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remembered that treating patients with leprosy is a long-term enterprise involving patients, their families, and health workers.

Areas where further research is needed

The epidemiology of leprosy still poses unanswered questions. Why are 70 per cent of all patients with leprosy in India? Is this due to living conditions, genetic susceptibilty, or particular environmental conditions in India?

Early detection of cases is vital both at an individual and population level. It is now recognized that substantial nerve damage occurs 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 currently limited to steroids. These are not effective for about 30 per cent cases. Thus trials of new immunosuppressants are urgently needed.

The WHO started the 1990s with the bold slogan of 'Eliminating leprosy as a public health problem by 2000'. This initiative galvanized leprosy control programmes worldwide, but the unique biology of *M. leprae* and its interaction with the human host meant that the target was unattainable. As the millennium approached the slogan was quietly dropped to the disappointment of many leprosy workers and governments. Leprosy is a bacterial disease with challenging immunological 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 conditions, and education.

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7.11.25 Buruli ulcer: *Mycobacterium ulcerans* infection

Wayne M. Meyers and Françoise Portaels

Introduction

Buruli ulcer, also known as Bairnsdale or Searles' ulcer (Australia), and Kakerifu or Toro ulcer (Congo), is an indolent, necrotizing infection of the skin, subcutaneous tissue, and bone, caused by *Mycobacterium ulcerans.* After tuberculosis and leprosy, Buruli ulcer is the third most common mycobacterial disease, and is recognized by the WHO as a re-emerging infection.

Aetiology

In 1948 MacCallum and colleagues first isolated the causative agent from patients in Australia. *M. ulcerans* is a slow-growing, acid-fast bacillus which grows optimally at 32°C, and elaborates mycolactone, a cytotoxic and immunosuppressive polyketide. Putatively, this toxin is the primary virulence factor of *M. ulcerans.* Data from 16S rRNA sequences define four groups of *M. ulcerans*: African, American, Asian, and Australian strains.

Epidemiology and transmission

All endemic foci of Buruli ulcer are near rural freshwater wetlands, especially still or slow-moving water (ponds and swamps). All foci except those in southern Australia and northern Asia are tropical. Major endemic areas are Benin, Ghana, Ivory Coast, Nigeria, Congo, Gabon, Uganda, and adjacent countries. There are minor foci in South and Central America and south-east and northern Asia.

Documented environmental sources of *M. ulcerans* include water in irrigation systems and water bugs that dwell in the roots of aquatic plants in the bottom mud of swamps. In Australia, koala, possum, and naturalized alpaca contract the infection naturally.

Outbreaks of disease often follow environmental changes that promote flooding or alter water courses, such as deforestation or construction of dams and irrigation systems. Increases in farming populations near wetlands may contribute to the rapid re-emergence of Buruli ulcer in Africa. Approximately 75 per cent of all new infections are in children, who often play semi-naked in swampy terrain.

We postulate that humans become infected by traumatic introduction of the bacillus into the dermis or subcutis from the overlying *M. ulcerans*-contaminated skin surface. The trauma may be as slight as a hypodermic injection or as severe as a land-mine wound or snakebite. Biting insects (e.g. water bugs) may serve as mechanical vectors. Aerosols arising from the surface of ponds and swamps may disseminate *M. ulcerans.* Patient-to-patient transmission is rare.

Pathogenesis

No predisposing host factors are known. Once introduced, the small amount of mycolactone produced by a few *M. ulcerans* bacilli causes tissue necrosis and suppresses local immune responses ensuring survival of the bacillus in a nidus of nutrient necrotic tissue. The toxin targets subcutaneous fat cells so that necrosis can spread in and just superficial to fascial planes. *M. ulcerans* invades lymphatics and probably blood vessels, causing metastatic spread.

Clinical features

Clinical effects may be localized or disseminated. Except for those with massive lesions, patients are usually surprisingly well without specific systemic symptoms or abnormal laboratory findings.

Localized disease

Typically the initial cutaneous lesion is a single, firm, painless, non-tender, movable subcutaneous nodule up to 3 cm in diameter. Limbs are most frequently affected, often around joints. There is marked variation in the natural history of the disease, but nodules usually ulcerate within 1 to 3 months of inoculation. A whitish necrotic slough develops in the base of the ulcer and the surrounding skin is indurated and hyperpigmented. Ulcer borders are undermined, sometimes extending 15 to 20 cm or more (major ulcerative disease) (Fig. 1 and Plate 1). Some small (1 to 2 cm in diameter) ulcerated lesions with shallow undermining self-heal early without sequelae (minor ulcerative disease). Without treatment, major ulcerative lesions tend to become inactive, usually after months or years, and heal by scarring. Typically the scars are depressed and stellate, often causing disfiguring and crippling cicatricial contractions.

Disseminated disease

Disseminated disease may pass only through the nodular stage or arise from localized major ulcerative lesions; however, following inoculation, the disease sometimes disseminates directly and rapidly. These patients present with indurated plaques of varying size, sometimes covering an entire limb or vast areas of the trunk. Without treatment, such lesions will eventually slough, leaving a large ulcer with continuing extension of disease at the borders. Structures such as eyes, breasts, and genitalia may be damaged or lost.

While metastatic spread may arise from localized disease, patients with the highly bacilliferous disseminated cutaneous form are more prone to develop metastatic lesions. Spread may be to distant skin sites or to bone. Bones of the limbs are affected most frequently. *M. ulcerans* osteomyelitis is an increasing problem in many endemic areas, and often leads to amputations and other disabilities.

Differential clinical diagnosis

Diagnosis of the nodular stage is often perplexing. Differential diagnoses include bacterial, mycotic, and parasitic infections, inflammatory lesions, and tumours. Ulcers resembling Buruli ulcer include tropical phagedenic ulcer (malodorous and not undermined), venous stasis ulcer (not undermined), and bites by venomous snakes or spiders (history helpful).

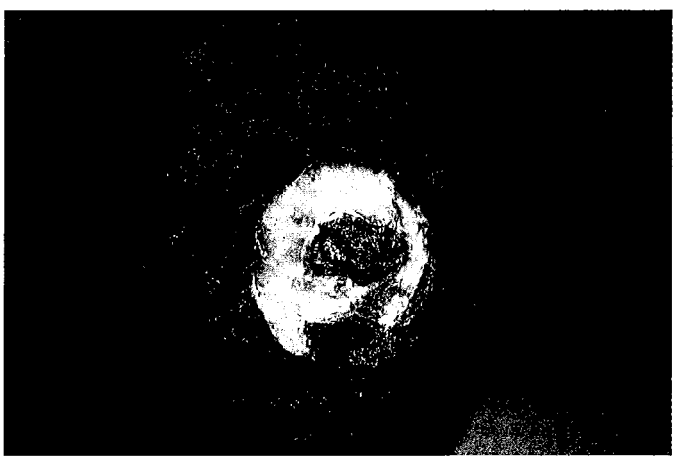

Fig. 1 Buruli ulcer on the left deltoid area in a 12-year-old Congolese boy who had received a hypodermic injection at this site 3 months previously. Note central necrotic slough in the base of the ulcer, and undermined edges. (See also Plate 1.)

Pathology

Optimal biopsy specimens contain the necrotic base of ulcers and undermined edge of lesions and subcutaneous tissue and fascia. Histopathological sections reveal a contiguous coagulation necrosis (non-caseating) of the deep dermis, panniculus, and fascia. Vasculitis and mineralization in these areas are common. Clumps of extracellular acid-fast bacilli are most plentiful in the base of the ulcer. Necrosis extends well beyond the location of the bacilli. Local and regional lymph nodes are often invaded and sometimes necrotic. In bone, the marrow is necrotic and contains acid-fast bacilli, and trabeculas are eroded. Development of delayed-type hypersensitivity granulomas heralds healing and eventual fibrosis.

Laboratory diagnosis

Smears stained by the Ziehl–Neelsen method from the ulcer base often reveal acid-fast bacilli in clumps. Cultures for *M. ulcerans* are often positive. Polymerase chain reaction is available for specific identification of *M. ulcerans*. Histopathological changes are characteristic.

Treatment

Wide surgical excision and skin grafting is the recommended treatment. Antimicrobial agents (e.g. rifampin and clarithromycin) should be administered before and after surgery to limit bacterial dissemination. Heating the lesion to 40°C is a useful adjunct. Oral antimycobacterial therapy without surgery may heal nodules and minor ulcerative lesions, but controlled trials are needed to establish efficacy. Physiotherapy is essential to prevent contraction deformities.

Prevention and control

Bacille Calmette-Guérin (BCG) vaccination provides short-lived protection. There are no practicable effective control measures for inhabitants of endemic areas. Tourists can avoid the wetlands in endemic countries.

Socio-economic impact

Patients are often disabled for life and require welfare services, often locally limited or unavailable. They require hospital stays of many months, taxing overburdened services.

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