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Mycetoma from the bench to the field

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1. Provide a forum for scientific and clinical medicine publications.
2. Serve the medical community in Sudan and the region in the field of continuing medical education.
3. Offer opportunities for the publication of service-oriented research and disseminate information aimed at the promotion of health services.
4. Encourage the development of medical and allied sciences research.

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Editorial

The International Research Collaboration: A room for improvement

In the era of global health, United Nations Sustainable Development Goals (SDGs), the WHO concept of leaving no one behind, increasing global competition and rapid technological changes, the International Research Collaboration (IRC) has been perceived as a dominant driving force for promoting good science, and research. Of the several clusters of research collaboration, inter-institutional is the most important and powerful. IRC is considered the robust approach for countries to foster and maintain such global innovation competitiveness. Countries with more international collaborative links easily attract international investments in Research and Development.

The **Mycetoma Research Center** (MRC), University of Khartoum, was established in 1991 as the only WHO Collaborating Centre on Mycetoma. It is an authoritative advisor on mycetoma management, scientific research and training. MRC has collaborated with more than **23 international research centers and institutes,** government and non-governmental bodies, sponsors and charities that culminated in good science production, and several innovative solutions for the patients' complicated medical, health and socioeconomic problems and complications. For example, the **first-ever clinical trial** for a new drug for eumycetoma was conducted in collaboration with the **DNDi,** Geneva, and Japan. The establishment of several **mycetoma satellites centers** in endemic villages where patients were treated locally, health education events were organised, and community engagement activities were conducted An innovative solution was produced to overcome the patients' post-treatment social stigma, social exclusion, physical deformities, and disabilities, such as the **Mycetoma Vocational and Entrepreneurship Training Centre (SAAI'D)**, which is a Japanese, businessmen and public-private partnerships project. This is in addition to the **NIHR Global Health Research Unit on Neglected Tropical Diseases.**

Difficulties facing MRC include ethical issues such as authorship guidelines breach, writing manuscripts on some MRC activities and issues without consulting the centre, imposing research proposals from overseas to be implemented locally in mycetoma endemic and obtaining biological material without offering support for the MRC human resources or research infrastructure.

In conclusion, no single country can achieve much without IRC as science, technology, and innovation. Many countries consider IRC a top priority and development of sound collaborative links between countries should be implemented with great respect to the research local environmental factors.

AH Fahal

Professor of Surgery,
The Mycetoma Research Center, University of Khartoum,
Khartoum, Sudan

Review article

Why is mycetoma still a public health dilemma and a unique neglected tropical disease?

Hyam Omar Ali[1,2], Ahmed Hassan Fahal[2]

[1]Faculty of Mathematical Sciences, [2]The Mycetoma Research Centre, University of Khartoum, Khartoum, Sudan.

***Correspondence to** ahfahal@mycetoma.edu.sd – ahfahal@hotmail.com*

HISTORICAL BACKGROUND

In 1842, the missionary John Gill reported the first clinical case of mycetoma in an Indian city named "Madurai".[1] Vandyke Carter first described the fungus form of mycetoma in 1860; thus, he proposed the name "mycetoma", which is driven from the Greek terms "mykes" and "oma", which means fungus and tumour, respectively.[2] Mycetoma is also known as "Madura Foot", referring to the first reported case, but this name is inappropriate as it is neither confided to the Madurai nor the foot. Chalmers and Archibald from Sudan formally classified mycetoma into two main groups, fungal and bacterial mycetoma,[3] after a suggestion made in 1913 to classify mycetoma based on the causative organisms.[4]

Mycetoma was one of the most neglected tropical diseases until 2013, when global mycetoma experts and the Drugs Neglected Diseases Initiative (DNDi) established the Mycetoma Consortium.[5,6] They made huge efforts to address mycetoma research priorities and to increase disease visibility globally. Then the Ministry of Health, Sudan, submitted a proposal to the WHO Executive Board to include mycetoma to the list of "top 17" WHO Neglected Tropical Diseases (NTDs) and on 28th May 2016, WHO included mycetoma in the NTDs list.[7,8] This global recognition attracted media attention and raised funding opportunities. The Mycetoma Research Center (MRC) in Khartoum, Sudan, is recognised as a world leader in mycetoma management and research. It has contributed massively to the international recognition of mycetoma. Currently, MRC is the only WHO Collaborating Center on Mycetoma.

Mycetoma is a chronic subcutaneous granulomatous and disabling inflammatory disease. It is classified into actinomycetoma and eumycetoma depending on the causative organisms, either bacteria or fungi, respectively. *Madurella mycetomatis (M. mycetomatis)* is the most common species causing eumycetoma, while *Streptomyces somaliensis (S. somaliensis), Actinomadura madurae (A. madurae), Actinomadura pelletieri (A. pelletieri),* and *Nocardia brasiliensis (N. brasiliensis)* are the common species for actinomycetoma.[5]

While mycetoma transmission mode is still unknown,[8] the literature suggests that causative organisms are present in the soil, thorns, or animal dunk and can enter the subcutaneous tissue through minor trauma such as stepping on a thorn, sharp objects or open wound.[6] No person-to-person transmission is reported; however, other transmission modes are not exempted.[9,10] After trauma, mycetoma infection starts with formation of grains within multiple cavities presenting clinically as nodules. The size of these nodules increases gradually, and they spread into the skin, deep tissues, and bone. Discharge of sero-purulent, purulent blood and grains of different sizes, colours, and textures through the sinus is frequent. The mycetoma lesions usually discharge grains, which can be black, yellow, white, or red in colour, and they are of different sizes and consistency. Mycetoma has slowly progressive course and can extend to different tissue planes leading to massive tissue destruction, deformity and disability (Figures 1,2).

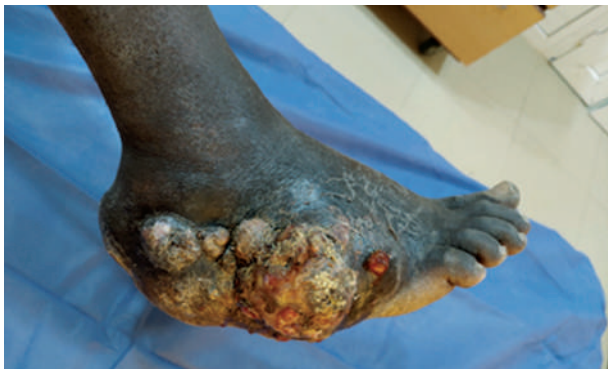

Figure1. Massive foot actinomycetoma

Mycetoma can spread through the lymphatic system and infrequently through the bloodstream. Thus, secondary satellite lesions are usually seen in the regional lymph nodes or beyond. This is more often linked to actinomycetoma as bacteria spread faster than fungi, and the lesion is not well encapsulated.[10,11] More tissue will be damaged as the disease progresses, and massive mutilating surgical excisions or amputation of the affected part may be the only available treatment.

In summary, mycetoma is characterised by a triad of painless subcutaneous mass, multiple sinuses formation, and discharge of grains containing colonies of the causative organism. The clinical presentation and symptoms for both types of mycetoma (fungus or bacterial) are similar,[8,12-14] although there are more than 70 microorganisms responsible for mycetoma infection.[5,11] However, mycetoma clinical presentation and treatment outcome might vary depending on disease duration, infection site, causative organisms, and the host immune system.[14]

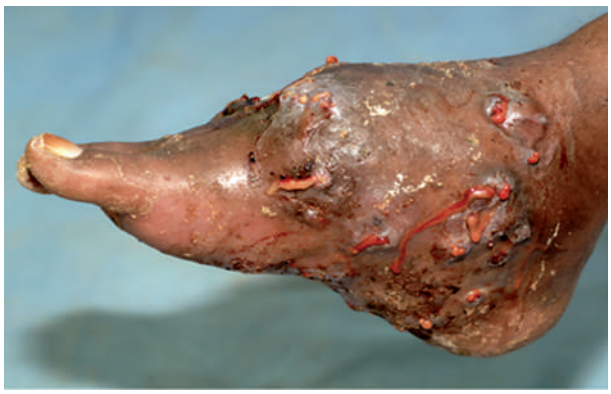

Figure 2. Massive mass with multiple sinuses and discharge

Mycetoma has a worldwide distribution, although the disease global burden is still unknown. The infection is endemic in tropical and subtropical areas. These regions are characterised by a short rainy and a long dry seasons.[11] The majority of mycetoma cases appear in a belt stretching between the latitudes of 15^0 south and 30^0 north, known as the Mycetoma Belt. The belt countries include Sudan, Somalia, Senegal, India, Yemen, Mexico, Venezuela, Colombia, Argentina and others.[12,16] (see Figure 3). The highest prevalence was reported in Sudan, India, and Mexico.[4,5] Sudan is the epicenter of mycetoma infection, with 355 new mycetoma cases/per year seen in the Mycetoma Research Center (MRC), University of Khartoum, WHO Collaborating Center on Mycetoma.[11,17,18] This number of cases is way less than the actual cases as it only counts the patients who managed to seek medical care at the MRC. Mycetoma was reported in temperate countries such as the USA, Germany, Turkey, Philippines, Japan, Netherlands, and France. [8,10,13,19] These cases are seen more often in immigrants who probably got infected in their homelands.[10,18] This belief is guided by the fact that the actual incubation period is unknown. The disease duration ranges from a few months up to 60 years up the presentation for medical consultation.[10,11,17,18]

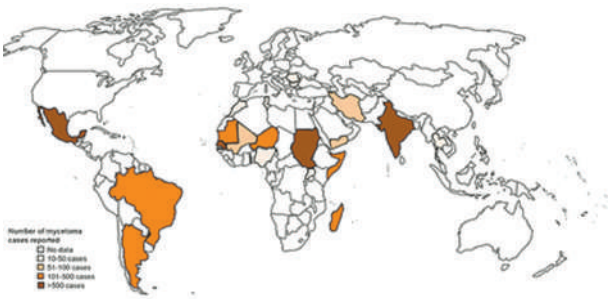

Figure 3. Prevalence of Mycetoma, adapted from van de Sande WWJ (2013) Global Burden of Human Mycetoma: A Systematic Review and Meta-analysis. PLoS Negl Trop Dis 7[11]: e2550. doi:10.1371/journal.pntd.0002550

The most susceptible group to mycetoma infection is young adults, particularly males aged between 20 and 40 years in remote rural areas. Mycetoma largely affects field labourers, agriculturalists, and herdsmen.[4,16,17] The lower extremity and hands

are the most frequently infected sites.[4,5,12] Women are less likely to be infected than men with a 1:3 ratio and the explanation is not clear.[12.17] Genetic, immunological, and environmental factors might increase infection susceptibility.[11,13,17] Most mycetoma patients are of low socioeconomic and health education status and reside in endemic regions with poor health and medical facilities. So, they usually seek medical advice late when the disease is advanced and hard to treat. Besides the painless nature of the disease, these factors might lead to chronic deformity and disability.

Mycetoma diagnosis

An initial diagnosis of mycetoma in endemic areas is often made clinically through physical examinations.[11,13,20] Advanced cases of infection with the classical clinical triad can be easily diagnosed as mycetoma. However, an earlier disease stage with small lesions may be difficult to distinguish from foreign body granulomas, soft tissue tumours and other infectious diseases that mimic mycetoma because of absence of the triad.[6] Confirmation of the infection as mycetoma alone is insufficient, and further investigations must be done to identify the causative agents and detect the spread of infection. These investigations are essential to plan the appropriate treatment strategy. Imaging and laboratory-based diagnostic tools are used to identify causative organisms and determine the extent of lesions. Usually, a combination of these tools is used to establish an accurate diagnosis. The clinicians approach the mycetoma diagnosis by eliciting history of trauma, located in an endemic area, the presence and number of sinuses, and the colour of grains, if any. These findings hint to the clinician the infection type, whether it is fungus or bacterial. Depending on the laboratory test requested, a sample is collected from the suspected tissue for further analysis. Table 1. summarises the major clinical differences between eumycetoma and actinomycetoma.[5,21]

Table 1. Comparison of eumycetoma and actinomycetoma clinical presentation

Feature	Eumycetoma	Actinomycetoma
Grain colour	Black, pale, white, yellow	Yellow, red, pink, white.
Grain size	Larger (0.5–2)µm	Smaller (20–100)µm
Grain texture	Coarse	Fine
Sinus (number; morphology)	Few sinuses, prominent	Many sinuses, flat
Progression	Slow	Quick
Geographic prevalence	Africa and India	South America and Asia

Imaging techniques

The disease extension into the different tissue planes and bones can be determined with imaging techniques. Furthermore, treatment and follow-up can be planned, and disease prognosis can be predicted.[11.13.14.20] Several radiological imaging techniques are used for mycetoma diagnosis, including conventional X-ray, ultrasound, Computed Tomography (CT scan), and Magnetic Resonance Imaging (MRI).[12,13,20,22-25] Currently, the lesion ultrasound examination is the first option in the imaging diagnosis. It is accurate, non-invasive, rapid and can differentiate the two types of mycetoma and the mycetoma lesion from the non-mycetoma ones; however, it is operator-dependent. Computerised Tomography (CT) scan can determine the bone affection accurately but not the soft tissue involvement. Magnetic resonance Imaging (MRI) is the technique of choice to determine the disease spread along the body planes, the treatment plans and outcome. MRI and CT are good techniques but are expensive and unavailable in low-resource settings (Figures 4,5).

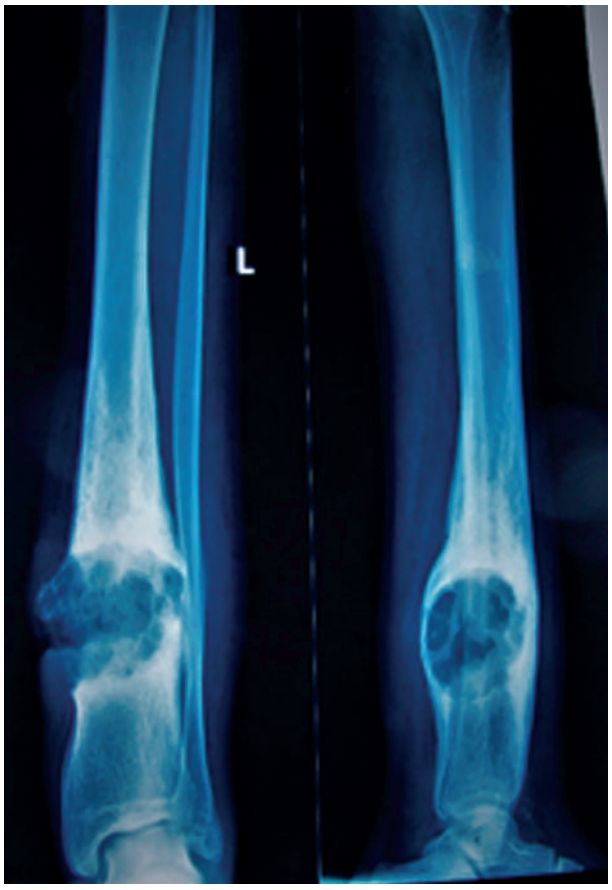

Figure 4. X-Ray in anteroposterior and lateral views of the leg shows a massive eumycetoma cavity with cortical thickness.

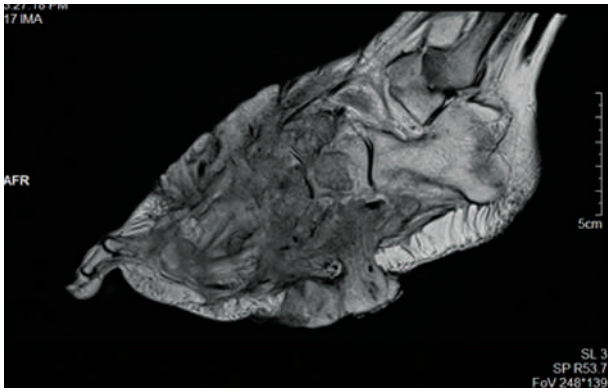

Figure 5. Magnetic Resonance Imaging (MRI) showing massive actinomycetoma affected most of the mid-foot with soft tissues and bones affection.

Identification of causative organisms' techniques

Grains and tissues must be examined to determine the causative organisms. Grains are obtained either directly from the opened sinuses, by fine-needle aspiration technique or surgically by tru-cut needle biopsy or deep-seated biopsies (Figure 6). Surgical biopsies are mostly used as grains obtained from the opened sinuses are frequently contaminated and dead.[11,14,20,26,27]

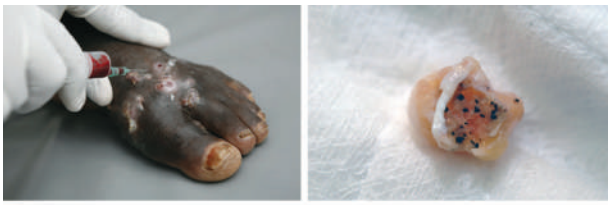

Figure 6a. Fine needle aspiration for Cytology

Figure 6b. Surgical Biopsy

Figure 6. Grains collection techniques[26]

Grain culture and direct microscopy

First, the grains are examined macroscopically for their size, colour, and consistency.[11,18,26] This can give a clue to the diagnosis but is inaccurate and can be deceiving and indefinite.[11,12,17,20,26] Grains are crushed and mounted under a glass slide for direct microscopy examination. For this, potassium hydroxide (10% KOH) is used to have a clear background, and then grains are examined under a light microscope.[20,26] The technique may differentiate between actinomycetes and fungi by their morphological characteristics, filament size, and pigment formation.[1] However, this method is not exclusive, and the use of an additional method is mandatory for conclusive diagnosis.[14,26]

In many centers, grains culture is a gold standard tool for identifying the causative organisms. The mycetoma grains are washed several times with normal saline before plating them into the appropriate culture media in a sterilised environment. Antibiotic-free culture media are used for actinomycetes identification, while eumycetes are inoculated into media containing antibiotics. The culture containers are incubated at 37^0C for three weeks on average. Causative agents and their species can be identified by their microscopic appearance and morphological properties.[26,28,29] In many instances, misdiagnosis and difficulty in distinguishing the different microorganisms based on morphological features are frequent.[20,26,29,30] In conclusion, grain culture is the core tool for

organism identification, but it is time-consuming and requires expert microbiologists to obtain accurate results. Also, this method is vulnerable to false-positive results because of contamination.

Molecular techniques

The use of molecular techniques allows the accurate identification of mycetoma causative agents to the species level. DNA analysis is the key to this technique.[6] Most commonly, the amplification of genes or gene fragments followed by sequencing are used for mycetoma molecular diagnosis.[31] Molecular techniques have become increasingly attractive as they provide rapid and reliable results to improve treatment outcomes.[10,20,26]

Histopathological examination

The histopathological examination of the surgical biopsies is useful for confirming the clinical diagnosis, but it remains ineffective for definitive species identification, particularly for eumycetoma species.[10,11,20,29] Primarily Haematoxylin and Eosin (H&E) stain is used for the mycetoma diagnosis based on histology, while special stains are crucial for species differentiation and inconclusive identification of grains by H&E staining.[11,20,26,32] These special staining includes Gram, Periodic acid–Schiff (PAS) stains, and others.

Deep surgical or tru-cut biopsies are needed for the histopathological examination. They must contain grains to establish the diagnosis.[26,29] Biopsies are fixed in a formalin solution and embedded in paraffin to prepare tissue blocks and histological sections. In mycetoma histopathological sections, the host tissue reactions and grains' morphological appearance are commonly seen.[12,14] Each causative agent has a distinct histological appearance.[4,18] The host tissue reactions against both the fungal and bacterial mycetoma causative organisms are the same. These are three tissue reaction types.[33] In Type I: The neutrophils are closely attached to the surface of grains resulting in grain disintegration. In Type II: the macrophages and multi-nucleated giant cells replace dead neutrophils. The fragmented grains are mostly seen within multi-nucleated giant cells. Type III is characterised by the formation of well-organised epithelioid granulomas with Langham's giant cells (Figure 7).

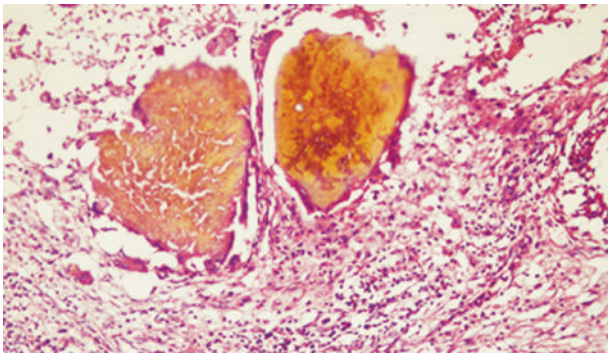

Figure 7. Photomicroscopy showing multiple *M. mycetomatis* grains surrounded by Type II Tissue Reaction in H&E stain, X10.

In general, in the histological sections, the host tissue reactions types I and II are more frequently seen, while type III is the least seen. The histological appearance of grains in H&E stain guides mycetoma differential diagnosis.[20,26,29,32,34,35] *M. mycetomatis* grains are usually large (> 0.5mm) and coloured brownish. They appear rounded, oval, or tri-lobed with irregular outlines and grains fracture (Figure 6). On the other hand, most of the actinomycetoma species grains are homogeneous with round and oval shapes. *S. somaliensis* grains range from 0.5 to 2 mm. They show longitudinal cracks and transverse fracture lines (Figure 8). Cottony shape characterises *A. madurae* grains, and their outlier appears opaque with deep purple colour and less dense stain in the center. *A. pelletieri* grains are compact and dyed dark violet.

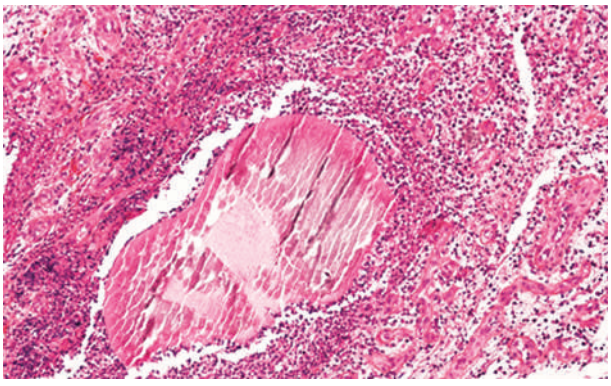

Figure 8. Photomicroscopy showing *S. somaliensis* grains surrounded by Type II Tissue Reaction in H&E stain, X10

Sometimes, grains are absent in histology sections; consequently, a conclusive diagnosis cannot be established. To avoid this, the surgical biopsy should always contain a good number of grains. Various cuts in the tissue blocks depth should be sectioned during the preparation of the histopathological sections.[29] Frequently pathologists report a background of mycetoma, taking into account inflammation and necrosis with grains absence which might be dropped out during the preparation of the sections. These reports are not conclusive for mycetoma diagnosis and necessitate repetition of the surgical biopsy.

Cytological examination

Fine-needle aspiration for cytology (FNAC) is a simple technique to obtain cells and grains for cytological examination. This technique is quite similar to histology in many aspects. First, grains must be present in the collected aspirates to establish the diagnosis. Moreover, cell blocks instead of tissue blocks are obtained from the collected sample and stained before examining smears or sections microscopically. A fine needle attached to a syringe is utilised to collect cytological samples. It is inserted into the suspected mycetoma lesion and negative pressure is applied while moving in for at least three different directions, as illustrated in Figure 6a. In practice, it can differentiate mycetoma from other subcutaneous lesions. In smears, we look for certain cytological properties such as; smears cellularity, inflammatory tissue reactions, and, obviously, the presence of causative organisms' grains.[26,29] Cytology techniques do not need surgical intervention to be collected and hence, can be used in the field and epidemiological surveys.[13,20,26,29]

Serology

Considering the long incubation time to determine causative organisms by culture and invasive surgical procedures to obtain grains in histology, efforts have been made to develop different serology assays.[8,20,26] Furthermore, serological methods are considered the most practical tests in developing countries because of their cost and quickness.[6,13,20] Yet there are no reliable serological tests for mycetoma diagnosis.[4,11,13,20] A common challenge with proposing such tests is the lack of standardised antigens and antigens' long and tedious preparation process.[6,10,20,26] Few studies have explored the use of certain serological tests to measure treatment response and early detection.[4,11,13]

In conclusion, both imaging tools and organism identification techniques are complementary. Nowadays, molecular techniques are considered the test of choice in many centers. They can provide authenticated results; it is expensive and cannot be afforded by most patients and centers. They require well-equipped infrastructure, which is unavailable in the endemic area.[26,35] On the other hand, cytological and histological techniques are simple, rapid, cost-effective methods commonly used in rural areas where most affected populations are located.[12,26,35] However, false-negative results are common in the cytological examination as the FNA is blindly performed, and it is possible to miss grains pockets. A recent comprehensive study conducted at the MRC showed that histology is more accurate than cytology in organism identification.[29] Furthermore, ultrasound-guided aspiration cytology had improved the test yield. In general, the minimum tools required to report the diagnosis are cytological and ultrasound examinations.[11] The recommended protocol for organism identifications shown in Figure 9.

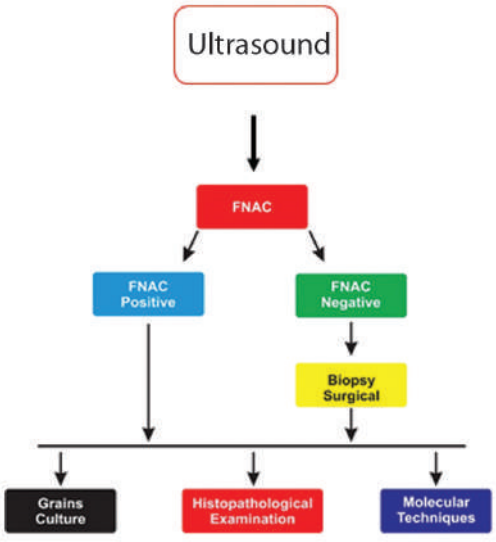

Figure 9. Mycetoma Diagnosis Flowchart

Mycetoma treatment and management

Although mycetoma was reported almost 200 years ago, no guidelines or protocols were approved by WHO for mycetoma treatment and management.[13,36] Thus, therapeutic programs are based on expert opinion and published case reports. The MRC developed various guidelines to assist health practitioners dealing with mycetoma based on its management experience with more than 10,000 patients, (www.mycetoma.edu.sd). The proper mycetoma treatment is highly dependent on the accurate identification of causative agents, as the two mycetoma types are treated differently.[10,12,26] In general, mycetoma treatment is difficult, challenging, and the outcome is disappointing. The available medicines are not very effective, have many side effects, expensive, and not accessible or available in many endemic mycetoma regions.[13,36] Furthermore, it requires prolonged treatment administration duration and thus the patients' low compliance and high dropout rates. Many patients present late with advanced disease; the only treatment option is massive surgical excisions with enormous deformities or amputations. Early cases without deep structure involvement are curable.[10,11] Although actinomycetoma is more aggressive than eumycetoma, with rapid progression and more rapid bone involvement, yet, it responds better to a combination of antibiotics with a cure rate of 70-90%.[7,10,12,13,35] In contrast, eumycetoma is difficult to cure; a combination of medical treatment with antifungals and surgical excisions is the recommended treatment regime.[18,37] In some rare cases, both types of infection occur, complicating treatment.

The surgical treatment of mycetoma ranges from wide local excision, repetitive surgical debridement for better response to medical therapy to amputation of the affected limb.[34,36,37] These aggressive surgical procedures are associated with higher morbidity, deformities, and disabilities[10,14]. Recurrence is high in eumycetoma patients. This is often due to the wide local disease spread along the tissue planes, disease biology, poor patient treatment compliance, late presentation, and poor surgical techniques.[10,11,37] The treatment outcome depends on the mycetoma type, site, size and tissue spread. Secondary bacterial infections are a common feature of mycetoma and frequently affect medical treatment.[7] Since treatment is prolonged, patients require long-term follow-up to monitor recovery, recurrence, and drug side effects.[36] This is often associated with a high patient dropout rate and irregular follow-up.[12] The MRC, the referral center in Sudan, schedules regular follow-ups every six weeks until the treatment endpoint. The cure is defined as (i) Sinuses closure, (ii) Lesions disappeared or massively decreased in size, (iii) Skin returns to normal, (iv) Improved disability, (v) No grains are seen on cytological or histopathological examination and (vi) Disappearance of masses and grains on ultrasound examination.[10,11,34,35] To improve treatment response to eumycetoma, in particular, *Madurella mycetomatis* species, the most common type, DNDi and MRC launched the world's first mycetoma clinical trial for a potential new drug for eumycetoma in 2017.[7,8]

Presently there is no control or prevention programme for mycetoma due to the knowledge gaps in its epidemiological characteristics. Hence, early detection and treatment have proved to be the effective tools for reducing the disease burden.[10,13,36] A survey conducted in one of the endemic villages in Sudan showed that barely half of the surveyed villagers used the acceptable practice in mycetoma management, and only 4% possess a good knowledge of mycetoma.[38] Therefore, MRC practices of health education and advocacy and encouraging reporting of suspected cases will improve prognosis and lower the severity of infection.[17]

Why is mycetoma still a public health dilemma and a unique neglected tropical disease?

Mycetoma is a destructive and devastating infection with either bacterial or fungus types. It mostly affects the poorest of the poor young adults in rural areas. Mycetoma is a common medical and health problem that might cause permanent deformity. The painless nature of mycetoma often leads to

late diagnosis with severe infection. Consequently, the disease might develop secondary bacterial infection leading to massive local and regional sepsis and occasionally septicemia.[4,7,34] Therefore, the correct diagnosis to the causative agentis important as the treatment varies for eumycetoma and actinomycetoma. However, the disease has been neglected by public health authorities, professionals, and the scientific community; hence, early diagnosis is quite difficult, and treatment is challenging and sometimes ineffective.

The mechanism of mycetoma transmission is still ambiguous. Furthermore, high-risk regions mapping is not yet accomplished, which restricts the designing of effective prevention and control programmes.[6] Presently, the active prevention mechanism considers lifting the awareness of the disease and the necessity of protecting exposed body parts in endemic areas, specifically feet and hands.[13,18,34] Also, promoting the importance of early reporting of suspected cases in primary care centers to be referred to specialist centers.[13,14]

Mainly, the feet are the most affected site, followed by the legs leading to chronic morbidity and loss of function.[5,39] With advanced disease or when treatment fails, amputation is very likely. This has major social and economic consequences.[7,10,12,39] There is a high probability of school/training dropouts for mycetoma patients, affecting their ability to secure a job and making them economically dependent. Psychologically, patients are also affected because of inadequate health centers in endemic areas, poor treatment response, and the social stigma of being physically disabled. Given this, mycetoma seriously impacts the patients, their families, and the communities.[36,39] In general, mycetoma patients live with the disease for quite a time and are rarely cured.

The mycetoma burden is concentrated in the "mycetoma belt", but the global burden is uncertain. The number of infected people worldwide and which countries are most infected are unknown[8]. Africa seems to be the most highly endemic continent, where health services and education are in crisis with limited staff and resources.[10] The number of mycetoma estimated cases is comparable to Buruli ulcer and African human trypanosomiasis; in the latter the data were from surveillance data.[5,6] It is believed that the approximated numbers of mycetoma cases are underestimated, but they give a general overview of prevalence and incidence. Unless surveillance data are gained for mycetoma, global burden and epidemiology would be missing.[5] Mycetoma has gone through a long journey to be globally recognised. This recognition attracts media attention and raises funding opportunities. WHO, Aljazeera, Global Health Innovative Technology Fund, BBC, and many other governmental and non-governmental organisations produced documentaries about mycetoma.[8] Also, the PLoS Neglected Tropical Diseases Journal had produced a special collection on mycetoma and accepted and published many papers. Despite this, numerous knowledge gaps still need to be investigated, particularly in epidemiology, transmission mode, diagnosis, and treatment.[6-9,11,13,17]

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Original Article

Are pharmacists neglecting the neglected Mycetoma in the most endemic area in Sudan? An opportunity for improvement

Kannan O Ahmed[1], Imtinan Abalgadr Osman[1], Alaa M. Abdalnabi[1], Sahar Mubarak Bakhiet[2,3], Abdalla Elkhawad[4], Ahmed Hassan Fahal[3*]

[1]*Faculty of Pharmacy, University of Gezira, Wad Medani, Sudan.*

[2] *Institute of Endemic Diseases, University of Khartoum, Sudan.*

[3]*Mycetoma Research Center, University of Khartoum, Sudan.*

[4]*Faculty of Pharmacy, University of Medical Sciences and Technology, Khartoum, Sudan.*

ABSTRACT

Background Mycetoma is a common medical and health problem endemic in many tropical and subtropical regions and is characterised by devastating deformities, disability, and high morbidity. It has serious negative medical, health, and socio-economic impacts on patients, families, communities, and health authorities in endemic regions. Yet, it enjoys scanty attention across the globe, culminating in massive knowledge gaps in various aspects of mycetoma. Hence, this study was set out to assess the knowledge of pharmacists in a highly mycetoma endemic area in Sudan.

Method This descriptive cross-sectional, community-based study was conducted in Sennar State using a validated web-based self-administrated questionnaire that included important and basic knowledge of mycetoma; 217 pharmacists were invited to participate, and 153 responded. The data were managed and analysed by appropriate statistical tests, and the overall knowledge scores were calculated.

Results The study population included 76 males (49.7%) and 77 females (50.3%). Their ages ranged from 20 to 50 years, with a mean of 31.7 years. Most of them (n= 134, 87.6%) were holders of bachelor's degrees in pharmacy, while 19 (12.4%) had higher degrees; 98 (64.1%) were community pharmacists; 38 (24.8%) were hospital pharmacists and their practice experience ranged from less than five years to more than 20 years. The majority of the participants (92.2%) had insufficient knowledge of mycetoma, and only 7.8% had good knowledge. There was no significant association between knowledge score and the participants' demographic characteristics.

Conclusion Mycetoma is a common problem in Sennar State, and despite that, most of the study participants had insufficient knowledge of the disease. A well-structured continuing professional development programme for pharmacists together with ‑ implementation of clinical pharmacy services in mycetoma endemic regions are badly needed

[*]***Correspondence to*** ahfahal@mycetoma.edu.sd, ahfahal@hotmail.com

INTRODUCTION

Mycetoma is a chronic granulomatous subcutaneous inflammatory disease caused by true fungi (eumycetoma) and certain bacteria (actinomycetoma).[1,2] Traumatic inoculation of the causative organism into the subcutaneous tissue is a popular route of entry theory.[3,4] The causative organisms are isolated worldwide, but most cases of mycetoma are reported from the so-called "mycetoma belt", which includes Brazil, Chad, Ethiopia, India, Mauritania, Mexico, Senegal,

Somalia, Sudan, Venezuela, Yemen, and others. Sudan has the highest disease burden worldwide.[5-7]

The Mycetoma clinical presentation is almost identical irrespective of the causal organism, and it is characterised by a triad of painless subcutaneous mass, multiple sinuses, and discharge containing visible grains.[8,9] Mycetoma usually spreads contiguously to involve the skin, deep structures, and bone resulting in destruction, disfigurement, and loss of function, which may be fatal.[10-12] Mycetoma commonly affects the extremities, back, and gluteal region, but no part is immune.[13-15] The patients' late presentation is the norm, and that is due to the mycetoma painless nature, the patients' low socio-economic status, lack of health education, and scarcity of medical facilities in remote areas where the disease is endemic.[16-18]

The diagnosis of the causative organisms is based on their identification on histopathological sections from surgical biopsies or cytological smears and the classical grains culture.[19-21] Other useful molecular techniques, such as DNA sequencing, are presently in use.[22,23] Various imaging techniques such as conventional radiology, ultrasound, and magnetic resonance can be used for disease extension determination.[24-26] However, most of the available mycetoma diagnostic tests and techniques are invasive, expensive, of low specificity and sensitivity and unavailable in mycetoma endemic regions compelling patients to travel to provincial hospitals.[27,28]

It is still challenging and hard to treat patients with Mycetoma, particularly eumycetoma. To treat eumycetoma, extensive and destructive surgery, mutilating amputation, a social stigma in developing countries, and prolonged antifungal treatment are required.[29-31] The available antifungals proved to be ineffective and have serious side effects. The currently available antifungal is itraconazole.[32] Treatment with itraconazole, which is not curative, lasts for more than two years, at the cost of approximately $5000 per year, making it expensive for patients and health authorities in endemic areas.[33,34] For actinomycetoma, a prolonged course, with a mean of 18 months, of combined antibiotics is mandatory, with a cost of $2000 per year is needed.[35]

Moreover, the treatment outcome is disappointing. It is characterised by a low cure rate (25%-35%), high amputation (15%), high patient follow-up dropout (55%), and high recurrence rates (27.5%).[29] Many Mycetoma patients, due to the suboptimal management, expensive medicines and diagnostic tests, embark on traditional and alternative treatments that commonly induce massive complications.[36] Hence, there is an urgent need for new medicines that are safe, effective, and appropriate for use in rural settings. Due to the patients' high follow-up dropout, counseling and health education support are also needed. To design such programmes, in-depth understanding of the practicing pharmacists in the mycetoma endemic areas disease knowledge is necessary. Hence this study was conducted.

MATERIAL AND METHODS

This descriptive cross-sectional survey was conducted in August 2022. It included 153 of the 217 Sudan Medical Council registered pharmacists in Sennar State. The study participants included practicing community, clinical and hospital pharmacists, sales representatives, and academics. A validated web-based self-administrated questionnaire was used to collect the required data. The questionnaire included important and basic knowledge of Mycetoma. A pilot endeavor was conducted prior to the study to validate the questionnaire. The questionnaire was distributed online to all pharmacists at Sennar State, and 153 of them responded. They gave informed consent.

The questionnaire consisted of three main parts; the first part was on the participants' demographic characteristics; the second was composed of 13 questions to determine their knowledge of the disease aetiology, symptoms, signs, transmission route, endemic area, treatment strategy and common drug prescribed for each mycetoma type and the third part was on their practice toward mycetoma

patients. The information is based on the most recent data on mycetoma. Participants who scored six or more than six out of 13 were considered to have good knowledge of mycetoma, while those with less than six were categorised as having insufficient knowledge.

Data analysis

The data were managed by the Statistical Package for Social Sciences (SPSS) version 26 (SPSS Inc., Chicago, IL). Descriptive statistics were executed, the categorical variables were presented as percentages and/or frequencies, while continuous variables were summarised as median and means. Association between variables was carried out using the chi-square test. A *p*-value of less than 0.05 was considered statistically significant.

RESULTS

Out of 217,153 (70.5%) Sudan Medical Council registered pharmacists practicing at Sennar State responded to the call and were included. There were 76 males (49.7%) and 77 females (50.3%). Their ages ranged between 20 and 50 years, with a mean ± standard deviation of 31.7 ± 6.3 years. Most participants (n=134, 87.6%), were holders of bachelor's degrees in pharmacy, while19 (12.4%) had higher degrees. The majority of study participants (n= 98, 64.1%) were practicing in community pharmacies; 38 (24.8%) were hospital pharmacist; 59 (38.6%) pharmacists had less than five years of practice experience, and 97 (63.4%) worked in Sennar city (Table 1).

Table 1. The pharmacists' demographic characteristics (n=153)

Characteristics	No	%
Sex		
Male	76	49.7
Female	77	50.3
Age group years		
20-30	80	52.3
31-40	60	39.2
41-50	13	08.5
Educational Level		
Bachelor	134	87.6
Master	14	9.2
PhD	01	0.7
Diploma	04	2.6
Practice locality		
Community Pharmacy	98	64.1
Hospital Pharmacy	38	24.8
Clinical Pharmacy	04	2.6
Medical Representative	07	4.6
Academia	06	3.9
Experience		
Less than 5 years	59	38.6
5-9 Years	47	30.7
10-14 Years	36	23.5
15-20 Years	08	05.2
More than 20 years	03	02.0
Residency		
Sennar city	97	63.4
Outside Sennar	56	36.6

Regarding the general knowledge of Mycetoma, 84 (54.9%) pharmacists knew Mycetoma types and causes, while 14 (9.2%) did not. Forty-four (28.8%) pharmacists reported that the age group 20 to 30 years is the most affected, and 43 (28.1%) did not recognise that.

For the Mycetoma gender distribution, 85 (55.6%) participants recognised males are affected most, and 16 (10.5%) did not know this characteristic. Only 36 (23.5%) participants did not know that central Sudan is the Mycetoma most affected part. Concerning the transmission route, 44 (28.8%) participants thought contaminated water was the main infection route, and 39 (25.5%) did not know

the route of transmission (Table 2).

Table 2. Pharmacists' general Knowledge of Mycetoma (n=153)

Characteristics		No.	%
Mycetoma aetiology			
	Fungal Infection	47	30.7
	Both Bacterial and Fungal	84	54.9
	Bacterial infection	07	4.6
	Non-infectious disease	01	0.7
	Don't know	14	9.2
Mycetoma patients' common ages			
	Less than 10 years	11	7.2
	10-20 years	19	12.4
	21-30 years	44	28.8
	31-40 years	24	15.7
	41- 50 years	07	4.6
	51-60	02	1.3
	More than 60 years	03	2.0
	Don't know	43	28.1
The most affected sex			
	Male	85	55.6
	Female	04	2.6
	No difference between sex	48	31.4
	Don't know	16	10.5
The most affected areas in Sudan			
	Central of Sudan	56	36.6
	East of Sudan	22	14.4
	West of Sudan	09	5.9
	North of Sudan	03	2.0
	South of Sudan	27	17.6
	Don't know	36	23.5
Transmission Route			
	Blood	22	14.4
	Orofecal Rout	16	10.5
	Implantation	30	19.6
	Unprotected Sex	02	1.3
	Contaminated Water	44	28.8
	Don't know	39	25.5

The collected data showed that 50 (32.7%) participants recognised that painless lesion is the commonest presentation of Mycetoma, and 24 (15.7%) did not know that. Furthermore, 103 (67%) knew the foot is affected most frequently in mycetoma, while 8 2% did not recognise this fact. Only 31(20.3%) pharmacists said that antibiotics combination is the treatment of choice for actinomycetoma, on the other hand, 15 (9.8%) did not know. For eumycetoma, 76 (49.7%) participants knew that antifungals followed by surgery are the treatment policy, and 23 (15%) did not. Of them, 39 (25.5%) did not know the drug of choice for actinomycetoma, but 94 (61.4%) knew that itraconazole is the most common drug used for

eumycetoma. The eumycetoma and actinomycetoma common drugs' side effects were unknown to 58 (37.9%) and 66 (43.1%) participants, respectively (Table 3).

Table 3. Pharmacists' Knowledge of Mycetoma clinical presentation and treatment (n=153)

Characteristics		No.	%
Signs and Symptoms of Mycetoma			
	Severe Pain lesion	37	24.2
	Painless lesion	50	32.7
	Grains	18	11.8
	Discharge	16	10.5
	Sinus	08	5.2
	Don't know	24	15.7
What are common Sites of Mycetoma			
	Foot	103	67.3
	Foot and hands	27	17.6
	Any sites in the body can be affect	13	8.5
	hands	01	0.7
	Head and Neck	01	0.7
	Don't know	08	5.2
Treatment strategy for Actinomycetoma			
	Combined antibiotics followed by surgery	57	37.3
	Surgery followed by combined antibiotics	40	26.1
	Combined Antibiotics	31	20.3
	Surgery	10	6.5
	Don›t know	15	9.8
Common Drugs for Actinomycetoma			
	Cephalosporin IV	28	18.3
	Trimethoprim/Sulfamethoxazole tablets	36	23.5
	Amikacin sulphate IV	24	15.7
	Antiviral	06	3.9
	Amoxicillin/clavulanic acid tablets	20	13.1
	Don't know	39	25.5
Treatment strategy for Eumycetoma			
	Antifungal followed by surgery	76	49.7
	Antifungal	43	28.1
	Surgery	11	7.2
	Don't know	23	15
Common Drugs for Eumycetoma			
	Itraconazole tablets	94	61.4
	Acyclovir tablets	10	6.5
	Ketoconazole tablets	20	13.1
	Don't know	29	19
Common SE of Actinomycetoma drugs			
	Hepatotoxicity	28	18.3
	Skin rash	43	28.1
	Renal failure	21	13.7

	Jaundice	01	0.7
	Adrenal failure	02	1.3
	Don't know	58	37.9
Common SE of Eumycetoma drugs			
	Hepatotoxicity	48	31.4
	Skin rash	17	11.1
	Renal failure	17	11.1
	Adrenal failure	01	0.7
	Jaundice	04	2.6
	Don't know	66	43.1
Mycetoma Patients in the Pharmacy			
	Yes	62	40.5
	No	91	59.5
Your First Response			
	Refer to the doctors	144	94.1
	Prepare my own pharmaceutical preparation	02	1.3
	Start treatment with antibiotics	07	4.6

SE = side effects

The study revealed that 141 (92.2%) participants had insufficient knowledge scores of Mycetoma, and only 12 (7.8%) had good knowledge. Further analysis demonstrated no significant association between knowledge score and the participants' demographic characteristics (p >0.01).

DISCUSSION

Mycetoma being one of the most common neglected tropical diseases (NTDs) enjoys all the characteristics of NTDs; it affects the poorest of the poor in poor and remote communities. The affected populations have low health education levels, poor socio-economic status, and a low political voice. Yet, there is no control or prevention measurement programme for mycetoma available worldwide, and that is due to knowledge gaps in its susceptibility, resistance, and infection route.[37] The treatment course is both long and difficult. The current medicines for mycetoma are few, have many side effects, expensive, and are not accessible or available in most disease-endemic areas.[37] The mycetoma treatment outcome is rather poor, characterised by a low cure rate, high recurrence, and patient follow-up dropout. The treatment duration may last several years with a mean of 18 months.[29] The disease burden is substantial, in developing countries, the diagnosis and treatment of one patient may amount to $6000 per year, with massive working days loss for the patient, the accompanying family members, and the community in general.[33] Mycetoma is an important cause of education attrition and poverty. Due to its devastating complications, the disease is considered a social stigma, particularly among the young and females.[38] To our knowledge, no specialised pharmacy service to patients with Mycetoma was reported worldwide. With this background, the present study was set to determine the knowledge of pharmacists in Sennar State (one of the most affected areas in Sudan), as they are key care providers whom we need to build on when designing mycetoma awareness and advocacy actions.

The obtained data showed the majority of the study participants (92.2%) had insufficient knowledge of Mycetoma. This is a serious finding as they are practicing in one of the badly affected states with this neglected disease in the country. The explanation may be multifactorial. Most pharmacists had less than five years of practice experience. Most of them were community pharmacists lacking continuing professional development (CPD) programmes and

training, as well as having insufficient courses and information on mycetoma and other NTDs in the undergraduate curricula.

Sennar State, part of the Sudan Mycetoma Belt, is a highly endemic state in the country,[1,2] and despite that, only 36.6% of the pharmacists knew this fact. This necessitates designing and implementing good CPD programmes to improve their knowledge of the disease.

Although the Mycetoma transmission route is not well documented, but the subcutaneous traumatic inoculation of the causative microorganisms is the most favoured theory.[1,2] For this reason, Mycetoma commonly affects farmers and shepherds in low socio-economic communities; however, only 19.6% of the pharmacists recognised this fact. Likewise, their knowledge of Mycetoma aetiology, clinical presentations, mostly affected gender and age groups was rather insufficient.

In general, actinomycetoma has a good therapeutic response to a combination of antibiotics and a better outcome, yet, the treatment policy was not well known to most of the study participants as only 20.3% recognised this fact. The most frequently used antibiotics for actinomycetoma are amoxicillin-clavulanate, cotrimoxazole, and amikacin based on the MRC treatment guidelines; only a minority of the pharmacists recognised these drugs and their side effects. The current treatment for actinomycetoma is a combination of amoxicillin-clavulanate and cotrimoxazole as a first-line treatment; for advanced cases, it is cotrimoxazole and amikacin sulphate; however, the latter is nephrotoxic and ototoxic, and needs close monitoring and observations.[35]

The treatment guideline for eumycetoma states that it is an antifungal treatment for six months, then surgical excision followed by antifungal therapy until cure. The preoperative antifungal treatment induces intensive fibrosis around the mycetoma lesion that can facilitate its surgical excision, and the postoperative treatment reduces the chance of surgical recurrence.[32]

Only a few antifungal drugs are available for eumycetoma treatment. Despite the good in vitro activity of voriconazole and posaconazole, their uses in clinical practice are limited because of their side effects with the longer treatment duration, cost-effectiveness, and relative lack of clinical studies to determine their cure rate.[39] Recently, fosravuconazole, a prodrug of ravuconazole, was tested in a double-blind clinical trial at the MRC, Sudan, and the result will soon be published. Itraconazole is the only drug for eumycetoma available in Sudan, but only 61.4% of the study participants knew this fact. However, it has many adverse effects, including transient elevation of serum transaminases due to hepatotoxicity, and its negative inotropic effects on the heart leading to congestive heart failure.[32] A few participating pharmacists knew about these adverse effects.

In conclusion, this study yielded important data and information on knowledge of the pharmacists practicing in an endemic area. Yet further study in other parts of the country with a large number of participants is needed. Mycetoma and other NTDs should be included in the medical and health professionals' undergraduate curricula. More structured objective CPD programmes for pharmacists are required, and the introduction of pharmacy clinical services in hospitals and centers in mycetoma endemic regions is vital.

Ethical approval

The Mycetoma Research Center IRB Committee approved the study.

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Original article

The value of tympanometry in diagnosis of ear disease in children's outpatient clinic in Khartoum

Osama M Khalid[1*], Somalia AM Ali[1], NaglaDafaa Allah[2], Hashim I Yagi[1]

[1]*Department of Otorhinolaryngology, Faculty of Medicine, University of Khartoum, Sudan*

[2]*International Hearing center, Khartoum Sudan*

ABSTRACT

Background Tympanometry is an acoustic evaluation of the ear drum and the conduction bones. It is an objective test of middle ear function. Typically, it is used to detect the presence of fluid in the middle ear and eustachian tube dysfunction. Tympanometry has been and remains one of the widely used tool especially in children because it is noninvasive and provides the information without interactive communication. This study assesses the value of the test in diagnosis of ear disease in children

Patients and methods This is a descriptive cross-sectional study conducted in Khartoum Ear Nose and Throat Hospital outpatient from October 2020 to October 2021.The participants were randomly selected from patients attending the otology clinic. Enrollment was optional with the right to withdrawal at any time. Consent was taken from guardians or participants. Ethical clearance was obtained. The data was collected by a well-structured questionnaire and analyzed using the Statistical Package of Social Sciences.

Results The total number of patients studied was 137. Females were 72 (52.6%) and males were 65 (47.4%). The patients ages ranged from 6 to 18 years with a mean age of 10.6years. The majority of the patients (n=78, 56.9%) were 6-10 of age. Decreased hearing was the most common presenting symptom; nasal obstruction and snoring were less common; 51.7% had no aural complaints. Otoscopic examination revealed normal and dull looking tympanic membranes in 77.7% and10.2% of cases, respectively. Out of the 274 examined ears type A tympanogram was found in 69.3% and type B in 14.5%. One third of ears with normal looking tympanic membranes showed abnormal tympanogram, mostly type B.

Conclusion Tympanometry is an easy useful test in diagnosis of diseases of the middle ear which are common in children. Diseases diagnosed by tympanometry could exist without aural symptoms. The look of the tympanic membrane alone does not always rule out healthy middle ear status. Non aural symptoms could correlate with an abnormal tympanogram and hence middle ear disease.

***Correspondance to** osamamk@yahoo.com*

INTRODUCTION

Acoustic immittance testing, an integral part of the test battery for diseases of the ear; consists of tympanometry, acoustic reflexes, and static compliance. These tests measure the function of the tympanic membrane, middle ear, and acoustic reflex arc pathway. They are not direct measures of hearing sensitivity[1].Tympanometry is a dynamic measure of immittance in the ear canal as a function of changes in air pressure in the ear canal above and below atmospheric pressure. A tympanogram is a graphical display of acoustic admittance, displayed on the y-axis, relative to ear canal air pressure, displayed on the x-axis. Ear canal pressure is expressed in units called deca-pascals (daPa). The unit of immittance is the millimho (mmho)[2].

Tympanometry is an acoustic evaluation of the middle ear and the conduction bones by creating variation of pressure in the ear canal. While the pressure is changing measurement of the ear drum movement will be recorded. It is a measure of energy transmission through the middle ear. It is an objective test of middle ear function. Identification of middle ear disorders by tympanometric measures has been a standard in audiology practice for decades. Examination of middle ear indices i.e., peak compensated static acoustic admittance [Ytm], equivalent ear canal volume [Vea], tympanometric peak pressure [TPP], and tympanometric width [TW]) are essential for the diagnosis of middle ear disorders, evaluating the efficacy of treatments for middle ear disorders, and for screening for middle ear disorders in children[3].

Types of tympanograms

Type A is normal tympanogram. Type As compliance is lower at or near ambient air pressure; seen in fixation of ossicles, e.g., otosclerosis or malleus fixation. Type Ad high compliance at or near ambient pressure; is seen in ossicular discontinuity or thin and lax tympanic membrane. Type B is a flat or dome-shaped graph. No change in compliance with pressure changes; seen in middle ear fluid, thick tympanic membrane or perforated tympanic membrane. Type C maximum compliance occurs with negative pressure in excess of 100 mm H2O; seen in retracted tympanic membrane and may show some fluid in middle ear[4]. Unfortunately, the diagnostic use of conventional Type As and Type C tympanograms has been limited because there is substantial overlap in the range of values recorded from normal and diseased ears[5].

Otitis media with effusion (OME) or "glue ear" is the most common cause of hearing loss in children in the developed world environment[6]. Otitis media with effusion is defined in recent international recommendations as the presence of liquid in the middle ear without any associated signs of ear infection[7]. Otitis media with effusion is prevalent among infants and young children. The disease is often associated with conductive hearing impairment, but the degree of this impairment varies. More-over, the course of this type of middle ear disease is also highly variable and generally unpredictable[8]. OME can lead to hearing loss that impairs the child's language and behavioral development[9].

MATERIALS AND METHODS

This is a descriptive cross-sectional hospital-based study of patients aged 6-18 years of age who presented to Khartoum Ear Nose and Throat (ENT)Teaching Hospital outpatient from October 2020 – October 2021. Participants were randomly selected from the otology clinic. Enrollment was optional with the right to withdrawal at any time. Informed consent was obtained with reassurance on the confidentiality, privacy, and consent of the data. Ethical clearance from the Ethical Committee of the Education Development Centre of Sudan Medical Specialization Board and the Research Committee of Khartoum Teaching Hospital was granted. Data was collected from the guardians or the participants using well-structured questionnaires. All participants were examined by otoscopy and tympanometry. In tympanometry the frequency was 226 Hz, and air pressure range: + 200 to – 300 mm.$H_2$0 was used. The data was analyzed using Statistical Package for Social Sciences (SPSS v.26) and P value of <0.5 is considered significant.

RESULTS

A total of 137 patients were included in this study. Females were 72 (52.6%) and males were 65 (47.4%). Patients' ages ranged from 6 to 18 years with a mean age of 10.6 years. Seventy-eight (56.9%) patients were 6 – 10 years old; 36 (26.3%) and 23 (16.8%) were aged 11 – 14 and 15 – 18 years, respectively. In the right ear, there was decreased hearing in 26 (19%) ears, sensation of aural fullness in 14 (10%) ears, otalgia in 20 (15%) ears and in 87 (63.5%) ears there was no complaints. In the left ear the decreased hearing, sensation of aural fullness and otalgia were seen in 18%, 7% and 10% of ears, respectively as seen in Figure 1; 133 (97.1%) patients had no delay in speech and 131 (95.6%) patients showed good social behavior.

Figure 1. Right and left ears presenting symptoms among patients in the study group

Nasal symptoms were present in 58 (42.3%) patients; 31 (22.6%), 39 (28.5%) and 16 (11.7%) of them experienced nasal obstruction, snoring and nasal discharge, respectively. Sore throat was encountered in 54 (39.4%), odynophagia in 19 (13.9%) and 74 (54%). patients had no throat symptoms

Out of 274 ears examined in this study, normal looking tympanic membrane (TM) was found in 213 (77.7%); 28 (10.2%) were dull, nine (3.2%) were bulging, 13 (4.7%) were retracted; one was thin; one was sclerotic with air fluid level seen through the TM and 12 (4.3%) were hyperemic. Of the 137 right ears 105 (76.6%) showed normal looking TM; 16 (11.7%) dull TM; 3 (2.2%) were bulging; and 6 (4.4%) retracted TM. Among the 137 left ears examined, the findings showed 108 (78.8%) normal looking TM, 12 (8.8%) dull; six (4.4%) bulging and seven (5.1%) retracted TMs as seen in Figure 2.

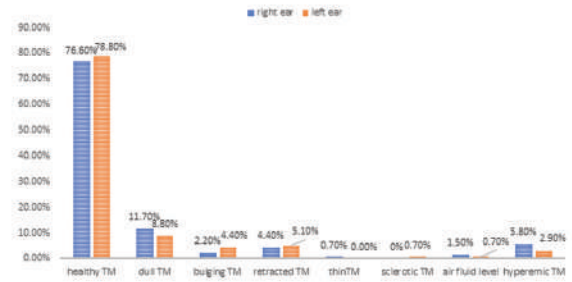

Figure 2. right and left ear examination findings of patients in the study group

Out of 274 tympanograms,190 (69.3%) the tympanograms were type A and 40 (14.6%) were type B. Type As, type Ad and type C tympanograms were seen in 22 (8,0%), 9 (3.2%) and 13 (4.7%) cases, respectively. In the right ear, 95 (69.3%) were type A tympanogram and 21 (15.3%) were type B. Type As, type Ad and type C were seen in 12 (8.8%), three (2.2%) and in six (4.4%) ears. In the left ear, the tympanograms seen in type A, type B, type As, type Ad and type C were 95 (69.3%), 19 (13.9%); ten (7.3%); six (4.4%) and seven (5.1%) ears, respectively. There is significant statistical difference when comparing between the types of tympanograms in right and left ears with P <0.00.

Thirty-nine patients complained of snoring in the right ear their tympanogram distribution was type A in 51.3%, type B in 33.3%, type As in 5.2%, type Ad in 2.5% and type C in 7.7% (Figure 3), while in left ear type A was in 53.8%, type B in 30.8%, type As in 2.6%, type Ad in 2.6% and type C was in 10.2% of cases (Figure 4). It was found that the only symptoms which had significant correlation with the types of tympanograms were poor social behavior (p<0.002) and snoring (P< 0.005 in right ear p< 0.001 in the left ear).

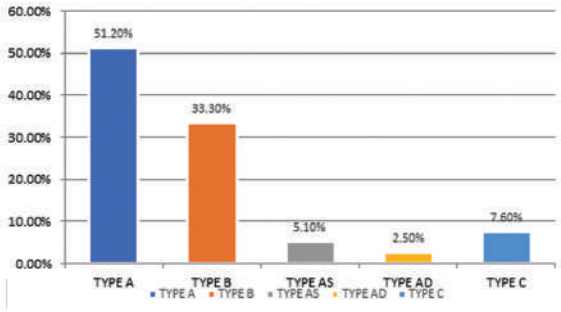

Figure 3. Types of tympanograms in the right ear among snoring patients in the study group

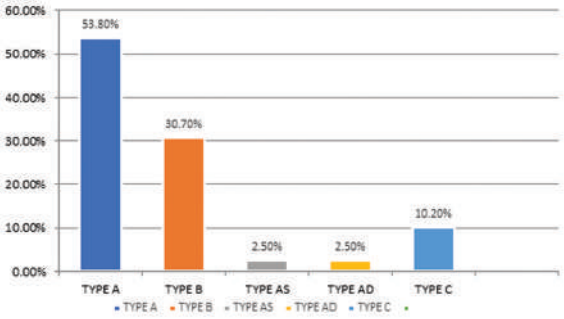

Figure 4. Types of left ear tympanograms in snoring patients the study group

Regarding the clinical examination findings of the 274 ears; in 213 ears there was normal looking TM; in 163(76.5%) of which the tympanogram was type

A and 17 (7.9%) were type B. Type As, type Ad and type C tympanograms were seen in 19 (8.9%), in seven (3.2%) and seven (3.2%) ears, respectively. In 28 ears with dull TM, eight (28.6%) of them showed type A tympanogram; fourteen (50%) were type B and five (17.8%) were type C. No ear with dull TM showed type As tympanogram with significant /value for both healthy and dull TMs (p<0.00 for both) (Table.).

Table. Correlation between ear examination findings and types of tympanograms

Ear examination	Tympanogram						
	Type A	Type B	Type AS	Type AD	Type C	Total	P value
Healthy TM	163	17	19	7	7	213	0.00
Dull TM	8	14	0	1	5	28	0.00
Bulging TM	4	4	1	0	0	9	0.177
Retracted TM	8	2	1	1	1	13	0.887
Thin TM	1	0	0	0	0	1	0.979
Sclerotic TM	1	0	0	0	0	1	0.132
Air fluid level	0	2	1	0	0	3	0.182
Hyperemic TM	5	4	2	0	1	12	0.234

DISCUSSION

This is a descriptive cross-sectional hospital-based study, in which 137 patients participated; their ages ranged from 6 years to 18 years. Both sexes were nearly equal. Decreased hearing was the most common ear complaint and it is an important symptom of OME which is common in pediatric patients, followed by otalgia and sensation of aural fullness. In this study there was no delay in speech nor abnormal social behavior. The most common nasal complaints were snoring and sore throat was presents in two-fifth of the cases. However, in the majority of ears, the tympanic membranes were normal and dullness (which was the most common abnormality) was seen in one tenth of the cases.

This study revealed that type A tympanogram was found in two-thirds of both right and left ears. This is comparable with Stefania study which reported type A in 76% in both right and left ears.The prevalence of type A is higher in Stefiana study probably because it was community-based study and done on healthy subject with larger sample size. However, our findings are compatible with Jorgen study which revealed type A in 68.7% of examined ears[10,11].

The most common abnormal type of tympanogram in this study was Type B (in 14.5% of assessed ears). This agrees with Jorgen and with Yousry EL Sayed study which reported prevalence of type B in 12.2% and 10.9%, respectively[11,12]. The incidence of type C in this study (i.e. 4.7%), is incompatible with Jorgen study which reflected type C in 19.1%. This could be explained by the disparity in age groups between the two studies and the larger sample size of the Jorgen study[11]. Bilateral type B tympanogram was present in 11.6% of the patients in this study group but it was 8.1% in Yousry El Sayed study[12]

Regarding types of tympanograms in ears with normal looking TMs in this study, three quarters were of type A; type B and type C were present in 8% and in 3%, respectively; in comparison with Fiellau study which reported type A in two-thirds, type B in 9.8%, type C in 27.4% [(13)] . It is difficult to explain the differences between the two studies.

In this study there is significant statistical difference when comparing types of tympanograms in right and left ears with p< 0.000, this is inconsistent with Aithal and Andrew Stuart studies who reported no statistically significant differences between right and left ear indices[3,14]. However, Li reported a statistically significant difference between right and left in equivalent ear canal volume only, with the left ears larger than the right[15]. But Haapaniemi found no statistically significant difference between right and left ear indices with the right ear canal was larger than that of the left ear by a mean difference of 0.05 ml[3]. Snoring and poor social

behavior are significantly associated with the types of tympanograms and this is consistent with Humaid study[16]

CONCLUSION

The number of patients studied was 137; of 274 tympanograms,14.5% showed type B diagnostic of OME. One third of the 77.7% normal looking TMs showed abnormal tympanogram, mostly type B. One third of patients with snoring showed type B tympanogram. Tympanometry is an easy useful test in diagnosis of diseases of the middle ear. Diseases diagnosed by tympanometry could exist without aural symptoms. The look of the tympanic membrane alone does not always rule out healthy middle ear status. Non aural symptoms: nasal obstruction and snoring could correlate with an abnormal tympanogram and hence middle ear disease. Tympanometry is recommended for screening in school health.

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Case report

Congenital venous malformation mimics actinomycetoma foot.

Alaa Tajeldeen Habeeb[1], Andreas Neumayer[2], Ahmed Hassan Fahal[1].

[1]*Mycetoma Research Center, University of Khartoum,Khartoum,Sudan*

[2]*Swiss Tropical and Public Health Institute, Switzerland*

***Correspondence to** ahfahal@mycetoma.edu.sd*

Case Report

The patient is a 24-year-old female, a housewife from West Kurdufan State, Sudan, who presented to the Mycetoma Research Center (MRC) with a history of painful right foot. Her condition started with a small painless swelling at the medial side of right foot accompanied by localised hyperhidrosis 16 years prior to presentation. There was no history of previous local trauma. In 2019, the swelling gradually increased in size and pain started at the medial side of her right foot aggravated by rest, especially at night, preventing her from sleep. She used pain killers, cold water, Henna (traditional paint), needle therapy and electric massage to relieve the pain.

In May 2019, fine-needle aspiration for cytology was performed, and was reported showing fragments of grains consistent with Actinomadura. she was started on amoxicillin/clavulanic and trimethoprim-sulfamethoxazole twice daily. In March 2020, she got pregnant, and stopped medication. In October 2022, she presented to the MRC with persisting pain and localised hyperhidrosis.

On general examination, the patient looked well, orientated calm with an antalgic gait. Examination of all other systems was normal. Local examination of the right foot showed intact skin with bluish discolouration. There were diffuse inhomogeneous soft tissue swellings extending from the medial part of the sole of the right middle foot to the inner ankle. On palpation, the patient complained of localised pain. There were several firm, smaller nodules and large compressible nodules. The refilling of these nodules after reliving pressure was noted, suggesting underlying blood vessels. There was localised hyperhidrosis and nodules with bluish disclouration overlying the soft tissue swelling. The swelling extended up to the ankle and lower leg with engorged vessels and multifocal nodules. The skin was warm and peripheral pulsations were intact (Figure 1).

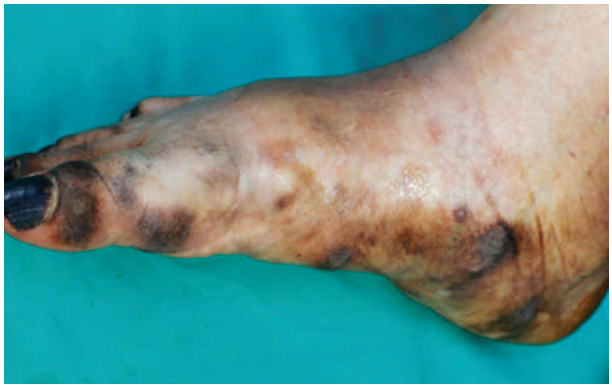

Figure 1. Showing the medial aspect of the right foot (after removal of the Henna) with diffuse inhomogeneous soft tissue swelling, localised hyperhidrosis and multifocal nodular surface with bluish-dark discolouration

The general laboratory investigations were within normal limits. Radiographs of the right foot and leg showed extensive tubular calcification anterior to the distal part of the tibia, while the bones of the right foot and lower leg were normal (Figures 2A, 2B & 2C).

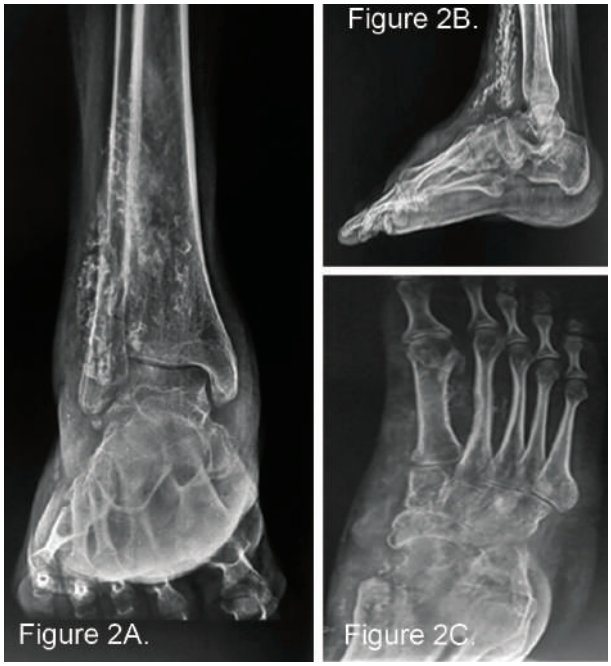

Figure 2A, 2B & 2C. X-rays of the right foot showing soft tissue masses with extensive tubular calcification anterior to the distal part of the tibia.

Lesional ultrasound examination revealed no evidence of mycetoma but multiple dilated, compressible vessels with a venous flow profile on the doppler ultrasound examination (Figure 3).

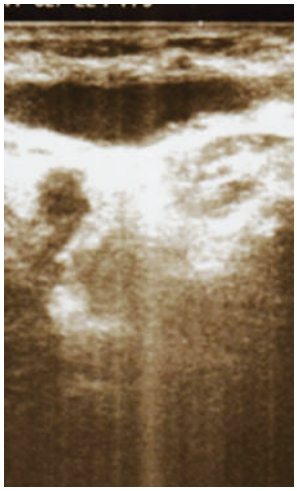

Figure 3. Showing lesional ultrasound examination with no evidence of mycetoma but multiple dilated, compressible vessels with a venous flow profile on doppler ultrasound examination.

Foot Magnetic Resonance Imaging (MRI) showed a 10x3x4.6 cm subcutaneous lesion at the distal 3rd of the leg encroaching over the medial and plantar aspects of the right foot. The lesion was heterogeneous, remarkably high on T2 and FLAIR images and intermediate on T1WIs demonstrating multiple foci signal voids representing calcific foci. Serpiginous tubular structures are along the medial aspect of the lesion. No pockets of fluid. No contained grains or foreign bodies (Figure 4).

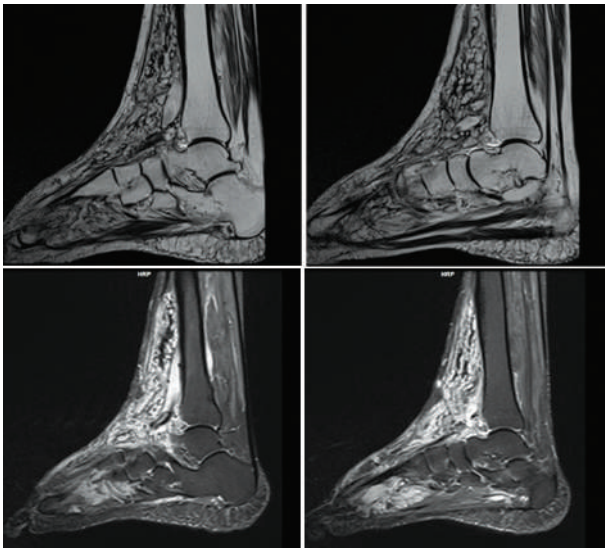

Figure 4. Magnetic Resonance Imaging (MRI) showing evidence of vascular malformation and no features of mycetoma.

DISCUSSION

Mycetoma is one of the neglected tropical diseases. It is caused by certain bacteria (actinomycetoma) or fungi (eumycetoma). The typical mycetoma clinical presentation is a painless subcutaneous swelling that appears on the foot, but no other body part is exempted. It is believed that mycetoma is a deep subcutaneous implanted infection following minor trauma and invasion of the causative microorganisms into the deep tissues and bones.[1]

A painless subcutaneous mass, multiple sinuses formation, and seropurulent and purulent discharge containing grains are pathognomonic of mycetoma[1]. The disease diagnosis depends on identifying causative microorganisms and the extent of the disease along the different tissue planes. This needs various diagnostic tools and techniques, including imaging, cytological, histopathological, serological, culture techniques, and molecular diagnostics.[2]

Venous malformation (VM) is the most common slow-flow congenital vascular malformation. It is a

cluster of twisted, ecstatic, and interconnected veins in soft tissue caused by congenital anomalies in the development of the venous network and occurs anywhere in the body.[3] VMs are frequently seen at the extremities and frequently have deep segmental extensions that are larger than their external appearance. These patients almost invariably have muscle involvement, and involvement of the joint and bone is not rare.[4] VMs can induce severe chronic pain and result in minor disfigurement and discolouration, depending on the lesion size. Treatments for VMs include surgical excision, sclerotherapy, and combined sclerotherapy and surgery.[5] Compression garments might reduce intravascular coagulation, improve symptoms and appearance, reduce oedema, and protect against minor trauma.[6] The first-line active intervention for VMs is generally sclerotherapy. It is typically a great method of symptom control for more extensive lesions and can decrease minor lesions extremely well. It hopes to reduce the mass effect and relieve venous congestion and thrombosis by scarring and closing the venous channels.[7]

In the reported patient, the misdiagnosis was due to the misinterpretation of the vascular calcifications as Actinomadura grains fragments. The patient was started on medical treatment for actinomycetoma for quite a time, which has serious medical and economic impediments. As the patient did not improve on actinomycetoma medical treatment, she was re-investigated, the diagnosis of mycetoma was revised, and venous malformation was established based on the MRI findings, the X-ray phleboliths and the dilated, compressible vessels with a venous flow profile on doppler ultrasound examination. Another cause for the misdiagnosis is the use of henna by the patient locally at the lesion site, where the physical examination was confusing. Sudanese women usually use henna as adornment; in this patient, it was used from the perspective of shame to hide the disease.

Learning points:

- Mycetoma and venous malformations share similarities with disease chronicity, subcutaneous swellings and local hyperhidrosis.
- A combination of diagnostic tests is needed to confirm the diagnosis of mycetoma not only smears cytological examination.
- Failure to respond to medical treatment in mycetoma demands revision of the diagnosis.
- Ultrasonography is an excellent diagnostic tool to differentiate mycetoma from other pathologies.

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