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1167 8.6.29 Buruli ulcer: Mycobacterium ulcerans infection arguments illustrate the difficulty in providing sound evidence for policy decisions when a decade-long wait to establish relapse rates is needed. Areas where further research is needed The epidemiology of leprosy still poses unanswered questions. Why are 64% of all patients with leprosy in India? Is this due to living conditions, genetic susceptibility, or particular environmental con- ditions in India? Early detection of cases is vital at both an individual and a popu- lation level. It is now recognized that substantial nerve damage oc- curs before diagnosis. A test for early infection might help detect individual cases before nerve damage is established and before the spread of infection. Leprosy-specific peptides for skin tests have been generated and are being evaluated. The medical management of reactions and nerve damage is cur- rently limited to steroids. These are not effective for about 30% of patients. Trials to determine the effectiveness of established and out-of-patent immunosuppressants, such as azathioprine and ciclosporin, are taking place. The WHO started the 1990s with the bold slogan of ‘Eliminating leprosy as a public health problem by 2000’. This initiative gal- vanized leprosy control programmes worldwide, but the unique biology of M. leprae and its interaction with the human host ren- dered this target unattainable. However, there is a strong perception that leprosy has been eliminated and this has hindered research and planning. The WHO policy for 2011–2015 focuses on sustaining leprosy work. Leprosy is a bacterial disease with challenging im- munological complications and will be a global and individual problem for many decades. It is unlikely to be eradicated until there is considerable improvement in general health, wealth, living con- ditions, and education. FURTHER READING Britton WJ, Lockwood DN (2004). Leprosy. Lancet, 363, 1209–19. Fine PE (2007). Leprosy: what is being ‘eliminated’? Bull

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Wayne M. Meyers ESSENTIALS Buruli ulcer is caused by Mycobacterium ulcerans, which secretes a cytotoxic and immunosuppressive toxin, mycolactone. The disease is characterized by necrosis of skin, subcutaneous tissue, and bone, and is re-emerging as a potentially disabling affliction of inhabitants of tropical wetlands. Major foci are in West and Central Africa, with an increasing focus in Australia, Mexico, South America, and Southeast Asia. It is not contagious; environmental sources include water, vege- tation, and insects, with humans probably becoming infected by traumatic introduction of the bacillus into the skin from the overlying M. ulcerans-contaminated surface in most instances. Clinical presen- tation may be as a cutaneous nodule, undermined ulcer, plaque, or widely disseminated oedematous lesion. Clinical diagnosis is often accurate by experienced clinicians, and smears for acid-fast bacilli, culture, polymerase chain reaction assays, and histopathology are confirmatory. Treatment was formerly by wide surgical excision and skin grafting, yet antibiotics (rifampicin with streptomycin given for 8 weeks) have now been found effective, including an all-oral regimen. Introduction Buruli ulcer is an indolent necrotizing infection of the skin, sub- cutaneous tissue, and bone caused by Mycobacterium ulcerans. In 1962 Clancey and Dodge described many patients from Buruli County, Uganda, with cutaneous ulcers reminiscent of those Cook described in 1897 from the same area, and named the disease Buruli ulcer. Since the World Health Organization (WHO) Buruli ulcer initiative there has been increased attention to efforts for the treatment and control of Buruli ulcer. Aetiology MacCallum and colleagues first isolated the causative agent in 1948 from patients in Australia. M. ulcerans, a slow-growing acid- fast bacillus, grows optimally at 32° C and produces mycolactone, a cytotoxic and immunosuppressive polyketide assembled by plasmid-encoded synthases of the aetiological agent. This toxin is the primary virulence factor of M. ulcerans. Data from whole genome sequencing define three major lineages of M. ulcer- ans that infect humans. Lineage 1 contains the South American strains, lineage 2 the Asian strains and lineage 3 the African and Australian subgroups. Single nucleotide polymorphism analysis through whole genome sequencing provides insights into the population structure and evolution of M. ulcerans across Africa. Portaels et al. were the first to culture M. ulcerans from the envir- onment, in 2008.

section 8 Infectious diseases 1168 Epidemiology and transmission Buruli ulcer is the third most common human mycobacterial in- fection worldwide, after tuberculosis (Chapter 8.6.26) and leprosy (Chapter 8.6.28). It occurs in humid, rural tropical, subtropical re- gions and temperate regions, and most endemic foci of Buruli ulcer are near rural freshwater wetlands, especially ponds and swamps. Presently, major endemic areas are Benin, Cameroon, Democratic Republic of Congo,

Gabon, Ghana, Ivory Coast, and adjacent coun- tries. Increasing case clusters have also been reported in Australia (Far North Queensland and Victoria, where it is known as Daintree or Bairnsdale ulcer) and sporadic cases in Mexico, South America, Malaysia, Japan, China, and Papua New Guinea. Documented environmental sources of M. ulcerans DNA include irrigation systems, water bugs living among aquatic plant roots in swamps, terrestrial vegetation, and mosquitoes. In Australia, koalas, possums, potoroos, rats, some domestic animals (dogs, horses, and one cat) and imported alpacas acquire the infection naturally. The mode of transmission is not fully understood, although dis- ease is known to be linked to contaminated water. Outbreaks of dis- ease often follow environmental changes that promote flooding or alter water courses, such as deforestation or construction of dams and irrigation systems. Increased farming activities near wet- lands and global climatic changes may contribute to the rapid re- emergence of Buruli ulcer. In West Africa the peak age of onset is 5 to 15 years, although the disease can affect any age group. In Australia the median age at presentation is 55–65 years. Transmission is probably via skin trauma, although insects may play a role. The trauma may be slight (e.g. hypodermic injection) or severe (e.g. land mine wound or snake bite). Biting insects (e.g. mosquitoes, water bugs) may serve as vectors. In Australia, risk for Buruli ulcer in humans is associated with the frequency of de- tection of M. ulcerans in the local possum faeces, as well as mos- quitoes, suggesting a possible role in transmission. Possums tend to be symptomatic with M. ulcerans ulcerations and are the likely reservoir in South Eastern Australia, with transmission possibly caused by mosquitoes that developed in water sources contamin- ated with possum faeces, or rested on M. ulcerans-contaminated vegetation. Possums may be useful sentinels to predict spread of Buruli ulcer in humans in South Eastern Australia, though no such link has been established in Far North Queensland. Extensive sur- veillance of rodents in Africa has failed to identify a similar res- ervoir to date. Mosquitoes do not seem to play a major role in ecology of M. ulcerans in Africa. Aerosols arising from ponds and swamp surfaces may disseminate M. ulcerans. Rare instances of person-to-person transmission of Buruli ulcer are anecdotal, and to our knowledge, none of these events has been established as M. ulcerans infection. Pathogenesis Predisposing host factors are poorly understood. Putatively, severity and course of infection are related to pathogen virulence, mode of infection, inoculum size, host genetic factors, and immunological response of the host. A T-helper 1 cell (Th1) response tends to lo- calize and heal infections while a T-helper 2 cell (Th2) type response is associated with dissemination. Once introduced, the small amount of mycolactone produced by inoculated M. ulcerans causes tissue necrosis and apoptosis, suppressing local immune responses, and ensuring survival of the bacillus in necrotic tissue. Mycolactone tar- gets subcutaneous fat cells, permitting necrosis to spread just super- ficial to fascial planes. M. ulcerans may invade lymphatic and blood vessels, causing metastatic spread of the mycobacterium despite its preference for cooler temperatures (32°C). Clinical features Except for those with massive lesions, patients are usually surprisingly well without systemic symptoms or abnormal laboratory findings. Meyers et al. have published a model for the natural history and inter- relationships of the forms of Buruli ulcer disease. Buruli ulcer may be localized or disseminated, and can be classified in three categories based on the extent of the ulceration, per WHO guidelines. Localized disease Typically, the initial cutaneous lesion is a single, firm, painless, nontender, movable, subcutaneous nodule up to 3 cm in diameter. Limbs are preferred sites, often around joints. The natural history of the disease is markedly variable, but nodules usually ulcerate within l to 3 months of inoculation. A whitish necrotic slough de- velops in the ulcer base with induration and hyperpigmentation of surrounding skin. Ulcer borders are undermined, sometimes extending widely (major ulcerative disease) (Fig. 8.6.29.1). Some small (1–2 cm in diameter) ulcerated lesions with shallow under-

mining self-heal (minor ulcerative disease). Without treatment, major ulcerative lesions tend to become inactive, after months or years, and heal by scarring. Scars are depressed and stellate, often causing disfiguring and crippling cicatricial contractures. Fig. 8.6.29.1 Pristine Buruli ulcer on the left deltoid area in a 12-year- old Congolese boy who had received a hypodermic injection at this site 3 months previously. Note central necrotic slough in the base of the ulcer and undermined edges.

1169 Disseminated disease Disseminated disease may develop from nodules, arise from local- ized major ulcerative lesions, or disseminate directly and rapidly from the site of inoculation, causing indurated plaques covering even an entire limb or vast areas of the trunk. Without treatment, such lesions will eventually slough, leaving a large ulcer with con- tinuing extension of disease at the borders. Eyes, breasts, and geni- talia may be damaged or destroyed. While metastatic spread may arise from localized disease, patients with the high bacterial loads and disseminated disease are most prone to metastatic lesions. Spread may be to distant skin sites or bone, especially bones of the limbs. In Africa, M. ulcerans osteomye- litis develops in approximately 10% of patients and often leads to amputations or other disabilities. Differential clinical diagnosis Clinical diagnosis is sometimes perplexing. Differential diagnoses include bacterial, mycotic, and parasitic infections, inflammatory lesions, and tumours. Ulcers resembling Buruli ulcer include trop- ical phagedenic ulcer (malodorous and not undermined), venous stasis ulcer (not undermined), and venomous snake bite or spider bite (history helpful). Pathology Optimal biopsy specimens contain the necrotic base of ulcers and undermined edge of lesions including subcutaneous tissue and fa- scia. Histopathological sections reveal a contiguous coagulation necrosis (noncaseating) of the deep dermis, panniculus, and fa- scia. Vasculitis and mineralization are common. Clumps of extra-cellular acid-fast bacilli are most plentiful in the base of the ulcer; however, intracellular M. ulcerans may be seen in inflammatory cells at the edge of necrotic foci. Necrosis extends well beyond the loca- tion of bacilli. Local and regional lymph nodes are often invaded and sometimes necrotic. In bone, the marrow is necrotic and con- tains acid-fast bacilli, and trabeculae are eroded. These features are distinct from those of osteomyelitis of all other known aetiologies. Development of delayed-type hypersensitivity granulomas heralds healing by fibrosis. Laboratory diagnosis Fine needle aspirates are often employed for laboratory studies on closed lesions. Smears stained by the Ziehl-Neelsen method from the ulcer base reveal acid-fast bacilli in clumps in around 30–60% of polymerase chain reaction confirmed Buruli ulcer le- sions. M. ulcerans is a slow-growing organism that can be cultured in vitro at 29–33°C, albeit with low rate of cultivability (20–60%). Polymerase chain reaction provides specific identification of M. ulcerans, with IS2404 as the most sensitive target given the pres- ence of over 200 copies per genome. Histopathological changes are characteristic. Treatment The former recommended treatment for most patients was wide surgical excision followed by skin grafting. Heating the lesion at 40°C can be a useful adjunct. Today, antimicrobial therapy (ri- fampicin 10 mg/kg by mouth plus streptomycin 15 mg/kg by intra-muscular injection, or rifampicin plus clarithromycin) without surgery is recommended and heals most nodular and minor ul- cerative disease, and some advanced lesions. Controlled trials have established efficacy. Physiotherapy is essential to prevent contrac- ture deformities. Prevention and control Bacille Calmette-Guérin (BCG) vaccination provides short-lived protection. Practical control measures for inhabitants of endemic areas are usually ineffective; however, use of a protected water supply is important. Tourists should avoid wetlands in endemic countries. Socioeconomic impact Patients are often stigmatized by disability or cosmetic damage, and may require welfare services for life, but such services are often locally limited or unavailable. They also often require protracted hospital stays, taxing overburdened services. Given certain similarities

between Buruli ulcer and leprosy, combined control and prevention strategies could be put in place in countries endemic for both diseases. FURTHER READING Alffenaar JW, et al. (2010). Pharmacokinetics of rifampin and clarithromycin in patients treated for Mycobacterium ulcerans infection. Antimicrob Agents Chemother, 54, 3878–83. Buultjens AH, et al. (2018). Comparative genomics shows that Mycobacterium ulcerans migration and expansion preceded the rise of Buruli Ulcer in Southeastern Australia. Appl Environ Microbiol, 84, e02612–17. Carson C, et al. (2014). Potential wildlife sentinels for monitoring the endemic spread of human Buruli ulcer in South-East Australia. PLoS Negl Trop Dis, 8, e2668. Converse PJ, et al. (2011). Treating Mycobacterium ulcerans disease (Buruli ulcer): from surgery to antibiotics, is the pill mightier than the knife? Future Microbiol, 6, 1185–98. Doig KD, et al. (2012). On the origin of Mycobacterium ulcerans, the causative agent of Buruli ulcer. BMC Genomics, 13, 258. Fyfe JA, et al. (2010). A major role for mammals in the ecology of Mycobacterium ulcerans. PLoS Negl Trop Dis, 4, e791. Kiszewski AE, et al. (2006). The local immune response in ulcerative lesions of Buruli disease. Clin Exp Immunol, 143, 445–51. Lavender CJ, et al. (2011). Risk of Buruli ulcer and detection of Mycobacterium ulcerans in mosquitoes in southeastern Australia. PLoS Negl Trop Dis, 5, e1305. 8.6.29 Buruli ulcer: Mycobacterium ulcerans infection

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