

Another case of *Aspergillus niger* mycetoma foot- Need to revisit causes of black grain eumycetomas

Yousuf Abd Mallick, Nausheen Yaqoob*

Dermatology Unit, The Indus Hospital, Karachi.

* Pathology Unit, The Indus Hospital, Karachi.

Abstract We are reporting a case of eumycetoma caused by *Aspergillus niger*, which is the second ever case-report to the best of our knowledge and search.

Key words

Aspergillus niger, eumycetoma, black grains, voriconazole.

Introduction

Mycetoma is chronic granulomatous infection of skin and subcutaneous tissues with involvement of underlying fasciae and bones in majority of cases. Causative agents are divided into two groups; actinomycetes and fungi. The clinical presentation is similar despite of a large number of organisms involved in the disease process. Mycetoma is a neglected disease in tropical and subtropical countries. There is complete scarcity of data from Pakistan regarding incidence, prevalence, types, causative organisms, behaviour and outcome of disease in the sufferers. Eumycetoma by different *Aspergillus* species is not new in the World's literature.

Case representation

A 41-year-old male, farmer by profession, presented to the Dermatology department of The Indus Hospital, Karachi with 12 years history of formation of nodules and discharging sinuses in his left foot. He had history of trauma 12 years back in wheat fields. He noticed development of

painless nodules on dorsum of left foot after few weeks of trauma. Nodules gradually enlarged and ruptured to release black-coloured grains. Gradually similar nodules and sinuses were formed on entire left foot. A diagnosis of eumycetoma was made because of black grains. He underwent multiple surgical procedures and received different antifungals for variable periods but there was no identification of species.

Slight improvement was noticed after every surgical procedure but condition relapsed as soon as the antifungal treatment stopped. Examination showed large, pigmented, firm nodules with active discharging sinuses and scar marks of previous surgeries (**Figures 1 & 2**). Spores extracted from sinuses revealed dichotomous septate hyphae on KOH mount. On examination all spores were black in colour, 1 to 2 mm in size, soft & fragile, and surface was smooth (**Figures 3**). Skin biopsy along with tissue culture and culture of extracted spores sent to laboratory.

Histopathology showed stratified squamous hyperplasia, hyperkeratosis and parakeratosis. Dermis showed dense lymphoplasmacytic infiltrate, foamy histiocytes and multiple

Address for correspondence

Dr. Yousuf Abd Mallick ,

House # R-386, Sector 16 A, Buffer Zone (Gulshan-e-Waseem), North Karachi, Karachi, Pakistan.

Ph: 0923432687716

Email: dryousuf2006@yahoo.com



Figures 1 & 2 Multiple, large, pigmented, ill-defined, firm nodules with discharging sinuses.



Figures 3 Small, 1 to 2 mm, black grains extracted from a sinus.

pigmented colonies with numerous dichotomously branched septate hyphae. These colonies were highlighted by special stain; Periodic acid-Schiff-diastase (PASD) stain. Cultures from both places revealed *Aspergillus*

niger species on Potato dextrose agar culture medium.

Routine labs and sugars were normal. Hepatitis B, C and HIV serology were negative. Voriconazole 400 mg/day was started in February 2019. MRI at the start of therapy showed numerous, heterogenous, lobulated cystic areas exhibiting classical dot-in-circle sign within soft tissues of fore and midfoot encasing many tendons. No bony involvement was identified.

Within 2 months of therapy his sinuses started to heal and after 6 months of treatment he became culture negative. For last 14 months he is on Voriconazole 400 mg/day. He underwent two surgical debulking procedures during this period. Repeat MRI after 2 surgical procedures and 1 year of complete therapy did not show any active or remaining signs of disease. During his treatment, his all labs remained under control and no serious side effect from voriconazole was reported. We decided to continue Voriconazole 400 mg/day for total of 24 months.

Discussion

The description of mycetoma is very old in the literature. The condition was described by John Gill in 1842 in Madurai district of Tamil Nadu in Southern India for the first time.¹ The term 'Madura foot' was coined by Colebrook in 1846, while Vandyke Carter, in 1874, gave the name 'Mycetoma' which means a 'fungal tumour'.² Elaboration of aetiology of mycetoma and its division into two subgroups was done by Chalmers and Archibald in 1916.³

Mycetoma presents with a classical triad of formation of multiple draining sinuses, presence of discharging grains and tumefaction of affected tissues.⁴ Causative agents are divided into two groups; aerobic actinomycetes and

saprobic fungi.⁵ When it is caused by a fungus it is termed as ‘eumycetoma’, while the one caused by actinomycete is called ‘actinomycetoma’. Clinical presentation is similar in both types of mycetoma and characterized by the discharge of ‘coloured grains’ which are considered as pathognomonic for diagnosis of mycetoma.

Mycetoma commonly presents between 20 to 50 years of age, with a male to female ratio of 2.2:1.⁶ The highest incidence is reported between latitude 15°S and 30°N, the so called “mycetoma-belt”.⁷ Rural areas are most affected and those who work barefoot are predominant victims like farmers, shepherds, livestock workers and daily labourers. It can involve any body part but foot is the predominant site involved.^{6,8}

Eumycetoma is classified into black grain eumycetoma and white grain eumycetoma. The black grain eumycetoma is commonly caused by *Madurella mycetomatis*, *Trematosphaeria grisea*, *Exophiala jeanselmei*, and *Curvularia geniculata* species.⁹ White grain eumycetoma is less common as compared to black grain eumycetoma and actinomycetoma.¹⁰ The white grain eumycetoma is caused by various species from genus *Acremonium*, *Pseudoallescheria*, *Aspergillus*, *Fusarium* and *Scedosporium*.⁷

Table 1 listed different causes of black grain eumycetoma reported in the literature.¹¹⁻¹⁹

However, along with black grain eumycetomas, some authors have also reported brown grain eumycetomas in the literature. Reported species are *Neoscytalidium dimidiatum*²⁰ and *Paecilomyces lilacinus*.²¹ The details and genetic makeup of these species have yet to be determined.

The dominance pattern of two different types of mycetomas differ largely throughout the World. Eumycetoma is more commonly observed in

Table 1 Cause of black grain eumycetomas

S. No.	Name of organisms	Reference
1	<i>Madurella mycetomatis</i>	11
2	<i>Madurella pseudomycetomatis</i>	11, 12
3	<i>Madurella tropicana</i>	11, 12
4	<i>Madurella fahalii</i>	11, 12
5	<i>Falciformispora senegalensis</i>	11, 13
6	<i>Falciformispora tompkinsii</i>	11, 13
7	<i>Medicopsis romeroi</i>	11, 13
8	<i>Biatrispora mackinnonii</i> (<i>Nigrograna mackinnonii</i>)	11, 13
9	<i>Pseudochaetosphaeronea larense</i>	11, 13
10	<i>Trematosphaeria grisea</i> (<i>Madurella grisea</i>)	11
11	<i>Parathyridaria percutanea</i> (<i>Rousoella percutanea</i>)	14
12	<i>Emarellia grisea</i>	14
13	<i>Emarellia paragrisea</i>	14
14	<i>Lasiodiplodia theobromae</i>	8, 14
15	<i>Alternaria alternata</i>	8
16	<i>Phanerochaete chrysosporium</i>	8
17	<i>Exophiala jeanselmei</i>	8
18	<i>Curvularia geniculata</i>	8
19	<i>Aspergillus niger</i>	6
20	<i>Rhytidhysterium rufulum</i>	14
21	<i>Chaetomium atrobrunneum</i>	15
22	<i>Curvularia lunata</i>	16
23	<i>Phialophora verrucosa</i>	17
24	<i>Phialophora parasitica</i>	18
25	<i>Cladophialophora bantiana</i>	19

African countries, while actinomycetoma is more frequently encountered in South American countries; Mexico and Brazil. In South India, actinomycetoma is more prevalent whereas eumycetoma is more common in North India, this is because of difference in ground vegetations and climatic conditions.⁵

In Sudan, *Madurella mycetomatis* has been implicated in more than 70% of all cases. *Trematosphaeria grisea* is most frequently reported from North American region. *Streptomyces somaliensis* is frequently associated with mycetoma in Middle East and Somalia. In Mexico and Central America, Nocardial species are most commonly encountered in mycetoma.²²

In our neighbouring country India, eumycetoma was principally caused by *Madurella mycetomatis* in the past. However, the trend has changed and many new black-grains producing species have been reported from different parts of India.^{8,20} Advancement in fungal culture techniques along with molecular identification by polymerase chain reaction (PCR) and loop mediated isothermal amplification (LAMP) have made a remarkable improvement in identification of proper species.⁵

In Iran, actinomycetoma (54.3% cases) is more common than eumycetoma, and in 3/4th of cases Actinomycete species were identified.²³ Mahmoudabadi and Zarrin reported 84.5% cases of mycetoma that were actinomycotic in origin and two most common species responsible were *Nocardia asteroides* and *Actinomadura madurae*.²⁴

In 1984, Khan *et al.* from Pakistan reported higher frequency of eumycetoma and 47.7% of all cases were caused by *Madurella mycetomatis* alone.²⁵ Faqir and Rehman in 2004, reported that 54.5% patients had actinomycetoma and most common species was Actinomycetes in their study.²⁶

Here, we are reporting a second case of *Aspergillus niger* eumycetoma. The first case was also reported by same authors.⁶ This demands a proper diagnosis of species by various culture techniques. This will help not only in identification of organisms but will also guide us in proper management of these cases. As *Aspergillus* is naturally resistant to many azoles and terbinafine, that's why authors decided to treat this case with a combination of voriconazole and surgical debulking. This combination treatment saved the patient from amputation and psychological comorbidity.

Conclusion

The exact incidence, prevalence, type and species for mycetoma in Pakistan remains to be elucidated. There is need of a national center and registry for mycetoma cases. Existing diagnostic methods are inadequate at most of the centers and cannot be used at point of care. Proper tissue culture facilities and molecular identification of species via PCR and LAMP is crucial for management of these cases.

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