

# Eumycetoma, A Report of Two Rare Cases

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## Abstract

Mycetoma is a chronic, slowly progressive, suppurative, granulomatous disease of the subcutaneous tissue characterized by a localized swelling with multiple sinuses discharging granules that are micro-colonies of the causative agents. Eumycotic mycetoma is caused by saprophytic fungi. It is responsible for considerable physical comorbidity, as many cases may require surgical interventions, including amputations. Facilities for tissue culture and sensitivity testing may not be available at resource poor settings, adding to the disease burden. Identification of organisms and appropriate therapy is essential for a successful treatment outcome. Here, we present two rare cases of eumycetoma caused by *Aspergillus*.

**Keywords:** *Aspergillus*, eumycetoma, fungal

## INTRODUCTION

Mycetoma has been acknowledged as a neglected tropical disease (NTD) by the World Health Organization (WHO) in 2016. It was first described in the Madurai district of Tamil Nadu, India. It is more common in males and usually presents between 20 and 50 years of age. It is classified into 2 types: Actinomycetoma and eumycetoma, depending on the causative agent. The highest incidence is reported from the “mycetoma-belt,” which includes the equatorial regions of Africa, Latin America, and Asia. The majority of cases in India are actinomycotic. In India, eumycetoma is more commonly reported from North India, whereas actinomycetoma is commonly reported from Andhra Pradesh, West Bengal, Madhya Pradesh, and Tamil Nadu.<sup>[1]</sup> The most common species of fungi causing eumycetoma are *Madurella* and *Leptosphaeria*. *Aspergillus* is a ubiquitous fungi, opportunistic, filament-forming with over 180 different species. These are found in water, soil, air, plants, etc., and it is a rare etiological agent for mycetoma. Appropriate diagnosis and effective therapy are essential to avoid the high morbidity resulting from the disease.

## CASE REPORT

### Case 1

A 60-year-old male resident of Jabalpur, working in the food industry, presented with a diffuse, ill-defined, indurated, tender, nodular, firm swelling studded with sinuses discharging purulent and serosanguineous discharge consisting of white grains affecting the dorsal and plantar aspects of the left foot for fifteen years. The overlying skin was hyperpigmented and indurated [Figure 1]. The regional lymph nodes did not show any significant enlargement and systemic examination was unremarkable. There was no history of preceding trauma. He was a known diabetic on oral hypoglycemic agents.

Histopathology of the grain revealed pale eosinophilic grains composed of multiple interlacing hyphae with club-shaped ends surrounded by an inflammatory infiltrate of neutrophils [Figure 2A]. Grocott–Gomori staining revealed numerous black-stained fungal hyphae

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**Figure 1:** (a) Case 1: Diffuse, ill-defined indurated tender firm swelling of the left foot. Discharging sinuses, and nodules are present on the medial aspect of the left foot. (b) Case 1: Discharging sinuses and a few healed sinuses on the left sole. (c) Case 1: Discharging sinuses and few healed sinuses on the dorsum of left foot with hyperpigmented and indurated skin

and larger thick chlamyospores [Figure 2B]. Periodic Acid Schiff (PAS) stain revealed pinkish-stained broad club-shaped hyphae [Figure 2C]. Fungal culture of grains revealed the growth of *Aspergillus* species sensitive to ketoconazole and fluconazole and resistant to itraconazole.

X-ray of the left foot (anteroposterior/lateral) showed soft tissue swelling without bony abnormality. Local ultrasonography revealed an ill-defined, hypodense collection in the subcutaneous plane with multiple sinuses. Laboratory investigations were normal.

The patient was treated with oral ketoconazole 200 mg twice daily and a saturated solution of potassium iodide, 5 drops 3 times a day, which was gradually increased to 40 drops 3 times a day with regular monitoring of liver function tests and thyroid function tests for 6 months. The patient started improving with a reduction of swelling and resolution of the sinuses [Figure 3]. He is currently under regular follow-up with continued medical treatment in the form of a tablet Ketoconazole and a saturated solution of potassium iodide.

### Case 2

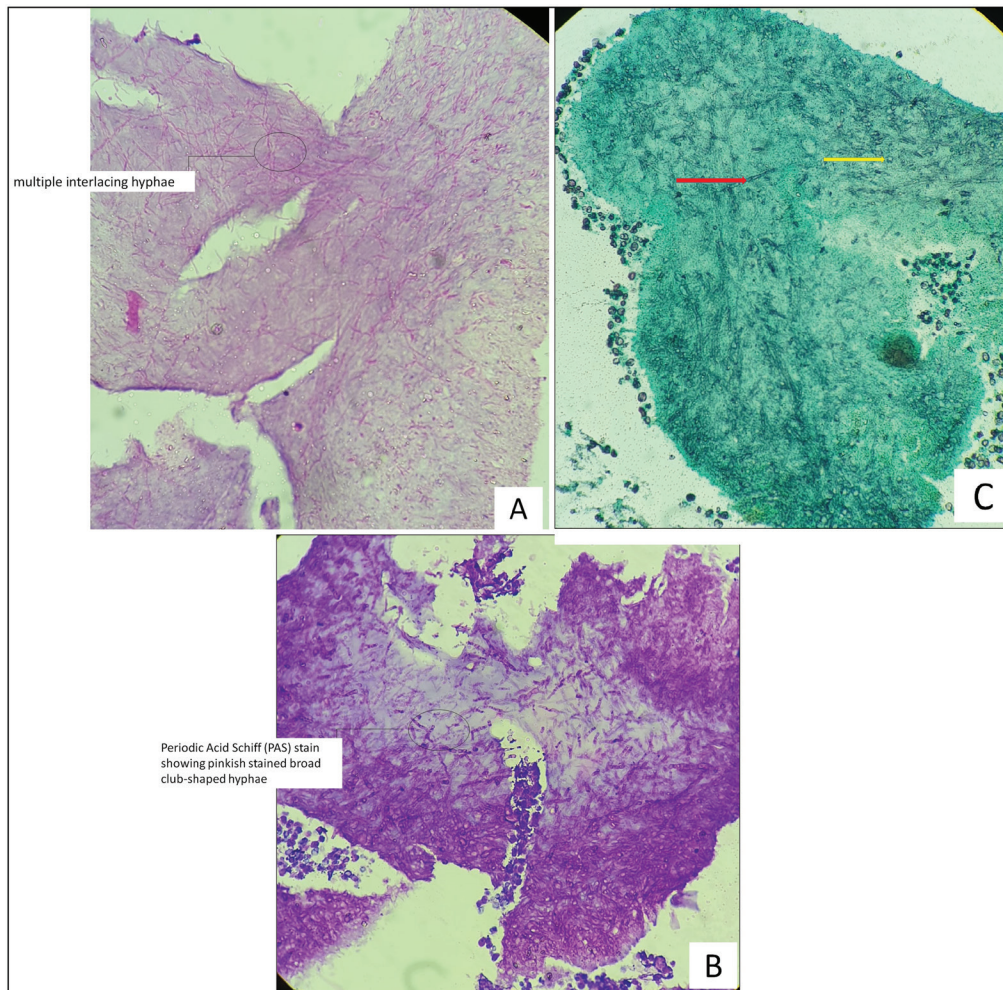
A 43-year-old married female, a housemaid from Mumbai, presented with a tender, ill-defined swelling of the right foot with firm induration and local warmth [Figure 4A] for 8 months, causing difficulty in walking. There was no history of any major medical or surgical illness.

USG of the local part showed multiple hypoechoic areas in the dermis and subcutaneous tissue [Figure 4B]. MRI revealed ill-defined marrow edema at the base of the fourth and fifth metatarsal bones without bony destruction. Skin biopsy revealed a chronic inflammatory infiltrate composed of lymphocytes, epithelioid cells, and histiocytes [Figure 4C]. Fungal culture of tissue samples revealed growth of *Aspergillus* species sensitive to itraconazole. Her routine hematological investigations, including blood sugars, were normal. The patient was treated with oral itraconazole 200 mg twice daily for 8 months, resulting in complete resolution of the lesion, which was confirmed on repeat ultrasonography [Figure 5]. The patient improved well with no signs of recurrence during a follow-up period of 3 years.

### DISCUSSION

The prevalence of eumycetoma in India is less than 0.01 cases per 100,000 inhabitants.<sup>[2]</sup> It most commonly affects field laborers. The most common site of infection is the lower extremity followed by the hand, head, neck, chest, shoulder, and arms. The most common causative organism is *Madurella mycetomatis*.

The disease is characterized by a triad of painless, firm, subcutaneous swelling, multiple sinuses, and discharging granules. Actinomycetoma is the closest differential diagnosis of eumycetoma. The differentiating features between the two diseases are mentioned in Table 1.<sup>[3]</sup> Skin biopsy with hematoxylin and eosin staining shows



**Figure 2:** (a) Histopathology of grain showed pale eosinophilic grains surrounded by inflammatory infiltrate of neutrophils. Grains were composed of multiple interlacing hyphae with club-shaped ends. (b) Periodic Acid Schiff (PAS) stain revealed pinkish-stained broad club-shaped hyphae. (c) Grocott–Gomori staining revealed numerous black-stained fungal hyphae (red arrow) and large thick chlamydospores (yellow arrow)

suppurative granulomas surrounding characteristic grains that are present in the subcutaneous tissue. In eumycetoma, these grains are aggregates of septate and branched, radially arranged broad hyphae. Periodic acid–Schiff and Grocott–Gomori staining may be performed for the demonstration of fungal hyphae. Culture of grains or biopsy samples in special media such as Sabouraud 4% dextrose agar or Kimmig’s agar at 37°C for 4–6 weeks provides identification of the causative agent.

Various imaging modalities may be utilized to assess the extent of the disease. X-ray studies may reveal periosteal erosion, osteoporosis, osteomyelitis, osteolysis, and osteosclerosis.

Further, ultrasonography may reveal single or multiple thick-walled cavities without acoustic enhancement, with grains having hyper-reflective echoes.

Magnetic resonance imaging (MRI) is the most detailed method for assessing bone and soft tissue involvement.<sup>[4,5]</sup>

Serological tests like enzyme-linked immunosorbent assay may be used for detecting circulating antibodies.<sup>[6]</sup>

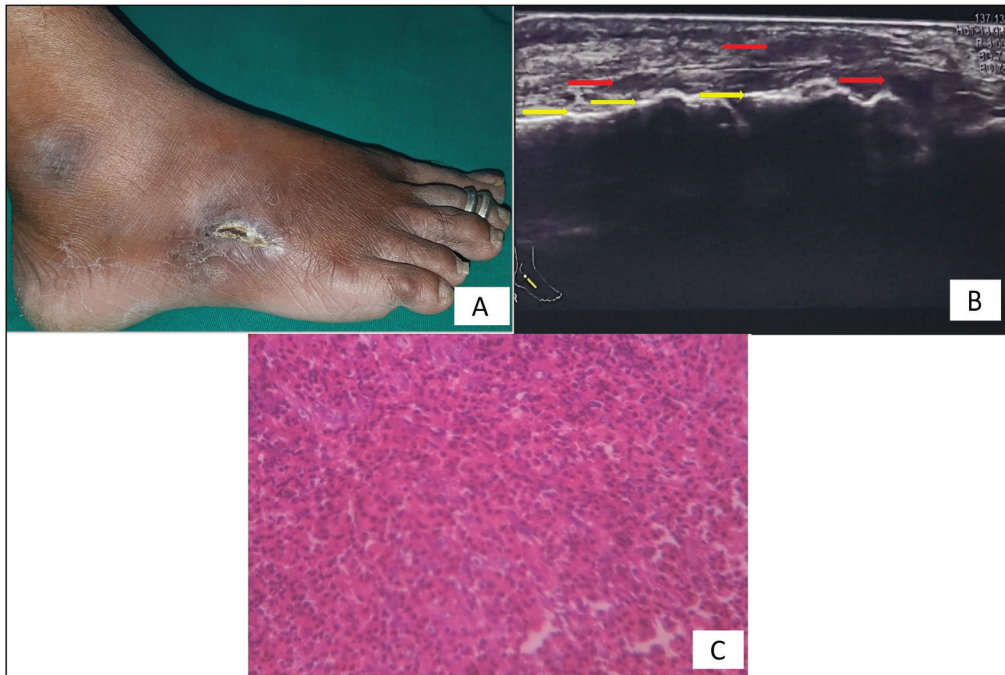
The appropriate treatment of mycetoma depends on precise species identification and the extent of the disease. Triazole antifungals (such as itraconazole) are the treatment of choice for eumycetoma, and usually, a prolonged treatment of 1–2 years is required.<sup>[7,8]</sup> Potassium iodide (KI) gets concentrated in infected granulomas and necrotic tissues, inhibiting further granuloma formation. Its combination with itraconazole leads to an enhanced therapeutic effect in eumycetoma.<sup>[7-9]</sup>

The fungal isolate in both of our cases was identified as *Aspergillus*. Species identification could not be done due to a lack of resources. *Aspergillus* is a rare cause of eumycetoma in India. A summary of cases





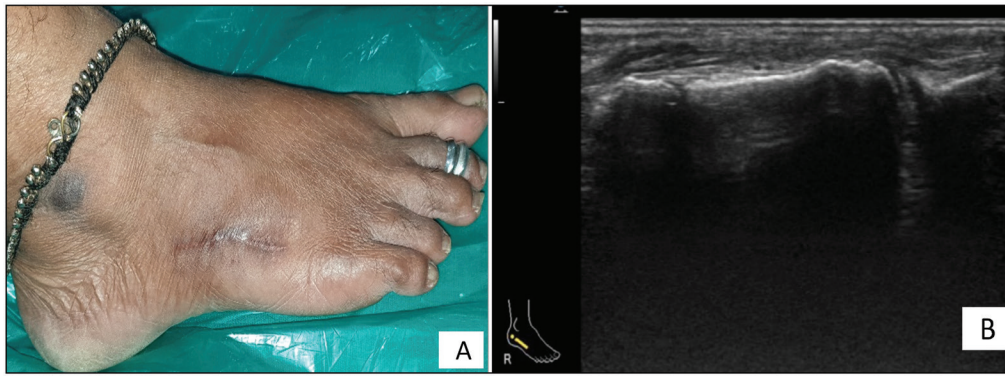
**Figure 3:** (a) Case 1: Healing of lesions on the medial aspect of the left foot. (b) Case 1: Healing of lesions on the medial aspect of the left sole. (c) Case 1: Healing of lesions on the dorsal aspect of the left sole



**Figure 4:** (a) Case 2: Tender ill-defined swelling studded with discharging sinuses, discoloration of the right foot with firm induration and local warmth. (b) Case 2: USG of the local part showed multiple hypoechoic areas (red arrows) in the dermis and subcutaneous tissue suggesting sinus formations with mild periosteal reaction (yellow arrows). (c) Case 2: Deep biopsy revealed a chronic inflammatory infiltrate composed of lymphocytes, epithelioid cells and histiocytes in the dermis

of eumycetoma caused by *Aspergillus* species is mentioned in Table 2. The reported cases have shown male preponderance, with the most common site of

involvement being the lower extremity. Most cases belonged to the age group of 45 to 65 years. *Aspergillus nidulans* and *Aspergillus flavus* grew in culture in two



**Figure 5:** (a) Case 2: Clinical improvement after 8 months of treatment. (b) Case 2: Ultrasonography of the foot post-treatment showing resolution of sinuses

**Table 1: The differentiating features of eumycetoma and actinomycetoma**

Salient Features	Eumycetoma	Actinomycetoma
Epidemiology	More prevalent in humid areas, usually seen in Africa and India	More prevalent in drier areas, usually seen in Central and South America
Causative agent	Fungi	Bacteria
Common species	<i>Madurella mycetomatis</i> (70% of cases), <i>Madurella grisea</i> and <i>Scedosporium apiospermum</i> .	<i>Nocardia brasiliensis</i> , <i>Actinomadura madurae</i> , <i>Actinomadura pelletieri</i> , <i>Streptomyces somaliensis</i>
Characteristics of the causative organisms	Gram-negative, septate hyphae 4–5 microns thick	Gram-negative, fine, branching filaments, about 1 micron thick
Clinical characteristics	Less severe inflammation with fewer sinuses. Rarely disseminative, only invades the primary location, slower spread to bone structures	More severe inflammation with multiple sinuses, more rapid progression, rapid spread to underlying bone causing osteomyelitis
Granule color	Commonly black, white	White, yellowish-white, light red, red, cream, to brownish-yellow.
Bone anomaly	Slower spread to underlying bone structures	Rapid spread to bone structures
Management	<ul style="list-style-type: none"> <li>•Ketoconazole</li> <li>•Itraconazole</li> <li>•Voriconazole</li> <li>•Posaconazole</li> </ul> Surgery is usually definitive	<ul style="list-style-type: none"> <li>•Trimethoprim-sulfamethoxazole</li> <li>•Amikacin-trimethoprim sulfamethoxazole</li> <li>•Amikacin</li> <li>•Rifampicin-gentamycin</li> <li>•Amikacin-impipenem</li> <li>•Linezolid</li> </ul>

cases each. Two patients were diagnosed with type 2 Diabetes mellitus, and one patient was diagnosed with myelofibrosis and underwent allogeneic hematopoietic stem cell transplantation 1 year before presenting with skin lesions. Five of the total cases were reported from India, and the rest from Pakistan, Sudan, and the United States. Most of the cases were managed with oral itraconazole.

Our cases highlight the importance of histopathology, fungal culture, and sensitivity in the appropriate management of eumycetoma. Also, the use of ultrasonography as a noninvasive and less expensive modality to monitor the treatment response in patients of eumycetoma.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**

There are no conflicts of interest.

