261 Agents of Mycetoma

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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]

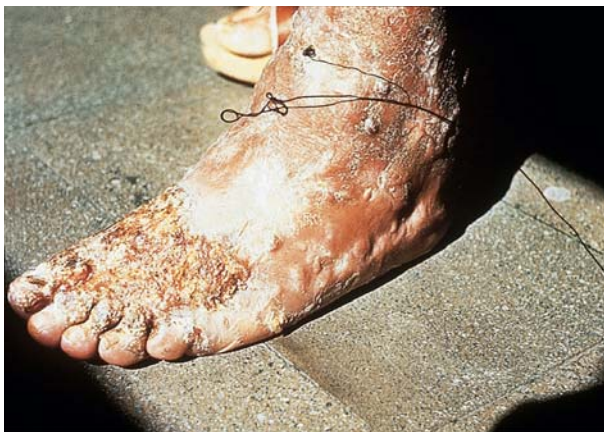

FIG. 261.1 Mycetoma of the foot. *(From Beneke ES, Rogers AL.* Medical Mycology and Human Mycoses. *Belmont, CA: Star Publishing; 1996.)*

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

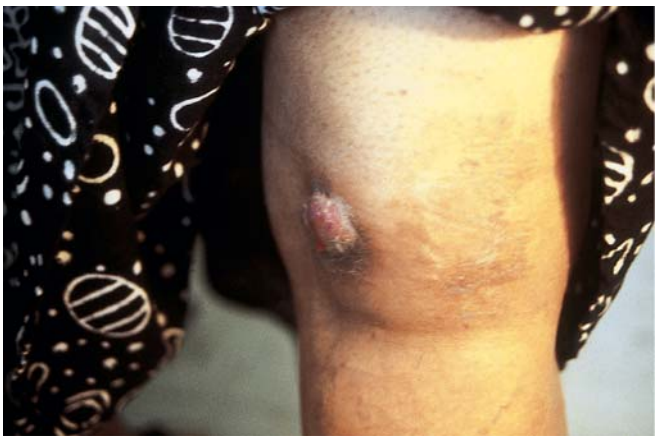

FIG. 261.2 Mycetoma of the leg (seen from back of knee). *(Courtesy Dr. Glenn W. Wortmann.)*

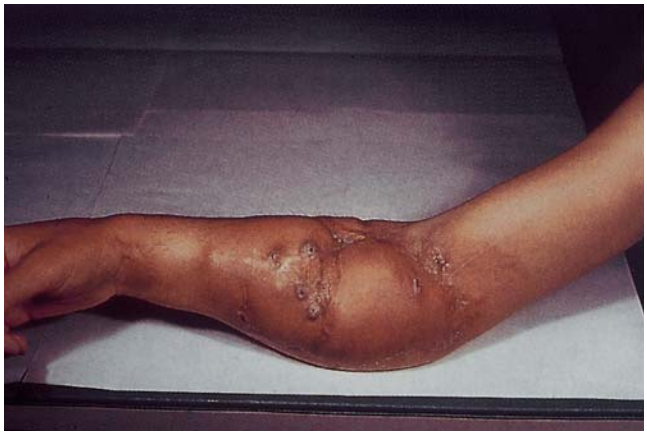

FIG. 261.3 Mycetoma of the arm caused by *Madurella mycetomatis.* *(From Chandler FW, Ajello L. Mycetoma. In: Connor DH, Chandler FW, Schwartz DA, et al, eds.* Pathology of Infectious Diseases. *Norwalk, CT: Appleton & Lange; 1997:1035–1044.)*

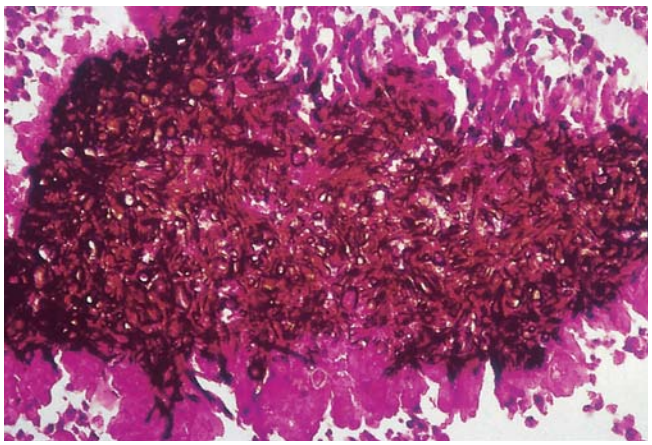

FIG. 261.4 Eumycetoma grain of *Fusarium (Acremonium) falciforme.* (Gomori methenamine silver and hematoxylin and eosin stains.) *(From Chandler FW, Ajello L. Mycetoma. In: Connor DH, Chandler FW, Schwartz DA, et al, eds.* Pathology of Infectious Diseases. *Norwalk, CT: Appleton & Lange; 1997:1035–1044.)*

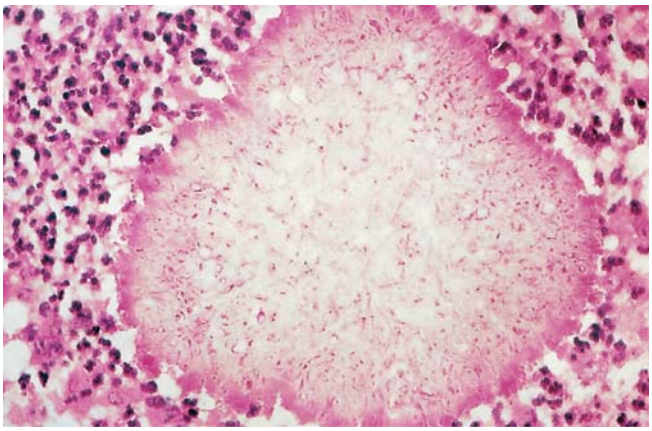

FIG. 261.5 Eumycetoma grain of *Scedosporium apiosperumum–Pseudallescheria boydii* complex. (Hematoxylin and eosin stain.) *(From Chandler FW, Ajello L. Mycetoma. In: Connor DH, Chandler FW, Schwartz DA, et al, eds.* Pathology of Infectious Diseases. *Norwalk, CT: Appleton & Lange; 1997:1035–1044.)*

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

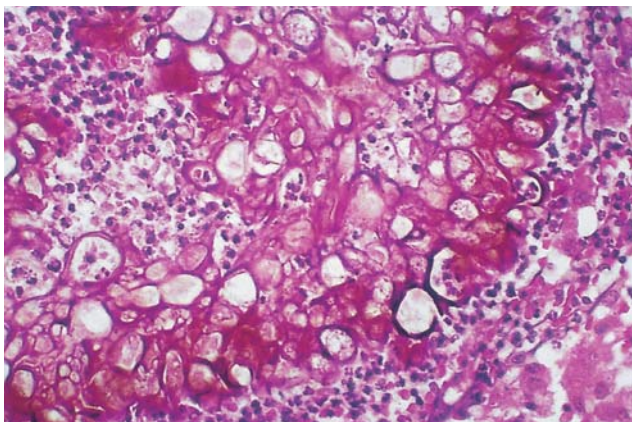

FIG. 261.6 Eumycetoma grain of *Curvularia geniculata*. (Hematoxylin and eosin stain.) *(From Chandler FW, Ajello L. Mycetoma. In: Connor DH, Chandler FW, Schwartz DA, et al, eds.* Pathology of Infectious Diseases. *Norwalk, CT: Appleton & Lange; 1997:1035–1044.)*

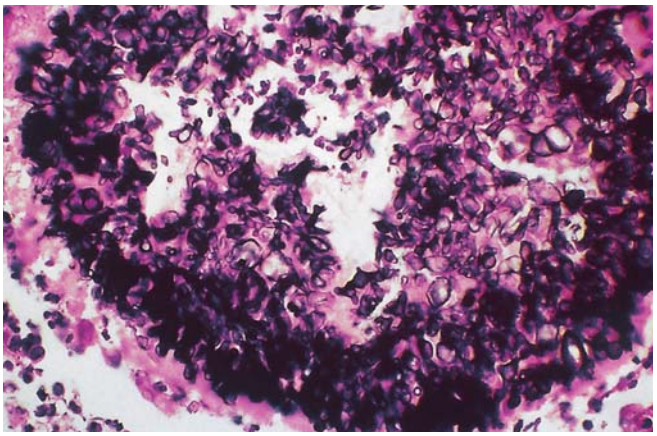

FIG. 261.7 Eumycetoma grain of *Neotestudina rosatii*. (Gomori methenamine silver and hematoxylin and eosin stains.) *(From Chandler FW, Ajello L. Mycetoma. In: Connor DH, Chandler FW, Schwartz DA, et al, eds.* Pathology of Infectious Diseases. *Norwalk, CT: Appleton & Lange; 1997:1035–1044.)*

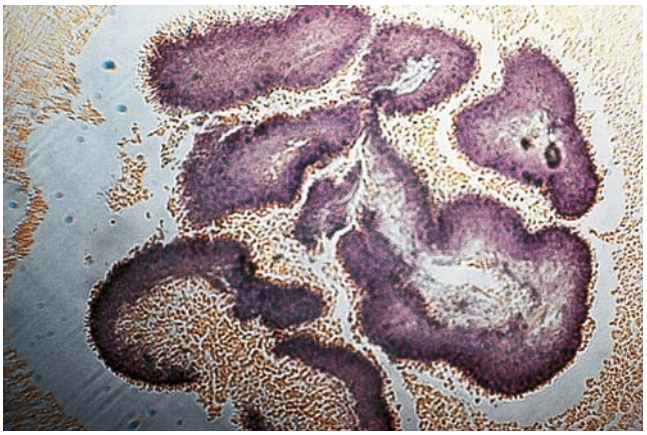

FIG. 261.8 Actinomycetoma grain. (Gridley stain.) *(From Beneke ES, Rogers AL.* Medical Mycology and Human Mycoses. *Belmont, CA: Star Publishing; 1996.)*

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.

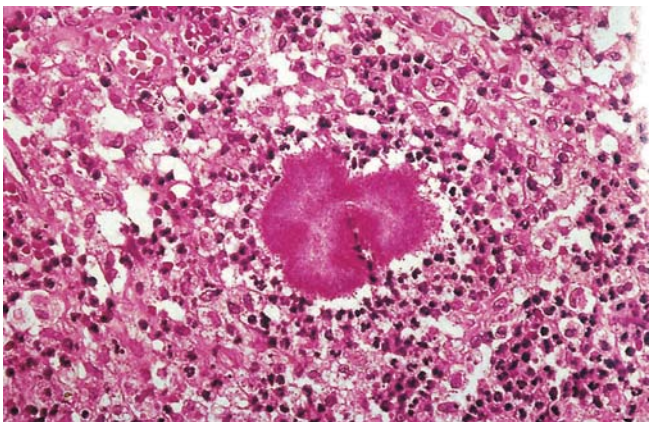

FIG. 261.9 *Nocardia brasiliensis* grain. (Hematoxylin and eosin stain.) *(From Chandler FW, Ajello L. Mycetoma. In: Connor DH, Chandler FW, Schwartz DA, et al, eds.* Pathology of Infectious Diseases. *Norwalk, CT: Appleton & Lange; 1997:1035–1044.)*

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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The complete reference list is available online at Expert Consult.

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