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Mycetoma: A report of 8 cases at tertiary care hospital in Central India with review of literature

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Original Article

Abstract

BACKGROUND: Mycetoma is introduced as a rare neglected disease in tropical areas. It is a chronic, localized, slowly progressive infectious granulomatous disease of soft tissue. It may be caused by true fungi such as eumycetoma or filamentous bacteria such as actinomycetoma. In India, there is variation in the species causing mycetoma according to geographical location. The purpose of this study was to review all currently available information to identify knowledge gaps and/or research priorities.

METHODS: The study was conducted retrospectively in the Department of Histopathology for biopsy-confirmed cases of mycetoma. Eight histopathologically confirmed cases were found in the two-year study period from 2018 to 2019, and a clinicopathological analysis of de-identified patient data was done.

RESULTS: Five cases were reported as mycotic mycetoma, and the rest were reported as actinomycosis. All patients were men, and the mean age of presentation was 41.37 years old. The foot, ankle, head, and neck were the sites that were the most infected regions.

CONCLUSION: Mycetoma is a rare disease but should be considered a differential diagnosis of any foot and ankle lump in a patient from the subtropics. An accurate and timely histopathological diagnosis is essential in mycetoma for its treatment and prognosis, as when left untreated, the disease progresses and leads to increased morbidity. Appropriate preventive and control measures can be utilized by health workers/community leaders to educate people at risk to reduce their exposure risk and report the cases as early as possible.

KEYWORDS: Mycetoma; Tropical Disease; Actinomycetoma; Eumycetoma

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Introduction

Mycetoma is a chronic, steadily progressive, localized soft tissue infectious granulomatous disease. It can be caused by true fungi (eumycetoma) or filamentous bacteria (actinomycetoma).

World Health Organization (WHO) introduced mycetoma as a 'neglected tropical disease'. The basis for negligence is that it often affects poor communities in countries with an insufficient number of skilled workers, health services, medical equipment, and care, especially in remote areas. The recurrent course of the disease and poor results of care for mycetoma further add to negligence.[1]

Mycetoma was not included on the WHO list until July 2013, despite its estimated prevalence of two per 100000 people being equivalent to other recognized neglected diseases.[2] South and Central America and Africa are more common places where actinomycetomas can be found there. The most endemic area for mycetoma is Sudan. [3, 4] Tissue

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mild trauma and subcutaneous tissue are the main signs of the disease, but most patients did not have a history of trauma. It can spread to the skin and deep tissues, resulting in the destruction and deformity of the tissue. Malignant neoplasia, tuberculosis, or nocardiosis are differential diagnoses of mycetoma since it often progresses continuously and gradually. Typically, penetration into deeper structures often leads to disfigurement as the infection progresses, prompting patients to seek medical advice. Within India, there is broad dissimilarity in the distribution of cases, as eumycetoma is common in Rajasthan. In contrast, other states, namely Andhra Pradesh, Punjab, Madhya Pradesh, Tamil Nadu, and West Bengal, report most cases of actinomycetoma.[2]

However, there is not much literature regarding the detailed epidemiology of the cases due to lack of reporting. Men are more infected by mycetoma (male to female ratio = 3:1), possibly due to the more common involvement of men in agricultural work.[5,6] Poor hygiene, low socioeconomic status, and inadequate nutrition are identified risk factors. Although mycetoma is generally considered a disease of the second to the fourth decade, no age group is exempted from it in endemic countries.[7,8] This disease has many unintended medical, socio-economic, and psychological impacts on the patients and their families in endemic regions.

The purpose of this study was to review all currently available information to identify knowledge gaps and research priorities. This study is significant because many people suffer from mycetoma, but basic epidemiological information is still lacking.

Methods

After getting approval from the institute ethics committee, this retrospective study was conducted in the histopathology section of the Department of Pathology. We received a total of 15000 specimens approximately in the histopathology section for two years from 2018 to 2019, of which 8 cases reported to have confirmed mycetoma who underwent surgical treatment in our hospital were included. The total number of chronic infections reported in the department of histopathology for the same period was approximately 720, out of which 8 cases were of mycetoma (1.11%). Except for these eight cases of mycetoma, the other chronically infected cases were considered under the exclusion.

Patients' case records were reviewed for age, gender, occupation, site of involvement, disease duration, and bone involvement. The clinical data from the hospital information system of these patients were carefully reviewed, and clinicopathological analysis was done after de-identification. Mycetoma was suspected on clinical examination, ultrasound, and conventional X-ray examination of the affected part, and the diagnosis was given by cytological and histopathological examination of the lesion.

The classic triad of tumefaction, discharging sinuses, and grain presence was used to make a clinical diagnosis. It was possible to perform a culture examination on one patient and a polymerase chain reaction (PCR) on two others.

This study was approved by the institutional ethics committee of Mahatma Gandhi Institute of Medical Sciences, Sevagram, Maharashtra, India (MGIMS/IEC/PATH/64/2020, 20/05/2020). Informed consent was also taken from every patient in their language regarding their willingness to participate in the study.

The data obtained were tabulated, and statistical analysis was performed. All statistical analyses were done using SPSS statistical software (version 20, IBM Corp. Released 2012. IBM SPSS Statistics for Window, Armonk, NY).

Results

A total of eight cases of mycetoma have

been reported over two years, including three cases of actinomycosis and five cases of mycotic mycetoma. The time from onset of signs and symptoms to seeking medical care ranged from three months to two years in our patients. All patients were men, and a history of trauma was reported in 4 cases. Comorbidities were present in two patients, including hypothyroidism and diabetes mellitus (DM). Three patients had to undergo amputation of the involved part.

The age group from 30 to 50 years showed the maximum number of cases correlated with the farming and working-age group. The mean age of presentation was 41.37 years (range: 26-52 years, the mean age for eumycetoma was 41.8 years and 40.6 years for actinomycetoma). The predominant site of involvement was the foot region (Figure 1), followed by one case affecting the ankle and head and neck region. Bone involvement was noted in two of the cases. Demographic details and clinical history and investigations are shown in table 1.

Figure 2 shows Exophiala jeanselmei microbiological characteristics, presenting slow-growing colonies ranging from green to greyish black.

Figure 3 shows histological features of eumycetoma and actinomycetoma. In the case of eumycetoma, suppurative granuloma or the characteristic 'grains' were composed of neutrophils, lymphocytes, plasma cells, multinucleated giant cells surrounding the septate, and branching fungal hyphae were seen. On periodic acid-Schiff (PAS) stain, delineated thick septate hyphae were seen. Actinomycetoma shows the homogenous eosinophilic material in a star-shaped manner (Splendore-Hoeppli reaction) which is a tangled mass of bacterial filaments in the center of granuloma.

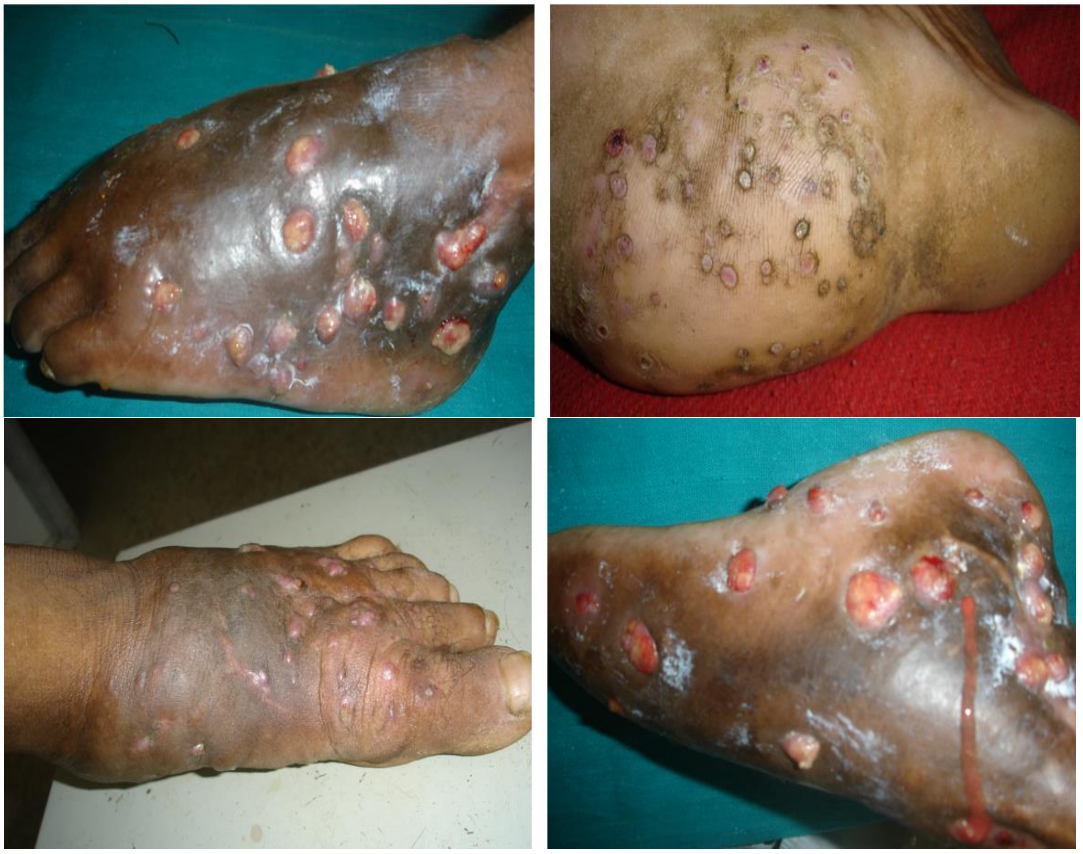

Figure 1. Lesion involving foot and ankle

Table 1. Demographic, clinical history, and investigation details

Age (year)	Sex	Clinical details	Duration (month)	Bone involvement	Culture	Grains	Histopathology reports diagnosis
31	Man	Growth over the right foot with multiple sinuses	4	+	-	+	Mycotic mycetoma
38	Man	Swelling over the left foot	6	-	-	-	Mycotic mycetoma
52	Man	Swelling over the right foot	24	-	-	+	Mycotic mycetoma
51	Man	Swelling over the left side of the face	8	-	-	-	Actinomycosis
26	Man	Lesion over the right foot	1	-	-	-	Actinomycosis
45	Man	Complains of swelling over the right foot	4	-	-	-	Actinomycosis
43	Man	Painful swelling over the left ankle	9	-	-	-	Mycotic mycetoma
45	Man	Swelling over the dorsum of left foot with pain and discharge	15	+	Exophiala jeanselmei	+	Mycotic mycetoma

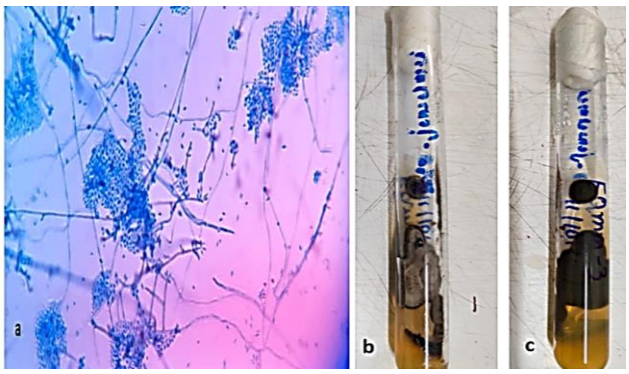

Figure 2. a, b, c) Microbiological features of Exophiala jeanselmei

Discussion

In ancient Indian Sanskrit texts, the earliest description of this disease process is found as "padavalmikam", which means 'anthill foot'.[9] The first clinical case in India, however, was documented in 1832. It was named Madura's foot in 1846 by Colebrook after field workers noted it in the Madurai district of Tamil Nadu.[10] We reviewed similar case series in India and found that around 399 cases had been reported in the last ten years, as shown in table 2. These studies[11-16] also show similar results with diagnoses of eumycetoma and actinomycosis with the following characteristics.[17]

Over 75% of patients showed lesions on the foot (70%), hands, head and neck, chest, shoulders, and arms. Mycetoma has an incubation period from 3 months to 9 years.[18] Mycetoma can spread to subcutaneous tissue, fat, ligaments, muscles, bones, and the fascial plane. Numerous punched-out lytic lesions in the bones of eumycotic mycetoma, osteolytic, and osteosclerotic lesions are characterized by actinomycotic mycetoma.

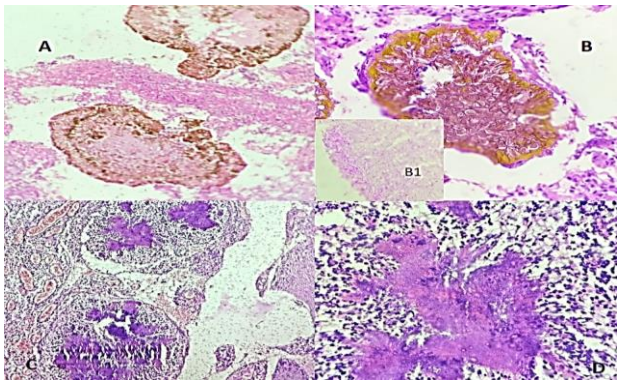

Figure 3. A) (Eumycetoma) Histological section showing eumycotic colony within fibro collagenous tissue; B) (Eumycetoma) Histological section showing interlacing hyphae and oval club-shaped ends; B1) Periodic acid-Schiff (PAS) stain 400X; C) (Actinomycosis) Biopsy skin (×10) – granuloma with a sulfur granule of actinomycosis; D) (Actinomycosis) High power (×40) – actinomycosis colony (sulfur granule) showing a tangled mass of filaments surrounded by radiating

Table 2. Studies on mycetoma from various parts of India in the last decade

Author	Total cases	Actinomycosis	Eumycetoma	Site(s) involved
Sawatkar et al.[11]	11	7	4	Foot (6), knee (2), leg (1), forearm (1), forehead (1)
Padhi et al.[12]	13	8	5	Foot and lower extremity (10), trunk (2), cheek (1)
Bakshi and Mathur[13]	73	25	48	Foot (73)
Maiti et al.[14]	264	197	67	Lower extremity (186), upper extremity (8), scalp (2), abdomen (3), chest (11), back (14), neck and shoulder (10), buttocks (5), upper thigh (12), upper arm (13)
Dubey et al.[15]	33	3	30	Foot (22), hands and trunk (11)
Chufal et al.[16]	5	3	2	Foot (5)

The usual outcome is the gross swelling of the affected portion with the resulting deformity.[18] One of the cases diagnosed as actinomycosis in the head and neck region presented clinically with a history of jaw swelling, which was insidious in onset, progressively increasing in size, and was associated with dull aching pain in the left mandibular region. The infective agent caused the pathogenesis of mycetoma. It occurs after penetration of fungi mycetoma through trauma sites. Some patients do not have any awareness of instigating factors.[1]

Agricultural occupation and living in rural environments are essential causes and farm workers are more exposed to mycetoma. Inoculation through standing on a splinter or thorn can allow penetration of the soil saprophyte.[19] Primary actinomyces of an extremity are very unusual due to the organism's endogenous habitat. It most likely occurs due to traumatic injury to the foot due to occupational exposure while farming barefoot, which is a widespread practice in rural India. In Streptomyces somaliensis (S. somaliensis) infection and after stimulation of peripheral blood mononuclear cells by Madurella mycetomatis (M. mycetomatis), antigens Th2-like responses [interleukin (IL)-10 and IL-4] were identified in primary lesions and in draining lymph nodes. Responses to Th1 are observed in the acute infection period and healthy endemic controls.[20] Humoral antibodies have an important role in disease; in immunocompetent BALB/c mice, immunoglobulin (Ig) M antibodies caused specific protection in experimental Nippostrongylus brasiliensis (N. brasiliensis) infection. The loss of IgM antibodies and the appearance of IgG is postulated to account for the slow onset of experimental actinomycetoma and the delay in development.[21] A biopsy is needed where it is impossible to obtain drainage material, and, in these situations, a deep punch biopsy should preferably be performed to include the subcutaneous tissue.[22]

Haematoxylin and eosin (H&E) stain indicates suppurative granulomas (composed of eutrophils), surrounding characteristic grains present in the subcutaneous tissue. Grains or druses are aggregates of separate and branched, radially arranged broad hyphae, and vacuole formation. Organisms are detected as broad, pink-stained hyphae surrounded by a sharp basophilic strand or filamentous bacteria forming tangled and radiating masses. The neutrophilic infiltrate is then surrounded by palisading histiocytes, and a mixed inflammatory infiltrate comprising lymphocytes, plasma cells, eosinophils, and macrophages is detected. In long-standing cases, fibrosis can also be recognized in the outermost layer. PAS and Grocott-Gomori staining can be performed. When an actinomycetoma is suspected, an additional Gram staining should be performed. An extra Gram staining is done when an actinomycetoma is suspicious. Mycetoma has to be distinguished from different infectious and non-infectious pathologies. Infectious

pathology usually includes 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. Non-infectious differentials include mossy foot or podoconiosis, malignant tumors, such as sarcoma of the skin and soft tissue or bones, and Kaposi sarcoma.[18]

Systemic antibiotics usually have a strong therapeutic response in actinomycetoma. Co-trimoxazole (TMP-SMX) is currently the gold standard for actinomycetoma therapy. Dapsone, netilmycin, and DA-7867 are some other medications that have been explored in combination with TMP-SMX (an experimental oxazolidinone, tried in vivo against N. brasiliensis). Oral linezolid (600 mg twice a day) in combination with TMP-SMX has been found to have a favorable clinical outcome, paving the path for patients to prefer oral treatment. TMP-SMX can be changed with amoxicillin-clavulanate or carbapenems such as imipenem or meropenem in non-responders or those allergic to the combination, and amikacin can be replaced with netilmicin in those who are allergic to the combination.[23]

Due to poor drug penetration through the fibrous encasement of the lesion, surgical debulking is an essential aspect of the treatment for eumycetoma. Nowadays, itraconazole (400 mg/day) in two divided dosages is regarded as the gold standard treatment; nonetheless, patient response and treatment duration vary. Terbinafine (250-500 mg/day) has shown minimal efficacy when administered alone. However, it can be used with itraconazole to improve effectiveness. Both voriconazole (400 mg/day in two divided dosages) and posaconazole (200-800 mg/day) have shown good in-vitro efficacy. Still, their use is limited due to the prolonged treatment period and a lack of data on their response. Fosravuconazole, a prodrug of ravuconazole, and isavuconazole, two newer medicines, have shown promise in vitro tests and are currently being evaluated in clinical trials.[24]

The main limitations of this study are the small sample size and the short duration of the study. Further studies are required to access accurate diagnosis, parmacotherapy and the use of substantial sample size. It would be beneficial to have a specific treatment plan for mycetoma.

Conclusion

Mycetoma is a rare disease but should be considered a differential diagnosis of any foot and ankle lump in a patient from the subtropics. Accurate identification of the mycetoma causative agent is required for treatment. Thus, there is a need for correct diagnosis of mycetoma after meticulous clinical examination supported by radiological examination, histological, and microbiological studies using special stains. The treatment of such cases and the response should minimize disease-related disfigurement. Health workers/community leaders can utilize appropriate preventive and control measures to educate people at risk to reduce their exposure risk and report the cases as early as possible.

Conflict of Interests

Authors have no conflict of interests.

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