Mycobacterium ulcerans: an unwelcome visitor

Mycobacterium ulcerans, the causative agent of Bairnsdale ulcer, made prime-time television in Victoria this July. Universally referred to in the media as the ‘flesh-eating bug’, M. ulcerans is creating considerable concern for local health authorities, residents and visitors to affected areas. A new cluster of at least 14 cases has been linked to the small coastal town of Point Lonsdale this winter.

Local and global epidemiology

The outbreak at Pt. Lonsdale highlights the continued westward march of M. ulcerans in Victoria. First described among residents in the Bairnsdale area in east Gippsland in the 1940s, there has been a step-wise expansion of its range. Locally acquired infections have been documented from around Westernport bay in the 1980s, Phillip Island and the Mornington Peninsula in the 1990s and in the last 5 years the towns of St. Leonards and Pt. Lonsdale on the Bellarine peninsula have experienced outbreaks (Figures 1 & 2).

In recognition of the increasing importance of M. ulcerans, the Victorian Department of Human Services made M. ulcerans infection notifiable from 1 January 2004.

Outside Victoria, M. ulcerans infection is endemic in far north Queensland between Mossman and the Daintree river, but is rare elsewhere in Australia. Overseas, the main endemic focus is in west and sub-saharan Africa where up to 10,000 cases of ‘Buruli ulcer’ – the African name for the disease – have been diagnosed in the last 20 years. The strange uneven distribution of M. ulcerans infection has yet to be explained, but remains a characteristic feature of M. ulcerans epidemiology.

Mode of transmission

M. ulcerans is acquired from the natural environment, typically swamps or slow flowing rivers, by people living nearby. The exact mode of transmission is unknown, but fascinating new data demonstrate that M. ulcerans is able to colonise the salivary glands of large carnivorous water bugs (Naucoridae). It is proposed that African children who swim in water inhabited by these insects may contract Buruli ulcer following insect bites. However, as M. ulcerans has also been found in biofilms adherent to aquatic plants in endemic areas, it is possible that other modes of transmission, including aerosol or direct inoculation, play a role. It is not yet clear whether Naucoridae or other insects act as a reservoir or vector in Australia.

Pathogenesis

The characteristic lesion of M. ulcerans infection – a slowly progressive deeply undermined ulcer – is explained by the production of a diffusible lipid toxin, mycolactone. Mycolactone is a toxic polyketide that reproduces many of the histological features of the disease when injected into guinea pig skin. Recent studies have shown that the polyketide synthase genes responsible for production of mycolactone reside on a large plasmid. The M. ulcerans whole genome sequencing project, initiated at the Pasteur Institute in Paris is now in the final annotation/completion phase at Monash University.

Diagnosis

Despite its recent fame, delayed diagnosis of M. ulcerans infection is common. Lesions typically progress slowly and are usually painless. Sufferers may take some weeks to seek assistance and doctors unfamiliar with the condition may lose valuable time by attempting to treat...
lesions with conventional antibiotics. Fortunately, once the possibility of M. ulcerans is considered, definitive diagnosis is relatively quick and straightforward.

The discovery of the insertion sequence IS2404 has led to the development of PCR diagnosis. The high copy number of the IS combined with the multi-bacillary nature of the disease, the specificity of IS2404 and the ease of obtaining ulcer swabs, make IS2404 PCR one of the best tests available for any infectious disease. We now have extensive experience with this PCR and have found it to have near perfect negative and positive predictive value, provided an adequate swab or tissue sample is obtained. The original method has been adapted to a real-time PCR format utilising a TaqMan MGB probe. In Victoria, almost all diagnoses are now made by PCR and our results correlate closely with culture and histology. The availability of this rapid accurate test has assisted the promotion of our main public health message – early diagnosis leads to simple effective therapy.

**Treatment**

M. ulcerans is sensitive to a range of antimicrobial drugs in vitro including rifampicin, macrolides, fluoroquinolones and aminoglycosides \(^{13, 14}\). However, not all of these are efficacious in the mouse footpad model of M. ulcerans infection \(^{15}\). When skin damage is extensive, surgery to debride necrotic tissue and apply grafts to obtain skin closure is required, but it is possible that early lesions or the uncommon acute oedematous form of M. ulcerans could be treated successfully with drugs alone.

A recent study in humans in Africa has shown that the combination of rifampicin and streptomycin is capable of sterilising early nodular lesions, and further studies are planned to better delineate the respective roles of surgery, drugs and other modes of therapy including the application of continuous local heat or hyperbaric oxygen.

**Immunity**

Even when treatment is not available, most sufferers are eventually able to arrest their own M. ulcerans infection, and are then relatively resistant to future attacks. However, extensive skin damage with consequent deformity may result during this period. There are also anecdotal reports of small lesions resolving spontaneously.

The basis of acquired immunity is unclear. Interestingly, patients with a past history of M. ulcerans infection typically have a strong TH-2 cytokine response when their lymphocytes are exposed in vitro to M. ulcerans. In contrast, household contacts of these patients who have not themselves developed clinical infection, exhibit a Th-1 immune response \(^{16}\), suggesting that natural resistance to clinical disease may be directed against small numbers of intracellular organisms that are somehow killed or held in check. In one fascinating case study, it has been shown that the development of ulcerative M. ulcerans disease is associated with a switch from the Th-1 to Th-2 phenotype \(^{17}\).
Research

There is an active research group working on M. ulcerans in Australia. We have members at Monash University Department of Microbiology, Austin Health, Austin Research Institute and the Victorian Infectious Diseases Reference Laboratory, and also have collaborations with the Pasteur Institute and other overseas groups. Current activities include annotation of the completed whole genome sequence, development of a diagnostic blood test for use in Africa, mode of transmission and basic vaccine research. Further information on M. ulcerans in Australia, including clinical photographs and diagnostic information for clinicians, is available on our webpage.

References