Differential Diagnosis of Buruli Ulcer

43

William R. Faber, Ghislain E. Sopoh, and Jim E. Zeegelaar

43.1 Introduction

Several studies have highlighted the fact that the clinical diagnosis of Buruli ulcer (BU) by health professionals is not as simple as one usually thinks, even in endemic countries [1–3]. Kibadi et al. (2010) found that 34% of patients in the Democratic Republic of Congo completing the clinical and epidemiological criteria of BU, as defined by WHO, could not be confirmed by microbiological examinations [4]. Siegmund et al. (2007) showed that even with the most sensitive tests, 22% of suspected cases of BU could not be confirmed [5]. Indeed, each of the clinical forms of BU can be confused with many other conditions. The differential diagnosis of BU depends on the stage of presentation of the disease and the pathologies existing in the area where the patient lives.

Although the disease is named "Buruli ulcer," clinical manifestations without ulceration also exist, and for each of these manifestations, there is a differential diagnosis.

The following clinical forms can be distinguished:

1. Papules
2. Nodules
3. Plaques

W. R. Faber (✉)
Amsterdam UMC, Department of Dermatology, Amsterdam, The Netherlands
e-mail: w.r.faber@amsterdamumc.nl; faber.aalders@hccnet.nl

G. E. Sopoh
Institut régional de santé publique, University of Abomey-Calavi, Ouidah, Benin
e-mail: gsopoh@irsp-ouidah.org

J. E. Zeegelaar
Flevoziekenhuis, Department of Dermatology, Almere, The Netherlands
e-mail: JEZeegelaar@Flevoziekenhuis.nl

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4. Inflammatory edema
5. Ulcers
   (a) Infectious
   (b) Noninfectious
6. Scars
7. Other BU forms
   (a) Mixed forms
   (b) Disseminated or multifocal forms
   (c) Paradoxical reaction

Osseous lesions are described under edematous lesions as they are frequently associated with edemas.

Most differential diagnoses are of infectious origin [3].

For most of the infectious conditions described in this chapter, laboratory tests are available to confirm them. Histopathological investigation may be important for the confirmation of some diseases such as subcutaneous mycoses. These tests are not included in this chapter.

It is important to know if a disease is geographically restricted or has a global prevalence. The differential diagnosis is therefore also dependent on the geographical area as a number of conditions covered in this chapter are geographically restricted.

43.2 Papules and Nodules

These two conditions are described together as their only distinction is the difference in size, a nodule being bigger than a papule.

Definition of a papule: circumscribed solid elevation of the skin <1 cm, heals without scar formation.

Definition of a nodule: firm and painless swelling under or elevated above the skin of about 3 cm maximum in diameter.

43.2.1 Cutaneous Leishmaniasis (CL)

CL is caused by protozoan parasites belonging to the genus *Leishmania*, which is divided into two subgenera, *L.* (*Viannia*) spp. and *L.* (*Leishmania*) spp.

In the Americas, CL is caused by at least eight different species, primarily of the *L.* (*V.*) *braziliensis* and *L.* (*L.*) *mexicana* complexes. Afro-Eurasia CL is caused by four species: *L. major*, *L. tropica*, *L. aethiopica*, and *L. infantum*. The parasites are transmitted to humans via the bite of the female phlebotomine sandfly which has fed on an infected mammal.

The disease occurs throughout the tropical and the subtropical regions. In the past decades, there is a definite increase in the incidence of CL. This is because of factors such as rural to urban migration, development of new agro-industrial

projects, re-locating non-immune communities in endemic areas, movement of army troops into endemic regions and the termination of insecticide spraying, and possibly also climate change. HIV infection does not seem to increase the risk of CL infection, but may influence treatment response.

It is estimated that 1–1.5 million cases of CL occur annually.

The clinical picture of CL varies with the endemic region and depends on the species involved, the immune status of the host, genetics, and probably the transmitting sandfly. The typical lesion is a painless ulcer although it starts with a circumscribed swelling which increases in size before ulceration occurs. They are generally localized on exposed body parts as they are the consequence of a bite of the sandfly [6].

43.2.2 Mycobacterial Infections

Infection with *M. tuberculosis* and a variety of so-called atypical mycobacteria may present skin manifestations.

43.2.2.1 Cutaneous Tuberculosis

Cutaneous tuberculosis is still endemic in some tropical countries. Several presentations of infection with *M. tuberculosis* may start with papules and nodules [7].

- Primary Infection

Primary infection accounts for only 2% of all cases of cutaneous tuberculosis. It is caused by exogenous inoculation of *M. tuberculosis* in the skin of a non-sensitized person. The lesion starts 2–4 weeks after inoculation as a smooth papule or nodule. After 3–8 weeks, non-tender regional lymphadenopathy develops, which may suppurate to form a "cold" abscess, which then may spontaneously drain with sinus tract formation. This process in general heals spontaneously with atrophic scarring in 3–12 months. Primary lesions are mainly located on the face and the extremities in children, but inoculation by injections and surgical procedures is also possible.

- Scrofuloderma

It is due to contiguous spread from a deeper localized infection such as lymph node or in some cases bone. Initially there is an indurated inflammatory area overlying the deeper infection. Due to suppuration, fluctuating nodules develop. In the course of time, cord-like scars or keloids develop. The lesions are mostly localized over the lymph glands in the neck.

- Lupus Vulgaris

It is caused by reactivation of the disease in patients with a high degree of cell-mediated immunity after earlier hematogenic dissemination. The lesions start as

brown-red papules. The most common location is the face; lesions on the legs and the buttocks are common in Asia and Africa.

- Tuberculous Gumma

Tuberculous gumma or metastatic tuberculous ulcer is caused by hematogenic dissemination from a primary focus during periods of lowered resistance. The lesion starts as a subcutaneous nodule or a fluctuant swelling.

A high index of suspicion is warranted because the clinical picture of mycobacterial infection of the skin can be non-specific. Investigation for mycobacteria is indicated in cases of persistent infiltrative lesions or non-healing ulcers.

43.2.2.2 *M. marinum* Infection (So-Called Swimming Pool Granuloma)

As initial reports of cutaneous disease by *M. marinum* were associated with swimming pools, it was called swimming pool granuloma. Infection in swimming pools nowadays is rare due to proper chlorination. The distribution is worldwide, occurring in fresh-brackish as well as salt water, and is prevalent in heated water (for instance, in tropical aquaria) in temperate climates and in pools and the sea in more tropical climates. In principle any water-related activity carries a potential risk for infection. Infection takes place through, in general superficially, traumatized skin.

As infection is preceded by trauma, majority of the lesions are located on the back of the fingers or the hand or around the knee. The initial lesions start as an inflammatory papule after a relatively long incubation period of 2–6 weeks. The papule then gradually enlarges into a bluish-red inflammatory nodule or plaque. There is generally a delay of months to even years before a doctor's opinion is sought because the lesions are painless and enlarge slowly. The lesions may heal spontaneously; this may take months to years. Less often deep infections such as tenosynovitis, osteomyelitis, arthritis, and bursitis occur. *M. marinum* infections are one of the causes of nodular lymphangitis (also called sporotrichoid extensions after the lymphatic spread of sporotrichosis). Clinically, there are nodules and/or ulcerating lesions resulting from spread along the lymphatic vessels. Deep infections and nodular lymphangitis do not heal spontaneously [8].

43.2.2.3 Other Mycobacteria

Other mycobacteria responsible for most cutaneous diseases are *M. fortuitum*, *M. chelonae*, *M. abscessus*, and *M. avium-intracellulare* which also may present with papules and nodules.

43.2.3 Leprosy

It has a variety of clinical presentations depending on the degree of cell-mediated immunity (CMI) of the host to infection with *M. leprae*. On the lepromatous part of the leprosy spectrum, ranging from mid-borderline to lepromatous leprosy, nodular

lesions can be seen. The number of lesions increases and the distribution becomes more widespread toward the lepromatous pole of the spectrum corresponding with the decrease in CMI.

During the type I or reversal reaction, increased inflammation leads to erythematous swelling of the lesions. As leprosy also affects peripheral nerves, this reaction is mostly accompanied by an acute neuritis with painful swelling of the involved nerves. In case of type II reaction or erythema nodosum leprosum, crops of painful erythematous nodules arise on normal-looking skin of especially the extremities and the face.

43.2.4 Non-venereal Endemic Treponematoses (Yaws, Pinta)

These diseases are widespread in many regions of the world, and millions of people, especially children, are at risk. They share evident cutaneous clinical manifestations and a chronic relapsing course. Yaws may nowadays present an atypical form or a milder, "attenuated" form in some regions, with less florid skin lesions, especially in areas with a low prevalence.

A serological test for treponemal and/or non-treponemal antibodies is required to make a definite diagnosis. There is no difference in this respect between the different non-venereal treponematoses.

43.2.4.1 Yaws

Yaws primarily affects children aged under 15 years who live in poor communities with poor hygienic conditions, warm, humid, and tropical forested areas of Africa, Asia, Latin America, and the Pacific islands in remote, often inaccessible, areas. It is spread by skin-to-skin contact.

After an incubation period of 9–90 days, the first (early stage) lesion, so-called mother yaw, appears. These primary lesions are mostly localized on legs, feet, and buttocks. Typically, it is a lesion with a papillomatous surface. Sometimes multiple primary lesions are present. They heal spontaneously in the course of 2–6 months. After or during spontaneous disappearance of initial lesions, relapses of more disseminated lesions can occur, which may be preceded or accompanied by fever, malaise, headache, and generalized lymphadenopathy. These early (secondary)-stage skin lesions often resemble the "mother yaw."

Tertiary lesions can present as nodular, nodulo-ulcerative, and gummas. Severe destruction of skin, bone, and joints can occur.

43.2.4.2 Pinta

Pinta is still prevalent in tropical Central and South America in remote rural regions.

In the early stage, a papule or an erythemato-squamous plaque occurs that is usually localized on the legs, feet, or hands. The initial lesions may become pigmented, hyperkeratotic, and scaly, accompanied by local lymphadenopathy. These initial lesions never ulcerate. After several months or even years, more extensive skin lesions may appear.

43.2.5 Syphilis

Disseminated papular and also nodular lesions are part of the clinical manifestations of the secondary stage which manifests 4–10 weeks after appearance of the primary lesion. In the late tertiary stage, nodules and ulcerative nodules can be seen. In these lesions it is difficult or impossible to demonstrate *Treponema pallidum* due the scarcity of the microorganisms. Treponemal and/or non-treponemal serological tests are required to make a definite diagnosis.

43.2.6 Erythema Nodosum

Erythema nodosum is considered to be an immunologic reaction to a variety of triggers. Well-known causes are sarcoidosis and streptococcal infections. However, in the majority of cases, no cause can be found. It has a worldwide distribution. It is more prevalent in females with a peak in the 15–40 age group.

Clinically it manifests as painful inflamed subcutaneous nodules, generally localized on the frontal part of the lower legs, although it may be localized elsewhere in the subcutaneous fat. It often resolves spontaneously in the course of 6 weeks when it is related to an infection; otherwise it may persist many months. Older lesions are more indurated.

43.2.7 Persistent Insect Bites (Fig. 43.1)

This is defined as a persistent local reaction after bite, sting, or contact with an "insect." Insects are Hexapoda (= six legs) comprising flies, fleas, lice, bugs, beetles, moths, bees, hornets, and ants. But for the definition of persistent insect bite, a reaction to other arthropods as, for instance, ticks and mites is also used. It has a worldwide distribution but is more common in regions with a tropical climate.

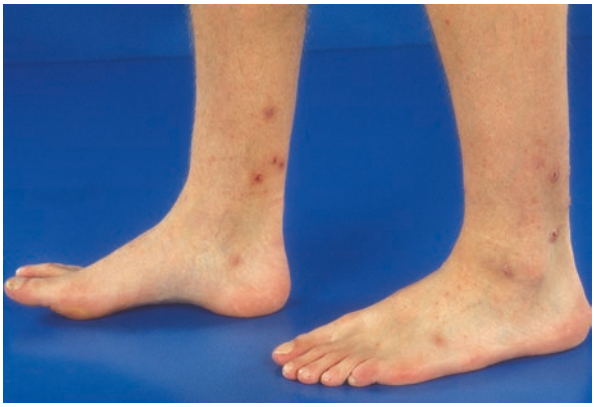

Fig. 43.1 Persistent insect bites

The clinical picture is that of papules and nodules. The duration can extend to weeks till (many) months and runs with spontaneous remissions and exacerbations. Characteristically they are more or less, but frequently severely, itching. Therefore, in the majority of the lesions, excoriations due to scratching are found. As it is a reaction to a contact, bite, or sting, they are localized on exposed body areas. A complication is bacterial infection due to scratching, especially of lesions localized on the legs. The diagnosis is clinical. Treatment is with topical strong steroids.

43.2.8 Subcutaneous or Furuncular Myiasis

Myiasis is infestation of the body tissues of humans and animals by the larvae (maggots) of flies (*Diptera*).

Cordylobia anthropophaga, the tumbu fly, a cause of furuncular myiasis, is widespread in tropical Africa, south of the Sahara. Eggs are laid on sand or soil, especially if contaminated by urine or feces, and also on laundry hanging out to dry. From these eggs, larvae develop that can survive in soil up to 9 days. These larvae can penetrate the skin of a host within 60 s.

Dermatobia hominis is a bluebottle-like fly found in the neotropical areas of the Americas, extending from southern Mexico to northern Argentina. It occurs where temperature and humidity are relatively high, principally in lowland forests. The female fly does not deposit her eggs directly on the host, but uses other insects, such as mosquitoes and blood-sucking flies, as vectors to carry her eggs to the host. When the vector subsequently feeds on a potential host, the eggs hatch and the larvae rapidly burrow into the skin.

After penetration of the skin, boil-like lesions develop gradually over a few days. Each lesion has a central punctum, which discharges serosanguinous fluid. The posterior end of the larva, equipped with a group of spiracles, is usually visible in the punctum, and its movements are usually noticed by the patient. In humans there is often an inflammatory reaction around the lesions. It may be accompanied by secondary infection, lymphangitis, and regional lymphadenopathy.

The larvae can often be expressed by firm pressure around the edges of the lesions, but the punctum may be enlarged surgically in order to remove the larva.

43.3 Plaques

Definition of a plaque: a solid flat elevated skin lesion with a diameter > 1 cm.

43.3.1 Cutaneous Tuberculosis

- Primary infection. This lesion enlarges during the course of several weeks into a plaque.
- Lupus vulgaris.

In the classical form, it extends into plaques with peripheral activity with an irregular border and central healing with atrophic scar formation and depigmentation. The clinical picture may be variable. Besides the plaque form, there is a hypertrophic form with nodules, which may form a hyperkeratotic mass.

Presentations of other mycobacteria may also evolve into plaques.

43.3.2 Leprosy

On the tuberculoid part of the spectrum, solitary or few flat plaques with a papular border and central healing can be found which are the result of enlargement of lesions in the context of a high degree of CMI, whereas at the lepromatous side, nodules can in time enlarge into infiltrated plaques.

43.3.3 Subcutaneous Mycoses

They are characterized by a heterogeneous group of infections that often result from direct penetration of the fungus into the dermis and subcutaneous tissue through traumatic injury. The most common presentations are plaque-like lesions [9].

Mycoses are restricted to certain regions. Most cases are encountered in those living and working in an endemic area with little availability of health resources. Sporotrichosis and basidiobolomycosis have a single specific etiological agent, whereas chromoblastomycosis and mycetoma are clinical syndromes with multiple fungal or bacterial etiologies.

43.3.3.1 Sporotrichosis

Sporotrichosis is caused by *Sporothrix schenckii*, which is a dimorphic fungus that occurs in nature as a saprophyte in soil, decaying organic material, and on surfaces of various plants. Infection results from traumatic inoculation of materials containing the fungus, particularly wood splinters or thorns through the skin. Zoonotic transmission has been described. The organism is particularly found in warm temperate and humid tropical climates and is one of the most common subcutaneous mycotic infections.

Individuals with activities, which expose them to the environment, are at risk. Sporotrichosis has a worldwide distribution. However, most cases at present are reported in South and Central America.

The incubation period is probably a few weeks. It is seen mostly as the lymphocutaneous or sporotrichoid form or less common as a localized or fixed cutaneous form. The primary lesions may appear as papular, nodular, or pustular lesions that develop into a superficial ulcer or a verrucous plaque. During progression, the lymphocutaneous form shows multiple subcutaneous nodules that are formed along the course of the draining lymphatics (sporotrichoid spread). The localized form shows no lymphatic spread and is characterized by indurated or verrucous plaques and occasional ulcers. Dissemination is rare and usually encountered in immunodeficient individuals.

43.3.3.2 Chromo(blasto)mycosis

Chromoblastomycosis is a chronic (sub)cutaneous mycotic disease that occurs more frequently in (sub)tropical areas. The disease is caused by saprophytic fungi that are found in soil and wood. It is most prevalent in tropical and subtropical America and Africa.

The disease occurs typically on the foot or the leg. It occurs mainly in farmers and rural workers who work barefoot. After inoculation of the fungus through the skin, slowly growing scaly wart-like nodules develop and ulceration may also occur. Clinically, it may be indistinguishable from verrucous cutaneous tuberculosis and localized sporotrichosis. It grows slowly and is painless, and lymphatic spread is only seen occasionally. Moderate itching is often mentioned. This may be relevant because scratching may contribute to inoculation of the fungus in adjacent areas. Scratching may also cause secondary infections, which are the most frequent complication of chromoblastomycosis.

43.3.3.3 Mycetoma (Fig. 43.2)

Mycetoma is a chronic granulomatous infection of the skin and the subcutaneous tissue characterized by deformation and increased volume of the involved subcutaneous tissue and, in the advanced stages, destruction of underlining bone structures. It is caused either by true fungi (eumycetoma) or filamentous bacteria (actinomycetoma). Nodules and openings of fistulae through which exudate containing grains *are discharged are* noticed on the skin surface. The grains, also known as sclerotia, are aggregation of hyphae produced by some species of fungi or the bacterial filaments from aerobic actinomycetes. Actinomycetic mycetoma is most common and accounts for 98% of the cases and is caused by aerobic species of the Actinomycetes group and the Streptomyces group. They are filamentous ramified bacteria that, when cultured, create colonies similar to fungi. The maduromycotic (eumycetic) mycetoma is caused by several fungi.

It is mainly a disease of the tropical climates and is more frequently seen in the rural areas where people work in farms under unprotected rudimentary conditions. Probably repeated punctures or abrasion of the skin are required for the inoculation of the organisms. The infection develops very slowly over the years. Its true incidence is unknown. Mycetoma is most often seen on the lower limbs (65%–70%).

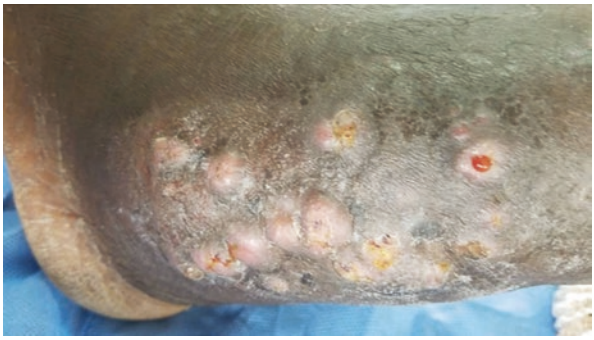

Fig. 43.2 Mycetoma

Clinically, the diagnosis is suspected in the presence of an increased volume of the affected tissue, formation of abscesses, and fistulae exudate containing grains.

43.3.3.4 Basidiobolomycosis

The Basidiobolomycosis is a rare deep mycosis of tropical and subtropical countries.

In early infection, the disease presents as inflamed and slightly painful nodules. In chronic infection, lesions are cold and painless. The edema is nonpitting and hard as wood, and the skin is rigid.

The evolution is slow and gradual, with periods of remissions over several months or years, in the form of an extensive plaque. Untreated infection may be fatal.

43.3.4 Panniculitis

Panniculitis is an (often painful) inflammation of subcutaneous tissue of the skin. Most patients have tender ill-defined red nodules and indurated plaques on the lower legs, thighs, and buttocks.

It includes a variety of diseases with different causes and therefore also different courses of disease. Diagnosis can be difficult and is based on clinical suspicion in combination with results from laboratory tests. A skin biopsy can be helpful for the classification of the panniculitis. The biopsy should include subcutaneous fat; therefore, a deep incisional biopsy is required. Treatment depends on the underlying cause.

43.4 Inflammatory Edema

43.4.1 Cellulitis

Cellulitis is an acute, spreading pyogenic inflammation of the dermis and subcutaneous tissue, caused most commonly by *Streptococcus pyogenes* and *Staphylococcus aureus* and usually complicating a wound, ulcer, or dermatosis.

The area, usually on the leg, is tender, warm, erythematous, and swollen, and demarcation from uninvolved skin is indistinct. Treatment is with antibiotics [10].

43.4.2 Erysipelas (Fig. 43.3)

It is a type of superficial cutaneous cellulitis. It presents with general malaise with high fever and a painful, bright red, raised, edematous, indurated plaque with advancing raised borders, sharply marginated from the surrounding normal skin. The most common localization is the lower leg, but it can also occur on the face.

It is usually caused by group A-hemolytic streptococcus (GAS) (very uncommonly group C or G streptococcus) and rarely by *S. aureus*. Treatment is with antibiotics

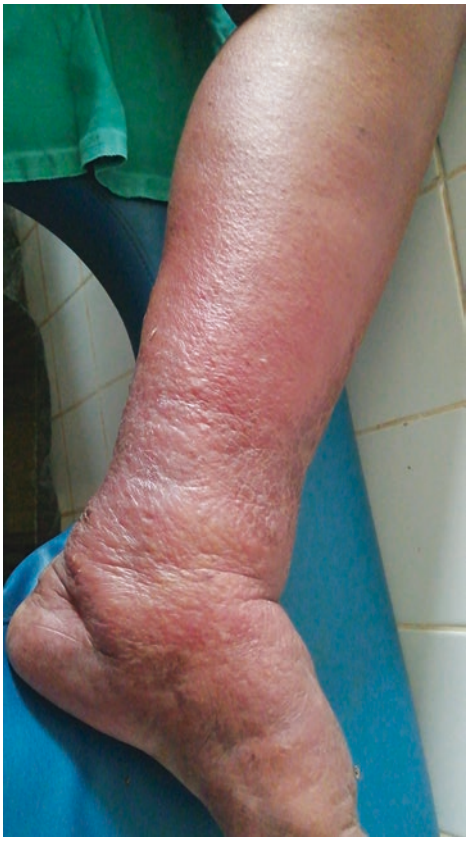

Fig. 43.3 Erysipelas

(penicillin). And as it is accompanied by marked dermal lymphatic vessel involvement, lymphedema may develop. The most common point of entry of the infection is the so-called toe web intertrigo, especially between the lateral toes, mostly due to a fungal infection, and treatment of this condition prevents a majority of erysipelas.

43.4.3 Necrotizing Soft Tissue Infections

Necrotizing soft tissue infections are infections of any layer of soft tissue compartment associated with necrotic changes and include necrotizing forms of cellulitis, myositis, and fasciitis. These infections are characterized clinically by fulminant tissue destruction, systemic signs of toxicity, and high mortality. It can be caused by a wide spectrum of organisms. It is associated with underlying conditions as, for instance, diabetes mellitus (DM), immune suppression, and obesity.

Clinical findings are initially swelling, erythema, pain, tachycardia; and it develops progressively with tense collateral edema, ecchymoses/blisters/bullae/necrosis, crepitus, and/or subcutaneous gas and is accompanied with disproportionate pain.

Treatment consists of early and aggressive surgical exploration and debridement of necrotic tissue, together with broad spectrum empiric antibiotic therapy and hemodynamic support [11].

43.4.4 Purulent Infectious Myositis (PIM)

Formerly known as tropical pyomyositis, PIM is an aggressive pyogenic infection of skeletal muscles which is also described from temperate climate zones. It affects all age groups, although young males are the most susceptible group. It is increasingly documented in persons infected with HIV.

It is usually a progressive febrile disease with pain in the affected muscle(s), and severe, life-threatening forms have been described, especially in immunosuppressed patients and children. Early diagnosis can be difficult due to lack of overlying skin changes [12].

Three clinical stages have been described:

1. *Invasive stage*. It is characterized by a subacute onset of variable fever and minimal systemic symptoms and a painful firm swelling, with or without erythema (as the infection is deep seated). The area is tender with a firm consistency. Aspiration yields no pus as this stage is a diffuse phlegmonous inflammatory process. About 2% of patients present in this stage. This stage lasts from 10 to 21 days. This stage may resolve itself, mimicking fibromyalgia or progressing to next stage of suppuration.
2. *Purulent or suppurative stage*. From the second week to third week, abscess forms in the muscle. The beginning of this stage is characterized by high fever and more severe systemic symptoms. Most cases present at this time. The classical signs of abscess, fluctuation, and erythema may be lacking because the process is localized within the muscle fascia. The involved muscle is usually tender, and the overlying skin may be normal or erythematous.

   Needle aspiration yields pus.
3. *Late stage*. High fever, severe pain, local signs of infection, and systemic manifestations of sepsis may be present. It is characterized by septicemia, metastatic abscesses, and multi-organ dysfunction and is associated with high mortality. There is exquisite tenderness of the involved muscle.

Atypical presentations exist. In some patients the invasive stage may be prolonged and the patient may present with pyrexia of unknown origin. Depending on the localization, it may present as an acute abdomen or spinal cord compression or compartment syndrome. When localized to neck muscles, it can be mistaken for cervicobrachial neuralgia. Noninvasive imaging techniques, ultrasound, CT scan, and MRI, are helpful in establishing the diagnosis. Treatment is by percutaneous or open surgical drainage along with antimicrobial therapy guided by culture results. *S. aureus* is the organism most commonly cultured.

43.4.5 Noma

A gangrenous infection of the mouth was a disease of the poor worldwide. But it nowadays especially affects children in underdeveloped countries in whom the constitution is altered by bad hygiene and serious (viral) illness. Most cases are reported from the so-called noma belt, ranging south of the Sahara from Senegal to Ethiopia. An increased incidence has been reported in patients with HIV infection. It starts with an ulcer of the mucous membrane with edema of the face, with salivation, and an unbearable stench; this phase generally lasts for a few days. A gangrenous necrosis rapidly destroys soft tissues and bone leading to gross deformity of the face. Mortality is still around 10%. Management consists of general measures, treatment of associated diseases, antibiotics and, in a later stage, reconstructive surgery [13].

43.4.6 Osteomyelitis

Osteomyelitis is an infection of the bone caused by bacteria, most commonly *S. aureus* but also by mycobacteria such as *M. marinum* and *Salmonella*. It can be the consequence of direct spread from an ulcer, an open fracture, or a surgical operation but also due to hematogenous spread. Clinical symptoms are pain in the bone, tenderness on palpation, and increase in pain by movement and weight bearing and signs as fever, swelling, and erythema. Acute and chronic forms of osteomyelitis exist.

Treatment is by antibiotics and also local measures depending on localization and other characteristics.

43.4.7 Bone Tumors

Bone tumors constitute 6%–10% of all tumors in children and adolescents. They are more frequent in adolescents around the age of 15, compared to younger children. Frequency decreases in young adults and then increases again around the age of 65. Boys are more affected than girls.

Clinical signs are bone pain and swelling of the bone or adjacent soft tissue related either to the extension of the tumor (inflammatory hourly pain) or with a fissure or fracture complication (mechanical schedule pain or mixed, i.e., combining intermittent and mechanical) and neurological signs (pain whose description follows a neurological pathway, suggesting nerve damage). Imaging techniques will aid in the diagnosis [14].

43.5 Ulcers

Definition of an ulcer: Ulceration is the absence of the normal tendency of a wound to heal, giving rise to tissue degeneration. There are many causes of ulceration which may be infectious or noninfectious or a combination.

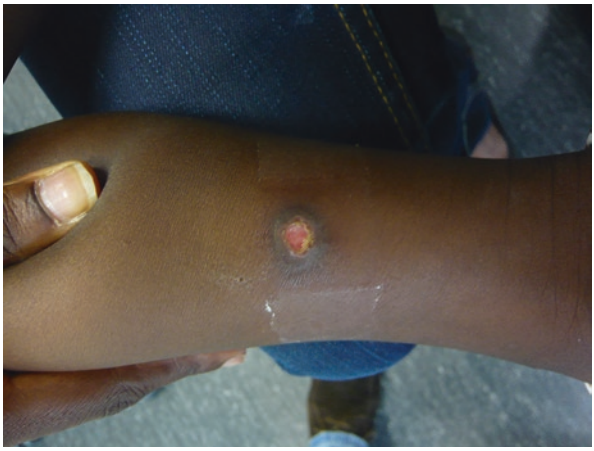

Fig. 43.4 Ulcerating pyoderma

43.5.1 Infectious Ulcers

43.5.1.1 Pyoderma (Fig. 43.4)

Pyoderma includes several clinically distinct types of skin lesions that are caused by *S. aureus* and/or *β-hemolytic streptococci group A*. It is a common cause of (purulent) ulcerative skin lesions in tropical countries.

Superficial skin infection may extend more deeply into the dermis and produce shallow ulcers known as ecthyma. The ulcer is covered with a dark-brown, bloody crust. A tender punched-out ulcer remains once the crust is removed. It is usually found on the dorsal feet, shins, and thighs, but less often on the upper part of the body. There are usually few lesions, but new lesions may develop without adequate treatment.

Ulcerating pyoderma is most commonly encountered as a secondary infection in skin lesions caused by environmental insults, such as insect bites, abrasions, and atopic dermatitis.

The diagnosis is often based on the clinical picture of persistent painful ulceration especially in the lower legs. One should perform a bacterial culture if facilities are available. Susceptibility tests in vitro are preferable. Methicillin-resistant *S. aureus* and tetracycline-resistant streptococci and staphylococci are frequently encountered in many areas of the tropics [15].

43.5.1.2 Cutaneous Leishmaniasis

CL is one of the most important causes of chronic ulcers in some parts of the tropical world.

Lesions are usually painless; if painful there is generally a secondary infection present.

CL in the Americas caused by species of the subgenus *Leishmania* will generally resolve, even without treatment, in 6 months, whereas lesions caused by the subgenus *Viannia* often do not resolve spontaneously. First a nodule develops which

enlarges and eventually ulcerates. A nodular lymphangitis may be present. Mucocutaneous leishmaniasis, although uncommon, may develop in approximately 3%–5% of patients as a complication of new-world CL caused by *Leishmania (V.) braziliensis*, but also occurs with *Leishmania (V.) panamensis*.

Afro-Eurasia CL lesions caused by *L. major* are often nodular, nodulo-ulcerative, and ulcerative. They develop slowly over months and generally resolve in 6 months. Lesions caused by *L. tropica* may persist as an erythematous papule for more than a year. Presentation is often as nodulo-ulcerative plaques with a necrotic base and indurated margin that are frequently covered by a firm adherent crust. The time period for spontaneous resolution is not well-known. It has been reported that leishmaniasis caused by *L. tropica* may affect the nose or the mouth. However, this is probably because of direct extension from skin lesions rather than from the dissemination of the parasite [15].

The initial diagnosis is based on the clinical picture of a non-healing painless ulcer in a patient who lives or visited an area where cutaneous leishmaniasis is endemic. BU and cutaneous leishmaniasis may have similar clinical presentation; therefore laboratory tests are important to differentiate between these two.

Laboratory tests include histopathological examination of biopsies, ulcer smears stained with Giemsa, and culture of the material obtained by needle aspiration or by biopsy. And if available PCR can be used [16].

43.5.1.3 Cutaneous Tuberculosis

- Cutaneous tuberculosis

  Cutaneous tuberculosis, especially primary infection, may show ulceration.

- *M. marinum* infections

  The primary lesion may ulcerate or show a warty surface. And also nodular lymphangitis may present with ulcerated nodules.

43.5.1.4 Subcutaneous Mycoses

Although plaques are the most common presentation, ulceration may occur.

The most common subcutaneous mycoses, which may show ulceration, are sporotrichosis, chromo(blasto)mycosis, and mycetoma.

43.5.1.5 Syphilis

Syphilis has a worldwide distribution in sexually active persons.

The incubation period is 10–90 days. Classically the primary stage is an indurated ulcer (= ulcus durum), but it starts with a papule-nodule before ulcerating. The lesions are typically painless. As it is sexually transmitted, the primary lesion is nearly always localized in the genital area, but extra-genital lesions do occur. In MSM also primary lesions in the peri-anal area can be found.

43.5.1.6 Diphtheria

Cutaneous diphtheria is an infectious bacterial disease caused by *Corynebacterium diphtheriae* or, more rarely, *C. ulcerans*. It is still endemic in many tropical countries and transmitted by direct contact with cutaneous carriers and to a lesser extent via vomit. *C. diphtheriae* produces a toxin which is responsible for the disease diphtheria. The microorganism (both toxigenic and non-toxigenic strains) may be harbored in the nasopharynx, skin, and other sites in asymptomatic carriers. *C. diphtheriae* is often found secondarily in pre-existing ulcers like ecthyma or as superinfection in eczema. In immunized individuals systemic toxic complications such as myocarditis and neuritis are rare. Skin lesions may be an important reservoir of infection. Contacts should be investigated and treated if necessary because there is a potential for secondary transmission. Cutaneous diphtheria is characterized by a chronic, non-healing ulcer with a punched-out appearance and an adherent membrane with a slightly undermined margin. In the first 2 weeks, it is painful; later the lesion becomes painless. After (spontaneous) removal of the adhering membrane, the hemorrhagic base appears. In many cases lesions are less distinctive. Secondary infection in any pre-existing wound and superinfection of eczematous skin lesions are common and often overlooked. Cutaneous diphtheria may persist for 6–12 weeks.

A high level of awareness among clinicians and microbiologists is necessary because cutaneous diphtheria ulcers are non-specific. The initial diagnosis is clinical.

43.5.1.7 Tropical Phagedenic Ulcer

Tropical phagedenic ulcer is a painful rapidly growing ulcer often on the lower leg, commonest in undernourished young people and particularly prevalent in the hot, humid tropical regions.

It may develop on abrasions, scratches, insect bites, or skin diseases such as pyoderma. Multiple factors as nutritional status, presence of fusiform bacilli, and spirochetes may contribute.

Its true prevalence is not known, but it seems to be quite rare these days.

It starts as a small papule or vesicle which becomes necrotic. The small ulcer rapidly enlarges. It is usually a 2–6 cm round punched-out ulcer with well-defined elevated borders. In the chronic stage, the ulcer is non-purulent, indolent, less punched out, and with a fibrotic border and may last for years.

43.5.2 Noninfectious Ulcers

43.5.2.1 Post-Traumatic Chronic Ulcer

Post-traumatic ulcers can be defined as a cutaneous lesion, resulting from acute exposure to energy (mechanical, thermal, electrical, chemical, or radiant). Road traffic injuries and intentional injuries (self-inflicted injuries, interpersonal violence, and war-related injuries) are most important causes of traumatic ulcers.

Injury is a significant health problem throughout the world. About 5.8 million people die each year as a result of injuries. This accounts for 10% of the world''s deaths, 32% more than the number of fatalities that result from malaria, tuberculosis, and HIV/AIDS combined. By far the greatest part of the total burden of injury,

approximately 90%, occurs in low- and middle-income countries [17]. The risk factors for road accidents are increasing in many developing countries. The global burden of disease due to road traffic injuries is expected to move from the ninth position in 2004 to the fifth position by 2030.

A carefully obtained medical history will reveal the origin of the ulcer.

If the ulcer is traumatic in origin, it should be defined in terms of high impact, low impact, repetitive, temperature related, caustic, radiation induced, type of bite, presence of drug abuse, and so on. In chronic ulcers, the age of the wound is important because long-standing wounds can be malignant (Marjolin's ulcer). Previous topical therapy to the ulcer should be delineated, because certain topical agents can contribute to the ulcer's chronicity (e.g., caustic agents such as hydrogen peroxide, 10% iodine, Dakin's solution, and so on).

43.5.2.2 Pyoderma Gangrenosum (PG)

PG is a rare reactive noninfectious inflammatory skin condition with a worldwide distribution that is difficult to diagnose. It is diagnosed clinically by exclusion of other causes of ulcers. Classical PG is the most common form (approximately 85% cases). This presents as an extremely painful erythematous lesion which rapidly progresses to a blistered or necrotic ulcer. There is typically a ragged undermined edge with a violaceous/erythematous border. The lower legs are most frequently affected although PG can present at anybody site. Subtypes include bullous, vegetative, pustular, peristomal, and superficial granulomatous variants. The differential diagnosis includes all other causes of cutaneous ulceration as there are no definitive laboratory or histopathological criteria for PG. As underlying systemic conditions are found in up to 50% of cases, thorough investigation for such conditions should be performed once a diagnosis of PG has been made.

43.5.2.3 Sickle Cell Ulcer (Fig. 43.5)

Sickle cell disease is caused by an abnormality in the gene encoding the β-chain of hemoglobin. When deoxygenated, sickle cell hemoglobin interacts hydrophobically

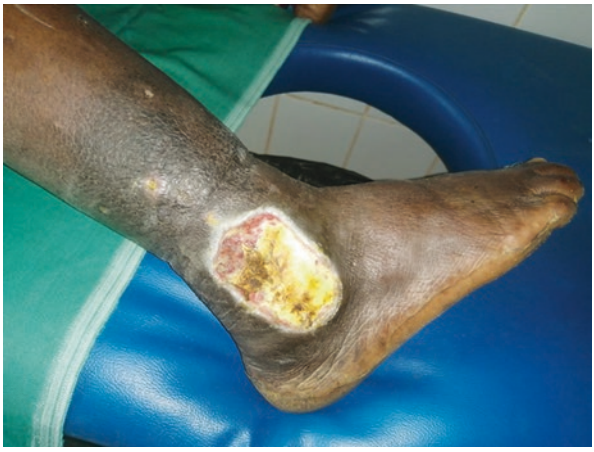

Fig. 43.5 Sickle cell ulcer

with other hemoglobin molecules and tends to aggregate and polymerize, resulting in the characteristic sickle shape. The pathogenesis of leg ulceration in sickle cell is not completely understood. Abnormal adherence of the sickle cell to endothelial cells has been postulated to be important in the initiation and/or progression of vaso-occlusive events leading to infarction of the skin. The sickle cell ulcers are commonly seen in adult males with homozygous sickle cell disease (HbSS) and are unusual in patients with sickle cell hemoglobin-C disease (HbSC) as well as those with sickle cell beta^{+} thalassemia [18].

Ulcers are a common cause of morbidity among North American and Jamaican patients with homozygous sickle cell (SS) disease in whom prevalence of 75% have been reported. The reported incidence from Africa is much lower, incidence varying from 5% to 9.6%. The cause of these differences is not known; however, age distribution of the population and genetic factors might play a role.

The incidence is very low in children under age 10 and markedly increased for those over age 50. Ulcers persist for months to years, heal slowly, and commonly recur. Most ulcers are located in the ankle area over the medial or lateral malleoli. The size of ulcers varies from a few millimeters to large circumferential ulcers. Ulceration is proceeded by prodromal pain and is often spontaneous or after minor trauma. The ulcer has a punched-out appearance with raised margins and a deep base. Radiographs often show some periosteal reaction which makes it difficult to rule out osteomyelitis. Secondary infection is found very often and might delay wound healing.

Pain is often very severe and probably the major problem. It has a great impact on the quality of life in these patients. Diagnosis is made on clinical observation of a painful leg ulcer, mostly in the ankle area in patients having sickle cell anemia. Edema is often present.

43.5.2.4 Vascular Ulcers

There are only very few epidemiological studies available on venous, arterial, or lymphogenic causes of ulcers in the tropics. Studies performed in the tropics reveal a very low or absent prevalence of vascular ulcers.

In the western world, the incidence of arterial disease is still increasing. As many people in developing tropical countries are changing their lifestyle into a more Western one, it is expected that arterial disease will become more prevalent.

Venous ulceration is the end stage of venous hypertension. Clinically edema, lipodermatosclerosis, hyperpigmentation, hyperkeratosis and atrophie blanche may be noticed in chronic venous insufficiency. Ulceration is often not painful.

Arterial insufficiency is occlusion that usually affects the entire femoropopliteal track, but may also affect only small-sized branches which may lead to limited infarction of skin and subcutaneous tissues.

Diagnosis of a venous ulcer is made on signs of venous insufficiency. Venous duplex scan may show superficial and/or deep venous reflux.

Diagnosis of arterial ulcers is made on history of the patient with ischemic disease. Clinical examination may reveal diminished peripheral pulsations. Doppler ultrasound measurements of the peak velocity of the peripheral bloodstream or

measurement of the systolic blood pressure at the feet are a useful parameter to calculate the degree of severity of the peripheral vascular disease. For visualization of the peripheral arterial tree, translumbar and transfemoral arteriography can be performed.

43.5.2.5 Malignant Ulcers

Cutaneous metastases originating from internal cancer or cancer originating in the skin may show ulceration. The three major types of skin cancer are basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and melanoma. These skin cancers are probably as a result of the protective effect of darker skin pigmentation far less prevalent in skin of color compared to the white population. Melanoma distribution in skin of color is often seen in sun-protected sites of the palms, soles, and nail bed.

Most important seems the development of SCC in chronic traumatized or inflamed skin as seen in chronic leg ulcers and traumatic scars. A large study in Nigeria showed a preponderance of SCC of the leg related to neglected, poorly managed, and chronic ulcers or scars from burns or injuries. Albino patients had a higher frequency of both SCC and BCC mostly on the head and neck. A study performed in Malawi showed a surprisingly large number of malignancies in skin ulcers. It is suggested that HIV disease of which the prevalence is very high in this population may be responsible. A three- to fivefold increased risk of developing a nonmelanoma skin cancer has been reported in persons with AIDS.

Signs and symptoms associated with the development of the carcinoma include a change in the scar with formation of a mass or ulcer, possibly with an increase in pain, increasing discharge, foul odor, and bleeding.

In all, non-healing ulceration of the skin biopsy remains the most important definitive diagnostic procedure, and it should be performed on any suspicious lesion or any chronic ulceration, especially those with any recent change in appearance.

43.5.2.6 Neuropathic Ulcers

Neuropathy can occur in several diseases; clinically most important is neuropathy of the feet. Most common causes of neuropathic feet worldwide are leprosy and DM.

Nerve invasion is a unique characteristic of *M. leprae* and results in nerve function impairment. It is estimated that 20%–30% of the leprosy patients have foot problems due to loss of nerve function. As a result, after trauma of the skin, ulceration of especially feet (and hands) may occur.

DM has become a worldwide pandemic, with two thirds of the global diabetic population living in developing countries.

Damage of peripheral nerves causes malfunction of the sensory, the motor, and the autonomic nerve fibers, thus increasing the vulnerability of the foot. Ulcers are usually localized at pressure points which result in deformity due to loss of function of motor nerves. In case of leprosy, ulcers have a chronic course. In case of DM, the clinical course is more acute as there is nerve function impairment in combination with metabolic disturbance and often vascular insufficiency. Also, a (progressive) bacterial infection is far more common. In leprosy as well as in DM, so-called

Charcot feet (= neuro-osteoarthropathy) can develop. This leads to gross deformity of the foot with ulceration on atypical localizations.

Management of neuropathic ulcers can be difficult. Most important is relief of pressure on the ulcer area to facilitate healing.

43.6 Scars

43.6.1 Ulcers

By definition all clinical conditions described under ulcers heal with, in general atrophic, scar formation. The clinical presentation depends on the depth and the size. When the extent of the ulceration is large, it may lead to deformities.

43.6.2 Third-Degree Burns (Fig. 43.6)

Third-degree burns are full thickness burns destroying the epidermis and dermis and may extend into the subcutaneous tissue. In burns up to 70% of patients develop hypertrophic scars.

43.6.2.1 Chronic Osteomyelitis

Deep or extensive ulcers that fail to heal with appropriate ulcer care should raise suspicion for osteomyelitis, especially if they are localized over bony prominences.

Following ulceration but also after surgical intervention, scars, sometimes extensive with deformities, develop.

43.7 Other Buruli Ulcer Forms

Apart from the classical forms, BU can present as unusual clinical forms that can induce misdiagnosis. These are the mixed forms, the disseminated or multifocal forms (see Chap. 42), and paradoxical reaction (see Chap. 45).

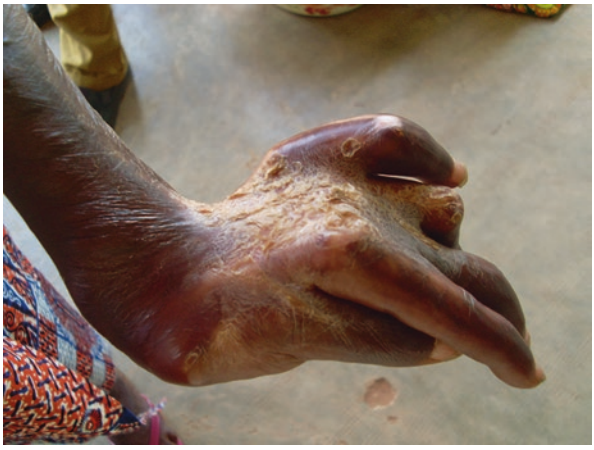

Fig. 43.6 Scar from thermal burn

43.7.1 Mixed Forms

The mixed forms can be defined as a combination of two or more types of primary lesions [19]. In settings where laboratory confirmation or X-ray is not always available, the diagnosis of BU can be difficult as differential diagnosis of deep fungal infections [20] or bone tumor [14].

43.7.2 Disseminated or Multifocal Forms

The disseminated or multifocal forms are defined as several identical or different types of lesions that coexist in the same patient, on the same or more body parts. Disseminated lesions usually present as an acute process, thus implying a differential diagnosis when the patient is seen at first consultation with multiple lesions. When they occur in a patient under antibiotic treatment for BU, they are referred to as paradoxical reaction. Most of the disseminated or multifocal forms at diagnosis are associated with HIV coinfection. However, also some cases without HIV coinfection have been described [21, 22]. The presence of multiple lesions at first consultation in a patient suspected of BU, in the absence of laboratory confirmation, suggests the differential diagnosis of cutaneous tuberculosis or cutaneous manifestation of bacterial sepsis. Cutaneous manifestations of systemic bacterial infections result from the bacteremia or septicemic dissemination or secondary to an infection at a cutaneous entry point [21]. Two main skin lesions are seen: "true" septic skin metastases which can be diagnosed clinically and above all bacteriologically by local samples and "aseptic" skin lesions only allowing a clinical diagnosis. The skin manifestations are polymorphic with ecthyma gangrenosum, subcutaneous abscess, and panniculitis.

43.7.3 Paradoxical Reaction

Paradoxical reactions are defined as new inflammatory lesions following an initial improvement of BU lesion during or after antibiotic treatment, leading to increased inflammation around lesions, extension of an ulcer, or a new lesion on a different part of the body. Paradoxical reactions are sometimes seen on parts of the body where there was no evidence of disease before antibiotic treatment, perhaps as a result of subclinical infection. Cultures of tissue or pus are usually sterile, although acid-fast bacilli can still be seen and PCR for *M. ulcerans* IS*2404* may remain positive. Paradoxical reactions occurred in 21%–22% of the patients, most of them were HIV or HBV coinfected [23, 24]. Paradoxical reactions per se do not give any problem with respect to differential diagnosis, since the diagnosis was already made, and the patient under treatment. However, the management of paradoxical reactions requires therapeutic abstention or, in the event of severe reaction, corticosteroid therapy. Other mechanisms which give similar clinical signs should be considered. This mainly concerns secondary bacterial infection of lesions, or bacterial sepsis [25]. Secondary infections can be misclassified as paradoxical reactions, since they also induce worsening of the lesion. They are all the more to be feared as the

so-called paradoxical reactions occur in patients presenting with immunosuppression. Secondary infections of BU lesions are common and can occur before (60%), during (65%), and after (75%) specific antibiotic treatment [25]. This will lead to worsening of lesions and delayed healing and should therefore be further investigated before drawing the conclusion of paradoxical reaction. The patient will present with pain, fever, anorexia, poor general condition, and other systemic symptoms. Culture from any new lesion should be performed to differentiate a relapse from a paradoxical reaction.

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