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Leprosy: A great imitator

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Abstract In recent years, advances in medical diagnosis and treatment have greatly attracted our attention, whereas some rare diseases, such as leprosy, have not found a place in the medical education curriculum; their existence may even be forgotten. Although the prevalence and incidence rates for leprosy have been significantly reduced as a result of the control strategies of the World Health Organization, new cases still appear. A total of 214,783 new cases were reported from 143 countries during 2016, corresponding to the global new-case detection rate of 2.9 per 100,000 population. Leprosy proves to be a very interesting model due to its immunologic properties. It joins with syphilis, mycosis fungoides, cutaneous tuberculosis, and sarcoidosis as one of the great imitators. The diagnosis of leprosy can be simple and practical, but considering the diagnosis of leprosy in the differential diagnosis is the first requisite again.

Leprosy

Leprosy is a chronic granulomatous infectious disease caused by the bacillus *Mycobacterium leprae (M leprae)*, an intracytoplasmic parasite for macrophages and Schwann cells. Depending on the immunologic status of the host, the clinical picture can range from being localized or broad-spreading and self-limiting or progressive. The disease primarily affects the superficial peripheral nervous system and the skin, but it also may involve the upper respiratory tract mucosa, the anterior camera of the eyes, bones, and testes.[1–6] (See Figs. 1–12.)

History

Leprosy is often described as an ancient disease of many cultures. It is not known where leprosy was first recognized, because it was often confused with other dermatologic and infectious diseases. The earliest written sources accurately describing the different types of the disease originated in India and China around 600 BCE to 400 BCE. It is believed that the disease first appeared in these regions and then migrated to the Middle and Near East, before invading European countries and the Americas, through various social movements such as trade routes, migrations, and wars. At the beginning of the 15th century, leprosy was extremely common in Europe, but the number has gradually decreased since the 19th century and has now almost entirely disappeared from that region of the world.[1,4–9]

Epidemiology

Currently, there are about 4 million active or inactive with sequelae of leprosy patients in the world. The number of new cases diagnosed annually approaches 250,000. The vast majority of cases being reported are in India, Brazil, Indonesia, Nepal, Myanmar, Madagascar, and the Democratic Republic of the Congo. India dominates the global picture of the world's

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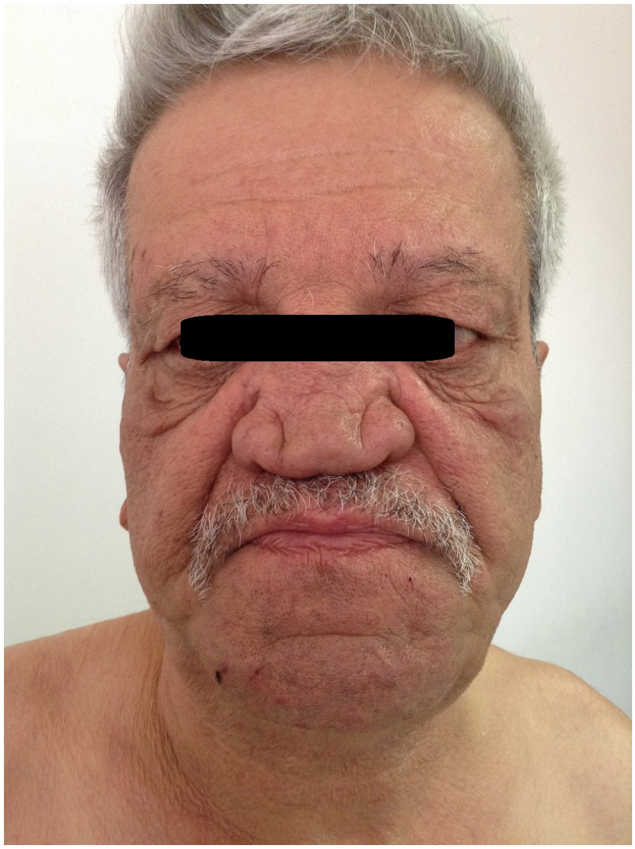

Fig. 1 Lepromatous leprosy, trilobed nose, madarosis, and maxillary bone resorption.

leprosy cases. A total of 214,783 new cases were reported from 143 countries during 2016, corresponding to the global new-case detection rate of 2.9 per 100,000 population.

In many countries where the prevalence has been reported below 1 per 10,000 population, the incidence has been reduced below these rates in recent years due to current strategies for fighting leprosy, including early diagnosis of new cases, completion of treatment, and monitoring complications that lead to a reduction in injuries.[3–6,8–11]

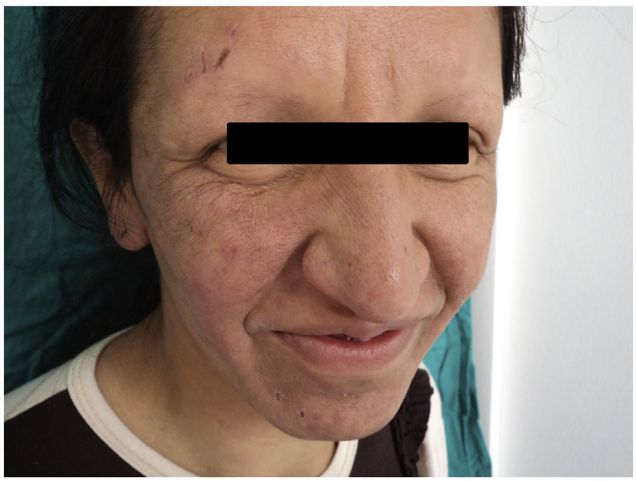

Fig. 2 Lepromatous leprosy, madarosis, and infiltration of the face.

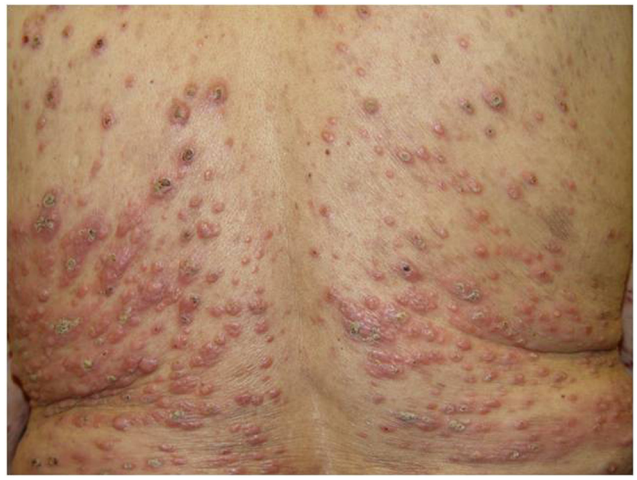

Fig. 3 Lepromatous leprosy, lepromas resembling guttate psoriasis, prurigo nodularis, or hypertrophic lichen planus.

Etiology

The etiologic agent *M leprae*, first shown by the Norwegian physician Gerhard Armauer Hansen (1841-1912) in 1873, is an acid-resistant, rod-shaped, slow-growing intracellular microorganism, which is an intracellular obligate parasitic organism that can grow and divide inside macrophages and Schwann cells. It can also be found in monocytes, endothelial cells, and neutrophils. The leprosy bacillus is the only one that infects the peripheral nerves, especially the Schwann cells.[2–6,9,12,13]

Transmission-infection route

The exact route of transmission of leprosy is still unknown. Even though transmission is reported through some types of African monkeys, the only reservoir of *M leprae* is humans. Transmission of leprosy depends on the infectivity of the infected person and the proximity, frequency, and duration of the contact. The most important problem in describing the transmission of the disease is the difficulty of determining when and how the "bacillus touch" occurs, because the illness is so slow and devious. The leprosy bacillus survives outside for a few days, sometimes up to 14 days. Because the bacteria mainly affect the skin and upper respiratory mucosa, it is believed that the main port of entry and exit of the pathogen are the upper respiratory tract and the skin lesions. *M leprae* can be spread through sweat, sebaceous secretions, and lepromatous skin ulcers, and, more rarely, it can be mechanically

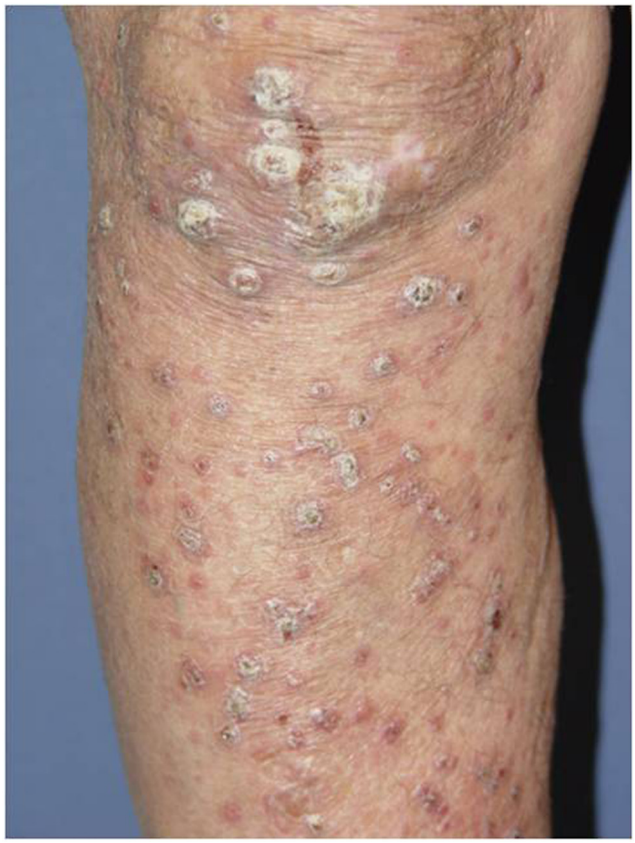

Fig. 4 Lepromatous leprosy, lepromas resembling guttate psoriasis, prurigo nodularis, or hypertrophic lichen planus.

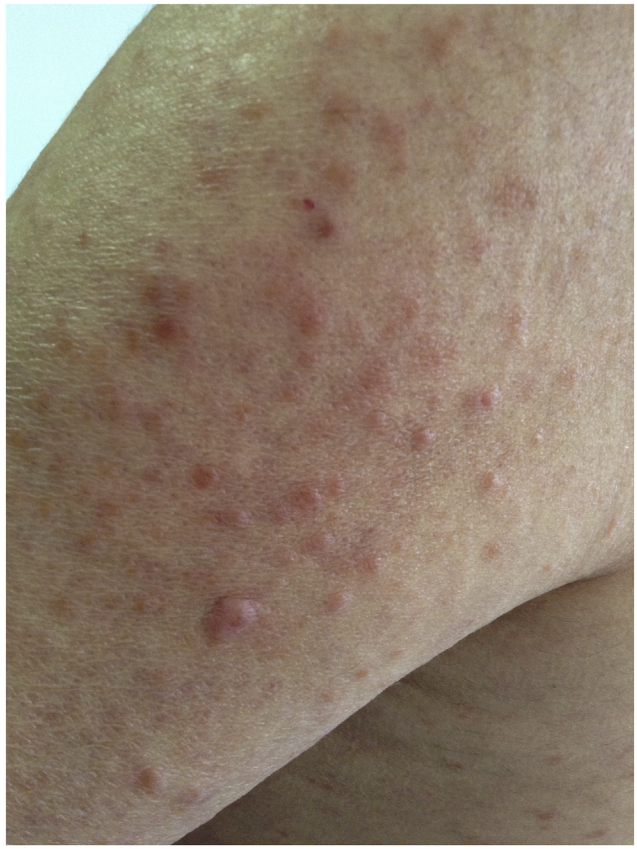

Fig. 5 Lepromatous leprosy, lepromas resembling micropapular sarcoidosis.

transplanted by insects. Bacilli can also be transmitted by the gastrointestinal tract, especially from untreated lepromatous nursing mothers via the milk pathway.[1–7,9]

The incubation period

Due to the insidious nature and slow evolution of the disease, it is not possible to give an exact incubation time. Various incubation periods have been reported, and they vary between 2 to 5 years for tuberculoid leprosy (TT) or between 9 to 11 years for lepromatous leprosy (LL). The average incubation period is 2 to 4 years. After this period, an initial lesion becomes indeterminate leprosy.[2,4,5,8,14–16]

Immunology: Immunopathology

Leprosy is not only a bacteriologic disease but also an immunologic disease. As the cellular immune system is primarily responsible for the protection of infections caused by intracellular microorganisms, such as *M leprae,* the immune response of the host determines the clinical expression of the disease. When the leprosy bacillus invades the body, it is first trapped by the Schwann cells, then released, and phagocytized by macrophages. Lymphokines, released by T lymphocytes, activate macrophages. Active macrophages phagocytize the bacilli and then turn into epithelial cells with a lifetime of several weeks. In this case, the primary infection is terminated without disease. A great majority of patients show resistance to the development of clinical disease, due to an effective innate immune response in combination with low virulence of the bacilli.[2–6,9,13,17–26]

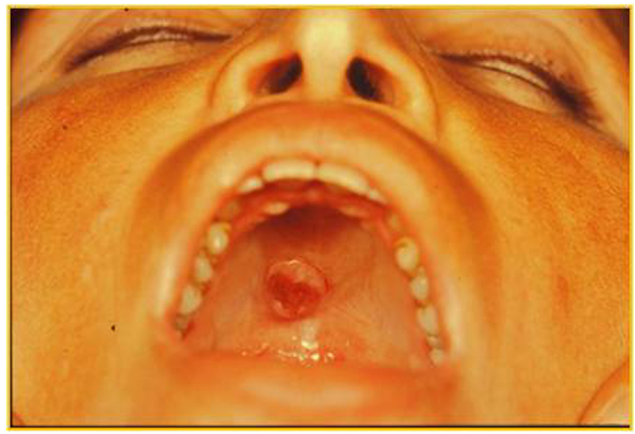

Fig. 6 Lepromatous leprosy, leproma on the palate.

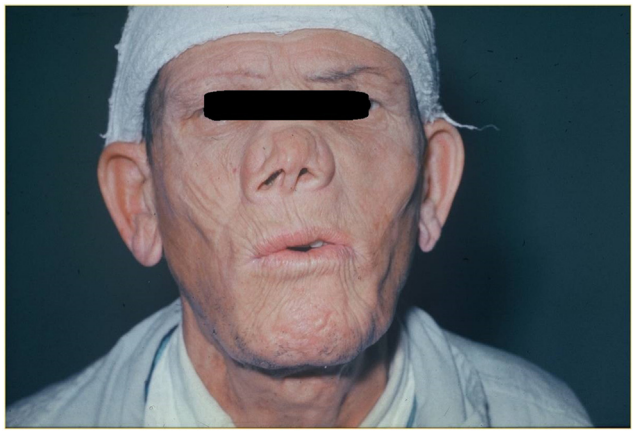

Fig. 7 Maxillary bone resorbtion and nose deformity as a sequelaeof LL leprosy.

AIDS/HIV infection and leprosy

In some areas where leprosy is endemic, the effects of AIDS and HIV infection on leprosy become an important problem. Due to the immunologic effects of HIV, subclinical leprosy infection becomes obvious, and a change of the clinical spectrum, chemotherapeutic adverse effects, erythema nodosum leprosum reaction, and, if used immunoprophylactically, BCG (Bacillus Calmette-Guerin) dissemination can be seen.[27]

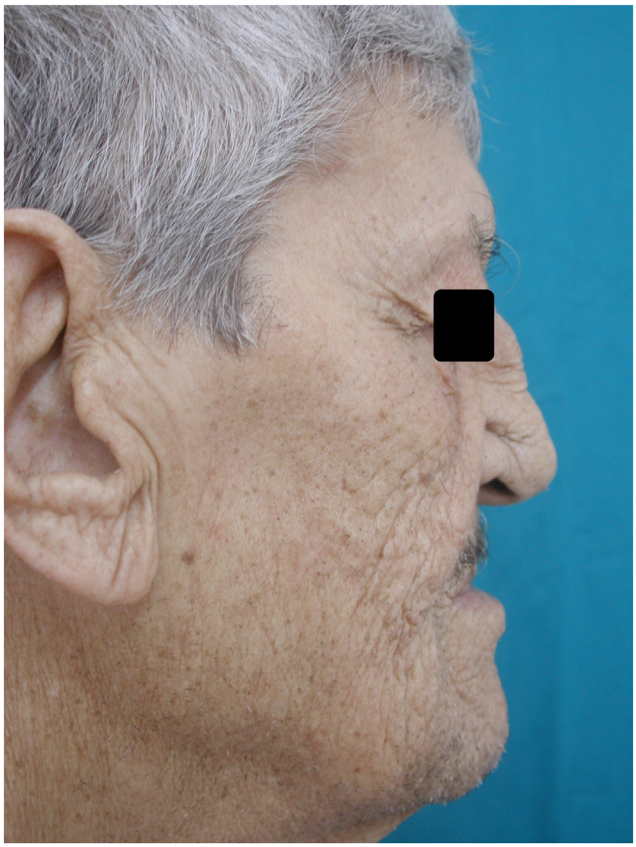

Fig. 8 Lepromatous leprosy, facial deformities, and typical facial appearance due to maxillary resorption and facial flattening.

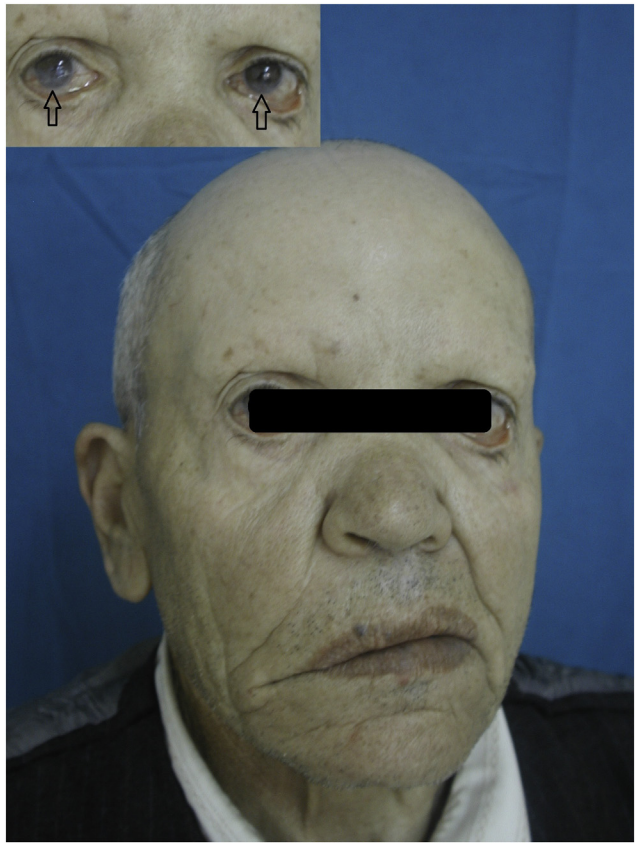

Fig. 9 Facial paralysis and lagophthalmus and corneal opacities at the lower part of the cornea, due to lagoftalmus.

Lepromin test

The lepromin test is an intradermal test that evaluates host resistance to the leprosy bacillus. Typically, a positive reaction is biphasic. The Fernandez reaction, a delayed-type hypersensitivity reaction, occurs after 24 to 48 hours and shows the expression of the organism's current sensitivity to leprosy; the Mitsuda reaction is measured after 21 days and shows the ability of the person being tested to respond to the leprosy bacillus. The lepromin test is positive in tuberculoid patients and negative in lepromatous patients, but it is not used to diagnose leprosy because both positive and negative results can be achieved in healthy subjects. It is used in the classification of the disease and has a prognostic value.[2,4,5,8,9] In the past, it was used in the classification of the disease but is not used routinely anymore.[28]

Dermatopathology

Because *M leprae* has a predilection for neural tissue, the first evidence of infection is often found in the peripheral

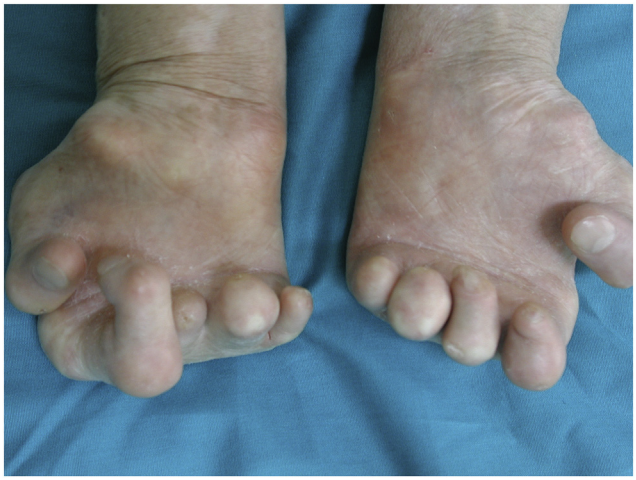

Fig. 10 Deformities of the hand due to bone resorbtions and clawing due to ulnar and median nerve involvement.

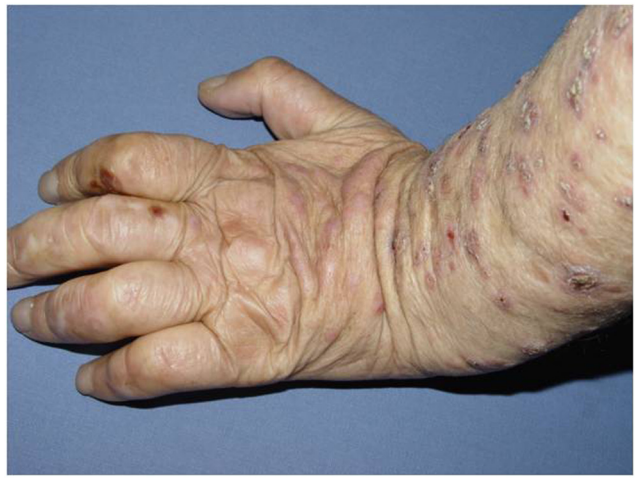

Fig. 12 Sausage-like thickening of fingers, atrophy in hand muscles, and clawing.

nervous system. Skin biopsies should contain the full thickness of the dermis and should be taken from the active side of the lesion.

Indeterminate leprosy

The epidermis is normal. There is a mononuclear cell infiltration, mainly consisting of lymphocytes and a few histiocytes scattered around the dermal veins, nerves, and skin appendages. There are no granuloma structures or Virchow cells. Sometimes, a few acid-resistant bacilli may be shown around dermal nerve fibrils and arrector pilorum muscles.

Tuberculoid leprosy

There is a granulomatous nodular infiltrate in the dermis, and typical tuberculoid structures of dermal epithelial cells, Langhans-type giant cells, and surrounding lymphocytes are seen. Granulomas appear in the epidermis, but acid-fast bacilli are not seen. Nerve involvement is characterized by an infrequent perineural infiltrate with lymphocytes, histiocytes, and plasma cells. There may be caseation within the nerves.

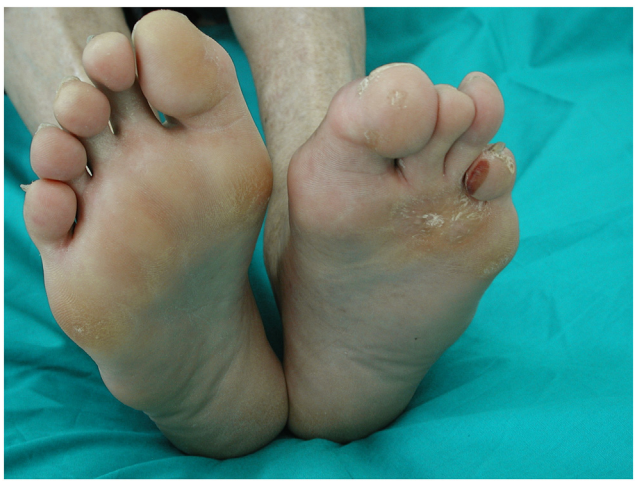

Fig. 11 Flexion deformities of the toes due to involvement of the nervus tibialis posterior, plantar hyperkeratosis, and plantar ulcers.

Borderline leprosy

Borderline leprosy shows histologic patterns of both lepromatous and tuberculoid forms. Epithelioid cell granulomas are more diffuse than those in TT leprosy. There is a subepidermal clear zone in all borderline lesions, especially in borderline leprosy (BB) and borderline lepromatous leprosy (BL) cases.

Lepromatous leprosy

The epidermis is thinned, Rete ridges are flattened, and there are diffuse granuloma formations (lepromas) in the dermis that contain abundant bacilli. The granulomas consist mainly of macrophages that do not convert into epithelial cells. Lymphocytes are scarce or absent. In advanced stages, oily changes occur in the cytoplasm of the macrophages, and Virchow's foamy cells (leprosy cells) occur. Cutaneous nerves show perineural inflammation.[3–6,9,29,30]

Classification of leprosy

The classification of leprosy has been a topic of debate for many years. From the beginning of the 20th century, different classifications have been proposed at meetings held in Manila (1931), Cairo (1938), Rio de Janeiro (1946), Havana (1948), and Madrid (1953). Clinical, bacteriologic, immunologic, and histopathologic criteria are taken into account in the Ridley–Jopling classification that was adopted. This classification includes tuberculoid and lepromatous forms that coincides

Table 1 Doses recommended in leprosy treatment by age

	0-5 years	6-14 years	15 years
Paucibacillary leprosy			
Dapsone/daily	25 mg	50 mg	100 mg
Rifampicin/monthly	300 mg	450 mg	600 mg
Multibacillary leprosy			
Dapsone/daily	25 mg	50 mg	100 mg
Rifampicin/monthly	300 mg	450 mg	600 mg
Clofazimine/monthly	100 mg	200 mg	300 mg
Clofazimine/daily	50 mg/twice weekly	50 mg/every other day	50 mg/day
Ethionamide	250-375 mg/day		

with the immunologic status of the patient and a borderline group between them.

In 1982, the World Health Organization (WHO) implemented multidrug therapy (MDT), resulting in two different treatment schemes that are based on the results of skin smears; in accordance with this, the disease was classified as paucibacillary (PB) and multibacillary (MB). In 1998, WHO repealed the use of slit skin smear examination for the classification of leprosy and adopted a new classification to make the treatment choice easier. When the skin smear is available and positive, the patient is classified as MB, but if it is not available, classification can be based only on the number of skin lesions. Patients with up to five skin lesions are classified as PB, and those with six or more skin lesions are classified as MB.[4,5,8,9,14,16,31]

Clinical aspects of leprosy

Clinical features of the disease depend on the bacterial proliferation, immunologic response of the host to leprosy bacilli, and peripheral neural involvement. Leprosy always involves peripheral nerves, almost always involves skin, and frequently afflicts the mucous membranes.

Clinical signs range from a single hypopigmented macule to a broad spreading involvement of skin and peripheral nervous system and deformities of the eye, bone, muscle, and other tissues. Bacilli prefer the cooler parts of the body. Warmer parts of the body, such as the axillae, groins, inner parts of thighs, perineum, and scalp, are usually spared and are known as the *immune zones.* These differences in clinical signs are the result of host immune response.

Indeterminate leprosy

The indeterminate form can be seen mostly in children or adults moving from leprosy-endemic countries. Indeterminate leprosy lesions are located in the cooler parts of the skin, such as the face, extensor surface of the arms and legs, buttocks, or trunk. The lesions are a few centimeters in size, few in number, and hypopigmented; sometimes, there are erythematous macules with poorly defined borders. These lesions are asymptomatic, with normal sweating and normal body hair. They usually have normal or slightly decreased thermal and tactile sensitivity and do not have characteristic diagnostic features. If the diagnosis cannot be made clinically, a histologic examination can be used for the definitive diagnosis. This lesion spontaneously heals in most of the cases, but a small fraction may progress to advanced clinical types. The disease completely heals with successful treatment in the indeterminate leprosy phase, and there is no reaction or neurologic sequelae.

Tuberculoid leprosy

TT leprosy mainly involves the peripheral nerves and skin. Skin lesions are few in number or solitary and have an asymmetric distribution. A typical tuberculoid lesion is a coppery erythematous or slightly purple raised plaque, with infiltrative borders and normal or hypopigmented center. The surface is dry, hairless, usually scaly, and insensitive. The lesions are large and can reach a diameter of 10 cm or more. They can be localized to any part of the body. Nerve damage occurs in early stages in TT leprosy, but the number of nerves involved is few, or even single, and asymmetrical. Borderline tuberculoid (BT) leprosy shows more deformities with early and more intense nerve involvement. Sensory loss may be difficult to demonstrate in lesions located on the face, because the face is rich in sensory innervation.

Borderline leprosy

Borderline spectrum of leprosy falls between tuberculoid and lepromatous leprosy. Most patients fall into this spectrum, and they also develop severe deformities due to the intense and widespread nerve lesions.

BT leprosy

Skin lesions in BT leprosy are similar to those in TT leprosy. The lesions are more numerous (may be 10-20 or more) and larger, and edge infiltration is weaker than TT lesions. Lesional anesthesia may be less than TT leprosy, and lesions are less dry and scaly. On the other hand, peripheral nerve damage is more common and serious.

BB leprosy

Lesions are macules, papules, plaques, and their combination in various forms and have a symmetrical distribution. Most are similar to those of lepromatous type. Nerve damage occurs in various ratios.

BL leprosy

Skin lesions are small and numerous. Peripheral nerve involvement is widespread. There are large macules of circinate lesions showing central healing. Mouth, nose, and eye lesions are very few; madarosis is absent or not severe. Peripheral nerves are thicker and nerve damage occurs earlier in BL than in LL patients.

Lepromatous leprosy

Early signs of LL are widespread, symmetrical, hypopigmented, becoming copper-red colored macules with indistinct edges. They are bright and damp, and if they are not examined carefully, they may be easily overlooked. Gradually, the skin lesions spread all over the body, but the scalp, perineum, underarms, groin, and middle parts of the body (warmer areas) are spared. In early lesions, there is no loss of sensation, but sweating may slightly be impaired; then the lesions become more infiltrated, and papules, tubercles, and nodules (lepromas) will develop. The lepromas located on the face lead to a diffuse infiltration (facies leonine, or "lion face"), and those located in the nasal mucosa cause nasal obstruction, bleeding, septum perforation, and resorption of the nasal cartilage (trilobed nose, or "clover nose"). Perforation in the palate, loss of uvula, and hoarseness due to thickening of vocal cords can also be seen in lepromatous patients. Retention of the alveolar projections of the maxillary bone causes the anterior and lateral incisors to fall off. The erosion of zygomatic protrusions leads to flattening of the cheeks and gives rise to a characteristic appearance of the upper lip and face. Nerve lesions develop slowly in this type of disease.

Although *M leprae* has a predilection for peripheral nerves and skin, it is also found in other organs via hematic and lymphatic systems. Lepromatous infiltration of the liver may be fatal. Hepatic amyloidosis has also been reported. During the course of the disease, jaundice can be seen due to viral hepatitis or drug-induced toxic hepatitis. LL leprosy may cause blindness through the lepromatous infiltration of the tissues around the eye (trichiasis), infiltration, and atrophy of the eye structures, and inflammatory disease of anterior segment (iridocyclitis). The destructive lesions of the bone are formed directly by leprosy bacilli. Mostly the small bones of the hands and feet are involved. The testes are small and soft. As a result of testicular atrophy, gynecomastia, sterility, and impotence can be seen, and the androgen-dependent hair follicle dispersion is disrupted. Glomerulonephritis is reported in 2% to 23% of the patients.

Lepromatous leprosy does not have spontaneous regression. With effective antileprosy treatment, death from this type of disease has been greatly reduced. In LL cases, infections, such as pneumonia, tuberculosis, and tetanus, and renal failure, are the main causes of mortality. Secondary amyloidosis may develop in LL leprosy, and leprosy patients are more likely to develop skin and other organ malignancies, although there are no sufficient data.[2–5,9,14–16,32–35]

Some rare clinical forms

Pure neural-type leprosy

Leprosy can sometimes appear with only peripheral neuropathy without any skin signs. After months or years, some patients develop skin lesions. This very rare type of leprosy is called *neural-type leprosy* or *pure neural leprosy.* Usually the prevalence is below 1%, but it occurs more frequently in India, with a prevalence of 18%. Because there are no other skin lesions, the diagnosis is difficult and is usually made by biopsy of sensorial nerves, such as the sural and superficial radial nerves.[3–5,28,33,36]

Histoid leprosy

Histoid leprosy is clinically different from the lesions in LL or BL leprosy. It has smooth hemispherical rigid nodules that are about 3 cm in diameter. They are bright copper-reddish in color and located in unconventional areas, such as the lower back, axilla, waist, chest, and neck. Histoid leprosy is seen during relapses in patients successfully treated with dapsone for a long period. The bacilli in these lesions are dapsone resistant. Rarely, histoid nodules can occur in patients who have not previously been treated.[3–5,33]

Localized lepromatous or borderline disease

There is a single nodule or a localized area of nodules and papules. These lesions have bacilli, and other routine sites sought for bacilli are negative.[4,5,14–16,33]

Lucio leprosy (*lepra bonita*)

The entire body has a uniform, diffuse, and bright infiltration. When the disease progresses, diffuse thickening of the eyelids gives the patient a sleepy or sad appearance. The first clinical manifestation is often madarosis. There may be mild anemia, numbness and edema of the hands and feet, nasal congestion, epistaxis, and hoarseness. This type of leprosy is associated with the Lucio phenomenon.[4,5,14–16,28,33]

Nerve involvement

M leprae is a compulsory intracellular microorganism with an affinity for macrophages and Schwann cells. Nerve damage

in leprosy is not only caused by peripheral nerves that are being infected with bacilli but is also due to immunologic and inflammatory response to *M leprae*. Intense involvement of nerves is associated with a high immunologic status. Autonomic, sensory, and motor fibers of the peripheral nerves are involved in priority order. Although sensory function is affected most, all three functions are impaired.

Ulnar nerve

The first sign of ulnar nerve injury is dryness due to autonomic dysfunction at the fourth and fifth fingers and the inner surface of the forearms. Depending on the damage of the sensitive fibers, anesthesia occurs in these regions. When motor fibers are involved, hypothenar atrophy and flexion contracture of the fourth and fifth fingers occur.

Median nerve

Median nerve involvement results in loss of sensation in hands, atrophy in thenar and elbow muscles, and deterioration of the opposition movement of the thumb.

Radial nerve

Radial nerve is rarely damaged. It causes sensory loss of the dorsomedial region of the hand and, if severely damaged, causes wrist drop.

Facial nerve

"Facies antonina" and lagophthalmos are the result of facial nerve damage.

Posterior tibial nerve

When the posterior tibial nerve is involved, dryness, paresthesia, anesthesia, and hyperkeratosis occur on the soles. Later, depression on the foot dome and clawing of the toes develops.

Common peroneal nerve

Common peroneal nerve damage causes anesthesia, hair loss, dryness, and impaired sweating of the lateral side of the legs and of the dorsal and lateral plantar surface of the feet. When motor deficit develops, the dorsiflexion movement of the foot fails. Drop foot, stepping gait, hyperkeratosis, ulcers, and infection on the anterolateral surface of the foot develop in the late phase.[3–5,9,14–16,33,37–41]

Leprosy reactions

In about half of the patients, inflammatory conditions called "reactions" develop during the clinical course of the disease. These inflammatory reactions are due to the immunologic response of the host to the bacilli.

Type I leprosy reaction (reversal reaction)

This type of reaction is related to delayed type hypersensitivity and is seen in TT and borderline (BT, BB, or BL) leprosy patients with immunologic recovery during or after treatment. Clinical manifestations include thickening of the nerves, neuralgia, edema on the face and extremities, exacerbation of preexisting skin lesions, and emergence of new skin lesions. Acute neuritis can cause loss of nerve functions.[2,4,5,9]

Type II leprosy reaction (erythema nodosum leprosum reaction)

Type II leprosy reaction (T2 R) is seen in LL and BL patients under treatment. The mechanism involves cytokine pattern and formation of immune complexes and may be accompanied by cell-mediated immunity. T2 R is a cutaneous and systemic small-cell vasculitis and can affect any tissue containing leprosy antigens. Fever, malaise, arthralgia or arthritis, erythema-nodosum-like skin lesions, iridocyclitis, glomerulonephritis, epididymoorchitis, lymphadenitis, and hepatosplenomegaly are the main clinical manifestations.[2,4,5,9,18,37]

Type III reaction (Lucio's phenomenon)

Patients with diffuse lepromatous leprosy (Lucio leprosy), seen in Central and South America, may develop the *Lucio phenomenon,* a thrombotic phenomenon, in addition to small vessel vasculitis.[42]

Pregnancy and leprosy

Women may present with any type of leprosy during pregnancy. When the patient is in the incubation period, the clinical disease appears or the current disease is exacerbated. Downgrading reactions are observed, especially in the third trimester, due to the suppression of cellular immunity during pregnancy. During the postnatal period, reversal reactions occur as a consequence of upgrading cellular immunity. T2 R is also common in the third trimester and postpartum period. Infants born to lepromatous patients have a low birth weight and show growth retardation.[4,43]

Differential diagnosis

Because the disease exhibits different dermatologic and neurologic manifestations within a wide clinical spectrum, many such diseases should be considered in the differential diagnosis. In areas where leprosy is endemic, the disease is

easily recognized, whereas it may be easily underdiagnosed in nonendemic countries.

Differential diagnosis of cutaneous findings

A variety of dermatologic diseases listed below can be considered in the differential diagnosis of leprosy presenting macular, papular, nodular, plaque, and annular lesions.

Macular lesions

Hypopigmented lesions: vitiligo, nevus anemicus, pityriasis simplex, tinea versicolor alba, sarcoidosis, hypopigmented mycosis fungoides, and postinflammatory hypopigmentation. Hyperpigmented lesions: tinea versicolor, café-au-lait stains, plaque-type parapsoriasis, and postinflammatory hyperpigmentation.[4,5]

Papular and nodular lesions

Sarcoidosis, disseminated granuloma annulare, lichen planus, papular treponemal lesions, leishmaniosis, leiomyomas, syringomas, acne vulgaris, xanthomatosis, erythema elevatum diutinum, pretibial myxedema, lichen myxedematous, neurofibromatosis, Kaposi sarcoma, and lymphoma cutis.[4,5]

Plaque lesions

Infiltrated plaques. Benign and malignant lymphocytic infiltrates, psoriasis, sarcoidosis, mastocytosis, and facial granulomas.[4,5,44–46]

Circinate and annular plaques. Tinea corporis, pityriasis rosea, lichen planus, figurated erythemas, facial granuloma, granuloma annulare, cutaneous lupus erythematosus, lymphocytoma cutis, psoriasis, sarcoidosis, and infectious granulomas (mycobacterial, treponemal, or leishmanial).[4,5,44,46–50]

Differential diagnosis of neurological findings

There are many neurologic findings, such as sensory loss, motor nerve deficits, muscle atrophy, deformities, and planter ulcers in leprosy. They are not usually associated with skin lesions. Neurologic examination is performed for the differential diagnosis. In leprosy, central nervous system is not involved. In many cases, leprosy is ruled out by detecting clinical manifestations such as nystagmus, pupil disorder, loss of reflexes, pathologic reflexes, loss of muscular tonus, and ataxia.

Differential diagnosis in a single nerve destruction

Surgical trauma, bone fractures, nerve tumors, compression neuropathies compression (carpal tunnel syndrome, cervicobrachial syndrome and others), local injections, and so on.

Differential diagnosis in multiple nerve destruction

Hereditary sensory neuropathy (Thevenard's syndrome), Dejerines Sottas disease, neurogenic musculoskeletal atrophy (Tooth-Charcot-Hoffman), syringomyelia, Gullian Barre syndrome, primary amyloidosis of nerves, polyneuropathies: various diseases with neuropathy (diphtheria, botulism, infectious mononucleosis, brucellosis, porphyria, paraproteinemias with impaired sensory function, Hodgkin disease, leukemia, ischemic neuropathies, diabetes, lupus erythematosus, scleroderma, amyloidosis, or pernicious anemia), drug poisoning (gold, arsenic, isoniazid, thallium, mercury, resorcinol, etc), and neurologic findings of AIDS.

Facial paralysis

Otitis media, herpes zoster, and parotid disease (Bell paralysis).[4,5,47,51]

Differential diagnosis of regional manifestations

Differential diagnosis of deforming acral features

Upper extremity/hand deformities. Carpal tunnel syndrome, cervical cot syndrome, Dupuytren contracture, and progressive systemic sclerosis.[47]

Lower extremity/foot deformities. Trophic ulcers, atypical mycobacterial infections, cutaneous tuberculosis, syphilis, leishmaniosis, pyoderma gangrenosum, diabetic ulcers, necrobiosis lipoidica diabeticorum, hypertensive ulcers, sickle cell anemia, chronic venous ulcers, and hereditary neuropathic disturbances.[47]

Differential diagnosis of leonine facies

Actinic reticuloid, chronic polymorphous light eruption, sarcoidosis, granuloma faciale, scleromyxedema, hematologic malignancies mainly mycosis fungoides and leukemia cutis, systemic mastocytosis, and neurofibromatosis.[47]

Differential diagnosis of madarosis

Other infiltrating pathologies such as skin lymphoma, follicular mucinosis, secondary syphilis, hypothyroidism, alopecia areata, trichotillomania, and thallium acetate intoxication.[47]

Differential diagnosis of nose deformities

Common cold, allergic rhinitis, mucocutaneous leishmaniosis, tertiary syphilis, yaws, rhinoscleroma, and relapsing polychondritis.[35,47]

Differential diagnosis of ear deformities

Diffuse cutaneous leishmaniasis, cutaneous lymphoma, lupus vulgaris, and lupus erythematosus.[47]

Differential diagnosis of type I leprosy reaction

Erysipelas, Sweet syndrome, vasculitis, and misdiagnosis as worsening of disease when subclinical lesions become apparent.[47]

Differential diagnosis of type 2 leprosy reaction

Other causes of erythema nodosum, panniculitides, and bacterial, mycobacterial, and other opportunistic fungal infections.[47]

Diagnosis

The greatest difficulty in the diagnosis of leprosy, especially in countries where leprosy is uncommon, is not to think of the disease. The diagnosis of leprosy is simple and practical, and if the diagnostic criteria of leprosy are fully applied, the probability of a false diagnosis will be greatly reduced.

There is no laboratory test that alone can make a diagnosis of leprosy. In the presence of suspicious clinical findings, patient history, clinical examination, investigation of peripheral nerve damage findings, and laboratory findings should be performed.[52,53]

Patient history

For the diagnosis of leprosy, history of contact with a lepromatous patient has vital importance. In countries where leprosy is uncommon, suspicious cases should be investigated for the last 10 to 15 years.[54] In the beginning, there may be no typical clinical manifestations; however, later in lepromatous leprosy, nasal obstruction and bleeding can be an important clue for upper respiratory tract involvement. Paresthesia and hyperalgesia may be noted as a result of peripheral neuropathy. Occasionally, localized itching may be the first presentation of neuropathy.[54,55]

Skin lesions

Skin lesions are present in all clinical forms. These are macular, papulo-nodular, or plaque-type lepromatous lesions (see Clinical Aspects of Leprosy section).[54,56] The most prominent features of skin lesions are dryness, loss of sweating, hair loss, and sensory loss, though they develop in a different way in tuberculoid and lepromatous disease. All these properties should be investigated in the course of skin examination.[54,56]

Findings of peripheric nerve involvement

Because leprosy primarily affects the peripheral nerves, this involvement should always be investigated by searching for peripheral nerve thickening and loss of sensation both on skin lesions and on the skin areas that are innervated by the peripheral nerves.[38,54] Although histamine and methacholine testing are suggested to demonstrate postganglionic nerve damage and sweating disturbances, in practice they are not routinely used.[52–54]

Radiologic examinations

Radiologic examinations, such as scintigraphy, ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), and electroneuromyography, can be used to evaluate peripheral neural involvement. Nerve biopsies (sural nerve biopsy) can be performed for the diagnosis of primary neural leprosy.

At the seventh meeting of the WHO in 1977, "three cardinal diagnostic criteria" were adopted by the expert committee to recognize leprosy[8,53]:

1. Hypopigmented or reddish skin lesions with loss of sensation
2. Involvement of the peripheral nerves, as demonstrated by their thickening and associated loss of sensation
3. Skin-smear positive for acid-fast bacilli

According to this proposal, the examinations that follow should be made for the diagnosis of leprosy.

Investigation of sensorial impairment

Testing for loss of sensation is a very simple test, and, when positive, it confirms the diagnosis of leprosy. Hot-cold, tactile, and pain sensations should be examined in suspicious skin lesions and all skin areas.[3–6,9,22,38,54]

Examination of peripheral nerve thickening

The peripheral nerves are assessed as thickened, stiff, or tender. Locations that can be palpated are between the olecranon and the median epicondyle, the ulnar nerve, between the tendons of the wrist the median nerve, at the lateral side of the wrist the radial cutaneous nerve, at the medial ankle the posterior tibial nerve, and at the lateral popliteal fossa the common peroneal nerve. Large auricular nerve thickening is palpable and visible on the outer edge of the sternocleidomastoid muscle and supraorbital nerve thickening on the upper part of the orbit.[3–6,9,22,38,54]

Skin smear microscopy

M leprae multiplies more easily in the cooler parts of body. The search for bacilli should be directed to:

- the outer parts of the eyebrows, chin, and ear lobes
- outer surface of the fingers and toes
- relatively cold skin areas such as elbows, knees, and nasal mucosa

At the outset, the skin area is wiped with an alcoholic cotton, and a skinfold is gripped firmly between thumb and index finger to prevent bleeding. An incision of 5 mm in length and 3 mm in depth is made with a scalpel, and the blade is turned at the right angle several times within the incision. Dermal tissue collected on the blade is smeared on a glass slide. For nasal mucosa, nasal swabs can be obtained by the aid of a curette or dry swab cotton. The smear is fixed and stained with Ehrlich-Ziehl-Neelson (EZN).[3–6,9,22,54]

Dermatopathologic diagnosis

Dermatopathologic diagnosis is the most valuable diagnostic method. A nerve biopsy taken from the cutaneous sensory

nerves (radial cutaneous nerve and sural nerve) is necessary for the diagnosis of primary neuritic leprosy.

Seroimmunologic diagnostic methods

Specific serologic tests are helpful in the diagnosis of early subclinical *M leprae* infection. By obtaining monoclonal antibodies against various antigenic determinants of *M leprae,* it is possible to distinguish the leprosy bacillus from other mycobacteria and provide great help for the serologic diagnosis of leprosy.[4,5,9]

Polymerase chain reaction

Polymerase chain reaction can be employed where modern molecular biology techniques are available, but it is not practical outside of medical centers.[52,57]

Prognosis of leprosy

Leprosy is not a life-threatening disease, except for glomerulonephritis, liver involvement, and severe leprosy reactions. Leprosy patients often die of causes other than their infection.[34,58]

Treatment of leprosy

M leprae is naturally resistant to most of the standard antimicrobials, because the structure of its cell wall prevents penetration of the agents. One of the first drugs used in leprosy treatment was Chaulmoogra oil. Certain components of this substance are effective against a few mycobacterial species but not *M leprae.*

There was no effective treatment against leprosy until the discovery of the use of dapsone in the mid-1940s. Between the 1940s and 1970s, antileprosy treatment was based on dapsone monotherapy, which was used 5 years for paucibacillary forms and for a lifetime for multibacillary patients. Unfortunately, primary and secondary resistance led to the need for new medications. Clofazimine, synthetized in the mid-1950s, was first proposed as a tuberculosis treatment, but then its effectiveness was demonstrated against *M leprae.* Rifampicin was discovered in 1967 and was first used as a tuberculosis treatment before it was recognized as an effective antileprosy agent. Subsequently, second-line agents (fluoroquinolones, minocycline, and clarithromycin) emerged as potential therapeutic agents. Recently new therapeutic agents, such as bedaquiline, have shown bactericidal activity against *M leprae* in mice, similar to that of moxifloxacin and rifampicin.[59,60] (See Table 1.)

WHO treatment plan 1982

WHO initiated the use of multidrug therapy with the aim of increasing treatment effectiveness, reducing the duration and frequency of treatment, preventing resistant bacilli, removing resistant strains, reducing side effects, and reducing the total cost of therapy. A study group was formed to evaluate treatment regimens, and this study group announced a MDT protocol in 1982. MDT has become the recommended standard therapy for leprosy patients.

According to these treatment protocols, patients are treated in two main groups.

Paucibacillary leprosy (I: Indeterminate, TT, and BT cases smaller than BI 2: Bacterial index 2) treatment

Dapsone 100 mg/daily/unsupervised, and rifampicin 600 mg/monthly/supervised, for 6 months.

Multibacillary leprosy (LL, BL, and BT cases greater than BI 2: Bacterial index 2) treatment

Dapsone 100 mg/daily unsupervised plus Rifampicin 600 mg/monthly supervised and clofazimine 100 mg/daily unsupervised, additional 300 mg/monthly supervised; for 2 years/or until bacteriologically negative.

Paucibacillary patients require 2 years, and multibacillary patients at least 5 years, of monitoring after treatment.

WHO 2003 leprosy treatment protocols

By taking the developments in leprosy treatment into consideration, the WHO technical advisory group announced changes, which they accepted in February 2003.

To facilitate implementation in diagnosis and treatment, the classification employs:

1. Skin smears (PB leprosy: smear-negative cases; MB leprosy: smear-positive cases)
2. Clinical findings: number of lesions (SLPB: Single lesion paucibacillary leprosy: single skin lesion; PB leprosy: 2-5 skin lesions; MB leprosy: more than 5 skin lesions)

It can also be assessed according to the number of nerves involved. In suspicious cases, MB treatment regimens are used.

This study group reduced the duration of treatment from 24 months to 12 months in multibacillary patients. If healing is delayed or if nerve damage is detected, an additional 12 months of treatment is recommended.

Substitution treatment

In cases where standard MDT is contraindicated or cannot be used due to drug resistance, different treatment schemes with new treatment combinations of quinolones (ofloxacin,

pefloxacin, sparfloxacin, and moxifloxacin), tetracyclines (minocycline), macrolides (clarithromycin), and rifampicin derivatives (rifapentine) can be recommended.

In addition to the standard treatment protocols, these antimicrobials have been used to obtain a broader range of options, to treat resistant cases, and to shorten the duration of treatment.[2–6,8,9,59–61]

Treatment of leprosy reactions

Type 1 leprosy reaction: Reversal reaction

In the reversal reaction, without neurologic manifestations, analgesics and nonsteroidal anti-inflammatory drugs (NSAID) may be sufficient. In addition to NSAIDs, systemic glucocorticoid therapy may be required. Azathioprine and cyclosporine are also effective. In the case of neuritis attacks, physical rest and immobilization are recommended. In some cases with severe neuritis, surgical decompression may be needed to prevent nerve damage and loss of function.

T2 R: Erythema nodosum leprosum reaction

In these patients, the antigenic load is reduced with antileprosy drugs. Clofazimine has antiinflammatory effects and suppresses T2 R. If only skin is involved and T2 R is mild, analgesics and NSAIDs are sufficient. Antimalarial drugs can be added when arthritic clinical manifestations arise. In severe T2 R, the drug of choice is 400 mg/d thalidomide for 2 doses per day.[3–5,9,37,59,61]

Prophylaxis

Elimination of leprosy cannot be achieved by MDT alone, and new tools are needed to prevent leprosy. In past times, the most common method to prevent disease spread was isolation of the patients at home or in sanatoria; however, strict isolation of a healthy and active patient can lead to several social as well as economic problems. The practical importance of this practice can be discussed as it is not possible to recognize all cases with early and active disease. Paucibacillary patients are considered noncontagious, and multibacillary patients become noncontagious after a single dose of 600-mg rifampicin.

Chemoprophylaxis with dapsone was given for extended periods; however, this provided only 50% protection. It is no longer used, as low doses of dapsone contribute to the development of resistant strains. Chemoprophylaxis with a single 25-mg/kg dose of rifampicin was implemented in 1988, with an overall protective effect of approximately 60%.

Apart from chemoprophylaxis, immunoprophylaxis with vaccination is an important issue. Two types of antileprosy vaccination are used: immunoprophylactic vaccination (correcting the known host response to mycobacterial antigens) and immunotherapeutic vaccination (targeting the immunologic mechanisms to achieve intracellular bacterial death).

Today, the most commonly used vaccine is BCG vaccine, which provides protection between 20% and 80%. Using SDR in combination with BCG vaccine provides an additional protective effect up to 80%.

In endemic areas where an effective vaccine against leprosy (primer protection) is unavailable, secondary prevention based on early detection and rapid treatment is used. Modern leprosy control programs comprise the diagnosis of the new cases, treatment of these patients, and patient and public education.[4,5,61,62]

Conclusions

Leprosy is a mutilating and stigmatizing disease with a low rate of infectivity and a wide range of clinical presentations. It causes a great diagnostic dilemma, justifying the description "the great imitator." In endemic areas, it is imperative to keep in mind the "many faces of leprosy" to prevent misdiagnosis. There is still a need for developing new and better diagnostic tools and treatment methods to achieve early diagnosis and treatment of leprosy and its complications. Today's modern leprosy control program comprises diagnosis of the new cases, treatment of these patients, and patient and public education.[1,2,60,61]

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