

Agents of Mycetoma

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Mycetoma is a chronic progressive granulomatous infection of the skin and subcutaneous tissue most often affecting the lower extremities, typically a single foot. Disease is unique from other cutaneous or subcutaneous diseases in its triad of localized swelling, underlying sinus tracts, and production of grains or granules (comprised 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, termed *actinomycotic mycetoma* or *actinomycetoma*. The term *mycetoma* can also be found in the literature incorrectly referring to a fungus ball found in a pre-existing 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 255), 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. In a rare form of ringworm called *dermatophyte mycetoma*, there are also loosely compacted clusters of hyphae in subcutaneous pus. 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.¹ The predominance of bacterial versus fungal causes of mycetoma varies among geographic location. 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 262-1). Color distinctions are made by observing unstained specimens. Among the fungi causing dark-grained mycetoma, the most common are *Madurella mycetomatis*, *Leptosphaeria senegalensis*, and *Madurella grisea*. Other agents include *Corynespora cassicola*, *Curvularia geniculata*, *Curvularia lunata*, *Exophiala jeanselmei*, *Exophiala oligosperma*, *Leptosphaeria tompkinsii*, *Phialophora verrucosa*, *Plenodomus avramii*, *Pseudochaetosphaeronea larense*, *Rhinocladiella atrovirens*, *Pyrenochaeta mackinnonii*, and *Pyrenochaeta romeroi*. *Pseudallescheria boydii* (anamorph *Scedosporium apiospermum*) is the most common cause of pale-colored grains. Other fungi in that category include *Acremonium falciforme*, *Acremonium kiliensis*, *Acremonium recifei*, *Aspergillus flavus*, *Aspergillus hollandicus*, *Aspergillus (Emericella) nidulans*, *Cylindrocarpon cyanescens*, *Cylindrocarpon destructans*, *Fusarium solani*, *Fusarium moniliforme* (*verticillioides*), *Neotestudina rosatii*, *Phaeoacremonium species*, and *Polycyttella hominis*.²⁻⁵ Actinomycetoma is caused by members of the order Actinomycetales, most commonly *Nocardia brasiliensis*, *Actinomyces madurae*, *Streptomyces somaliensis*, and *Actinomyces pelletieri*. Cases have been reported that were caused by *Actinomyces latina*, *Nocardia asteroides*, *Nocardia caviae*, *Nocardia farcinica*, *Nocardia otitidiscaviarum*, *Nocardia mexicana*, *Nocardia*

transvalensis, *Nocardia veterana*, *Nocardiosis dassonvillei*, and *Streptomyces sudanensis*.^{2,6-8} Actinomycetoma grains are typically white or pale yellow, except those caused by *Actinomyces pelletieri*, which are red to pink.

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.”² 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 being reported from endemic areas in the India subcontinent, the Middle East, Africa, and Central and South America. One of the largest current group 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 be in part the result of decreased 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 affliction, but *A. madurae*, *M. mycetomatis*, and *S. somaliensis* are more commonly reported from drier regions, whereas *P. boydii*, *Nocardia* species, and *A. pelletieri* are more common in those areas with higher annual rainfall. In India, *Nocardia* species and *M. grisea* are the most common causes of mycetoma; in the Middle East, *M. mycetomatis* and *S. somaliensis*; in West Africa, *L. senegalensis*; and in East Africa, *M. mycetomatis* and *S. somaliensis*. In Central and South America, *M. grisea* and *Nocardia* species are the common causes of mycetoma, and in the United States, *P. boydii* (*S. apiospermum*) is the most commonly recovered causative agent.⁹

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.¹⁰ 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 *P. boydii*) and actinomycotic (*S. somaliensis*) antigens in vitro.¹¹ Cells of the innate immune system attempt to engulf and inactivate these organisms, but in disease ultimately fail to accomplish this goal. Abscesses containing grains are seen in association with granulomatous inflammation and fibrosis. Three types of

*The views expressed are those of the author and do not reflect the official policy or position of the Department of the Army, the Department of Defense, or the U.S. Government.

TABLE 262-1 Typical Morphologic Features of Mycetoma Grains

Grain Color	Causative Agent
Eumycetoma (Eumycotic Mycetoma)*	
Black grains	<i>Madurella</i> spp., <i>Leptosphaeria</i> spp., <i>Curvularia</i> spp., <i>Exophiala</i> spp., <i>Phaeoacremonium</i> spp., <i>Phialophora verrucosa</i> , <i>Pyrenochaeta mackinnonii</i> , <i>P. romeroi</i>
Pale grains (white to yellow)	<i>Pseudallescheria boydii</i> (<i>Scedosporium apiospermum</i>), <i>Acremonium</i> spp., <i>Aspergillus</i> spp., <i>Fusarium</i> spp., <i>Neotestudina rosatii</i>
Actinomycetoma (Actinomycotic Mycetoma)†	
Pale grains (white to yellow)	<i>Actinomadurae madurae</i> , <i>Nocardia</i> spp.
Yellow to brown grains	<i>Streptomyces</i> spp.
Red to pink grains	<i>Actinomadurae pelletieri</i>

*2- to 5- μ m diameter hyphae are observed within grain.

†0.5- to 1- μ m diameter filaments are observed within grain.

immune responses have been described in response to the grains of mycetoma.¹² The type I response is seen as neutrophils degranulate and adhere to the grain surface, leading to gradual disintegration of the grain. Type II response is characterized by the disappearance of neutrophils and arrival of macrophages to clear grains and neutrophil debris. Type III 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. 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.^{13,14} Recent work examining genes responsible for innate immune functions has identified polymorphisms that appear to predispose people to this infection, may be linked with neutrophil function.¹⁵ 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*, *P. romeroi*, and *N. brasiliensis*.^{16,17} In the study of *N. brasiliensis*, estradiol limited disease produced in animals.¹⁶

Clinical Manifestations

Over 75% of persons with mycetoma have a lesion of a lower extremity, most commonly in the foot (70%) (Figs. 262-1 and 262-2). Next 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. 262-3). 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 *M. grisea*.¹⁸

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 hypo- or hyperpigmented, with signs of both old healed and active sinuses, displaying the cycle of spontaneous healing of older sinuses tracts and simultaneous spread of infection to new areas typical



Figure 262-1 Mycetoma of the foot. (From Beneke ES, Rogers AL. *Medical Mycology and Human Mycoses*. Belmont, Calif: Star Publishing; 1996.)



Figure 262-2 Mycetoma of the leg (seen from back of knee). (Courtesy of Dr. Glenn W. Wortmann.)



Figure 262-3 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, Conn: Appleton & Lange; 1997.)

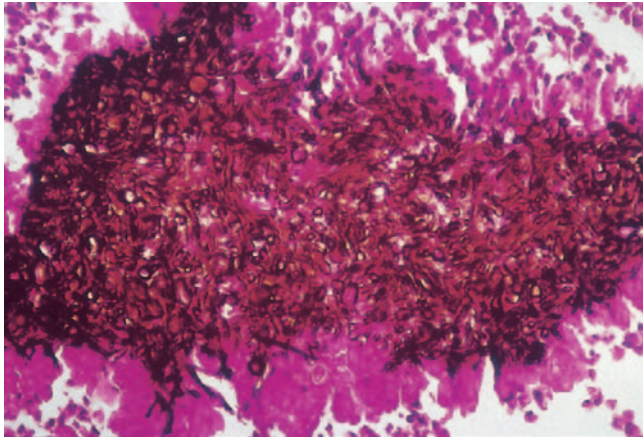


Figure 262-4 Eumycetoma grain of *Acremonium falciforme*. (Gomori methenamine-silver and hematoxylin and eosin stain.) (From Chandler FW, Ajello L. Mycetoma. •• In: Connor DH, Chandler FW, Schwartz DA, et al, eds. Pathology of Infectious Diseases. Norwalk, Conn: Appleton & Lange; 1997.)

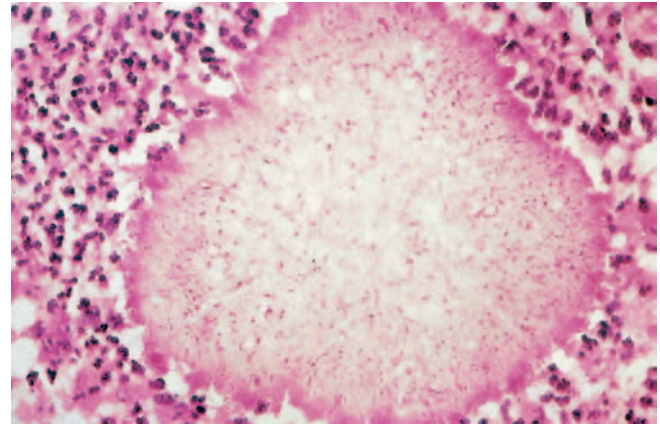


Figure 262-5 Eumycetoma grain of *Pseudallescheria boydii*. (Hematoxylin and eosin stain.) (From Chandler FW, Ajello L. Mycetoma. •• In: Connor DH, Chandler FW, Schwartz DA, et al, eds. Pathology of Infectious Diseases. Norwalk, Conn: Appleton & Lange; 1997.)

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. 262-4 to 262-9). Organisms are usually not seen outside the grain. An alternate strategy is the aspiration of grains directly from an unopened sinus tract for microscopic observation and culture. Evaluation of spontaneously extruded grains may not allow diagnosis, because these grains may be composed of dead organisms and are frequently associated with contaminating bacteria that grow more rapidly than the mycetomatous agent.

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- μ m-wide filaments and fungi

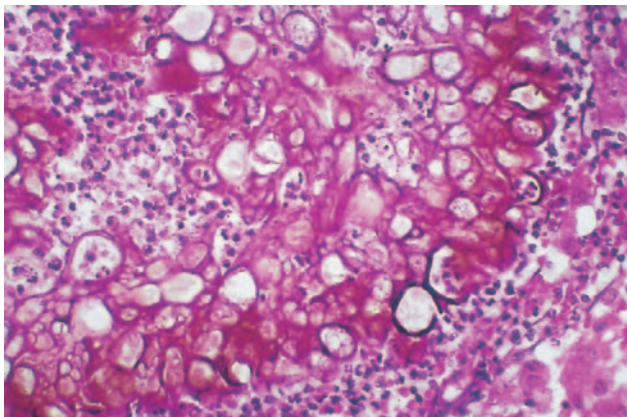


Figure 262-6 Eumycetoma grain of *Curvularia geniculata*. (Hematoxylin and eosin stain; ••.) (From Chandler FW, Ajello L. Mycetoma. •• In: Connor DH, Chandler FW, Schwartz DA, et al, eds. Pathology of Infectious Diseases. Norwalk, Conn: Appleton & Lange; 1997.)

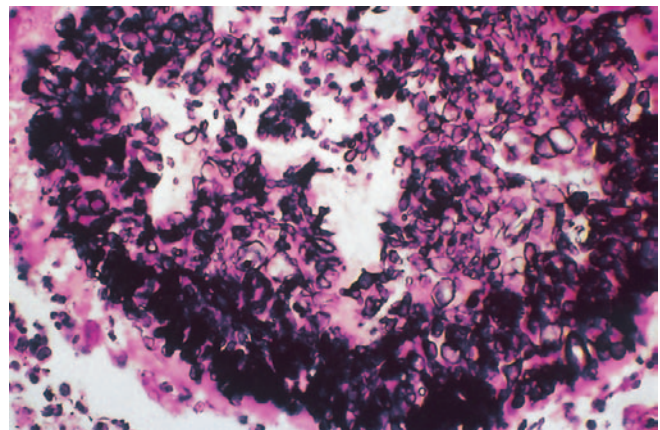


Figure 262-7 Eumycetoma grain of *Neotestudina rosatii*. (Gomori methenamine-silver and hematoxylin and eosin stain.) (From Chandler FW, Ajello L. Mycetoma. •• In: Connor DH, Chandler FW, Schwartz DA, et al, eds. Pathology of Infectious Diseases. Norwalk, Conn: Appleton & Lange; 1997.)

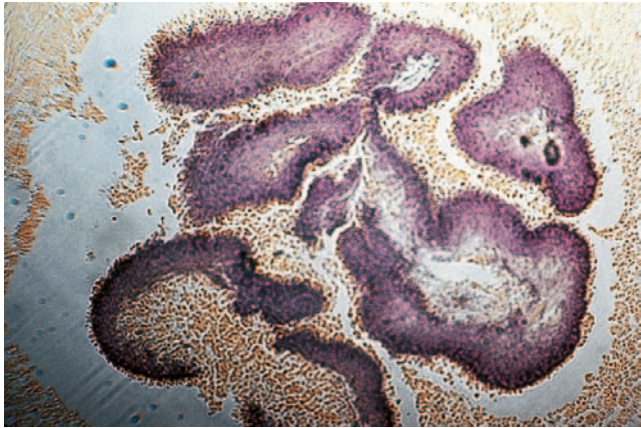


Figure 262-8 Actinomycetoma grain (Gridley stain.) (From Beneké ES, Rogers AL. *Medical Mycology and Human Mycoses*. Belmont, Calif: Star Publishing; 1996.)

by 2- to 5- m-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, 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 x-ray 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 prior to surgical excision, these lesions were found to have distinct characteristics that distinguished them from other diseases.¹⁹ 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 (CT) 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.²⁰ When compared directly, CT 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.²¹ 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.

The use of serology has been advocated by some authorities in the diagnosis and long-term management of this disease. Of the tests described, counterimmunoelectrophoresis has been the most commonly used. Lack of standardization or widespread availability limit 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 renders serology of no practical use.

Treatment

Treatment of this disease has proven to be difficult, and typically includes antimicrobial agents and surgery. Short of amputation, surgery alone is rarely successful in the treatment of mycetoma, but removal of smaller lesions or debulking of larger ones does play an important role, especially in the management of fungal disease. 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 receive 3 to 24 months of therapy to obtain an adequate response.

The most commonly described regimens for actinomycetoma include streptomycin plus either trimethoprim-sulfamethoxazole (TMP-SMX) or dapsone. In this regimen, streptomycin (14 mg/kg/day IM) is given for the first month (and sometimes three times weekly thereafter for several months) in addition to a long course of TMP-SMX, usually one double-strength tablet (160 mg trimethoprim and 800 mg sulfamethoxazole) twice daily, or dapsone (1.5 mg/kg/day twice daily). Alternate regimens include TMP-SMX plus dapsone⁶ and amikacin plus TMP-SMX. The patient should be tested for glucose-6-phosphate dehydrogenase (G6PD) deficiency before dapsone use. Cycled dosing of amikacin (15 mg/kg/day, divided into two daily doses for 3 weeks) in addition to TMP-SMX for 5 weeks has also been described.²² Most patients improved with only one or two cycles of this therapy. Gentamicin (1.5 mg/kg IV) plus TMP-SMX (two double-strength tablets) given twice daily for 4 weeks followed by continuation of TMP-SMX plus doxycycline (100 mg twice daily) has more recently been reported.²³ Response to TMP-SMX alone has also been reported.²⁴ 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 amoxicillin²⁵ and regimens that include amoxicillin-clavulanate,²⁶ fusidic acid, clindamycin, or imipenem-cilastatin.

Antifungal therapy of eumycetoma most commonly includes the use of azole antifungals, because amphotericin B has not been effective in producing long-term cures. Itraconazole (400 mg/day) or ketoconazole (200 to 400 mg/day) are considered first-line azole agents in the treatment of this disease. Early study using ketoconazole, 200 mg twice daily, noted marked improvement or cure in 72% of a group of 50 patients with mycetoma secondary to *M. mycetomatis* receiving 9 to 36 months of therapy.⁶ Itraconazole at a dosage of 100 mg twice daily in

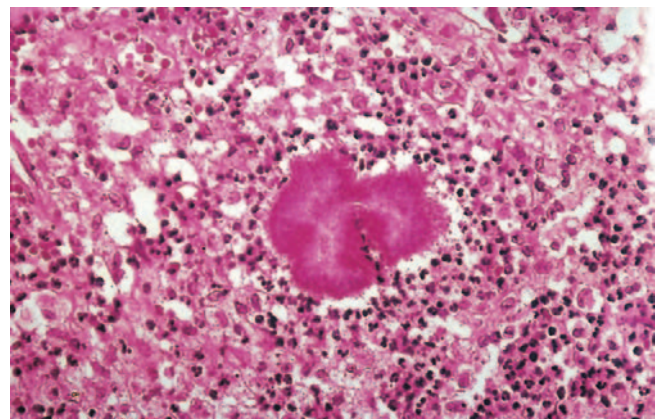


Figure 262-9 Nocardia brasiliensis grain (Hematoxylin and eosin stain.) (From Chandler FW, Ajello L. *Mycetoma*. •• In: Connor DH, Chandler FW, Schwartz DA, et al, eds. *Pathology of Infectious Diseases*. Norwalk, Conn: Appleton & Lange; 1997.)

the same population produced marked improvement in 42% of subjects, but no cures.²² Multiple case reports and case series have reported mixed success with the use of itraconazole in a range of doses.^{6,27,28} Fluconazole has proven to be even less effective for the treatment of mycetoma. *P. boydii* (*S. apiospermum*) is not responsive to ketoconazole therapy and is often resistant to itraconazole in vitro and in clinical therapy. In vitro, both of the newer azoles, posaconazole and voriconazole, have good activity against many of the causative agents of eumycetoma. Case reports of successful therapy with voriconazole have been published,²⁹⁻³¹ as has a small case series of successful therapy of previously azole refractory disease that responded to posaconazole.³² 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).³³

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 of 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.

REFERENCES

- Ahmed A, Adelman D, Fahal A, et al. Environmental occurrence of *Madurella mycetomatis*, the major agent of human eumycetoma in Sudan. *J Clin Microbiol*. 2002;40:1031-1036.
- Kwon-Chung KJ, Bennett JE. Mycetoma. In: *Medical Mycology*. Philadelphia: Lea & Febiger; 1992:560-593.
- Smith MD, McGinnis MR. Subcutaneous fungal infections (chromoblastomycosis, mycetoma, and lobomycosis). In: Hespenthal DR, Rinaldi MG, eds. *Diagnosis and Treatment of Human Mycoses*. Totowa, NJ: Humana Press; 2008:383-392.
- Desnos-Ollivier M, Bretagne S, Dromer F, et al. Molecular identification of black-grain mycetoma agents. *J Clin Microbiol*. 2006;44:3517-3523.
- Hemashettar BM, Siddaramappa B, Munjunathaswamy BS, et al. *Phaeoacremonium krajdienii*, a cause of white grain eumycetoma. *J Clin Microbiol*. 2006;44:4619-4622.
- Welsh O, Salinas MC, Rodriguez MA. Treatment of eumycetoma and actinomycetoma. *Curr Top Med Mycol*. 1995;6:47-71.
- Quintana ET, Wierzbicka K, Mackiewicz P, et al. *Streptomyces sudanensis* sp. nov., a new pathogen isolated from patients with actinomycetoma. *Antonie van Leeuwenhoek*. 2008;93:305-313.
- Rodriguez-Nava V, Couble A, Molinard C, et al. *Nocardia mexicana* sp. nov., a new pathogen isolated from human mycetomas. *J Clin Microbiol*. 2004;42:4530-4535.
- Green WO, Adams TE. Mycetoma in the United States: A review and report of seven additional cases. *Am J Clin Pathol*. 1964;42:75-91.
- Wethered DB, Markey MA, Hay RJ, et al. Ultrastructural and immunogenic changes in the formation of mycetoma grains. *J Med Vet Mycol*. 1986;25:39-46.
- Yousif MA, Hay RJ. Leucocyte chemotaxis to mycetoma agents—the effect of the antifungal drugs griseofulvin and ketoconazole. *Trans R Soc Trop Med Hyg*. 1987;81:319-321.
- Fahal AH, el Toum EA, el Hassan AM, et al. The host tissue reaction to *Madurella mycetomatis*: New classification. *J Med Vet Mycol*. 1995;33:15-17.
- Bendl BJ, Mackey D, Al-Saati F, et al. Mycetoma in Saudi Arabia. *J Trop Med Hyg*. 1987;90:51-59.
- Mahgoub ES, Gumaa SA, El Hassan AM. Immunological status of mycetoma patients. *Bull Soc Pathol Exot Filiales*. 1977;70:48-54.
- van de Sande WWJ, Fahal A, Verbrugh H, et al. Polymorphisms in genes involved in innate immunity predispose toward mycetoma susceptibility. *J Immunol*. 2007;179:3065-3074.
- Hernández-Hernández F, López-Martínez R, Méndez-Tovar LJ, et al. *Nocardia brasiliensis*: In vitro and in vivo growth in response to steroid sex hormones. *Mycopathologia*. 1995;132:79-85.
- Méndez-Tovar LJ, de Biève C, López-Martínez R. Effets des hormones sexuelles humaines sur le développement in vitro des agents d'eumycétomes. *J Mycol Méd*. 1991;1:141-143.
- Maiti PK, Ray A, Bandyopadhyay S. Epidemiological aspects of mycetoma from a retrospective study of 264 cases in West Bengal. *Trop Med Int Health*. 2002;7:788-792.
- Fahal AH, Sheik HE, Homeida MM, et al. Ultrasonographic imaging of mycetoma. *Br J Surg*. 1997;84:1120-1122.
- Sharif HS, Clark DC, Aabed MY, et al. Mycetoma: Comparison of MR imaging with CT. *Radiology*. 1991;178:865-870.
- Sarris I, Berendt AR, Athanasous N, et al. MRI of mycetoma of the foot: Two cases demonstrating the dot-in-circle sign. *Skeletal Radiol*. 2003;32:179-183.
- Hay RJ, Mahgoub ES, Leon G, et al. Mycetoma. *J Med Vet Mycol*. 1992;30(Suppl 1):41-49.
- Raman M, Bhat R, Garg T, et al. A modified two-step treatment for actinomycetoma. *J Dermatol Venereol Leprol*. 2007;73:235-239.
- Khatri ML, Al-Halali HM, Fouad Khalid M, et al. Mycetoma in Yemen: Clinicoepidemiologic and histopathologic study. *Int J Dermatol*. 2002;41:586-593.
- Ramam M, Garg T, D'Souza P, et al. A two-step schedule for the treatment of actinomycetoma. *Acta Derm Venereol*. 2000;80:378-380.
- Wortman PD. Treatment of a *Nocardia brasiliensis* mycetoma with sulfamethoxazole and trimethoprim, amikacin, and amoxicillin and clavulanate. *Arch Dermatol*. 1993;129:564-567.
- Resnik BI, Burdick AE. Improvement of eumycetoma with itraconazole. *J Am Acad Dermatol*. 1995;33:917-919.
- Smith EL, Kutbi S. Improvement of eumycetoma with itraconazole. *J Am Acad Dermatol*. 1997;36:279-280.
- Lacroix C, de Kerviler E, Morel P, et al. *Madurella mycetomatis* mycetoma treated successfully with oral voriconazole. *Br J Dermatol*. 2005;152:1062-1094.
- Loulergue P, Hot A, Dannaoui E, et al. Short report. Successful treatment of black-grain mycetoma with voriconazole. *Am J Trop Med Hyg*. 2006;75:1106-1107.
- Porte L, Khatibi S, El Hajj L, et al. *Scedosporium apiospermum* mycetoma with bone involvement successfully treated with voriconazole. *Trans R Soc Trop Med Hyg*. 2006;100:891-894.
- Negróni R, Tobón A, Bustamante B, et al. Posaconazole treatment of refractory eumycetoma and chromoblastomycosis. *Rev Inst Med Trop S Paulo*. 2005;47:339-346.
- N'Diaye B, Dieng MT, Perez A, et al. Clinical efficacy and safety of oral terbinafine in fungal mycetoma. *Int J Dermatol*. 2006;45:154-157.

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