Abstract
Mycetoma is a localized chronic, supplicative, and deforming granulomatous infection seen in tropical and subtropical areas. It is a disorder of subcutaneous tissue, skin and bones, mainly of feet, characterized by a triad of localized swelling, underlying sinus tracts, and production of grains or granules. Etiological classification divides it into eumycetoma caused by fungus, and actinomycetoma caused by bacteria. Since the treatment of these two etiologies is entirely different, a definite diagnosis after histopathological and microbiological examination is mandatory, though difficult. Serological test exists but is not so reliable; however, molecular techniques to identify relevant antigens have shown promise. The disease is notoriously difficult to treat. Eumycetoma may be unresponsive to standard antifungal therapy. Actinomycetoma responds to antibiotic therapy, but prolonged treatment is necessary. This review focuses on the etiopathogenesis, clinical features, laboratory diagnosis, and treatment of mycetoma.

Key Words: Actinomycetoma, eumycetoma, Madura foot

Introduction and Historical Aspects
which is amenable to prolonged treatment.[1,2] Mycetoma is a chronic supplicative infection affecting skin, subcutaneous tissue, and bones prevalent in tropical and subtropical regions. The oldest description of this disease dates back to the ancient Indian Sanskrit text Atharva Veda in which reference is made to padavalmikam, meaning “anthill foot.”[3] In more modern times, Gill first recognized mycetoma as a disease entity in 1842 in the southern province of Madura[4] from where the commonly used name “Madura foot” got prevalent. Godfrey first documented a case of mycetoma in Madras, India. However, the term “Mycetoma” (meaning fungal tumor) was proposed by Carter, who established the fungal etiology of this disorder.[5] He classified his cases by the color of the grains. Later, Pinoy recognized the possibility of classifying the cases of mycetoma by grouping the causative organisms, and the formal classification was put into place by Chalmers and Archibald who divided them into two groups.[5,6]

Group 1: Maduramycosis, caused by true fungi, and Group 2: Actinomycosis, caused by actinomyces which belongs to higher bacteria.

Etiology
Mycetomas are caused by various species of fungi and bacteria, which occur as saprophytes in soil or on the plants. Actinomycotic mycetoma is caused by aerobic species of actinomycetes belonging to the genera Nocardia, Streptomyces and Actinomadura with Nocardia brasiliensis, Actinomadura madurae, Actinomadura pelletieri, and Streptomyces somaliensis being most common.

Eumycotic mycetoma is associated with a variety of fungi, the most common being Madurella mycetomatis.

Clinically, the different species produce grains of different colors[7,8] in Table 1.

Epidemiology
Mycetoma is reported to occur worldwide. It is endemic in tropical and subtropical regions, particularly between latitudes 15° S and 30° N, also known as the “Mycetoma belt” (Sudan, Somalia, Senegal, India, Yemen, Mexico, Venezuela, Colombia, and Argentina); however, the

What was known?
- Diagnosis of mycetoma can be made by the classic triad of painless soft tissue swelling, draining sinus tracts, and extrusion of grains
- A diagnosis of actinomycetoma or eumycetoma can be made on outpatient basis based on morphology of grains
- Treatment of actinomycetoma involves long-term use of antibiotics whereas that of eumycetoma is surgery followed by antifungals.

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### Table 1: Mycetoma causing organisms and the color of grains they produce

| Agent                        | Grain color          |
|------------------------------|----------------------|
| Actinomycotic                |                      |
| Nocardia asteroides          | White                |
| Nocardia brasiliensis        | White                |
| Nocardia otitidiscaviarum    | White                |
| Actinomadura madurae         | White                |
| Actinomadura pelletieri      | Red to pink          |
| Streptomyces somalensis      | White to yellow      |
| Eumycotic                    |                      |
| Madurella mycetomatis        | Black to brown       |
| Madurella grisea             | Black to brown       |
| Leptosphaeria senegalensis   | Black                |
| Curvularia lunata            | Black                |
| Neotestidina rosatii         | Yellow               |
| Acremonium spp.              | White to yellow      |
| Fusarium spp.                | White to pale yellow |
| Scedosporium apiospermum     | White to pale yellow |

actual endemic area extends beyond this belt. Most cases are reported from Sudan and Mexico with Sudan being the most endemic country.\(^\text{[9]}\) The species causing mycetoma vary from country to country, and agents that are more common in one region are rarely seen in other areas. Worldwide, \(M.\) \textit{Mycetomatis} is the most common cause of this affliction. \(A.\) \textit{madurae}, \(M.\) \textit{mycetomatis}, and \(S.\) \textit{somaliensis} are more commonly reported from drier regions, whereas \(Pseudallescheria\) \textit{boydii}, \(Nocardia\) species, and \(A.\) \textit{pelletieri} are more common in those areas with higher annual rainfall. In India, \(Nocardia\) species and \(Madurella\) \textit{grisea} are the most common causes of mycetoma.\(^\text{[10]}\)

Overall, most cases occur in arid and hot climates, which have a short period of heavy rainfall with milder temperatures. Actinomycetoma is more prevalent in drier areas, whereas eumycetoma is more common in sites with more rainfall.

Around 75% of mycetomas are actinomycotic in certain parts of India.\(^\text{[11]}\) However, eumycotic mycetoma accounts for the majority of cases reported from the Northern region.\(^\text{[12]}\) Mycetoma is more commonly reported in males than females (3:1), probably attributable to men being more commonly involved in agricultural work.\(^\text{[13,14]}\) The condition is most common in young adults (16–40 years old)\(^\text{[15]}\) and is uncommon in children.

### Pathogenesis

Although antibodies against the causative organism are found in number of individuals, only few develop the disease and this may be attributable to a complex interplay of factors between the host and pathogen.

### Host factors

The organism is usually implanted after a penetrating injury while performing agricultural work barefoot or through preexisting abrasions. Increased number in tropical regions may be due to decreased use of protective clothing, chiefly shoes, and due to the warmer, poorer conditions. Usually, some predisposing condition may be found such as poor general health, diabetes, and malnutrition, and this may lead to a more invasive and widespread infection. Complement-dependent chemotaxis of polymorphonuclear leukocytes has been shown to be induced by both fungal and actinomycotic antigens \textit{in vitro}.\(^\text{[14]}\) Cells of the innate immune system attempt to engulf and inactivate these organisms but in disease ultimately fail to accomplish this goal. Three types of immune responses have been described in response to the grains of mycetoma.\(^\text{[17]}\)

1. Type a: Neutrophil degranulation and adherence to the grain surface, leading to gradual disintegration of the grain. Outside the zone of neutrophils is a zone of granulation tissue containing macrophages, lymphocytes, and plasma cells
2. Type b: Disappearance of neutrophils and arrival of macrophages to clear the grains and neutrophil debris
3. Type c: Marked by the formation of epithelioid cell granulomas.

T-cell responses also seem to play an important part in the development of mycetoma. Th2-like responses (interleukin (IL)-10 and IL-4) were found in primary lesions and in draining lymph nodes in \(S.\) \textit{somaliensis} infection and after stimulation of peripheral blood mononuclear cells by \(M.\) \textit{mycetomatis} antigens. Th1 responses are found in the acute phase of infection and in healthy endemic controls.\(^\text{[18]}\)

Humoral antibodies also have a role in pathogenesis; in immunocompetent BALB/c mice, IgM antibodies induced specific protection in experimental \(N.\) \textit{brasiliensis} infection. The disappearance of IgM antibodies and the appearance of IgG are postulated to account for the slow onset and the delay in development in experimental actinomyctoma.\(^\text{[19]}\)

Recently, it has also been suggested that the greater frequency of disease in men may be due to progesterone inhibiting the growth of organisms.\(^\text{[20,21]}\) In another study, estradiol was seen to limit the disease produced in animals.\(^\text{[20]}\)

### Factors related to pathogen

It has been found that certain species are more commonly found in the immunocompetent individuals such as \(N.\) \textit{brasiliensis}, whereas others such as \(Nocardia\) \textit{faricina}, \(Nocardia\) \textit{nova}, and \(Nocardia\) \textit{cyriacigeorgica} mostly affect immunosuppressed individuals, and this may be due to ability of \(N.\) \textit{brasiliensis} to survive the first-line innate
immune response by phagocytes. The persistence of the organism after an initial inoculation appears to be related to its ability to evade host defenses through a variety of adaptations such as cell wall thickening and melanin production which protect microorganisms against ultraviolet radiation and destruction by alveolar macrophages, enzymatic lysis, and oxidants and might protect against antifungal drugs.

Ekizlerian et al.[22] studied the pathogenesis of mycetoma in animals injected with *N. brasiliensis*. It was suggested that the fractions of organisms are chemotactic for granulocytes, and the resultant influx of leukocytes to the site of inoculation is attributed to chemotactic activity induced by products of complement activation, formyl-methionyl peptides, leukotriene B\(_4\), and a soluble low molecular weight factor produced by macrophages. The lipid and polysaccharide constituents of bacteria probably participate in this inflammatory response inducing the liberation of products of complement activation or by inducing macrophage to secrete potent mediators of the acute inflammatory response. 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.

**Clinical Presentation of the Disease**

Over 75% of patients have a lesion of lower extremity, most commonly in the foot (70%) followed by hand involvement. Other sites include the head, neck, chest, shoulder, and arms. The incubation period is variable, from 3 months to 9 years in natural infections. Since the mean duration before the first medical evaluation is long, patients often do not remember the preceding trauma.[23,24] The clinical features are fairly uniform, regardless of the organism involved.[25,26] The pathognomonic feature is a triad of painless firm subcutaneous mass, multiple sinus formation, and a purulent or seropurulent discharge containing grains.

Most cases start as small, painless, subcutaneous nodule at the site of injury which over time softens and ulcerates to discharge a viscous, purulent, or serosanguinous fluid [Figure 1a and b] containing characteristic granules. The granules, composed of colonies of causative organism, are hallmark of mycetoma and vary in size, color, and consistency depending on the etiological species. With time papules, pustules and nodules appear which also break down to form draining sinuses developing on the skin surface [Figure 2a and b]. Overlying skin appears smooth and shiny and is commonly fixed to the underlying tissue. Skin may be hypo- or hyper-pigmented, 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 typical of this disease. Sometimes, the overlying skin may display an increase in sweating secondary to sweat gland hyperplasia and increased local temperature due to increased blood flow secondary to inflammatory process.

The disease progresses to involve the surrounding tissues which become swollen, indurated, and deformed by fibrous tissue reaction and multiple sinus formation. The condition is usually painless but may become very painful with the involvement of bones or as a result of secondary bacterial infection. Nerves and tendons are rarely affected till late in the disease.

Mycetoma is usually localized but may extend slowly by direct contiguity along the fascial planes, invading the subcutaneous tissue, fat, ligaments, muscles, and bones. In eumycotic mycetoma, there may be multiple punched out lytic lesions in bones whereas actinomycotic mycetoma is characterized by both osteolytic and osteosclerotic lesions. The result is gross swelling of the affected part with deformity. Actinomycetoma tends to progress more rapidly, with greater inflammation and tissue destruction and earlier invasion of bone than implantation mycosis.

Spread of the infection may also occur through the lymphatics, resembling sporotrichosis.[27] Metastatic lesions can also occur at various distant lymph nodes, which might become suppurative. These lymph node lesions are more common in actinomyctoma than in eumycetoma. Hematological spread has also been described.

**Figure 1:** (a and b) A female patient with gross swelling of the left foot and ulcers in various stages of healing, with serosanguinous discharge from the active ulcer. Furthermore, evident is the pigmentary changes on the overlying skin

**Figure 2:** (a and b) A male patient with mycetoma with multiple papules, pustules, and nodules breaking down to form draining sinuses on the skin surface. Dorsum of foot of the same patient showing hyperpigmentation of skin with signs of both old healed and active sinuses
Complications
The disease causes disfigurement but is rarely fatal. When left untreated, disease continues to progress, and bacterial superinfection leads to increased morbidity from local abscess formation, cellulitis, and bacterial osteomyelitis. In advanced cases, deformities or ankylosis may occur.

Differential Diagnosis
Mycetoma has to be differentiated from various infectious and noninfectious pathologies. Infectious pathology would usually include chronic infections such as cutaneous tuberculosis, nontuberculous mycobacterial infections of the skin, osteomyelitis (bacterial or tubercular), actinomycosis, chromomycosis, sporotrichosis, blastomycosis of the skin, dermatophyte pseudomycetomas, and botryomycosis.

Noninfectious differentials would include mossy foot or podoconiosis, malignant tumors, such as sarcoma of the skin and soft tissue or bones, and Kaposi sarcoma.

Laboratory Diagnosis
A diagnosis of mycetoma can be made by the classic triad. Diagnosis of the causative organism can be made by microscopic observation of a grain only. Histopathology and culture is usually not necessary. Finally, various serological and molecular tests have also found place in diagnosis of mycetoma.

Specimen collection
Ideally, the discharging fluid, scrapings of sinus walls, and tissue biopsy should be examined for the presence of grains. Saline dressings applied overnight over the swelling or aspiration of grains directly from an unopened sinus tract can also be used. Evaluation of spontaneously extruded grains may not allow diagnosis because these grains may be composed of dead organisms.

The grains extracted are evaluated in three ways to confirm the diagnosis: direct clinical examination, microscopy, and culture. Direct clinical examination involves evaluating the variation in size, color, and consistency of the grains, which can be helpful in rapid but provisional identification of the etiological agent.\(^7,^8\)

Direct microscopy
A Gram's stained preparation is of considerable value in distinguishing between actinomycetoma and eumycetoma in Table 2.\(^{26,28}\) The study of discharged granules crushed on the slide and stained with special stains, most notably lactophenol blue, particularly allows differentiation between the thin filaments of actinomycetoma and the thicker hyphae of eumycetoma.

Histology
It is usually needed when the drainage material cannot be obtained, and in these cases, ideally a deep punch biopsy should be taken to include the subcutaneous tissue.

Hematoxylin and eosin (H and E) stain shows [Figure 3] suppurative granulomas (composed of neutrophils), surrounding characteristic grains which are present in the subcutaneous tissue. Grains or druses are aggregates of septated and branched, radially arranged broad hyphae, sometimes with vacuole formation. They are seen as broad, pink-stained hyphae surrounded by a sharp basophilic strand. The neutrophilic infiltrate is, in turn, surrounded by palisading histiocytes, beyond which a mixed inflammatory infiltrate comprising lymphocytes, plasma cells, eosinophils, and macrophages is seen. In long-standing cases, fibrosis may also be appreciated in the outermost layer.

In eumycetomas apart from H and E, periodic acid–Schiff and Grocott–Gomori staining may be performed for finer details. When an actinomycetoma is suspected, an additional Gram staining should be performed.

Table 2: Difference between mycetoma causing organisms on basis of Gram stain

| Actinomycetoma       | Eumycetoma              |
|----------------------|-------------------------|
| Gram-positive        | Gram-negative           |
| 0.5-1 µm-wide filaments | 2-5 µm-wide hyphae    |
| Septate fine-branching filaments | Septate hyphae         |
| Stained better with Gram stain | Stained better with Gomorimethamine silver or PAS stains |

PAS: Periodic acid-Schiff

\[32\]

Figure 3: Skin biopsy, stained with H and E. ×40 view showing granulomas surrounded by a mixed inflammatory infiltrate comprising lymphocytes, plasma cells, eosinophils, macrophages are seen. Some amount of fibrosis can be seen in the periphery.
Sabouraud 4%, dextrose agar, or Kimmig’s agar is capable of providing an accurate identification of the causative agent. Culture can be performed on grains or from biopsy sample, and incubation at 37°C is necessary because the isolates are human pathogens and probably will grow at 37°C. Fungal cultures should be kept for a longer time, approximately 4–6 weeks, in order not to overlook slowly growing fungi. \textit{M. mycetomatis}, an important causative agent of eumycetomas, grows very slowly. First, growth of colonies is usually not seen before 10–15 days of cultivating.

Cultivation of actinomycetes requires special media and a longer duration than other bacterial cultures (10 days). Recommended culture media for actinomycetes are Lowenstein–Jensen media, thioglycollate broth, Columbia agar, and brain heart infusion agar. Incubation time should comprise approximately 48–72 h and longer at 35°C–37°C.

**Serology**
Serological tests are not usually required; however, they can prove useful in the early stages of the disease, even before granule formation. At present, no useful serological test exists that can reliably diagnose mycetoma. However, several serological assays have been used, including immunoblots, indirect hemagglutination assays, immunodiffusion, counterimmunoelectrophoresis, and ELISA. ELISA appears to be a sensitive test for the detection of circulating antibodies and has been especially used in epidemiological studies. Serological diagnosis has been used in few studies for \textit{N. brasiliensis}, \textit{M. mycetomatis}, and \textit{P. boydii}; however, their sensitivity and specificity is low and may be positive in healthy endemic controls.

**Recent advances in diagnostic techniques**
The development of rapid and inexpensive species-specific polymerase chain reaction (PCR) analyses permits identification of new species and phylogenetic relationships. PCR is done directly on the biopsy specimen, and sequencing of gene regions, for example, internal transcribed spacer 1 (ITS1), ITS2 is usually sufficient in most isolated fungi. In distinct cases, to identify the mold species, however, it will be necessary to use other gene regions as a multilocus sequence analysis, for example, of the large subunit, small subunit 18S nrDNA, β-tubulin, and chitin synthase 1 regions.

**Imaging techniques**
Radiology and ultrasonography enable assessment of disease extent and bony involvement if any. Standard X-ray studies can reveal bony involvement such as periosteal erosion secondary to invasion, osteoporosis, and changes consistent with osteomyelitis, osteolysis, and osteosclerosis. Ultrasonography successfully differentiates the mycetoma from osteomyelitis or tumor. Subtle differences between actinomycetoma and eumycetoma can also be picked up. Eumycetoma produces single or multiple thick-walled cavities, without acoustic enhancement, with grains represented as distinct hyper-reflective echoes. Actinomycetoma produced similar results except grains produced fine echoes that were found at the bottom of the cavities.

The use of helical computerized tomography has recently been shown to provide detailed assessments of soft tissue and visceral involvement and appears to be more sensitive for detecting early changes. However, magnetic resonance imaging (MRI) provides the most comprehensive method for assessment of the bone and soft tissue involvement and may also be useful in evaluating the differential diagnosis of the swelling. A “dot-in-circle sign” has been described as a potentially specific diagnostic finding seen with MRI. 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.

Table 3 briefly summarizes the various diagnostic tests.

**Treatment**
Treatment of mycetoma has proven to be difficult and typically includes antimicrobial agents and surgery. Surgery alone is rarely successful, but the removal of smaller lesions or debulking of larger ones does play an important role, especially in the management of fungal disease. As chemotherapeutic options for actinomycetoma and eumycetoma vary, the clinician must confirm the diagnosis before starting the treatment.
Treatment of actinomycetoma

Actinomycetomas are usually amenable to antibiotic treatment. Several antibiotics, among these cotrimoxazole, dapsone, streptomycin, trimethoprim (TMP), rifampicin, and amoxicillin-clavulanic acid combination, have been used and found to be effective. In addition, combinations such as netilmicin with cotrimoxazole, amikacin with cotrimoxazole and rifampicin, and meropenem have also been used. In vitro sensitivity of actinomyces to ciprofloxacin and linezolid has also been demonstrated, but these are currently not used as a first-line therapy. Today, the common consensus is that cotrimoxazole should be administered as a gold standard therapy in all actinomycetoma patients. Combination antibiotic therapy is preferable to monotherapy to avoid development of drug resistance and to eradicate residual infection. Surgery may be required for some patients unresponsive to medical therapy alone.

Table 3: Summary of diagnostic investigations

| Method         | Advantages                                                                 | Salient points                                                                 | Disadvantage             |
|----------------|-----------------------------------------------------------------------------|-------------------------------------------------------------------------------|--------------------------|
| Direct microscopy | Simple outpatient procedure                                                 | Quick diagnosis of causative organism and hence classification as eumycetoma or actinomycetoma | Expertise required is not available at most places |
| Histology      | In case of eumycetoma, suppurative granulomas composed of neutrophils are seen surrounding characteristic grains | Actinomycetoma histopathology shows the homogeneous eosinophilic material around the grain in a star-shaped manner (Splendore-Hoeppli reaction) | Expertise required is not available at most places |
| Culture        | Species-specific diagnosis is possible                                       |                                                                                | Readily not available Long growth time |
| Serology       | Detection of circulating antibodies                                          | Good sensitivity for detection of cases early in the course                   | Readily not available Costly |
| Radiology      | Reveal bony involvement such as periosteal erosion secondary to invasion, osteoporosis, lytic cavities, and changes consistent with osteomyelitis |                                                                                |                          |
| Ultrasonography| Differentiates the mycetoma from osteomyelitis or tumor                     | Eumycetoma produces single or multiple thick-walled cavities, without acoustic enhancement. In actinomycetoma, the grains produce fine echoes that are usually found at the bottom of the cavities |                          |
| CT             | Good sensitivity for early detection of bone involvement                    |                                                                                |                          |
| MRI            | Most comprehensive method for assessment of the bone and soft tissue involvement | A dot-in-circle sign has been described as a potentially specific diagnostic finding seen with MRI |                          |

CT: Computerized tomography, MRI: Magnetic resonance imaging

In 1987, Welsh demonstrated excellent therapeutic response with amikacin alone and in combination with TMP-SMX (Welsh regimen) in the treatment of 15 patients with poorly responsive actinomycotic mycetoma and those with systemic involvement. The regimen included cyclical dosing of amikacin 15 mg/kg/day, in two divided doses in cycles of 21 days for 1–3 cycles with intervals of 15 days between cycles while cotrimoxazole (one DS tablet BD) was administered continuously for 35–105 days. The 2-week interval of amikacin in the 5-week cycle is used for renal and audiometric monitoring. All patients achieved remission with this regimen with most patients requiring two cycles (42 days) of amikacin and 70 days of cotrimoxazole therapy. Damle et al. in 2008 introduced the modified Welsh regimen in unresponsive patients by adding rifampicin as the third drug.

Ramam et al. initially described a two-step regimen consisting of an intensive phase with penicillin, gentamicin, and cotrimoxazole for 5–7 weeks, followed by maintenance therapy with amoxicillin and cotrimoxazole continued 5–6 months after clinical remission; however, they later modified this to gentamicin (1.5 mg/kg IV) plus TMP-SMX (two DS tablets) given twice daily for 4 weeks followed by continuation of TMP-SMX plus doxycycline (100 mg twice daily). This modified approach had the advantage of reducing the number of injections and duration of intensive phase
and reducing the cost of therapy but still maintaining the efficacy.\cite{48}

Some other combinations that have been found useful are cotrimoxazole with penicillin,\cite{49} dapsone with ampicillin and amikacin,\cite{50} and tetracycline or chloramphenicol.\cite{51}

As a general rule, actinomycetomas should be treated with a combination of cotrimoxazole and dapsone; however, in case of widespread infections, amikacin can be added for 3–5 pulses in the intensive phase.

In case of resistance or allergy to co-trimoxazole or amikacin, co-amoxiclav can be used as an alternative to co-trimoxazole and netilmicin to amikacin. Co-amoxiclav can also be used alone during pregnancy; however, chances of resistance are there. Amikacin combined with a carbapenem, such as imipenem or meropenem, could also be used in refractory cases.\cite{30}

**Treatment of eumycetoma**

Eumycotic mycetomas usually respond less well to drug therapy, and therefore, a combined approach of both medical and surgical therapy is usually undertaken. Complete surgical excision of the lesion followed by long courses of antifungals should form the first line of management in eumycotic mycetoma. Triazole antifungals (itraconazole) are the treatment of choice and usually a prolonged treatment of 1–2 years is required, however, due considerations should be made at appropriate intervals about the response and treatment side effects. Various treatments available for eumycotic mycetomas are in Table 4.

**End point of treatment**

Since the treatment is prolonged, few indicators may be used to define the end point of treatment including skin becoming normal, disappearance of mass, healing of sinuses, and elimination of organisms from the tissue evidenced by the absence of grains in fine-needle aspiration cytology with a type 3 tissue reaction and the disappearance of the grains and cavities on ultrasonography.\cite{17} Radiological examination is essential for follow-up of patients on medical treatment and to assure cure. It usually shows reappearance of normal bone pattern and the disappearance of the soft tissue mass.

**Conclusion**

Mycetoma, being a relatively painless condition, is often diagnosed at an advanced stage where permanent deformity of affected part has already occurred. The chronic nature of the disease leads to a high possibility of superimposed bacterial infection which can worsen the disease. This can cause increased pain and disability as well as septicemia which may be fatal if untreated. Thus, there is a need for correct diagnosis of mycetoma after meticulous clinical examination, assisted by histological and microbiological studies along with the use of special stains and a proper treatment.

Table 5 summarizes the important differences between actinomycetoma and eumycetoma.

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Nil.

**Conflicts of interest**

There are no conflicts of interest.

**Table 4: Treatment options for eumycotic mycetoma**

| Treatment                  | Dose                        | Efficacy                                                                 |
|----------------------------|-----------------------------|--------------------------------------------------------------------------|
| Itraconazole\cite{51,55}   | 400 mg/day in 2 divided doses | Gold standard therapy, however, failures have been reported              |
| Ketoconazole\cite{53,54}   | 400-800 mg/day              | Mainstay of therapy in the past but now use restricted due to potential side effects |
| Terbinafine\cite{51,52}    | 250-500 mg/day              | Has been used in small number of patients with limited efficacy, combination with itraconazole has been found to be successful in few patients |
| Voriconazole\cite{54}      | 400 mg/day in 2 divided doses | Both have been assessed in a very limited number of patients with promising results; however, despite good in vitro activity, long duration of treatment seems to be needed |
| Posaconazole\cite{57}      | 200-800 mg/day              | An expensive option for third world countries                            |
| Newer antifungals: Isavuconazole\cite{58} and ravuconazole\cite{59} |                             | Excellent in vitro activity, however in vitro trials lacking               |
| Liposomal amphotericin B\cite{60} |                             | Poor in vitro activity, toxicity on prolonged use                        |
| Echinocandins\cite{61}     |                             | No in vitro activity against *Madurella mycetomatis*                     |

**What is new?**

- Greater frequency of disease in men may not be just attributable to environmental factors but also to hormonal factors
- Various serological and molecular tests have also found place in diagnosis of mycetoma allowing early diagnosis and identification of new species and phylogenetic relationships
- Magnetic resonance imaging provides the most comprehensive method for assessment of the bone and soft tissue involvement and may also be useful in evaluating the differential diagnosis of the swelling
- Combination antibiotic therapy is a must in case of actinomycetomas
- Several newer antifungals have been tried for eumycetomas though in vivo studies are lacking.
Aerobic species of actinomycetes belonging to the genera *Nocardia*, *Streptomyces*, and *Actinomadura*.

**Epidemiology**
- 75% of Indian cases
- More common in northern India

**Course**
- Rapid progression
- Slow progression

** Destruction**
- More destructive
- Less destructive

**Bone involvement**
- Early bone invasion
- Late bone invasion

**Lymph node spread**
- More common
- Uncommon

**Histopathology**
- Homogeneous eosinophilic material around the grain in a star-shaped manner
- Suppurative granulomas composed of neutrophils seen surrounding characteristic grains

**Culture**
- Lowenstein-Jensen media, thioglycollate broth, Columbia agar, and brain heart infusion agar, at least for 10 days
- Sabouraud 4% dextrose agar or Kimmig's agar, for 4-6 weeks

**Ultrasonography**
- Grains produce fine echoes that are found at the bottom of the cavities
- Produce single or multiple thick-walled cavities, without acoustic enhancement, with grains represented as distinct hyper-reflective echoes

**Treatment**
- Antibiotics, surgery sometimes needed
- Surgery usually needed along with antifungals

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### Table 5: Summary of differences between actinomycetoma and eumycetoma

| Features                  | Actinomycetoma                                                                 | Eumycetoma                                                                 |
|---------------------------|-------------------------------------------------------------------------------|----------------------------------------------------------------------------|
| Etiological agent         | Aerobic species of actinomycetes belonging to the genera *Nocardia*, *Streptomyces*, and *Actinomadura* | Fungi                                                                      |
| Epidemiology              | Prevalence more in drier areas                                                | Prevalence more in sites with rainfall                                     |
| Epidemiology (India)      | 75% of Indian cases                                                           | More common in northern India                                              |
| Course                    | Rapid progression                                                             | Slow progression                                                           |
| Destruction               | More destructive                                                             | Less destructive                                                          |
| Bone involvement          | Early bone invasion                                                          | Late bone invasion                                                        |
| Lymph node spread         | More common                                                                   | Uncommon                                                                   |
| Gram stain                | Tabulated above                                                               |                                                                           |
| Histopathology            | Homogeneous eosinophilic material around the grain in a star-shaped manner    | Suppurative granulomas composed of neutrophils seen surrounding characteristic grains |
| Culture                   | Lowenstein-Jensen media, thioglycollate broth, Columbia agar, and brain heart infusion agar, at least for 10 days | Sabouraud 4% dextrose agar or Kimmig’s agar, for 4-6 weeks                  |
| Ultrasonography           | Grains produce fine echoes that are found at the bottom of the cavities       | Produce single or multiple thick-walled cavities, without acoustic enhancement, with grains represented as distinct hyper-reflective echoes |
| Treatment                 | Antibiotics, surgery sometimes needed                                         | Surgery usually needed along with antifungals                              |

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