often on a distal extremity, but almost any site may be involved, including such central locations as the nose and the ocular adnexa.[2,19,20] This preference

FIG. 259.1 Sporotrichosis of the fifth finger in a gardener. Three nodular lesions are visible on the hand and arm.

FIG. 259.2 Sporotrichosis of the bones of the wrist.

for cooler parts of the body corresponds to the known intolerance of some strains of *S. schenckii* to growth at 37°C.[21] Initial lesions are papulonodular, often erythematous, and range in size from a few millimeters to 2 to 4 cm. The lesions may be smooth or verrucous, and they often ulcerate and develop raised erythematous borders.[19] Lesions often develop proximally along lymphatic channels—these secondary lesions evolve in the same fashion as the primary lesion (Fig. 259.1). Secondary lesions do not usually involve a lymph node, although lymphadenopathy may develop. The lesions are typically painless, even after they ulcerate. The fixed, or plaque, form of sporotrichosis differs by not demonstrating any tendency to spread locally. Although spontaneous resolution of fixed sporotrichosis has been described,[19] the lesions of sporotrichosis usually wax and wane over months to years. The patient will not have systemic symptoms, and laboratory examinations will be normal.

The indolent progression and physical examination features suggesting both lymphocutaneous and fixed sporotrichosis are also produced by a number of other organisms (Table 259.1). Cultures of the drainage from skin lesions are occasionally helpful, but culture of biopsy material is preferred and is diagnostic when positive. Microscopic examination will reveal pseudoepitheliomatous hyperplasia in the epidermis with pyogranulomas and granulomas, often with areas of liquefactive necrosis in the mid and upper dermis.[22] Gomori methenamine silver stain will detect yeast cells in about one-third of cases, particularly if multiple sections are examined.[23]

Extracutaneous Sporotrichosis

Osteoarticular involvement is the most common form of extracutaneous sporotrichosis.[2,24] Involvement is of the major joints of the extremities—wrist (Fig. 259.2), elbow, ankle, and knee (Fig. 259.3); the hip, shoulder, and spine are not involved.[25] Most patients present with involvement of a single joint without previously having had sporotrichosis at any other site. The joint is swollen and painful on motion, an effusion is present, and a sinus tract may develop. The overlying skin may or may not be erythematous. Systemic symptoms are minimal and, other than elevation of the erythrocyte sedimentation rate, laboratory examinations are unrevealing. Untreated, other joints may become involved. Tenosynovitis associated with carpal tunnel syndrome or nerve entrapment has been reported.[26] The radiologic changes of osteomyelitis develop slowly and include loss of articular cartilage, periosteal reaction, and periarticular osteopenia and cystic changes. Failure to consider the diagnosis has resulted in an average 25-month delay before diagnosis.[27] Repeated culture of fluid from joint aspiration, as well as culture and microscopic examination of tissue from synovial biopsies, is often required to make the diagnosis. Differential considerations include pigmented villonodular synovitis, tuberculosis, gout, osteoarthritis, and rheumatoid arthritis.

TABLE 259.1 Differential Diagnosis of Sporotrichoid Lesions

Lesions Resembling Lymphocutaneous Sporotrichosis
(papulonodular lesions with or without central ulceration and with one or more nodules in the proximal skin along paths of presumed lymphatic spread)

- Nocardiosis due to *Nocardia brasiliensis*
- Cutaneous leishmaniasis
- Mycobacterial infection due to:
  - *M. tuberculosis* (tuberculosis cutis verrucosa)
  - *M. marinum*
  - *M. chelonae*
  - *M. kansasii*
  - *M. fortuitum*
- Infections that may rarely resemble lymphocutaneous sporotrichosis:
  - *Mycobacterium leprae*
  - Cowpox
  - *Staphylococcus aureus*
  - *Streptococcus pyogenes*
  - *Francisella tularensis*
  - *Scedosporium apiospermum*
  - *Fusarium* species

Lesions Resembling Plaque Sporotrichosis
(chronic, indurated hyperkeratotic plaques)

- Infections—as for lymphocutaneous disease and also:
  - Blastomycosis
  - Paracoccidioidomycosis
  - Chromoblastomycosis
  - Lobomycosis
- Neoplasms
  - Squamous carcinoma
  - Basal cell carcinoma
  - Mycosis fungoides
- Other
  - Psoriasis
  - Lupus vulgaris
  - Pyoderma gangrenosum

Modified from Kostman JR, DiNubile MJ. Nodular lymphangitis: a distinctive but often unrecognized syndrome. Ann Intern Med. *1993;118:883–888; and Smego RA Jr, Castiglia M, Asperilla MO. Lymphocutaneous syndrome—a review of non-sporothrix causes.* Medicine. *1999;78:38–63.*

Pulmonary sporotrichosis is well described and may present with multifocal noncavitary disease as part of the syndrome of multifocal extracutaneous infection (see later) or primary cavitary disease following fungal inhalation.[28,29] The typical patient with primary cavitary disease is a 30- to 60-year-old-male. Approximately one-third of the patients are alcoholic; one-third have a concomitant medical illness such as pulmonary tuberculosis, diabetes mellitus, sarcoidosis, and steroid use; and one-third are apparently normal. Patients are occasionally asymptomatic but will usually have a productive cough, low-grade fever, or weight loss. Other than elevation of the erythrocyte sedimentation rate, laboratory abnormalities are minimal. The chest radiograph reveals unilateral or bilateral cavitary lesions, usually with an associated parenchymal infiltrate

FIG. 259.3 Sporotrichosis of the knee with formation of a Baker cyst. *(From Kwon-Chung KJ, Bennett J.* Medical Mycology. *Philadelphia: Lee & Febiger; 1992:712.)*

FIG. 259.4 Chest roentgenogram demonstrating extensive bilateral cavitation due to sporotrichosis.

(Fig. 259.4). Pleural effusions and hilar lymphadenopathy are occasionally noted. Gram stain or cytologic examination of sputum or bronchial washings will sometimes reveal elongated budding yeast,[30] and sputum culture will usually yield the organism. With some patients, however, repeated cultures and long-term follow-up are necessary in order to make the diagnosis.[31] Untreated, the cavities of pulmonary sporotrichosis gradually enlarge and produce progressive pulmonary dysfunction. A single case of spontaneous resolution of noncavitary infection has been reported.[32] The differential diagnosis includes mycobacterial infections (due to both *Mycobacterium tuberculosis* and other mycobacteria), histoplasmosis, and coccidioidomycosis.

FIG. 259.5 Hematogenously disseminated skin lesions scattered over the skin of a previously normal male farmer who also had joint lesions.

An indolent meningitis due to *S. schenckii* has been described, with skin lesions or other extra–central nervous system foci noted in about half of cases.[33–36] Cerebrospinal fluid (CSF) analysis demonstrates a lymphocytic pleocytosis, an elevated protein, and hypoglycorrhachia. Cultures of the CSF are positive, although repeated cultures of large volumes of CSF or serologic studies may be required to make the diagnosis. Infections of a variety of other sites have been reported but are uncommon. Involvement of the ocular adnexa, sometimes with spread to the eye, has been described.[20,37] Endophthalmitis may even occur without prior trauma or other evidence of sporotrichosis.[38] Cases of isolated involvement of the sinuses, kidney, testes, and epididymis have also been reported.[24,39]

Multifocal Extracutaneous Sporotrichosis

In otherwise normal patients with extracutaneous sporotrichosis, the lesions are generally restricted to a single site and are only locally progressive. Occasionally a patient with osteoarticular sporotrichosis will have involvement of several joints, but the presentation is otherwise identical to that in patients with involvement of only a single joint. A much smaller group of patients, on the other hand, present with weight loss or variable low-grade fever and often have several widely scattered cutaneous lesions without necessarily showing a single primary distal extremity lesion with the pattern of lymphangitic spread (Fig. 259.5). Mild anemia, leukocytosis, and elevation of the erythrocyte sedimentation rate may be present. Osteolytic bone lesions and arthritis are common, and spread to the palate, eyes, and central nervous system may develop.[24,40] Noncavitary lung lesions may also be seen.[41] Untreated infection is ultimately fatal. Patients with this form of sporotrichosis almost always have some form of immunosuppression, commonly hematologic malignancy,[24,40] or human immunodeficiency virus (HIV) infection (see later). Cultures of skin lesions and joints are usually positive, whereas blood and bone marrow cultures are occasionally positive. Immunosuppressed patients with what appears to be simple cutaneous sporotrichosis should be examined for other sites of infection, and a technetium pyrophosphate bone scan or positron

emission tomography/computed tomography (PET/CT) should be performed.[41a]

CLINICAL MANIFESTATIONS OF SPOROTRICHOSIS IN THE HIV-INFECTED PATIENT

Infection with HIV predisposes to invasive, atypical, or disseminated manifestations of sporotrichosis. When $CD4^+$ counts are relatively well preserved, localized infection may follow direct cutaneous inoculation in a pattern analogous to that in immunocompetent patients.[42] However, widespread lymphocutaneous sporotrichosis or multifocal extracutaneous disease may be seen in patients with more advanced HIV infection. In a review of patients with acquired immunodeficiency syndrome (AIDS) with disseminated sporotrichosis,[43] almost all had fewer than 100 $CD4^+$ T cells/μL. Multiple ulcerative skin lesions are usually present. Sporotrichosis may also present as multifocal tenosynovitis and arthritis with or without overt cutaneous disease or systemic dissemination and thus may resemble disseminated gonococcal infection or the seronegative spondyloarthropathies such as reactive arthritis or psoriatic arthritis (Fig. 259.6), which are seen with a higher frequency in the setting of AIDS.[44] Widespread visceral dissemination also occurs, as evidenced by reports of meningitis with parenchymal brain lesions[35,36]; lung abscess, liver, and spleen involvement[45]; endophthalmitis[46]; and fungemia with spread to esophagus, colon, testes, bone marrow, and lymph nodes.[46] Dissemination may manifest as part of the immune reconstitution inflammatory syndrome.[47] Sinusitis with invasion of the contiguous bone and soft tissues has also been described,[48] and emphasizes the potential for the respiratory tract as the initial focus of infection in HIV-infected patients.

DIAGNOSIS

Diagnosis is best made by culture of the affected site, though repeated attempts at culture may have to be made. A positive culture from any site is ordinarily diagnostic of infection, although a case of saprophytic involvement of the respiratory tract has been described.[49] A positive blood culture strongly suggests the multifocal form of sporotrichosis seen in immunocompromised hosts, and the lysis-centrifugation system may be more sensitive in detecting fungemia in nonimmunocompromised patients.[50] Serodiagnosis has been described[51] but has often been complicated by the presence of antibodies in individuals without evidence of sporotrichosis[52] and by cross-reactivity with other fungi.[2] Molecular diagnostic techniques such as polymerase chain reaction have also been described.[53]

Examination of biopsy specimens reveals a pyogranulomatous response and is diagnostic if characteristic 1- to 3-μm × 3- to 10-μm cigar-shaped yeast forms are seen. Unfortunately, the yeast may be difficult to detect unless multiple sections are examined,[23] although lesions from immunocompromised hosts may contain numerous yeasts (Fig. 259.7). In addition, *S. schenckii* often assumes a more rounded tissue form, making the biopsy suggestive but not diagnostic. The organisms may be surrounded by a stellate, periodic acid–Schiff-positive, eosinophilic material known as an *asteroid body.* In the brain or eye, a capsule has sometimes been demonstrable around the yeastlike cells.

As with other immunosuppressed patients, individuals with advanced AIDS may have a high fungal load that results in positive smears and cultures.[30] Skin biopsy may reveal fungal elements with a limited inflammatory response, and this should prompt the clinician to initiate a search for a systemic immunodeficiency.[54]

THERAPY

Treatment guidelines for sporotrichosis have been proposed.[55] Due to its convenience and consistent efficacy,[56] itraconazole at 100 to 200 mg/day (or 65 mg to 130 mg/day if using the enhanced bioavailability SUBA-itraconazole formulation; see Chapter 40B) has become the therapy of choice for cutaneous sporotrichosis.[55] Therapy with itraconazole is given for 2 to 4 weeks beyond complete resolution of all lesions and usually requires 3 to 6 months to effect a clinical cure. Relapse has been observed on occasion after cessation of therapy. Should relapse develop, a higher dose of itraconazole (200 mg twice daily), or terbinafine or iodide, may be tried. Terbinafine has been effective in adults at doses of 250 to 1000 mg/day for 12 to 24 weeks,[37,57] but direct comparative data do not exist and the limited data suggest more frequent and more durable cures with higher doses. Further, the maximum US Food and Drug Administration–approved terbinafine regimen is 250 mg daily for 12 weeks; the safety of extended higher-dose therapy has not yet been extensively validated. Iodides are an effective and inexpensive but poorly tolerated therapy for cutaneous sporotrichosis[58] and have been effective in cases of therapeutic failure of itraconazole.[59] Iodide therapy is prescribed as a saturated solution of potassium iodide (SSKI), with therapy begun at 5 to 10 drops taken orally three times per day. The dose is gradually advanced to 25 to 40 drops three times daily (for children) or 40 to 50 drops three times daily (for adults). SSKI has a bitter taste and is made more palatable by taking it in milk, juice, or a carbonated beverage. Side effects include nausea, anorexia, diarrhea, parotid or lacrimal gland enlargement, and an acneiform rash. These side effects will remit with reduction of the dose of SSKI or temporary

FIG. 259.6 Extensive multifocal sporotrichosis with tenosynovitis of the toes, arthritis of the ankles, and associated lymphedema in a patient with advanced acquired immunodeficiency syndrome. This patient also had tenosynovitis of the wrists and hands along with arthritis of the wrists and knees.

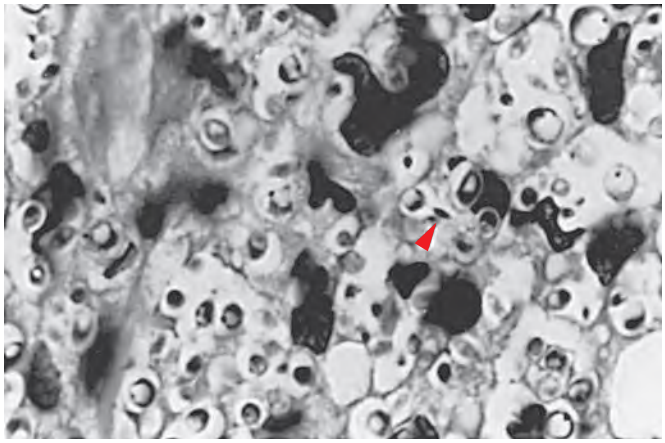

FIG. 259.7 Numerous yeasts of sporotrichosis in a cutaneous lesion from an immunosuppressed patient. In the normal host, organisms are usually difficult to locate. Although a single cigar-shaped form is present *(arrowhead),* most of the yeasts have a rounded form that is consistent with, but not diagnostic of, sporotrichosis. *(Courtesy Dr. Ronald Rapini, Houston, TX.)*

cessation of therapy. For both terbinafine and iodide, therapy should be continued until 2 to 4 weeks after the cutaneous lesions have resolved, a process that usually takes 3 to 6 months. Some patients are allergic to iodides, and in others cutaneous disease may respond slowly to iodide therapy or rarely fail to respond at all.

Ketoconazole has not proven to be effective, and amphotericin B is too toxic to be used in this setting. Consistent with its limited in vitro activity, fluconazole has only modest clinical activity and should be used only if other therapies are not tolerated.[60–62] Clinical data with the newer azoles are sparse,[63] and elevated minimum inhibitory concentrations have been reported with both voriconazole and posaconazole.[60–62,64] Due to the temperature sensitivity of this organism, local application of heat is a useful adjunct therapy and on occasion has been curative.[65] Given the toxicity of both the azoles and the iodides in pregnant women (skeletal bone deformities and goiter, respectively),[66] use of heat may be especially valuable during pregnancy.[55,67]

Therapy of extracutaneous sporotrichosis is often difficult. Osteoarticular sporotrichosis has been treated with intravenous amphotericin B (a lipid-associated preparation is recommended due to the improved safety profile of these formulations),[55] but itraconazole at 200 mg twice daily for at least 1 year is the preferred approach. Ketoconazole (400–800 mg/day) and fluconazole (200–400 mg/day) appear less efficacious, and ketoconazole is hepatotoxic.[55,68] As noted previously, very few clinical data are available with the newer azoles (voriconazole and posaconazole), and the echinocandins do not appear consistently active.[2,60,61,69] Intraarticular amphotericin B is sometimes given, although its role has not been clearly defined. Surgical débridement is often employed, but its utility is also uncertain. SSKI has rarely been reported to be effective but usually is not.

If diagnosed prior to the development of cavities, pulmonary sporotrichosis may be treated with itraconazole, SSKI, or amphotericin B.[28,29] Cure of cavitary disease typically requires pulmonary resection plus a perioperative course of itraconazole or amphotericin B.[55] Treatment failure is often associated with incomplete resection.[4]

Sporothrix schenckii meningitis does not consistently respond to amphotericin B, and the addition of 5-fluorocytosine may be warranted. Limited data suggest that itraconazole might be useful as suppressive or step-down therapy.[55] The number of reported cases of involvement of other specific sites is too limited to permit generalization. Extracutaneous sporotrichosis in the immunocompromised host usually responds at least partially to either amphotericin B or itraconazole, although relapse is common.

Therapy of Patients With Acquired Immunodeficiency Syndrome

Therapy of sporotrichosis in AIDS should be tailored to the presenting syndrome. Itraconazole appears to be the drug of choice, and individuals with limited cutaneous disease can be treated with 200 mg twice daily. Amphotericin B should be used as initial therapy of disseminated disease, with lipid-associated formulations preferred over amphotericin B deoxycholate.[55] Based on the observation of frequent relapse and dissemination, chronic suppressive therapy with itraconazole appears warranted following initial control of infection. Although unsupported by direct data, it is appears reasonable to discontinue therapy in individuals who have been treated for itraconazole for at least 1 year and whose $CD4^+$ cell counts have been about 200 cells/μL for at least a year.[55]

Both anecdotal and published experience suggest that multifocal extracutaneous disease in HIV-infected patients may respond poorly, if at all, to current therapies.[70,71] Therapy should be initiated with amphotericin B followed by lifetime suppression with itraconazole. Progression may occur despite amphotericin therapy. Because disseminated disease has been reported to develop despite ongoing fluconazole being given for other indications,[72] fluconazole is not a first-line choice. As has been demonstrated for other opportunistic pathogens, the use of highly active antiretroviral therapies may also assist in clearing the infection.[73]

Itraconazole Blood Level Monitoring

When itraconazole is used for noncutaneous infection or in HIV-infected subjects, confirmation of adequate blood levels is recommended (see Chapter 40B). In HIV in particular, levels may be reduced by achlorhydria, malabsorption, or diarrhea due to other opportunistic pathogens. As for other fungal infections, target levels of the parent (unmetabolized) itraconazole molecule of at least 500 ng/mL by high-performance liquid chromatography generally appear adequate. The increased bioavailability of itraconazole cyclodextrin suspension is helpful in achieving such blood levels.

PROGNOSIS

Cutaneous sporotrichosis responds well to therapy and has an excellent prognosis. Osteoarticular sporotrichosis may require prolonged therapy but is not life threatening. Other forms of extracutaneous sporotrichosis can be difficult to treat and may have substantial morbidity and mortality.

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260 Agents of Chromoblastomycosis

Duane R. Hospenthal

SHORT VIEW SUMMARY

Definition
- Chromoblastomycosis (chromomycosis) is a chronic fungal infection limited to the skin and subcutaneous tissue.
- It produces scaly nodular, tumorous, verrucous, plaque or cicatricial lesions, typically affecting the lower extremities.
- It is defined by the microscopic presence of muriform cells.

Epidemiology
- Chromoblastomycosis has a worldwide distribution, with most cases occurring in tropical and subtropical regions.
- The largest numbers of cases are reported from Madagascar, Brazil, Mexico, Venezuela, and Costa Rica.
- The disease has a male predominance and is more prevalent in those aged 40 to 69. It is commonly associated with outdoor activities such as farming or woodcutting and with absence of footwear.

Microbiology
- Infection is most commonly caused by species of *Fonsecaea (F. pedrosoi, F. monophora, F. nubica)* or *Cladophialophora (C. carrionii).*
- Less commonly it is caused by *Exophiala, Phialophora,* or *Rhinocladiella* species.
- Other dark-walled fungi are rarely reported as causative agents.

Diagnosis
- The presence of muriform cells (also called sclerotic, "copper penny," or Medlar bodies) is pathognomonic.
- Muriform cells are observed microscopically in skin scrapings prepared with potassium hydroxide or in routinely stained skin biopsy specimens.
- Culture on standard mycologic media is possible but not always necessary.

Therapy
- No proven treatment has been identified.
- Small lesions may be treated successfully with surgical excision, liquid nitrogen or topical heat application, or photocoagulation. Use of curettage and electrocautery is discouraged because of reports of disease spread after their use.
- Oral itraconazole 200 to 400 mg daily or terbinafine 250 to 500 mg daily in combination with local liquid nitrogen is the most effective therapy.
- Posaconazole has been used successfully in a small number of patients with disease that is refractory to itraconazole or terbinafine.

Prevention
- No vaccine is available.
- The need for footwear and proper protective clothing should be stressed.

Chromoblastomycosis (chromomycosis) is a chronic, localized fungal infection of the skin and subcutaneous tissue that produces raised scaly lesions, usually of the lower extremities. The lesions of chromoblastomycosis are frequently warty or cauliflower-like in appearance, with pathognomonic muriform cells (also called "copper penny" or sclerotic bodies) found at histologic examination. This disease of tropical and subtropical distribution is produced by inoculation of the infecting fungi in association with minor trauma. Alexandrino Pedroso, for whom the major etiologic agent is named, first noted the disease in 1911, although the first publication to describe what was likely chromoblastomycosis appeared in 1914, authored by Max Rudolph.[1,2] The first reports to include identification of the fungal cause of this disease were published 1 year later by Medlar and Lane, who described a patient with disease acquired not in the tropics but in the United States.

ETIOLOGIC AGENTS

Infection is caused by one of several dark-walled (dematiaceous) fungi found in the soil and in association with cacti, thorny plants, and other live or decaying vegetation. *Fonsecaea pedrosoi* is the most common cause of chromoblastomycosis. Other *Fonsecaea* species (*F. monophora* and *F. nubica*) and *Cladophialophora carrionii* are also common etiologic agents. *Phialophora verrucosa* and *Rhinocladiella aquaspersa* are less commonly reported. In the largest reports from Brazil,[3] Mexico,[4] Sri Lanka,[5] India,[6] and Japan,[7] *F. pedrosoi* has been responsible for 66% to 96% of all infections. With the more recent recognition of *F. monophora* and *F. nubica* as new species, identification of these organisms as the cause of both new cases and old cases (with reidentification of isolates previously identified as *F. pedrosoi*) of chromoblastomycosis continues to increase.[8–12] *Fonsecaea compacta* is currently believed to be a variant of *F. pedrosoi* and not a distinct species. Rare or isolated reports of disease caused by *Botryomyces caespitosus, Chaetomium funicola, Cladophialophora arxii, Cladophialophora boppii, Cyphellophora ludoviensis, Exophiala (Wangiella) dermatitidis, Exophiala jeanselmei, Exophiala spinifera, Fonsecaea pugnacius, Phaeosclera dermatioides, Rhinocladiella phaeophora, Rhinocladiella similis, Rhinocladiella tropicalis,* and *Rhytidhysteron* species have been published.[1,2,13–19]

EPIDEMIOLOGY

Chromoblastomycosis has been described to occur throughout the world, although most cases arise in tropical and subtropical regions, especially those with high annual rainfall. Large numbers of cases have been described from Madagascar, Brazil, Mexico, Venezuela, and Costa Rica. Disease is more prevalent in males (4:1 ratio), in those aged 40 to 69,[3] in association with outdoor activities such as farming and woodcutting, and in the absence of footwear. In Madagascar, a unique epidemiology has been described in what is probably the largest focus of endemic disease.[20] Madagascar has two distinct foci of infection, with disease secondary to *F. pedrosoi* occurring in the humid, rainy, northern evergreen forest region and disease secondary to *C. carrionii* found in the arid southern desert region. In a study of 1343 cases of disease over 40 years in that country, the prevalence of 1 case per 1920 inhabitants in the southern desert region has been described, with an incredible 1 in 910 prevalence in a single district of that region.

PATHOLOGY AND PATHOGENESIS

Traumatic inoculation of these fungi results in a mixed chronic suppurative and granulomatous host response.[21] The epidermis typically becomes thickened in a process called pseudoepitheliomatous hyperplasia,

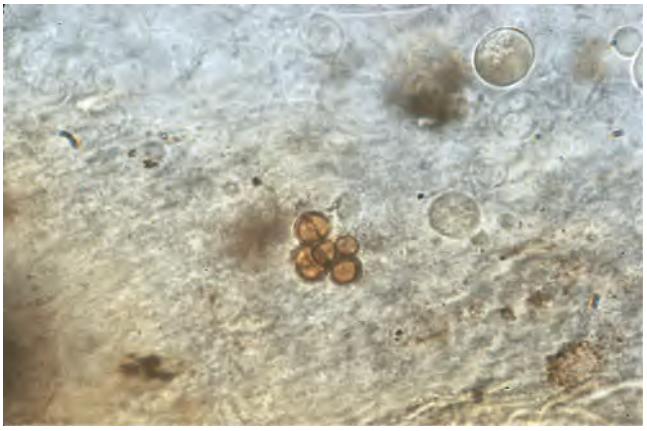

FIG. 260.1 Sclerotic bodies of chromoblastomycosis. *(From Beneke ES, Rogers AL.* Medical Mycology and Human Mycoses. *Belmont, CA: Star Publishing; 1996.)*

FIG. 260.2 Chromoblastomycosis of the foot. *(From Beneke ES, Rogers AL.* Medical Mycology and Human Mycoses. *Belmont, CA: Star Publishing; 1996.)*

a histologic morphologic appearance that may be misidentified as malignancy by more inexperienced microscopists. Foci of polymorphonuclear cells and microabscesses are seen in both the epidermis and dermis. In the dermis, granulomas that include multinucleated giant cells and epithelioid cells are present, along with varying amounts of fibrosis. Fibrosis is increased in older lesions and can extend into the subcutaneous tissue, although disease rarely extends deep into the subcutaneous tissue. The hallmark of chromoblastomycosis, the muriform cells—also called sclerotic, copper penny, or Medlar bodies—may be found intracellularly in macrophages or extracellularly in abscesses. These are darkly pigmented (brown-golden), thick-walled, rounded cells, 4 to 12 µm in diameter, with cross walls in one or two planes (Fig. 260.1). Hyphae may also occasionally be seen, usually in the epidermis. The host response to these structures results in a process termed *transepithelial elimination,* in which fungi and damaged tissue are expelled through the epidermis, a process similar to that seen in calcinosis cutis.[22] The immunologic response of the host in this mycosis is still not well understood. Disease appears to be associated with an ineffective immune response to the organism, with chronic inflammation produced in response to persistence of the fungi in tissue. The cell-mediated immune response appears to play a central role. High interleukin-10 (IL-10) levels, low interferon-γ levels, and inefficient T-cell proliferation have been noted in patients with severe disease, with the opposite seen in those with milder chromoblastomycosis.[23] This ineffective response has been linked to lack of recognition of these fungi by Toll-like receptors (TLRs) in a murine model.[24] Antibody responses have shown association with disease chronicity and extent but do not appear to provide any degree of protection in this infection.[25]

CLINICAL MANIFESTATIONS

Weeks to months after inoculation of the causative organisms through minor trauma, subjects typically develop a small scaly papule on the lower extremity at the site of the trauma (Figs. 260.2–260.4). This lesion slowly develops into a superficial nodule, commonly with an irregular friable surface. Frequently, these nodules later spread out to become purplish, irregular, raised plaques. In descriptions by Carrion,[26] lesions of chromoblastomycosis were categorized into five types: (1) early nodular lesions, described as soft and pink-violaceous, with smooth, verrucous, or scaly surfaces; (2) tumorous lesions—large, papillomatous, often lobulated masses with crusting, sometimes described as cauliflower-like; (3) verrucous lesions with prominent hyperkeratosis; (4) plaque lesions; and (5) cicatricial lesions. Most lesions have black dots associated with their outer surface that are composed of fungi and necrotic debris, the products of transepithelial elimination. Although not typically painful, lesions may be associated with pruritus, are easily traumatized, and bleed readily. Ulceration is generally limited to those lesions with bacterial superinfection. Large lesions may become hyperkeratotic, and limb distortion, including elephantiasis, can occur as a result of blockage of normal lymphatic drainage.

FIG. 260.3 Chromoblastomycosis with multiple verrucous nodules. *(From McGinnis MR, Chandler FW. Chromoblastomycosis. In: Connor DH, Chandler FW, Schwartz DA, et al, eds.* Pathology of Infectious Diseases. *Norwalk, CT: Appleton & Lange; 1997.)*

FIG. 260.4 Chromoblastomycosis of the lower leg with lobulated, confluent nodules with focal ulcerations. *(From McGinnis MR, Chandler FW. Chromoblastomycosis. In: Connor DH, Chandler FW, Schwartz DA, et al, eds.* Pathology of Infectious Diseases. *Norwalk, CT: Appleton & Lange; 1997.)*

Although lesions have been described to occur chiefly on the lower extremities (80%–85%) in most regions of the world,[3,27] an exception to this pattern is reported from Japan. Evaluation of 290 lesions from that country found that chromoblastomycosis occurs most commonly on the upper extremities of male subjects and on the face or neck of females.[7]

Persistence of the lesions of chromoblastomycosis for 30 years has been reported, and delays in diagnosis of 1 to 3 years are not unusual. Although most lesions remain localized without spread to deeper structures, localized dissemination may occur via autoinoculation or via the lymphatics. Hematogenous spread has only rarely been described but does include reports of dissemination to the central nervous system.[7] The occurrence of secondary bacterial infection has been reported to affect as many as 63% of persons with chromoblastomycosis.[4] Although apparently rare, at least 14 cases of squamous cell carcinomas and 1 case of melanoma have been reported; all occurred after 8 or more years of disease.[28,29]

The differential diagnosis of chromoblastomycosis includes psoriasis, other mycoses (e.g., blastomycosis, coccidioidomycosis, lobomycosis, mycetoma, paracoccidioidomycosis, cutaneous phaeohyphomycosis, sporotrichosis, tinea), cutaneous tuberculosis, leprosy, leishmaniasis, protothecosis, keratoacanthoma, squamous cell carcinoma, and sarcoidosis.

DIAGNOSIS

Chromoblastomycosis should be suspected in persons with chronic scaly or friable lesions of the extremities, especially in rural tropical climates. Microscopic examination of skin scrapings can provide a rapid diagnosis of chromoblastomycosis because the characteristic muriform cells can be seen in potassium hydroxide preparations, especially those containing black dots (see Fig. 260.1). These unique structures may also be readily observed with standard staining of skin punch biopsy specimens with hematoxylin and eosin (Fig. 260.5). Although not absolutely necessary, culture can be performed to identify the specific cause of infection. Standard mycologic media (Sabouraud glucose agar), with and without cycloheximide, should be used and cultures incubated for at least 4 weeks. In culture, the fungal agents of chromoblastomycosis appear as dark molds. Under standard culture conditions, these fungi may be identified by the microscopic appearance of hyphae and reproductive structures. The muriform structures seen in tissue have been produced in vitro with low pH and the addition of propranolol, but this is not necessary for clinical diagnosis.[30] Exoantigen testing of the fungus has been developed to aid in identification, although this is not commonly used.[31] Serologic and skin tests have also been developed, but their use in this rare disease is limited to specialized centers in more endemic regions of the world.

THERAPY

Although spontaneous resolution has been reported,[32] this is only a rare occurrence, and most chromoblastomycosis is a chronic indolent infection. When caused by its most common agent, *F. pedrosoi,* it is difficult to eradicate, even with prolonged therapy. Multiple modalities have been used to treat patients with chromoblastomycosis, including surgery, local (physical) treatments, and antifungal agents.[33] Unfortunately, no single reproducibly successful treatment strategy has been identified. Surgical removal of small lesions appears to be effective, as does local application of liquid nitrogen, topical heat, and photocoagulation. Local curettage or electrocautery has been reported sometimes to result in disease spread and is to be discouraged. Heat therapy (42°C–46°C) with pocket warmers and other devices providing prolonged daily warmth directly to the lesions has been described as effective with 2 to 12 months of treatment.[34] Cryotherapy with liquid nitrogen sprays or applied with soaked cotton swabs or balls has been successful in the cure of small early lesions and may be used effectively in combination with antifungal medications on larger lesions. Topical imiquimod has been used successfully in four cases of disease secondary to *F. pedrosoi.*[35] The use of topical ajoene (a garlic extract) and 5-fluorouracil has been reported to be effective against disease secondary to *C. carrionii.*[36]

Currently, the best therapy appears to be itraconazole or terbinafine, perhaps with adjunctive cryotherapy with liquid nitrogen or other local treatments.[37,38] Other antifungal agents, including amphotericin B (intravenous or intralesional), 5-fluorocytosine, ketoconazole, and fluconazole, have been used with poor to mixed success, alone or in combination.

Itraconazole has been reported to be effective in many patients in uncontrolled, nonrandomized studies. Early study with lower doses (100 to 200 mg daily) of itraconazole documented high response rates with this azole antifungal agent, but the numbers of cures were small (3 of 10 patients treated for 12 to 24 months).[39] Treatment of chromoblastomycosis caused by *C. carrionii* with itraconazole has met with much greater success than treatment of that caused by other agents. One study reported cure in 2 of 5 patients with disease secondary to *F. pedrosoi* and 8 of 9 patients with *C. carrionii,* all given 100 to 400 mg of the drug daily for 4 to 8 months.[40] Queiroz-Telles and colleagues have reported the cure of 42% of patients (8 of 19) treated with 200 to 400 mg of itraconazole for a median of 7 months.[41] Another group described the therapy for 10 patients with disease secondary to *F. pedrosoi,* 4 of whom had experienced failure of prior therapy with ketoconazole.[42] All patients received 200 to 400 mg of itraconazole daily, and 8 also received monthly cryotherapy with liquid nitrogen. Nine patients were cured with 3 to 12 months of therapy; 2 of these responded with sustained cures after only 3 months of itraconazole at the lower dose of 200 mg daily. The remaining patient had marked improvement without cure. Recurrence was noted in a single patient who had been cured with a 6-month course of itraconazole (400 mg daily) and cryotherapy. Decreased in vitro susceptibility to itraconazole has been reported in one study of sequential clinical isolates of *F. pedrosoi,* potentially accounting for treatment failures.[43] Bonifaz and associates described good success with smaller lesions treated with itraconazole or cryosurgery and in larger lesions treated with itraconazole followed by cryosurgery.[44] In that study, which included 4 patients in each group and dosage of itraconazole at 100 mg three times daily for 5 to 14 months, 8 of 12 patients (67%) were cured and the remaining 4 showed improvement. In addition to daily therapy, success with itraconazole given as pulse therapy, 400 mg daily for 7 days/month for 6 to 12 months, has also been reported.[45] If the better-absorbed SUBA-itraconazole forumation is used, 65-mg capsules would be equivalent to 100-mg capsules of the older formulation.

The allylamine antifungal agent terbinafine has produced excellent results in the treatment of chromoblastomycosis. In the largest study to date, terbinafine, 500 mg daily, was given to 35 patients for up to 12 months.[46] In that study, 16 patients had experienced failure of thiabendazole in the past and almost half had lesions of longer than 10 years' duration. Improvement, defined as lack of bacterial superinfection and resolution of edema, was seen after 2 to 4 months of therapy and, after 12 months, 86% obtained mycologic cures (72% with clinical cures).[27] Patients with *C. carrionii* infections were noted to respond more quickly than those with *F. pedrosoi* infection in that study. Unexpectedly, partial reversal of fibrosis of the lesions of chromoblastomycosis has also been reported to occur with terbinafine therapy. This reversal has been suggested to be independent of mycologic cure of infection in those receiving terbinafine.[47,48] Terbinafine used in alternate-week or

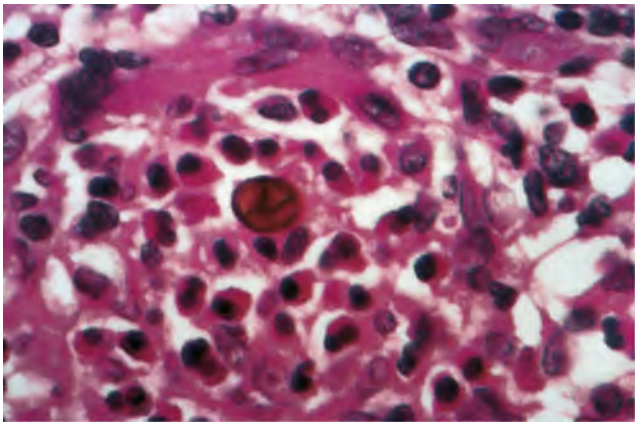

FIG. 260.5 Dermal abscess with quadrate cluster of organisms in a mixture of neutrophils, macrophages, eosinophils, and a giant cell (hematoxylin and eosin). *(From McGinnis MR, Chandler FW. Chromoblastomycosis. In: Connor DH, Chandler FW, Schwartz DA, et al, eds.* Pathology of Infectious Diseases. *Norwalk, CT: Appleton & Lange; 1997.)*

combination therapy with itraconazole to treat 4 patients with resistant infections successfully has also been reported.[49]

The newer broad-spectrum azole antifungal agents may potentially be useful in this disease. In vitro testing has shown that the minimum inhibitory concentrations of voriconazole for *F. pedrosoi* and *F. compacta* are lower than those seen with itraconazole.[50] *F. pedrosoi* has also been shown to be susceptible to the echinocandin caspofungin in one small in vitro study.[51] Posaconazole (800 mg/day of the suspension in divided doses for 6 to 12 months) has been used to successfully treat a small number of patients (five of six) with disease refractory to itraconazole and terbinafine.[52]

No vaccinations exist to prevent chromoblastomycosis. Proper protective clothing, especially footwear, and early treatment of the lesions are the only available preventive measures against this disease.

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The complete reference list is available online at Expert Consult.

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261 Agents of Mycetoma

Duane R. Hospenthal

SHORT VIEW SUMMARY

Definition

- Mycetoma is an infection of the skin and subcutaneous tissue characterized by a triad of localized swelling, draining sinuses, and grains (aggregates of infecting organisms). Unlike actinomycosis, which also forms grains in lesions, mycetoma enters the body through the skin.
- It most commonly affects a single site, typically involving the lower extremity and especially the foot.
- Eumycetoma (eumycotic mycetoma) is mycetoma caused by fungi, most commonly *Madurella mycetomatis.*
- Actinomycetoma (actinomycotic mycetoma) is mycetoma caused by bacteria, most commonly *Nocardia brasiliensis.*

Epidemiology

- Distribution is worldwide, with most cases occurring in tropical and subtropical regions.
- Largest numbers of cases are reported from Africa, Latin America, and the Indian subcontinent.
- Mycetoma occurs predominantly in men, ages 20 to 40, typically with occupations that expose them to the environment.

Microbiology

- *Madurella* spp., *M. mycetomatis, Trematosphaeria grisea,* and *Scedosporium apiospermum* complex are the most common causes of eumycetoma, although *Falciformispora senegalensis, Falciformispora tompkinsii, Exophiala jeanselmei,* and many other genera and species of fungi have been reported as etiologic agents.
- *Nocardia brasiliensis, Actinomadura madurae, Streptomyces somaliensis,* and *Actinomadura pelletieri* are the most common causes of actinomycetoma, although disease secondary to other species of *Actinomadura, Nocardia,* and *Streptomyces* has been described.

Diagnosis

- Clinical presentation of the classic triad of chronic, painless soft tissue swelling with draining sinuses that discharge grains is pathognomonic.
- Microscopic examination of the grains can differentiate between eumycetoma and actinomycetoma.
- Culture of causative agent from grains can better direct selection of antimicrobial therapy.
- Radiographic techniques (plain radiographs, ultrasound, computed tomography, and magnetic resonance imaging) can be used adjunctively in making (or excluding) the diagnosis and determining its extent.

Therapy

- Small lesions may be treated successfully with surgical excision alone.
- Actinomycetoma is typically treated with medical therapy alone.
- Eumycetoma commonly requires combined medical and surgical therapy, but results are poor.
- No single therapy has proved most effective for either form of mycetoma.
- Most actinomycetoma regimens include parenteral aminoglycosides and oral sulfa drugs.
- Less severe actinomycetoma may be treated with 6 to 24 months of trimethoprim-sulfamethoxazole.
- Eumycetoma is typically treated with a regimen of an oral azole antifungal drug for 6 to 24 months, perhaps combined with debulking surgery.

Prevention

- No vaccine is available.
- Use of footwear and proper protective clothing should protect against this infection.

Mycetoma is a chronic progressive granulomatous infection of the skin and subcutaneous tissue most often affecting the lower extremities, typically a single foot. The disease is unique from other cutaneous or subcutaneous diseases in its triad of localized swelling, underlying sinus tracts, and production of grains or granules (composed of aggregations of the causative organism) within the sinus tracts. These infections may be caused by fungi and termed *eumycotic mycetoma* or *eumycetoma*, or by filamentous higher bacteria and termed *actinomycotic mycetoma* or *actinomycetoma.* The term *mycetoma* can also be found in the literature incorrectly referring to a fungus ball found in a preexisting cavity in the lung or within a paranasal sinus, most often caused by *Aspergillus* spp. Grain formation by infecting organisms is restricted to the diseases mycetoma, actinomycosis (see Chapter 254), and botryomycosis. Actinomycosis is a disease produced by the anaerobic and microaerophilic higher bacteria that normally colonize the mouth and gastrointestinal and urogenital tracts. The portal of entry in actinomycosis is from those colonized sites, whereas in mycetoma the portal is the skin and subcutaneous tissue into which the organism was inoculated by minor trauma. Botryomycosis is a chronic bacterial infection of soft tissues in which the causative organism, often *Staphylococcus aureus,* is found in loose clusters among the pus.[1] In a rare form of ringworm called *dermatophyte mycetoma,* there are also loosely compacted clusters of hyphae in subcutaneous pus.[2] In contrast, mycetoma grains are dense clusters of organisms.

ETIOLOGIC AGENTS

The agents of mycetoma are fungi and aerobic filamentous bacteria that have been found on plants and in the soil.[3,4] The predominance of bacterial versus fungal causes of mycetoma varies among geographic locations. Eumycotic (true fungal) disease is caused by a variety of fungal organisms. These can be divided into those that form dark grains and those that form pale or white grains (Table 261.1). Color distinctions are made by observing unstained specimens. Among the fungi causing dark-grained mycetoma, the most common are *Madurella mycetomatis, Falciformispora* (formerly *Leptosphaeria*) *senegalensis,* and *Trematosphaeria grisea.* Other agents include *Corynespora cassicola, Curvularia geniculata, Curvularia lunata, Emarellia grisea, Emarellia paragrisea, Exophiala jeanselmei, Exophiala oligosperma, Falciformispora* (formerly *Leptosphaeria*) *tompkinsii, Madurella fahalii, Madurella pseudomycetomatis, Madurella tropicana, Phialophora verrucosa, Plenodomas avramii, Pseudochaetosphaeronema larense, Rhinocladiella atrovirens, Medicopsis* (formerly *Pyrenochaeta*) *mackinnonii, Biatriospora* spp., *Roussoella* spp., *Rhytidhysteron* spp., and *Medicopsis* (formerly *Pyrenochaeta*) *romeroi. Scedosporium apiospermum* complex species are the most common cause of pale-colored grains. Other fungi in that category include *Fusarium* (formerly *Acremonium*) *falciforme, Sarocladium* (formerly *Acremonium*) *kiliense, Acremonium recifei, Aspergillus flavus, Aspergillus hollandicus, Aspergillus nidulans, Phialophora* (formerly *Cylindrocarpon*) *cyanescens, Cylindrocarpon destructans, Diaporthe phaseolorum, Fusarium solani,*

TABLE 261.1 Typical Morphologic Features of Mycetoma Grains

GRAIN COLOR	CAUSATIVE AGENT
Eumycetoma (Eumycotic Mycetoma)[a]	
Black grains	*Madurella* spp., *Biatriospora* spp., *Trematosphaeria* spp., *Pseudochaetosphaeroma* spp., *Roussoella* spp., *Rhytidhysteron* spp., *Curvularia* spp., *Exophiala* spp., *Falciformispora* spp., *Medicopsis* spp., *Phaeoacremonium* spp., *Phialophora verrucosa*
Pale grains (white to yellow)	*Scedosporium apiospermum* complex, *Aspergillus* spp., *Diaporthe phaseolorum, Fusarium* spp., *Neotestudina rosatii, Pleurostomophora ochracea*
Actinomycetoma (Actinomycotic Mycetoma)[b]	
Pale grains (white to yellow)	*Actinomadura madurae, Nocardia* spp.
Yellow to brown grains	*Streptomyces somaliensis*
Red to pink grains	*Actinomadura pelletieri*

[a]Hyphae of 2- to 5-μm diameter are observed within grain.
[b]Filaments of 0.5- to 1-μm diameter are observed within grain.

Fusarium moniliforme, Fusarium keratoplasticum, Fusarium pseudensiforme, Neotestudina rosatii, Phaeoacremonium spp., *Pleurostomophora ochracea,* and *Polycytella hominis.*[5–13]

Actinomycetoma is caused by members of the order Actinomycetales, most commonly *Nocardia brasiliensis, Actinomadura madurae, Streptomyces somaliensis,* and *Actinomadura pelletieri.* Cases have been reported that were caused by *Actinomadura latina, Nocardia aobensis, Nocardia farcinica, Nocardia harenae, Nocardia otitidiscaviarum* (formerly *N. caviae*), *Nocardia mexicana, Nocardia transvalensis, Nocardia veterana, Nocardia yamanashiensis,* and *Nocardiopsis dassonvillei.*[4,14–18] Actinomycetoma grains are typically white or pale yellow, except those caused by *Actinomadura pelletieri,* which are red to pink.

Some reports use species names that are not currently recognized, leaving in doubt the identification.[19] The modern use of molecular techniques, including polymerase chain reaction, DNA sequencing, and matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF), has both assisted in better identifying and classifying the agents of mycetoma, and made comparisons between current and previous pathogen identification difficult to track.[20–22]

EPIDEMIOLOGY

The oldest description of this disease appears to date back to the ancient Indian Sanskrit text *Atharva Veda,* in which reference is made to *pada valmikam,* translated to mean "anthill foot."[5] More modern descriptions from Madras, India, in the 19th century led to this disease initially being called "madura foot," or *maduromycosis,* a term still used by some today to describe eumycotic mycetoma. Mycetoma is most commonly found in tropical and subtropical climates, with the highest incidence reported from endemic areas in the Indian subcontinent, the Middle East, Africa, and Central and South America. One of the largest current groups of cases is in Sudan. Only scattered reports describe cases originating in the United States, Europe, and Japan. Disease occurs around five times more frequently in males, commonly in the 20- to 40-year-old age range. Disease is more common in agricultural workers and outdoor laborers but is not exclusively seen in rural areas. Disease occurs sporadically throughout most areas of the world, and some postulate that the increased numbers in tropical regions may also result in part from less use of protective clothing, chiefly shoes, in the warmer, poorer endemic regions.

The causative agents of mycetoma vary from region to region and with climate. Worldwide, *M. mycetomatis* is the most common cause of this disease, but *A. madurae, M. mycetomatis,* and *S. somaliensis* are more commonly reported from drier regions, whereas *S. apiospermum* complex spp., *Nocardia* spp., and *A. pelletieri* are more common in those areas with higher annual rainfall. In India, *Nocardia* spp. and *T. grisea* are the most common causes of mycetoma; in the Middle East, *M. mycetomatis* and *S. somaliensis;* in West Africa, *F. senegalensis;* and in East Africa, *M. mycetomatis* and *S. somaliensis.* In Central and South America, *T. grisea* and *Nocardia* spp. are the common causes of mycetoma, and in the United States, *S. apiospermum* complex spp. are the most commonly recovered causative agent.[23]

FIG. 261.1 Mycetoma of the foot. *(From Beneke ES, Rogers AL.* Medical Mycology and Human Mycoses. *Belmont, CA: Star Publishing; 1996.)*

PATHOLOGY AND PATHOGENESIS

Infection follows inoculation of organisms, frequently through thorn punctures, wood splinters, or preexisting abrasions or trauma. After inoculation, these normally nonpathogenic organisms grow and survive through the production of grains (also called granules or sclerotia), structures composed of masses of mycelial fungi or bacterial filaments and a matrix component. The matrix material has been shown to be host derived with some pathogens. In eumycetoma, hyphal elements often have thickened cell walls toward the periphery of grains, potentially conferring protection against the host immune system.[24] Grains are seen in histopathology within abscesses containing polymorphonuclear cells. Complement-dependent chemotaxis of polymorphonuclear leukocytes has been shown to be induced by both fungal (*M. mycetomatis* and *S. apiosperumum* complex) and actinomycotic (*S. somaliensis*) antigens in vitro.[25] Cells of the innate immune system attempt to engulf and inactivate these organisms, but in disease they ultimately fail to accomplish this goal. Abscesses containing grains are seen in association with granulomatous inflammation and fibrosis. *Nocardia brasiliensis* has been shown to be resistant to human neutrophil peptides.[26] Three types of immune responses have been described in response to the grains of mycetoma.[27] The type 1 response is seen as neutrophils degranulate and adhere to the grain surface, leading to gradual disintegration of the grain. Type 2 response is characterized by the disappearance of neutrophils and arrival of macrophages to clear grains and neutrophil debris. Type 3 response is marked by the formation of epithelioid granuloma. This host response does not appear to be able to control infection but likely accounts for the partial spontaneous healing that is seen in the disease.

It is not clear whether persons who develop mycetoma have predisposing immune deficits.[4] Disease does not appear to be more common in immunocompromised hosts, and early studies of immune function in persons with mycetoma have not clearly documented a common deficit.[28,29] Recent work examining genes responsible for innate immune functions has identified polymorphisms that appear to predispose people to this infection, which may be linked with neutrophil function.[30] It has been suggested that the greater frequency of disease in men is not completely explained by increased frequency of exposure to soil and plant material. Progesterone has been shown in vitro to inhibit the growth of *M. mycetomatis, M. romeroi,* and *N. brasiliensis.*[31,32] In the study of *N. brasiliensis,* estradiol limited disease produced in animals.[31]

CLINICAL MANIFESTATIONS

More than 75% of persons with mycetoma have a lesion of a lower extremity, most commonly the foot (70%) (Figs. 261.1 and 261.2). Next

FIG. 261.2 Mycetoma of the leg (seen from back of knee). *(Courtesy Dr. Glenn W. Wortmann.)*

FIG. 261.3 Mycetoma of the arm caused by *Madurella mycetomatis.* *(From Chandler FW, Ajello L. Mycetoma. In: Connor DH, Chandler FW, Schwartz DA, et al, eds.* Pathology of Infectious Diseases. *Norwalk, CT: Appleton & Lange; 1997:1035–1044.)*

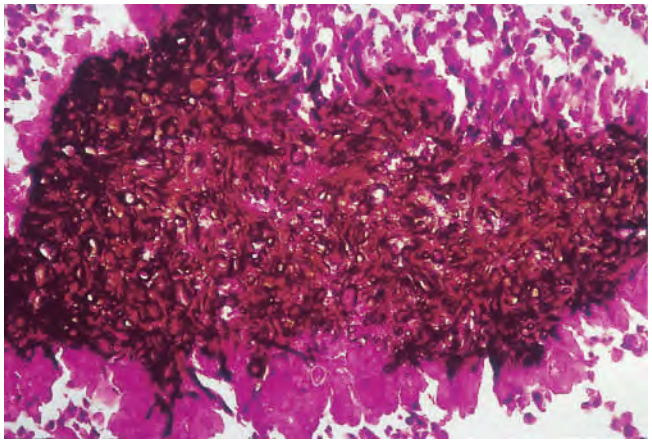

FIG. 261.4 Eumycetoma grain of *Fusarium (Acremonium) falciforme.* (Gomori methenamine silver and hematoxylin and eosin stains.) *(From Chandler FW, Ajello L. Mycetoma. In: Connor DH, Chandler FW, Schwartz DA, et al, eds.* Pathology of Infectious Diseases. *Norwalk, CT: Appleton & Lange; 1997:1035–1044.)*

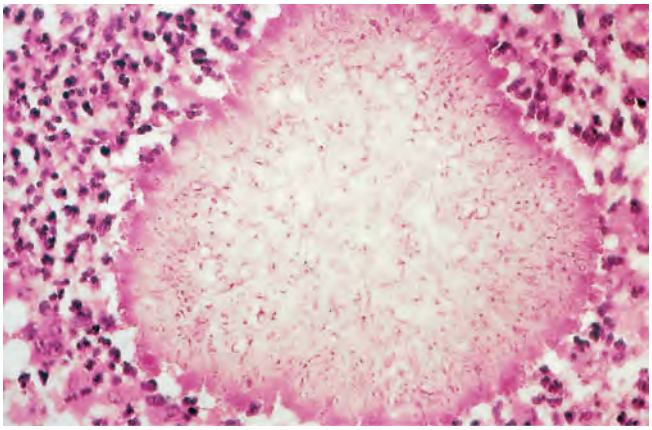

FIG. 261.5 Eumycetoma grain of *Scedosporium apiosperumum–Pseudallescheria boydii* complex. (Hematoxylin and eosin stain.) *(From Chandler FW, Ajello L. Mycetoma. In: Connor DH, Chandler FW, Schwartz DA, et al, eds.* Pathology of Infectious Diseases. *Norwalk, CT: Appleton & Lange; 1997:1035–1044.)*

in frequency is disease of the hand (15%), followed by the upper extremities and other areas of the body that may be exposed by carrying firewood or thorny brush, including the upper back and adjacent neck, top of the head, and, rarely, the face (Fig. 261.3). Lesions in more than one anatomic site are extraordinarily rare. Disease begins in most cases as a single, small, painless subcutaneous nodule. This nodule slowly increases in size, becomes fixed to the underlying tissue, and ultimately develops sinus tracts beneath the lesion. These tracts open to the surface and drain purulent material with grains. Grains are several millimeters in diameter and may be seen by close inspection of a gauze bandage covering the sinus tract. Progression to draining sinus tracts can take weeks, months, and even years, occurring more rapidly in actinomycetoma. In a study of patients in India, the average time to presentation with disease from history of probable inciting trauma was 3 years for *N. brasiliensis,* 7 years for *A. madurae,* and 9 years for *T. grisea.*[33]

Disease can affect the skin, subcutaneous tissue, and eventually contiguous bone, spreading along fascial planes. Overlying skin appears smooth and shiny and is commonly fixed to the underlying tissue. Skin may be hypopigmented or hyperpigmented, with signs of both old healed and active sinuses, displaying the cycle of spontaneous healing of older sinus tracts and simultaneous spread of infection to new areas that is typical of this disease. Swelling is often firm and nontender, and the overlying skin is not erythematous. Muscle, tendons, and nerves are generally spared direct infection, but extensive local damage may lead to muscle wasting, bone destruction, and limb deformities. Lymphatic spread is rare, although it may follow surgical manipulation. Hematogenous spread has not been documented. This disease and its effects are generally localized, and thus no signs or symptoms of systemic illness are usually seen in mycetoma unless secondary bacterial infection occurs. When left untreated, disease continues to progress, and bacterial superinfection can lead to increased morbidity from local abscess formation, cellulitis, bacterial osteomyelitis, and, rarely, septic death.

Differential diagnosis includes botryomycosis, chronic bacterial osteomyelitis, tuberculous osteomyelitis, chromoblastomycosis, phaeohyphomycosis, and soft tissue or bone tumor.

DIAGNOSIS

A diagnosis of mycetoma can be made by the classic triad of painless soft tissue swelling, draining sinus tracts, and extrusion of grains. Diagnosis of the causative organism can be made by microscopic observation and culture of a grain. Deep biopsy with histopathology and culture is usually not necessary, although obtaining a deep tissue biopsy avoids the bacterial contamination of surface cultures. Grains may not be seen in any one histopathologic section because they are scattered along the tracts. When a grain is present in the section, its large size and surrounding cluster of neutrophils make it difficult to miss, even without fungal or bacterial stains (Figs. 261.4 through 261.9). Organisms are usually not seen outside the grain. An alternate diagnostic strategy is the ultrasound-guided needle aspiration of grains directly

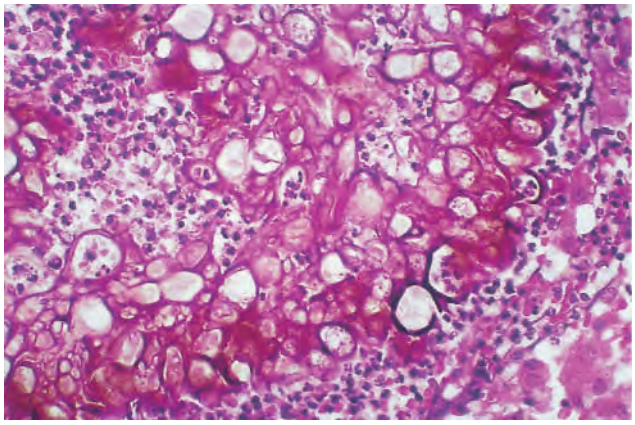

FIG. 261.6 Eumycetoma grain of *Curvularia geniculata*. (Hematoxylin and eosin stain.) *(From Chandler FW, Ajello L. Mycetoma. In: Connor DH, Chandler FW, Schwartz DA, et al, eds.* Pathology of Infectious Diseases. *Norwalk, CT: Appleton & Lange; 1997:1035–1044.)*

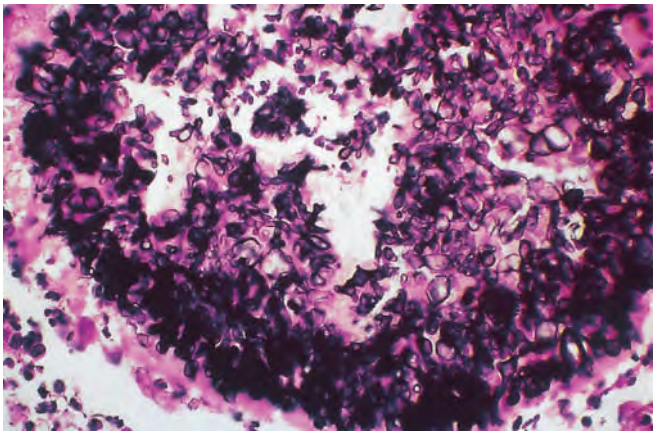

FIG. 261.7 Eumycetoma grain of *Neotestudina rosatii*. (Gomori methenamine silver and hematoxylin and eosin stains.) *(From Chandler FW, Ajello L. Mycetoma. In: Connor DH, Chandler FW, Schwartz DA, et al, eds.* Pathology of Infectious Diseases. *Norwalk, CT: Appleton & Lange; 1997:1035–1044.)*

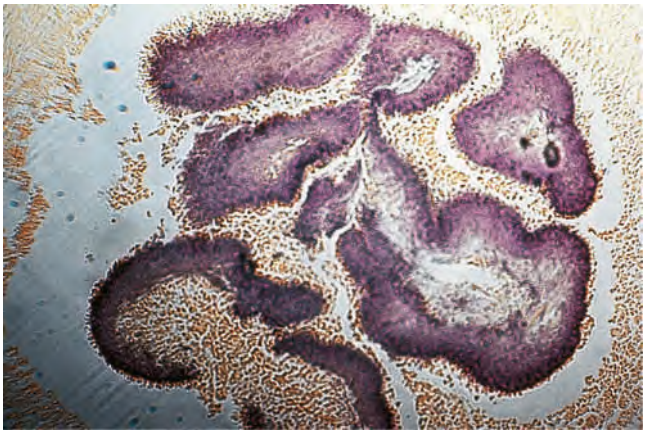

FIG. 261.8 Actinomycetoma grain. (Gridley stain.) *(From Beneke ES, Rogers AL.* Medical Mycology and Human Mycoses. *Belmont, CA: Star Publishing; 1996.)*

from an unopened sinus tract for microscopic observation and culture.[34] Evaluation of spontaneously extruded grains may not allow diagnosis because these grains are often composed of dead organisms and contaminated with skin surface bacteria that outgrow the mycetomatous agent in culture.

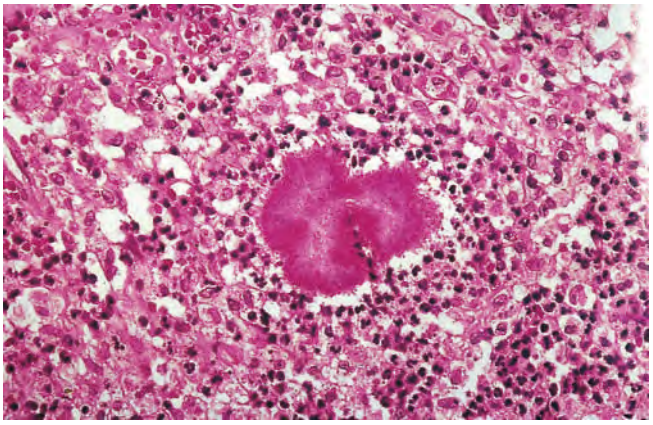

FIG. 261.9 *Nocardia brasiliensis* grain. (Hematoxylin and eosin stain.) *(From Chandler FW, Ajello L. Mycetoma. In: Connor DH, Chandler FW, Schwartz DA, et al, eds.* Pathology of Infectious Diseases. *Norwalk, CT: Appleton & Lange; 1997:1035–1044.)*

The grains (or granules or sclerotia) of mycetoma are usually 0.2 to 5 mm in diameter and thus may be observed grossly, without magnification. Microscopic evaluation of crushed grains prepared with potassium hydroxide or stained with Gram stain is useful in differentiating fungal from bacterial causes. On inspection, actinomycetes are recognized by the production of 0.5- to 1-μm-wide filaments and fungi by 2- to 5-μm-wide hyphae. Many reports and reviews have detailed the use of grain color, size, and consistency to diagnose the specific cause of mycetoma, but recovery of the causative agents in culture is more accurate and of greater clinical usefulness when resources are available.

Culture of grains recovered from aspirated material or biopsy specimens can be used to diagnose the specific cause of mycetoma. If extruded grains are used, most experts suggest rinsing these in 70% alcohol or with antibiotic-containing saline solutions to decrease bacterial contamination. Specimens should be cultured on mycologic and mycobacteriologic media and held for at least 4 weeks.

The role of radiology in the management of mycetoma is that of adjunctive assessment of disease extent and involvement of bone, and perhaps long-term follow-up of disease regression or progression. Radiographic studies can help define the extent of disease and aid in the differentiation of mycetoma from other disease. Standard radiographic studies can reveal bony involvement such as periosteal erosion secondary to invasion, osteoporosis, and changes consistent with osteomyelitis, including lytic lesions. Ultrasonography has been used successfully in the differentiation of mycetoma from osteomyelitis or tumor. In a study of 100 patients with foot swelling who underwent ultrasonography before surgical excision, these lesions were found to have characteristics that distinguished them from other diseases.[35] Eumycetoma were found to produce single or multiple thick-walled cavities, without acoustic enhancement, with grains represented as distinct hyperreflective echoes. Actinomycetoma produced similar results, except grains produced fine echoes that were found at the bottom of the cavities. Magnetic resonance imaging (MRI) and computed tomography have also been evaluated in the management of mycetoma. Both modalities provide accurate assessment of disease extent when compared with surgical findings, especially in the soft tissues.[36] When compared directly, computed tomography appears to be more sensitive for detecting early changes consistent with bone involvement. A *dot-in-circle sign* has been described as a potentially specific diagnostic finding seen with MRI.[37,38] The dots are tiny hypointense foci (believed to be grains) within spherical, high-intensity lesions (the circle) surrounded by low-intensity matrix on T2-weighted imaging, which represent granulomas scattered in areas of fibrosis. T1-weighted, fat-saturated, postgadolinium images may also produce this appearance. An MRI grading system has been developed by the Mycetoma Research Centre (Khartoum, Sudan) for use in the diagnosis and management of mycetoma.[39]

The use of serology in the diagnosis and long-term management of this disease has been advocated by some authorities. Of the tests

described, counterimmunoelectrophoresis has been the most commonly used. Lack of standardization or widespread availability limits the use of these tests to centers that see a large volume of such patients. In the United States, the infrequency of the diagnosis and the diverse number of pathogens render serology of no practical use.

THERAPY

Treatment of mycetoma has proved to be difficult and typically includes prolonged courses of antimicrobial agents, often with surgical debulking.[40–42] Surgery alone has a limited role in the treatment of mycetoma.[43] In addition to limb amputation, surgical excision of smaller lesions may be successful as monotherapy. Typically, surgery is employed adjunctively in fungal mycetoma to debulk large lesions after weeks to months of azole antifungal therapy has been given. Because chemotherapy varies for actinomycetoma and eumycetoma, at a minimum the clinician must differentiate whether a mycetoma is caused by actinomycetes or fungi. Ideally, recovery of the causative organism can allow identification of species, and perhaps even susceptibility testing, to guide therapy. Treatment regimens are currently based on expert opinion because no randomized controlled trials have been performed. Duration of therapy is also not defined, and most patients require 3 to 24 months of therapy to obtain an adequate response.

The most commonly described regimens for actinomycetoma include parenteral aminoglycosides combined with oral sulfonamide drugs or dapsone. Therapy with 5-week cycles of oral trimethoprim-sulfamethoxazole (TMP-SMX) (2 double-strength tablets twice daily) with parenteral amikacin (15 mg/kg/day divided into 2 daily doses) given during the first 3 weeks has been reported to produce successful results in all treated patients.[4,14,44] More than half of 56 patients treated with this regimen were cured with one or two cycles; none required more than four cycles, and only one relapsed. The single patient with relapse was treated successfully with three cycles of TMP-SMX combined with netilmicin, an aminoglycoside. Other aminoglycoside-sulfonamide regimens include gentamicin or streptomycin in combination with either TMP-SMX or dapsone.[40,41,44,45] TMP-SMX alone may be successful in the treatment of smaller lesions. Other regimens that have been used include streptomycin with either sulfadoxine-pyrimethamine or rifampin; a combination of penicillin, gentamicin, and TMP-SMX followed by TMP-SMX and amoxicillin; and regimens that include amoxicillin-clavulanate, tetracycline, rifampin, fusidic acid, clindamycin, or imipenem-cilastatin.[a] Success with linezolid therapy has also been reported in one patient.[4,14]

Antifungal therapy for eumycetoma most commonly includes the use of azole antifungals because amphotericin B has not been effective in producing long-term cures. The first-line agent in the treatment of this disease is considered to be itraconazole (200–400 mg/day). Cure rates with this drug are quite variable, and it is suggested that all patients be evaluated for surgical debulking after their disease is controlled with azole therapy, typically after a year of therapy.[41,48,49] In vitro, all three of the newer azoles—isavuconazole,[50] posaconazole, and voriconazole—have good activity against many of the causative agents of eumycetoma. Case reports of successful therapy with voriconazole have been published,[51–53] as has a small case series of successful therapy for previously azole-refractory disease that responded to posaconazole.[54] Because of its susceptibility pattern, mycetoma secondary to the *S. apiospermum* complex should be treated with voriconazole. Successful therapy with terbinafine, an allylamine antifungal, has also been reported. Improvement or cure was seen in 16 of 20 patients who completed 24 to 48 weeks of terbinafine therapy (500 mg twice daily).[55] There are very little safety data on doses this high. In vitro, terbinafine has limited activity against *M. mycetomatis* compared with that observed with itraconazole, ketoconazole, or posaconazole.[56]

PREVENTION

No preventive vaccine is available against any of the causative agents of mycetoma. Disease prevention is best accomplished by reduction of the incidence of the traumatic inoculation of the causative organisms. Wearing shoes and clothing to protect against splinters and thorn pricks should be stressed. Debilitating disease can be prevented by early identification and treatment of lesions, usually with minor surgery and chemotherapy.

[a]References 4, 14, 40, 41, 46, 47.

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262 Cryptococcosis (*Cryptococcus neoformans* and *Cryptococcus gattii*)

John R. Perfect

SHORT VIEW SUMMARY

Life Cycle
- The life cycle represents both asexual (clinical) and sexual (recombination) cycles, with the impact of the sexual cycle on pathogenesis.

Taxonomy
- There are 19 cryptococcal species with two major pathogenic species, *Cryptococcus neoformans* and *Cryptococcus gattii.*
- At present, the following taxonomic divisions have been proposed, but this area continues to evolve in the molecular era: *C. neoformans* var. *grubii* (serotype A), with five genotypes (VNI, VNII, VNBI, VNBII, and the hybrid VNIII); *C. neoformans* var. *neoformans* (serotype D or genotype VNIV); and five other cryptic species: *Cryptococcus gattii, Cryptococcus bacillisporus, Cryptococcus deuterogattii, Cryptococcus tetragattii,* and *Cryptococcus decagattii* (serotypes B/C or VGI–VGV).[1]

Identification
- Biochemical tests, including urease production, melanin formation, and appearance of a capsule
- Antigen tests, cultures, DNA-based tests, or matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF)

Ecology
- *C. neoformans* (serotypes A and D) found in pigeon guano or associated with certain trees (mopane trees)
- *C. gattii* found around trees from eucalyptus to coniferous species (landscape of niche may be changing related to climate changes)

Epidemiology
- Not a routine constituent of human microbiota but can colonize humans without evidence of disease
- Widespread asymptomatic infections occur in the exposed populations
- Risk factors for disease: acquired immunodeficiency syndrome (AIDS), corticosteroid treatment, transplantation, cancer, monoclonal antibodies (from anti–tumor necrosis factor to anti-CD52), sarcoidosis, autoantibodies to granulocyte-macrophage colony-stimulating factor, idiopathic CD4 lymphocytopenia, and new tyrosine kinase inhibitors for cancer treatment; identifies primarily cell-mediated immunity defects but humoral perturbations may also be a factor (see Table 262.1)
- Antiretroviral therapy (ART) impact on appearance of clinical cryptococcosis is impressive in patients with AIDS. However, even widespread availability of ART does not eliminate high numbers of cryptococcosis in some populations.
- A million new cases of cryptococcosis per year, with more than 600,000 deaths worldwide at the peak of the human immunodeficiency virus (HIV) epidemic; now reduced although not yet eliminated with ART availability, with an estimated present census of over 200,000 new cases per year worldwide with over 100,000 deaths per year.

Pathogenicity
- Virulence factors (examples include but not limited to: capsule, melanin, high temperature growth, urease, phospholipase)
- Many understandings of cryptococcal disease at the genetic and molecular level have been acquired.

Host Responses
- Efficient protection requires intact and coordinated cell-mediated, innate, and humoral immunity networks.

Pathogenesis
- Three factors: (1) host defenses, (2) virulence of strains, and (3) size of infectious inocula
- Cryptococcosis is considered primarily a reactivation clinical disease but disease can occur with the initial infection.

Clinical Manifestations (see Table 262.2)
- Major body sites for infection are the central nervous system and lung.
- Other body sites with unique infection considerations are the skin, prostate, peritoneum, and eye.
- Cryptococci have produced infection within any organ of the human body.
- Disease primarily depends on host immunity—either too little or too much (immune reconstitution inflammatory syndrome [IRIS]).

Laboratory Diagnosis
- Microscopy: India ink and histopathologic stains, including a general fungal Gomori methenamine silver stain, or the specific capsular polysaccharide stains (mucicarmine or alcian blue)
- Culture of cerebrospinal fluid (CSF), blood, bronchoalveolar lavage
- Cryptococcal antigen detection in CSF and serum is sensitive and specific as determined by either latex agglutination assay, enzyme-linked immunosorbent assay, or a lateral flow assay.

Management
- The Infectious Diseases Society of American Guidelines in 2010 established road maps for therapies and strategies (https://academic.oup.com/cid/article/50/3/291/392360); most of its principles are still intact but a few updates can be made.
- Direct antifungal drug resistance uncommonly arises during therapy, but relapse/persistent isolates should have in vitro antifungal susceptibility testing performed and compared to original isolate.
- Treatment strategies are outlined in this chapter for (1) cryptococcal meningitis in AIDS patients, transplant recipients, and non-AIDS, nontransplant patients and (2) pulmonary infections.
- Treatment has been best studied for cryptococcal meningitis in HIV-infected patients (2018 US Department of Health and Human Services guidelines at https://aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-oi-prevention-and-treatment-guidelines/333/cryptococcosis). Treatment is initiated with amphotericin B, preferably with the liposomal formulation at 3 to 4 mg/kg daily, the alternatives being the lipid complex at 5 mg/kg or conventional amphotericin B at 0.7 mg/kg/day. Any one of these can be used plus flucytosine 25 mg/kg every 6 hours (100 mg/kg/day with normal renal function) for at least 2 weeks and until clinically improved. In cryptococcal meningitis, delaying ART during these 2 weeks may prevent IRIS from complicating management and increased early deaths. Patients who respond to induction-phase combination antifungal therapy may then be switched to fluconazole, 400 to 800 mg/day, for 8 to 10 weeks as a consolidation phase. Finally, a suppressive phase is begun with fluconazole 200 mg once daily. Antifungal therapy in HIV-infected patients can be stopped after 1 to 2 years in patients who respond to ART with a CD4 count above 100/μL for at least 3 months, a nondetectable viral load, and a negative or low serum cryptococcal antigen. In non–HIV-infected patients who improve, therapy is also generally extended for 1 year.
- Complications of cryptococcal meningitis requiring special attention are (1) early increased intracranial pressure, which can lead to blindness, permanent dementia, and death; (2) development of hydrocephalus, which may require placement of a ventriculoperitoneal shunt; and (3) IRIS, which may be mistaken for therapeutic failure.