Textbook of
Tropical Surgery

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172 Buruli Ulcer

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Since 1980, Buruli ulcer (BU), caused by *Mycobacterium ulcerans*, has emerged as an important cause of human morbidity. BU is the third most common mycobacterial disease of humans after tuberculosis and leprosy. Both the medical community and the general public are poorly informed about the disease. From their experiences in Australia, MacCallum and colleaguespublished the first clinical description of the disease in 1948. Sir Albert Cook described cases consistent with BU in Uganda in 1897, but these observations were not published until 1970 (BMJ ii: 378–379). In response to the growing spread and impact of BU, the World Health Organization (WHO) established the Global Buruli Ulcer Initiative (GBUI) in 1998.

Etiology

M. ulcerans is a slowly growing environmental mycobacterium. The microorganism is an acid-fast bacillus (AFB). It grows on common mycobacterial media (e.g. Löwenstein–Jensen), at low temperatures (30–32°C), at low oxygen tension (pO_2 <2.5 kPa) and within a pH range of 5.4–7.4, in 6 weeks or longer for primary culture. Recent molecular studies using specific primers have revealed *M. ulcerans* in water, fish, aquatic insects and snails. *M. ulcerans* secretes a polyketide macrolide toxin, mycolactone, that destroys tissues and has local immunosuppressive activity.

Epidemiology and transmission

BU is endemic in at least 31 countries, mostly in tropical and subtropical regions; however, West Africa currently is the most affected region (Figure 172.1). The disease most often prevails near rivers and stagnant water. Koalas and possums are naturally infected in Australia. Exact modes of transmission are not known, but aquatic insects (*Naucoris* and *Dyplonychus* spp.) may transmit the disease. Patient-to-patient transmission is rare. Infection with the human immunodeficiency virus (HIV) is not a known risk factor. Mortality is low, but the suffering and long-term social and economic impacts are considerable.

All ages and social groups and both sexes are affected, but the highest incidence (70%) is in children under 15 years of age. The disease most frequently afflicts the limbs – the lower limb twice as often as the upper limb. The trunk, head, neck and genitalia may also be affected.

Living close to endemic foci, travelling to BU-endemic areas, having regular contacts with the contaminated aquatic environment and local trauma to the skin are some of the important risk factors for developing infection or disease.

Pathogenesis and pathology

Following inoculation of *M. ulcerans*, the organism proliferates and produces cytotoxin(s) that cause necrosis of the dermis, panniculus,

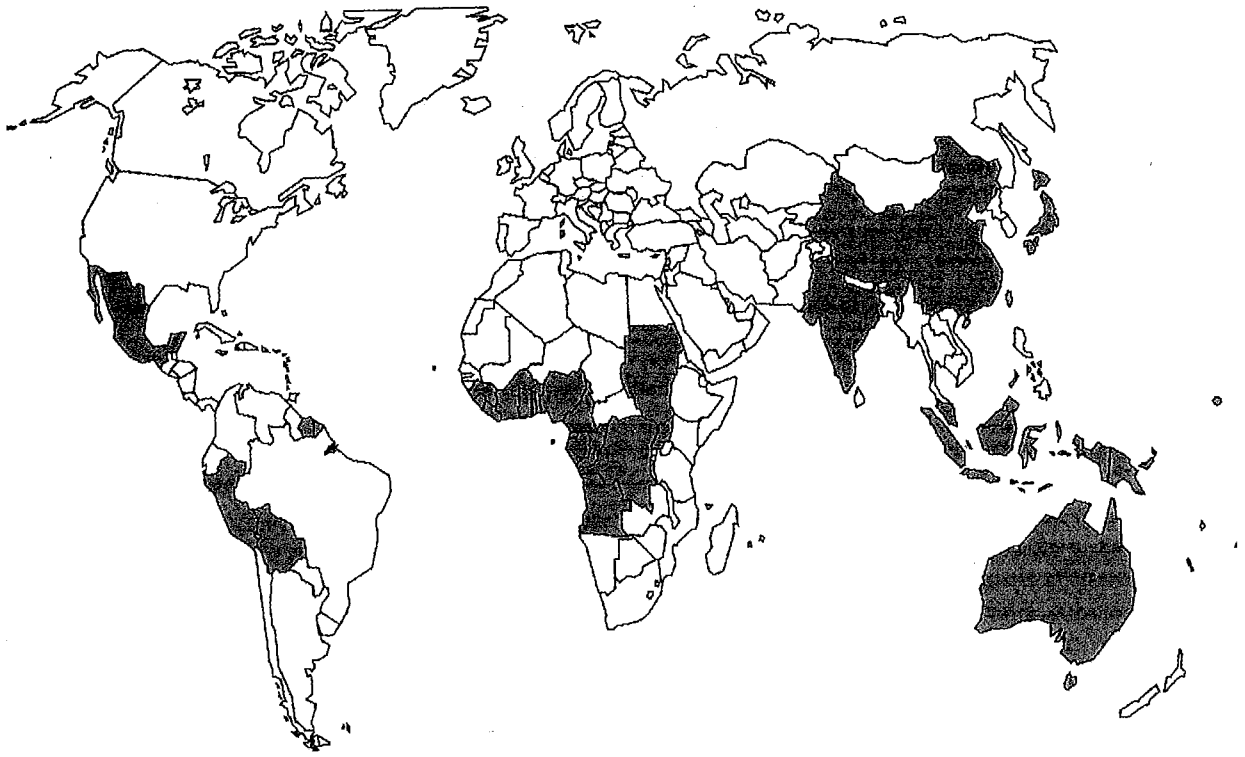

Figure 172.1 Map of the worldwide distribution of *M. ulcerans* disease. Reproduced with permission from Crofts K (ed). Management of *Mycobacterium ulcerans* disease. World Health Organization, 2001.

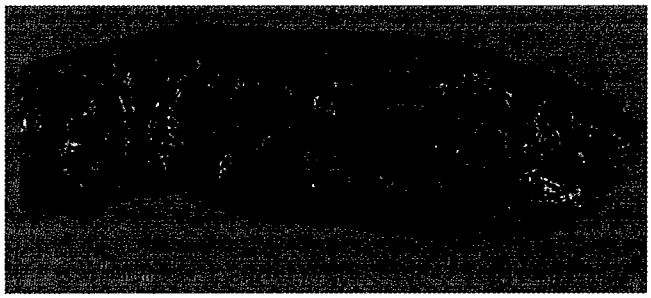

Figure 172.2 A section of surgically excised nodule of *M. ulcerans* disease. The central whitish area represents coagulation necrosis. Photograph courtesy of John Hayman.

Figure 172.3 Nodular form of *M. ulcerans* disease. Photograph courtesy of Samuel Etuaful.

and deep fascia. The most well characterized cytotoxin is mycolactone, which targets subcutaneous tissue, especially fat cells. *M. ulcerans* invades lymphatics and blood vessels, potentially leading to metastatic spread to bone and distant skin sites.

Specimens for pathologic study are best taken from the edges of ulcers or from the centers of closed lesions, and should include skin, subcutaneous tissue and fascia. Histopathologic sections reveal contiguous coagulation necrosis of the deeper layers of the skin and subcutaneous tissue (Figure 172.2), vasculitis and, in Ziehl–Neelsen (ZN)-stained sections, clumps of extracellular acid-fast bacilli (AFB) are abundant in deep necrotic tissue.

M. ulcerans-specific osteomyelitis shows necrosis of marrow and destruction of bony trabeculae. In early lesions, cellular exudates are scarce, but eventually chronic inflammatory cells infiltrate necrotic tissue and delayed-type hypersensitivity granulomas develop, heralding the beginning of healing, which culminates in depressed scars.

Figure 172.4 Extensive *M. ulcerans* disease. Photograph courtesy of Kingsley Asiedu.

Clinical manifestations

The median incubation period is about 2 months but may be much longer. In cases of reactivation, the incubation period could be 2–4 weeks.

In primary disease, following inoculation of M. ulcerans into the skin, lesions may be localized or disseminated. In Australia, a papule may develop at the inoculation site, but in Africa, localized disease appears first as a painless subcutaneous nodule (Figure 172.3) that may itch. The nodule may self-heal early, but this has not been well documented. Usually, the nodule ulcerates, sometimes leaving small undermined ulcers that self-heal or lead to large, well-defined, widely undermined ulcers with central necrosis, having a cotton wool appearance and induration of the surrounding skin (Figures 172.4 and 172.5). The disseminated form usually bypasses the nodular stage and presents as a painless, elevated indurated plaque or diffuse nonpitting edema that sometimes covers vast areas of the body, even an entire limb or much of the trunk. Disseminated lesions eventually ulcerate, but without the localizing features described above.

Bones and joints may be affected by direct spread from an overlying lesion of BU or via the blood stream. Extensive areas of ulceration are often debilitating and there may be continuing minor bleeding or sudden hemorrhage. Secondary infection may lead to dangerous septicemia.

Long-neglected or poorly managed patients usually present with scars, partially healed areas or disabling joint contractures (Figure 172.6). Apart from scar contractures, patients may develop hypertrophic scars or keloids, usually on their limbs. Marjolin's ulcer (squamous cell carcinoma) may develop in unhealed areas or in chronic nonpigmented scars.

M. ulcerans disease should always be borne in mind when a patient with a localized chronic inflammatory skin condition has recently visited an endemic area.

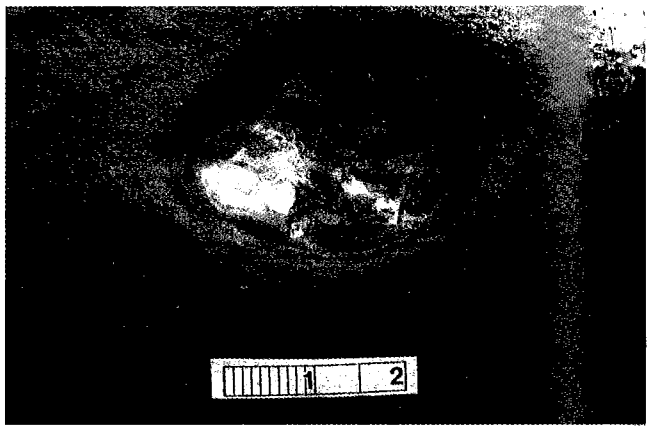

Figure 172.5 Typical features of *M. ulcerans* disease, showing undermined edges and central necrotic slough. Photograph courtesy of John Hayman.

Diagnosis and differential diagnosis

Diagnosis is mainly clinical by experienced physicians. ZN-stained smears from the necrotic base of ulcers usually reveal clumps of extracellular AFB (Figure 172.7).

Incisional rather than punch biopsy specimens are recommended. Specimens that include the necrotic base of active ulcers, the undermined edge of lesions and subcutaneous tissue are nearly always diagnostic. Biopsy specimens from nonulcerated lesions are best obtained from their presumed centers. *M. ulcerans* can often be cultured from exudates or biopsy specimens, but visible growth requires incubation at 32°C for 6

Figure 172.6 A contracture deformity resulting from *M. ulcerans* disease. Photograph courtesy of Marcel Crozet.

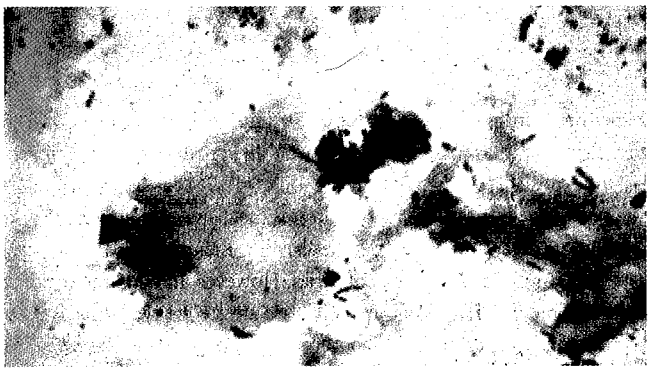

Figure 172.7 Ziehl-Neelsen-stained smear from *M. ulcerans* disease showing acid-fast bacilli. Photograph courtesy of Bernard Carbonnelle.

weeks or longer. Molecular biologic techniques (i.e. polymerase chain reaction, PCR) are often useful in establishing the diagnosis, especially when culture and histopathologic analysis are negative.

The differential diagnosis of *M. ulcerans* disease includes:

- for minor infections: insect bites and a variety of dermatologic conditions;
- for nodules: cysts, lipomas, boils, onchocercomas, lymphadentis and mycoses;
- for plaques: leprosy, cellulitis, mycoses and psoriasis;
- for edematous forms: cellulitis, elephantiasis and actinomycosis;
- for ulcers: tropical phagedenic ulcer, leishmaniasis, neurogenic ulcer, yaws, squamous cell carcinoma and noma.

Management

Although drug treatment has been disappointing in the past, recent evidence has shown that treatment of early small lesions in humans with a combination of rifampicin and streptomycin was successful in causing excised lesions to be culture-negative after 4, 8 and 12 weeks, but not after 2 weeks. Most lesions also decreased in size. Further studies are needed to determine the optimal duration of treatment and role of antibiotics in curing early lesions or complementing surgery. Other investigational treatments have included continuous local heating to 40°C (e.g. by circulating water jackets) and hyperbaric oxygen.

Surgery is the mainstay of treatment, possibly associated with specific antibiotics. Secondary infection requires treatment according to the sensitivities of the organisms. The margins of the involved tissues are determined by inspection and palpation: excision should include margins of healthy tissue. Small skin defects may be closed directly, but most excisions require split skin grafts. For small skin defects, free full-thickness skin grafts may be preferable, but primary flap repair should be infrequent. When extensive areas are involved, excision and grafting should be staged. When areas over or near joints are affected, splinting is essential to prevent contractures.

Bone involvement by direct extension is managed conservatively by excision of infected soft tissue followed by sequestrectomy. Specific antibiotic therapy is recommended. *M. ulcerans*-specific osteomyelitis putatively acquired by dissemination is best managed by conservative drainage procedures and specific antibiotic therapy. External fixation may assist in the treatment of disease involving or near joints.

Contractures are easier to avoid by splinting than to treat. Surgical treatment involves division of tight superficial and deep scar tissue (tenotomy may be necessary) followed by free skin grafts or flaps. The joint is extended as far as possible without damaging vessels and nerves. Prolonged postoperative splinting is essential. Subsequently, leg calipers may be needed.

Surgical treatment of *M. ulcerans* disease involving the face, eye, breast or genitalia requires specialized management.

Primary amputation is performed to save life, when bone is destroyed or when reconstruction is not possible. Secondary amputation may be unavoidable. Much ongoing care is essential following a leg amputation.

Socioeconomic impact

BU often occurs in poor communities with poor health service coverage. Because of superstition, lack of knowledge and poverty, patients often seek treatment very late, resulting in prolonged costly hospitalization leading to disruption of work or schooling. In some areas, 20–25% of people with healed lesions have functional disabilities that have long-term social and economic impacts, especially for children. BU imposes a considerable burden on patients, care and health services.

Prevention and control

There are no effective prophylactic measures but a single bacille Calmette–Guérin (BCG) vaccination may provide protection for approximately 6 months or delay the onset of lesions. This is the only currently acceptable strategy for field studies of the immunoprophylaxis of BU. Disease management should be aimed at early detection and treatment.

Conclusions

BU is a growing public health problem, particularly in Africa, requiring urgent control. The disease may appear in non-endemic areas because of international travel; thus, health care providers, especially dermatologists, surgeons and general practitioners, around the world should be aware of the presentation and treatment of this disease.

Further reading

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