Review Article

A Review of Mycetoma and the Importance of Research for Effective Preventive Strategies

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Abstract

Mycetoma is a tropical disease caused by the subcutaneous infection of an open wound with Actinobacteria (Actinomyctoma) or fungi (Eumycetoma). When allowed to progress without intervention, it can damage tissues deep tissue and cause severe disability in the impoverished populations that it affects. It has remained severely neglected since the 17th century but has recently been added to The World Health Organizations List of Neglected Tropical Diseases. This has positive implications for gaining additional resources for public health. There are, however, still uncertainties concerning its global incidence and prevalence, its mode of transmission, and current treatments are inadequate. Effective implementation of treatment and preventive strategies at the community level require additional research into mechanisms of transmission, rapid diagnostic tools, and establishment of accurate and thorough epidemiological data. This paper will aim to review what is already known about mycetoma, questions that still have to be answered, and research considerations.

Keywords: mycetoma, neglected tropical disease

Introduction

Mycetoma is a tropical disease caused by subcutaneous infection of certain bacteria or fungi, that elicit a progressive and chronic inflammatory process at the site of infection which can spread to deeper tissues [1,2]. If allowed to continue without treatment, amputation of the affected limb is performed, and even then, there is still potential for the causative agent to continue to spread especially if it is a fungus. Left neglected, this disease has extremely negative consequences that affect all aspects of health as well as productivity of individuals and communities. This also makes it more difficult for these communities to better themselves economically.

Englebert Kaempfer first described mycetoma in western literature in 1694 [3], and the first reported case was in the Southern Indian town of Madura and hence was called “Madura Foot” [4]. It was not until 1860 that Vandyke Carter established the fungal etiology of the disease, naming the disease “Mycetoma” for the first time. Since these pioneering discoveries, there has been a hospital and research center opened dedicated to mycetoma in Sudan. Despite their establishment, this disease has not received the attention that it should have since its documentation in the literature, but it recently became the 18th disease on the World Health organization’s list of neglected tropical
diseases [4]. This was as a result of the development of a systematic process for evaluating diseases for their potential addition to this list in April 2016 [4]. According to these guidelines, diseases that disproportionately affect impoverished populations, occur primarily in tropical and subtropical regions, can be adequately controlled using public health strategies of the Department for Control of Neglected Tropical Diseases, and have not been allocated resources relative to its impact on morbidity and mortality, are candidates for inclusion [5].

**Etiology and Transmission**

The phylum of bacteria implicated in mycetoma is Actinobacteria. Mycetoma caused by bacteria is called Actinomycetoma (AM), represents about 60% of the cases of mycetoma, and it is most often found in Middle and South America [6]. Actinomycetes are gram-positive bacteria often found in soil, and 18 species have been identified, the most common belonging the genera of *Norcardia, Actinomadura* and *Streptomyces* [2]. When a fungus is the causative agent it is referred to as eumycetoma (EM), represents 40% of cases, and is more commonly seen in Africa [6]. Seven types of fungi have been implicated, the most common being *Maduralla mycetomatis* and *P. boydii*. EM progresses more slowly than AM, and it is often more debilitating. It is more of a concern medically than AM because it is difficult to treat, and the treatment is inadequate. Though AM is more easily treatable, it is more aggressive, and affects deeper tissues at a much faster rate [6].

There are various theories surrounding possible modes of transmission of these causative agents, but there has not been one fully agreed upon in the literature. The most historically and accepted mode of transmission are thorn pricks from Acacia trees [2], which easily penetrate skin, and if its contaminated with the bacteria or fungi, transmission of the agent can occur. As well as anecdotal evidence, there have been thorn pieces found at the site of infection [7]. Community interventions have identified practices that may contribute to transmission via thorns, such as the use of thorny plants as domestic fencing [8] and use of thorns to extract guinea worms. Minor injuries that cause a break in the skin such as insect and snakebites have also believed to contribute to transmission. Whether there are any intermediate vectors involved as well is still being investigated, and there are still some questions regarding the natural habitat of the organisms involved. There have been both bacterial and fungal causative agents isolated from soil samples [7], and fungal agents isolated from dung [6]. It is unclear whether animals excrete the fungus, or the agents inhabit dung after excretion to facilitate their growth, but currently soil is assumed to be the primary reservoir. It is also unclear whether transmission will always cause mycetoma, or if there are factors that predispose the host to its development. These include nucleotide polymorphisms in the promoter region of chemokine ligand 5 (CCL5) and interleukin-10 [6], as well as insertion mutations in the chitotriosidase gene [8]. Both of these possible genetic predispositions are found in inhabitants of Sudan. What is certain is that there has to be injury, and the causative agent has to reach the subcutaneous tissue. There has not been any documented human-to-human transmission to date [9].

**Clinical Presentation and Pathology**

AM and EM are both identifiable by the clinical trial of tumefaction, multiple sinuses draining pus, and blood, and granules with of the causative agent present, which also drain from the sinuses [9,10]. Initially, it presents as a painless and subcutaneous swelling at the site of infection, and gradually develops from a localized nodule into an extensive subcutaneous mass with sinuses tracts that heal and develop as progression ensues [11]. Other than the clinical trial, there are rarely other signs and symptoms one may expect such as fever or malaise.

If left untreated, the infection can spread to deeper tissues such as the muscles and bone lead to irreversible destruction and disability, necessitating amputation. This is often the stage that people affected with mycetoma present with, because of a lack of health facilities in endemic areas. The foot is affected 70-80% of the time, and this is
expected because of the implicated reservoirs, but anywhere on the body can be affected. More commonly affected regions after the foot include the legs, arms, knee, neck and head, thigh and perineum [11]. In rare cases, the infection may spread to the lymph nodes, the vulva or scrotum, facial structures [12], or in the case of Norcardia and Streptomyces, become blood borne. It is not unusual for a secondary bacterial infection to complicate clinical presentation.

**Differential Diagnosis**

There are three levels of differential diagnosis one must undertake in the case of suspected mycetoma. The first level would require differentiation of mycetoma from other similar diseases called implantation mycoses, which have similar clinical presentations with regards to subcutaneous swelling [13], as well as bacterial osteomyelitis, soft tissue tumours, and granulomas [7]. It is also necessary to differentiate AM from EM, as well as identify the specific causative agent for treatment and epidemiological surveillance purposes [7]. There are a range of techniques that are used for differential diagnosis, including imaging, histological, cytological and microbiological and molecular methods, and it is often necessary to perform at least one of each type of test to obtain a definitive diagnosis [7]. Magnetic resonance imaging (MRI) allows initial recognition of mycetoma if it has invaded the bone, as there is a “dot-in-circle” sign that is specific to mycetoma [11]. This technique also allows practitioners to determine the degree of damage to the bone to decide whether there is a need for surgical intervention. Another feature unique to mycetoma used for differential diagnosis is that fact that when the swelling is investigated using an ultrasound, there are hyperreflective echoes that are not accompanied by acoustic enhancement. These echoes are classified as either fine or sharp, corresponding to actinomycetoma and eumycetoma respectively [7].

Initial differentiation between AM and EM is also made possible by examination of the discharged grains, as these are black, pale or green in fungal infections, and red, yellow pink, or white in AM [7,11]. These granules also differ in shape and size, and this difference can assist with narrowing the list of the specific causative agent. Differentiation of AM from EM using a MRI depends on the characteristic of bone lesions. In EM, there will be few, large number of lesions with distinct margins, whereas in AM, lesions will be more numerous, small, with less distinct margins [11].

At the third level of diagnosis, fine need aspiration cytology or a deep-seated biopsy is often carried out to obtain a sample of granules containing the causative agent. The samples are then washed in saline, crushed, and plated. Due to the facultative anaerobic characteristic of Actinobacteria, they may not grow in culture, and should not be ruled out as a causative agent based on a negative culture. Specialized stains such as gram, periodic acid-Schiff (PAS) and Gomori methenamine silver (GMS) stains [7], can also assist with observing micromorphological properties.

**Treatment**

There are various antibiotics that are given depending on the causative agent. Patients are usually treated in two phases. There is an initial intensive phase in which a combination of two antibiotics - streptomycin, trimethoprim–sulfamethoxazole, gentamicin, rifampicin, or dapsone - is given intravenously or orally every day for 5-week cycle. The cycle may or may not be repeated depending on the condition of the patient. After this phase, the patients are released and required to continue taking antibiotics long term. When streptomycin, trimethoprim–sulfamethoxazole, and rifampicin, are used in combination, the change for reoccurrence is decreased significantly [11].

The treatment for fungal infections is highly unsatisfactory and expensive. Standard treatment involves surgical removal or reduction of the lesions, and then long-term used of anti-fungals [7]. While the most commonly
used antifungal is itraconazole, there are more suitable alternatives depending on the causative agent. For example, voriconazole is best used when the causative agent is \textit{P. bodydii}, while posaconazole is preferred for treatment of \textit{M. mycetomatis} [11]. Quite recently, there was a response to a journal article that spoke to the usefulness of nonsteroidal inflammatory drugs when treating eumycetoma, as it counteracts the inflammatory processes that are thought to contribute to the disease [13]. The reason that the treatment is unsatisfactory is that these medications can become toxic after being used for an extended period of time and there have been reports of acute liver failure, and hearing loss. Even with long term treatment and surgery, there is a high chance of reoccurrence.

\textbf{Distribution and Vulnerable Populations}

Mycetoma is endemic in twenty-three countries that lie within what has been termed the mycetoma belt, which lies between 30 degrees north and 10 degrees south of the equator [9]. Countries affected include Venezuela, Chad, Ethiopia, Sudan, India, Senegal, Somalia, Mexico, Mauritania, Yemen, Congo, Argentina, Nigeria, Niger, Togo, and Pakistan. The climate in the mycetoma belt is tropical and subtropical, and tends to be hot and dry with short, heavy rainy seasons. The estimated prevalence of the disease is from a meta-analysis in which 49 full papers reporting cases from 1960 were reviewed, and the cases for each country were totaled and divided by the current population to estimate the prevalence [10]. Mauritania was found to have the highest prevalence with 3.49 per 100,000, and Sudan, which is considered the epicenter of disease, had a prevalence 1.81 per 100,000. They also reported on the ages groups that are most affected, and the highest number of cases were reported in 21-30-year olds. The author’s effort gives some indication of which countries and age groups are most affected, but an obvious shortfalt is that it is based on cases reported in the literature, and not all reported cases would have necessarily been published.

Vulnerable populations are of low socioeconomic status and have little to no health education. It particularly affects those that walk or work with barefoot [1]. Sheppards and farmers are at even higher risk because they work barefoot with animals whose dung may harbor the causative agents. These are often roles for men, which may be why the male to female ratio for mycetoma is about 5:1 [10]. Inadequate housing and living close to livestock also increases vulnerability. A community intervention in Sudan documented poor construction of living quarters, which had with mud walls and dirt floors. This allows for bacteria and fungi to flourish in dwellings area, and there is also constant exposure to animal dung [8]. Exacerbating this is poor hygienic practices, inadequate nutrition, and individuals that may be immuno-compromised due to co-infections such as HIV.

\textbf{Discussion}

\textbf{Research at the Primary and Secondary Levels of Prevention}

Given the suspected reservoirs and transmission of infection, community-based interventions are crucial. Those at the Mycetoma Research Center have already realized this, and they educate communities about mycetoma, as well as plan community-based interventions. The importance of community interventions has already been demonstrated by the success of such ventures [8]. Though mycetoma is hard to treat in some cases, primary prevention seems to be achievable in a reasonable time frame. This level of prevention is highly reliant on research regarding the knowledge, attitudes and practices in endemic regions afflicted by mycetoma. There is also a need to confirm the mode of transmission and identify the primary reservoirs of infection to help prevent transmission. This will allow for implementation of effective improvement of community infrastructure to decrease exposure to potential agents. The One Health One Medicine paradigm can also be applied at this level of prevention, given that causative agents have been isolated from domestic animal dung, and persons in these communities tend to live in close proximity to these animals. Veterinary research approaches discerning whether fungi are a part of normal flora and is excreted, and whether the agents are essential for the wellbeing of the animal, would be useful. It would also be wise
to investigate whether treating animals with specific antifungals could decrease the spread of agents to humans. Supporting this idea is that fact that animals are known reservoirs for other subcutaneous infections such as leishmaniasis, and Lyme disease [2]. This, of course, would coincide with improved hygiene measures and adequate separation of dwelling areas from livestock.

It is evident from discussion of the methods of differential diagnosis that this process is tedious and hinders rapid case identification and collection of accurate epidemiological data. At the secondary level, there is a need for developing fast and cheap diagnostic tools for early case detection. Molecular techniques such as PCR are currently showing the most promise for achieving this goal. This is important not only for epidemiological data, for but improving prognoses and evaluating therapeutic outcomes. While imaging techniques are non-invasive and rapid and can be used in the low-income settings in which mycetoma wreaks havoc, tools for efficient identification of the causative agent are too costly for affected regions [7].

Research at the tertiary level of prevention

Finally, at the tertiary level, there is a need for establishing more healthcare facilities in endemic areas, and the development of safer and more effective drugs. As previously stated, there are questions concerning genetic predispositions to the development of mycetoma, and this may be helpful in drug research, such as the polymorphisms in the promoter regions of CCL5 [6]. This gene encodes for a chemokine protein present of the surface of platelets that is responsible for leukocyte recruitment [14], as well as the activation of natural killer cells. The CCL5 protein also mediates monocyte adhesion by undergoing a protein-protein interaction with neutrophils, implicating a role in chronic inflammation [14]. These inflammatory processes are thought to contribute significantly to the development of mycetoma. Given the high chance of reoccurrence of mycetoma despite antibacterial or antifungal treatment, drugs that can temper this interaction, or the expression of CCL5, may lessen the chances of reoccurrence. Before this option is pursued therapeutically, however, the fact that this chemokine regulates several other immune responses, and inhibition of its function may negatively exacerbate other conditions, should be considered [14]. Though the immune system of animals and humans are not directly comparable, in vivo studies of the effects of antagonizing CCL5 could be studied in mice models of mycetoma [15]. As expected for a neglected disease, there is not extensive research into the best animal model for mycetoma, compared to diseases such as diabetes, cardiovascular conditions, and cancer. Larger animal models may prove the most useful for studying the pathogenesis of mycetoma, as well as CCL5 antagonism, as they have already been shown to be efficient models for investigating infectious disease pathogenesis and immunity, and outcomes in animal models are more likely to provide clinically significant results [16]. Similar studies can also be carried out by addressing the mutation in the chitotriosidase gene. This gene produces host immune system enzyme chitinases that are responsible for clearance of fungal infections by degrading fungal chitin, and the mutation described previously results in decreased activity [17]. Drugs that can restore or compensate for this loss of function may prove beneficial at the tertiary level of prevention.

Conclusion

Classification of mycetoma as a neglected disease will increase global attention, as well as advocacy, funding, research and intervention efforts. Additionally, because it has been neglected for so long there are not appropriate surveillance and reporting systems in place, but now that WHO has officially listed it as a neglected tropical disease, epidemiologists may be able to obtain more accurate data to assist in targeting these efforts efficiently. At all of the levels of prevention, there is a need to provide incentives for research, especially because strategies to combat this disease are still in the nascent stages and requires a great deal of effort from researchers to secure funding for developing innovative research and intervention strategies [18].
References