Journal of Pakistan Association of Dermatologists. 2019; **29(4)**: 428-432.

Case Report

Eumycetoma due to aspergillus niger: First case report and successful treatment with voriconazole

Yousuf Abd Mallick

Dermatology Unit, The Indus Hospital, Karachi.

Abstract Mycetoma is an uncommon, chronic granulomatous infection of skin and subcutaneous tissues with involvement of underlying fasciae and bones in majority of cases. Lower extremities are the most common site involved by mycetoma. The classical triad consists of formation of multiple draining sinuses, presence of discharging grains and tumefaction of affected tissues.1 Causative agents are divided into two groups; actinomycetes and fungi. When it is caused by a fungus it's termed as eumycetoma, while the one caused by actinomycete is called as actinomycetoma. Eumycetoma by different Aspergillus species is not new but I am reporting a case of eumycetoma caused by Aspergillus niger, which is the first ever case-report to the best of my knowledge and search.

Key words
Acantholytic, ATPC2,'dilapidated brick wall appearance'.

Introduction

A 49-year-old male, farmer by profession, presented to the Dermatology department of the Indus Hospital, Korangi campus, Karachi on 3rd of February 2018, with 8-year history of formation of nodules and recurrent discharging sinuses in his right foot. He had history of trauma to right foot 8 years back. After 2-3 months of trauma he noticed formation of nodules on sole of right foot. These ruptured to release pus and black-coloured grains. Later on similar nodules and sinuses were formed on dorsum and medial aspect of foot. He received multiple treatments from different places including terbinafine, itraconazole, fluconazole, ampicillin, and co-trimoxazole. Minimal improvement was noticed and condition relapsed as soon as the treatment was stopped. On examination, he had firm nodules and active discharging sinuses **(Figures 1a & 1b)**. Spores were extracted from sinuses and nodules and examined under microscope. Fungal hyphae were seen on KOH mount. Deep skin biopsy and cultures were sent to laboratory and terbinafine 500 mg/ day was began. On examination all spores were black in colour; small-sized, soft & fragile, surface was smooth. This is in contrary with typical black-spores of Madurella species which are rough, hard and slightly larger than spores which I extracted, although my prime diagnosis was eumycetoma with one of the Madurella species.

Biopsy report showed hyperplastic stratified squamous epithelium along with hyperkeratosis and parakeratosis. Dermis showed dense lymphoplasmacytic infiltrate along with hyaline budding, septate fungal hyphae and spores surrounded by multinucleated giant cell reaction, neutrophils and eosinophils **(Figure 2)**. These colonies were highlighted by special stain; Periodic acid-Schiff (PAS) stain. Features were suggestive of eumycetoma due to Aspergillus species. Later on culture also showed *Aspergillus niger* species. A second culture also

Address for correspondence
Dr. Yousuf Abd Mallick
House # R-386, Sector 16 A, Buffer Zone ,
(Gulshan-e-Waseem), North Karachi, Karachi.
Ph: 03343276953
Email: dryousuf2006@yahoo.com

Figure 1a Nodule was excised for biopsy and cultures, showing black grain at the base

Figure 1b Sinus showing discharge of black grains

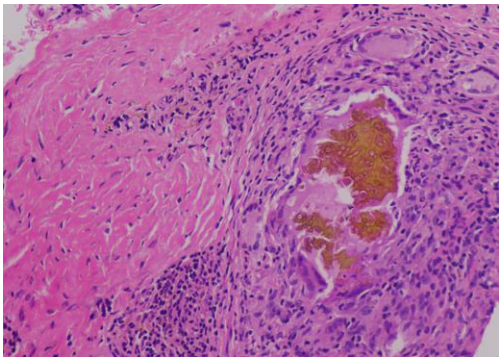

Figure 2 Septate fungal hyphae and spores with hyaline budding surrounded by multinucleated giant cells, neutrophils, eosinophils and lymphocytes

confirmed the same species in Potato dextrose agar culture medium.

After 1 month when cultures confirmed the species and patient had no improvement on terbinafine 500 mg/day, I decided to switch to Voriconazole 400 mg/day. MRI at the start of therapy showed dot in circle sign in right medial cuneiform bone. Rest of the bony and soft tissues were spared. Within 1 month his sinuses were started to heal. So, I continued the same dose. After 6 months of treatment he became culture negative, all sinuses were healed, edema was reduced and he was pain free.

Figure 3a

Figure 3b

Figures 3a & 3b Showing complete recovery and healing of all sinuses after 12-months therapy with voriconazole

I continued voriconazole in same dose for 12 months. Repeat MRI after 1 year did not show any enhancement or active signs of inflammation in medial cuneiform bone.

During treatment, he reported repeated flu like symptoms, oral ulcers, burning in eyes and gastrointestinal upsets but all his lab tests remained under control and no serious side effect from voriconazole was reported. After completing one-year therapy he was symptom free and clinically there was no finding besides post inflammatory pigmentation **(Figures 3a & 3b)**. So, his therapy was discontinued.

Discussion

Mycetoma (Madura foot) was first described by Gill in 1842 in Madura district of Tamil Nadu in Southern India.[2] It commonly presents between 20 to 50 years of age, with a male to female ratio of 2.2:1.[3] Foot is the predominant site involved that is why the term "Madura foot" was given by Gill.[4] Mycetoma foot is prevalent in almost all parts of the world, but the highest incidence is

Table 1 The colour of grains in different types of mycetomas and their species

Eumycetoma	
Black grains	Madurella mycetomatis, M. grisea, Leptosphaeria senegalensis, L. tompkinsii, Exophiala jeanselmei, Pyrenochaeta romeroi, Curvularia lunata, Phialophora verrucosa, Phytophthora parasitica, Cladophialophora bantiana, Aspergillus terreus, A. niger*
White grains	Pseudallescheria boydii, Aspergillus nidulans, A. flavus, A. fumigatus, Fusarium Sp, Acremonium Sp, Neotestudina rosatii, Scedosporium apiospermum
Actinomycetoma	
Red grains	Actinomadura pelletieri, Streptomyces somaliensis (sometimes)
White grains	Nocardia brasiliensis, N. asteroides, N. otitidiscaviarum, N. yamanashiensis, Actinomadura madurae
Yellow grains	Streptomyces somaliensis (mostly)

* Recently added by the author; Sp = Species

Table 2 Taxonomic position of Aspergillus niger[8]

Kingdom	Fungi
Division	Ascomycota
Class	Eurotiomycetes
Order	Eurotiales
Family	Trichocomaceae
Genus	Aspergillus
Subgenus	Circumdati
Section	Nigri
Species	A. niger

reported between latitude 15ºS and 30ºN, the so called "mycetoma-belt".[5] Depending upon the aetiology, the disease is classified into two types; actinomycetoma and eumycetoma. The eumycetoma is classified into black grain eumycetoma and white grain eumycetoma. The black grain eumycetoma is most commonly caused by Madurella mycetomatis, Madurella grisea, Exophiala jeanselmei, and Curvularia geniculate species.[6] The white grain eumycetoma itself is very rare as compared to black grain eumycetoma and actinomycetoma.[1] The white grain eumycetoma is caused by various species from genus Acremonium, Pseudoallescheria, Aspergillus, Fusarium and Scedosporium.[5] Different causes of eumycetoma and actinomycetoma are shown in **Table 1**.

Aspergillus fungi are ubiquitous, opportunistic, filament forming moulds, comprises of over 180 different species.[7] These are globally distributed and present in water, soil, air, plants, dust, fields, deserts etc.[8] Many species are responsible for causing infections in humans.[9] Aspergillus niger (also known as Black Mould) belongs to the Section Nigri which includes 15 related black-spored species which shared many physical and chemical properties.[10] Taxonomic position of Aspergillus niger is shown in **Table 2**.

In the literature Aspergillus fumigatus, A. flavus, A. nidulans, A. terreus, and A. ustus had been reported with human eumycetoma infections.[1,8,11-18] However, Aspergillus niger is reported to be responsible for mycetoma of maxillary sinus[19] and lungs,[20-21] but not outlined as a cause of eumycetoma foot to the best of my literature search and knowledge.

Eumycetoma due to Aspergillus species is considered as most difficult to treat as most species of Aspergillus are naturally azoles and terbinafine resistant.[22] The same occurred in my case. He received many treatments but all in vain. The decision to start voriconazole was made after thorough literature (medical, surgical, paediatric, oncology and infectious diseases) search for drugs used against Aspergillus infections and especially A. niger infections. Our patient responded very well to voriconazole and his foot was saved from amputation. He experienced no serious side effects and his labs always remained in normal limits during therapy.

Conclusion

Mycetoma is a disease mostly concentrated in tropical and subtropical countries. Detection of organism by tissue culture and PCR analysis is cornerstone in the management of these cases. Early referral to tertiary care centers, identification of species by proper tissue culture and adequate treatment might decrease the disease-related morbidity in mycetoma cases. Furthermore; this case also enlarges the list of organisms from Aspergillus group which are causing human eumycetoma.

References

1. Prasanna S, Grover N, Bhatt P, Sahni AK. A case of Aspergillus nidulans causing white granule mycetoma. Med J Armed Forces India 2016; 72(1): 88–90.
2. Angeline AK, Sangeetha MA. Mycetoma madura foot – case report. Int J Orthop Nurs 2017; 2(1): 15-9.
3. Alam K, Maheshwari V, Bhargava S, Jain A, Fatima U, Haq EU. Histological diagnosis of madura foot (mycetoma): a must for definitive treatment. J Glob Infect Dis 2009; 1(1): 64–7.
4. Magana M. Mycetoma. Int J Dermatol 1984; 23: 221-36.
5. Verma P, Jha A. Mycetoma: reviewing a neglected disease. Clin Exp Dermatol 2019; 44(2): 123-9.
6. Chander J. Subcutaneous mycosis mycetoma. In: A Textbook of Medical Mycology. 3rd ed. Mehta publishers; 2009: 148–162.
7. Mowat E, Williams C, Jones B, McChlery S, Ramage G. The characteristics of Aspergillus fumigatus mycetoma development: is this a biofilm? Med Mycol 2009; 47 Suppl 1: S120-6.
8. Ahmed SA, Abbas MA, Jouvion G, Al-Hatmi AM, de Hoog GS, Kolecka A, Mahgoub el S. Seventeen years of subcutaneous infection by Aspergillus flavus; eumycetoma confirmed by immunohistochemistry. Mycoses 2015; 58(12): 728-34.
9. Perrone G, Susca A, Cozzi G, K. Ehrlich, J. Varga, J.C. Frisvad et al. Biodiversity of Aspergillus species in some important agricultural products. Stud Mycol 2007; 59: 53–66.
10. Aspergillus niger [Internet]. [Place unknown]: Wikipedia The Free Encyclopedia [updated 2018 Oct 30; cited 2019 Mar 15]. Available from: https://en.wikipedia.org/wiki/Aspergillus_niger
11. Kotwal N, Yanamandra U, Badwal S, Nair V. Mycetoma foot caused by Aspergillus in a diabetic patient. Intern Med. 2012; 51(5): 517-8.
12. Veraldi S, Grancini A, Venegoni L, Merlo V, Guanziroli E, Menicanit C, et al. Mycetoma caused by Aspergillus nidulans. Acta Derm Venereol 2016; 96(1): 118-9.
13. Sawatkar GU, Narang T, Shiva Prakash MR, Daroach M, Sharma M, Nahar Saikia U, et al. Aspergillus: an uncommon pathogen of eumycetoma. Dermatol Ther. 2017 Jan;30(1). doi: 10.1111/dth.12411. Epub 2016 Sep 9.
14. Verma R, Vasudevan B, Sahni AK, Vijendran P, Neema S, Kharayat V. First reported case of Aspergillus nidulans eumycetoma in a sporotrichoid distribution. Int J Dermatol 2015; 54: 74–7.
15. Mahgoub ES. Can Aspergillus flavus cause maduromycetoma? Bull Soc Pathol Exot Filiales 1973; 66: 390–5.
16. Bassiri-Jahromi S. Mycetoma in Iran: causative agents and geographic distribution. Indian J Dermatol 2014; 59(5): 529.
17. Witzig RS, Greer DL, Hyslop NE Jr. Aspergillus flavus mycetoma and epidural abscess successfully treated with itraconazole. J Med Vet Mycol 1996; 34: 133–7.
18. Padhi S, Uppin SG, Uppin MS et al. Mycetoma in South India: retrospective analysis of 13 cases and description of two cases caused by unusual pathogens: Neoscytalidium dimidiatum and Aspergillus flavus. Int J Dermatol 2010; 49: 1289–96.
19. S Zaman, D Sarma. Maxillary sinus mycetoma due to aspergillus niger. Internet J Otorhinolaryngol 2006; 6(1): 1-4.
20. Longbottom JL, Pepys J, Clive FT. Diagnostic precipitin test in aspergillus pulmonary mycetoma. Lancet 1964 Mar 14; 1(7333): 588-9.
21. Kurrein F, Green GH, Rowles SL. Localized deposition of calcium oxalate around a pulmonary Aspergillus niger fungus ball. 1975; 64(4): 556-63.

22. Krishnan-Natesan S, Chandrasekar PH, Manavathu EK, Revankar SG. Successful treatment of primary cutaneous Aspergillus ustus infection with surgical debridement and a combination of voriconazole and terbinafine. Diagn Microbiol Infect Dis 2008; 62: 443-6.