Miscellaneous skin deseases

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Buruli ulcer

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

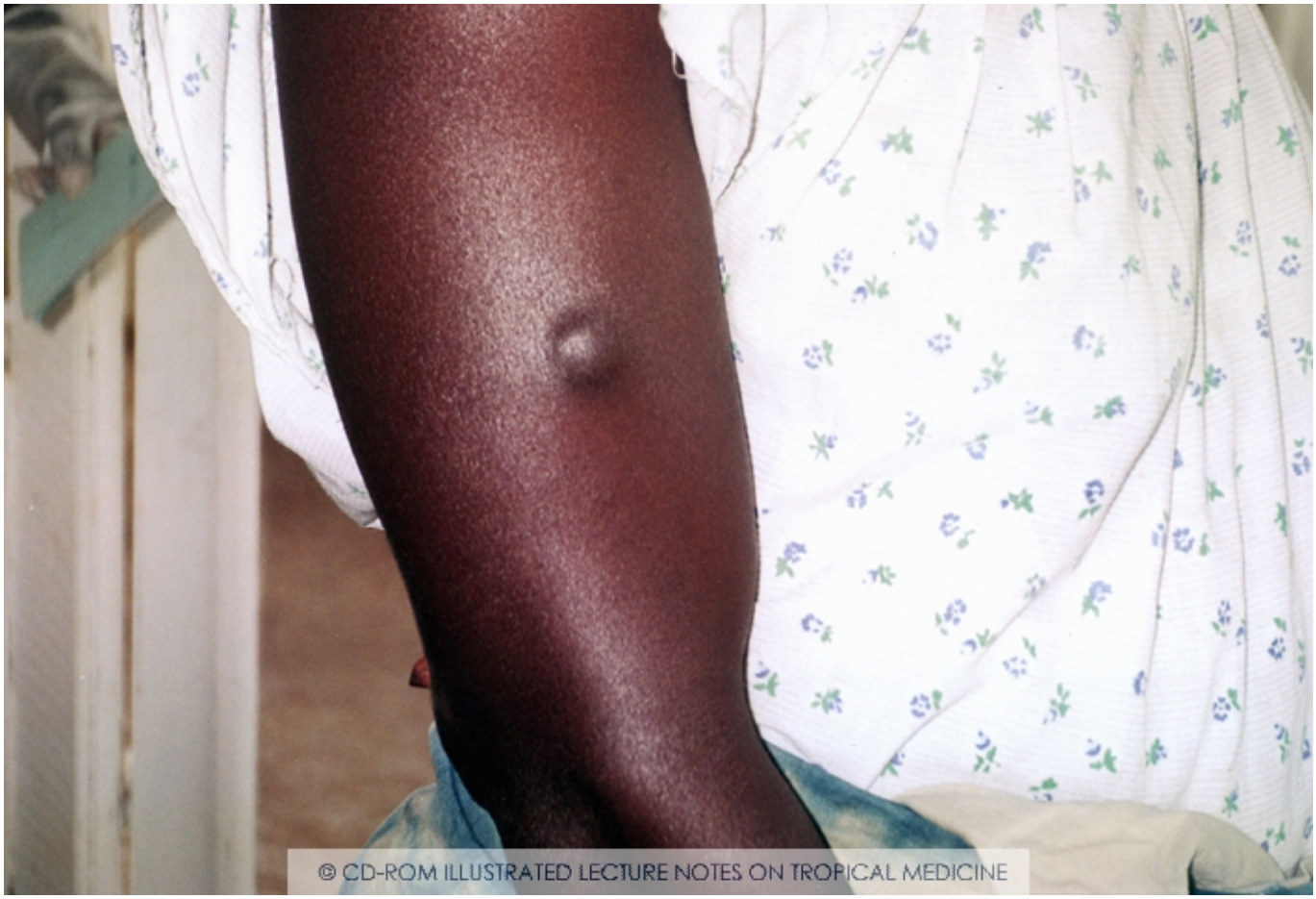
Buruli ulcer is caused by *Mycobacterium ulcerans*, an organism that is closely related to *M. tuberculosis*. These bacteria are acid-fast rods, 3-7 µm long. The generation time is 20 hours (slow-growing organism). The reservoir and the route of transmission remain unknown. Regular reference is made 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

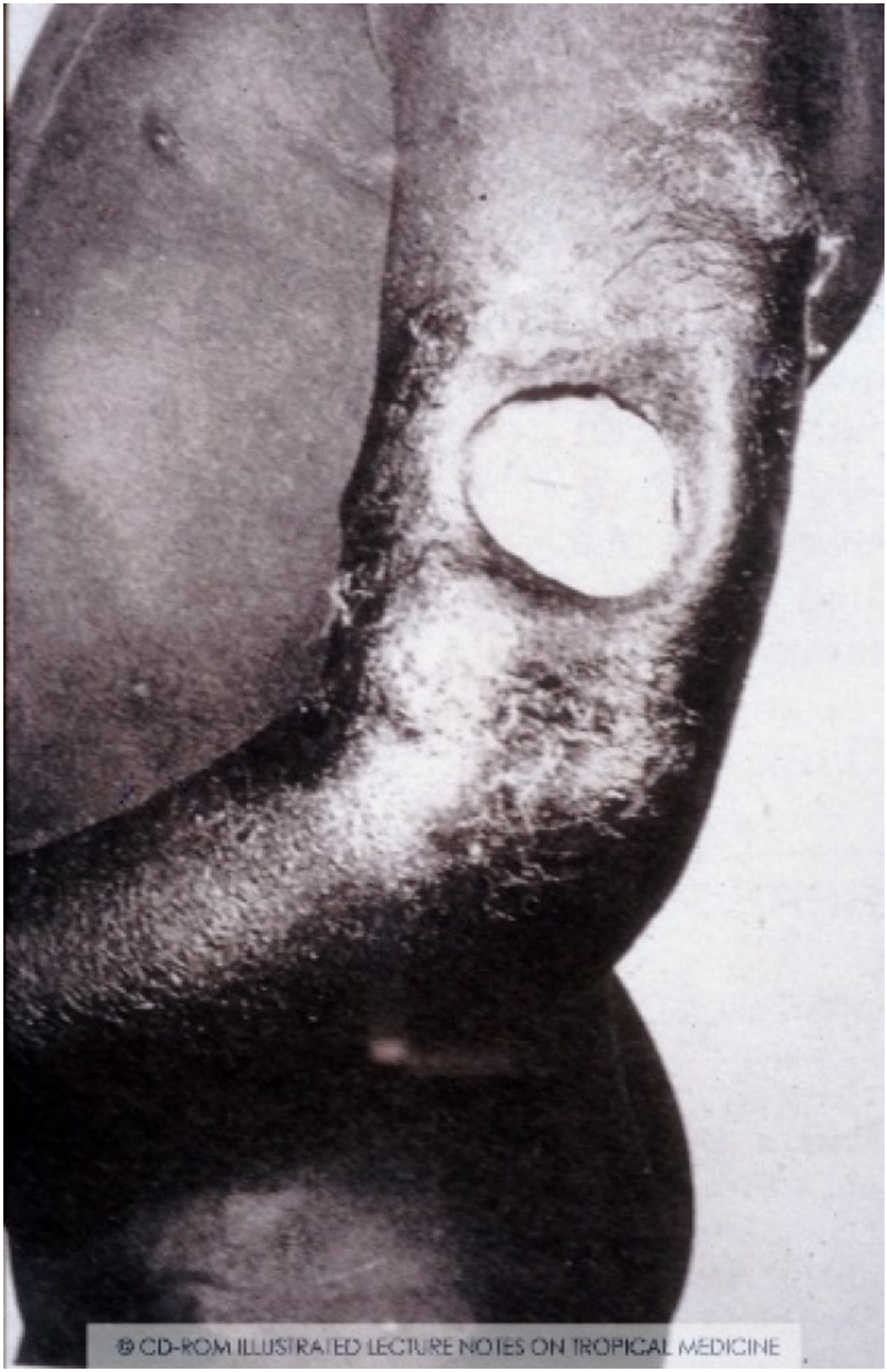
M. ulcerans is a mycobacterium that grows extracellularly in the human body. The earliest lesion is a necrotic zone in subcutaneous fatty tissue. There is typically surprisingly little inflammatory reaction in the surrounding tissues. Clumps of acid-fast bacilli are found in the necrotic fatty tissue (“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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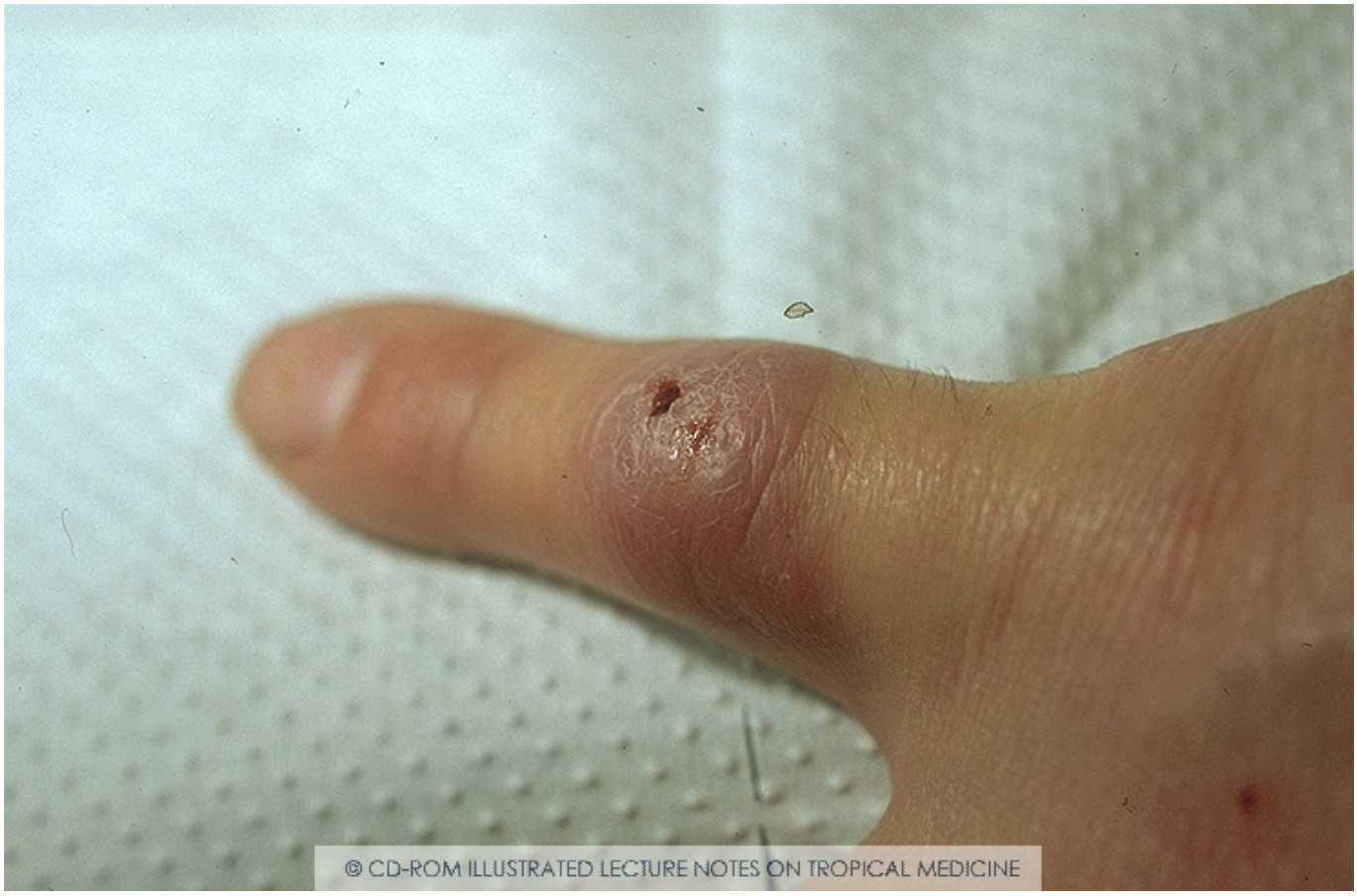
Mycobacterium marinum



Mycobacterium marinum, ulcer on finger. Copyright ITM

Mycobacterium marinum (*M. balnei*) causes swimming pool granuloma. The condition was first described in Sweden and was later observed in most Western countries. It involves papules with central ulceration which heal spontaneously after a few months with the formation of a small scar. Infection occurs during bathing by rubbing the skin against the rough cement lining of a swimming pool or aquarium or by touching tropical fish. For treatment, a combination of rifampicin (600 mg/day on an empty stomach) with minocycline or doxycycline (100-200 mg per day) is used, together with clarithromycin (500 mg twice daily), cotrimoxazole (twice 800/160) or ethambutol (max. 2.5 g/day).

The disease must not be confused with Erysipeloid (Rosenbach's disease), an infection caused by the Gram-positive bacterium *Erysipelothrix rhusiopathiae.* Infections with this organism also occur frequently in fishermen and people who handle crabs. Pig slaughterers represent another risk group. Cat scratch disease, leishmaniasis and sporotrichosis are to be considered in the differential diagnosis.

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Tropical ulcer

Summary

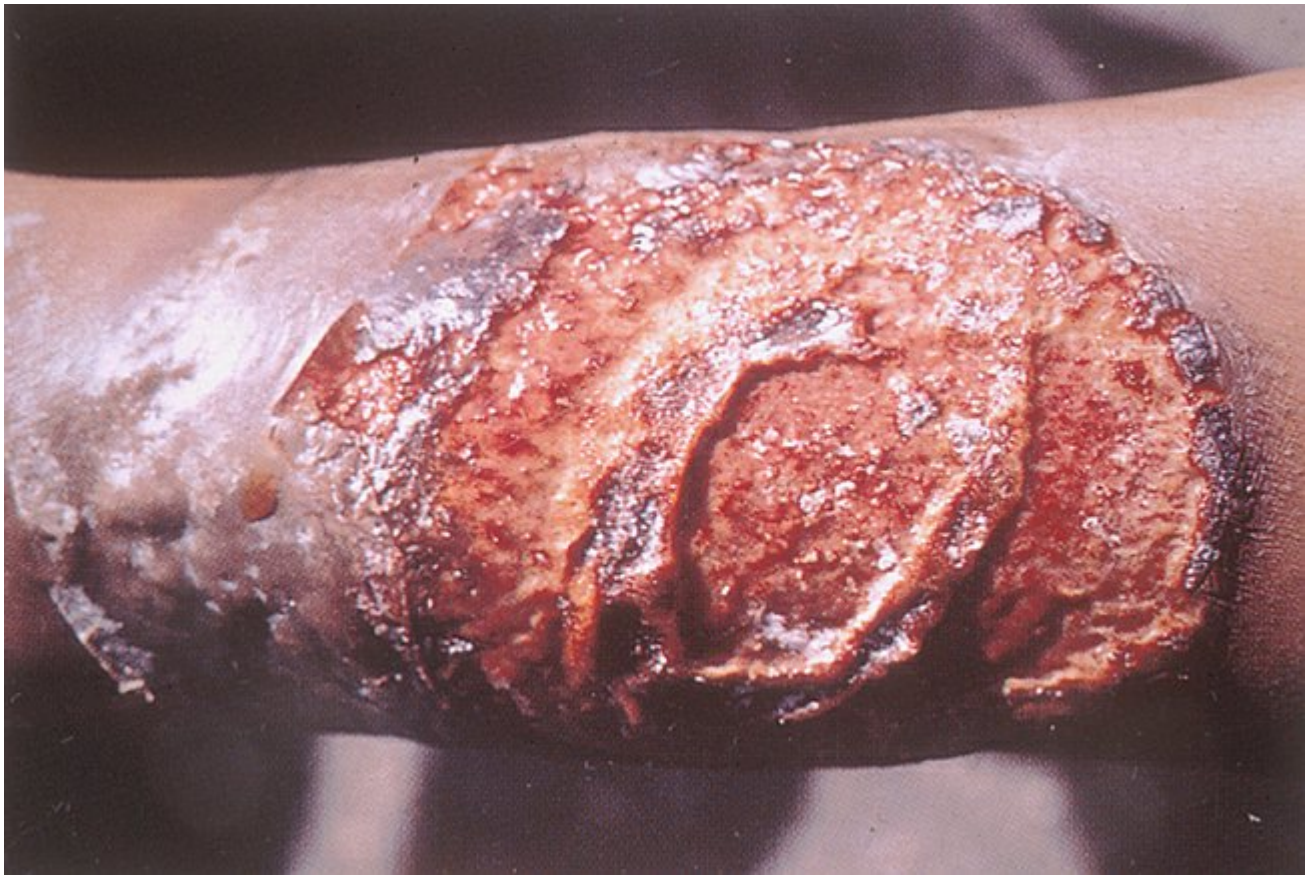
- Fusospirillary association (*Fusobacterium* + *Borrelia*)
- Initially very painful, subsequently painless ulcer on feet or lower leg
- Bad smell in early stage
- Very chronic course with frequent relapses
- Treatment with antibiotics, local care and skin grafts

Introduction

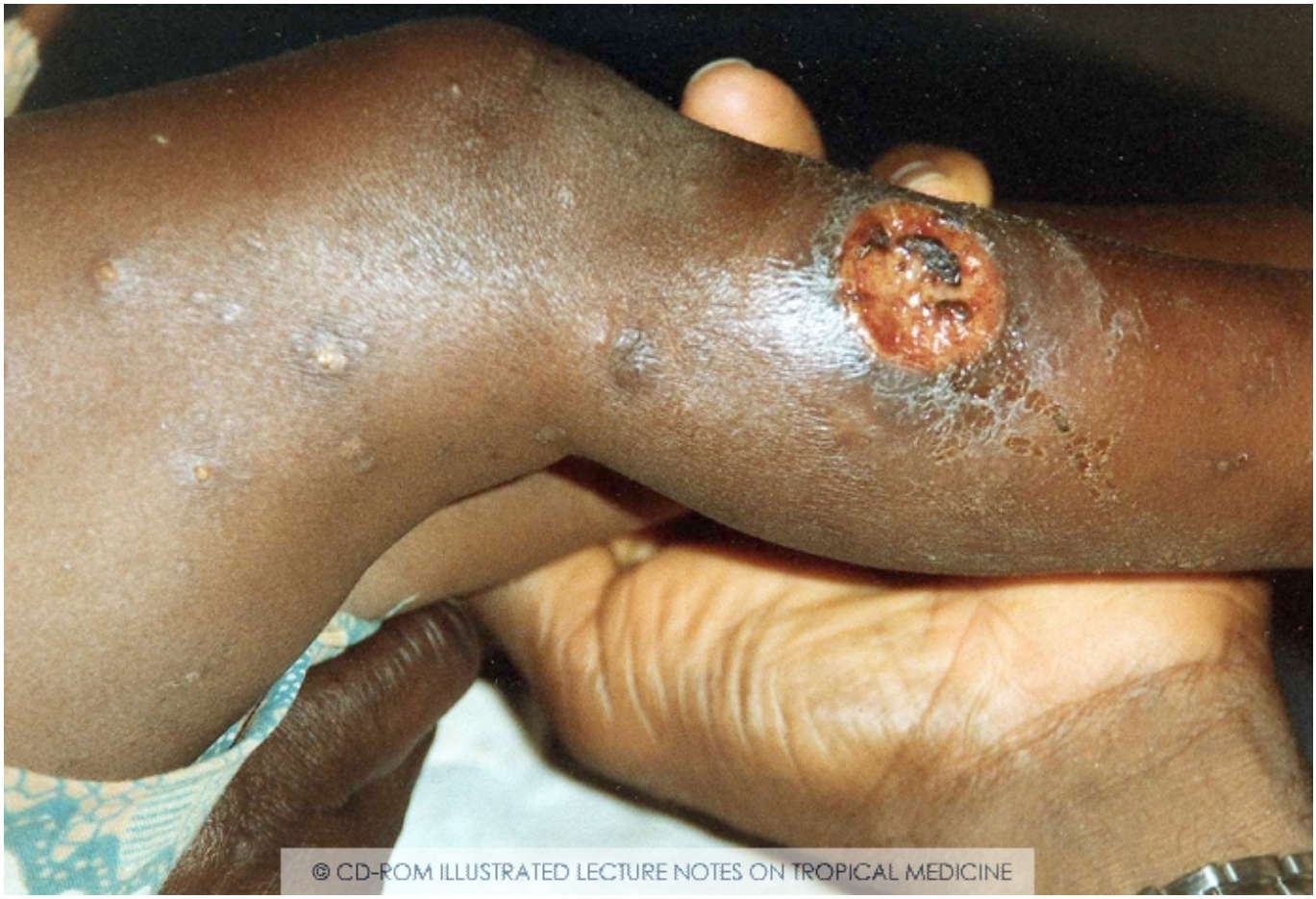
Tropical ulcer or phagedenic ulcer is a disease of warm and moist geographical regions. There is an association with poor living conditions: lack of clean water, lack of basic health services, carelessness in the treatment of small wounds, abundance of flies, etc. The role of malnutrition and lack of hygiene is clear. For example, in 1942-1945 the disease was extremely common and severe in Western prisoners of war in Japanese camps in Southeast Asia.

In early lesions, Vincent's fusospirillary bacterial association is usually detected: ***Fusobacterium fusiformis*** and ***Borrelia vincenti***. The same organisms are isolated from the mouth in a third of the patients, from which it is deduced that the cause of tropical ulcer might probably be transmitted to small wounds by saliva. In 1989, two new species of *Fusobacterium* were isolated from tropical ulcers but their exact role in the aetiology has not been determined. In more chronic cases the flora is non-specific. The histological presentation is non-specific. It is possible that tropical ulcer is initially caused by a trivial infection or secondary infection with streptococci or staphylococci in an undernourished person.

Clinical aspects



Tropical ulcers



Tropical ulcer.

Tropical ulcers

The primary localizations are on the lower leg, the front of the ankle and the dorsum of the foot. These are sites where the bone lies immediately beneath the skin and where the blood supply is less extensive. In this respect they resemble stasis ulcers in venous insufficiency. In tropical ulcer there are no signs of venous insufficiency. Ulcers occur less often on other parts of the body. Schematically, the disease progresses in three stages:

Acute stage: Local swelling of the skin, oedematous, violently painful and pruritic, sometimes with general symptoms such as fever. A blister with serous or bloody content forms and rapidly bursts. The small ulcer then extends both peripherally and inwards. The patient sometimes reports a recent minor trauma e.g a thorn prick or an insect bite at this site.

Subacute stage: On the ulcer, a superficially necrotic, evil-smelling, purulent, yellow-green or haemorrhagic black coating forms. The base is granular and bleeds easily. Deep in the ulcer the tendons, aponeuroses and periosteum can be seen. The edge of the ulcer is raised but with little if any undermining (in contrast to Buruli ulcers). After a few weeks, the ulcer's diameter is on average 10-12 cm. The form is or becomes regular, round or oval. Painful lymphadenitis may be present.

Chronic stage: After approximately one month, the swelling and pain decrease. The edge becomes flatter. The base is now coarsely granular, less haemorrhagic and forms less exudate, but the odour persists. Bacteriologically, the flora is now non-specific. Beneath the base of the ulcer there is reactional periostitis in chronic cases. The ulcer gradually heals spontaneously. The longer the disease course, the more difficult healing becomes and the more readily a relapse occurs, as the scar always consists of a small amount of connective tissue lined with fragile, smooth, shiny, often depigmented and atrophic skin. If the lifestyle is not changed, the ulcer flares up again at the first opportunity.

Complications are numerous:

Malformations and functional disorders. Scars with fibrosis of the deeper muscles and stiffness of the ankle joint cause all kinds of problems, of which the most common is retraction of the Achilles tendon with club feet of the equinovarus type.

Secondary infection can lead to tetanus, gas gangrene or cellulitis. Thrombosis of the large arteries can result in distal gangrene. Bleeding can occur as a result of erosion of blood vessels.

Osteomyelitis. There is often a limited cortical reactional osteitis. Extensive destruction of the bone under the ulcer is suggestive of cancer.

Carcinoma. Almost always involves spinocellular epithelioma of the skin with a starting point in the border of the ulcer ("Marjolin' ulcer"). Cancer occurs after a prolonged course, whether as the gradual degeneration of an active ulcer or in a scar after one or more recurrent episodes of the ulcer. The cancer then develops in the scar itself but also sometimes in the apparently healthy skin. The edges are partially or completely raised. The base is irregular and bleeds readily. There is induration and the ulcer becomes irregular. Spontaneous fractures and spontaneous complete amputation of the lower leg can occur. In 85% of cases the ipsilateral lymph nodes are enlarged, but only a third of these by metastases, the remainder as a result of lymphadenitis. Histological examination provides formal diagnosis. The biopsy site must be carefully chosen as not all the ulcer is necessarily degenerated. Metastases in the lymph nodes can also only be confirmed by biopsy.

Tropical ulcer, differential diagnosis

See differential diagnosis ‘Buruli Ulcer’

Prognosis and social importance

The importance of this rural disease is usually underestimated. Allowance must be made for the following factors:

- High prevalence, which is rapidly reduced as living conditions are improved: better nutrition, clean water, primary health care services, etc.
- Numerous health centre consultations for tropical ulcer. The disease takes up much of the personnel’s time for treatment, disinfection and bandages.
- Multiple and long-term admissions.
- Frequent relapse.
- Severe invalidity in many patients.
- High incidence of cancer formation, which is a potentially fatal complication. The risk of cancer formation in a poorly treated or untreated tropical ulcer is estimated at 10-15%.

Treatment

Acute cases

Local and systemic treatment with penicillin is indicated. The results are good if the ulcer is recent and its diameter is less than 2.5 cm. Some tropical ulcers heal in 2-3 weeks after administration of metronidazole for 7 days. Metronidazole is effective against anaerobic organisms.

Chronic ulcers

Antibiotics improve the case but do not heal the ulcer. Immobilisation and local treatment e.g. by bathing with Dakin’s solution (aqueous sodium hypochlorite solution) and parenteral antibiotics can result in healing after a few weeks. Effective treatment of a chronic tropical ulcer involves complete excision followed by skin transplants. This can be performed under either general or epidural anaesthesia. The ulcer is curetted until there is diffuse bleeding from the whole underlaying surface. The skin is cut away for up to 0.5 cm at the edges of the ulcer. The underlying bone is vigorously curetted in order to remove sequesters and irregularities and to obtain a flat area. Powder with sulphonamides or antibiotics is then sprinkled on the wound and a pressure bandage applied on top. If

the ulcer is next to a joint, this is immobilised with a plaster of Paris. At the same time antibiotics are administered parenterally. After one week the bandage is removed, the wound cleaned, and skin grafts applied. These are obtained with a dermatome from the heterolateral thigh.

In this way up to 90% of tropical ulcers can heal in less than 3 weeks and leave an acceptable scar.

Malignant degeneration

Treatment consists of conservative amputation with adaptation of the stump for a simple prosthesis. The inguinal lymph nodes are removed for histological examination. These tumours metastasise haematogenous and the prognosis is unfavourable.

Prevention

Peripheral health centres should provide proper wound care. It is important to promote:

- Decentralisation of primary health care services which can tend small wounds effectively: antiseptics, simple, clean, non-hermetic bandage, penicillin if necessary
- Proper diet with sufficient animal proteins
- Good water supply
- Health education
- Monitoring at the workplace of people with tropical ulcer scars or who suffer a deterioration in their nutritional or health status

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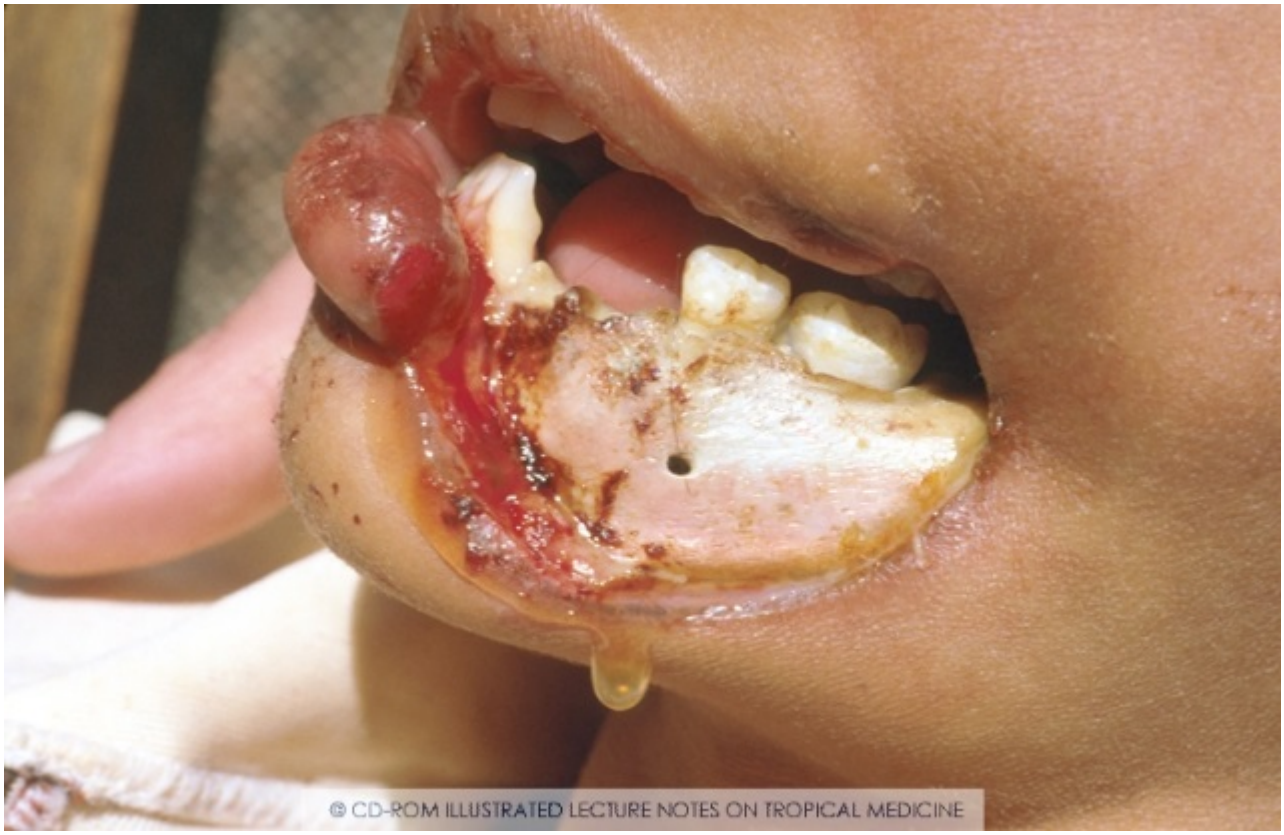
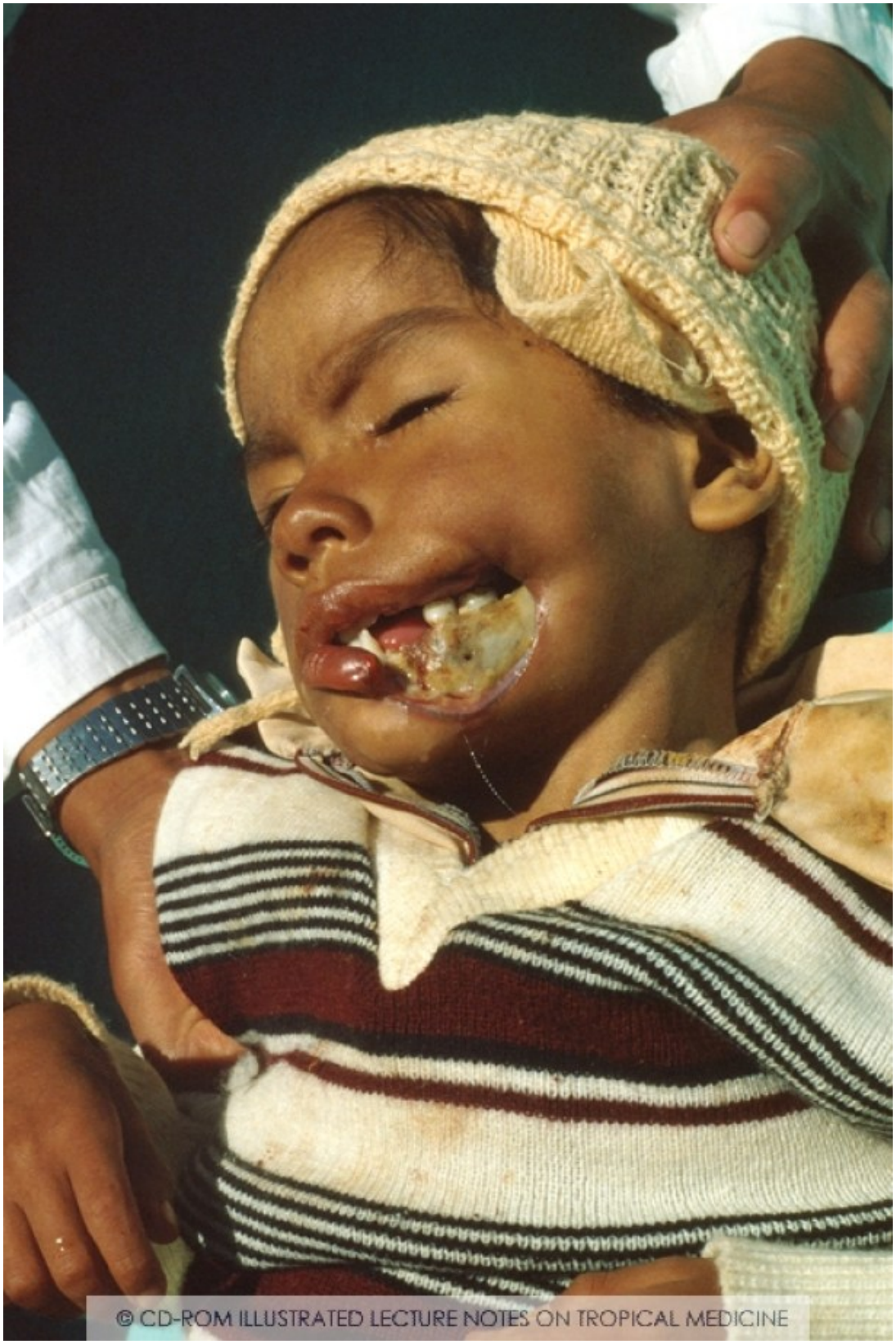
Noma

Noma (Gr. numein: to devour) or cancrum oris is a terrible gangrenous disease which leads to severe soft and hard tissue destruction in the face (mouth, teeth, lips, nose, cheeks) with lasting disfigurement. It is associated with a high mortality. The exact aetiology is not yet known, but it is thought that several factors contribute to this devastating illness. It is clearly a disease of poverty and social deprivation. Improvements in general socioeconomic status, public health and nutrition made that noma disappeared from all places except the most desperately poor and where severe malnutrition occurs. Several factors contribute, such as malnutrition with associated vitamin and trace element deficiencies, poor oral hygiene, a compromised immune status (malnutrition, measles, CMV

infection, blood dyscrasia such as leukaemia), a lesion of the gingival mucosal barrier, a (bacterial?) trigger and inappropriate initial treatment. They probably act together to cause noma. Bacteria such as spirochaetes, *Prevotella intermedia* and *Fusobacterium necrophorans* are suspected to play a role in the acute pathology. However, it should be remembered that at present, most bacteria in the mouth cannot be cultured in vitro. Although the disease existed in Europe and other parts of the globe, at present it is most common in Africa. The disease affects mostly children between 2-6 years but can occasionally appear in older children and even in debilitated adults (Auschwitz!). It is thought that the disease starts as an acute painful necrotising gingivitis (“trench mouth”), evolving to a necrotising stomatitis with ulceration and oedema of the cheek. The lesion tends to start at the alveolar margin in the premolar-molar region. It spreads very fast (1-2 days). Within a couple of days, a greyish area appears on the cheek. This becomes black and necrotic and has well defined margins. There is an offensive odour. The necrotic zone penetrates the cheek and has a typical cone shape (“cône gangréneux”). After the necrotic tissue has sloughed away, bone is exposed. Large bone sequesters may form, sometimes with destruction of maxilla and/or mandibule. It should be distinguished from pyogenic abscesses and Burkitt’s lymphoma. Secondary infection occurs rapidly, as can be expected. Fever occurs in some patients. Many patients die due to starvation, septicaemia, or aspiration pneumonia. Because of the high mortality in acute noma and the fact that it occurs in the poorest among us in areas with inadequate reporting, the burden of disease is difficult to determine for epidemiologists.



Noma, cancrum oris. Photo Cochabamba, Bolivia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Noma, cancrum oris. Face ulcer. Photo Cochabamba

The tissue defects are classified in 4 types:

- Type I is the most common and consists of a localised cheek and commissural defect. It can be bilateral.
- Type II includes the upper lip, and in some cases the nose and the palate.
- Type III is located on the lower lip ± the mandible and floor of the mouth.
- Type IV consists of major defects of the whole cheek, lips, palate, maxilla and can extend up to the orbit, eyelids and nose.

Treatment in the acute phase encompasses proper oral hygiene, mouth rinses with chlorhexidine, antibiotics including penicillin and metronidazole against anaerobic bacteria, proper nutrition and vitamin/trace element supplements and treatment of any underlying medical conditions. The healing is characterized by ugly scars with fibrous tissue which tends to provoke strictures. After the acute phase, physiotherapy should be initiated to limit the strictures, fibrous scarring, trismus and to avoid bony ankylosis (bridging) between upper and lower jaw. Bundles of wooden spatulae in the mouth or more sophisticated devices (e.g. the Therabite) are used. At least a year after the initial disease, reconstructive craniomaxillofacial surgery for the sequelae can be considered. This should be done by experienced teams including specialised surgeons and anaesthesiologists (tracheostomies, fiberoptic intranasal intubation). Each case will require an individual approach.

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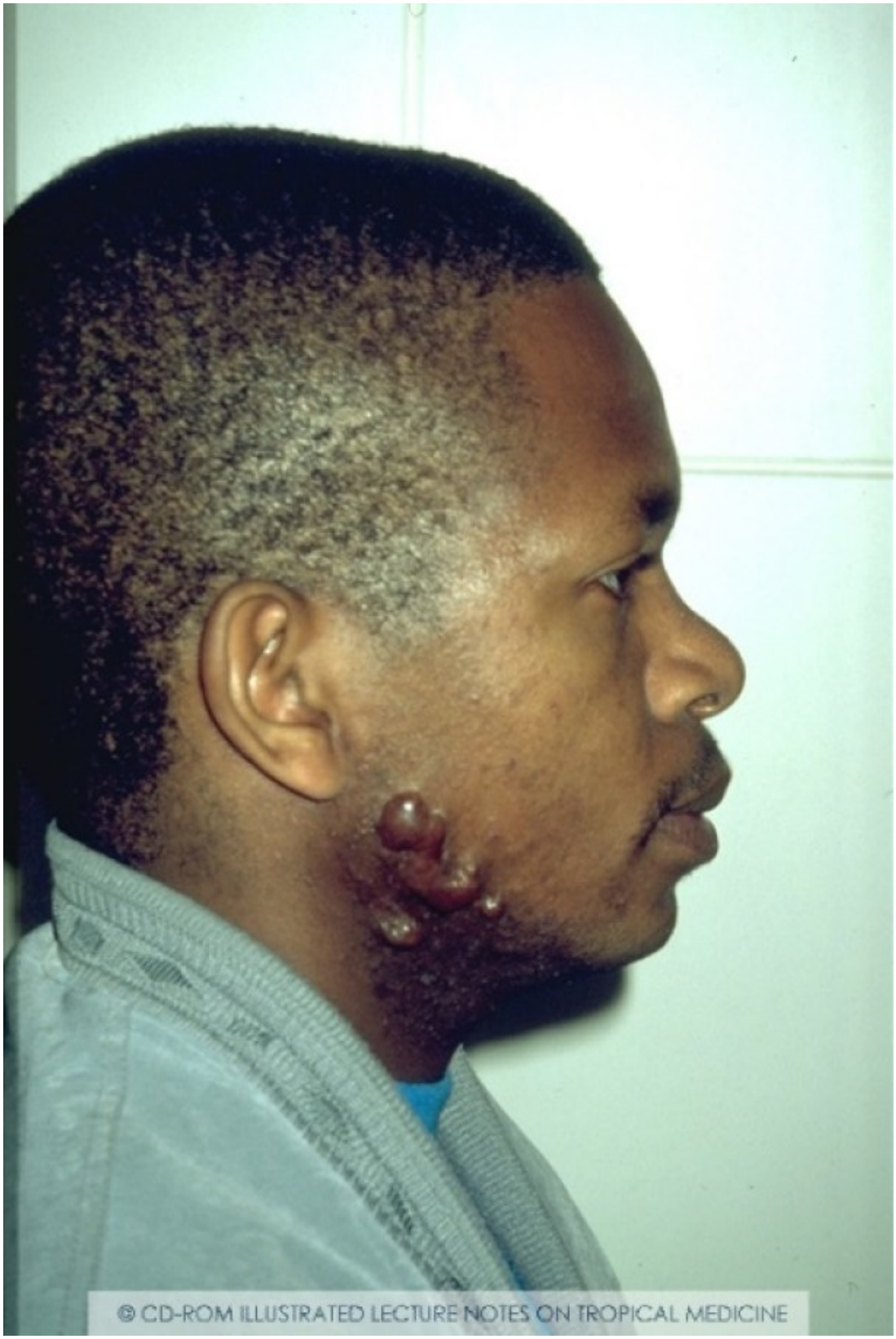
Keloids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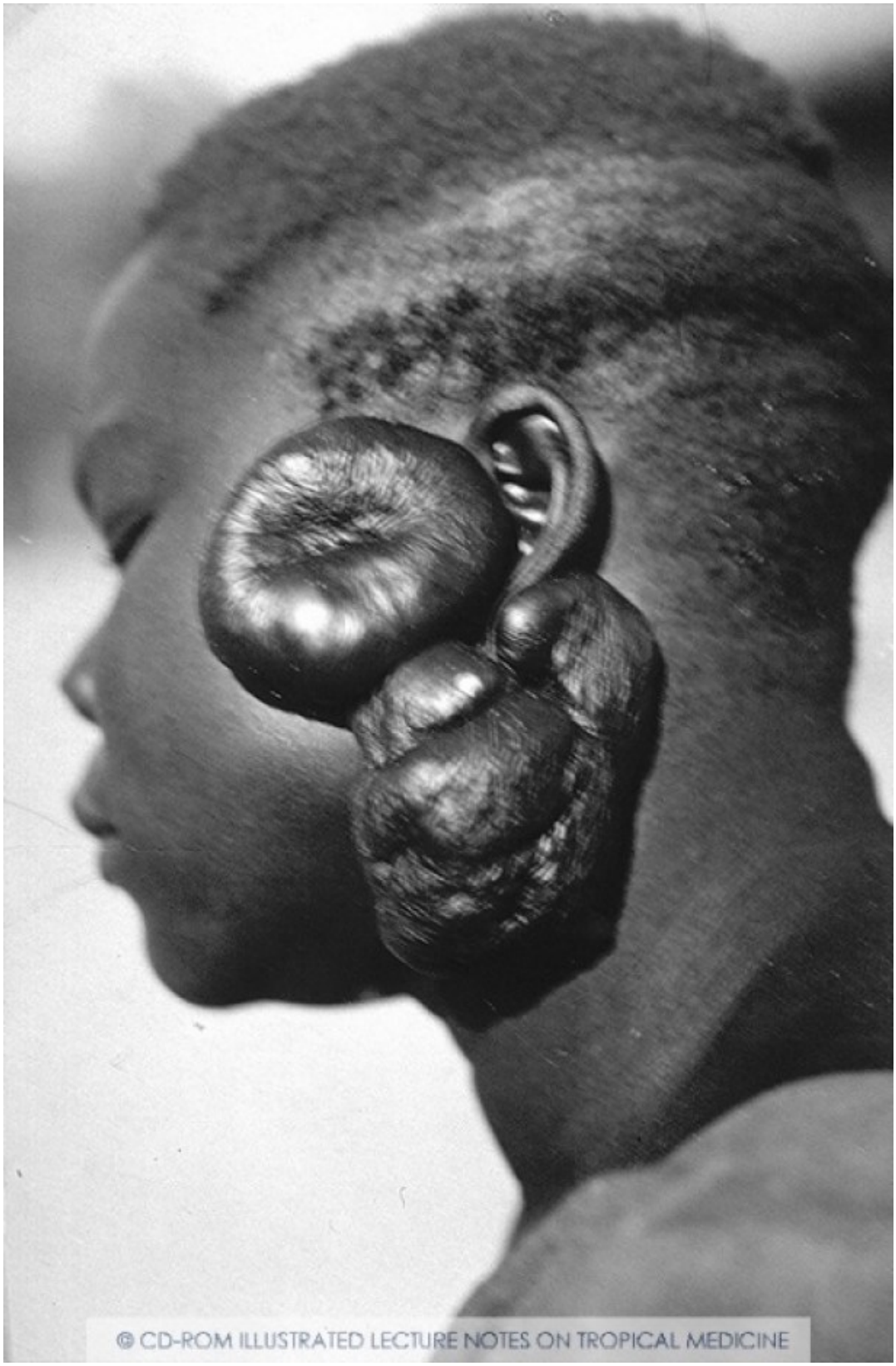
Keloids on the face, shaven area (microtraumata). Copyright ITM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Keloid of the ears, as reaction to perforations for aesthetic reasons. Copyright ITM

Keloids are nodular, often lobulated, firm to hard but movable, non-encapsulated masses of hyperplastic scar tissue. It is a result of an overgrowth of granulation tissue (collagen type 3, early) at the site of a healed skin injury which is then slowly replaced by collagen type 1 (late). The pathogenesis is complex and involves both genetic and environmental factors and the exact mechanism is still unknown. Growth factors like VEGF, TGF-β1, TGF, β2, CTGF and PDGF-α play are overexpressed, but it remains unclear if this is the cause or the consequence of the excessive scarring. Keloids can closely resemble lobomycosis but can also be confused with lepromata and less likely with lesions of diffuse cutaneous leishmaniasis. Africans are particularly susceptible to keloids. The tribal scar pattern following scarification is based on this property. Keloids occur in all types of conditions, for example after burns, cauterisation, vaccinations, on in-growing beard hair, folliculitis or even spontaneously. Keloids are raised and sharply delineated. The overlying skin is reddish and shiny. The lesion can be itchy or painless and the dimensions can be unexpectedly large. Keloids can develop later, up to years after the initial trauma. Treatment is difficult. Treatment options include resection, cryotherapy, intralaesional corticosteroids, 5-fluorouracil or bleomycin. Complete excision is followed by recurrence in 70% of cases. Excision within the edges of the lesion is recommended but the result is aesthetically unsatisfactory. Corticosteroids have no effect on the fixed lesions, but can prevent their recurrence by injections localised around the site of the original lesion if started 3 weeks after surgery and repeated weekly for the following 8-12 weeks. Bigger and horizontally growing keloids are more likely to recur after treatment.

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Diphtheria

Summary

- Caused by the gram-positive bacillus *Corynebacterium diphtheriae*
- Infection leads to respiratory or cutaneous disease or an asymptomatic carrier state
- The pseudomembranes in combination with neck swelling can cause life threatening croup
- Diagnosis in most low-resource settings is clinical
- Treatment with erythromycin or penicillin
- Antitoxin and airway protection in severe cases
- Worldwide vaccination lead to a significant decrease in diphtheria cases

General

Diphtheria is an infectious diseases caused by the gram-positive bacillus *Corynebacterium diphtheriae.* Symptoms range from mild to severe. Whereas in the 1980s about 100,000 cases were reported worldwide, in 2015 this number had dropped to 4,500 cases with >80 percent vaccination rates worldwide. Regions mostly affected are sub-Saharan Africa, the Indian subcontinent and Indonesia where mostly children are affected. In 2015, 2,100 deaths were reported, down from 8,000 in 1990. The disease has become rare in high-income countries thanks to widespread vaccination but re-emergence is a threat when vaccination rates decrease. Diphtheria death rate in those diagnosed varies from 5% to 10%.

There are four types of *C. diphtheria: gravis, intermedius, mitis* and *belfanti*. All four can cause Diphtheria, although mitis strains cause less severe disease. Symptoms are caused by bacterium's toxin. In rare occasions toxigenic strains of other *Corynebacterium* species (*C. ulcerans, C. haemolyticum, C. pseudotuberculosis*) evoke respiratory symptoms.

The name comes from the Greek word "diphthera" which means "leather" referring to the appearance of the pseudomembrane in the throat.

**History of Diphtheria (Source: Wikipedia, https://en.wikipedia.org/wiki/Diphtheria*)*

The disease was first described in the 5th century BC by Hippocrates
In 1613, Spain experienced an epidemic of diphtheria. The year is known as El Año de los Garrotillos (The Year of Strangulations) in the history of Spain.
Before 1826, diphtheria was known by different names across the world. In England, it was known as Boulogne sore throat, as it spread from France. In 1826, Pierre Bretonneau gave the disease the name diphthérite (from Greek diphthera "leather") describing the appearance of pseudomembrane in the throat.

In 1878, Queen Victoria's daughter Princess Alice and her family became infected with diphtheria, causing two deaths, Princess Marie of Hesse and by Rhine and Princess Alice herself.
In 1883, Edwin Klebs identified the bacterium causing diphtheriahttps://en.wikipedia.org/wiki/Diphtheria – cite_note-34 and named it Klebs-Loeffler bacterium. The club shape of this bacterium helped Edwin to differentiate it from other bacteria. Over the period of time, it was called Microsporon diphtheriticum, Bacillus diphtheriae, and Mycobacterium diphtheriae. Current nomenclature is Corynebacterium diphtheriae.

Friedrich Loeffler was the first person to cultivate C. diphtheriae in 1884. He used Koch's postulates to prove association between C. diphtheriae and diphtheria. He also showed that the bacillus produces an exotoxin.
Joseph P. O'Dwyer introduced the O'Dwyer tube for laryngeal intubation in patients with an obstructed larynx in 1885. It soon replaced tracheostomy as the emergency diphtheric intubation method.
In 1888, Emile Roux and Alexandre Yersin showed that a substance produced by C. diphtheriae caused symptoms of diphtheria in animals.
In 1890, Shibasaburo Kitasato and Emil von Behring immunized guinea pigs with heat-treated diphtheria toxin. They also immunized goats and horses in the same way and showed that an "antitoxin" made from serum of immunized animals could cure the disease in non-immunized animals. Behring used this antitoxin (now known to consist of antibodies that neutralize the toxin produced by C. diphtheriae) for human trials in 1891, but they were unsuccessful. Successful treatment of human patients with horse-derived antitoxin began in 1894, after production and quantification of antitoxin had been optimized. Von Behring won the first Nobel Prize in medicine in 1901 for his work on diphtheria.
In 1895, H. K. Mulford Company of Philadelphia started production and testing of diphtheria antitoxin in the United States Park and Biggs described the method for producing serum from horses for use in diphtheria treatment.
In 1897, Paul Ehrlich developed a standardized unit of measure for diphtheria antitoxin. This was the first ever standardization of a biological product, and played an important role in future developmental work on sera and vaccines.
In 1901, 10 of 11 inoculated St. Louis children died from contaminated diphtheria antitoxin. The horse from which the antitoxin was derived died of tetanus. This incident, coupled with a tetanus outbreak in Camden, New Jersey, played an important part in initiating federal regulation of biologic products.
In the 1920s, each year an estimated 100,000 to 200,000 diphtheria cases and 13,000 to 15,000 deaths occurred in the United States. Children represented a large majority of these cases and fatalities. One of the most infamous outbreaks of diphtheria was in Nome, Alaska; the "Great Race of Mercy" to deliver diphtheria antitoxin is now celebrated by the Iditarod Trail Sled Dog Race.
In 1926, Alexander Thomas Glenny increased the effectiveness of diphtheria toxoid (a modified version of the toxin used for vaccination) by treating it with aluminium salts. Vaccination with toxoid was not widely used until the early 1930s.
In 1943, diphtheria outbreaks accompanied war and disruption in Europe. The 1 million cases in Europe resulted in 50,000 deaths.
In 1974, the World Health Organization included DPT vaccine in their Expanded Programme on Immunization for developing countries

About a million cases a year are believed to have occurred before the 1980s

Transmission

Diphtheria is airborne and spreads between people by coughing and sneezing. In rare occasions, direct contact with diphtheria skin lesions can transmit the bacteria. Indirect transmission is possible when an infected person touches an object on which the bacteria can remain viable. Asymptomatic carriers exist and they can still spread the infection to others. Immunity from past infection or vaccination does not prevent carriage of the bacterium.

Diphteria toxin

C. diphtheria produces and exotoxin when it is infected with a bacteriophage that integrates the toxin-encoding gene (*tox*+) into the bacteria. Diphtheria toxin is composed of two peptide chains: fragment A and fragment B. Fragment B facilitates toxin entry into host cells by binding the heparin-binding EGF-like growth factor on the cell membrane. Once inside the cell's endosome, a trypsin-like protease splits the toxin in the A and B fragments. The low pH in the endosome causes fragment B to create pores in the endosome membrane through which fragment A can enters the cytoplasm. Fragment A catalyses ADP-ribosylation of elongation factor EF-2, a protein that moves tRNA from the A-site to the P-site of the ribosome during the translation step in protein synthesis. The final result is a disturbed protein synthesis leading to cell death.

Clinical aspects

The incubation period is usually two to five days and the disease starts with a gradual onset of sore throat with pharyngeal erythema and fever. In more severe cases diphtheria destroys the respiratory tract tissues with dead tissues forming a thick, grey, friable and tightly adhering coating in the throat. This is called a pseudomembrane which is composed of necrotic fibrin, white- and red blood cells, epithelial cells and bacteria. The pseudomembrane may expand from the nose to the tonsils, the throat up to the bronchial tree. This can lead to dysphagia and can obstruct the airways provoking hoarseness, stridor and sometimes suffocation when membranes are aspirated. This can be exacerbated with extreme neck swelling ("bull neck") due to enlarged lymph nodes causing external pressure on the airways. This clinical picture is referred to as "diphtheritic croup" or "true croup" (= laryngotracheobronchitis caused by diphtheria). Children who have smaller airways are more vulnerable to the complications of diphtheritic croup. Nowadays, croup is mostly related to viral infections causing milder respiratory symptoms.

Diphtheria can be complicated by myocarditis (in two-thirds of severe cases) and nerve inflammation (in up to 75 percent of severe diphtheria). Paralysis of the soft palate and posterior pharyngeal wall can occur, as well as cranial nerve paralysis. Cardiac and neurological symptoms often arise from the moment respiratory symptoms are improving. A peripheral polyneuropathy can develop weeks or months after the acute illness.

Cutaneous diphtheria presents as chronic, non-healing ulcers with a grey membrane. The infection is often preceded by local trauma. Epidemics of cutaneous diphtheria have occurred in populations living in poor hygienic conditions. The ulcers can serve as a reservoir from which the infection spreads to others.

Diagnosis

Diagnosis is often made considering the setting and clinical manifestations in a non-vaccinated person. Positive cultures confirm the diagnosis, but the need for special culture media (Loffler's or Tindale's media), the need for appropriate transport media and the necessity of quick inoculation, make the confirmation challenging, even in high-resource settings. Toxin detection with PCR is possible and confirms that the strain is toxicogenic.

A probable case is a clinically compatible case that is not laboratory-confirmed nor epidemiologically linked to a confirmed case. A confirmed case is a clinically compatible case that is laboratory confirmed or epidemiologically linked to a laboratory-confirmed case. It is important that the antitoxin and antibiotics are administered prior to confirmation when diphtheritic croup is suspected. Cases of diphtheria should be reported to the World Health Organization (WHO).

Differential diagnosis

Several diseases can give a clinical picture that can resemble pharyngitis with pseudomembranes: infectious mononucleosis, group A streptococcal tonsillopharyngitis, epiglottitis, viral pharyngitis, Vincent's angina (= acute necrotizing ulcerative gingivitis), oral candidiasis, pertussis (100-day cough).

Treatment

When diphtheria is suspected, prompt initiation of antibiotics is needed since severe untreated diphtheria has a mortality rate of 40% to 50%. Erythromycin (500 mg 4 times daily, 14 days) and penicillin G (300,000 IU IM daily for patients < 10 kg and 600,000 IM IU daily for patients > 10 kg) followed by penicillin V (250 mg 4 times daily, oral) for a total of 14 days are the antibiotics of choice.

In severe diphtheria with pseudomembranes or cardiac involvement, diphtheria antitoxin is indicated. These antibodies are produced in horses that have been challenged with diphtheria toxin. The antitoxin does not neutralize toxin that is already bound to tissues, hence a delay in administration increases mortality rates. In about 10 percent of patients receiving antitoxin hypersensitivity or serum sickness arises.
In case of (threatening) respiratory failure airway protection with intubation is necessary. This procedure can be difficult if there is extensive throat oedema and mucosal friability. There is a risk of dislodging the pseudomembranes into the bronchi. In rare occasions a tracheotomy is needed. After recovery, vaccination is still needed since pharyngeal infections do not protect against future infections. Skin infections are an exception since they evoke a strong antibody response.

Prevention

An effective vaccine exists with different available formulations. In childhood, three or four doses are given along with tetanus and pertussis in a penta-, sexta- or heptavalent vaccine. A booster vaccination, together with tetanus, is recommended every ten years.

Close contacts can be given prophylaxis with a single dose of penicillin G benzathine (1.200.000 IU IM) or oral erythromycin 500 mg 4 times daily for 1 week.

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