Mycetoma: an old and still neglected tropical disease

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Received 22 December 2014; accepted 8 January 2015

Keyword: Mycetoma, Neglected tropical disease

Mycetoma is a chronic infection caused by either fungi or filamentous bacteria that are known as eumycetoma or actinomyce-
toma, respectively. It is characterised by massive deformity and severe disability. Although described from antiquity in Indian writings, it was first described in the western literature by the naturalist, historian and physician, Engelbert Kaempfer, who, while his ship had moored off the coast of Southern India, travelled through the local area describing a variety of unusual illnesses, one of which was mycetoma. While seldom common, it is a continuing source of consultation by patients in many tropical regions of the world from Mexico to Thailand.\textsuperscript{1} But the largest numbers of cases have been reported from Mexico, Sudan and India. Despite the increasing interest of a small group of active investigators and clinicians, mycetoma has remained a disease that is generally inaccurately diagnosed and poorly managed except in a few centres where special interest has led medical teams to make a closer study of this infection. In 2013, it was listed by WHO as a neglected disease.\textsuperscript{2}

There remain a large number of mysteries surrounding this condition. The causative organisms can be found in the environment in soil or plant material such as Acacia thorns. Penetrating injury was always assumed to be the prelude to infection. However, it has recently become clear that distribution is by no means uniform, and even in endemic areas there are hyperendemic communities where the prevalence rate can exceed 10% of the population.\textsuperscript{3} Equally there may be a small shift in the pattern of organisms within the same country. For instance, in Mexico in the state of Monterrey the cause of infection is overwhelmingly the actinomycete, \textit{Nocardia}, whereas in parts of the Costa Chica, Guerrero state, fungi dominate as the causative organisms.\textsuperscript{4} Attention has therefore focused on possible co-factors involved in the pathogenesis disease. These include the presence of cattle and cattle dung in areas of high endemicity and the finding that there is a population prevalence of mutations found by single nucleotide polymorphisms in patients with mycetoma from endemic areas in Sudan, in genes encoding CC chemokine ligand S and interleukin-10 promoter regions.\textsuperscript{5} These suggest underlying susceptibility involving macrophage recruitment and function may play a role in determining the outcome of an initial injury and implantation of potentially causal organisms.

Once the organisms invade, they assume a new growth pattern characteristic of mycetoma, forming micro-colonies called grains in subcutaneous tissues. The morphology of the organisms in these structures alters dramatically with both cell wall thickening and replication as well as unfolding of the carbohydrate cyto-skeleton that allows binding of adjacent cells.\textsuperscript{6} In the case of eumycetomas, confirmation of the clinical diagnosis is frequently hampered by the slow growth of the organisms in culture and, often, the lack of identifying features such as conidia (spores). But the advent of molecular diagnostic methods has begun to change the situation with a reclassification of the organisms and recognition that many more fungi can cause this disease. Whereas previously there were only two \textit{Madurella} species implicated in mycetoma, \textit{M. mycetomatis} and \textit{M. grisea}, three more \textit{Madurella} species have been added, \textit{M. pseudomyctomatis}, \textit{M. fahalii} and \textit{M. tropicana},\textsuperscript{7} and speciation appears to have implications for both epidemiology and drug sensitivity. Imaging investigations have also advanced with magnetic resonance imaging playing an increasingly important role in disease assessment,\textsuperscript{8} but cheaper alternatives such as ultrasound are also being used with effect to define the extent of the infection.

Treatment remains a major cause for concern. In \textit{Nocardia} actinomyctomas there is increasing interest in using agents other than cotrimoxazole and rifampicin, a former staple approach to treatment, with newer antibacterials such as amikacin, moxifloxacin and imipenem being found to have greater efficacy.\textsuperscript{9} For the fungal mycetomas, though, the antifungal choice is limited with older drugs such as itraconazole being widely used. Another azole antifungal, ketoconazole, has some efficacy in mycetoma but its recent removal from the market in Europe, where it was used for superficial mycoses, may have an adverse effect of drug availability for deep infections in other parts of the world. There is limited evidence that newer azoles such as voriconazole may be more active, largely through the fact that they
lack the melanin binding properties of other drugs; as a conse-
sequence voriconazole is more bioavailable per unit dose.10
However, cost remains a potent bar to the use of the newer anti-
fungals in resource-poor countries. In addition, uncertainty sur-
rounding the continued development of other antifungals that
may appear promising in vitro, such as ravuconazole, does not
provide a healthy prospect for the availability of new therapies
in the near future. Finally, there are currently neither preventive
control measurements nor any vaccine for mycetoma due to
the current state of knowledge of its route/source of infection,
susceptibility and resistance.

What are the needs for mycetoma? The list is long,11 although
international recognition, long in coming, may add an incentive to
further work. Our understanding of the global distribution of
mycetoma is patchy although recent efforts to improve this situ-
ation may well bear fruit.1 However, top clinical priorities are the
introduction of systems that allow early recognition of new cases
at rural health-post level; early institution of treatment may well
provide a more successful answer to management.12 This needs
to be coupled with increased availability of effective medications
subject to cost. The burden of this disease falls on a relatively
small number of patients in the poorest of countries, which
makes the delivery of therapies for mycetoma a potentially
achievable target for focused donor programmes. Engagement
with the pharmaceutical industry and international bodies such
as WHO may create the necessary structure to implement this
type of action. This needs to be coupled with two other initiatives.
Understanding the pathogenesis of mycetoma could potentially
provide the basis for new treatments or treatment combinations.
Assessing the burden of mycetoma as a global disease is also a
key element of this plan. At present, the Global Burden of
Disease study13 does not include this infection as a separate
entity and yet data arising from such work would provide further
impetus to control and possibly eliminate this troublesome
infection.

Authors’ contributions: RJH and AF contributed to the writing of this
paper. Both authors read and approved the final manuscript. RJH is the
guarantor of the paper.

Funding: None.

Competing interests: None declared.

Ethical approval: Not required.

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