

Treatment criteria for madura foot: Case report and literature review

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Mycetoma is a chronic granulomatous infection of the skin and underlying tissues, which affects remote populations in tropical and subtropical countries. We report the case of a 35-year-old male with an over 10 year history of left foot mycetoma, who initially presented with diffuse non-draining papules, edema, and dull chronic pain of the left foot. Radiographic imaging depicted erosive changes throughout the left midfoot and forefoot, while bone biopsy of the left navicular and first metatarsal confirmed actinomycetes. After being prescribed amoxicillin-clavulanate and trimethoprim-sulfamethoxazole and undergoing surgical debridement, the patient had marked improvements with less frequent pain and fewer blisters. One year later, the patient's ankle joint remained untouched by mycetoma, yet his condition began to deteriorate with the reemergence of draining granules and chronic pain. As of now, the patient has been scheduled for below-the-knee limb amputation. The treatment of mycetoma aims to preserve limb function and prevent recurrences, but further research and investigations are necessary.

Keywords: Actinomycetoma, eumycetoma

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Mycetoma, also known as Madura foot, is a neglected tropical disease that induces a granulomatous inflammatory response in the subcutaneous tissue or deep dermis. The etiology of mycetoma can be fungal or bacterial, respectively termed as eumycetoma or actinomycetoma. Even though mycetoma is dispersed throughout the world, it was found to be indigenous to tropical and subtropical areas between latitudes 15° South and 30° North, an area commonly known as the "Mycetoma Belt". Male populations living in these rural areas earn for their families by engaging in manual labor without proper footwear. Thus, transmission most commonly occurs through lacerations from cactus thorns, corn husks, or acacia trees. Manifestation includes foot pain with swelling and firm lesions to the site of laceration; raised ulceration sites; draining sinus tracts; and induration

[1]. Diagnosis is best approached with biopsy, organism granule evaluation, serological and molecular methods, and imaging [1,2]. Magnetic resonance imaging (MRI) is generally more sensitive than radiographs, especially at earlier stages [1]. An antifungal or antibiotic regimen in conjunction with surgical debridement is considered to be the gold standard for treatment [1,2]. In its advanced stages, mycetoma may invade deeper structures including muscle, fascia, and bone and increase the risk of mortality or severe disability via amputations [1].

Treatment and management of mycetoma have been difficult in rural regions due to factors such as low health education, poor access to health care, social stigma, and socioeconomic burden; thus resulting in late presentation to clinical care and poor compliance

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to treatment [3]. It has been difficult to correct these factors as there is a limited bank of research and knowledge about mycetoma around the world. There is an increased need for more epidemiological studies to obtain a clear understanding and accurate data on transmission, prevalence, and incidence of this condition [4]. Though advanced diagnostic techniques are available in resourceful regions, health care professionals in endemic regions mostly rely on visual inspection for diagnosis thus increasing the need for more accessible diagnostic modalities [5]. Research on more aggressive treatments for mycetoma and the implementation of prevention methods may be required to improve the quality of life of the patient. However, when medication and surgical debridement are not the solution, health care professionals may resort to amputation to reduce the risk of mortality in these patients [6].

In the present report, we describe a 35-year-old male presenting with an advanced manifestation of this uncommon clinical condition. A review of the condition, including presentation, conservative treatment options, and surgical treatment options, is then discussed.

Case Report

A 35-year-old male construction worker with a history of a heart murmur and streptococcal pharyngitis presented for podiatry consultation for left foot pain and swelling in December, 2017. He was unclear on how the pain occurred. However, there was a high suspicion for Madura foot on this patient by his primary care physician (PCP). Further discussion in a follow-up visit revealed injuring himself from a corn husk while working on a corn field in Mexico. The symptoms had been slowly progressing over the preceding 10+ years before he presented to our care in 2017. The patient reported the pain to be chronic and dull. He had no known allergies, pertinent surgical history and pertinent family history. His medications included 875mg-125 mg per tablet of oral amoxicillin-clavulanate (Augmentin) which needs to be taken 2x day and 800mg-160mg per tablet of oral trimethoprim-sulfamethoxazole which needs to be taken 2x day. His physical exam of the extremities revealed hyperpigmentation and rigidity on the entire left foot with pain on the medial aspect (Figures 1 and 2). Papules were evident diffusely with no obvious purulence or drainage. This consultation ended with discussions and informed consent for his left foot bone biopsy as requested by his PCP.



Figure 1 Clinical image at presentation, Left dorsal foot. Hyperpigmentation noted diffusely from digits, extending proximally to the ankle with patches of fibrotic hypopigmentation.



Figure 2 Clinical image at presentation, Left plantar foot. Roughened, plantar bumps and papules of mycetoma with contour irregularity and hyperpigmentation.

A bone biopsy was performed on the left first metatarsal and the navicular. The first metatarsal biopsy was 0.5 cm in length and 2 mm in diameter for a dumbbell shaped portion of brown-colored osseous tissue. The pathology report of the first metatarsal identified benign-appearing fibro-osseous tissue however it was in part non-viable. The navicular bone biopsy was several fragments of light tan-colored osseous tissue measuring in aggregate of 0.5x0.2x0.2 cm. The report identified osseous tissue with numerous plasma cells, acute inflammation, periosteal

fibrosis, and aggregates of filamentous microorganisms indicative of actinomycetes. Wound cultures were positive for *Staphylococcus aureus*.

Radiographic images demonstrated destructive and erosive changes throughout the left midfoot and forefoot (Figure 3). An MRI revealed rounded lesions of intermediate signal with low signal central foci in the talar neck and body, calcaneus, cuboid, navicular, tarsal bones, cuneiforms, and metatarsals. Nodules were present in the dorsal soft tissue, medial soft tissue adjacent to the first metatarsal, and the plantar soft tissue adjacent to first and second metatarsals. Soft tissue edema was also noted extending to sinus tarsi. Bone marrow edema and intraosseous/extraosseous lesions surrounded by subcutaneous edema were identified with enhancement. Increased signal intensity on T2 views was evident of the intrinsic musculature and of the distal aspect of flexor hallucis longus muscle.

Three months later, he demonstrated marked improvements with only 1-2 blisters resurfacing with intermittent throbbing pain for 1-2 times per month. At this point, his surgical history included left foot biopsy, irrigation, and debridement of his left foot. He was still on the same medication plan however has not been consistent with his management of Madura foot. His physical exam revealed improved edema on his left foot but mild serous drainage from the dorsal aspect were present. And, indurated skin was present from digits to rear foot without any pain. Given the slow progression of the infection at that point, it was decided to continue his medications and closely monitor his conditions to see whether it reached the ankle joint.

After one year has passed, he presented with worsening pain over the past 4 months with granules which open and close. His current medications included a 500mg capsule of oral cephalexin (Keflex) which needed to be taken 1 capsule 2x daily. Next medication was 5-325mg per tablet of oral hydrocodone-acetaminophen (NORCO) which needed to be taken 1 tablet every 6 hours prn. Next medication included an 800 mg tablet of oral ibuprofen which needed to be taken 1 tablet every 8 hours prn. His physical exam of the lower extremity revealed improved edema on the left foot however with an appreciable amount of drainage. Indurated skin was present from digits to rear foot. Pain was noted on midtarsal joint range of motion.



Figure 3 Radiographic images taken in June, 2017. Left foot dorsoplantar view. Degeneration and erosions throughout the midfoot and forefoot with superimposed sclerosis and significantly narrowed joint spaces.

His recent x-ray images taken in December of 2019 have revealed the extent of erosions from phalanges to calcaneus however erosions still have not penetrated the ankle joint.

He continued to cycle between improvements and deterioration of symptoms. This may be attributable to his non-compliance to the given recommendations such as taking the appropriate medications in a timely manner and frequent visits to the health care providers. At this time, he has been experiencing deterioration of his symptoms with worsening pain and granule drainage. Therefore, he consented to a below the knee amputation (BKA) in hopes of obtaining permanent relief of his symptoms. As of now, the amputation was scheduled to take place sometime in 2020.

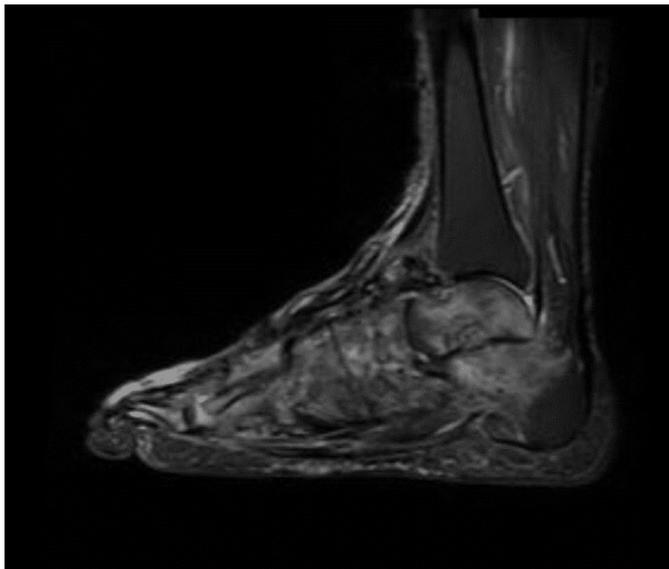


Figure 4 MRI image, sagittal view of the left foot. Rounded lesions of intermediate signal with low signal central foci were present in the talar neck and body, calcaneus, cuboid, navicular, tarsal bones, cuneiforms, and metatarsals. Soft tissue nodules were present in the dorsal soft tissue, medial soft tissue adjacent to the first metatarsal, and the plantar soft tissue adjacent to first and second metatarsals.

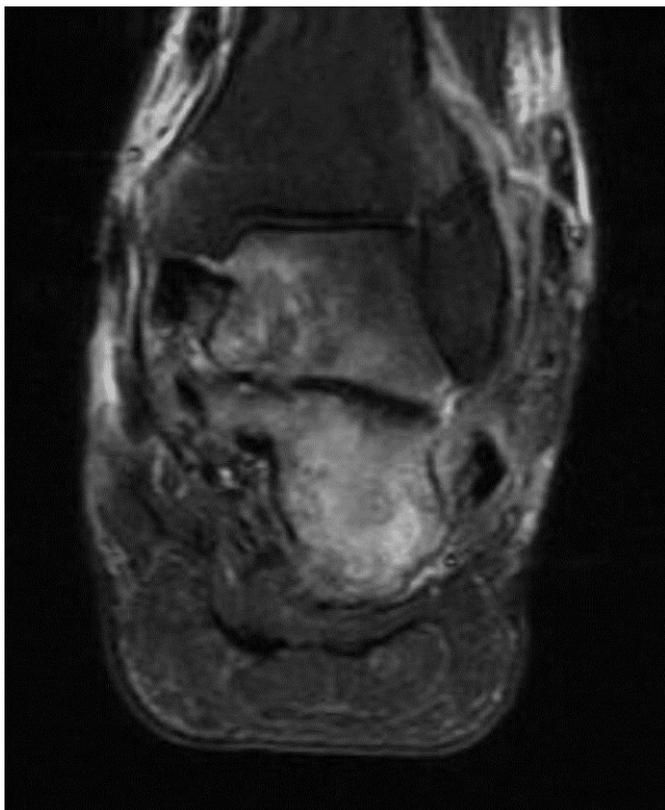


Figure 5 MRI axial view of the calcaneus, depicting rounded lesions of low to intermediate signal intensity with low signal central foci, characteristic of mycetoma.



Figure 6 X ray images taken December, 2019. Degeneration and erosions have increased in number throughout midfoot and forefoot with superimposed sclerosis and significantly narrowed joint spaces. The erosions had extended to involve the rear foot with involvement of talus and calcaneus. However, his erosions still have not reached the ankle joint.

Discussion

Mycetoma is a chronic granulomatous infection of the subcutaneous tissue caused by true fungi (eumycetoma) or filamentous bacteria (actinomycetoma) residing in various habitats, including soil and residing organisms such as earthworms. Thus, mycetoma poses an occupational hazard to cultivators, farm laborers, shepherds, or agricultural workers. Offending bacterial or fungal pathogens penetrate via an abrasion site to permeate subcutaneous tissues. The infection remains dormant until spreading to deeper tissues and skeletal systems. Early diagnosis may be essential for better prognosis of these conditions however patients seeking medical treatment are usually at late stages making management extremely difficult [1]. Some of the contributing factors may include misdiagnoses and the lack of resources, trained health care professionals, and familiarity of the condition [4].

Clinical manifestations of mycetomas are similar despite the causative microorganism. Current research does not define a precise incubation period but suggests that it may range from three months to 50 years. During early stages, pain is not an essential component of the clinical picture. Overall the initial appearance of mycetoma can be characterized by papules, nodules, abscesses or indurated tissue without clear boundaries [3]. With time, draining nodules expel grains from interconnected sinuses tracking from the innermost abscesses [7]. Fungal organisms tend to generate different colors but mostly white or black granules, whereas bacterial granules generate a range of colors except black. Even though these granules help the offending organisms

to evade immune detection, granule colorations are not pathognomonic for diagnostic purposes [8].

The advanced stage is characterized by a triad of symptoms including swollen, indurated, and deformed tissues; numerous communicating sinus tracts; and discharging aggregates of granules [9,10]. The affected skin retains the ability to heal draining sinus tracts, however, new tracts continuously form with discharge from various deep abscesses [1]. As the granuloma enlarges, the affected skin continuously deforms as a result of stretching of skin, pigmentation, and hyperhidrosis. Sweat gland hyperplasia and hypertrophy may be a consequence of overactivation of sympathetic nerves and/or rise in temperature due to extensive vascularization of the enlarging lesion [1,7]. During the period preceding highly advanced stages, this vascularization is apparent on angiography as dilated and convoluted arterial branches and veins proximal to the affected skin [1]. Blood supply is sufficient to preserve nerves and tendons until advanced stages of mycetoma [3,7]. During the advanced stages, pain may result from subsequent bacterial infections, metastasis to bone, and nerve damage. Despite the shared similarities in clinical presentation of mycetoma, it is notable that actinomycetoma is rapidly destructive and tends to extend to bone faster than eumycetoma [3]. Actinomycetoma was reported to invade the lymphatic system in rapid fashion leading to enlarged region lymph nodes [7]. Ultimately, delayed care can limit options and lead to poor outcomes, which may include severe disability, limb amputation or the need for multiple staged surgical excisions [4].

According to Hay et al., many health care professionals in endemic regions mostly rely on dermatological manifestations of the affected region for diagnosis due to lack of a required training and availability and economic burdens of other diagnostic tools [5]. This may contribute to numerous false positive outcomes and delays in accurate treatment for patients [11]. Since patients present in advanced stages of mycetoma, other diagnostic modalities are imperative to determine the extent of disease, staging of the disease, rule out differential diagnoses, such as Yaws and elephantitis, and confirm the exact causative treatment before starting treatment [12]. Cultures can be isolated via swab of sinus drainage or fine needle aspiration to distinguish the etiological agent, but cultures tend to be unreliable due to species variation, time needed for specimen growth, and high risk of contamination. Serological diagnosis

via immunoelectrophoresis and enzyme-linked immunosorbent assay (ELISA) is another diagnostic option but is costly and unreliable with the need for purified antigens and the cross-reactivity between organisms. Yet, these disadvantages may be overcome via histopathology [7].

Histopathology is a required diagnostic procedure with the potential to distinguish between eumycetoma and actinomycetoma before starting treatment [3,7]. Specimens need to be obtained from a deep surgical biopsy from a deep sinus tract or abscess to avoid contamination [7]. Grains can be visualized via Hematein-eosin-safran (HES), Periodic acid Schiff, and Gomori silver staining. More specifically, H&E staining illustrates eumycetoma as branched hyphae that arrange in groups and form vacuoles. Actinomycetoma with H&E staining demonstrates granules that are surrounded by eosinophilic fringe. Despite these benefits of histopathology, a major drawback includes the ability to only identify the mycetoma type not the causative agent [6].

In Western countries, molecular systematic protocols have been adapted to identify particular species and genera, allowing accurate selection of appropriate treatment options [11]. For actinomycetoma, 16S rRNA gene sequencing, PCR coupled with restriction endonuclease analyses, DNA fingerprinting with PCR amplification, or mass spectrometry can be employed to ascertain etiological species. For eumycetoma, fungal species can be recognized through PCR on an internal transcribed spacer sequence on fungal ribosomal DNA regions, PCR-restriction fragment length polymorphism analysis, and molecular typing via restriction endonuclease analyses and amplified fragment length polymorphism analyses [1,11]. Despite these advantages, molecular diagnostics should not be a substitute for traditional methods, as molecular techniques are typically unavailable and costly in endemic regions [3]. Thus, traditional methods in conjunction with diagnostic imaging should be ordered initially if possible.

Diagnostic imaging is essential for confirmation of appropriate pathology and disease severity. Radiographic evaluation of mycetoma can be characterized by soft tissue edema, periosteal reactions, thickened and eroded cortex, destroyed joints, moth eaten appearance, osteopenia, and osteolysis [13]. Radiographic details suggestive of eumycetoma include a small number of bone lesions which are typically ≥ 1 cm in diameter while actinomycetoma contains more numerous, but

smaller bone cavities [8]. Radiographic stages are defined in order to determine the severity and direction of metastasis. Radiographic stages are defined in order to determine the severity and direction of metastasis. Stage 1 features an enlarging granuloma with external pressure on bone. Stage 2 demonstrates periosteal reaction or reactive sclerosis. Stage 3 depicts the first indication of osseous involvement with erosion or cavitation on a single bone. Stage 4 demonstrates vertical progression into a single bone. Stage 5 is characterized by metastasis in horizontal direction to affect neighboring structures. Stage 6 is the most advanced stage of progression with metastasis of multiple planes [13].

Ultrasound is preferred for an accurate diagnosis of mycetoma even though it might not be readily available in endemic regions [1]. Granuloma containing granules adapt unique appearances which may aid in ruling out differential diagnoses and distinguishing actinomycetoma from eumycetoma [12]. The most distinguishing feature to confirm mycetoma diagnosis from ultrasound images is the “dot in the circle sign”. This sign can be defined by multiple round hypoechoic lesions with a hyperechoic focus in the center [4]. Doppler ultrasound can demonstrate the effect on mycetoma on vasculature of the affected region. Also, bacterial and fungal grains with a capsule and the accompanying granuloma have distinguishing ultrasound features which may be helpful in ruling out differential diagnoses [12]. Ultrasound can be helpful to determine the severity of mycetoma which may be essential for surgical planning [3].

In addition to ultrasound, MRI images are accepted to be highly essential in examining the extent of lesions and metastasis to adjacent structures [1]. Dot in the circle sign is not solely seen on ultrasound as it may be seen on MRI as oval hyperechoic lesions with a hypoechoic center [14]. On MRI images, high signal regions represent inflammatory granuloma while low signal regions within represent the granules. This is highly pathognomonic of mycetoma. Despite these advantages, MRI is expensive in rural regions, requires a high level of expertise to interpret the results and cannot be used to discriminate between actinomycetoma and eumycetoma [3,12].

Medical Management

The treatment and outcome of mycetoma depend on the causative agent and stage of disease progression [7]. Generally, patients with actinomycetoma have

more favorable prognoses to medical treatment than those with eumycetoma [13]. Greater drug penetrance, due to the smaller granules (~1µm diameter) in actinomycetoma, effectively supports a wider array of antibiotic regimen options [15,16]. Since the 1960s, trimethoprim-sulfamethoxazole (TMP-SMX) has been the gold standard for first-line treatment of actinomycetoma, either as monotherapy or in conjunction with dapsons, a penicillin, or an aminoglycoside for more resistant organisms [17]. Currently, combination drug therapy is recommended to avoid resistance and enhance efficacy [7,18]. Antibiotic sensitivity testing should be performed to select the most optimal combination, treatment duration, and number of cycles, all of which vary from case-to-case and depend on soft-tissue or osseous involvement [6,16].

The Welsh regimen is a well-acknowledged combination therapy that has achieved cure rates of more than 90% in previous studies [16,19]. Interestingly, most of the cases from Welsh’s studies were from Mexico, where 98% of mycetoma is due to actinomycetes (86% is further classified as *Nocardia brasiliensis*) [20]. During the intensive phase, intramuscular amikacin (15 mg/kg/day) is administered in two divided doses, combined with oral TMP-SMX (7+35 mg/kg/day) in three divided doses for 21 days. One to three cycles are performed at 15-day intervals. While in the maintenance phase, oral TMP-SMX (7+35 mg/kg/day) is administered at the same dose for 15 days after the last cycle [3,16,21]. Using the Welsh regimen as a template, other case studies have published modifications to optimize drug efficacy [16].

Damle et al. modified the Welsh regimen by incorporating rifampicin, which resulted in successful remission of all 16 patients included in the study who had all previously had unsatisfactory responses to therapy [16,22]. Rifampicin was specifically selected for its potency as a second-line drug and its medical familiarity within developing regions in the treatment of leprosy and tuberculosis. Agarwal et al. then modified the procedure presented by Damle et al. by increasing the number of cycles to three cycles in cases with soft-tissue involvement and up to five cycles in those with osseous involvement.

Another well-established treatment schedule is the modified two-step Ramam regimen, which consists of intravenous gentamicin (80 mg) twice daily and oral cotrimoxazole (320/1600 mg) twice daily for 4 weeks in the intensive phase. The successive step includes

oral doxycycline (100 mg) twice daily and oral cotrimoxazole (320/1600 mg) twice daily in the maintenance phase until five-six months after the complete healing of all sinus tracts is noted [3,16,23]. Although amikacin is the preferred aminoglycoside due to less nephrotoxicity and its characteristic resistance to bacterial aminoglycoside-inactivating enzymes, the Ramam regimen instead utilizes gentamicin primarily due to cost [16,23].

In patients with allergy or noted drug resistance, TMP-SMX can be substituted with amoxicillin-clavulanate, and amikacin can be replaced by netilmicin [1,6]. Additionally, amoxicillin-clavulanate can be used as monotherapy during pregnancy. Amikacin can also be combined with a carbapenem in cases refractory to sulfonamides [1,24]. Importantly, patients must be routinely monitored during and in between treatment cycles for any adverse effects from antimicrobial usage [6]. Especially for amikacin or other aminoglycosides, testing for renal, liver, and auditory function should be performed every three to five weeks to detect potential toxicity [25]. Surgery is rarely indicated in actinomycetoma, but may be advantageous for reducing disease load in larger lesions to enhance drug response or to control secondary bacterial infections in unresponsive patients [19,26].

Eumycetoma is associated with larger granules and extensive fibrosis, thus requiring more prolonged treatment durations ranging from one-to-three years for eumycetoma, compared with three months to one year for actinomycetoma due to lower drug penetrance [8,15]. Itraconazole (200-400 mg daily) for 9 to 12 months followed by surgical intervention has demonstrated favorable clinical responses in many studies and is currently the gold standard for treating eumycetoma [8,27]. In prior decades, Ketoconazole (400-800 mg daily) was a popular antifungal regimen, but has more recently fallen out of favor due to the risk for liver and adrenal toxicity [1,6]. It should be noted that disappointing and inconsistent results are common in pharmacotherapy of eumycetoma with recurrence rates between 20% and 90% [11,13]. Itraconazole and ketoconazole may not necessarily be curative, but their extended usage has exhibited the formation of thick fibrous capsules around the lesions, thus promoting the localization of disease for an easier and more complete surgical excision [7,26]. In a 20-patient open-label study, high-dose terbinafine (1000 mg daily) was administered for 24-48 months and demonstrated moderate efficacy. Results stated

that 25% of patients were cured, while 55% had notable clinical improvement by the completion of the study [27,28]. Newer antifungal drugs from the azole class are currently being investigated for their promising potential, featuring broad spectra, low toxicity and favorable bioavailability [6,11].

Treatment therapies for both actinomycetoma and eumycetoma must be continued until the conditions for complete cure are met. Those criteria include clinical healing of sinus tracts, complete resolution of soft tissue masses both clinically and radiologically, restoration of normal osseous appearance with radiological evidence of remodeling, cytological absence of granules, and ultrasonographic absence of cavities [7,26].

Surgical Intervention

Generally, mycetoma of fungal origin requires more extensive surgical management than that of bacterial etiology [19]. In cases with no osseous involvement, wide surgical excision is indicated for localized early lesions to reduce disease burden and to facilitate therapeutic response [7,19,29]. If osseous involvement is confirmed, surgical debridement can be carefully performed to remove granules and damaged tissue from the cavities [6].

Amputation may be considered in advanced stages of mycetoma, when massive osseous destruction, secondary bacterial infection, or sepsis occur [6]. Still, it is important to note that amputation will not necessarily result in a complete cure, as noted by high postoperative recurrence rates of 25% to 50% [2]. In a 1013 patient retrospective study by Wadal, et al., several indicators were correlated to predicting post-operative recurrences, including lesion size greater than 10 cm at initial presentation, positive family history of mycetoma, previous surgeries, and disease duration of more than five years [30]. In addition, surgeons must meticulously excise with wide margins to ensure adequate excision of infected tissues or there may be a risk of new satellite lesions forming from lymphatic spread [2,6,26].

Limb amputation is accompanied by significant socioeconomic, functional and psychological consequences. Mycetoma most commonly affects young men between 20 and 40 years of age, who are generally the highest producers and earners in endemic communities [1]. Disabilities and deformities resulting from mycetoma can compromise employment and relationship opportunities in adults,

while children are susceptible to becoming socially rejected and discontinuing education [3]. In a 2015 case study of two drug-resistant patients, Maiti, et al., examined the outcomes between an actinomycetoma patient who had undergone amputation after 9 years of treatment and an eumycetoma patient who continued to manage the slow progression of disease for 16 years after refusing amputation. The actinomycetoma patient was diagnosed with moderate depression post-amputation and also developed disease recurrence on her amputated stump 3 years later. The eumycetoma patient, however, maintained sufficient functionality for daily activities and was spared from anxiety or depression associated with amputation [31]. Thus, Maiti, et al., proposed that symptomatic management of drug-resistant mycetoma may perhaps be more beneficial to a patient's quality of life than amputation and the corresponding morbidities [31].

Conclusion

Mycetoma is an exceedingly rare condition that is most commonly encountered in underdeveloped regions. Experimental studies and randomized clinical trials may help determine the efficacy of various treatment regimens to prevent the progression of Mycetoma to more advanced stages [11]. Further, there exists a need for further research and development of a standardized treatment regimen available at low cost in endemic countries.

References

- Zijlstra EE, Van de Sande WW, Welsh O, Mahgoub ES, Goodfellow M, Fahal A. Mycetoma: a unique neglected tropical disease. *Lancet Infectious Disease* 16:100-112, 2016.
- Suleiman SH, Wadaella ES, Fahal AH. The Surgical Treatment of Mycetoma. *PLOS Neglected Tropical Diseases* 10:6, 2016.
- Emmanuel P, Dumre SP, John S, Karbwang J, Hirayama K. Mycetoma: a clinical dilemma in resource limited setting. *Annals of Clinical Microbiology and Antimicrobials* 17:35, 2018.
- Fahal AH. Mycetoma: A global medical and socio-economic dilemma. *PLOS Neglected Tropical Disease* 11:4, 2017.
- Hay R, Denning DW, Bonifaz A, Queiroz-Telles F, Beer K, Bustamante B, Chakrabarti A, Chavez-Lopez M, Chiller T, Cornet M, Estrada R, Estrada-Chavez G, Fahal A, Gomez BL, Ruoyu Li, Mahabeer Y, Mosam A, Ramarozatovo LS, Andrianarivelo MR, Rabenja FR, Van de Sande W, Zijlstra EE. The Diagnosis of Fungal Neglected Tropical Diseases (Fungal NTDs) and the Role of Investigations and Laboratory Tests: An Expert Consensus Report. *Tropical Medicine and Infectious Disease*. 4:122, 2019.
- Reis CMS, Reis-Filho EG. Mycetoma: an epidemiological, etiological, clinical, laboratory and therapeutic review. *An Bras Dermatol* 93:8-18, 2018.
- Fahal AH, Shaheen S, Jones DHA. The orthopaedic aspects of mycetoma. *The Bone and Joint Journal* 96B:420-425, 2014.
- Verma P, Jha A. Mycetoma: reviewing a neglected disease. *Clinical and Experimental Dermatology* 44(2):123-129, 2018.
- Harrington TL, Eldredge D, Benson EK. Immigration Brings New Pathology with No Standardized Treatment Protocol. *Journal of the American Podiatric Medical Association* 108:517-522, 2018.
- Hjira N, Boudhas A, Bouzidi AA, Boui M. Madura foot: Report of a eumycetoma Moroccan case. *Journal of Dermatology and Dermatological Surgery* 19:143-145, 2015.
- Ahmed AAO, Van de Sande WWJ, Fahal A, Woudenberg IB, Verbrugh H, Belkum A. Management of mycetoma: major challenge in tropical mycoses with limited international recognition. *Current Opinion in infectious Diseases* 20:146-151, 2007.
- Guerra-Leal JD, Medrano-Danes LA, Montemayor-Martinez A, Perez-Rodriguez E, Luna-Gurrola CE, Arenas-Guzman R, Salas-Alanis JC. The importance of diagnostic imaging of mycetoma in the foot. *International Journal of Dermatology* 58:600-604, 2019.
- White EA, Patel DB, Forrester DM, Gottsegen CJ, Rourke EO, Holtom P, Charlton T, Matcuk G. Madura Foot: two case reports, review of the literature, and new development with clinical correlation. *Skeletal Radiology* 43:547-553, 2014.
- Sen A, Pillay RS. Case Report: Dot-in-circle sign-An MRI and USG sign for "Madura Foot". *Indian Journal of Radiology and Imaging* 21:264-266, 2011.
- Salim AO, Mwita CC, Gwer S. Treatment of Madura foot: a systematic review. *JBHI Database System Rev Implement Rep* 16(7):1519-1536, 2018.
- Agarwal US, Besarwal RK, Gupta R, Agarwal P. Treatment of actinomycetoma foot--our experience with ten patients. *J Eur Acad Dermatol Venereol* 27(12):1505-13, 2013.
- Scolding P, Fahal A, Yotsu RR. Drug therapy for Mycetoma. *Cochrane Database of Systematic Reviews* 7:1-6, 2018.
- Relhan V, Mahajan K, Agarwal P, Garg VK. Mycetoma: An Update. *Indian J Dermatol* 62(4):332-340, 2017.
- Sampaio FM, Wanke B, Freitas DF, Coelho JM, Galhardo MC, Lyra MR, Lourenco MC, Paes RA, do Valle AC. Review of 21 cases of mycetoma from 1991 to 2014 in Rio de Janeiro, Brazil. *PLoS Negl Trop Dis* 11(2):1-14, 2017.
- Welsh, O. Mycetoma. *International Journal of Dermatology* 30(6):387-398, 1991.
- Vongphoumy I, Dance DA, Dittrich S, Logan J, Davong V, Rattanavong S, Blessmann J. Case report: Actinomycetoma caused by *Nocardia aobensis* from Lao PDR with favourable outcome after short-term antibiotic treatment. *PLoS Negl Trop Dis* 9(4):1-7, 2015.

22. Damle DK, Mahajan PM, Pradhan SN, Belgaumkar VA, Gosavi AP, Tolat SN, Gokhale NR, Mhaske CB. Modified Welsh regimen: a promising therapy for actinomycetoma. *J Drugs Dermatol* 7(9):853-856, 2008.
23. Ramam M, Bhat R, Garg T, Sharma VK, Ray R, Singh M K, Banerjee U, Rajendran C. A modified two-step treatment for actinomycetoma. *Indian J Dermatol Venereol Leprol* 73:235-239, 2007.
24. Ameen M, Arenas R, Vásquez del Mercado E, Fernández R, Torres E, Zacarias R. Efficacy of imipenem therapy for *Nocardia actinomycetomas* refractory to sulfonamides. *Journal of the American Academy of Dermatology* 62(2):239–246, 2010.
25. Welsh O, Al-Abdely HM, Salinas-Carmona MC, Fahal AH. Mycetoma Medical Therapy. *PLoS Negl Trop Dis* 8(10):1-14, 2014.
26. Zein HA, Fahal AH, Mahgoub el S, El Hassan TA, Abdel-Rahman ME. Predictors of cure, amputation and follow-up dropout among patients with mycetoma seen at the Mycetoma Research Centre, University of Khartoum, Sudan. *Trans R Soc Trop Med Hyg* 106(11):639-44, 2012.
27. Nenoff P, van de Sande WWJ, Fahal AH, Reinell D, Schöfer H. Eumycetoma and actinomycetoma – an update on causative agents, epidemiology, pathogenesis, diagnostics and therapy. *J Eur Acad Dermatol Venereol* 29:1873-1883, 2015.
28. N'Diaye B, Dieng MT, Perez A, Stockmeyer M, Bakshi R. Clinical efficacy and safety of oral terbinafine in fungal mycetoma. *International Journal of Dermatology* 45(2):154–157, 2006.
29. Gismalla MDA, Ahmed GMA, Mohamed Ali MM, Taha SM, Mohamed TA, Ahmed AE, Hamed LS. Surgical management of eumycetoma: experience from Gezira Mycetoma Center, Sudan. *Trop Med Health* 47(6):1-6, 2019.
30. Wadal A, Elhassan TA, Zein HA, Abdel-Rahman ME, Fahal AH. Predictors of Post-Operative Mycetoma Recurrence Using Machine-Learning Algorithms: The Mycetoma Research Center Experience. *PLoS Negl Trop Dis* 10(10):1-11, 2016.
31. Maiti PK, Chakraborty B, Ghosh S, De A. Does the benefit of salvage amputation always outweigh disability in drug-failure mycetoma?: A tale of two cases. *Indian J Dermatol* 60:74-76, 2015.