

Fusarium as a Cause of Mycetoma: A Case Report and Review of the Literature

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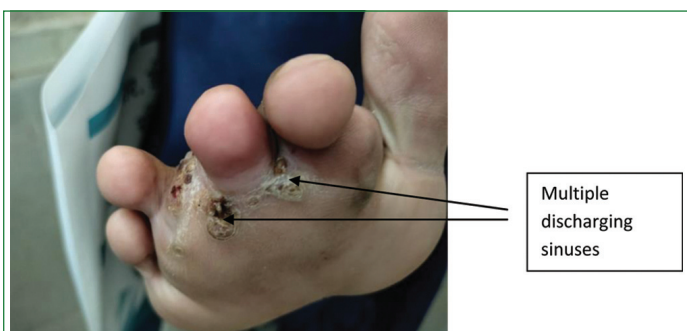
ABSTRACT

Mycetoma is a chronic, slow progressive granulomatous infection of skin and subcutaneous tissue; is classified into Eumycetoma (caused by fungi) and Actinomycetoma (caused by Actinomycetes). *Fusarium*, is a known cause of mycetoma. This case report describes the isolation and identification of *Fusarium* sp. from a lesion on the right foot of a female patient. This case report is about a 23-year-old female with complaints of gradual enlarging nodular swelling with multiple discharging sinuses along with granules on the right foot, on and off for last seven years. The granules obtained from the lesions are the best specimen for culture as they contain microcolonies of causative agents and it's a hallmark of mycetoma. Granules were collected aseptically, crushed and examined microscopically on 20% KOH preparation. Plenty of thin hyaline, septate hyphae were seen. Granules were washed with sterile saline and inoculated on Sabouraud's Dextrose Agar (SDA) and potato dextrose agar and incubated aerobically at 25°C and 37°C in two sets of each. Colonies grew at inoculated site, pinkish in the centre and whitish in the periphery. The isolate was identified as *Fusarium* sp. on the basis of morphology. The patient was started on Itraconazole 200 mg and is currently on the same treatment, improving and under follow-up. Mycetoma is a rare disease caused by both fungal and bacterial microorganisms. Definitive diagnosis should be made on the basis of culture or histopathological examination. Once the diagnosis is made, use of appropriate anti-fungal therapy with or without surgical interventions can result in complete cure without recurrence.

Keywords: Actinomycetoma, Eumycetoma, Potato dextrose agar, Sabouraud's dextrose agar

CASE REPORT

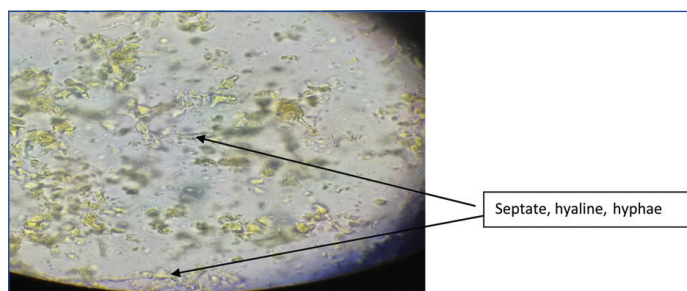
This case involves a 23-year-old female with history of painless multiple nodular lesions associated with discharging sinuses along with granules on the plantar aspect and inter-digital spaces of right foot for seven years [Table/Fig-1]. She had no complaints seven years back when she got injured by a thorn prick on the plantar aspect of the right foot. Initially, small elevated lesions were formed at the site of injury, which gradually increased in size. Later on, these developed into multiple discharging sinuses. The discharge was blood stained, seropurulent in nature and associated with granules. There was no history of diabetes or hypertension or any other co-morbidities and no significant family history was found. The patient took, on and off medications for the past seven years that were prescribed by her local doctor but she had no documents regarding past treatment. She did not get any respite, and rather the lesion got aggravated.



[Table/Fig-1]: Multiple discharging sinuses on right foot.

On clinical examination, her vitals were stable and there was no significant systemic finding. On local examination of the right foot, the swelling was gradually progressive in nature, solid, nodular, smooth, firm in consistency and non tender on palpation. The size of swelling was approximately 8x9 cm² with hyper-pigmented plaque present on the dorsal surface of same foot with ill-defined borders that were irregular in shape and size. There were multiple discharging sinuses present on the plantar surface and inter-digital aspect of the right foot. Discharge was blood stained, sero-purulent in nature and contained

granules [Table/Fig-1]. Granules and discharging pus were collected in sterile container and were sent to the Microbiology Laboratory for diagnosis. In the laboratory, the granules were examined; they were approximately 2-4 mm in size and were easily crushable. The granules were washed with normal saline, crushed between two slides and were examined by using Gram stain and 20% KOH. On Gram staining, Gram positive hyphae were seen. On 20% KOH examination, plenty of thin, hyaline septate hyphae were seen [Table/Fig-2]. The granules were then inoculated on Sabouraud's Dextrose Agar (SDA) and potato dextrose agar in two test tubes each; one of each was kept at 37°C and other at 25°C. Growth appeared in the tube, which was kept at 25°C after 48 hours; it was initially whitish, cottony on obverse and no change was observed on reverse. After 10 days of incubation on the obverse pink coloured colonies were seen in the centre with lighter periphery [Table/Fig-3a]. The reverse was pale to yellow [Table/Fig-3b]. Lactophenol Cotton Blue (LPCB) mount preparation from the colonies showed, thin septate, hyaline, hyphae with short branched and unbranched conidiophores. The conidiophores were arising from the single phialides and arranged singly and in clusters at the tip of the phialides. Sickle shaped macroconidia with 3-5 septa also arise from phialides. On the basis of culture characteristics and microscopic features, isolate was phenotypically identified as *Fusarium* sp. The genotyping of isolate was not done. [Table/Fig-4] showing hyphae from which monophialides extend and producing microconidia accumulated at



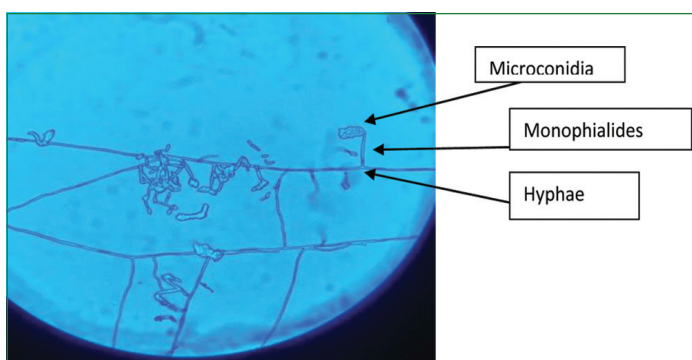
[Table/Fig-2]: Wet mount of crushed granules showing septate, branched, hyaline hyphae with swelling at some points (400X 20% KOH mount).



[Table/Fig-3a]: Growth of *Fusarium* sp. on SDA (Obverse).



[Table/Fig-3b]: Growth of *Fusarium* sp. on SDA (Reverse).



[Table/Fig-4]: *Fusarium* sp.- Showing septate, hyphae from which monophialides extend and from monophialide microconidias are arising and accumulated at the tips (1000X LPCB).

the tips. Anti-fungal susceptibility testing was not done. The patient was started on Itraconazole 200 mg daily for one year and is currently on the same treatment and under follow-up and improving. We do not have photographs of follow-up condition.

DISCUSSION

Mycetoma, also known as Maduramycosis or Madura foot, is a chronic, slow progressive granulomatous infection of skin and subcutaneous tissue with involvement of underlying fasciae and bones, usually affecting extremities [1]. It is caused by certain bacteria and fungi present in soil and water [2]. It usually affects young adults

(20-40 years) with male preponderance (M:F ratio 3.5:1) attributed to higher risk of exposure after splinter or thorn prick injury during field work [3]. In more than 80% patients' lower limbs are affected [4]. Clinically, it manifests as triad of swelling, discharging sinuses and presence of granules in the discharge whose colour depends on the causative agents [5]. Granules are the hallmark of mycetoma, which are micro colonies of the aetiologic agents [6]. The disease evolves slowly; initially micro-abscesses are formed by the polymorphs that are replaced later by chronic granulomatous tissue in skin and subcutaneous tissue [6]. Mycetoma is more common in tropical and subtropical countries. The area lying between 15°S and 30°N is said to be the Mycetoma belt. Three countries viz., Sudan, Mexico and India are predominantly affected [1,7].

Fusarium sp. are common worldwide and are causative agents of many fungal infections. This is one of the major causes of sinopulmonary and disseminated infection in profoundly neutropenic patients. In these cases, the microorganism can often be cultured from characteristic cutaneous lesions, as well as blood culture [8]. Many *Fusarium* sp. are plant pathogens that can be traumatically inoculated into the cornea and subcutaneous tissues [9]. Mycetoma cases attributed to *Fusarium* sp. have rarely been reported from India in the past decade. Hence, this is a rare case of mycetoma caused by *Fusarium*.

We searched various case reports on PubMed. We used the MeSH terms mycetoma, India and case reports from 2012 to 2021 and found 17 case reports that were published from India during this 10-year-period that met the inclusion criteria. The articles that fell under the exclusion criteria included case series, articles that were not from India and articles that were not fully accessible. In the past 10 years, we found that *Fusarium* sp. was rarely isolated as an agent of eumycetoma in India, indicating that it's not a common agent of mycetoma in India. The mean age of these cases was 39.6 years and male to female ratio was 5:3. Most common site affected was lower extremities followed by upper extremities. Granules were present in 12 cases out of which five were black or dark coloured grains. Most cases were treated with Itraconazole, followed by Cotrimoxazole. Twelve cases showed clinical improvement while the prognosis was not known in five cases. The details of the case reports reviewed by us are mentioned in [Table/Fig-5] [1,7,10-24].

Mycetoma has been acknowledged as a Neglected Tropical Disease (NTD) by the World Health Organisation (WHO) in 2016 [25] and continues to evade efforts to estimate its true burden. The differential diagnoses of eumycetoma are actinomycetoma, botryomycosis, chromoblastomycosis, sporotrichosis and

S. No.	Author	Year of publication	Age/ Sex	Name of State	Occupation	Im-munity status	Clinical features	Trauma	Site	Granules	Sam-ples	Histopathology/culture findings	Treatment	Outcome
1.	Bhandari M et al., [10]	2021	35 y/F	North India	Not known	Not known	7y history of painful nodule and sinuses on left arm	No	Left arm	Absent	Pus sample	<i>Nocardia africana</i> sp. nov.	Cotrimoxazole and Moxifloxacin	Improved
2.	Kaur M et al., [1]	2021	61 y/F	North India	Not known	Not known	Swelling of right foot with nodules and discharging sinuses	No	Right foot	White coloured granules	Tissue biopsy	<i>Aspergillus candidus</i>	Itraconazole	Not known
3.	Singh G et al., [11]	2020	30 y/M	Rajasthan	Company worker	ic	Left middle sole multiple discharging sinuses for 15y duration	No	Left middle sole	Black grains	Tissue biopsy	<i>Madurella</i> sp.	Itraconazole Terbinafine Posaconazole and surgical excision	Improved but recurred. Foot amputation done
4.	Sharma P et al., [7]	2020	35 y/F	Chhattisgarh	Not known	ic	5y history of multiple discharging sinuses of foot	Not known	Left foot	Yellow grains	Punch biopsy	<i>Actinomadura</i> sp.	Itraconazole	No improvement

5.	Das L et al., [12]	2021	45 y/M	Himachal Pradesh	Cement factory worker	id (Diabetic)	3y history of painless, multiple nodular lesions of foot	Not known	Right foot	Not known	Tissue biopsy	<i>Fusarium solani</i>	Itraconazole, Voriconazole and surgical debridement	Improvement
6.	Ankad BS et al., [13]	2019	46 y/M	Not known	Not known	Not known	2y history of skin lesion	Yes	Left wrist	Black grains	Tissue biopsy	<i>Madurella grisea</i>	Itraconazole	Resolved significantly
7.	Sandhu G et al., [14]	2019	39 y/M	Not known	Not known	ic	8y history of discharge and lesions on right thigh	Yes	Right thigh	Black grains	FNAC	Histopathology suggested fungal infection	Itraconazole	Improved
8.	Maihotra R et al., [15]	2018	37 y/M	Uttar Pradesh	Daily wager	Not known	Multiple painless nodules and discharging sinuses on left leg	Not known	Left leg	Yellow grains	Excised tissue	<i>Madurella mycetomatis</i>	Not known	Not known
9.	Nayyar N et al., [16]	2018	45 y/M	Sub-Himalayan region	Farmer	Not known	5-6y history of pain swelling discharging sinus in right foot	Not known	Right foot	Present	None	Radiologically diagnosed	Not known	Not known
10.	Grover A et al., [17]	2017	40 y/M	Not known	Not known	Not known	Left plantar swelling for 4 months	No	Left foot	Absent	Excised mass	Left plantar swelling-mycetoma	Excision and antifungal therapy	Complete resolution
11.	Neelakantan S et al., [18]	2016	36 y/M	Not known	Not known	Not known	2y history of nodular swelling with no discharging sinuses	not known	Right foot	Present	Punch biopsy	Filamentous fungal grain with amorphous brown matrix	Itraconazole	Responded well
12.	Kothiwala SK et al., [19]	2015	26 y/F	Rajasthan	Not known	Not known	4y history of subcutaneous nodule	No	Right breast	Black grains	Excision biopsy	Chronic granulomatous inflammatory reaction with giant cells with grains	Itraconazole	Lost to follow-up
13.	Shinde RS et al., [20]	2015	27 y/F	Karnataka	Housewife	ic	12y multiple discharging lesions	No	Left shoulder	Absent	Tissue biopsy	<i>Curvularia</i> and superinfection <i>Staphylococcus</i>	Itraconazole	Responded well
14.	Chander J et al., [21]	2015	50 y/F	Not known	Not known	ic	Suppuration and swelling with exuding pus in left upper cervicofacial region for 6 months	Not known	Left cervical and cheek	Not mentioned	Pus sample	<i>Streptomyces griseus</i>	Crystalline Penicillin	Improved
15.	Vaishya R et al., [22]	2015	21 y/M	Not known	Farmer	ic	4y history of pain and nodular swelling. Presence of bone osteomyelitis	Yes	Right foot	Dark coloured granules	Granules	Dense tender meshwork of slender hyphae interspersed with spore like structure	Itraconazole and Terbinafine	Improved
16.	Prasanna S et al., [23]	2016	45 y/M	Not known	Not known	id	4 months painful swelling of leg till knee with discharging fluid	No	Right leg	White coloured granules	Skin biopsy	<i>Aspergillus nidulans</i>	Itraconazole	Improved
17.	Gooptu S et al., [24]	2013	60 y/M	Maharashtra	Not known	Not known	11 month history of swelling and nodule on foot dorsum	Not known	Left foot	Yellow grains	Tissue biopsy	<i>Nocardia</i> sp.	Cotrimoxazole, Dapsone, Rifampicin and surgical debridement	Improved
18.	Present case	2022	23 y/F	Madhya Pradesh	House wife	ic	7y history of painless, nodular lesion, multiple discharging sinuses with granular discharge on right foot	Yes	Right foot	Present	Granules	<i>Fusarium</i> sp.	Itraconazole	Under follow-up

[Table/Fig-5]: Review of literature [1,7,10-24].

y: years; F: female; M: male; ic: immunocompetent; id: immunodeficient; FNAC: Fine needle aspiration cytology

malignancy etc. Eumycetoma is differentiated from other conditions on the basis of histopathological examination, culture and microscopic characteristic features. For complete resolution without recurrence of the disease, clinicians need to distinguish between the bacterial and fungal forms of mycetoma [4]. Current therapy for eumycetoma is a combination of anti-fungal agents with surgical procedure. Triazole anti-fungal therapy is the first line therapy for eumycetoma. The effective dose of Itraconazole for eumycetoma is 400 mg per day [26]. Treatments are indicated for an extended time, that may be up to one and half years [26]. Anti-fungal treatment is always necessary to localise the lesion and complete curing of the disease. Surgical intervention is needed to reduce the lesion size for better response to medical treatment [26].

In Northern India, including Rajasthan, eumycetoma is more prevalent with commonest agent being *Madurella mycetomatis* [6]. On the other hand, actinomycetoma is more common in Southern part of India [6]. From Eastern India *Streptomyces viridis* has also been found in patients of actinomycetoma [6]. *Fusarium* sp. is an ubiquitous fungi and infection is acquired through mild penetrating trauma. Clinically, our case is very similar to other eumycetomas. The patient had history of thorn prick injury, located on the right foot with the classic clinical triad and characteristic culture and microscopic features. The patient did not present with any immunodeficient condition.

Fusarium sp. have been reported from a variety of clinical conditions like keratitis, skin infection in burns, variety of skin lesions, arthritis, peritonitis, systemic infection in immunocompromised hosts, systemic- and granulomatous diseases and in aplastic anaemia [9].

CONCLUSION(S)

Mycetoma cases are quite common in India and thus need light to be shed upon. In the present case report, the *Fusarium* sp. isolated is not commonly reported in India. Early definitive diagnosis, with or without surgical intervention and opting for appropriate anti-microbial agent is a must for complete resolution, depending on the causative agents. Eumycetoma is commonly caused by the fungi *Madurella* sp., *Aspergillus* sp., *Curvularia*, *Fusarium*, *Pseudoallescheria boydii* and *Scedosporium*. *Nocardia* is the commonest pathogen responsible for Actinomycetoma worldwide. The burden of the disease is not well established and more studies and reporting of mycetoma cases are needed in India.

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