Buruli ulcer

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Summary

- Skin ulcers caused by *Mycobacterium ulcerans*
- Role of mycolactone, the Buruli toxin secreted by the organism
- Extensive involvement of subcutis and underlying tissue
- Little pain
- Surgical intervention is the first choice for treatment
- Add rifampicin plus streptomycin if early diagnosis/lesion

Historical note

In 1897, a disease was noted in Africa by Sir Albert Cook that is most likely to have been Buruli ulcer. Between 1923-35 the condition was also observed by Kleinsmidt in north-east Congo. The disease was seen in 1940 and subsequently (1948) described by MacCallum in Australia as Bairnsdale ulcer. Afterwards similar ulcers were found in Africa, Papua New Guinea and other parts of the world. In 1961 a focus was discovered in Uganda along the White Nile in Buruli County near Lake Kyoga, hence the name Buruli ulcer which has since been used extensively. After 1980, important new foci were discovered in West Africa. Since December 1997, the condition has been recognised by the WHO as an important emerging disease. The “Global Buruli Ulcer Initiative” was launched in February 1998 with the intention of improving knowledge and control of this disease.

Geographical distribution

The geographical range of the disease is still incompletely known. In the year 2000, the condition was known to occur in:

Benin, Burkina Faso, Cameroon, Ivory Coast, Ghana, Guinea, Liberia, Nigeria, Sierra Leone, Togo, Angola, Congo, Gabon, Sudan, Uganda

Australia, Papua New Guinea

China, India, Indonesia, Japan, Malaysia

Bolivia, French Guyana, Mexico, Peru, Surinam

Aetiology

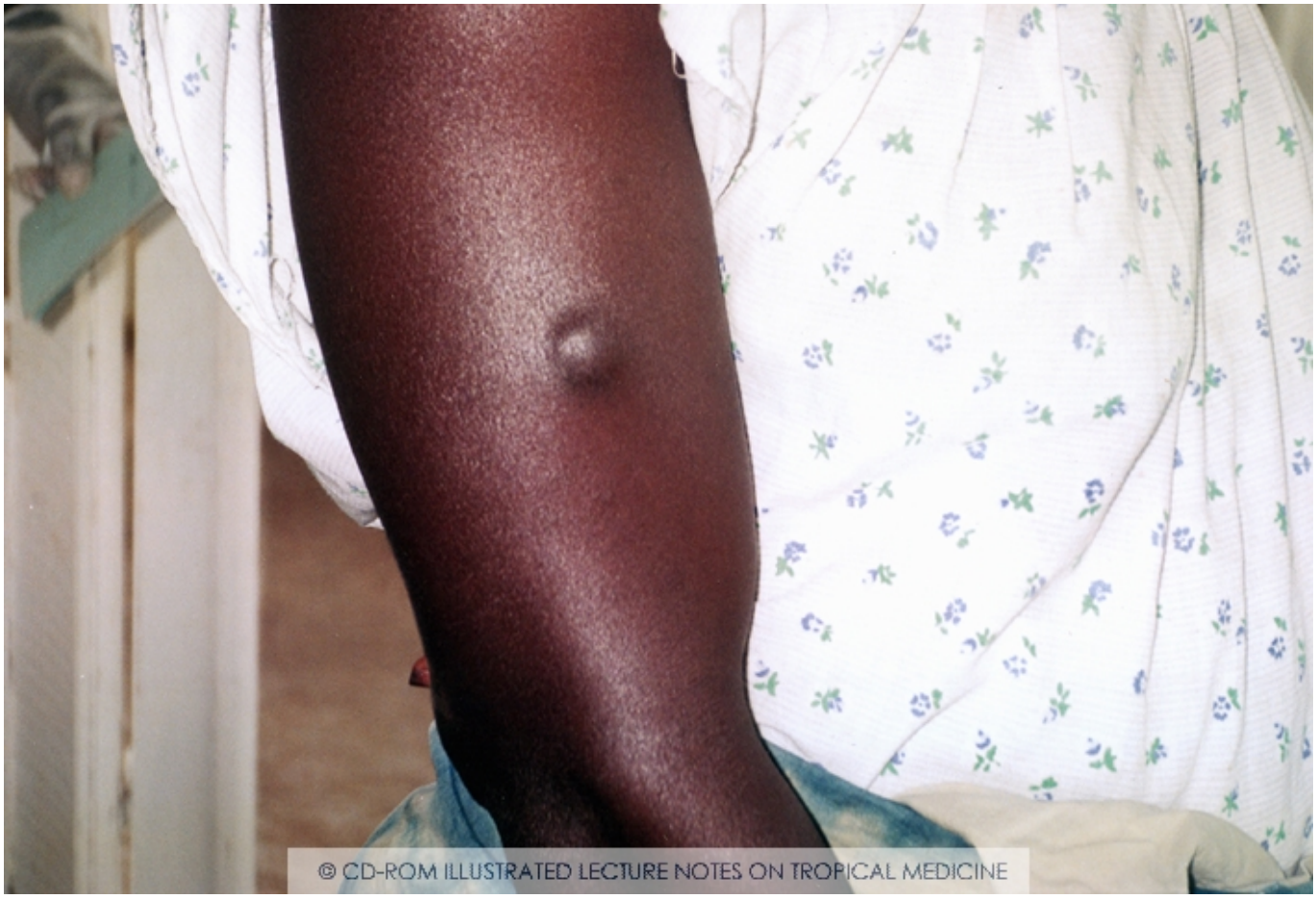
Buruli ulcer is caused by *Mycobacterium ulcerans*, an organism that is closely related to *M. tuberculosis*. These bacteria are acid-fast rods, 3-7 µm long. The generation time is 20 hours (slow-growing organism). The reservoir and the route of transmission remain unknown. Regular reference is made to the presence of the disease in marshy areas along large rivers. *M. ulcerans* grows best at low oxygen concentrations, such as are found in the mud of marshy ground. The clinical history often includes a report of minor trauma, an insect bite or a hypodermic injection at the site of the original solitary lesion. It is suspected that transmission might occur via the bite of infected water bugs. These insects are possibly infected by filter feeding on micro-organisms in the water, subsequently serving as mechanical vectors. This however is still only a hypothesis. The mycobacteria are detectable in those insects by PCR. Mosquitoes were suspected in a large outbreak in Australia (PCR-positive). As a rule, attempts to isolate the organism from the environment (e.g. streambeds of slow-flowing rivers or marshes) fail. The interval between sampling and culture, the transport media, the temperature and the aggressive decontamination procedures that are used possibly play a part in this.

Pathology

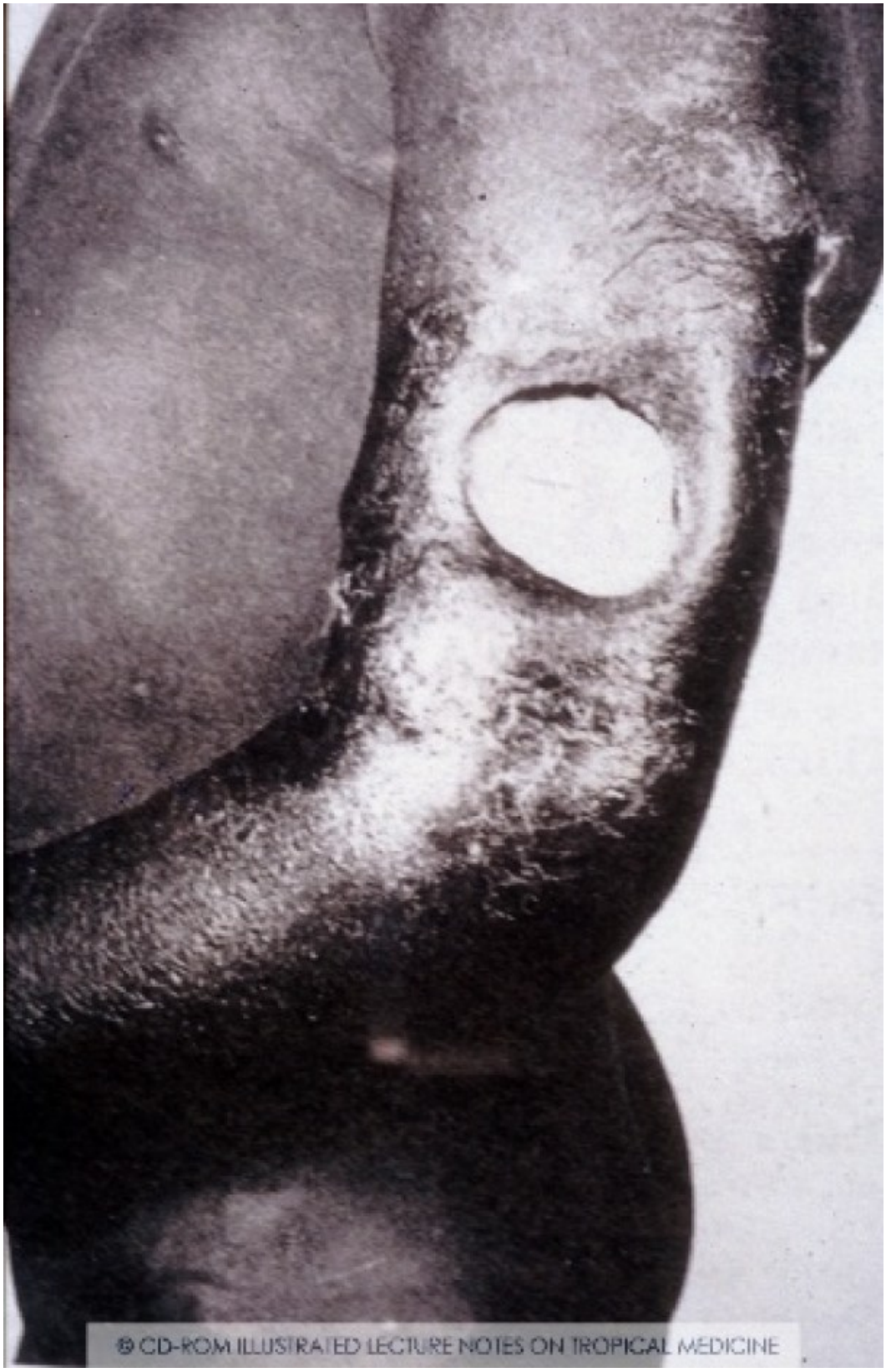
M. ulcerans is a mycobacterium that grows extracellularly in the human body. The earliest lesion is a necrotic zone in subcutaneous fatty tissue. There is typically surprisingly little inflammatory reaction in the surrounding tissues. Clumps of acid-fast bacilli are found in the necrotic fatty tissue (“steatonecrosis”), sometimes in huge numbers. Calcifications can also form. Eventually the lesion ulcerates as a result of necrosis of the overlying skin. Necrosis of the fatty tissue is always more extensive than the ulcer itself so that the edges are undermined and become detached over a considerable distance. Multiple ulcers can form, connected at the deeper level by necrotic subcutaneous channels. From the edges of the ulcer there is a tendency to re-epidermalisation of the lowest level of the detached skin, which is pathognomonic for this disease. The base of the ulcer is coated with a layer of necrotic, purulent material in which for the most part no *M. ulcerans* is found. In contrast to tropical ulcers, these ulcers show no tendency to malignant degeneration.

The tissue necrosis extends further than the colonies of acid-fast rods. Following injection in experimental animals, a sterile ultrafiltrate of *M. ulcerans* can cause lesions that are very similar to Buruli ulcers. A cytotoxic necrotic toxin that is responsible for the steatonecrosis is found in the culture medium of *M. ulcerans*. This substance probably also has a bacteriostatic effect, which would explain the rarity of secondary infection. The toxin is a polyketide macrolide: mycolactone ($C_{44}H_{70}O_9$). *M. ulcerans* strains that produce no mycolactone are avirulent to guinea pigs. Mycolactone is probably locally immunosuppressant

Clinical Aspects



Infection with Mycobacterium ulcerans. Subcutaneous lesion on arm. There is no break-through (yet) to the surface. Copyright ITM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Buruli ulcer results from infection with Mycobacterium ulcerans. Notice the undermined edges.

It is estimated that the incubation time is 6 weeks or longer. The ulcers are predominantly found on the limbs, more above the elbow and knees, but in 10% of cases it can be found the trunk and the abdominal wall and very rarely on the face or scalp.

The disease course can be divided into 4 stages: nodule, cellulitis, ulceration, scar. It begins as a pruritic, painless or slightly painful subcutaneous swelling that gradually becomes attached to the skin. A papulonecrotic or vesicular lesion then appears on the skin that progresses to an open ulcer with a gelatin-like coating. The skin around the ulcer is dark, sometimes with slight desquamation or with a deep reddish-purple colour (Caucasians) or hyperpigmentation (darker skin). The edges are slightly raised and rolled. The undermining of the wound edges can be established by probing. Satellite lesions and metastatic lesions in the skin or bone sometimes occur. In addition, there can be numerous lesions at the time of the first examination. The general state of health remains excellent, without fever or malaise, irrespective of how extensive the ulcer is.

When the ulcer is finally formed, it remains and becomes generally painless unless a secondary infection is involved. Sometimes localised pain is present. At the deeper level muscle, bone and joint tissue are destroyed with the accompanying formation of sequesters. Calcifications can be detected radiologically:

in any lesion, irrespective of its location or whether it is ulcerative.

in the skin near a lesion either before ulceration or in the subsequent scars.

In the long-term, after months or years, the ulcer tends to heal, but extensive deformities, ankylosis or lymphoedema remain. The scars are reminiscent of old burns or the consequences of late treponematoses.

Diagnosis

The diagnosis of the ulcerative form is somewhat easier than that of the non-ulcerative form. The undermining of the wound edges is a characteristic of Buruli ulcer. Radiologically, subcutaneous fat calcifications and/or osteomyelitis are observed in a large percentage of patients.

The acid-fast rods are examined with Ziehl stain in smears of curettage products from the edges of

the ulcer (preferably from the underside of the skin edges and not from the centre of the ulcer). The Ziehl stain of a smear demonstrates bacilli in ± 75% of cases. The histological features on biopsy are characteristic on condition that the sample has been taken sufficiently deeply to include the necrotic fatty tissue. Punch biopsies are usually not sufficient. Serodiagnosis is still experimental. Culture is possible but slow (several months). The organism grows optimally at 32°C. Higher temperatures inhibit the organism (important when transporting). Semisolid transport media such as PANTA (polymyxin B, amphotericin B, nalidixic acid, trimethoprim, azlocillin) can be used, although growth is not always obtained. The organism cannot be frozen although storage at 4°C is possible. Löwenstein-Jensen medium is best used as a culture medium in an atmosphere with little oxygen.
Additionally, clinicians with Buruli ulcer experience state that the ulcers have a characteristic unpleasant smell, which can contribute to the diagnosis.

There are a few other non-tuberculous mycobacteria that can cause skin abscesses and ulcers, e.g. *Mycobacterium avium intracellulare* in AIDS patients, as well as *M. szulgai, M. terrae, M. fortuitum, M. chelonae, M. malmoense and M. xenopi. M. abscessus* is a fast-growing organism that can cause tissue necrosis after accidental contamination of a deep inoculation (injection). Of course tuberculosis and leprosy need to be ruled out.

Infection induces cross sensitivity with tuberculin. It is possible that the opposite is also true, and that tuberculosis provides partial protection against *Mycobacterium ulcerans*. Patients with active lesions often have no local skin reaction after injection of *M. ulcerans* antigen (burulin). After recovery they test positive (cell immunity).

There are various PCR methods for detecting *M. ulcerans* but the technique is expensive and only available in a few places. False positive results can be reduced by developing a meticulous technique. False negatives (e.g. as a result of the presence of PCR inhibitors) are detected by carrying out simultaneous controls with known positive samples.

Buruli ulcer, differential diagnosis:

1. Cutaneous tuberculosis: scrophulus, lupus vulgaris
2. Atypical mycobacteriosis e.g. Swimming pool *granuloma (M. marinum), M. abscessus* (post-surgery or deep injection), *M. avium-intracellulare* in AIDS-patients
3. Leprosy (less ulceration)
4. Cat scratch disease
5. Tropical ulcer
6. Tertiary syphilis (gumma)

7. Framboesia (= Yaws = Pian): Treponema pertenue
8. Rat-bite fever or sodoku: Spirillum minus
9. Ecthyma: Streptococcus pyogenes, β-haemolytic (also known as Group A Strep)
10. Cutaneous diphtheria
11. Actinomycosis or mycetoma (incl. phycomycosis), deep mycosis: histoplasmosis, blastomycosis, chromomycosis, maduramycosis, sporotrichosis
12. Cancrum oris (= Noma)
13. Cutaneous leishmaniasis
14. Cutaneous amoebiasis (Acanthamoeba, Entamoeba histolytica)
15. Pyogenic abscess with e.g. pyomyositis
16. Fistula of classic osteomyelitis
17. Trauma, residual foreign body and burns, decubitus
18. Cancer: spinocellular carcinoma (also secondary to chronic ulcer), Marjolin ulcer, Kaposi, melanoma, basocellular
19. Arterial, diabetic or venous ulcer
20. Haematological abnormalities, e.g. sickle cell anaemia
21. Vasculitis (leukocytoclastic, Behçet, microscopic polyangitis, Churg-Strauss, cryoglobulinemia)
22. Pyoderma gangrenosum. This can be difficult to distinguish from Buruli. Both have undermined edges. Pyoderma gangrenosum is often secondary to chronic inflammatory conditions such as ulcerative colitis, Crohn’s enteritis, rheumatoid arthritis, pulmonary abscesses, paraproteinemia. Acid-fast bacilli will be absent of course and the infiltration will be mainly neutrophilic.
23. Botryomycosis: S. Aureus or other bacteria
24. Inoculation chancre: tryponosomiasis, rickettsia (tache noir)
25. Dracunculiasis (Guinea worm)
26. Anthrax
27. Tularemia
28. Snake bite (viperidae)
29. Loxosceles bites (spider)

Prognosis

The prognosis is unfavourable because of the severe skin and bone lesions, scars, tendency to infectious metastases and the problems of surgical treatment. Many lesions heal spontaneously, although with severe sequelae.

Treatment

Drug treatment is disappointing in the late stages. In vitro *M. ulcerans* is susceptible to rifampicin, clarithromycin, amikacin and streptomycin. Cycloserine, dapsone and clofazimine are active, but the organism is resistant to isoniazid. Clinical results however are often disappointing, possibly because the antibiotics do not diffuse to the bacillus itself. Treatment therefore is principally surgical: excision of the tissue followed by curettage, followed by immobilisation in a functional position. In most cases, excision of the tissues is carried out under broad-spectrum antibiotic cover. The previously mentioned antimycobacterial antibiotics can be administered at the same time to prevent the emergence of metastatic lesions. The combination rifampicin, clarithromycin and amikacin is practical. Studies suggest that an antimicrobial regimen of rifampicin plus streptomycin may be effective against early forms of Buruli ulcer. After the formation of healthy granulation tissue, skin transplants are applied (split skin grafts). Amputation may sometimes be the only possible treatment. Tetanus vaccination should not be overlooked. Good results can be obtained with local thermotherapy by surrounding the ulcer with water bottles at 40°C. This can cause logistical and technical problems. Healing of ulcers is obtained after an average of 41 days. There is little experience with hyperbaric oxygen therapy. Intensive physiotherapy can improve the function of a mutilated limb. Relapse of Buruli ulcer is not exceptional. Follow-up is important to rapidly identify those cases. Delays in seeking medical advice can lead to severe complications, including dissemination of disease and especially the development of bone lesions.

Prevention

In two studies in Uganda, BCG vaccination was shown to have about 50% efficacy against *M. ulcerans*. Protection nevertheless was temporary, on average lasting only a year. The ulcers that developed in vaccinated patients were smaller than those in controls. Possibly this merely involves non-specific immunostimulation by BCG.

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