Leprosy

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Alireza Firooz, Mansour Nassiri Kashani,
Lila Izadi Firouzabadi, and Mohammad Shizarpoor

11.1 Epidemiology

Leprosy (*Hansen's disease*) is a chronic infection caused by *Mycobacterium leprae*. It predominantly involves the skin and the peripheral nervous system. Although in multibacillary forms of the disease the agents can be detected in a majority of body organs, (except the central nervous system, the gastrointestinal system, and the lungs), their dissemination causes no clinical symptoms [1].

A recent WHO report has shown that the global prevalence of leprosy is 0.32 per 10,000, i.e., a total of 180,618 cases at the beginning of 2014. The exact incidence is unknown because of the number of subclinical infections present in endemic areas, the long incubation period, and the possibility of self-cure, particularly in children. The number of new detected cases in 2013 was 215,656 (3.81 per 100,000), with the highest prevalence in tropical parts of Southeast Asia (India, Nepal, Bangladesh, Myanmar, and Indonesia), South America (Brazil), and Africa (Ethiopia, Tanzania, Congo, and Madagascar), mostly in overpopulated countries with high rates of poverty. More than 80% of all new cases of leprosy are registered in India, Brazil, and Indonesia [2]. In 1991, the World Health Organization introduced the target of eliminating, not eradicating, leprosy reducing its prevalence rate to <1 case per 10,000 persons, achieved in 2013 [3].

The incubation period of leprosy is long, with an average of 2–5 years in paucibacillary and 8–12 years in multibacillary clinical forms. The disease affects preferably men in most parts of the world; paucibacillary forms of the disease are more common, with two peak ages at 10–15 and 30–60 years [4].

11.2 Etiology

In 1873, the Norwegian scientist, Armauer Hansen, discovered the infectious agent of leprosy, *Mycobacterium leprae*. This acid-fast bacillus has several exclusive features. Its reservoir is only in humans and probably armadillos in some parts of the world. It is an obligatory intracellular organism, and cell-mediated immunity is the only mechanism of defense against it. The division time of the bacilli is long (12–14 days), thus expanding the incubation period of the disease to several years. The best temperature for its growth is 30–33 °C; therefore, the agents grow in the cooler regions of the body such as the skin and the peripheral nerves. In vitro culture is not available to date, and mouse foot pads or armadillos are used for replication in vivo. This has led to difficulties in the laboratory diagnosis, evaluation of sensitivity and resistance to antibiotics, and discovery of new anti-leprosy drugs. Unlike the *Mycobacterium tuberculosis*, its genetic mutational rate is low and the DNA genome rather stable, as completely sequenced in 2001 [5].

The main reservoir in humans is the upper respiratory tract of untreated patients with multibacillary leprosy; the disease is transmitted to the healthy via close and lengthy contact through nasal secretions. After inhalation, *Mycobacterium leprae* replicates in the upper respiratory tract of the new host, has a short phase in blood, and finally binds to the Schwann cells of the peripheral nerves and skin macrophages. Undamaged skin is resistant to transmission, but rare cases of leprosy have been reported after traumatic inoculation such as vaccination, penetrating trauma, tattoo, and surgery. In the USA, some rare cases of leprosy have been described in patients who had no history of travel to or contact in endemic areas but had contact with armadillo.

A. Firooz, M.D. (✉) · M. Nassiri Kashani, M.D.
L. Izadi Firouzabadi, M.D. · M. Shizarpoor, M.D.
Center for Research and Training in Skin Diseases and Leprosy, Tehran University of Medical Sciences, Tehran, Iran
e-mail: firozali@tums.ac.ir

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Overall, the significance of armadillo for a transmission of leprosy is not clearly elucidated [6].

About 90% of humans are genetically resistant to leprosy. Others may acquire the disease only if they have close, prolonged, and continuous household contact with multibacillary patients for months or years.

11.3 Classification

There are several systems for classifying the clinical forms of leprosy, the two most commonly used are the WHO and Ridley-Jopling classifications. The classification of WHO [7] is more practical, especially for healthcare providers in endemic areas. It is primarily based on skin smear results, dividing patients into two groups: *Paucibacillary* (PB) forms with negative smear and *multibacillary* (MB) with positive smear. Due to the absence of facilities for preparing and evaluating skin smears in many medica in poor endemic areas, WHO later recommended a new scheme of classification based on the number of skin lesions. Patients who have five or fewer skin lesions are considered as *paucibacillary*, and those with >5 lesions are considered *multibacillary*. The main obstacle for such classification is that some MB patients might have less than five skin lesions, be classified as PB group, and receive insufficient treatment. As a result, if there is any doubt regarding MB or PB, the patient should be considered as MB for treatment.

A system based on clinical and histopathological findings has been proposed by Ridley and Jopling [8], taking into account the cell-mediated immune reaction against the agent. The patients are divided into six groups: *Indeterminate* (I), *tuberculoid* (TT), *borderline tuberculoid* (BT), *mid-borderline* (BB), *borderline lepromatous* (BL), and *lepromatous leprosy* (LL). The first three groups almost match with paucibacillary, whereas the last three are compatible with multibacillary patients. The skin smear is usually negative in the first three groups and positive in the rest. After a strong immune response, the patient develops tuberculoid leprosy (TT), a moderate response results in borderline, and minimal or lacking response to lepromatous leprosy [9, 10]. Patients in the tuberculoid pole of leprosy have few asymmetric cutaneous and nervous lesions. Toward the lepromatous pole of the disease, there is an increase in the number of lesions with more diversity and symmetry in the morphology of the lesions. Although an involvement of the peripheral nerves is more obvious in the first group, such symptoms can also be seen in advanced stages of the second group.

11.4 Clinical Features

A wide spectrum of clinical signs and symptoms can be seen in patients with leprosy, depending on the immune response of the patient [11, 12].

Indeterminate (I) leprosy: This is the early phase of the infection, usually seen in children. It usually presents with a single hypopigmented patch, particularly in dark-skinned patients, with an ill-defined margin. In fair-skinned patients, there is a fade erythema within this patch. The lesion often develops on the face, upper arm, upper leg, and buttock. It does not involve the scalp, axilla, and inguinal areas as these areas are warmer. The patient may complain from paresthesia, but there is no sensory impairment. Indeterminate leprosy generally improves spontaneously; a few cases develop into progressive disease.

TT leprosy: This type involves the skin and peripheral nerves only. There is usually a single elevated annular plaque or a few asymmetric macules or flat patches, sometimes showing a prominent border. The center may be erythematous in light skin or hypopigmented in dark-skinned individuals (Fig. 11.1). The scalp, axillae, and inguinal areas are usually spared. On physical examination, the TT lesions are hypo- or anesthetic. Temperature sensation is the first to get lost, followed by loss of sensation of light touch, pain, and deep touch. As a rule, a peripheral nerve close to the skin lesion is enlarged and palpable. Involvement of the autonomic innervations can lead to lack of perspiration and decrease in hair growth.

BT leprosy: Likewise in TT type, the lesions have a well-demarcated border and hypopigmented center. There is a possibility for erythematous appearance in fair skin. The number of lesions in BT leprosy is higher than in TT patients but usually less than five. Small satellite lesions may be seen at their periphery, revealing a symmetric pattern of distribution. Peripheral nerve involvement is common, and large nerve trunks are asymmetrically involved. Impairment of the sensory function is a significant feature.

BB leprosy: This form is usually unstable, and the patient often upgrades or downgrades to other types of leprosy. The

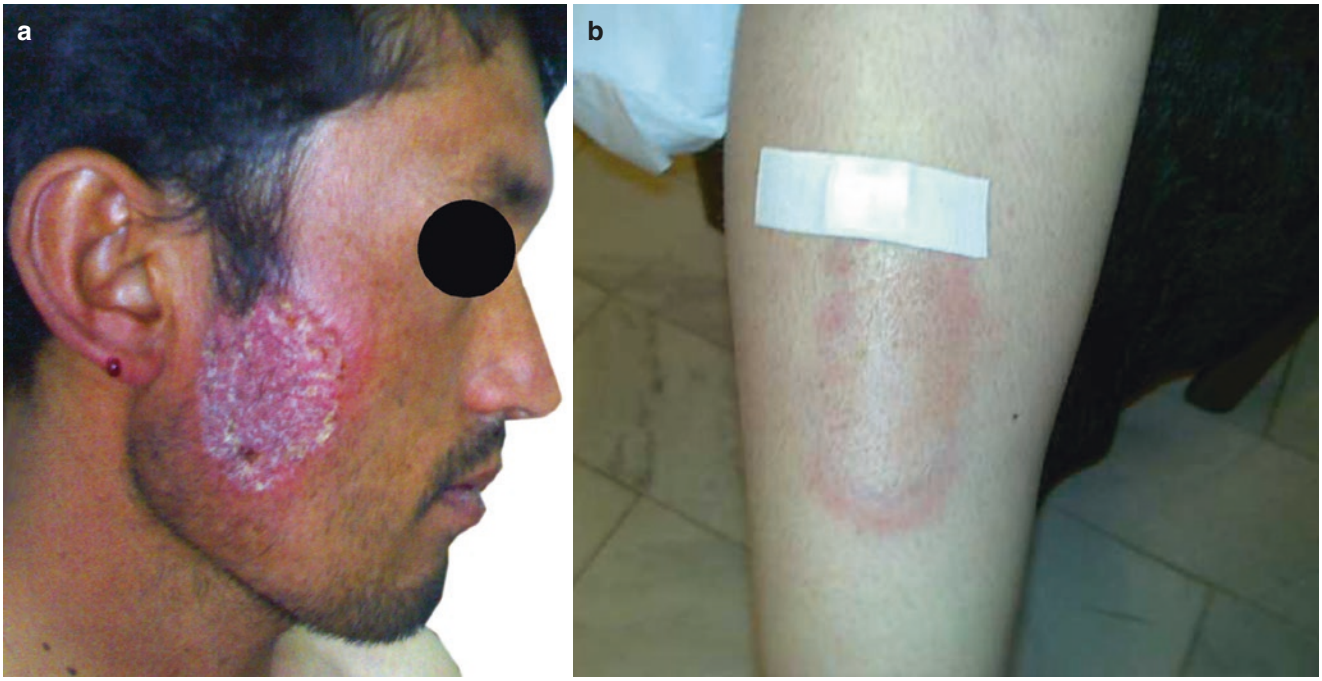

Fig. 11.1 Patients with *TT leprosy*. (**a**) Single erythematous plaque, (**b**) asymmetric dissemination of hypopigmented, hypoanesthetic macules on the trunk

number of lesions is high, but not as much as in LL leprosy. Their distribution tends to be more symmetric than BT, presenting macules, papules, and plaques. A rare but typical feature is a punch out erythematous plaque with well-demarcated inner border and a fade, nonspecific outer border. Nerve enlargement and symmetrical peripheral neuropathy is often found.

BL leprosy: Involvement of the skin is in this type diffuse, multiple, and almost symmetric. Fade macules are followed by papules, plaques, and nodules (Fig. 11.2), often with ill-defined borders and asymptomatic symmetric enlargement of large peripheral nerves. Patients also show distal sensory loss in a stock-and-glove pattern, reduced sweating, and in late stages muscle atrophy and contractures (Fig. 11.3). In early stages, there are no signs and symptoms of oral and nasal involvement such as epistaxis, septal perforation, saddle nose, and madarosis (thinning or loss of eyebrows and lashes). The incidence of immunological reactions, both types 1 and 2, is high in BL leprosy.

LL leprosy: High and unrestrained replication of *Mycobacterium leprae* in the skin, nerve tissue, and several other organs is the cause for the clinical features of lepromatous leprosy. Widespread and symmetric papules, nodules, and plaques are seen, but still the scalp, axillae, and groins are spared. Diffuse infiltration of bacillus in the skin leads to multiple lesions and in some cases to the typical and characteristic feature of leonine facies (Figs. 11.4, 11.5 and 11.6). Saddle nose deformity, destruction of nasal bridge, and epistaxis may occur due to heavy infiltration of the agent. Madarosis, lagophthalmos due to facial nerve paralysis, and ichthyosis-like xerosis are also features in late-stage LL. The auricle may be infiltrated, enlarged, and swollen. Neuropathy in the form of glove-and-stocking anesthesia is seen in the late and progressive stages of lepromatous leprosy. The nerve damage permits blisters, cuts, burns, and infections of the extremities due to repetitive or unsuitable traumas. Later secondary infections, cellulitis, osteomyelitis, loss of tissue, and permanent deformities and disabilities may occur.

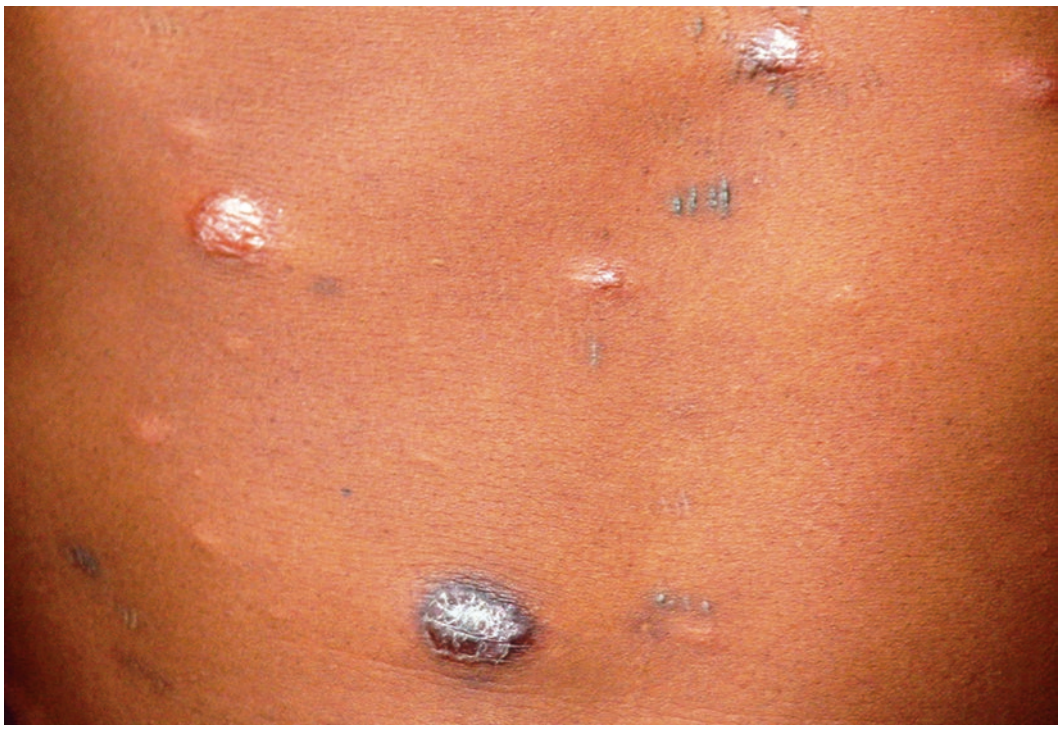

Fig. 11.2 *BL leprosy* showing macules plaques and nodules

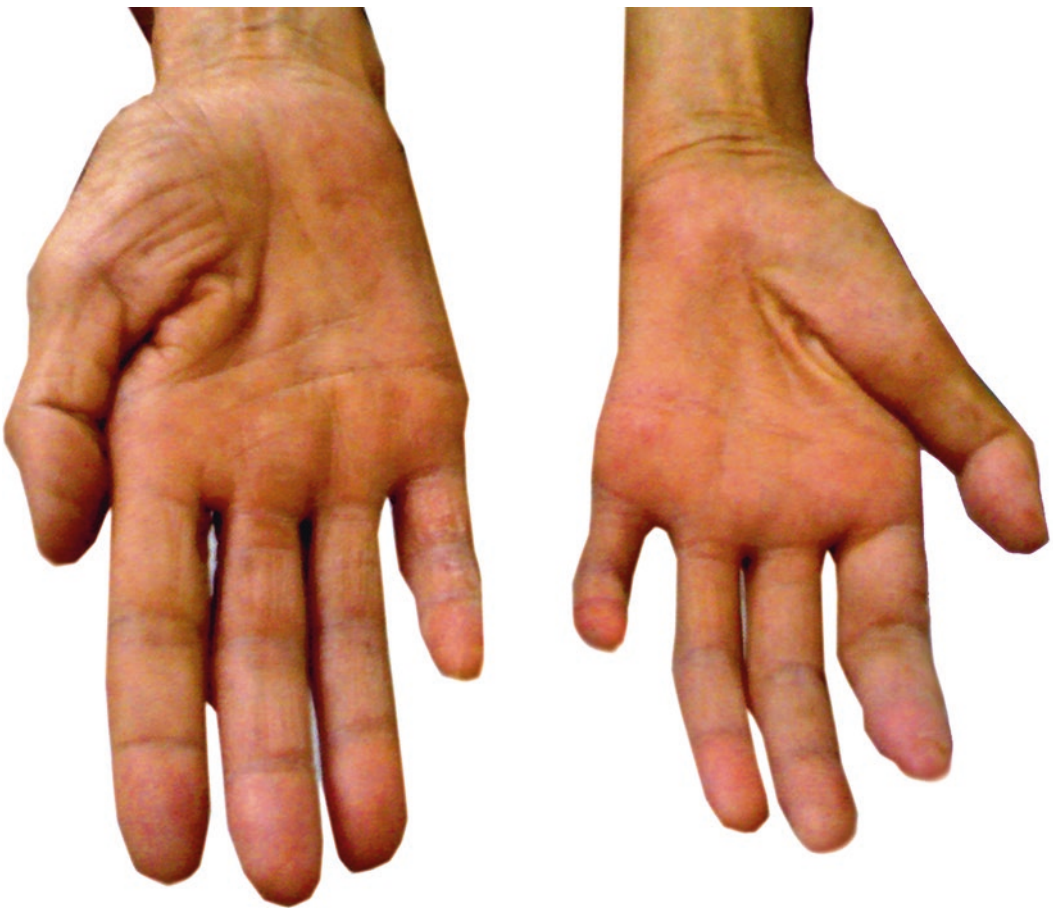

Fig. 11.3 Muscle atrophy and contractures in *BL leprosy*

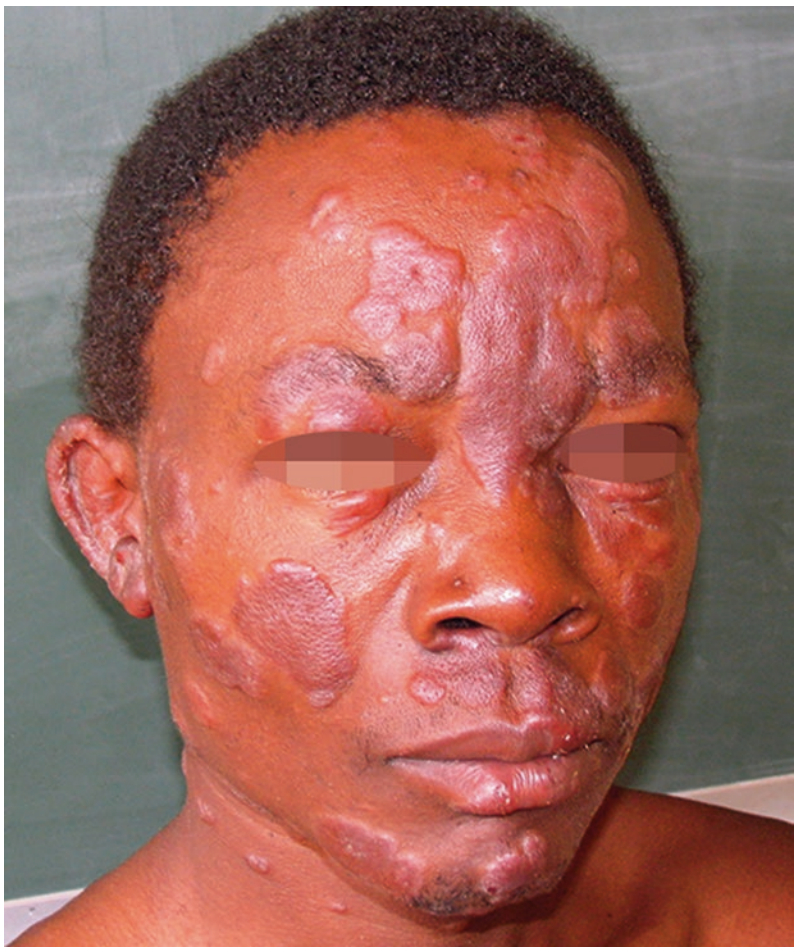

Fig. 11.4 Elevated plaques and leonine aspect of the face in *lepromatous leprosy* (Courtesy RDTC in Moshi, Tanzania (Photo: CEO))

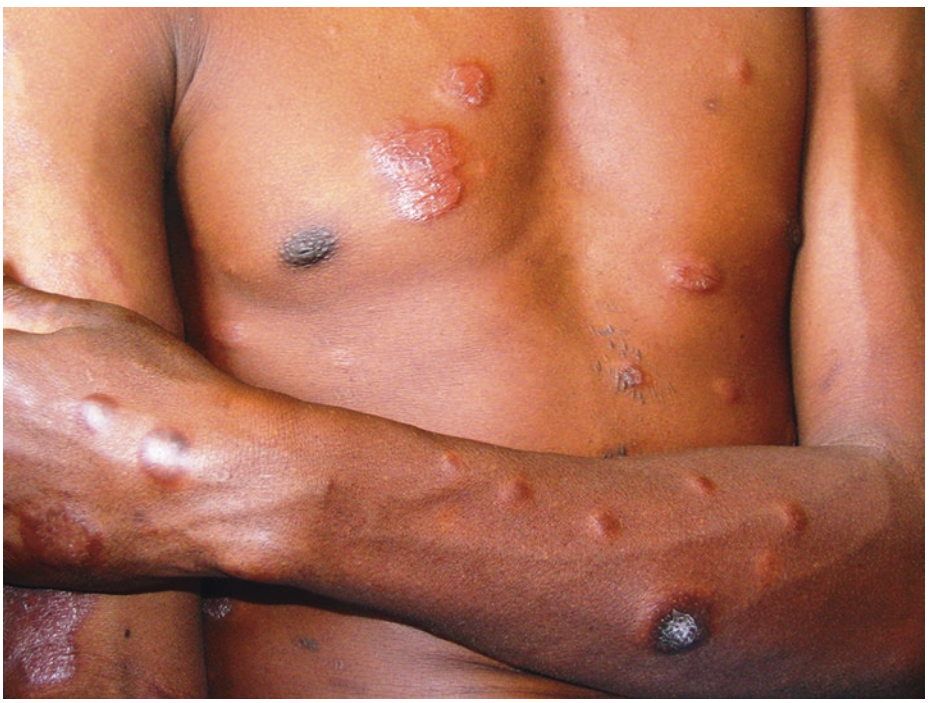

Fig. 11.5 *LL leprosy*. Characteristic lesions on the trunk and extremities (Courtesy RDTC Moshi, Tanzania (Photo: CEO))

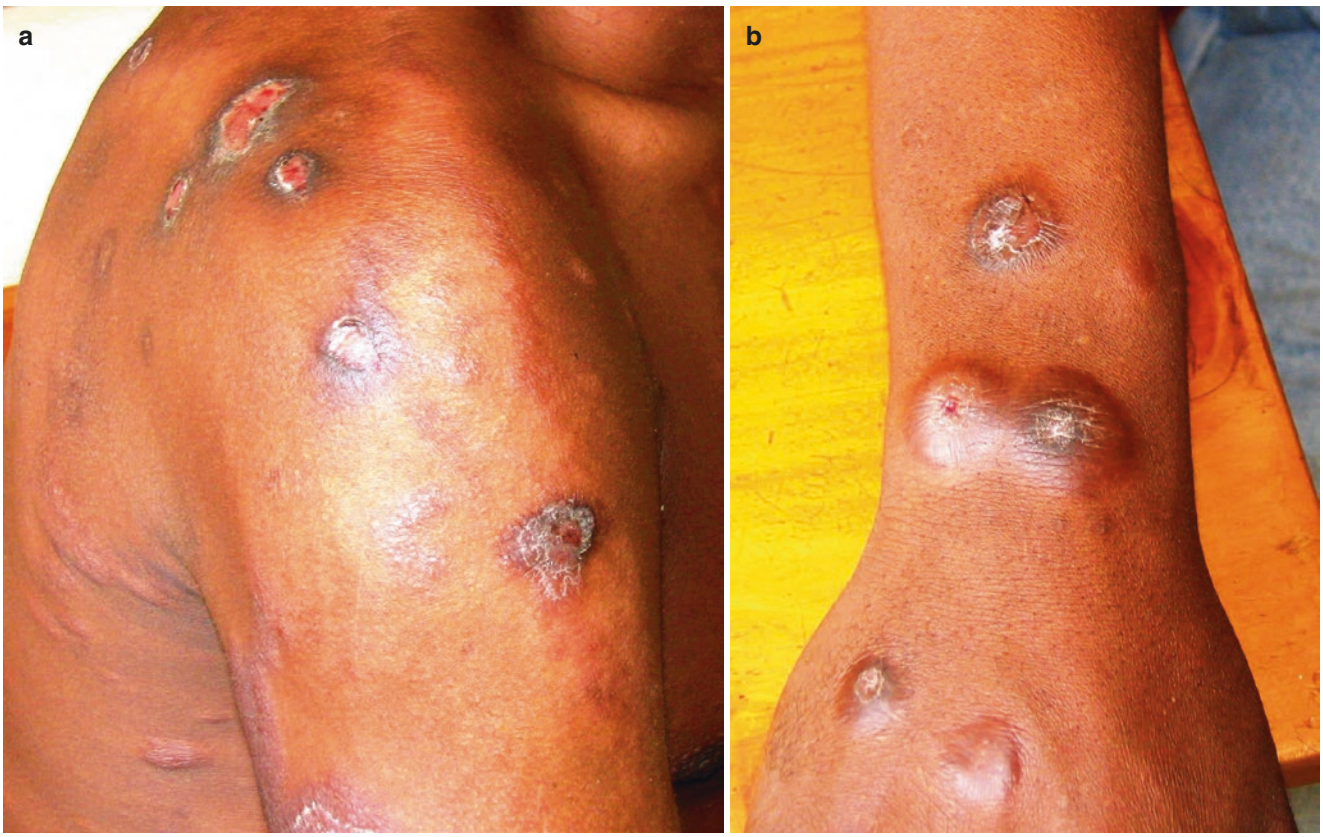

Fig. 11.6 (**a**, **b**) Tumor-like lesions in late *lepromatous leprosy*

11.5 Immunologic Reactions

Type 1 reactions can occur in borderline leprosy patients before, during, or even after treatment due to changes of the cell-mediated immune response, considered as a type IV hypersensitivity reaction. Patients develop acute symptoms of inflammation in the skin and peripheral nerves. On examination, pain, swelling, and erythema in cutaneous lesions and/or in nerve fibers occur. New skin lesions can appear abruptly with inflammation and erythema (Fig. 11.7a). This phenomenon is a destructive process and can damage nerves permanently.

Type 2 leprosy reactions are due to the formation and deposition of antigen-antibody complexes (type III hypersensitivity) and occur in around 50% of the patients with BL and LL types of the disease, particularly after the onset of oral medication. It is a multi-systemic process representing leukocytoclastic vasculitis. Uveitis, orchitis, arthritis, lymphadenopathy, and hepatosplenomegaly may be diagnosed. *Erythema nodosum leprosum* (ENL) is a cutaneous manifestation of type 2 reaction, consisting of multiple, painful subcutaneous nodules (Fig. 11.7b). Unlike ordinary erythema nodosum, the nodules in ENL last shorter and involve the upper limbs, face, and trunk, in addition to the lower limbs. Occasionally, ENL may be the first manifestation of the infection.

The immune reactions in patients with leprosy are of significant importance and considered as an emergency condition to be instantly diagnosed and treated. If they remain untreated, persistent complications and disabilities may follow. Both physicians and patients should be aware that reactions arising during treatment are not side effects of the drugs or signs of failure of the medication and that treatment must continue. It may be difficult to differentiate mild type 2 reaction from a relapse after termination of treatment; however, immune reactions are always acute and show rapid response to corticosteroids. In contrast, relapses are much less frequent and usually arise years after the treatment is stopped; they do not respond to corticosteroids and slowly progress.

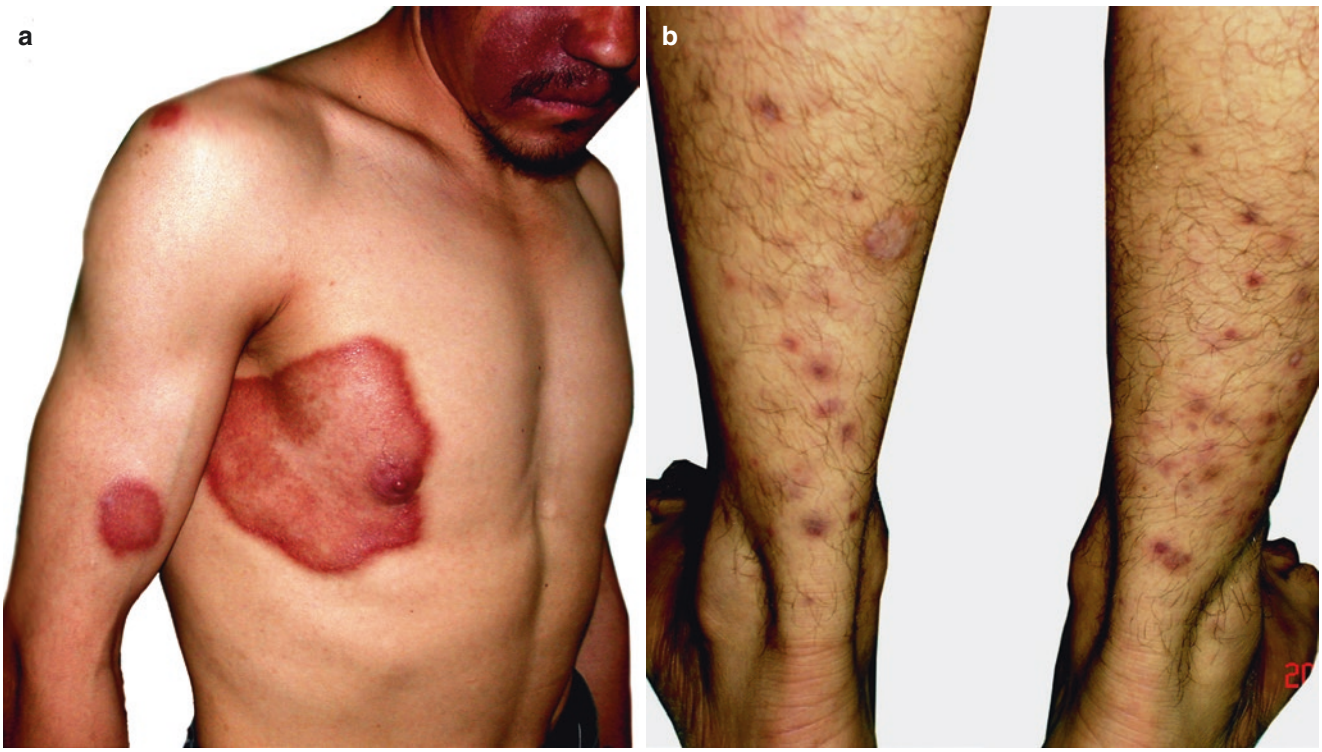

Fig. 11.7 (**a**) Elevated plaques representing type 1 reaction and (**b**) erythema nodosum leprosum (ENL) as a type 2 reaction in leprosy

11.6 Diagnosis

The diagnosis of leprosy is usually clinical, based on the history and accurate examination of the patient. When leprosy is suspected, a complete and thorough physical examination of the entire skin is necessary. None of the existing laboratory methods are sensitive enough or available in endemic areas.

The main diagnostic criteria are (*a*) presence of cutaneous lesions compatible with leprosy, (*b*) sensory impairment on skin lesions in tuberculoid pole or extremities in lepromatous pole, and (*c*) palpable thickening of peripheral nerves. Due to the diverse features in its different clinical types, almost any skin lesions can be related to leprosy. The peripheral nerves should be then palpated for thickening and tenderness. Following that, the sensory function should be thoroughly examined and carried out by test tubes containing warm and cold water for thermal sensation, a cotton wool or feather for light touch, pinprick for pain, and pinch test for deep sensation. Examinations should be performed on the cutaneous lesions of paucibacillary leprosy; for excluding multibacillary forms, all limbs should be examined, together with evaluation of strength of the distal muscles and the presence of atrophy or muscle contractures. Hypohidrosis or loss of hair can be a sign of impairment of autonomic nerves. Examination of the eyes is mandatory in all patients suspected for leprosy.

Hypopigmented lepromatous lesions must be differentiated from pityriasis alba, vitiligo, post-inflammatory hypopigmentation, and achromic or anemic nevi. The well-demarcated erythematous lesions of paucibacillary forms can imitate dermatophytosis, granuloma annulare, cutaneous tuberculosis, mycosis fungoides, or allergic contact dermatitis; erythematous lesions in multibacillary forms may resemble psoriasis, pityriasis rosea, secondary syphilis, cutaneous lymphoma, and sarcoidosis. The leonine facies is most characteristic for LL, but not pathognomonic; it can be also seen in leishmaniasis, lymphoma, and pseudolymphoma.

Although the WHO does not recommend any laboratory evaluation for confirming the diagnosis, slit skin smears, histopathology of the skin and/or the peripheral nerves with special stains, and PCR investigations will be helpful.

11.7 Management

A multidrug regimen (MDT) has been introduced by the WHO for treatment of leprosy [7, 13], and monthly packages of the necessary drugs are distributed free of charge. The combination of drugs recommended is highly effective

Table 11.1 Multidrug therapy (MDT) for leprosy recommended by the WHO

Type of leprosy	Monthly supervised	Daily oral intake	Duration
Paucibacillary	Rifampin 600 mg + clofazimine 300 mg	Dapsone 100 mg + clofazimine 50 mg	6 months (over 6–9 months)
Multibacillary	Rifampin 600 mg + clofazimine 300 mg	Dapsone 100 mg + clofazimine 50 mg	12 months (over 12–18 months)

(Table 11.1). The side effects are tolerable; the most common are gastrointestinal complaints due to rifampicin, hypersensitivity reactions to dapsone, and hyperpigmentation due to clofazimine, particularly in dark-skinned patients. The rate of posttreatment relapses is less than 1:1000, mostly not due to loss of the efficacy of the drugs; therefore, re-administration of MDT is recommended for relapsed patients. MDT is also recommended for pregnant and breastfeeding women. For children, the dosage must be adjusted according to the age or body weight.

Leprosy reactions should be treated promptly since there is a possibility of rapid destruction and permanent damage of nerves; MDT medication should be continued. Mild reactions without nervous involvement are treated with nonsteroidal anti-inflammatory drugs, whereas in cases with nerve involvement, prednisolone is given instantly (40–60 mg/day). The dose should be gradually tapered, particularly in type 1 reactions, and be withdrawn when the reaction is controlled. Thalidomide (100–200 mg/day) is a drug of choice for type 2 reactions including ENL, with or without prednisolone. Its use in childbearing women is limited due to high risk of teratogenicity. High-dose clofazimine (300 mg/day) might be effective in some ENL patients. When it is difficult to differentiate between immune reactions and relapse, it is advised to administer corticosteroids in order to avoid possible nerve injury [12].

11.8 Prevention

Early diagnosis, prompt treatment, and patient education are the main strategies of WHO for prevention of leprosy and its complications. Household contact persons of leprosy, particularly in multibacillary cases, should be followed for the development of signs and symptoms of the infection. Regular monitoring of the sensory and motor functions of the hands, feet, and eyes is mandatory to early diagnose nerve damage. Patients should be instructed to apply ointments on the skin to prevent xerosis, wear appropriate shoes, massage the muscles and do physiotherapy to prevent contractures, and clean all abrasions. In cases with lagophthalmos, frequent use of artificial tears and occlusion of the eyes with an ointment at night are recommended [13]. Efforts to develop a vaccine for leprosy were unsuccessful before the introduction of MDT. The protective effect of BCG vaccination was quite variable in different communities [14].

Conclusions

Leprosy is a chronic infection with highest prevalence in developing countries in hot climate zones of Asia, America, and Africa. *Mycobacterium leprae* is an obligatory pathogenic intracellular organism, and the cell-mediated immunity is the only mechanism of defense. About 90% of humans are genetically resistant to the agent; their immune response inactivates and destroys the bacilli after entering the body. A wide spectrum of signs and symptoms can be seen on the skin of patients affected, resulting into various clinical pictures depending on the immune response of the host. Early diagnosis and prompt introduction of treatment sustainable over several months are the main strategies for prevention. The multidrug regimen (MDT) introduced and supported by the WHO for the management of leprosy is highly effective; however, profound education of patients and all health workers involved is an essential precondition for eradicating the disease in developing countries under the circumstances of poverty.

Immunological reactions in patients under antilepromatous treatment must be diagnosed instantly and treated appropriately as emergencies, in order to prevent persistent complications and disabilities.

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