Original Article

Mycetoma: A Common Yet Unrecognized Health Burden in Central India

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Abstract

Context: Mycetoma is a chronic suppurative infective disorder of skin, subcutaneous tissue, fascia, and bones caused by the traumatic inoculation of either fungal (eumycotic) or bacterial (actinomycotic) organisms present in the soil. Triad of tumefaction, discharging sinuses, and grains characterizes the disease. **Aims:** This study was undertaken to study the clinical spectrum and treatment response of mycetoma in central India. **Settings and Design:** It was a retrospective study of clinical and/or biopsy-proven and treated cases of mycetoma from November 2015 to October 2016. **Subjects and Methods:** Medical records of diagnosed and treated mycetoma patients were enrolled retrospectively during November 2015 and October 2016. Case records of patients were evaluated with respect to demographic, clinical, microbiological details, bone involvement, and treatment. Type of therapies and outcome, wherever available, were also assessed. **Statistical Analysis:** Statistical analysis was done using proportion, mean, and percentages. **Results:** Eleven cases (male = 8) were seen during the study period (seven actinomycetoma and four eumycetoma). Foot and lower extremity was the most common site (9/11), whereas upper extremity and forehead were involved in one case each. On culture, the organisms isolated were *Phialophora* and *Fusarium*. Modified Welsch regimen was started in six of seven patients with actinomycetoma, whereas one was started on sulfamethoxazole–trimethoprim and a combination of amoxicillin and clavulanic acid therapy. All four cases of eumycetoma were treated with itraconazole. On follow-up, six cases of actinomycetoma cases showed significant improvement. Two cases of eumycetoma showed mild to moderate improvement and one case required surgical intervention. One case each of actinomycetoma and eumycetoma were lost to follow-up. **Conclusion:** Mycetoma has been recognized as a neglected tropical disease by the World Health Organization, recently. There are very few case reports from the central part of India. Prominent case detection in our study emphasizes the need of larger studies to know the extent of disease in this part of India.

Keywords: *Actinomycetoma, eumycetoma, itraconazole, modified Welsh regimen*

Introduction

Mycetoma is a chronic infectious disease of the skin, subcutaneous tissue, and bone with high morbidity. The lesion is characterized by the triad of tumefaction, discharging sinuses, and the grains that are formed by the colonies of causal organisms. Depending on the organism, it can be either actinomycotic or eumycotic. The disease is common in people with low socioeconomic status, mostly who are field workers. Although it is prevalent worldwide, it continues to be a major health problem in the tropical and subtropical countries such as India.[1-3]

Dry areas are more facilitative for actinomycetoma, whereas eumycetoma is more common in areas with more rainfall.[3] Within India, there is wide variation in the cases, as eumycetoma is common in Rajasthan, whereas other states, namely, Andhra Pradesh, Punjab, Madhya Pradesh, Tamil Nadu, and West Bengal report most cases of actinomycetoma.[2] However, there is a dearth in literature regarding the exact epidemiology of the cases due to lack to reporting. Herein, we present our experience of cases of mycetoma which we came across at the Government Medical Institute, Nagpur (Maharashtra), which is in the central part of India.

Subjects and Methods

It was a retrospective study of clinically suspicious cases of mycetoma from November 2015 to October 2016. Institutional ethical committee clearance was taken. Clinical diagnosis was made by

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the classic triad of tumefaction, discharging sinuses, and presence of grains. Case records of patients were evaluated with respect to age, gender, occupation, site of involvement, duration of disease, and bone involvement. KOH, Gram stain, Periodic acid–Schiff stain, fine-needle aspiration cytology, and biopsy were performed in all cases. Imaging modalities such as X-ray, ultrasonography, and MRI were performed wherever applicable. Categorization of the lesion into eumycotic or actinomycotic was based on either clinical and/or histopathological and culture characteristics. Microbiological parameters such as grain size, color (by direct examination with 10% KOH), and culture results were correlated wherever available. All patients with eumycetoma were treated with itraconazole 400 mg daily. Six patients with actinomycetoma were treated with modified welsh regimen.[4] Each cycle comprised amikacin (15 mg/kg/day) in two divided doses 12 h apart for 21 days at a interval of 15 days along with daily administration of sulfamethoxazole–trimethoprim (35 + 7 mg/kg/day) and rifampicin at a dose of 10 mg/kg/day.[4] Six patients with actnomycetoma received five such cycles. The demographic details, clinicopathological, microbiological, and therapeutic outcome data of all 11 patients are represented in Tables 1 and 2. Statically analysis was done using mean, median, and proportion.

Results

Seven patients belonged to Nagpur city and its rural area, whereas two patients each belonged to the adjacent states of Madhya Pradesh (Balaghat) and Chhattisgarh (Rajnandgaon). Among the 11 patients, 7 cases were of actinomycetoma (actinomycetoma: eumycetoma = 7:4). The male-to-female ratio was 8:3 with a mean age of patients being 32 years (age range = 18–55 years). The average duration of reporting to our institute was 43.2 months (range = 8–120 months). Foot and lower extremity was the most common site of involvement (9/11) [Figure 1a and b]. Upper extremity and forehead were involved in one patient each [Figure 1c and d]. Black grains were isolated in three patients and KOH, examination of which showed fungal elements, suggestive of eumycetoma [Figure 2a-d]. Histopathology from discharging sinuses of clinically suspected eumycotic lesion revealed sulfur granule showing thick septate hyphae at the periphery of granules surrounded by infiltrate comprising lymphoid cells, histiocytes, neutrophils, eosinophils, plasma cells, and fibroblasts in

Table 1: Demographic details and clinical history details

Age (years)	Sex	Residence	Occupation	Site	History (months)	Grains
24	M	Nagpur	Worker	Foot	12	+
35	F	Gondia	Farmer	Right forearm	60	−
36	M	Gondia	Driver	Knee	8	−
55	M	Rajnandgaon (Chattisgarh)	Farmer	Foot	120	−
24	F	Balaghat (Madhya Pradesh)	Farmer	Foot	24	−
45	M	Nagpur	Farmer	Foot	36	+
38	F	Nagpur	Worker	Leg	84	−
20	M	Gondia	Student	Foot	32	−
32	M	Balaghat (Madhya Pradesh)	Farmer	Forehead	20	−
18	M	Chattisgarh	Student	Knee	36	−
19	M	Amravati	Student	Foot	48	+

Table 2: Investigation details, treatment details, and outcome

		Culture	Bone involvement	Diagnosis	HP	Follow-up
1	+	−	+	Eumycetoma	Itraconazole 200 mg BD Addition of SSKI for 2 months	Mild to moderate
2	−	−	−	Actinomycetoma	Modified Welsh regime	Good improvement
3	+	−	+	Actinomycetoma	Modified Welsh regime	Good improvement
4	−	−	+	Actinomycetoma	Modified Welsh regime	Good improvement
5	−	−	+	Actinomycetoma	Septran plus amoxicillin and clavulinic acid combination	Lost to follow-up
6	+	*Exophila* species	+	Eumycetoma	Itraconazole 200 mg BD	Referred to surgery
7	+	−	−	Actinomycetoma	Modified Welsh regime	Good improvement
8	+	−	+	Actinomycetoma	Modified Welsh regime	Good improvement
9	+	−	+	Eumycetoma	Itraconazole 200 mg BD	Lost to follow-up
10	−	−	-	Actinomycetoma	Modified Welsh regime	Good improvement
11	−	*Fusarium* species	+	Eumycetoma	Itraconazole 200 mg BD	Mild to moderate improvement

HP=Histopathology, SSKI=Supersaturated Potassium Iodide

deep reticular dermis [Figure 3a and b]. Biopsy taken from the discharging sinuses of actinomycotic lesion revealed epidermis with acanthosis and irregular colony comprising filamentous bacteria surrounded by mixed inflammatory cells in dermis [Figure 4a and b]. Culture was done in all patients and was positive only in two patients with eumycetoma. Fungal growth of two organisms, namely, *Exophiala jeanselmei* and *Fusarium*, were identified on sabouraud dextrose agar culture. Slide culture of *E. jeanselmei* species showed septate hyphae with tubular conidiophore bearing clusters of conidia at the tips and also along the sides of hyphae [Figure 5a and b]. Slide culture of *Fusarium* species showed septate hyphae with sickle-shaped multiseptate macroconidia [Figure 5c and d]. All patients with actinomycetoma and one case of eumycetoma had underlying bone involvement. Ill-defined permeative pattern of bony destruction along with soft tissue swelling was the most common radiological finding [Figure 6a and b]. Modified Welsh regimen was initiated in six patients with actinomycetoma, whereas one pregnant patient was treated with sulfamethoxazole–trimethoprim and a combination of amoxicillin and clavulanic acid therapy.

All four patients with eumycetoma were treated with oral itraconazole at a dose of 400 mg daily. On follow-up, six patients with actinomycetoma showed significant improvement after five cycles of modified Welsh regimen [Figure 7a-d]. Two patients with eumycetoma showed moderate improvement [Figure 8a and b]. Surgical debridement was required in one patient with eumycetoma. One case each of actinomycetoma and eumycetoma were lost to follow-up.

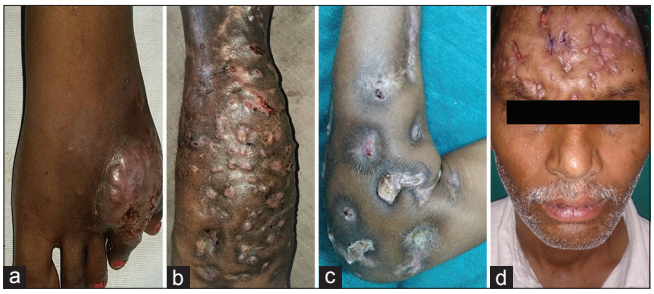

Figure 1: Swelling with multiple discharging sinuses of foot (a), lower leg (b), upper extremity (c), and forehead (d)

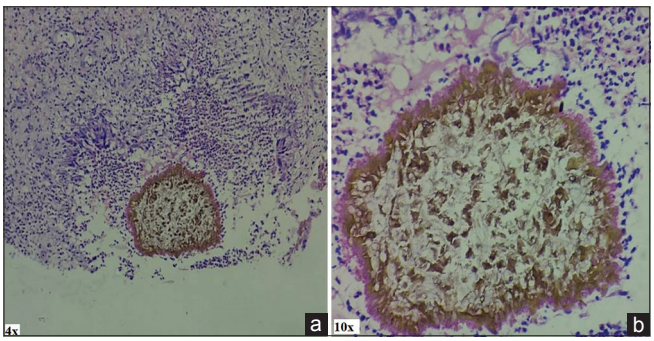

Figure 3: (a and b) Histopathology from discharging sinuses of clinically suspected eumycotic lesion revealed sulfur granule showing thick septate hyphae at the periphery of granules surrounded by infiltrate comprising lymphoid cells, histiocytes, neutrophils, eosinophils, plasma cells, and fibroblasts in deep reticular dermis (×40, ×100)

Discussion

Mycetoma, caused by bacteria (actinomycetoma) or fungi (eumycetoma), is a devastating, neglected tropical disease characterised by extensive tissue destruction, deformities, and disabilities in the affected patients.[5] It is also commonly referred as "Madura Foot" as it was first described in Madurai in South India, in 1842. It typically affects poor communities in the tropical and subtropical belt such as Sudan, Mexico, and India.[3] Prevalence of mycetoma can be generalized over

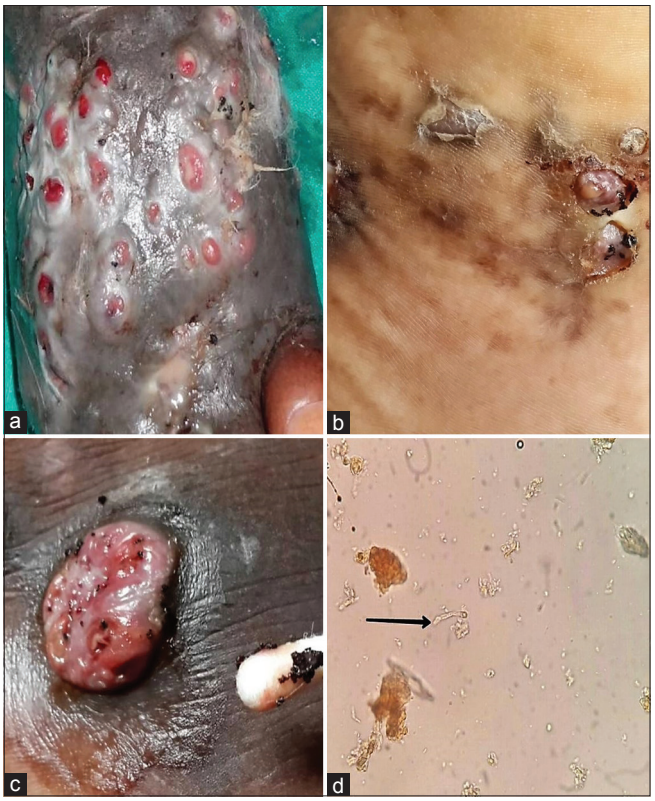

Figure 2: Black grains isolated from discharging sinuses over dosum of foot (a), plantar aspect of foot (b and c), and fungal elements seen on KOH examination of grains suggestive of eumycetoma(d)

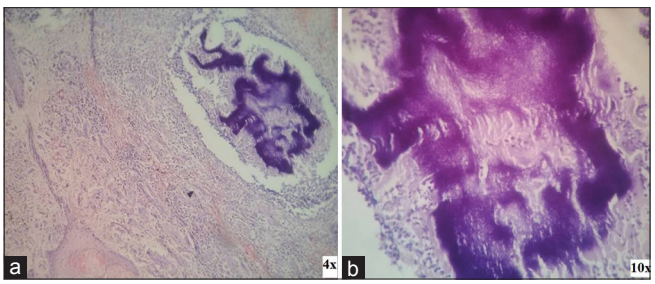

Figure 4: (a and b) Biopsy taken from discharging sinuses of actinomycotic lesion revealed epidermis with acanthosis and irregular colony comprising filamentous bacteria surrounded by mixed inflammatory cells in dermis (×40, ×100)

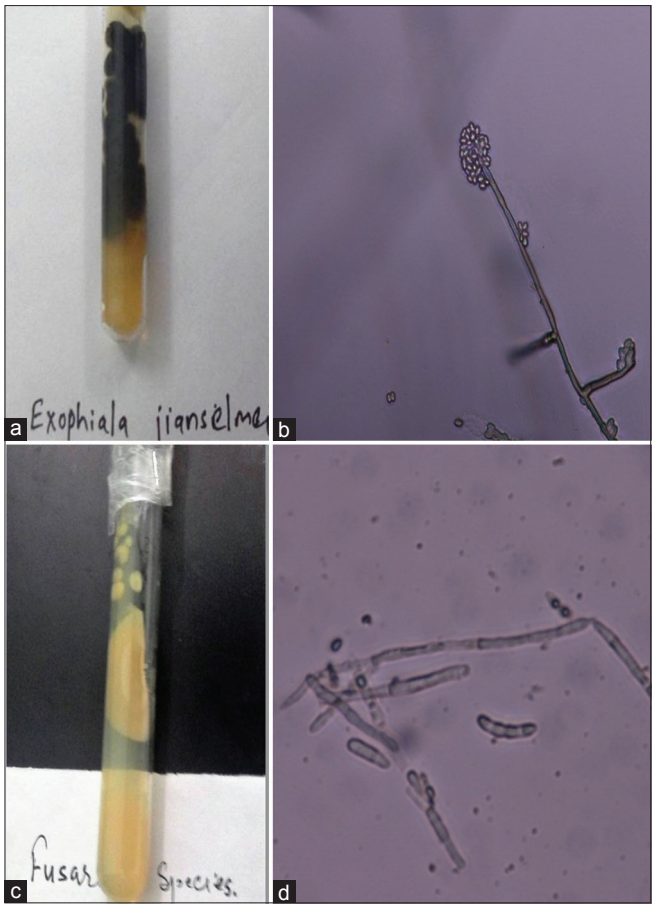

Figure 5: (a and b) Slide culture of *Exophiala jeanselmei* species showing septate hyphae with tubular conidiophore bearing clusters of conidia at the tips and also along the sides of hyphae. (c and d) Slide culture of *Fusarium* species showing septate hyphae with sickle-shaped multiseptate macroconidia

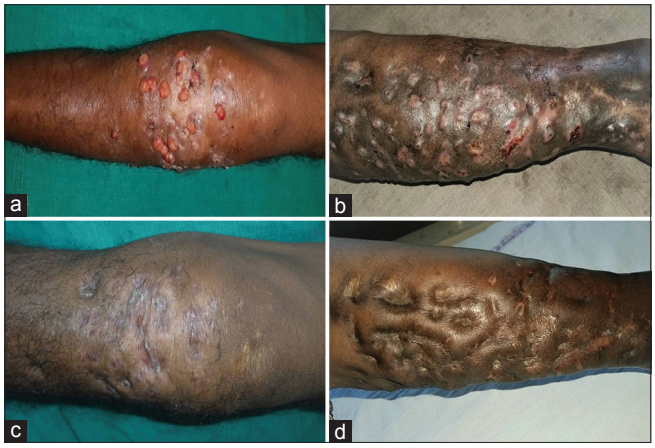

Figure 7: Pretreatment and posttreatment images of case of actinomycetoma over right knee (a and b) and right leg lesions (c and d)

these countries except one, India.[2] These may be because of the variation in the climate, socioeconomic factors, and the variations in reporting in the literature.

The male-to-female ratio of mycetoma ranges from 1.6 to 6.6:1 in adults,[6-8] a finding similar to ours.

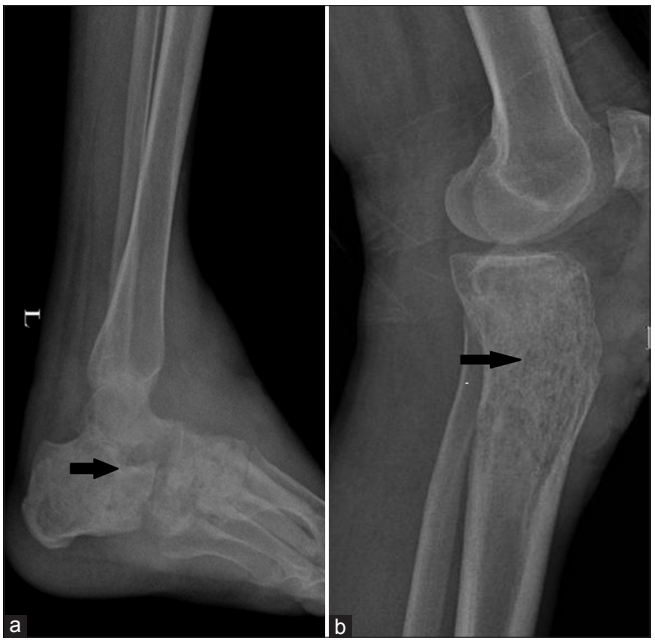

Figure 6: Ill-defined permeative pattern of bony destruction along with soft tissue swelling over upper tibia (a) and talus, calcaneum, and cuboid bones (b)

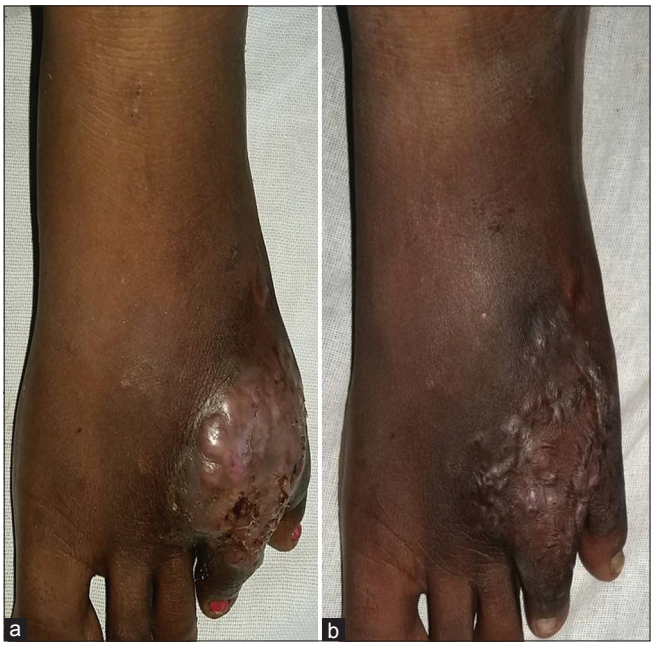

Figure 8: Pretreatment (a) and posttreatment (b) images of case of eumycetoma over foot

Mycetoma is predominantly a disease of men in rural areas, who work barefoot, putting them at a greater risk of acquiring trauma and infection by these pathogens. As the disease does not produce pain or any other discomfort, it usually goes unnoticed for a long period of time, until it produces a significant deformity. Poor hygiene, low socioeconomic status, and low nutrition are the suggested risk factors. Although mycetoma is generally considered a disease of second to fourth

decade, children and adolescents can also be affected in endemic countries.[4,9,10]

In this series, seven were farmers and field laborers by occupation, whereas other three were students and one was driver. A strong history of injury was available only in three patients. The average duration of reporting was found to be 43.2 months (range = 8–120 months). This can be ascribed to asymptomatic, painless, slow progressive nature of the disease, low health education, improper/inadequate treatment from local healthcare provider and social stigma associated with the disease.

Foot and lower extremities followed by hand have been mentioned as the commonest sites of mycetoma.[4] In our series, seven patients had involvement of foot, two had involvement of knee, one had involvement of right forearm, and one had involvement of forehead. Involvement of uncommon sites such as upper extremity, trunk, buttocks, face, head, and neck[4,11,12] suggest that mycetoma is not just a disease of lower extremities. It further highlights that if prompt diagnosis and treatment is not made, then deformity is certain. The majority of published literature on mycetoma showed actinomycetoma outnumbering eumycetoma cases which correlated with our study (7:4).[13] The common organisms causing mycetoma in the Indian scenario are *Actinomadura madurae*, *Nippostrongylus brasiliensis*, and *Actinomadura pelletieri*. However, we could only get growth of *Phialophora* and *Fusarium* in our series. Cultures for all cases of actinomycetoma were negative. Bakshi and Mathur found *Madurella mycetomatis* as the most common eumycotic agent in their histopathological analysis.[14] Padhi *et al.* found *Madurella mycetomatis*, *Neoscytalidium dimidiatum*, and *Aspergillus flavus* as the most common agent of eumycetoma.[13] Precise identification of causative organism was difficult in our setup due to lack of facilities and/or partial treatment of patients from outside, stringent growth requirements, as well as the small numbers of viable organisms present in a long-standing, inflammatory lesion. Radiological findings of bone involvement include periosteal erosion secondary to invasion, osteoporosis, and changes consistent with osteomyelitis, osteolysis, and osteosclerosis. Subtle radiographic features such as few, larger (≥1 cm in diameter) lytic lesions prompt toward eumycetoma, whereas multiple, smaller lytic lesions are found in actinomycetoma.[9]

Polymerase chain reaction (PCR) is rapid and inexpensive method used in diagnosis of mycetoma. PCR is done directly on the biopsy specimen, and sequencing of gene regions, for example, internal transcribed spacer 1 (ITS1) and ITS2, is usually sufficient in most isolated fungi.[15] But this facility is not available at our institution.

Complete therapeutic cure of mycetoma is a major challenge. Actinomycetomas are usually well-responsive to antibiotic treatment. Several antibiotics such as cotrimoxazole, dapsone, streptomycin, trimethoprim, rifampicin, and amoxicillin–clavulanic acid combination have been used and found to be effective.[16] Various regimens such as Ramam regime, modified Ramam, Welsh regime, and modified Welsh regime have been found to be effective in treatment of actinomycetoma. Irrespective of the regime used, the duration of treatment is individualized and depends on the clinical response to treatment. The number of cycles of Welsh regimen can be three only if soft tissue involvement is present and can be increased to five in case of bone involvement.[9] In our case series, six patients with actinomycetoma showed significant improvement after five cycles of modified Welsh regimen. One case of actinomycetoma lost to follow-up.

Eumycetoma is refractory to treatment, and no standard guidelines or regime are available at present. Itraconazole is being used but is unable to eradicate the fungus and needs to be given for a longer duration and is expensive. Voriconazole and posaconazole have been assessed in a very limited number of patients with some promising results. Isavuconazole and fosravuconazole were reported to have excellent *in vitro* activity. Amputations and recurrences in patients with eumycetoma are common.[3] Oral itraconazole showed mild to moderate improvement, though surgical intervention was required in one case with eumycetoma. Long duration of treatment is another important factor for noncompliance of patients to follow-up. Similarly, in our series two patients were lost to follow-up. This emphasizes the importance of proper counseling of such patients.

Conclusion

Among the 11 patients, 7 cases were of actinomycetoma (actinomycetoma: eumycetoma = 7:4), in our study. This prominent case detection in a short period of time signifies burden of mycetoma in this part of Maharashtra. A radiological screening should be done in all cases of mycetoma as it is one of the most important factors determining the duration of treatment. Modified Welsh regimen showed excellent response in all of our cases of actinomycetoma and can be considered as first-line therapy for the same. Precise identification of organisms by newer diagnostic techniques such as PCR can lead to better treatment outcomes reducing the disability and disfigurement associated with this condition. To the best of our knowledge, this is the first study of mycetoma from the central part of India.

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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Nil.

Conflicts of interest

There are no conflicts of interest.

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