Clinical Review

Clinical Review identifies issues in the medical literature of interest to clinicians in Africa. Essential references are given at the end of each section

Dermatology

Mycetomas: A neglected tropical disease

Mycetomas were designated a neglected tropical disease (NTD) by the World Health Assembly in 2016. Mycetomas are chronic, disfiguring, subcutaneous granulomatous infections that can lead to significant disability. They are characteristically difficult to treat. They are endemic in many tropical and subtropical regions and generally afflict those of low socioeconomic status. Early recognition and treatment of mycetomas will improve prognosis. However, given their chronic, slow progression, patients commonly present late when the skin lesions either begin to cause pain or functional impairment.

Epidemiology & aetiology: The true global incidence and prevalence of mycetomas is not known. Most of the reported data comes from hospital cases. Mycetomas are mainly endemic in the 'mycetoma belt', which extends from 30°N to 15°S around the Tropic of Cancer and includes the following countries, which have the highest burden of cases: the Indian subcontinent, Yemen, Sudan, Somalia, Senegal, Mexico, Venezuela, Colombia and Argentina. India, Sudan and Mexico have produced the greatest data on disease prevalence and therapy. The Mycetoma Research Centre established in 1991 at Soba University Hospital, Khartoum, Sudan, is a WHO collaborating centre on mycetoma (www.mycetoma.edu.sd). It has produced an impressive body of literature on mycetomas and has extensive experience of managing hundreds of severe and advanced cases.

There are two main types of mycetomas: Eumycetomas are caused by eumycetes fungi, most commonly *Madurella mycetomatis*; Actinomycetomas are caused actinomycetes bacteria, mainly *Nocardia brasiliensis* and *Streptomyces somaliensis*. Climatic and ecological factors determine the geographic distribution of causative species. Eumycetomas generally predominate in sub-Saharan Africa and Southern Asia: *Madurella mycetomatis* is the most prevalent eumycete, responsible for 70% of cases in Sudan.[1] Actinomycetomas predominate in the Americas: *Nocardia brasiliensis* is the commonest actinomycete, responsible for more than 80% of cases in Mexico.[2]

Mycetomas are believed to be acquired via traumatic inoculation of the pathogen into the skin from a contaminated thorn, stick or other plant matter. The disease is not contagious between humans or from animals to humans. More than 80% of cases involve the limbs, particularly the feet in those who walk barefoot. Indeed the 'Madura foot' was the first description of mycetomas, which were first recognised in the Madura region of India in the mid 1800s. Infections may occur on other parts of the body too, such as the trunk and back as a consequence of local agricultural practices where loads of wood or hay are carried on backs. Mycetomas may also affect the head, neck and perineum regions. All age groups and both sexes may be affected. However, it most frequently affects men working in agriculture.[2,3]

Clinical presentation: The initial lesion of a mycetoma is usually a painless, subcutaneous nodule, which goes on to suppurate and drains through sinus tracts. As lesions progress, they begin to look more tumourous with several draining sinuses. The sinuses may discharge visible 'grains', which are aggregates of fungal hyphae or bacterial filaments. Grains are of various sizes and colours, which may help to identify the causative species before an attempt is made at bacteriological and fungal culture (Table 1). Without effective treatment infection can slowly spread to deeper structures such as soft tissue and bone, causing osteomyelitis. Lymphatic spread to regional lymph nodes is rare. Contiguous spread of severe infection of the trunk can affect viscerae such as the lungs and peritoneum. There have been cases too of infection of the vertebral bodies leading to spinal cord compression. Actinomycetomas are generally more aggressive than eumycetomas in speed of progression and involvement of local structures. Mycetomas are usually painless unless there is secondary bacterial infection. The bacterial infection is often treated by a local doctor or health care practitioner with standard courses of antibiotics. Initially there may appear to be improvement of the skin lesions but the underlying diagnosis of mycetoma is often missed and therefore the mycetoma will continue to slowly progress. Skin lesions may also be misdiagnosed as abscesses and therefore there may be attempts at treating them by surgical excision. However, without effective antimicrobial therapy, mycetoma lesions will recur.[2,3]

Diagnosis and treatment: The diagnosis is often clinically apparent in advanced mycetoma infection where there are multiple sinuses. An important differential diagnosis is scrofuloderma where skin lesions develop secondary to an underlying tuberculous lymphadenitis. However, the history of disease progression should be able to differentiate between these two conditions, as mycetomas (particularly eumycetomas) may take years to evolve and progress to the stage when discharging sinuses become clinically evident. Also in the case of mycetomas, patients may describe seeing grains discharging from sinuses. The differential diagnosis also includes other causes of soft tissue masses, skin cancers such as malignant melanoma and squamous cell carcinomas, foreign body granuloma, and other deep cutaneous fungal infections.

If the diagnosis of a mycetoma is suspected an attempt should be made to try to manually extract a grain by gentle compression of the lesion in order to 'milk' the grain towards the sinus opening. Grains can also be obtained by fine needle aspiration and skin biopsy.

Species	Grain colour	Region
EUMYCETOMA		
Madurella mycetomatis	Black	Africa, S. Asia
Madurella grisea	Black	Americas
Fusarium sp.	White	Worldwide
Acremonium sp.	White	Worldwide
ACTINOMYCETOMA		
Nocardia brasiliensis	White	Americas
Nocardia asteroides	White	Worldwide
Streptomyces somaliensis	White	Africa, S. Asia
Actinomadura madurae	White	Worldwide
Actinomadura pelletieri	Red	Africa, S. Asia

Identifying characteristic grains on direct microscopy of the seropurulent discharge confirms the clinical diagnosis in which case a skin biopsy is not required. If a skin biopsy is performed, histopathology reveals a granulomatous inflammatory reaction with abscesses containing grains. Culture of grains enables species identification but can take many weeks and sometimes fails due to contamination or poor morphological differentiation. Species-specific PCR analysis is available for certain species at a few tertiary centres. However, in many endemic regions adequate laboratory facilities are often not available. Nonetheless, some clinicians in endemic regions develop expertise in identifying the causative species as usually there are only one or two species in their region that are responsible for mycetoma infection: they suspect a species based on the colour, size and consistency of a grain that is known to be endemic in their region. Performing an Xray of the affected region on a limb is important as it will detect any bony involvement, which can manifest with a loss of the normal trabecular pattern, sclerosis or osteolytic lesions. Ultrasound examination can be useful in diagnosing lesions with no sinuses, and may even differentiate between the grains of eumycetomas and actinomycetomas, as well as assess their degree of spread. CT and MRI scanning, if available, will also establish the extent of underlying infection.[2,3]

Treatment is usually initiated when characteristic grains have been identified and before the results of any other microbiological investigations, if performed, become available. Treatment consists of long course of antimicrobial therapy, which may be combined with surgery. Drug therapy is much more effective for actinomycetomas than eumycetomas. Long periods of drug therapy are usually required especially when there is bone or visceral involvement. Generally much longer courses of antifungal drug therapy are required for treating eumycetomas than antibiotic drug therapy for treating actinomycetomas. Cure is defined by a lack of clinical activity, the absence of grains, and negative cultures. With effective drug therapy, skin lesions should decrease in size with a reduction of purulent discharge and eventual healing of sinuses with scar formation.[4]

Surgery is sometimes necessary in addition to drug therapy, especially for the management of eumycetomas. This may involve simple wide excision of early well-defined lesions, debulking, or amputation, as in the case of bony involvement unresponsive to treatment. Surgical management has sometimes been the only option for patients when there has been no access to prolonged antifungal therapy or the high cost of antifungal drugs is prohibitive. Surgery as monotherapy has historically been associated with a recurrence rate of 25-50% at the Mycetoma Research Centre in Sudan.[5] Therefore drug therapy is recommended in addition to surgery in order to eradicate infection. Drug therapy should begin several months before surgery to try to reduce the size of the skin lesions, which may help to limit the extent of surgery required. Drug therapy also needs to continue for several months after surgery to achieve microbiological cure and to prevent any risk of relapse.[2,4,6]

There are no large randomised controlled trials evaluating the efficacy of antifungal therapy for eumycetomas. Several antifungals have been tried. Fluconzole, griseofulvin and terbinafine are ineffective. Both itraconazole and ketoconazole demonstrate efficacy. However, itraconazole (400mgs daily combined with surgical excisions) is currently the treatment of choice as prolonged itraconazole therapy is much better tolerated than prolonged ketoconazole therapy, since the latter is more likely to lead to adverse hepatotoxic effects.[6] There are reports of the high tolerability and efficacy of the newer broad-spectrum triazoles such as voriconazole and posaconazole. However, their high costs and/or lack of availability preclude their use in most endemic settings. Despite long courses of antifungal therapy together with extensive surgical resection, large and extensive eumycetomas are rarely completely cured. Furthermore, cases of apparent clinical cure of smaller eumycetoma lesions are often associated with clinical relapse several months or years later even when drug therapy had been continued for at least one year after apparent cure.

Actinomycetomas are much more likely to achieve cure with antibiotic drug therapy although cure rates still vary widely from 60-90%. Combined antibiotic drug therapy is recommended in order to prevent the risk of development of drug resistance associated with long treatment courses as well as to eradicate any residual infection. Various antibiotic regimes are used depending on the causative actinomycete. Treatment with sulfonamides and sulfonamide combinations such as trimethoprim–sulfamethoxazole (co-trimoxazole) are usually first line. Aminoglycosides, tetracyclines, rifampicin, ciprofloxacin and amoxicillin-clavulanate have also been successfully used.[4] Parenteral amikacin and oral co-trimoxazole combination therapy is especially advocated for cases at risk of bone or visceral involvement.[7] Antibiotic drug therapy is often given for 2-3 years with a mean treatment period of 18 months. In contrast to eumycetomas, actinomycetomas seldom require surgical management.

It is important to recognise that long courses of drug therapy required to treat mycetomas can be associated with the risk of non-compliance, which can increase the potential to develop drug resistance. Therefore treatment schedules and duration need to be carefully explained to patients to ensure that treatment interruption is avoided.

In conclusion, treating mycetomas is very challenging. In advanced cases of eumycetomas in resource limited regions of the world, clinicians often have to resort to amputation of the limb, which can have devastating socioeconomic consequences for the patient. Therefore early recognition and intervention is essential in ensuring the best treatment outcomes. Mycetomas' status now as an NTD will push forward an agenda to improve disease recognition and management. In March 2017, the WHO identified several strategic priorities for mycetoma management, which include epidemiology, case management, prevention, health system strengthening, and capacity building.

Mahreen Ameen
Consultant Dermatologist
Department of Dermatology
Royal Free London NHS Foundation Trust
United Kingdom
Email: m.ameen@nhs.net

References

1 Ahmed AO, Van Leeuwen W, Fahal A et al. Mycetoma caused by Madurella mycetomatis: a neglected infectious burden. Lancet Infect Dis 2004; 4: 566-74.
2 Welsh O, Vera-Cabrera L, Salinas-Carmona MC. Mycetoma. Dermatol Clin 2007; 25(2): 195-202.
3 Ahmed AO, van Leeuwen W, Fahal A et al. Management of mycetoma: major challenge in tropical mycoses with limited international recognition. Curr Opin Infect Dis 2007; 20(2), 146-51.
4 Ameen M, Arenas R. Emerging therapeutic regimes for the management of mycetomas. Expert Opin Pharmacother 2008; 9(12): 2077-85.
5 Zein HAM, Fahal AH, Mahgoub ES et al. The Predictors of Cure, Amputation & Follow-up dropout among Mycetoma Patients as seen at The Mycetoma Research Centre, University of Khartoum. Trans R Soc Trop Med Hyg 2012; 106(11): 639-44.
6 Fahal AH, Rahman I A, El-Hassan AM et al. The efficacy of itraconazole in the treatment of patients with eumycetoma due to Madurella mycetomatis. Trans R Soc Trop Med Hyg 2011; 105(3): 127-32.
7 Welsh O, Sauceda E, Gonzalez J, Ocampo J. Amikacin alone and in combination with trimethoprim-sulfamethoxazole in the treatment of actinomycotic mycetoma. J Am Acad Dermatol 1987; 17: 443-8.

Tuberculosis

Urgent response needed to end TB by 2030

WHO 2018 Global TB Report released on 18 September in New York revealed that fewer people fell ill and died from tuberculosis in 2017. During this period, 1.6 million deaths (including among 300,000 HIV-positive people) occurred. Since 2000, 44% reductions in TB deaths were registered among people with HIV compared with a 29% decrease among HIV-negative people.

Globally, an estimated 10 million people developed TB in 2017. The number of new cases was falling by 2% per year, although faster reductions have occurred in Europe (5% per year) and Africa (4% per year) between 2013 and 2017.

Some countries are moving faster than others – as evidenced in Southern Africa, with annual declines (in new cases) ranging from 4% to 8% in countries such as Lesotho, Eswatini, Namibia, South Africa, Zambia, and Zimbabwe.

Drug-resistant TB remains a global public health crisis: In 2017, 558,000 people were estimated to have developed disease resistant to at least rifampicin – the most effective first-line TB drug. The vast majority of these people had multidrug-resistant TB (MDR-TB), that is, combined resistance to rifampicin and isoniazid (another key first-line TB drug).

Underreporting and under-diagnosis of TB cases remains a major challenge. Of the 10 million people who fell ill with TB in 2017, only 6.4 million were officially recorded by national reporting systems, leaving 3.6 million people undiagnosed, or detected but not reported. Ten countries accounted for 80% of this gap, with India, Indonesia and Nigeria topping the list. Less than half of the estimated one million children with TB were reported in 2017. It further observed that countries were still not doing enough to end TB by 2030. WHO warned that, although global efforts had averted an estimated 54 million TB deaths since 2000, TB remained the world's deadliest infectious disease.[1]

Launching the 2018 TB report, Dr Tedros Adhanom Ghebreyesus, WHO Director-General, said, 'we have never seen such high-level political attention and understanding of what the world needed to do to end TB and drug-resistant TB. We must capitalise on this new momentum and act together to end this terrible disease.' The report called for an unprecedented mobilisation of national and international commitments.

Consequently, in 2018 the UN General Assembly held the first-ever high-level meeting on the fight against tuberculosis, under the theme 'United to end tuberculosis: an urgent global response to a global epidemic'.[2] The political declaration was the culmination of recent leadership commitments at global and regional level – including the 2017 Moscow Declaration to End TB[3] – to drive universal access, sufficient and sustainable financing, intensified research and innovation, and accountability across all sectors. The meeting aimed at accelerating efforts in ending TB and reaching all affected people with prevention and care. The leaders committed to ensure that 40 million people with TB received the care they needed by end 2022. They also agreed to provide 30 million people with preventive treatment to protect them from developing TB.

Dr Ghebreyesus described the occasion as a landmark in the long war on TB and that these were bold promises and to keep them, partnerships were vital. He committed WHO to work with every country, every partner and every community to get the job done.

Heads of state and government who attended the meeting agreed to mobilise US$13 billion a year by 2022 to implement TB prevention and care, and US$2 billion for research. They committed to take firm action against drug-resistant forms of the disease and build accountability mechanisms.

To urgently improve detection, diagnosis and treatment rates, WHO, the Stop TB Partnership and the Global Fund launched the new initiative in 2018, which set the target of providing quality care to 40 million people with TB from 2018 to 2022.

'The political declaration proposed for this meeting set a roadmap for accelerated action to end TB in line with the vision and targets for 2030. We have before us the opportunity for a clear wins – a chance to save the lives of millions, to preserve billions in resources,

to demonstrate the success of the Sustainable Development Goals, and to reaffirm the utility, efficacy and necessity of multilateralism and the UN System.'[4]

The political declaration is the culmination of recent leadership commitments at global and regional level – including the 2017 Moscow Declaration to End TB – to drive universal access, sufficient and sustainable financing, intensified research and innovation, and accountability across all sectors. Taking note of the Global Tuberculosis Report 2017 of WHO, the UN Assembly emphasised that current global actions and investments fall far short of those needed to end the global tuberculosis epidemic. Treatment coverage lagged behind at 64% and must increase to at least 90% by 2025 to meet the TB targets.

A half of the estimated 920,000 people with HIV-associated TB were reported in 2017. Of these, 84% were on antiretroviral therapy. Most of the gaps in detection and treatment were in the WHO African Region, where the burden of HIV-associated TB is highest.

In addition several months ago, WHO issued a Rapid Communication on key changes to treatment of drug-resistant TB based on the latest scientific evidence, which should result in better treatment outcomes and more lives saved. WHO predicted that at least 30 million people should be able to access TB preventive treatment between 2018 and 2022. Although preventive treatment for latent TB infection was expanding, most people who needed it were not yet accessing care. WHO strongly recommended preventive treatment for people living with HIV, and children under 5 living in households with TB.[5]

The timing of the UN High-Level Meeting was critical as ending the TB epidemic required action beyond the health sector. The commitments made by the Heads of State were essential to galvanise multi-sectoral action. Furthermore countries must ensure that their leaders will be held accountable for the actions they promised to take. Finally all stakeholders must be kept accountable and under check for keeping the pressure on until we achieve the end to TB by 2030. This will require dedicated efforts by all stakeholders to focus on the 30 high-burden countries, of which 50% are from sub-Saharan Africa.

Peter Eriki: MB:ChB (MU); M.Med. (MU); DTCD (Cardiff) MPH (Harvard)
Director Health Systems
African Centre for Global Health and Social Transformation (ACHEST)

References

1 WHO Global Tuberculosis Report 2018
2 See www.who.int/UNHLMonTB
3 Global Ministerial Conference on Ending TB Moscow, 16-17 November 2017
4 H.E. Ms Maria Fernanda Espinosa Garcés, President of the 73rd Session of the UN General Assembly.
5 New guidance was issued by WHO in 2018, to facilitate greater access to preventive services