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 Itroconazole 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.

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 aspect of the 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, sero-purulent 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.

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, cotty in 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

Keywords: Actinomycetoma, Eumycetoma, Potato dextrose agar, Sabouraud’s dextrose agar
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 others [26].

### Table/Fig-4: Fusarium sp. - Showing septate, hyphae from which monophialides extend and monophialide microconidia are arising and accumulated at the tips (1000X LPCB).
<table>
<thead>
<tr>
<th>Case</th>
<th>Year</th>
<th>Age (y)</th>
<th>Sex</th>
<th>Residence</th>
<th>Occupation</th>
<th>History</th>
<th>Side</th>
<th>Lesion</th>
<th>Treatment</th>
<th>Follow-up</th>
<th>Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.</td>
<td>2021</td>
<td>45</td>
<td>M</td>
<td>Himachal  Pradesh</td>
<td>Factory worker</td>
<td>4y history of nodular lesions of foot</td>
<td>Right</td>
<td>Not known</td>
<td>Not known</td>
<td>Present</td>
<td>Fusarium solani</td>
</tr>
<tr>
<td>6.</td>
<td>2019</td>
<td>46</td>
<td>M</td>
<td>Andhra Pradesh</td>
<td>Factory worker</td>
<td>2y history of skin lesions</td>
<td>Left</td>
<td>Wrist</td>
<td>Black grains</td>
<td>FNAC</td>
<td>Histopathology suggested fungal infection</td>
</tr>
<tr>
<td>7.</td>
<td>2018</td>
<td>37</td>
<td>M</td>
<td>Uttar Pradesh</td>
<td>Daily wager</td>
<td>5-6y history of painless discharging sinus in right foot</td>
<td>Left</td>
<td>Leg</td>
<td>Yellow grains</td>
<td>Excision</td>
<td>Improved</td>
</tr>
<tr>
<td>8.</td>
<td>2018</td>
<td>45</td>
<td>M</td>
<td>Uttarakhand region</td>
<td>Farmer</td>
<td>4y history of nodular lesions of foot</td>
<td>Right</td>
<td>Not known</td>
<td>Present</td>
<td>None</td>
<td>Radiologically diagnosed</td>
</tr>
<tr>
<td>9.</td>
<td>2017</td>
<td>40</td>
<td>M</td>
<td>Himachal Pradesh</td>
<td>Housewife</td>
<td>2y history of nodular lesion</td>
<td>Left</td>
<td>Foot</td>
<td>Absent</td>
<td>Excised mass</td>
<td>Left plantar swelling-mycetoma</td>
</tr>
<tr>
<td>10.</td>
<td>2016</td>
<td>36</td>
<td>M</td>
<td>Uttarakhand region</td>
<td>Farmer</td>
<td>4y history of nodular lesions of foot</td>
<td>Right</td>
<td>Not known</td>
<td>Present</td>
<td>Punch biopsy</td>
<td>Itraconazole</td>
</tr>
<tr>
<td>11.</td>
<td>2015</td>
<td>26</td>
<td>F</td>
<td>Rajasthan</td>
<td>Worker</td>
<td>3y history of nodular lesion</td>
<td>Left</td>
<td>Shoulder</td>
<td>Absent</td>
<td>Tissue biopsy</td>
<td>Conulata and superinfection</td>
</tr>
<tr>
<td>12.</td>
<td>2015</td>
<td>27</td>
<td>F</td>
<td>Karnataka</td>
<td>Housewife</td>
<td>12y multiple discharging lesions</td>
<td>No</td>
<td>Left</td>
<td>Not known</td>
<td>Not mentioned</td>
<td>Streptomyces griseus</td>
</tr>
<tr>
<td>13.</td>
<td>2015</td>
<td>50</td>
<td>F</td>
<td>Uttar Pradesh</td>
<td>Worker</td>
<td>Suppuration and swelling with exuding pus</td>
<td>Not known</td>
<td>Cervical</td>
<td>Not known</td>
<td>Not known</td>
<td>Crystalline Penicillin</td>
</tr>
</tbody>
</table>
| 14.   | 2015 | 21      | M   | Maharashtra | Farmer | 4y history of pain and nodular swelling | Yes | Right | Dark coloured granules | Granulomas | Fusarium solani, Zonulae 
| 15.   | 2016 | 45      | M   | Himachal Pradesh | Farmer | 4 months painful swelling of leg till knee with discharging fluid | No | Right | White coloured granules | Skin biopsy | Improved |
| 16.   | 2013 | 60      | M   | Maharashtra | Farmer | 11 month history of swelling and nodule on foot dorsum | Not known | Left | Yellow grains | Tissue biopsy | Nocardia sp. |
| 17.   | 2012 | 23      | M   | Madhya Pradesh | Housewife | 7y history of painless, nodular lesion | Yes | Right | Present | Granulomas | Fusarium sp. |

**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 therapy 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 actinomyctoma [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 trauma. Clinically, our case is very similar to other eumycetomas. 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 reviews of mycetoma cases are needed in India.

REFERENCES