Clinical Diagnosis of Leprosy

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Introduction

Leprosy, which is caused by the *Mycobacterium leprae* (see Chapter 5.1), is a disease of low contagion that presents with protean manifestations. In its usual presentation, it is a chronic disease whose slow clinical progression is often punctuated by hypersensitivity reactions (lepra reactions; see Chapter 2.2). The disease ranges from a singular patch or single nerve thickening to the diffuse involvement of the skin, multiple nerves, and even the internal organs. The neurological involvement (see Chapter 2.5) in leprosy results in sensory-motor deficits leading to deformities and disability (see Chapter 4.1). These deformities lead to stigmatization (see Chapter 4.5) and the socioeconomic-emotional isolation of leprosy patients.

A lack of awareness about the signs and symptoms of the disease makes the diagnosis of leprosy very challenging, especially for practitioners in areas of low endemicity. In the UK, the clinical diagnosis of leprosy was not suspected in 80% or more of patients on their first visit, and the diagnostic delay averaged 1.8 years (1). Hence, it is imperative to recognize, classify, and appropriately treat the disease to prevent complications that are more difficult to manage.

The clinical recognition of the subtle signs of leprosy is of great value in its diagnosis, as that recognition clinches the diagnosis in most of the cases. Laboratory tests (see Chapter 7.1) are often unavailable in highly endemic nations and polymerase chain reaction (PCR; see Chapter 7.2) is currently not adequately reliable. As a result, slit-skin smears (SSS) and histopathology (see Chapter 2.4) are simple but important investigative tools in the diagnosis of leprosy. The WHO expert committee on leprosy has defined a case of leprosy as an individual who has one of the following cardinal signs of leprosy but who has not received a full course of multi-drug therapy (MDT) for the type of leprosy identified (2):

- A definite loss of sensation in a pale (hypopigmented) or reddish skin patch
- A thickened or enlarged peripheral nerve with a loss of sensation and/or weakness in the muscles supplied by the nerve
- The presence of acid-fast bacilli in an SSS

The diagnosis of leprosy is often complicated by what have been defined as the 'spectral' manifestations of the disease, which are due to the variability in the type and strength of the body's immune response (see Chapter 6.2) to *M. leprae*. A strong cell-mediated immune response leads to a milder form of presentation, whereas a weaker cell-mediated immune response leads to a more severe form of the disease. This spectral presentation has resulted in the development of several classification systems for leprosy, two of the most important being the Ridley and Jopling classification (see Chapter 2.4) and the WHO classification.

In 1966, Ridley and Jopling (3) proposed a classification system for leprosy (shown in Table 1). This classification was developed for research purposes and is still used in clinical practice in many parts of the world, including the U.S. and most European countries. The Ridley-Jopling system classifies leprosy as an immune-mediated spectral disease with tuberculoid leprosy (TT) at one end of the spectrum and lepromatous leprosy (LL) at the other end. These two ends of the spectrum are considered to be clinically stable. Immunologically, strong cell-mediated immunity (CMI) correlates with the TT type and weak CMI correlates with the LL type of the disease. Between these two ends lies the clinically unstable borderline spectrum, which can be further subdivided into borderline tuberculoid (BT), mid-borderline (BB), and borderline lepromatous (BL), of which BB is the least stable. Leprosy as a disease frequently undergoes changes in clinical presentation depending on the immune status of the individual. If the disease is moving up the spectrum, i.e., towards TT, it is upgrading, and if the disease is moving down the spectrum, i.e., towards LL, it is downgrading. Hence, the Ridley-Jopling classification helps correlate the disease pathophysiology with the clinical features and describes leprosy as a spectral disease from a clinical, immunological, and histopathological perspective. The Ridley-Jopling classification, however, does not include the indeterminate and pure neuritic forms of leprosy.

The WHO classification system (1981), which is an operational classification system, was developed to simplify the institution of chemotherapy (Table 1). The WHO classifies leprosy as multi-

bacillary (MB) or paucibacillary (PB) leprosy. This distinction was initially made on the basis of SSS positivity, in which patients with a bacillary index (BI; see Chapter 2.4) of more than 2 are treated as MB and the rest as PB. The BI is directly related to the bacterial load, and it denotes the total number of bacilli, regardless of their shape and staining (Table 2).

TABLE 1 Leprosy classification: Ridley Jopling and WHO

Ridley Jopling Classification (1966)	WHO Classification (1981)
Tuberculoid leprosy (TT) Borderline tuberculoid (BT)	Paucibacillary Leprosy up to 5 skin lesions SSS negative on all sites
Borderline borderline (BB) Borderline lepromatous (BL) Lepromatous leprosy (LL)	Multibacillary Leprosy 6 or more skin lesions SSS positive at any site

TABLE 2 Bacillary Index (see Chapter 2.4)

BI is expressed in logarithmic scales:
1 + (1 bacillus in every 100 fields),
2 + (1 bacillus in every 10 fields),
3 + (1 bacillus in every field),
4 + (1–10 bacilli in every field),
5 + (10–100 bacilli in every field),
6 + (More than 100 bacilli and even globi in every field).

The current WHO classification of leprosy as MB or PB is simply based on the total number of leprosy lesions in a given individual. Initially, for feasibility and operational purposes, all of the patients who had SSS positivity were regarded as MB. However, when SSS was applied globally, quality control issues emerged. Hence, in 1998, SSS was omitted as a basis for the distinction between MB and PB leprosy.

The sensitivity and specificity of the WHO classification has been reported to be around 90% (4). Nerve involvement is not part of the WHO's clinical classification. In India, the number of nerves involved, along with the number of skin lesions, is taken into consideration in the classification of leprosy into PB and MB cases. This classification system was developed by the National Leprosy Eradication Program (NLEP) of the Government of India, the Global Alliance for Leprosy Elimination, and the WHO (Table 3) (5). Single nerve involvement is labeled PB; more nerve involvement is labeled MB (5).

TABLE 3 NLEP classification, India (2009)

Paucibacillary leprosy	Up to 5 skin lesions; No nerve / single nerve involvement with five lesions (including nerve). Skin smear negative at all sites.
Multibacillary leprosy	6 or more skin lesions. More than one nerve involvement, irrespective of the number of skin lesions. Skin smear positive at any site.

INDIAN CLASSIFICATION

The Indian classification was accepted and adopted in India in 1955 (6). The aim of the Indian system was to include all levels of leprosy workers from grass-root workers to researchers. The Indian classification includes six groups: (i) tuberculoid, (ii) borderline, (iii) lepromatous, (iv) indeterminate, (v) pure neuritic, and (vi) maculoanesthetic. In 1981, the Indian classification was modified and accepted by the Indian Association of Leprologists (IAL) and the new five-group classification was named the New IAL classification of leprosy (7). Maculoanesthetic leprosy was later removed from this classification.

Clinical Features of Leprosy

Detecting the clinical features of leprosy in a patient requires a meticulous approach. The presentation is subtle in many patients, especially in the indeterminate and tuberculoid portions of the spectrum. The patient should be fully exposed and observed under adequate lighting to detect the clinical signs of leprosy.

According to the Eighth Report of the WHO Expert Committee on Leprosy, leprosy should be suspected in people with any of the following symptoms and signs (2):

- Pale or reddish patch(es) on the skin
- Loss, or decrease, of feeling in the skin patch(es)
- Numbness or tingling of hands, feet
- Painful or tender nerves
- Swelling of or nodules on the face or earlobes
- Painless wounds or burns on the hands or feet

The various clinical types of leprosy are described below.

INDETERMINATE LEPROSY (I)

The earliest clinical presentation in leprosy often is in the form of an ill-defined hypopigmented macule or patch, situated on the lateral / outer aspect of the thigh, face, and extensor aspect of the limbs. The color, however, may vary within the same individual or between individuals depending on skin type. In fair-skinned patients, the lesions may be erythematous, and in dark-skinned patients, they may be coppery brown. The body hair appears normal on these lesions, but the macule may be slightly dry as compared to the surrounding skin. This initial clinical presentation is known as indeterminate leprosy and is observed as the first sign of the disease in about 20–80% of the patients, often in the examination of family contacts of an index case. However, it is generally believed that the CMI response against *M*. *leprae* is not well developed in this early presentation.

There might be single or multiple lesions, no more than 3–4 cm wide, with a smooth surface that might occasionally have a slightly creased or wrinkled appearance. The larger lesions are fairly well defined, whereas the smaller lesions have an indefinite border that fades imperceptibly into the surrounding skin (Figure 1). The number of lesions depends on the CMI of the patient, which is genetically determined (see Chapter 8.1). Patients with a stronger CMI usually present with few skin lesions, have a strong tendency to self heal without treatment, and have a higher tendency to evolve towards the TT or BT forms of leprosy. Patients with a weaker CMI usually present with multiple skin lesions and, without treatment, they have a higher tendency to evolve towards the BB, BL, or LL forms of leprosy.

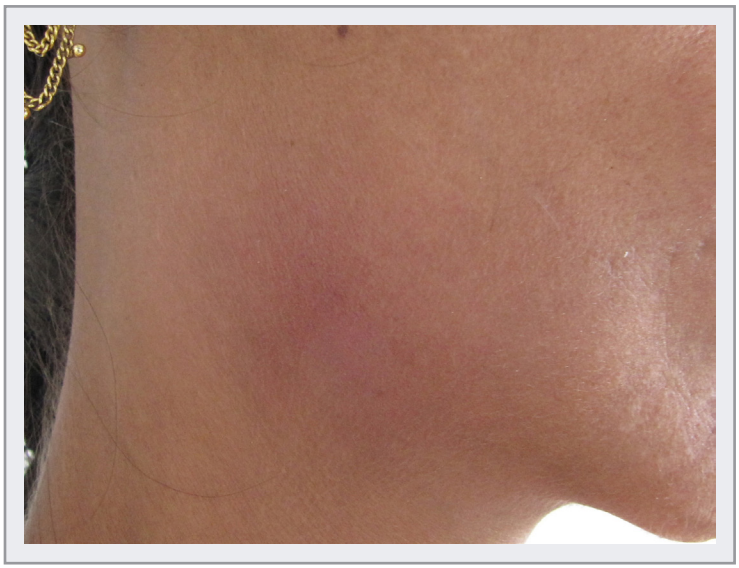


FIG 1 Indeterminate leprosy. An ill-defined erythematous patch over the face.

Sensory loss is unusual in indeterminate leprosy. However, patients commonly present with a loss of thermal sensation, i.e., an inability to differentiate between hot and cold water in a test tube. Hyperalgesia may often precede the detection of skin lesions. The slit-skin smear (SSS) is usually negative.

The absolute confirmation of the diagnosis of indeterminate leprosy is a demonstration of acid-fast bacilli in Fite-stained sections in a biopsy; perineurovascular infiltration (see Chapter 2.4) is highly suggestive. The histamine test is very useful in the diagnosis of indeterminate leprosy in fair-skinned individuals. The triphasic skin reaction known as the triple response of Lewis is not observed in the leprosy lesion. The triple response depends on the local response to histamine,

which is in the form of erythema, wheal, and flare. For the response to completely manifest itself, the integrity of the sympathetic system should be well preserved, which is not true in the leprous lesion.

The common differentials (see Chapter 2.3) for lesions of indeterminate leprosy are pityriasis alba, a hypochromic variant of P. *versicolor*, early vitiligo, post inflammatory hypopigmentation, and a hypopigmented variant of polymorphic light eruption.

In our experience with the prognosis of indeterminate leprosy, three out of four indeterminate cases heal on their own and the rest become 'determinate' and enter the clinical spectrum of leprosy. However, when the clinical suspicion is doubtful and the histology is inconclusive, the patient should be kept under close supervision. There should be no hurry to label the patient as a case of leprosy, as the disease is often associated with severe social stigma. The key features of indeterminate leprosy are summarized in Table 4.

TABLE 4 Indeterminate leprosy

Hypopigmented, ill to well defined macules or patches of variable sizes.
Hypoesthesia is not predominant.
Cell mediated immunity is not well developed.
Slit-skin smear is negative.
Histopathology shows infiltrate around neurovascular bundle, few bacilli may be found.
Histamine test can be used for diagnosis in fair-skinned individuals.
With treatment, prognosis is good, without reactions or neurological sequelae.
Without treatment, three out of four cases heal by themselves.

TUBERCULOID LEPROSY (TT)

Tuberculoid leprosy forms one end of the spectrum in the Ridley-Jopling classification. The CMI is high in patients with tuberculoid leprosy and the lepromin test is reactive. Due to the high CMI (see Chapter 6.2), lesions may heal on their own in the majority of patients (8). The symptoms in TT might be cutaneous or neural or both.

Cutaneous lesions in TT do not number more than 3, are up to 10cm in diameter, and are well defined. The lesions are rarely very large. The lesions may occur on any part of the body, but often there is a predilection for exposed/uncovered areas of the body. The lesions are in the form of erythematous papules or plaques with a well-defined outer border (Figure 2A). Less commonly in early stages, clinical presentation is in the form a macular lesion. The macular lesions are hypopigmented but can also be erythematous. Erythema of the lesion may not be well appreciated in dark skinned individuals in whom the lesions may appear to have coppery hue. The lesions are

hypopigmented and never depigmented, having dry mild scaly surface and well defined borders (Figure 2B). They may have papular lesions on the outer edges (9, 10). Plaques often show central flattening or clearing, which gives the lesion annular morphology. In case of such presentations, the border slopes towards the inner margin and is abrupt on the outer margin. These characteristics are due to the central clearance and peripheral spread of the disease activity (10). Often, there is an enlarged nerve at the border of the macule or plaque. Light palpation around the border of the lesion helps to detect this subtle clinical sign, which may otherwise be missed.

Neural involvement in TT is uncommon and usually occurs as a result of the extension of the infection through cutaneous superficial branches. Hence, the nerve involvement is usually patchy, unilateral, and asymmetrical. The neural symptoms can present as pain, sensory loss, tingling, and muscle weakness or paralysis. Nerve pain may be the first presentation of TT (11). Very rarely, TT may present solely as anesthetic areas without changes of skin color or peripheral nerve enlargement (11).

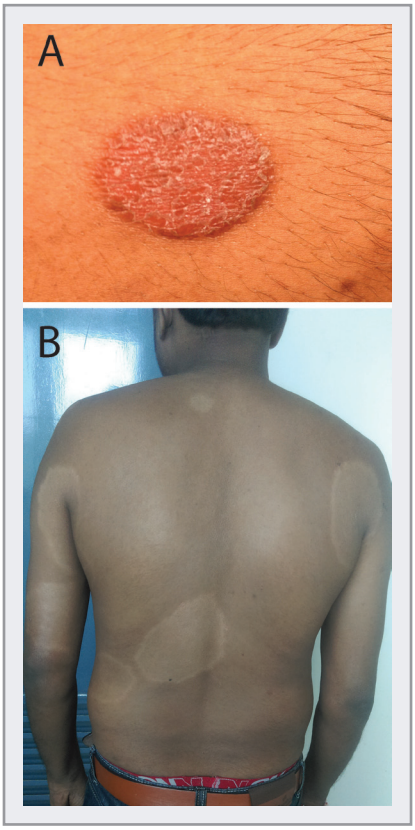


FIG 2A TT leprosy, with well-defined, erythematous, hairless, dry, anesthetic plaque.

FIG 2B Maculoanesthetic BT leprosy, hypopigmented, hypoesthetic, dry patch with loss of appendages.

The lesion is often completely anesthetic. First the temperature sensitivity is lost, followed by pain and finally the loss of tactile sensitivity. On the face, the sensory impairment is difficult to demonstrate because of the rich sensory innervations that may compensate for the damaged nerves. In an individual lesion, the sensory loss is more marked in the center than in the periphery. Due to the involvement of autonomic nerves, the surface is dry and sweating is lost. Well-organized epithelioid granulomas are characteristic histopathologic findings (see Chapter 2.4) in a skin biopsy of the lesion, but acid-fast organisms are difficult to demonstrate in Fite-stained sections and skin smears are usually negative. The lesions are often dry to the touch, and the lesions may be devoid of hair (9).

There might be nodular swellings along the course of thickened nerves (see Chapter 2.3), which may be caused by localized nerve abscesses. The nerve abscess formation is more common in the tuberculoid portion of the leprosy spectrum. The type of abscess seen in TT is a ‘cold abscess’ with scanty lepra bacilli, whereas in the rest of the spectrum the abscess is of the inflammatory type with a large number of inflammatory cells and plenty of degenerating bacilli (12). The nerve abscess may be present in the nerve trunk and can occasionally be very large in size, mimicking a tumor. The nerve abscess may find its way out of the sheath and pro-

duce swelling beside the nerve. It might also rupture through the skin, producing a discharging sinus. Eventually, the abscess may calcify and the calcification can spread over long stretches of the nerve, which can be detected by X-rays (12).

The common differentials (see Chapter 2.3) of tuberculoid leprosy are often the lesions which show annular morphology such as tinea, subacute lupus erythematosus (SCLE), annular sarcoid, syphilis, and a herald patch of pityriasis rosea. Clinical examination and histopathology secure the diagnosis. The sweat test demonstrates anhidrosis and the complete triple response is not seen in the histamine test (13).

The prognosis is good, as a TT lesion can even self-heal. However, nerve damage-related disability can occur. The key features of TT are summarized in Table 5 (see next page).

BORDERLINE LEPROSY

Globally, the borderline form contributes the majority of the disease burden due to leprosy. Immunologically, the disease is unstable and may either upgrade to the tuberculoid portion of the spectrum with treatment, or downgrade to the lepromatous portion of the spectrum if untreated. The CMI in BL ranges between the tuberculoid and lepromatous poles. This immunological instability is reflected in the variability of clinical features seen in this spectrum. This immunological instability increases the tendency to develop lepra reactions (see Chapter 2.2) and 30% of the patients with BL are at risk of developing type I reactions (Figures 3A, 3B) (9). This risk translates to a higher chance of developing crippling deformities in the borderline cases.

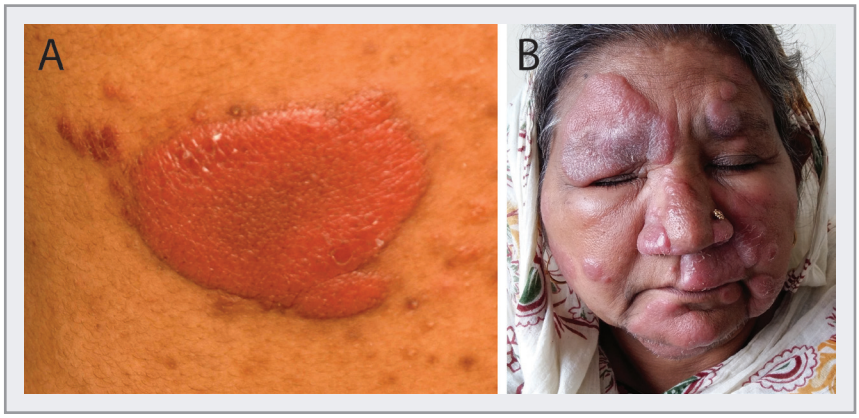


FIG 3 BT leprosy in reaction.

A. BT leprosy in reaction. Erythematous, indurated, succulent, shiny plaque. Note the finger like projection (pseudopodia) and satellite lesions.

B. BT leprosy in reaction (face) showing downgrading to BL. Multiple succulent erythematous, edematous, shiny plaques can be observed.

The skin lesions also vary in numbers and morphology as we move from BT to the BL type of the disease. Skin lesions in BT are clinically closer to skin lesions in TT, and the lesions in BL are closer to those in LL. Skin lesions are fewer in number, asymmetrical, better defined, dry, and less shiny

and smooth, with an absence of appendages in the BT spectrum. As the disease downgrades, skin lesions become more numerous and ill-defined and are shiny in appearance. Loss of appendages is prominent higher up in the BT spectrum. However, the loss of sensation in BT is never as severe as that seen in TT. The loss of sensation in the limbs tends to become more symmetrical in the extremities if the disease progresses from BT to BL.

The involvement of the nerves is prominent in borderline lesions. The nerve involvement is asymmetrical and seen in fewer nerves in BT lesions. With numerous nerves involved, the nerve involvement becomes more symmetrical towards the BL portion of the spectrum. The borderline portion of the disease spectrum is extremely unstable and can move towards any pole. But, when left untreated, the disease has a tendency to deteriorate and move towards the lepromatous end of the spectrum (13). The key features of BL are summarized in Table 5.

BORDERLINE TUBERCULOID (BT)

Lesions in BT often resemble those in TT, but are more numerous, larger in size, and less well defined. Unlike TT, where the outer margin is well defined, lesions in BT have an outer margin that at places slopes towards the surrounding skin. BT lesions are characterized by 'finger like' extensions, known as pseudopodia. There may be satellite lesions surrounding the plaque (Figure 3A). The lesions are often dry, scaly, hypoesthetic plaques with a loss of appendages and decreased sweating (Figures 3C–3F); however, these features are not as prominent as those seen in TT. In the maculoanesthetic presentation of BT, there are pale macules with decreased sensation, mostly on the face, lateral aspect of extremities, buttocks, and scapulae. These are large and asymmetrical hypopigmented lesions with well-defined edges and a dry surface with decreased sweating (14).

The nerves are asymmetrically and irregularly thickened in BT leprosy. The patient may present with anesthesia and motor deficits. The nerves are severely involved in episodes of reaction in BT (14). During a reaction episode, the nerve function may deteriorate rapidly and the patient may present for the first time because of the nerve function impairment. In the absence of prompt treatment, this reaction might lead to paralysis, followed by deformity and disability (Figure 3G).

Fite staining for AFB is often positive and the BI ranges between 0 and 2+ in skin smears.

BORDERLINE BORDERLINE (BB)

BB is the most immunologically unstable portion of the borderline spectrum (9). Patients quickly move either towards the lepromatous or the tuberculoid poles. Dimorphous lesions, i.e., lesions characteristic of both the tuberculoid and lepromatous types, are seen in this part of the spectrum. Skin lesions, which are in the form of infiltrated papules, plaques, and even nodules at times, tend to be symmetric. The characteristic lesion of BB leprosy is an annular plaque with a well-demarcated 'punched-out' inner margin and a sloping outer margin, giving a 'swiss cheese' appearance (Figures 4A, 4B).

TABLE 5 Characteristics of Ridley Jopling classification through the whole spectrum.

	Number and type of lesion(s)	Size of lesion(s)	Surface of lesion	Sensations	Peripheral Nerves
TT	One to three well defined macule(s) or plaque(s)	Variable size, usually large	Dry, scaly, and infiltrated	Absent	Asymmetrical, single nerve enlargement. Nerve to patch may be palpable.
BT	Macules or plaques, variable in number, up to ten. Occasionally showing finger-like extensions (pseudopodia) or satellite lesions.	Variable size, some lesions are large	Dry, scaly, and infiltrated (but less than in TT lesion)	Markedly diminished	Asymmetrical enlargement of few nerve(s)
BB	Macules or plaques with annular, 'swiss cheese' appearance. Variable number (10–30).	Variable	Dry, scaly, and slightly shiny	Moderately diminished	Asymmetrical enlargement of several nerves
BL	Macules, papules, plaques, and some nodules, lesions with variable morphology, asymmetrical in distribution.	Variable, usually small	Shiny (less than LL)	Slightly diminished	Increasingly symmetrical enlargement of nerves
LL	Macules, plaques, and nodular lesions. Innumerable lesions showing tendency to symmetry in distribution.	Small	Shiny	May be normal	Symmetrical involvement of nerve trunks with 'glove and stocking anesthesia'. Nerves may feel normal on palpation or may be thickened.

TT: Tuberculoid; BT: Borderline tuberculoid; BB: Borderline borderline; BL: Borderline lepromatous;

TABLE 5 ▯ continued

	Hair	Bacteriology on SSS	Typical reaction	Lepromin reactivity	Histopathology
TT	Absent	Negative	Type 1	Strongly positive (+++)	Granuloma consisting of lymphocytes epithelioid and giant cells erodes the epidermis. Small nerves are completely effaced by caseating granuloma. AFB are not seen.
BT	Markedly diminished	Negative or scanty bacilli	Type 1	Weakly positive (+ or ++)	Granuloma consists of epithelioid cells and an admixture of macrophages and lymphocytes. Giant cells are also seen. Clear SEZ present. Nerves are replaced by granuloma. Fragmented bacilli are seen with AFB stain.
BB	Moderately diminished	Moderate number of AFB present	Type 1/ Type 2	Negative/ weakly positive	Granuloma consisting of predominantly epithelioid cells and macrophages and scattered lymphocytes are also seen. SEZ is always clear. Transverse section of the nerve shows cut onion appearance. AFB are always present.
BL	Slightly diminished	Large number of AFB visualized	Type 1/ Type 2	Negative	Granuloma around nerve neurovascular bundle consists primarily of macrophages and isolated clumps of epithelioid cells. Lymphocytes are scattered sparsely. SEZ is clear. Nerves show concentric perineural cell infiltration and more conspicuous cut onion appearance. AFB are plentiful, including small globi.
LL	Almost normal (initially)	Plenty of AFB including globi are seen	Type 2	Negative	Expansive and loose granuloma is distinct, with plenty of macrophages loaded with AFB. Few lymphocytes are also seen. AFB are seen in endothelial and also Schwann cells. SEZ is always clear. Nerves are minimally involved.

LL: Lepromatous leprosy; SSS: Slit-Skin Smear; AFB: Acid Fast Bacilli; SEZ: Sub Epidermal Zone.

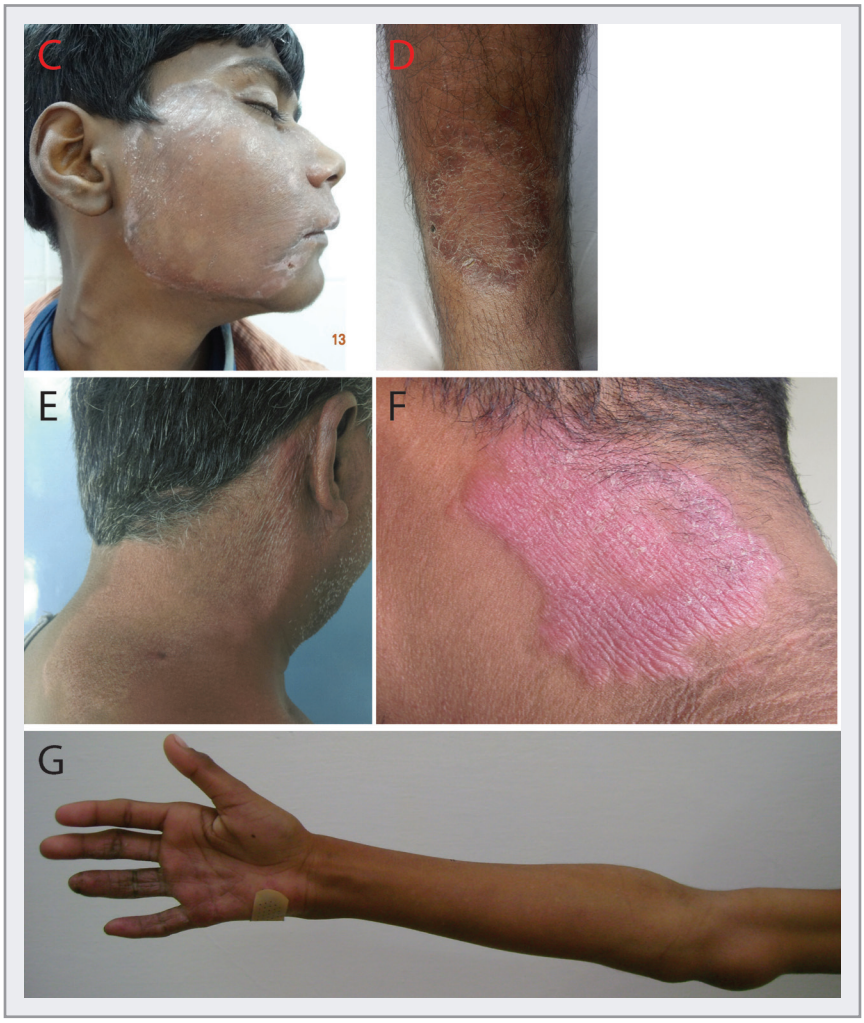


FIG 3 BT leprosy.

C. BT leprosy. Hypopigmented, hypoesthetic, dry plaque with well-defined outer border and loss of appendages. Enlarged greater auricular nerve can be observed on neck.

D. BT leprosy on the leg. Hypopigmented to coppery brown, hypoesthetic, dry patch with decreased hair density.

E. BT Leprosy on nape of neck – large, hypigmented to erythematous plaque with central clearing and elevated borders. Xerosis, wrinkling, and loss of hair can be seen.

F. BT leprosy on the nape of neck. Erythematous, well-defined, dry plaque with well-defined outer border and loss of appendages. Satellite lesions can be observed surrounding the large plaque.

G. BT leprosy in type 1 reaction presenting with ulnar nerve abscess and subsequent deformity in the form of ulnar clawing.

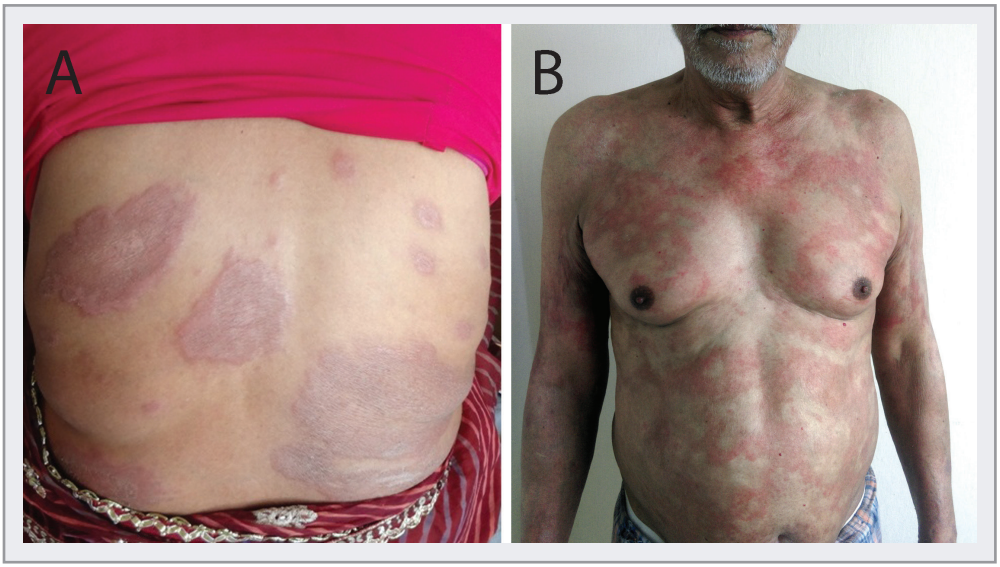


FIG 4 BB leprosy.

A. BB leprosy. Multiple erythematous, dry plaques, some of them show the hallmark annular morphology with a 'punched out' inner edge giving the 'Swiss cheese' appearance. Note the presence of well-defined plaque reminiscent of the Tuberculoid spectrum, suggesting downgrading.

B. BB leprosy. Multiple, symmetrically distributed erythematous, ill-defined annular plaques with some of the plaques showing a 'punched out' inner margin.

The nerve involvement is variable in BB. If downgrading from BT, there may be asymmetrical nerve thickening, and if upgrading from BL, the nerve thickening may be more symmetrical. Nerve involvement may be severe in the case of type 1 reactions. On histopathology, the Fite stain for AFB is positive. On microscopy, BI on SSS usually ranges between 2+ and 4+ (15).

BORDERLINE LEPROMATOUS (BL)

Lesions in BL are multiple and there is an increased tendency for symmetry. Lesions often begin as hypopigmented to coppery-hued macules that are multiple in number, more symmetrical in distribution, and smaller in size and that have indistinct borders that merge into the intervening normal skin (16). A decrease in appendages and sweating, which are features of the disease in the BT and TT spectrums, are not prominently seen in BL. With time, the macules undergo induration/infiltration beginning from the center and forming plaques and nodules. Often the lesions in BL have downgraded from the higher spectrum, which is evident due to the presence of lesions of variable morphology and large size (Figures 5A, 5B).

In BL, the peripheral nerve trunks are thickened and tend to be symmetrical. The nerve damage is not as severe as that seen in BT, and the corresponding anesthesia and paresis is usually not seen

in the early stages of the disease. Symmetrical anesthesia involving hands and feet is seen later in the course of the disease. Severe nerve deficits can occur in the case of reactional episodes.

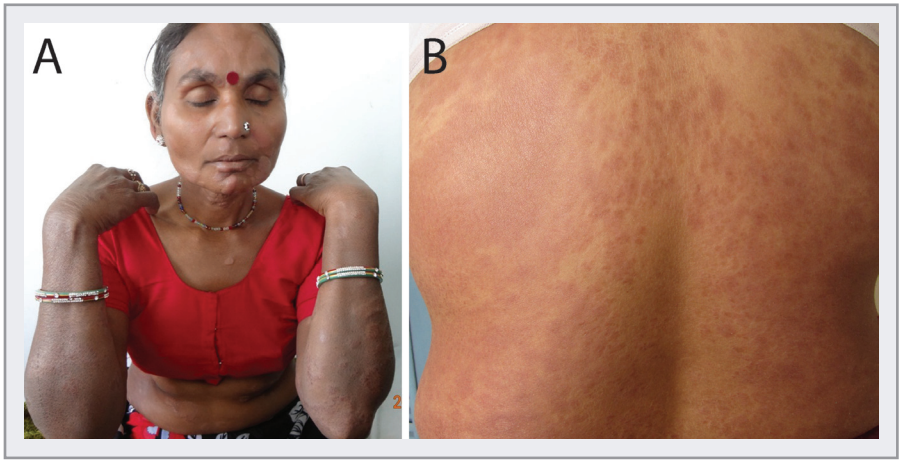


FIG 5 BL leprosy.

A. BL leprosy downgraded from BT. Multiple well-defined dry plaques with decreased appendages. Lesions show symmetry in their distribution.

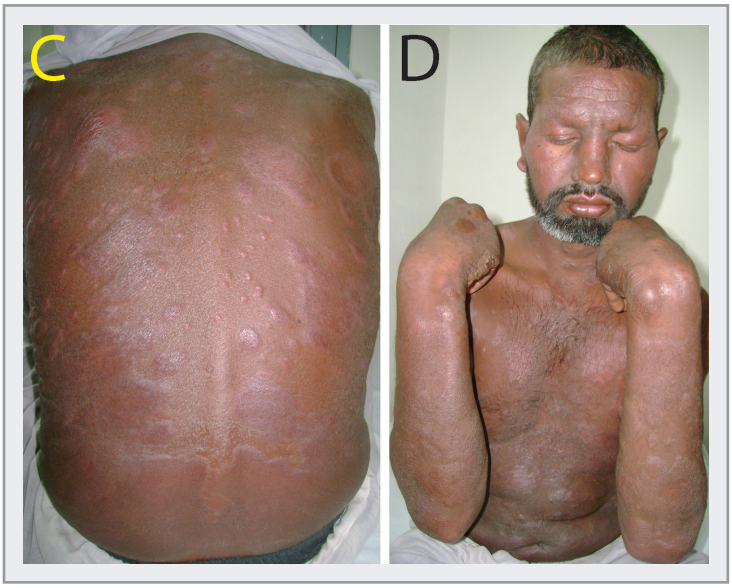
B. BL leprosy. Multiple ill-defined, but distinct erythematous maculo-plaque lesions with a tendency to symmetry in their distribution.

Patients may manifest with type 1 reactions (reversal reaction; see Chapter 2.2) after starting treatment (Figures 5C, 5D). Type 2 reactions (see Chapter 2.2) or erythema nodosum leprosum affect about 10% of patients in BL. The lepromin reaction is almost always negative. Fite staining for AFB is strongly positive and BI can reach 6+ with globi (15).

FIG 5 BL leprosy.

C. BL leprosy in type 1 reaction. The pre-existing lesions appear as erythematous, indurated, shiny lesions.

D. BL leprosy in type 1 reaction. The pre-existing lesions appear as erythematous, indurated, shiny lesions. Crops of new lesions appear on previously un-involved skin. The face appears edematous.



LEPROMATOUS LEPROSY (LL)

The CMI is severely impaired in LL. This impairment results in the uncontrolled multiplication and dissemination of lepra bacilli. LL can appear de novo due to the highly anergic state of the individual or may downgrade from the BT or BL spectrum in the absence of treatment. LL with a de novo appearance is called polar lepromatous leprosy (LLp), and when a result of downgrading, it is called subpolar lepromatous leprosy (LLs) (14). The subpolar group can regain its lost CMI and upgrade in the spectrum (17). Fite stains reveal large numbers of acid-fast bacilli and globi. Also, bacteriologically, the subpolar group clears earlier than the polar group after therapy.

The cutaneous lesions of LL are multiple with bilateral symmetrical distribution over the arms, legs, buttocks, face, and trunk. Warm areas of the body such as the axillae, groin, perineum, and hairy scalp of the body are relatively spared, as lepra bacilli favor the cooler areas of the body. Often these areas of the body have been described as 'immune zones' in leprosy. But the sparing of these areas has nothing to do with immunity per se and simply occurs due to the temperature preference of lepra bacilli. Clinically, the LL disease may present with any of the stages described below or with a mix of these lesions.

Early macular stage

During the initial phase of presentation, lesions are often in the form of many macules. In light-colored individuals, the macules are slightly erythematous, and in darker individuals, the macules may be hypopigmented to mildly erythematous with a coppery hue. These macules are indistinct and coalesce with one another; they have indistinct borders and merge inconspicuously in the surrounding skin. There is little difference in texture between these macules and the surrounding normal skin; however, they have a shiny appearance and exhibit the impairment of sweating. There is no loss of sensations and the skin appendages are almost normal. (Note that the macules seen in BT lesions are anesthetic, have dry texture, and exhibit an absence of appendages and a lack of sweating.)

Infiltrated stage

In due course, if left untreated, the macular lesions progress to develop induration. Due to minimal infiltration and a shiny appearance, the lesions are often better visualized in oblique lighting. The minimal infiltration of these lesions is better appreciated by pinching the lesions rather than by simple inspection/palpation of the lesions. The infiltration is more marked on the face and the ear lobules. The infiltration of the ear lobules is better seen by standing behind the patient (Figures 6A, 6B).

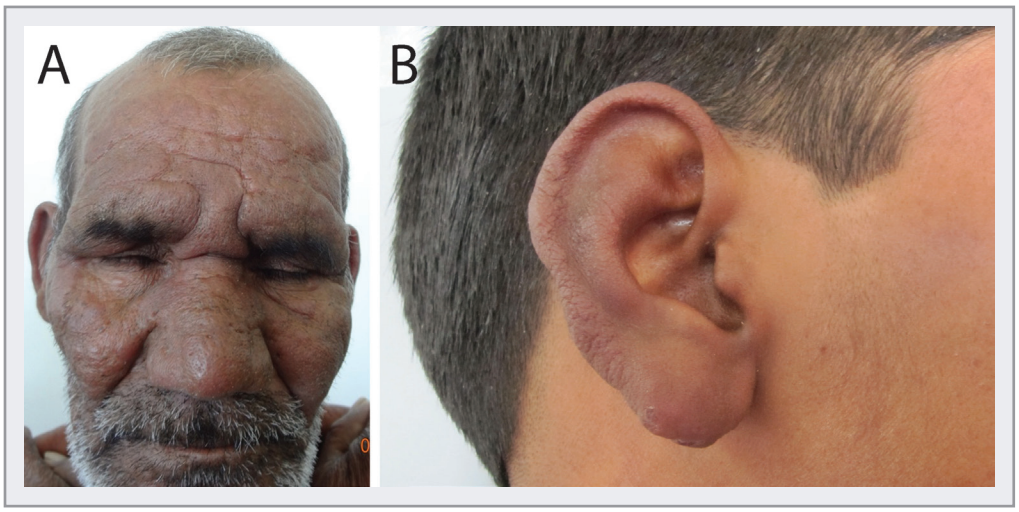


FIG 6 LL leprosy.

A. LL leprosy. Diffuse infiltration of the face. Slit-skin smear was highly positive.

B. LL leprosy. Thickening, infiltration and nodulation of the ear.

Late nodulo-plaque stage

If left untreated, the infiltration increases and the macules progress to form papules, nodules, and even plaques. Even with increasing infiltration, the characteristics of the lesions remain essentially the same, i.e., they have ill-defined outer borders that merge into the surrounding skin. The nodules make their first appearance on the ear lobes and, as the disease spreads, appear anywhere on the body. They are commonly seen over the buttocks and extremities, especially over the elbows, fingers, joints, and genitals. These nodules, and occasionally the areas of thick induration, may break down to produce ulcers, especially during episodes of type 2 reaction (Figure 6C) (12). These repeated episodes of ulceration and healing, when the ear cartilage is involved, lead to what has been described as the 'rat-bitten' appearance of the ears. These ulcers are rich in lepra bacilli and the patient is highly infectious. The ulcers are more commonly found in the nose, mouth, and throat (see Chapter 2.4) due to the breaking down of the mucous membranes. Involvement of the nose results in nasal stuffiness, crusting, and epistaxis. A history of epistaxis is often an early pointer for LL but has to be specifically sought in the patient's history. The involvement of the upper respiratory tract is seen in about 80% of patients. Progressive induration, thickening, and nodulation of the face accentuate the skin folds, producing classic 'leonine facies'. The nodules are initially movable over the underlying subcutaneous tissue, but later they become fixed.

An untreated patient with LL has leonine facies, thickening and nodulations of ear lobes, and a broad and swollen nose, which may be a collapsed thinning of eyebrows (superciliary madarosis) and eyelashes (ciliary madarosis), and may have characteristic facies leprosa (Figure 6D). 'Facies leprosa' is characterized by the resorption of the nasal bone, anterior nasal spine, supra-incisive

alveolar region, and anterior alveolar process of the maxilla, with associated sensory or motor damage depending on the type of nerve(s) involved.

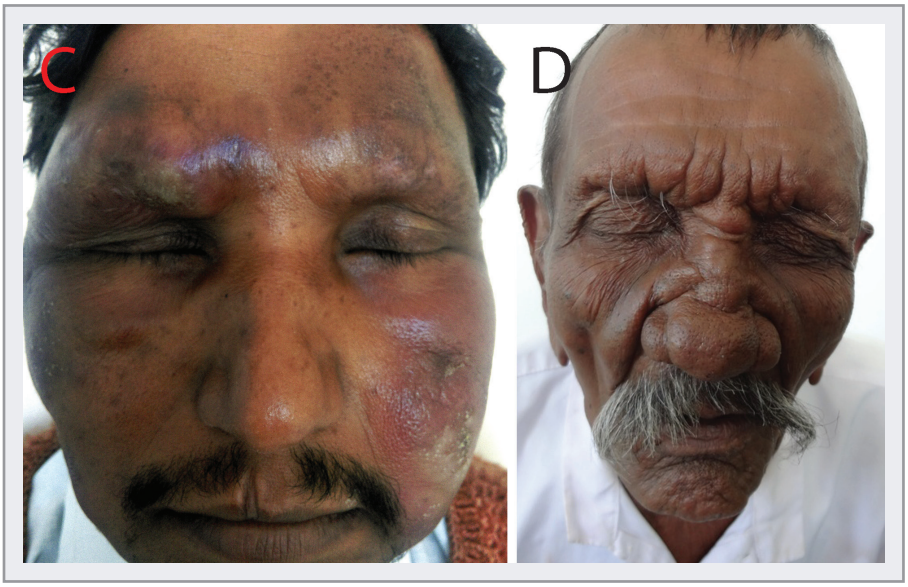


FIG 6 LL leprosy.

C. LL leprosy in type 2 reaction. There are multiple erythematous nodules on the face showing central necrosis.

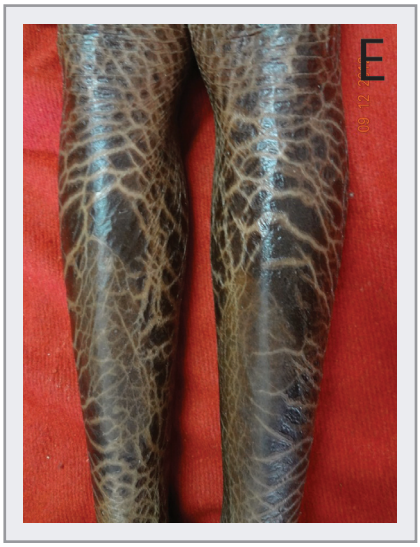
D. LL leprosy. The bridge of the nose is collapsed and the eyebrows are lost.

Early in LL progression there may be no nerve thickening, in contrast to the BT or TT types, where nerve thickening is predominant even early in the course of the disease. If patients are diagnosed and treated early, they may have no residual nerve thickening, but the same may not be true of the nerve deficit. The peripheral nerves (see Chapter 2.5) are the first to be affected, and they become firm, hard, and eventually fibrotic at the sites of predilection, i.e., where the nerves are closer to the surface (ulnar groove, radial groove, neck of fibula, and radial styloid). The well known 'glove and stocking' anesthesia is a late manifestation of LL. With time, the peripheral anesthesia becomes extensive and there is almost complete anhidrosis of the limbs. The dry skin appears ichthyotic, which may be further worsened by clofazimine administered as part of MDT (Figure 6E). Before the development of frank anesthesia, the digits may appear to have fusiform swelling and are hypersensitive to even minor stimuli or trauma. The patient often experiences severe neuralgic pain, even at the slightest touch. This sensitivity is followed by frank anesthesia, which is bilaterally symmetrical, although it may develop earlier in one limb than the other. The anesthesia may be patchy at first. Testing for anesthesia should be performed for pain, temperature, and light touch using a pin, hot and cold water, and a wisp of cotton. Sensory examination of leprosy patients should be done for all three components, as there might be a loss of only one aspect (dissociated anesthesia). Thermal sensation is the first to be affected, followed by touch and then pain. This outcome is of grave consequence because the patient, now unable to per-

ceive sensations, has repetitive traumatic ulcerations that are slow to heal. This insensitivity leads to chronic non-healing ulcers and resorption of the fingers and toes. Also, trophic ulcers develop at pressure-bearing sites. There might be a secondary infection of these ulcers, which may further lead to cellulitis or osteomyelitis.

FIG 6 LL leprosy.

E. LL leprosy. Severe, dry, plate-like ichthyotic scales observed on the lower legs in an LL patient on treatment. The ichthyosis in leprosy may be attributed to the disease itself or the clofazimine therapy, secondarily to the settling of pedal edema and nutritional deficiency.



Damage to the motor neurons leads to muscle weakness, wasting, and paralysis. The damage also results in classic deformities, such as the claw hand deformity (due to the involvement of the median and ulnar nerves), ape thumb deformity (due to the involvement of the median nerve), wrist drop (due to the involvement of the radial nerve), foot drop (due to the involvement of the lateral popliteal nerve), and facial palsy (facial nerve palsy).

As a result of hematogenous dissemination, LL can affect several organ systems apart from the skin, including the eyes, bones, oral cavity, testes, reticulo-endothelial system, muscles, and bones. They can be affected directly by LL or secondarily in reaction episodes.

The prognosis of LL in the absence of treatment is poor. The disease progressively worsens and affects the entire body. The patient is left with many non-healing ulcers and several deformities. Even with the institution of treatment, remission is often punctuated by several episodes of type 2 reactions. Death from leprosy is mainly due to superadded infections, severe and recurrent type 2 reactions, amyloidosis, and renal failure. The key features of LL are summarized in Table 5.

Rare Variants of Leprosy

HISTOID LEPROSY

Histoid leprosy was first described by Wade in 1960. The term was coined after the classic histopathological appearance of histoid lesions, which have histiocytes that form interlacing bands, curlicules, and whorls. Histoid leprosy was initially reported to manifest after the failure of long-term dapsone mono-therapy, irregular therapy, or inadequate therapy. However, it is now well

known that histoid leprosy develops de-novo as well (21, 22). Histoid leprosy is considered by some to be a subtype of lepromatous leprosy, whereas others consider it to be an independent type (21). It is characterized by a very high lesional bacillary load but with a relative absence of globi. The CMI and humoral immunity are probably higher than those found in LL. There is an increased expression of CD36 by the keratinocytes, and increased CD4 cells and B cells surround the histoid granuloma (22). This increase in inflammatory cells surrounding the granuloma may explain the containment of most of the lepra bacilli to the lesional skin in histoid leprosy (22).

Clinically, the lesions appear as firm, erythematous, shiny, smooth, hemispheric, round to oval non-tender nodules on the background of normal skin located on the face, back, buttocks, and extremities as well as over bony prominences. When localized on the face, they have a characteristic centrofacial distribution. Occasionally, the lesions may appear pedunculated or ulcerated (18). The nodules may be superficially or deeply placed on the skin, or subcutaneous. Lesions may manifest as plaques and pads that are well defined and scaly, especially around pressure points such as elbows (Figures 7A–7C). Rare presentations include xanthomatous lesions, umbilicated nodules resembling molluscum contagiosum, and scrotal sinus (18). Two types of histoid facies can be seen. In one subgroup, the facies resembles that of LL, in which patients have an old, wrinkled, atrophic face with scanty eyebrows and depressed nasal changes with scant histoid lesions on face. In the next subgroup, patients have histoid lesions on apparently normal skin with no nasal or ocular changes.

Reaction episodes are considered to be uncommon in histoid leprosy; however, episodes of ENL have been observed (18).

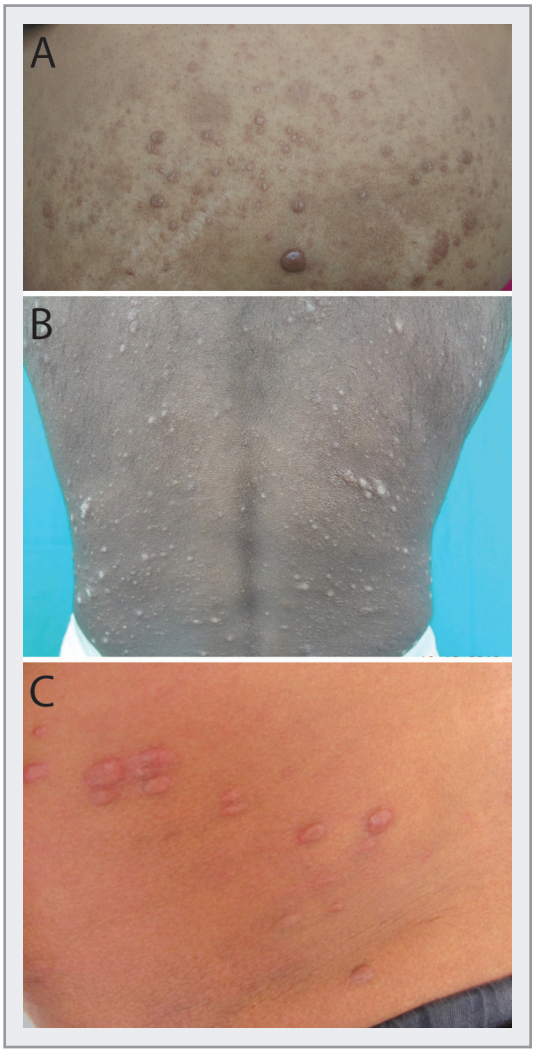


FIG 7 Histoid leprosy.

A. Histoid leprosy. Nodules and noduloplaque lesions; some of the lesions show central umibilication.

B. Histoid leprosy. Multiple nodules and noduloplaque lesions distributed on normal-appearing skin on back.

C. Histoid leprosy. Multiple well-defined, dome-shaped, hemispherical nodules on normal-appearing skin.

The differential diagnosis (see Chapter 2.3) includes progressive nodular histiocytosis, conventional leprosy nodules, molluscum contagiosum, and neurofibromas. The histoid lesions show a high BI and have a typical histopathological appearance.

PURE NEURITIC LEPROSY (PNL)

PNL is a variant of leprosy characterized by the isolated involvement of peripheral nerve trunks in the absence of skin lesions. This form of leprosy is more common in Nepal, Brazil and India (19, 20, 21, 22). Seven percent (7%) of total leprosy cases in Nepal and 4.3% of total leprosy cases in India are diagnosed as PNL (20, 21, 22). The clinical features of this variant of leprosy include nerve thickening, pain, tenderness, and sensory-motor impairment. Sensory neuropathy is more predominant in PNL, with a loss of heat and pain sensitivities (23). Occasionally, PNL may present with nerve abscesses. Mononeuritis is the most common presentation and is asymmetric in nature (22, 23, 24). Nerve trunks in the upper limb are more commonly involved (22). The nerve trunks commonly involved are the ulnar nerve, superficial radial nerve, sural nerve, common peroneal nerve, and posterior tibial nerve. PNL can have a spectral presentation ranging from TT to LL. Clinically, PNL is likely to be TT if only one or two nerve trunks are thickened and borderline if there are several thickened nerves.

The diagnosis of PNL is clinched by histopathological, bacteriological, and immunological evaluation. In difficult situations, a nerve biopsy serves as the “gold standard” for the diagnosis of PNL (25). However, the nerve biopsy needs to be approached with caution.

LUCIO’S LEPROSY

A diffuse form of polar LL, now known as diffuse leprosy of Lucio and Latapi (LuLp), was first described by Lucio and Alvardo in 1852 and further elaborated by Latapi and Zamora in 1948. It is common in Mexico (23% of leprosy cases) and Costa Rica, but very rare in other countries. However, it has been reported in Argentina, Brazil, and India. This form of leprosy has been associated with both *M. leprae* and a newly described organism in the *M. leprae* complex, *Mycobacterium lepromatosis* (26, 27).

LuLp is characterized by a diffuse infiltration of the skin, which in the initial period might go unnoticed. There is diffuse infiltration of the face and hands that may mimic a “myxedema”-like appearance, often giving the impression of a “moon face” or “healthy look”, and imaginatively called Lepra bonita (beautiful leprosy). The skin of the extremities may appear edematous, is smooth and devoid of hair, and may have violaceous erythema, especially on the hands and feet. As the disease progresses, the infiltration persists but the skin becomes thinner and atrophic and, consequently, the patient appears to have prematurely aged. The lower limbs appear xerotic and have ichthyosiform changes; the earlobes become saggy and stretched; and the face and trunk often have telangiectasia with a rosacea-like appearance. Hair loss is observed and involves the

eyebrows, eyelashes, and body hair. Occasionally, the scalp may be involved, in which case the hair loss may mimic alopecia areata.

Nasal mucosa is involved insidiously with an initial congestive phase in which the mucosa is swollen with numerous telangiectasia. This phase is followed by the formation of microsanguineous crusts. In an advanced stage, the symptoms are similar to those observed in LL, with nasal obstruction and epistaxis followed finally by the ulceration of the septum, leading to a deformed 'saddle-nose' appearance. The involvement of the larynx is rare and may present as dysphonia and rarely as a respiratory obstruction.

Pan-neuritis is observed and somehow the equilibrium of muscles is preserved due to which "claw hand" deformity is usually not seen, even though there is atrophy of the lumbricals and the interosseus muscles (28). Due to pan-neuritis, there is generalized hypoesthesia and hypohidrosis. In advanced stage there can be systemic involvement, with infiltrations of the spleen and liver leading to hepatosplenomegaly. Ocular involvement can occur and often there is madarosis with exaggerated shining of the eyes, known as "children eyes" (28).

A peculiar phenomenon that characterizes LuLp is the lucio phenomenon (See Chapter 2.2). It is often the onset of lucio phenomenon that unmasks lucio leprosy. Lucio phenomenon is akin to Type 2 lepra reaction and is characterized by well-defined, angular, jagged, purpuric lesions evolving into ulcerations and spreading in ascending fashion and healing with atrophic white scarring.

Conclusion

Leprosy is a disease that has spectral presentation; it is also a great mimicker. Some points to consider when making a diagnosis of leprosy are the following:

1. An ill-defined, normo-anesthetic, hypopigmented to erythematous patch situated on the face or the outer aspect of arms and legs may often be the presenting feature of indeterminate leprosy.
2. Leprosy lesions are characterized by macules, papules, and plaques that are hypopigmented to erythematous, often hypo-anesthetic, dry lesions with scanty hair.
3. As the lesions progress from the Tuberculoid to the Lepromatous spectrum, they become more numerous in number and gain symmetry in distribution.
4. Patients suspected of having leprosy should always be fully exposed and examined in a well-lit room.
5. A nerve examination is an integral part of assessing patients with leprosy and should never be skipped. Nerves should be examined for their thickness and tenderness, and a sensory examination of cutaneous lesions has to be performed.

6. The pure neuritic variant of leprosy can present with isolated neural involvement in the absence of cutaneous involvement.

7. Histoid leprosy is a rare variant of leprosy presenting as erythematous, non-tender, hemispherical or pedunculated nodules, which can be mistaken for nodular histiocytosis, molluscum contagiosum, xanthoma, or neurofibroma.

8. Lucio leprosy is another rare variant of leprosy caused by *Mycobacterium lepromatous*, which is characterized by the diffuse infiltration of the skin that can often be mistaken for myxedema.

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