CASE REPORT

An Unusual Case of Mixed Mycetoma by Actinomycete and Aspergillus Species

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ABSTRACT

Mycetoma is a chronic granulomatous infection of skin and subcutaneous tissues. It is a neglected disease worldwide with severe physical and psychological consequences as many cases end up with amputation. Proper diagnosis with tissue culture is the cornerstone in management of these cases. Mycetoma can occur anywhere on body but feet are the most commonly reported affected part. Walking bare foot is the main predisposing factor. Delay in diagnosis, lack of expertise and diagnostic facilities in remote areas, poor patient compliance, and resistant nature of almost all the causative organisms contribute towards the difficulty index in the management of mycetoma cases. Mycetoma is caused by either fungi or actinomycetes with a very similar clinical presentation. Mixed infection with both is a rarity. This is a case report of mixed mycetoma caused by actinomycetes and fungi both, and author's experience is shared to manage this difficult and unusual case.

Keywords: Mixed Mycetoma; Aspergillus fumigates; Actinomadura madurae; Voriconazole.

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INTRODUCTION

Mycetoma is an uncommon, mutilating, chronic granulomatous infection of skin and subcutaneous tissues with involvement of underlying fasciae and bones in majority of cases[1]. Young and adults are affected most but no age is immune, with a male to female ratio of 2.2:1[2]. Feet are the predominant site involved that is why the term "Madura foot" was given by Gill in 1842[3]. Mycetoma is most frequently reported in farmers, shepherds and workers of low socio-economic status[2]. Mycetoma foot is prevalent in almost all parts of the world, but the highest incidence is reported between latitude 15ºS and 30ºN, the so-called "mycetoma-belt" [4].

CASE PRESENTATION

A 44 years old female, housewife, presented to the Dermatology department of the Indus Hospital, Karachi in January 2018, with 14-year history of formation of nodules and recurrent discharging sinuses in her right foot (Figure 1). She had history of accident and severe damage to her right foot in 2004. After few weeks of trauma, she noticed formation of nodules on dorsum of right foot. These ruptured to release pus and white-colored grains. Later on, these nodules developed on different parts of foot, around ankles and lower leg. She had four biopsies done during this period but no cultures were performed. She received long courses of many antibiotics and antifungals, mostly alone and sometimes in combination without any knowledge of species causing this problem. During treatment, she also developed 3 episodes of fixed drug eruption (FDE) but the drug was not identified. Despite on proper antibiotic and antifungal therapy she continued to develop new nodules, which ruptured to release white colored grains all the time.

She came to me first time in January 2018. A nodule was completely excised and sent to laboratory for histopathology and all types of cultures. Histopathology revealed dense neutrophilic infiltrate along with pigmented granules in the center of neutrophilic abscesses. These colonies were highlighted on periodic acid-Schiff (PAS) and Silver stains. A heavy lymphoplasmacytic infiltrate, palisaded histiocytes and multinucleated giant cells were present surrounding the granules. Findings were suggestive of Splendore–Hoeppli phenomenon.

The most striking feature of the biopsy was presence of two different types of colonies. The first one showed multilobated colony with knobby projections, intense basophilic border with central pale eosinophilic amorphous material highly suggestive of Actinomadura madurae colony (Figure 2A). Gram stain showed thin filaments 1 µm thick with sharp twists (Figure 2B). The other colony revealed fungal mycelium, which was intensely, stained with Gomori Methenamine-Silver (GMS) and Periodic Acid-Schiff (PAS) stains, showing gray-black colored colonies. These colonies showed dense collection of septate hyphae, with dichotomous branching pattern at peripheries (Figure 3). Multiple scattered fungal spores also identified stained with PAS and GMS.

Based on clinical and histopathological reports, a diagnosis of mixed mycetoma infection was made, and itraconazole 400 mg/day, amoxicillin 1000 mg/day and co-trimoxazole 1920 mg/day were started. Routine labs, sugars, electrocardiography and echocardiography were normal. Hepatitis B, C and HIV serology were negative.

Just after 2 weeks, she presented with FDE patches which were similar to last 3 episodes and at same places. Co-trimoxazole was presumed to be the cause and stopped. In the mean time, cultures showed Actinomadura madurae growth on special media sensitive to amoxicillin and linezolid, so linezolid 1200 mg/day was added to the regimen. Cultures failed to identify fungus after prolonged incubation. So, triple regimen (itraconazole, amoxicillin and linezolid) was continued in same doses.

MRI at the start of therapy showed osteomyelitis in calcaneum and talus bones along with multiple, multiloculated abscesses involving lower leg, Achilles tendon and forefoot. Involvement of the tibiotalar joint was also appreciated. Incision and drainage (I&D) done, and again cultures failed to identify fungus species but actinomycotic species was reported on special media.

After 6 months of triple regimen, she became culture negative, all sinuses were healed, edema was reduced and pain was minimal. Therefore, itraconazole was stopped but other two drugs were continued. 6 months later, the disease relapsed again with discharge of white grains while she was on dual therapy (amoxicillin and linezolid). MRI was repeated and showed disease that is more extensive this time. An extensive I&D and sequestrectomy were performed by orthopaedics department, sent everything for culture, and at last a fungus; Aspergillus fumigatus was grown on culture from grains and sequestrum. All cultures failed to grow actinomycetes this time. Linezolid was stopped but amoxicillin was continued. Voriconazole 400 mg/day was added as soon as the culture reported *Aspergillus fumigatus*. Within 2 months, her sinuses started to heal. So, two drugs were continued in same doses. After 6 months of treatment with amoxicillin and voriconazole, she became culture negative, all sinuses were healed, edema was reduced, pain was bearable, and she regained her all routine activities. Amoxicillin was stopped after a total of 18 months but voriconazole was decided to continue in same dose for 24 months at least.

During treatment, she reported repeated flu like symptoms, oral ulcers, burning in eyes and photo-sensitivity but her all labs remained under control and up until now, and no serious side effect from voriconazole has been reported. Since February 2019, she is on voriconazole 400 mg/day.

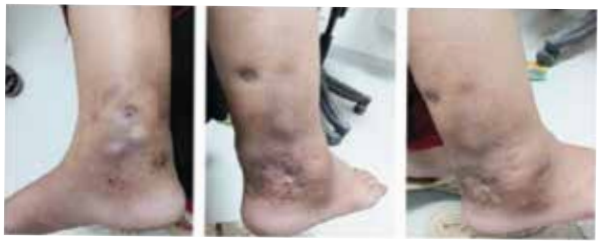

Figure 1: Discharging sinuses in right foot before treatment.

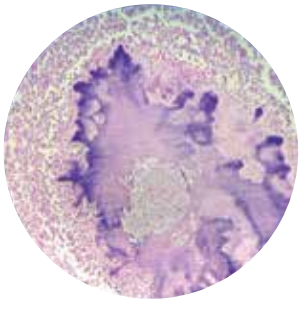

Figure 2A: *Actinomadura madurae* colony.

Figure 2B: Gram-positive thin filaments with sharp twists *(Actinomadura madurae)*.

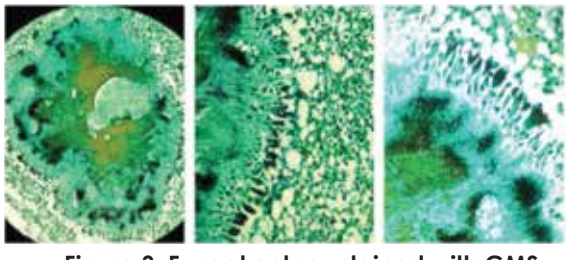

Figure 3: Fungal colony stained with GMS

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DISCUSSION

Mycetoma is a neglected disease with slightly higher prevalence in tropical countries as compared to rest of the world. Mycetoma has a classical triad, which consists of formation of multiple draining sinuses, presence of discharging grains and tumefaction of affected tissues[2]. Causative agents are divided into two groups; aerobic actinomycetes and saprobic fungi[3]. When it is caused by a fungus it's termed as "eumycetoma", while the one caused by actinomycete is called as "actinomycetoma." Clinical presentation is similar in both types of mycetoma and characterized by discharge of coloured grains which are considered as pathognomonic for diagnosis of mycetoma. The disease has been reported in both immunocompetent and immunocompromised patients from different countries.

The eumycetoma is further divided into black grain eumycetoma and white grain eumycetoma. The "black grain eumycetoma" is frequently reported from all over the world and most common species responsible for this are *Madurella mycetomatis, Madurella grisea, Exophiala jeanselmei and Curvularia geniculata.* The "white grain eumycetoma" is caused by various species from genus Aspergillus, Fusarium, Acremonium, Pseudoallescheria, and Scedosporium[4]. Actinomycetoma is uncommon as compared to eumycetoma. Grains in actinomycetoma show white, yellow, cream, red and brown colours. Most common species for producing actinomycetoma worldwide are Nocardia brasiliensis, *Actinomadura madurae, Streptomyces somaliensis, Actinomadura pelletieri and Nocardia asteroides*[4]. *Actinomadura pelletieri* is characteristically associated with red-colored grains.

Mycetoma is a chronic, painless, slowly progressive, non-communicable disease, but multiple family members, relatives and residents living in the same territory have been reported with same disease due to predisposing environmental factors. The portal of entry is commonly via thorn prick, a wood splinter or a stone cut.That is why walking bare foot is considered as the main persuading factor for mycetoma[1].

Diagnosis requires a deep biopsy for histopathology and tissue culture along with extraction of spores from sinuses, their microscopic examination and culture of spores. Histopathology is not always diagnostic, as in very long-standing cases; there is dense fibrosis, which subsidizes the diagnostic findings. The demonstration of classical Splendore-Hoeppli's phenomenon helps to confirm diagnosis of mycetoma but failed to recognize species in many cases. Detection of species is very important as completely different ways and drugs manage two types of mycetoma. X-rays, ultrasound, computed tomography and MRI scans can only help in detection of depth and extent of disease. Actinomycetoma is managed by antibiotics usually in combination for prolonged periods followed by surgical resection in majority of cases. On the other hand, eumycetoma is resistant to antifungals most of the times and surgical resection or debulking is considered as first line treatment followed by oral antifungal therapy until complete clinical and microbiological cure. List of antifungal agents include fluconazole, itraconazole, terbinafine, voriconazole and posaconazole. The prognosis is better in actinomycetoma while it is grave in eumycetoma.

The description of mixed mycetoma infection with actinomycetes and fungi both is rare in the literature. Although mixed mycetoma caused by two different organisms simultaneously has been reported by Bonifaz from Mexico and Fahal from Sudan more often than others[2,4,5]. Both of them belong to high endemic countries for mycetoma. These endemic areas have a Savannah type of vegetation and frequently have trees with numerous thick and long thorns[1]. Albornoz et al. reported the first case in the literature in 1977. It was very similar with my case. Their patient also had mixed infection with an actinomycete and a true fungus. Organisms were Actinomadura madurae and Pyrenochaeta species, detected on cultures[6].

In 2012, Gulati et al. from the United Kingdom reported a case of eumycetoma having concurrent infection with Scedosporium apiospermum and Madurella grisea in an immune-competent host[7]. Beniwal and colleagues from India in 2014 highlighted a case with coexistent actinomycosis and eumycetoma in an immune-competent patient. Different organisms were identified on histopathology and special staining but failed to grow on cultures[8].

Similarly, few others have also reported mixed mycetoma infection with two fungi and occasionally with two actinomycetes. Buot et al. in 1987 reported a case of mixed fungal mycetoma infection with Fusarium and Acremonium species. Recently from Mexico, Bonifaz and colleagues reported two cases of mycetomas with unusual double infections. The first case in 2017 reported an adult male with double eumycetoma caused by Fusarium verticillioides and Madurella mycetomatis species in his both feet and lower legs[9]. The second case of abdominal actinomycetoma with double aetiology was reported in 2018. Nocardia brasiliensis and Actinomadura madurae were found on cultures[10].

Still in the era of modern medical science, there is no vaccine available for prevention of mycetoma. People who are associated with soil related activities are instructed to wear protective clothing during working. Currently, no rapid and reliable

serologic or immunologic tests are available for diagnosis of mycetoma. Therefore, we have to wait for culture reports for a proper diagnosis. Molecular tests like polymerase chain reaction (PCR) and loop mediated isothermal amplification (LAMP) have been made for rapid detection and confirmation of species but are only available in highly equipped research laboratories[3]. There is no definite curative treatment available for both types of mycetoma.

This unusual case presented with a diagnostic and therapeutic challenge. Lack of complete work up in terms of cultures along with unavailability of facilities at most centers were the main reason for diagnostic delay. She was managed with combined antibacterial and antifungal therapies, and surgical debulking. She is planned to be on antifungal therapy until complete clinical and microbiological cure. Mycetoma is not considered as a reportable disease in our country, so the exact prevalence, real burden of mycetoma in Pakistan is not known. The clinics and primary care centers of high reported territories must be trained and guided accordingly along with a proper and early referral system to a well-equipped tertiary care center must be planned. This will not only decrease economic burden over patient, but also save patient from amputation and subsequent psychological consequences. Furthermore, guidelines should be prepared which focus on management of different types of mycetomas. There is a need for development of novel treatments, as current treatments for eumycetoma are mostly disappointing.

CONCLUSION

In summary, in a resource-limited country where the diagnosis is not established, treatment is not usually curative for mycetoma cases, along with poor compliance of many patients; the result is mostly amputation of the affected part. Tissue culture facilities for uncommon and unusual organisms are available at few tertiary care centers. The author recommends sending all types of cultures along with histopathology if you are suspecting a case with mycetoma that will certainly help your patients.

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CONFLICT OF INTEREST

Author declared no conflict of interest.

ETHICS APPROVAL

Ethical approval was taken from ethical review committee.

PATIENT CONSENT

Patient consent was taken before starting the procedure and for publishing.

AUTHOR'S CONTRIBUTIONS

YM had collected the data; performed the analysis, drafting the literature and written the case report.

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