Tuberculosis and Leprosy
Classical Granulomatous Diseases in the Twenty-First Century

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KEYWORDS

• Granuloma • Atypical mycobacteria • Tuberculosis • Lupus vulgaris • Leprosy • Hansen disease • Leprosy reaction • Cell-mediated immunity

KEY POINTS

- Cutaneous lesions are rare in tuberculosis but are common in leprosy.
- *Mycobacterium tuberculosis* is cultivable; *Mycobacterium leprae* is not.
- Both infections are curable, but optimal multidrug regimens for them are different.
- Standard Ziehl-Neelsen staining may fail to stain many *M leprae,* because they are weakly acid-fast compared with *M tuberculosis.*
- A delay or failure to diagnose cutaneous tuberculosis may be associated with mortality if there is concomitant systemic disease; delay or failure to diagnose leprosy is associated with a high risk of peripheral neuropathy and disability.
- Hypoesthesia and intraneural or perineural localization of granulomas are helpful in distinguishing leprosy from tuberculosis clinically and histologically.

INTRODUCTION

Tuberculosis (TB) and leprosy, the 2 major mycobacterial infections of humans, are classic granulomatous diseases that still affect millions of people. Both infections are now curable, but no highly effective vaccine is yet available for either of them. Both are ancient scourges with a wide range of cutaneous manifestations, and both are infamous for their ability to mimic other diseases and sometimes fool even the most skilled diagnostician.

Etiopathogenesis

TB and leprosy are both chronic infections, but they are very different diseases (**Table 1**). *Mycobacterium tuberculosis* is cultivable; *Mycobacterium leprae* is not. *M leprae* infects peripheral nerves; *M tuberculosis* does not. Untreated tuberculosis has a high mortality; untreated leprosy has a high disability rate due to peripheral neuropathy. Cutaneous lesions are typical of leprosy, but rare in tuberculosis.

The cell-mediated immune response (CMI) to these agents is the critical determinant in individual susceptibility to these infections and in the range of clinical and histologic appearances of their cutaneous lesions (**Fig. 1**). The organisms express pathogen-associated molecular patterns on their surfaces, which are recognized by pattern recognition receptors of macrophages and

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Table 1
A comparison of tuberculosis and leprosy

	TB	Leprosy
Etiologic agent	*M tuberculosis*	*M leprae*
Acid-fastness	Strong (Ziehl-Neelsen stain)	Weak (Fite stain preferred)
Growth in tissue	Extracellular or in macrophages	Obligate intracellular pathogen, in macrophages and Schwann cells
Cultivable	Yes	No
Growth temperature	37°C	33°C
Number of protein genes	3993	1614
Number of pseudogenes	6	1133
Transmission	Airborne droplets	Probably airborne
Initial site of infection	Periphery of lung	Nose and nasopharynx
Cutaneous infection	Uncommon	Typical, very common
Infection of peripheral nerves	No	Yes
Infection is curable	Yes	Yes
CMI	Mainly 2 polar types; strong and weak CMI	Full spectrum from strong to none
Outcome if untreated	High mortality	Very low mortality; high disability rate from peripheral neuropathy
Vaccine	BCG (variable protection)	BCG (variable protection)

dendritic cells, facilitating phagocytosis.[1] Innate immunity to mycobacteria is mediated by macrophages and dendritic cells, including Langerhans cells in the skin, and may be sufficient to prevent further progression of the infection.

If innate immunity is insufficient, mycobacterial antigens are presented to CD4+ T cells, initiating the acquired CMI.[2] Based largely on inherited immunologic capabilities, CMI in most individuals will be driven by activated CD4+ T lymphocytes

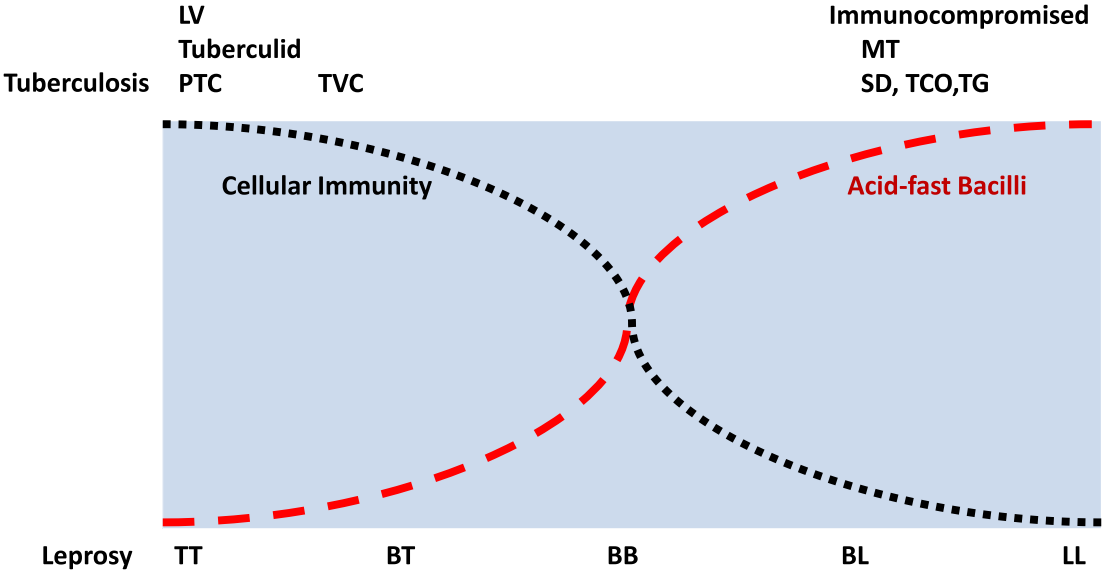

Fig. 1. Immunopathologic patterns of cutaneous tuberculosis and leprosy. The cellular immune status and bacterial load of different forms of cutaneous tuberculosis compared with the broad, continuous spectrum in leprosy. Cutaneous tuberculosis: MT, miliary tuberculosis; PTC, primary tuberculous chancre; SD, scrofuloderma; TCO, tuberculosis cutis orifacialis; TG, tuberculous gumma.

elaborating tumor necrosis factor-α (TNF-α) and interleukin-2 (IL-2), stimulating macrophage release of interferon-γ (IFN-γ), the TH1 pattern of cytokines.[3] TH1 responses are associated with the formation of well-organized granulomas. The epithelioid macrophage is a specialized cell producing large quantities of cytokines, with enhanced microbicidal activity. Such granulomas are associated with limited proliferation of mycobacteria.[4,5] Caseous necrosis is thought to be a result of the death and regeneration of the epithelioid cells within the granuloma, a process mediated by TNF-α and proteases.[6]

Although granuloma formation has been understood as a host-protective strategy to limit spread of the mycobacteria, recent studies suggest that *M tuberculosis* may use the granuloma to shield itself from the host's immunologic killing mechanisms and antimicrobial agents.[7] Therapies targeting granuloma formation are being studied as adjunctive therapies for the treatment of TB.[8]

Such a shielding effect of granulomas may play a role in the human tuberculosis and leprosy, but it is also apparent that in these 2 infections the well-organized epithelioid granuloma is associated with a high degree of CMI and a limited bacterial load. When CMI is weak or absent, a TH-2 response to mycobacterial infection results, characterized by the production of IL-4 and IL-10. In such individuals, well-organized granulomas do not develop, and mycobacteria proliferate and may reach large numbers, such as in lepromatous leprosy or tuberculosis in immunosuppressed individuals.

Antibodies play no role in protective immunity to *M tuberculosis* or *M leprae*. Negligible antibody production is elicited by either agent in individuals who have strong CMI and granulomatous responses. In general, therefore, tests for antibodies are not useful in the diagnosis of these infections, whereas assays for CMI mediators such as IFN-γ[9] are sensitive and specific for tuberculosis, and measurements of CXCL-10 show promise for use in leprosy.[10,11]

CUTANEOUS TUBERCULOSIS

Epidemiology

TB remains the second leading cause of death worldwide, despite concerted measures to improve detection and treatment. The World Health Organization (WHO) estimates that 8.6 million people were diagnosed with TB in 2012 (122 cases per 100,000 population) and 1.3 million died of the disease.[12] Although the incidence of TB has decreased 2% over the last decade, global efforts to reach the 2015 Millennium Development Goal of decreasing TB-related mortality by 50% are unlikely to succeed,[12] and the increase in multidrug-resistant TB (MDR-TB) raises concerns of an epidemic of untreatable cases.[6]

Skin involvement is a relatively rare extrapulmonary manifestation of systemic TB, comprising less than 1% to 2% of all cases.[13–18] However, cutaneous TB is still an important differential diagnosis to consider in the age of HIV/AIDS, MDR-TB, and immunosuppressive therapies.[19]

Etiopathogenesis

Cutaneous TB in humans is primarily caused by *M tuberculosis*, although rarely this is due to *Mycobacterium bovis*.[20–24] The development of cutaneous TB depends on multiple factors, including the route of infection, duration of exposure and previous sensitization, and the individual's CMI.[22]

Cutaneous manifestations of TB are immunologically driven; individuals without effective CMI face a higher risk of active disease with exudative lesions and disseminated miliary TB.[5] The tuberculin skin test (purified protein derivative [PPD]), reflecting delayed hypersensitivity to *M tuberculosis* antigens, becomes positive 3 to 8 weeks after infection.[6]

Histopathology

Typically, 3 to 6 weeks after infection, the classic tuberculoid granuloma develops, with a central focus of epithelioid histiocytes and Langhans giant cells surrounded by a mantle of lymphocytes. Caseation necrosis occurs in the center of the granuloma, often with calcification and fibrosis. The number of bacilli is roughly proportional to the amount of necrosis present. The histopathological features of different forms of cutaneous TB depend on source of infection (exogenous vs endogenous) and the host's CMI.

Both sarcoidosis and lupus vulgaris (LV) are characterized by granulomas, but sarcoidal granulomas typically have minimal lymphocytic inflammation and no caseation necrosis. Perineural involvement helps to distinguish tuberculoid leprosy from cutaneous TB (see later discussion). The causative organism must be identified in other infections with a prominent granulomatous infiltrate (ie, atypical mycobacteria, leishmaniasis, blastomycosis, and chromomycosis). Tertiary syphilis can also be granulomatous; however, increased plasma cells and endothelial swelling help differentiate it from TB. Rosacea and panniculitis can exhibit a nonspecific nodular granulomatous infiltrate, but typical tuberculoid granulomas are absent.[6] Rare cases of lupus miliaris disseminatus faceii, a controversial entity generally understood as a rosacea variant, have shown evidence of TB.[6,13]

Classification and Clinical Presentations

The classification of cutaneous TB has evolved from a model based on clinical morphology to one incorporating the route of transmission and immune status (**Table 2**).[13,25] In an individual with high CMI, few bacilli are noted histologically, and they are difficult to culture. Patients with low CMI have many mycobacteria, easily seen in Ziehl-Neelsen–stained sections and cultured.[26] The presence of numerous acid-fast bacilli (AFB) indicates impaired CMI and suggests consideration of other entities such as leprosy (see **Fig. 1**).

High immune forms

Tuberculosis verrucosa cutis (TVC) is a warty plaquelike form occurring most commonly on the extremities as a result of direct cutaneous inoculation in a previously sensitized individual (**Fig. 2**). TVC can occur by accidental inoculation (ie, "prosector's wart"), by autoinoculation from sputum in a patient with active TB, and in children with some immunity exposed to infected sputum.[6] Clinically, TVC starts as an asymptomatic indurated papule, gradually evolving into a brownish-red verrucous plaque with a soft center, sometimes with keratinous discharge; this may spontaneously involute, forming a hypopigmented and atrophic scar, or it can become a large, exophytic, keloidal plaque, with rare sporotrichoid spread or lymphadenitis.[6] Histologically, TVC shows epidermal hyperplasia with a mixed dermal infiltrate of neutrophils, lymphocytes, and some giant cells. Bacilli may or may not be identified. The differential diagnosis is broad, including fungal infections (sporotrichosis, blastomycosis, and chromomycosis) as well as leishmaniasis, tertiary syphilis, hypertrophic lichen planus, psoriasis, and squamous cell carcinoma.[27]

LV is a chronic and progressive form of cutaneous TB that occurs in patients with moderate to high CMI. Historically, LV has been the most common presentation of cutaneous TB in Asia and South Africa.[15,28–30] It presents with multiple red-brown papules coalescing into plaques (**Fig. 3**), developing a gelatinous quality centrally; its appearance on diascopy resembles "apple jelly."[6,13] Lesions run a variable course and may cause significant tissue destruction, heal with atrophic scarring, or have a prolonged course with minimal cutaneous damage.[6,26] The most commonly affected areas were the head and neck in Europe,[31] and the extremities, trunk, and buttocks in Asia.[15,32] LV may originate from an underlying focus of TB in a lymph node, bone, or joint, by direct contiguous extension, or via lymphatic spread.[6] It may result from reactivation of latent cutaneous TB or after exogenous inoculation, including Bacille Calmette-Guérin (BCG) vaccination.[21] Involvement of the face may result from hematogenous spread, and acral lesions may result from reinoculation.[13] Clinical variants include classic plaque-type, ulcerative, vegetating, tumorlike, papular, and nodular forms.[6] Histologic findings often include typical tuberculoid granulomas surrounded by numerous lymphocytes, sparse caseation necrosis, and fibrosis (**Figs. 4** and **5**). Bacilli may or may not be identified by acid-fast staining.

LV is morphologically diverse and can mimic a plethora of cutaneous conditions, such as Spitz nevus and lupus erythematosus,[6] in early stages as well as rosacea[33] and port-wine stains[34] in chronic disease. Verrucous and vegetating lesions (**Fig. 6**) can resemble deep fungal infections or other mycobacterial infections. Differentiating the "apple-jelly" lesions of LV from those of sarcoidosis and leprosy can be challenging, and subtle nuances such as the firm texture of leprosy nodules versus the more grainlike quality of sarcoid lesions may be the only clinical clues.[6]

Tuberculids, first described by Darier in 1896,[35] are hypersensitivity reactions to *M tuberculosis* or other mycobacterial antigen in a person with strong CMI against TB. Tuberculids classically include lichen scrofulosorum (**Fig. 7**), papulonecrotic tuberculid (**Fig. 8**), nodular tuberculid, erythema induratum (Bazin disease), and the more recently described nodular granulomatous phlebitis.[17,36–38] Tuberculids tend to run a relapsing and remitting course, appearing in crops and healing with scarring. Although the histology of tuberculids can vary, they generally show granulomatous inflammation (**Fig. 9**) and some degree of necrosis and vasculitis (**Figs. 10** and **11**), suggesting that they are the result of released mycobacterial antigens from concurrent or distant TB.[38] Tuberculids fail to show evidence of mycobacteria with special stains or cultures, but polymerase chain reaction (PCR) has detected mycobacterial DNA in some specimens.[6,39]

Low immune forms

A tuberculous chancre results from cutaneous or mucosal inoculation in a person with a low level of CMI. It most commonly presents in children as an inflammatory papule at the site of inoculation on the face or extremities; after 2 to 4 weeks, this develops into a firm, shallow solitary ulcer with regional lymphadenopathy. Histologically, abundant neutrophils and numerous AFB are seen, with necrosis involving skin and lymph nodes. Later, lesions demonstrate more granulomatous inflammation with fewer bacilli. The

Table 2
Clinical and histologic classification of cutaneous tuberculosis

TB Type	Host Immunity to *M tuberculosis*	Clinical Presentation	Histologic Features	PPD
TVC	High	Hyperkeratotic papule or plaque, resolves spontaneously with scarring, often with lymphadenopathy	Pseudoepitheliomatous hyperplasia of epidermis with intense dermal infiltrate of neutrophils, lymphocytes, and some giant cells; ± bacilli	+
LV	Moderate to high	Plaque: gelatinous Hypertrophic: soft nodules Ulcerative: necrotic Vegetative: papule with ulceration or necrosis Commonly involving face/neck; "apple-jelly" appearance on diascopy	Tuberculoid granulomas embedded in sheets of lymphocytes, sparse or absent caseation, extensive fibrosis with healing; increased risk of developing nonmelanoma skin cancer in lesions; ± bacilli	±
Tuberculids	Moderate to high	Papulonecrotic tuberculid, dusky small papules with central necrosis Lichen scrofulosorum, multiple grouped lichenoid papules Erythema induratum (Bazin), painful ulcerated nodules on posterior legs Nodular tuberculid, bluish-red nontender, nonulcerating nodules on legs Nodular granulomatous phlebitis, nonulcerating, subcutaneous nodules along leg veins of anterior and medial leg	Superficial granulomatous infiltrate, wedge-shaped necrosis, granulomatous vasculitis Variable dermal granulomas Granulomatous vasculitis at junction of deep dermis/subcutis Septal and lobular panniculitis with granulomatous vasculitis Epithelioid granulomas with Langhan giant cells in walls of cutaneous veins No bacilli	+
Scrofuloderma	Low	Nodule over affected cervical lymph node, suppurates and ulcerates with fistulae progressing to scarring	Ulcerated dermal abscess with scattered histiocytes, few lymphocytes, marked caseation necrosis containing numerous bacteria in the deeper structures; ++ bacilli	+
Tuberculosis cutis orificialis	Low	Painful papule that ulcerates with "punched-out" borders; usually oral cavity or genitourinary	Ulceration with underlying caseating granulomas; ++ bacilli	±
Miliary tuberculosis	Low	Numerous discrete minute red to violaceous papulopustules, umbilication, hemorrhagic necrosis, crusting; heal with atrophic scarring	Focal necrosis with microabscesses surrounded by chronic inflammation; in HIV patients more pustular with numerous neutrophils; ++ bacilli	±
Tuberculous gumma (metastatic tuberculous abscess)	Low	Indurated deep nodule(s) on trunk, face, extremities, becoming fluctuant with draining sinuses, ± ulceration	Tuberculous granulation tissue, massive necrosis, and abscess formation; ++ bacilli	±
Tuberculous chancre	Naïve host	Usually follows penetration injury; inflammatory papule progresses to nontender, shallow, undermined ulcer with painless lymphadenopathy	Acute neutrophilic inflammation with necrosis in skin and affected lymph nodes. Granulomatous inflammatory infiltrate in later lesions; ++ bacilli (early), ± late	±

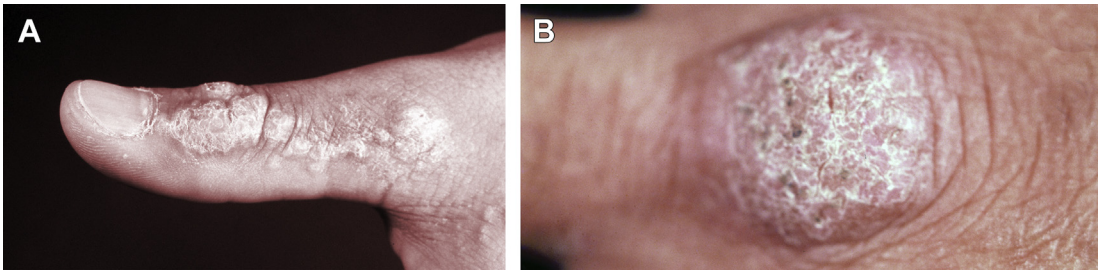

Fig. 2. (*A,B*) TVC ("prosector's wart") occurring on the hand.

differential diagnosis includes tularemia, other mycobacterial infections (especially *Mycobacterium marinum*), sporotrichosis, and actinomycosis.[6]

Scrofuloderma results from breakdown of skin overlying a contiguous tuberculous focus, most commonly a lymph node, bone, or joint, or a lacrimal gland or duct (**Fig. 12**).[6] It has been reported as the most common form in children,[28] but is also seen in adults.[14] Clinically, an abscess or fistula draining purulent material forms from an underlying focus of infection with subsequent induration and ulceration of the site. Histologically, an ulcerated dermal abscess with marked caseation necrosis is present, with scattered histiocytes, lymphocytes, and numerous AFB. The differential diagnosis includes sporotrichosis, hidradenitis suppurativa, actinomycosis, and syphilitic gumma.[6,27]

Tuberculosis cutis orificialis (**Fig. 13**) is a form of autoinoculation TB occurring in mucosal or orificial sites after local trauma. Patients are typically immunocompromised and are often severely ill with advanced visceral TB.[6] Lesions present on the nose, mouth, tongue, lips, and infrequently, on the vulva, as small erythematous papules that rapidly break down, forming undermined and painful ulcers with violaceous edges. Histology demonstrates ulceration with underlying caseating granulomas. The clinical differential diagnosis is broad and includes herpes simplex, Crohn disease, malignancy, aphthous ulcers, paracoccidioidomycosis, and the Melkersson-Rosenthal syndrome.[27,40]

Cutaneous miliary TB is a rare manifestation due to hematogenous spread of mycobacteria to the skin, usually from a pulmonary or meningeal focus.[41] It primarily affects young children and immunocompromised patients.[32,41] Lesions present as crops of widespread, minute (1–4 mm) papulopustules and vesicles on the trunk and extremities. The initial diagnosis of systemic TB may sometimes be made from a skin biopsy in this form,[41] showing focal necrosis and microabscesses. Lesions can mimic folliculitis[42] as well as lymphomatoid papulosis, disseminated herpes infection, bacterial endocarditis, disseminated cryptococcosis, and papulopustular syphilis.[27,41]

Tuberculous gumma (metastatic tuberculous abscess) occurs as a result of hematogenous spread of TB from a primary focus that remains latent until a period of lowered resistance (ie, malnutrition, immune compromise).[13] Lesions begin as solitary or multiple subcutaneous nodules or abscesses, usually on the extremities, which break down forming an ulcer with draining sinuses.[6] Histology shows granulation tissue, massive necrosis, and abscess formation with

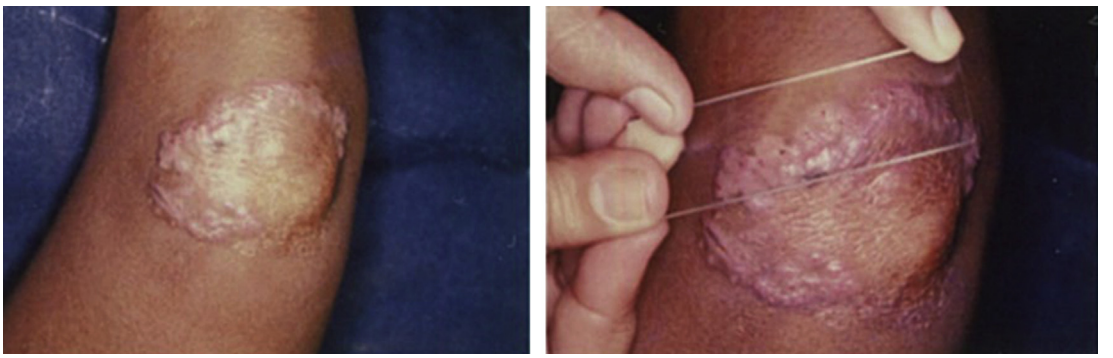

Fig. 3. LV, classic plaque-type, which demonstrated a classic "apple-jelly" appearance on diascopy.

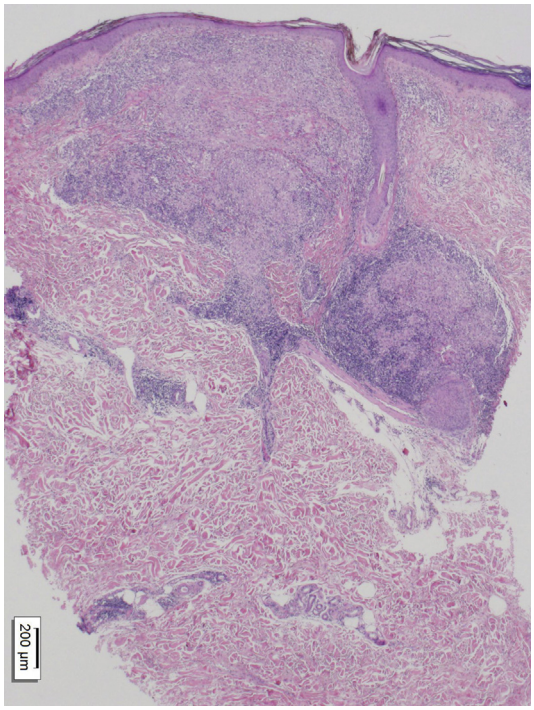

Fig. 4. Histology of LV, showing dermal granulomas accompanied by a dense lymphocytic infiltrate (H&E, ×20).

numerous AFB. Histologically, the differential diagnosis includes deep fungal infections, syphilitic gumma, and leishmaniasis.[27]

Systemic Associations

Transmission of *M tuberculosis* is primarily via respiratory droplets; therefore, the most common site of primary infection is the pulmonary system. Although primary inoculation of the skin with tuberculosis is possible, most cases of cutaneous TB are related to tuberculous disease of other organs.[13]

Extrapulmonary disease occurs more commonly in immunocompromised patients and may affect lymph nodes, meninges, eyes, peritoneal cavity, and intra-abdominal organs.[5,43–45] Kivanç-Altunay and colleagues[46] observed that spread of visceral TB to skin was rare.

Comorbidities that increase the risk of both systemic and cutaneous TB include HIV/AIDS, young age, solid organ transplantation, poorly controlled diabetes mellitus, intravenous drug abuse, renal failure, underlying systemic malignancy, vitamin D or A deficiency, and chronic immunosuppressive therapies.[4,5,47,48] In a patient with diabetes mellitus

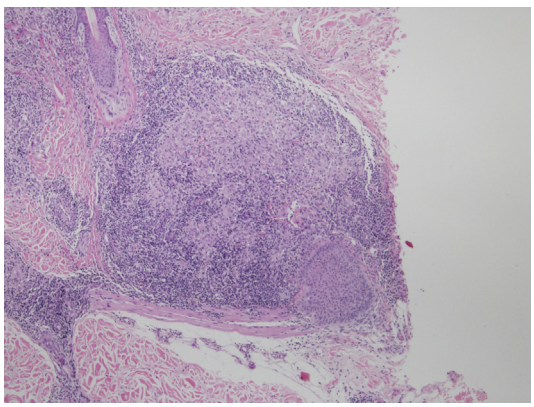

Fig. 5. LV with well-formed epithelioid granulomas in the papillary and reticular dermis (H&E, ×40).

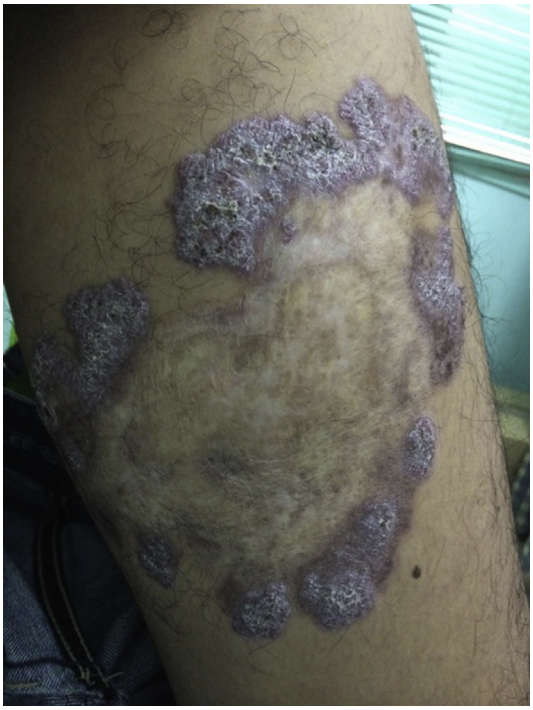

Fig. 6. Hyperkeratotic lesions of LV may clinically resemble a deep fungal infection or other mycobacterial infection.

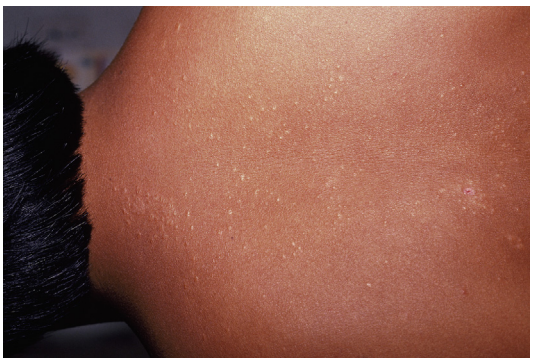

Fig. 7. Lichen scrofulosorum with scattered lichenoid papules, characteristically healing with varioliform scarring.

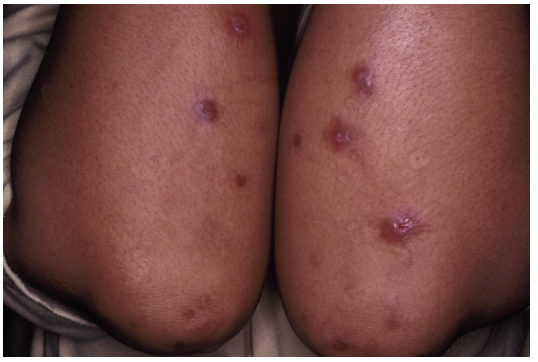

Fig. 8. Papulonecrotic tuberculid from a TB hypersensitivity reaction in a person with strong immunity.

and taking corticosteroids, atypical gangrenous or vegetating forms of TB and tuberculous cellulitis-like lesions have been seen.[49] Cutaneous TB in immunodeficient patients often elicits a less granulomatous inflammatory response, and more bacilli are identified.[6]

Cutaneous tuberculosis in immunocompromised patients

The frequency of extrapulmonary TB in patients with advanced HIV infection is high when there is concomitant pulmonary TB; the incidence of coinfection is up to 20% in the United States.[43,50,51] Despite this, the coexistence of cutaneous TB and HIV is relatively rare.[41] However, the clinical features of cutaneous TB in HIV+ patients are highly variable and unusual. In India, scrofuloderma and LV were the most common presentations of cutaneous TB in HIV+ patients[51]; LV has also presented with erythematous plaques on the cheek and pinna,[51] ulcerated lesions, cellulitis-like lesions, subcutaneous abscesses, and tuberculids.[42,49,52] These patients are more likely to develop acute fulminant miliary TB in the skin,[42,53,54] often associated with drug-resistant strains[55] and carrying a poor prognosis.[42]

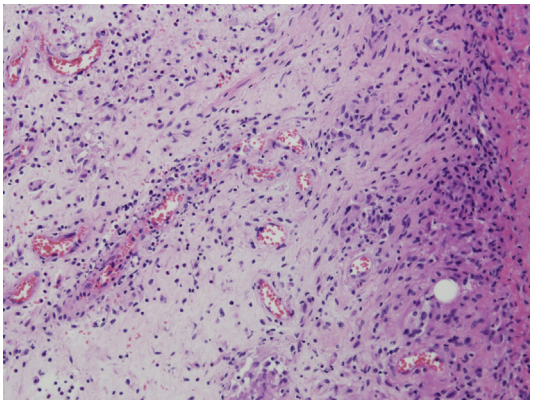

Fig. 10. Chronic granulomatous small-vessel vasculitis in a papulonecrotic tuberculid (H&E, ×100).

Renal transplant patients are 5 times more likely to acquire TB, with an incidence of 0.5% to 1% in the United States, most commonly during the first year after transplantation.[56,57] Although rare, cutaneous miliary TB has been described in renal transplant recipients presenting with multiple erythematous papules on the lower extremities[47,57] or with erythematous and violaceous lesions on the legs, subcutaneous nodules, and necrotizing tuberculous fasciitis of the gluteus muscle.[42]

Evaluation and Management

Definitive diagnosis of TB requires a positive culture of *M tuberculosis* or identification of mycobacterial DNA by PCR.[6,22] Skin biopsy, smear, and acid-fast stains should be performed in all suspicious cases. Notably, recent data suggest that in latent infection with distinct cell-wall alterations, *M*

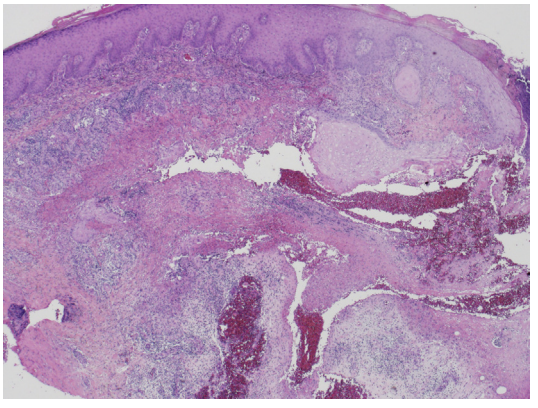

Fig. 9. Histology of papulonecrotic tuberculid. Epidermal ulceration, necrosis, and palisading histiocytes in the dermis. No AFB are identified (H&E, ×20).

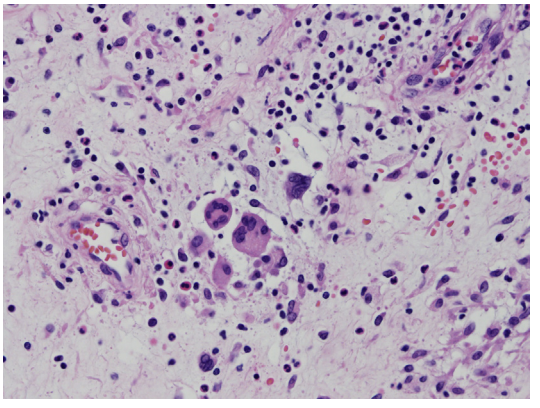

Fig. 11. Papulonecrotic tuberculid. Langhans giant cells and a mixed inflammatory infiltrate adjacent to a small blood vessel (H&E, ×200).

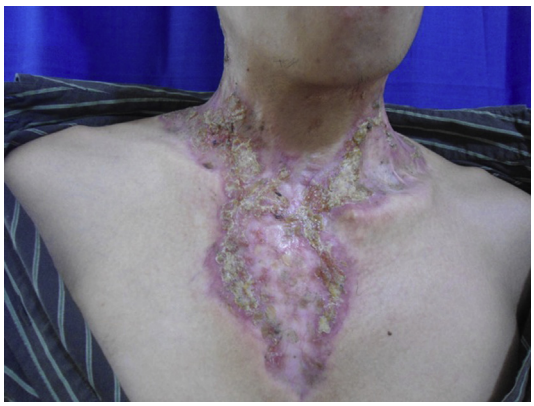

Fig. 12. Late-stage scrofuloderma of the neck and anterior chest.

tuberculosis may lose Ziehl-Neelsen staining, and tissue samples with negative AFB stains may be positive by culture and PCR analysis.[58]

A positive PPD reaction is helpful in diagnosis, but different degrees of induration are significant in different groups, (eg, immunocompetent individuals, young children, immigrants, injection drug users, immunosuppressed patients, or those who have chest radiograph findings of prior TB).[13,59] Serum QuantiFERON-TB Gold (QFT-G; Cellestis Inc, Valencia, CA, USA), which measures IFN-γ release by sensitized lymphocytes in vitro, is highly specific and has been recommended by the Centers for Disease Control and Prevention (CDC) for use in all circumstances in which the PPD skin test is used.[59]

PCR techniques are highly sensitive and specific and are helpful in detecting *M tuberculosis* when the bacterial load is extremely low.[6] Mycobacterial DNA has also been identified in papulonecrotic tuberculid and erythema induratum.[39] Because PCR can be positive due to bacteremia and not necessarily cutaneous disease, it must be interpreted within the clinical context.[60]

Treatment of cutaneous TB consists of multiple drug treatment (MDT) to prevent the emergence of bacterial resistance, for a length of time sufficient to eliminate the mycobacteria (**Table 3**). Because many patients with skin findings also have simultaneous systemic TB, the treatment regimens are identical.[61] The CDC recommends a 2-phase regimen: (1) initial intensive bactericidal treatment for 8 weeks with daily isoniazid, rifampin, pyrazinamide, and either ethambutol or streptomycin; and (2) maintenance for 16 weeks with isoniazid and rifampin given daily or 2 or 3 times weekly.[62] Surgical excision may be effective in cases of LV, scrofuloderma, and TVC. Plastic surgery can be helpful when cutaneous TB is complicated by severe scarring and disfigurement.[6,22,23]

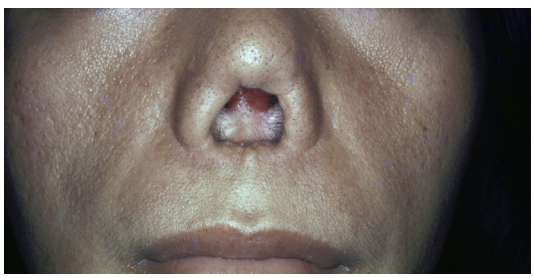

Fig. 13. Tuberculosis cutis orificialis of bilateral nares with violaceous papules and plaques that ulcerate and heal with atrophic scarring.

Clinical results/outcomes in the literature

Cutaneous TB usually responds well to MDT, and clinical improvement should be expected after 4 to 6 weeks.[63] It is important to individualize the therapy, taking into account overall health, immune status, type and degree of cutaneous involvement, stage of disease, patient compliance with medication administration, and side effects.[27] Although MDR-TB and extensively drug-resistant TB pose serious threats to management,[64,65] it is extremely rare for resistant strains to develop in the context of cutaneous TB.

Summary

Although cutaneous TB is relatively rare, the increase in new cases of pulmonary TB has led to an increase in incidence of cutaneous TB. This increase in incidence is especially true in high-risk populations, such as in endemic and resource-poor areas and in patients with HIV coinfection or other forms of immunosuppression. A diagnosis of cutaneous TB warrants a rigorous search for systemic disease and concurrent immunosuppression such as HIV infection. Given its often-elusive clinical and histopathological findings, physicians must maintain a high level of diagnostic suspicion to accurately recognize, diagnose, and manage cutaneous TB.

LEPROSY (HANSEN DISEASE)

Epidemiology

Leprosy remains one of the important neglected tropical diseases. The WHO estimates that approximately 220,000 new cases occur annually,[66] based on passive case-finding; active case finding studies have indicated that the actual number may be 6-fold greater than this.[67] India and Brazil report the greatest number of new cases each year. Approximately 200 new cases are diagnosed annually in the United States.[68] Most new cases in the United States are in patients with a history of foreign birth or travel.

Table 3
First-line medications for tuberculosis

Agent	Interval and Doses	Adverse Reactions	Monitoring
Isoniazid	Initial phase: 5 mg/kg daily, max 300 mg 5 mg/kg daily, BIW or TIW, max 900 mg	Paresthesias, peripheral neuropathy, elevated LFTs, nausea, vomiting	Baseline CMP; monthly LFTs for patients >35 y old, history of hepatic disease or alcoholism, or IV drug abuse; women in postpartum period; optional ophthalmologic examination
Rifampin	10 mg/kg daily, BIW or TIW, max 600 mg	Nausea and vomiting, diarrhea, pyrexia, abdominal pain, orange/red discoloration of bodily fluids, flulike symptoms, elevated LFTs	Baseline CBC, CMP; LFTs every 2–4 wk if hepatic impairment
Pyrazinamide	20–25 mg/kg daily, max 2 g Recommended adult dosages by weight, using whole tablets (MMWR)	Malaise, joint pain, rash, photosensitivity, anorexia, hyperuricemia, gout, elevated LFTs	Baseline uric acid and CMP, then periodically
Ethambutol	15–20 mg/kg daily, Recommended adult dosages by weight, using whole tablets (MMWR)	Blurred vision, blindness, flulike symptoms, nausea, vomiting, anorexia, pruritus, rash, elevated LFTs	Baseline CBC, CMP; baseline ophthalmologic examination, then periodically

Abbreviations: BIW, 2 times weekly; CBC, complete blood count; CMP, comprehensive metabolic panel; LFT, liver function test; TIW, 3 times weekly.

Data from Treatment of Tuberculosis, American Thoracic Centers for Disease Control and Prevention. Society, CDC, and Infectious Diseases Society of America. MMWR 2003;52(No. RR-11):3–5;19–25.

However, 20% to 24% of new cases each year are seen in persons who have never traveled outside the United States. Most of these are in the Gulf coast states, and substantial evidence now indicates that leprosy is a zoonosis in North America, carried by the 9-banded armadillo (*Dasypus novemcinctus*).[69] Preliminary evidence indicates that this may also be true in other regions in the Western hemisphere.

Prolonged, close contact seems to be the greatest risk factor for infection.[70] Most individuals have native immunity to *M leprae* and will not develop disease when exposed. Transmission of *M leprae* is probably via airborne droplets expelled from the nasopharynx[71]; this site is also suspected of being the major route of entry as well. Some evidence indicates that skin-to-skin transmission may also occur.[71]

Etiopathogenesis

M leprae, the causative agent of leprosy, is a noncultivable, obligate intracellular pathogen that has a very slow division time of approximately 13 days. In contrast with *M tuberculosis,* *M leprae* is weakly acid fast: Ziehl-Neelsen stains may be negative, whereas Fite stains will demonstrate abundant organisms (**Fig. 14**). *M leprae* has optimal growth in cool skin sites (32–34°C) (**Fig. 15**) and is the only bacterial pathogen capable of infecting peripheral nerves, where it inhabits Schwann cells and intraneural macrophages (**Fig. 16**).

The genome of *M leprae* has only half as many coding genes as *M tuberculosis*, and a large percentage of these are pseudogenes (see **Table 1**).[72] Genes for key enzymes of several metabolic pathways are missing from the *M leprae* genome,[73] consistent with its obligatory intracellular existence. The precise details of this metabolic dependency are not clear and this is a topic of continuing investigation.

Most individuals have native immunity to infection with *M leprae,* but among susceptible individuals, this pathogen elicits an extraordinarily broad spectrum of CMI in man based on the immunologic mechanisms described in the Introduction. This immunologic spectrum is manifested clinically as a wide range of lesions ranging from macules to nodules to diffuse infiltration, and

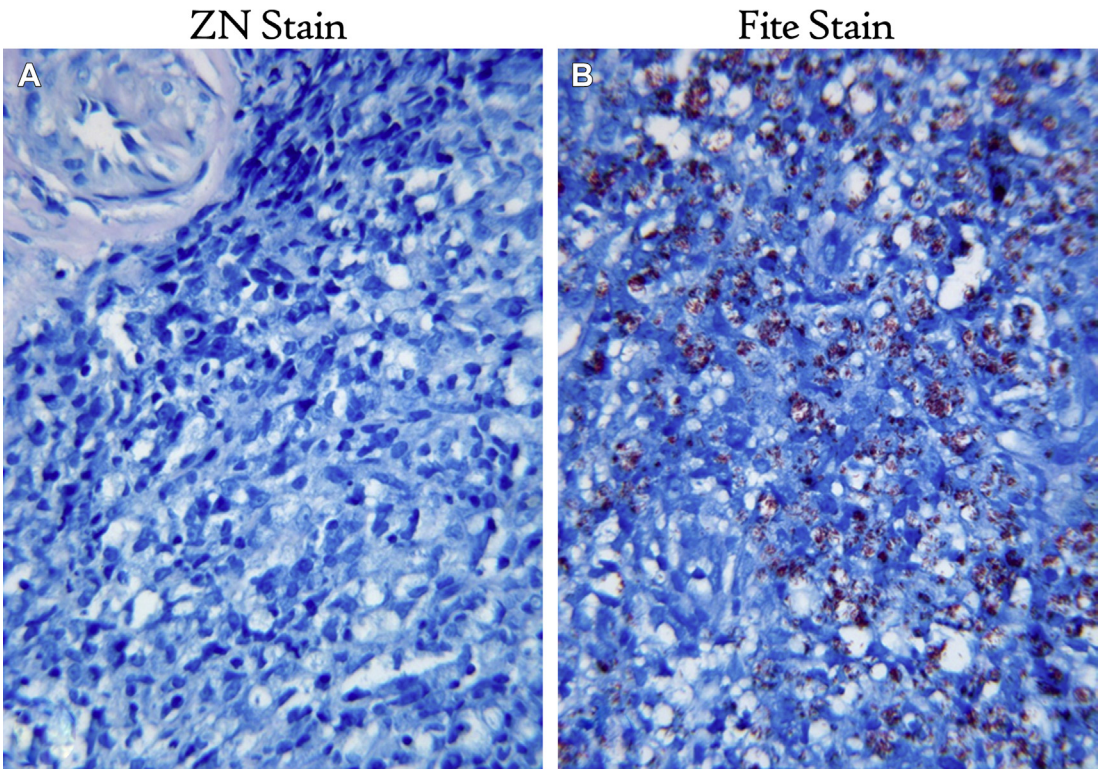

Fig. 14. Comparison of Ziehl-Neelsen (Z-N) and Fite stains. *M leprae* is weakly acid-fast, and a standard Z-N stain revealed few or no bacilli in this specimen (*A*). Fite staining of another section of the same specimen revealed abundant *M leprae* (*B*) (A, B: original magnification, ×1000).

histologically as a correspondingly wide range of appearances in the skin (**Fig. 17**). Based on clinical and pathologic criteria, this spectrum is divided into 5 types: polar tuberculoid (TT), borderline tuberculoid (BT), mid-borderline (BB), borderline lepromatous (BL), and polar lepromatous (LL).[74] Most patients are classified into the BT, BL, and LL groups. Because the immunologic underpinnings of this spectrum are genetically determined, the classification in any individual patient does *not* typically start at TT and then "slide down" in the spectrum. Rather, the established infection in any one patient will generally remain in a particular portion of the spectrum; slight upgrading or downgrading may occur and present as clinical reactions (see later discussion).

Classification and Clinical Presentations

Clinically, hypoesthesia or anesthesia within or adjacent to skin lesions is highly suggestive of leprosy. Associated findings include enlarged or

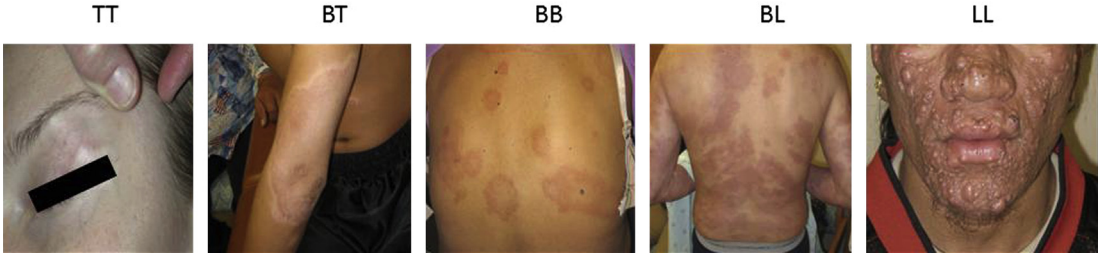

Fig. 15. Variations in leprosy lesions across the spectrum. Cutaneous lesions in leprosy are usually found at cool sites of the face, torso, and extremities. Lesions range from well-defined macules in tuberculoid disease to elevated plaques and "target" lesions in the BB leprosy, to diffuse infiltration and nodular lesions in lepromatous patients. (Abbreviations as in **Fig. 1**.) (*Courtesy of* Stryjewska B, MD, Baton Rouge, LA; and *From* Joyce MP. Leprosy. In: Walker PF, Barnett ED, editors. Immigrant medicine. Philadelphia: Elsevier; 2007. p. 460; with permission.)

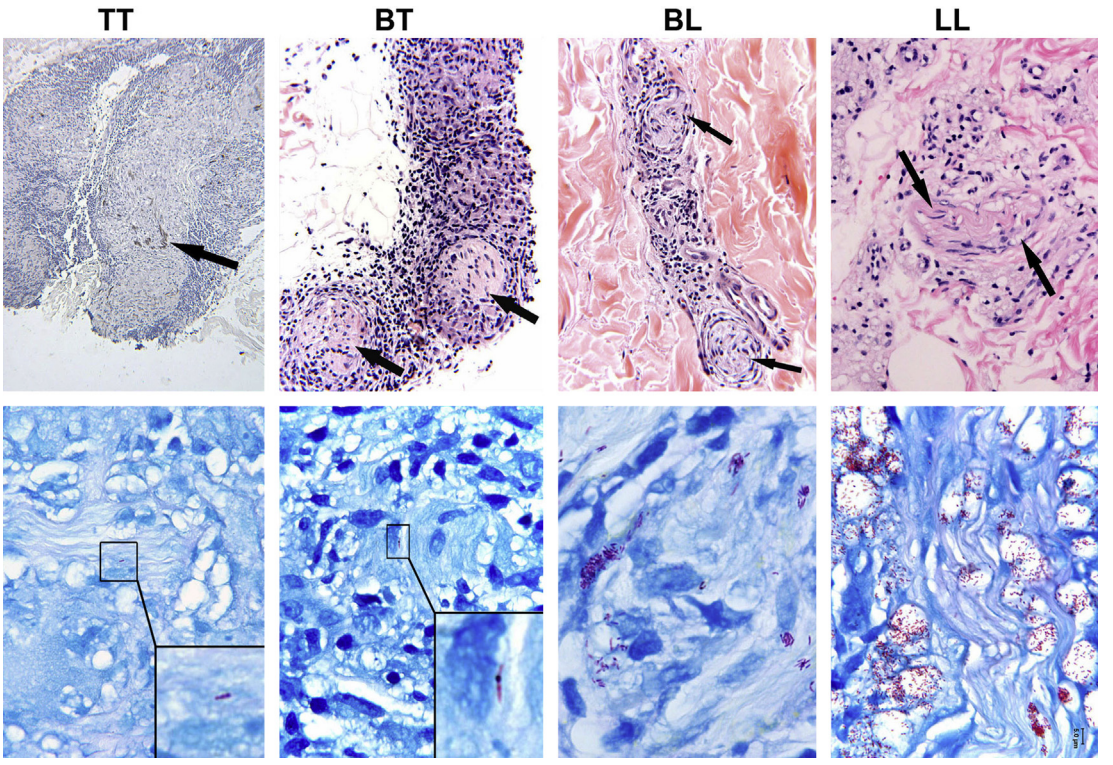

Fig. 16. *M leprae* in cutaneous nerves. Perineural inflammation (*upper panel*) and intraneural AFB (*lower panel*) are shown in cutaneous nerves from lesions ranging from TT to LL. Severe granulomatous inflammation in TT lesions may render nerves difficult to detect. *M leprae* may be difficult to demonstrate within nerves in TT-BT lesions, but are abundant in nerves in LL-BL lesions. (*Arrows* in upper panel indicate cutaneous nerves). (*Upper panel*, TT: S-100, ×20; BT, BL, LL: H&E, ×20. *Lower panel*: Fite stain, ×1000. Abbreviations as in **Fig. 1**.)

tender peripheral nerves, or history of painless cuts or burns on the hands or feet. In individual patients, across the spectrum from TT to LL, there is a progressive increase in the number of lesions and a gradual change from flat, sharply defined macules in tuberculoid lesions to diffuse infiltration and indurated plaques and nodules in lepromatous lesions (**Table 4**). Macules also characterize BT leprosy, but they are more numerous and usually distributed asymmetrically on the face, trunk, and limbs.

In BB patients, highly dimorphic patterns of lesions are seen, combining macules, plaques, and nodules. BL patients typically have numerous infiltrated macular and papular or nodular lesions, with poorly defined margins. They are seen on both sides of the body, often somewhat symmetric. Hypoesthesia may be present but is not seen as consistently as in tuberculoid lesions.

Polar LL patients have numerous, diffuse or nodular lesions with variable hypoesthesia. In advanced disease, diffuse thickening and wrinkling of the skin of the face may produce classic "leonine facies," but in less advanced disease, thickening of the skin may be subtler. Madarosis and nodular thickening of the earlobes are typical in LL and BL leprosy but may not be evident in early cases.

Histologically, across the leprosy spectrum, there is a concomitant decrease in organization of the infiltrates, from well-organized epithelioid granulomas in TT lesions to totally disorganized aggregates of foamy histiocytes in LL lesions (see **Fig. 16** and **Table 4**). Perineural inflammation is characteristic in all types. The infiltrates can also destroy dermal appendages, leading to loss of hair (eg, eyebrows) and dryness within the lesions (see **Table 4**). In contrast with tuberculosis, necrosis is rare in leprosy and is seen almost exclusively in granulomas in nerves in TT-BT lesions.

The bacterial load increases across this spectrum, from rare AFB in TT lesions to enormous numbers of bacilli in LL lesions (see **Fig. 17**). The papillary dermis is an especially favorable site in which to find the rare bacilli in both TT and BT lesions. A Fite stain should be performed in all biopsies with perineural inflammation to try to identify acid-fast organisms. *M leprae* is the only bacterium to infect peripheral nerves, and the finding of AFB within nerves is pathognomonic of

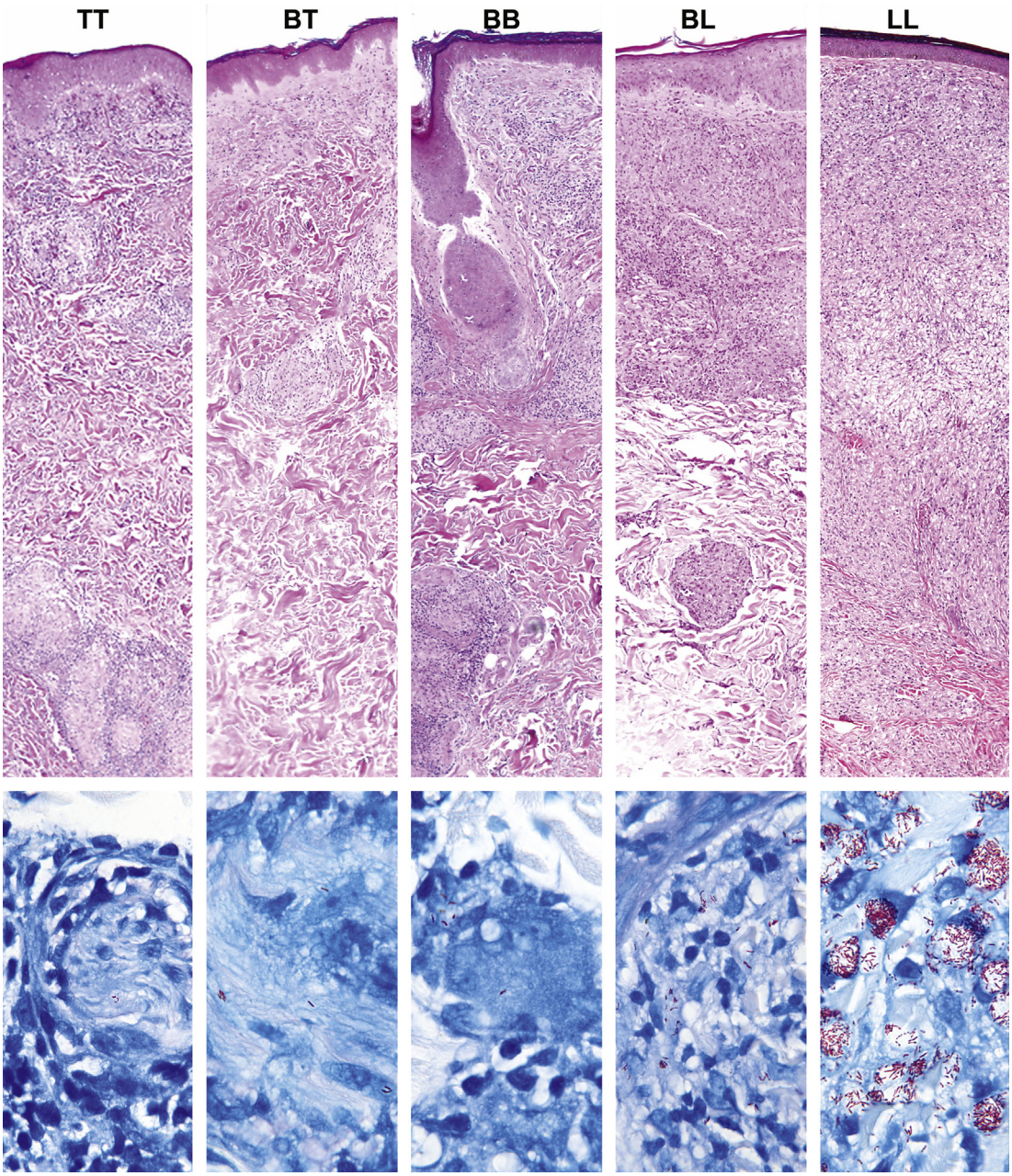

Fig. 17. The immunopathological spectrum of leprosy. Representative fields from each of the histopathological types of leprosy in the Ridley-Jopling classification are presented in the upper panel, in H&E stained sections (original magnification, ×63), and in the Fite-stained sections in the lower panel (original magnification, ×1000). TT leprosy is so named because the well-formed epithelioid granulomas are virtually identical to those seen in tuberculosis; acid-fast organisms are rare and difficult to demonstrate. In BT lesions, the granulomas are not as highly organized as in TT lesions, but acid-fast organisms are rare. In BB lesions, some foci of inflammation show epithelioid granulomatous organization, while other foci are disorganized and contain foamy histiocytes. Acid fast organisms are readily demonstrated but may not be abundant. BL infiltrates are composed of poorly organized aggregates of lymphocytes and foamy histiocytes, many of which have foamy cytoplasm. Numerous AFB can be found in any field. Polar LL lesions reveal confluent aggregates of foamy histiocytes. (Abbreviations as in **Fig. 1**.) (*From* Scollard DM, Adams LB, Gillis TP, et al. The continuing challenges of leprosy. Clin Microbiol Rev 2006;19:341; with permission.)

Table 4
Classification of leprosy

Leprosy Type	Cellular Immunity to *M leprae*	Clinical Presentation	Histologic Features	AFB (Fite Stain)	Frequency[a] (%)
Indeterminate[b]	Uncertain	Single lesion, often pale macule	Nonspecific perineural inflammation	Rare	2.9
TT	High degree of delayed hypersensitivity (DTH); strong Th-1 immune response	One to 3 macules (may be large), pale or erythematous, dry, sharply defined margins; sensation often reduced	Well-organized epithelioid granulomas involving nerves, occasional giant cells, necrosis is rare	Rare	3.2
BT	Moderately strong DTH; strong Th-1 immune response	Many macules, bilateral, pale or erythematous, dry, sharply defined margins; sensation often reduced	Moderately organized epithelioid granulomas involving nerves, occasional giant cells, necrosis is rare	Rare, but often in small cluster when found	24.3
BB	Weak DTH; weak Th-1 type immune response, some antibody production	"Dimorphic": mixed macules, plaques, "target lesions"; some margins sharp, others diffuse; sensation often reduced	"Dimorphic": epithelioid granulomas as well as aggregates of foamy histiocytes; nerves involved	Some bacilli in most fields	3.2
BL	Very weak delayed hypersensitivity; Th-2 type immune response; polyclonal antibody response	Multiple plaques and nodules, diffuse margins, bilateral and often widespread; sensory loss in some but not all lesions	Disorganized aggregates of lymphocytes and foamy histiocytes; nerves involved	Many bacilli in all fields; some globi	31.4
LL	Absent DTH to *M leprae*; Th-2 immune response; strong polyclonal antibody response	Multiple plaques, papules, and nodules, diffuse margins; sometimes diffuse thickening; bilateral and often widespread; sensory loss in some but not all lesions	Disorganized aggregates of lymphocytes and foamy histiocytes, sometimes confluent sheets of histiocytes; nerves involved	Very large number of bacilli in all fields; many globi	34.9

[a] Frequency (%) in 678 biopsies of new cases of leprosy. Biopsies processed at the NHDP from 2004 to 2013.
[b] Indeterminate means that a *definite diagnosis of leprosy* is made, but histologically the infiltrate is small and classification is uncertain.

leprosy. PCR can be used to identify *M leprae* in biopsies. PCR for *M leprae* is very specific but is not appreciably more sensitive than Fite staining and examination by an experienced microscopist.

Disorders commonly mistaken clinically and histologically for tuberculoid leprosy include sarcoidosis, granuloma annulare, and various superficial fungal infections. The diffuse infiltrates and macules of lepromatous leprosy are sometimes mistaken clinically for cutaneous lymphoma, and histologically for histiocytic neoplasms.

Considerable information has been gained regarding the immunologic status of leprosy lesions,[75,76] but there is still no single unifying hypothesis that can explain the wide spectrum of this disease. At the tuberculoid end of the spectrum, a Th-1 cytokine profile is present, similar to that in tuberculous granulomas,[3,5] while at the lepromatous pole, a Th-2 profile is seen.[77]

Current evidence suggests that the immunologic responses to *M leprae* are controlled genetically at 2 levels: native and acquired immunity. Most people have native immunity to *M leprae*, determined by several genes, such as PAKRG,[78,79] and mediated by Langerhans cells and dendritic cells.[3,80] Individuals who do not express native immunity may become infected with *M leprae* if sufficiently exposed, and an acquired immune response develops. This acquired immune response is regulated and determined by several genes, including many that are HLA-linked and expressed largely through T-cell functions, as indicated by cytokine profiles.[81] Although genetic determinants of both native and acquired immunity have been identified in many studies, at this time there are no clinically available genetic tests that can identify who is susceptible, nor what type of T-cell response a susceptible individual will develop if infected.

Lepromatous patients, who generate little or no CMI to *M leprae*, do produce a strong polyclonal antibody response. This strong polyclonal antibody response is the basis of attempts to develop serologic tests for leprosy,[82] but such methods do not detect most TT-BT patients and so they are not useful as general diagnostic tests.[83] However, this polyclonal antibody response may result in false positive serologic tests for syphilis, HIV, and other similar diseases.

Systemic Associations

Leprosy reactions represent the major burden of leprosy today, complicating the course of disease in 40% to 50% of patients. These reactions are spontaneous immunologic phenomena occurring as part of the natural course of infection in some patients; they are not drug reactions and are not caused by MDT. Two major types of reactions occur: "reversal" (type 1, T1R) reactions and *erythema nodosum leprosum* (type 2, T2R).

T1Rs occur in borderline patients (BT, BB, and BL) and are a manifestation of spontaneously enhanced cellular immunity, with expression of Th-1 cytokines and the chemokine, CXCL10.[10,84] Clinically, T1R presents as increased erythema and induration of pre-existing lesions, often with acute neuritis as well as acral edema, joint pain, and systemic symptoms that often suggest an autoimmune disease. Although they often present with severe, dramatic cutaneous lesions, the skin biopsy may show only subtle, nonspecific pathologic changes, such as edema or an increased number of giant cells. Clinical diagnosis is paramount, because there are no reliable histologic criteria for diagnosis. If the underlying diagnosis of leprosy is not recognized, such patients are frequently referred to rheumatologists and may be given corticosteroid regimens for many months. This regimen may provide transient relief of symptoms, but also enhances the growth of *M leprae*.

T2Rs present as crops of tender, erythematous nodules on any part of the body, not necessarily related to pre-existing lesions. This reaction occurs among lepromatous (LL-BL) patients, who have a high bacterial load and also have abundant circulating anti-*M leprae* antibodies. The pathogenesis of T2R is not understood. Although widely considered to be an antigen-antibody complex phenomenon,[85] the evidence supporting this is not fully convincing. Acute inflammatory infiltrates are characteristic of T2R, however, and the mechanisms of neutrophil recruitment are under investigation.[86] Clinically, in addition to the typical nodules, these patients experience acute neuritis, fever, leukocytosis (leukocyte counts sometimes ranging from 15,000 to 20,000/mm^3), and moderate to severe malaise. Skin biopsy of a lesion less than 24 hours old may reveal focal infiltrates of polymorphs superimposed on the disorganized lymphohistiocytic infiltrate of lepromatous leprosy (**Fig. 18**). Circulating C-reactive protein is also usually elevated.[87] Patients with T2R sometimes present to emergency rooms so acutely ill that they are evaluated for sepsis, if the underlying diagnosis of leprosy is not recognized.

Both types of reactions respond well to corticosteroids, but if the reaction is severe, high doses may be required. Tapering of corticosteroids is often difficult, because the reaction may reappear as the dose is lowered. There are no reliable laboratory tests to evaluate regression of the underlying immunologic phenomena. Thalidomide is

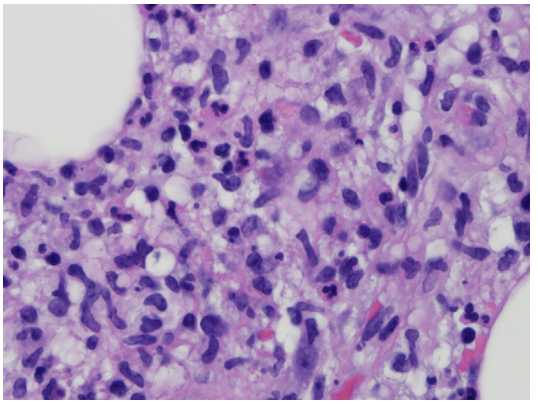

Fig. 18. Erythema nodosum leprosum, with foci of polymorphonuclear leukocytes superimposed on the disorganized, chronic inflammatory infiltrates of lepromatous leprosy (H&E, original magnification, ×400).

remarkably effective in the treatment of T2R[88]; it was this single benefit of thalidomide that kept the drug from being totally banned from all formularies for nearly 20 years, until newer uses for it were recognized. Medically, thalidomide is the drug of choice for T2R. However, because of its cost and the many precautions necessary to avoid the risk of phocomelia, in practice thalidomide is usually used for T2R only when corticosteroids do not control the reaction or if they cannot be tapered satisfactorily. Thalidomide has no beneficial effect in T1R.

All of the clinical-histopathological types of leprosy pose serious consequences for the patient who is not treated. Although the granulomatous inflammation in tuberculoid types of disease is associated with greatly limited bacterial growth and thus makes these patients far less infectious to others, the granulomas can destroy tissue. Because bacilli localize to peripheral nerves, these slender structures are especially vulnerable to damage and destruction by the granulomatous inflammation of TT-BT leprosy.[89] Thus, even though acid-fast organisms are rare in Fite-stained sections of TT-BT disease, signs and symptoms of clinical sensory and motor neuropathy are often observed earlier in tuberculoid patients than in lepromatous ones. In BB, BL, and LL forms of the disease, an increasing bacterial load is observed within nerves. Although the immune responses to *M leprae* in these patients are ineffective and are less damaging to nerves in the short term, eventually the combined effects of chronic infection and inflammation result in nerve injury, demyelination, and fibrous scarring.

These nerve injuries, if untreated, may progress functionally from slight sensory loss to complete anesthesia of hands or feet, or of the cornea. Motor weakness follows and ultimately may result in paralysis affecting fingers and toes as well as the musculature of the eye. Such nerve injury occurs to some degree in all cases of leprosy (ie, reduced sensory perception in skin lesions), and this may be seriously aggravated by leprosy reactions.

AFB and characteristic histopathological lesions of leprosy are usually *not* seen in the affected hand or foot or eye; these clinical findings are distal effects of nerve injury *proximal* to the affected site. The pathogenesis of the anesthetic foot, and the pressure ulcers that may result, was worked out in studies of neuropathy in leprosy[90] and has now been widely applied to the management of neuropathic injuries in diabetes mellitus.[91]

Evaluation and Management

Uncomplicated leprosy is treated with a MDT regimen of dapsone, rifampin, and clofazimine. For tuberculoid (TT-BT) disease, daily dapsone and rifampin are recommended for 1 year in the United States (**Table 5**). For lepromatous disease, daily clofazimine is added to this regimen, and the 3 drugs are given for 2 years. The WHO distributes these drugs in blister packs, but rifampin is provided only once monthly (see **Table 5**). These basic recommendations were made empirically by a WHO committee in 1982,[92] but in 1998 the WHO recommended reducing the duration of treatment by half[93,94] (see **Table 5**); many experienced physicians prefer the longer duration of treatment.

Clofazimine is not available commercially; it is distributed globally by the WHO in blister packs with dapsone and rifampin. In the United States, clofazimine is currently classified by the Food and Drug Administration as an investigational drug. The National Hansen's Disease Programs (NHDP) holds the Investigational New Drug Application for the use of clofazimine to treat leprosy, and the NHDP is the sole distributor of this drug in the United States. Additional information is available at www.hrsa.gov/hansensdisease.

Alternative drugs that are known to be effective against *M leprae*, both in laboratory tests and in clinical trials, are minocycline, clarithromycin, ofloxacin/levofloxacin, and moxifloxacin. Any of these can be substituted for any of the first-line drugs if necessary because of intolerance or interaction with other drugs the patient is taking.

Dapsone, rifampin, and clofazimine have been used extensively and are safe and well-tolerated in the vast majority of patients. Dapsone may cause mild anemia in many patients and should not be used at all in patients with G6PD deficiency.

Table 5
Treatment of leprosy: US and World Health Organization regimens

Agent	USA/NHDP[a]	WHO[b]
Tuberculoid (paucibacillary)		
Dapsone	100 mg/d for 12 mo	100 mg/d for 6 mo
Rifampin	600 mg/d for 12 mo	600 mg once monthly under supervision for 6 mo
Lepromatous (multibacillary)		
Dapsone	100 mg/d for 24 mo	100 mg/d for 12 mo
Rifampin	600 mg/d for 24 mo	600 mg once monthly given under supervision for 12 mo
Clofazimine	50 mg/d for 24 mo (if refused, may substitute daily Minocycline)	50 mg/d, plus 300 mg each month given under supervision for 12 mo

[a] The US-recommended MDT protocol has been evaluated in a retrospective study.[92]
[b] The MDT drug combination was recommended by a WHO committee in 1982[86]; no randomized controlled trial has been performed. In 1998, the WHO recommended reducing the duration of MDT treatment by half.[87,88]
From Scollard DM, Joyce MP. Leprosy (Hansen's disease). In: Rakel RE, Bope ET, editors. Conn's current therapy. St Louis (MO): Elsevier Science; 2003. p. 103; with permission.

Hemoglobin and hematocrit values should be checked during treatment. Possible hepatotoxicity with rifampin should be evaluated with periodic tests of liver function, and it may be necessary to avoid this drug in patients with hepatitis or other liver disease. Clofazimine causes bluish-black pigmentation of lesions as well as diffuse darkening of the skin in sun-exposed areas, and compliance with this drug is sometimes poor as a result of patients' cosmetic concerns.

Clinical Results/Outcomes

Notably, because *M leprae* is not cultivable, it is not possible to demonstrate killing of bacilli by routine culture or other methods. The bacteriostatic and bacteriocidal effects of antimycobacterial agents against *M leprae* have been documented in laboratory studies (reviewed in Ref.[69]). Recent reports indicate that measurements of RNA from *M leprae* extracted directly from biopsies may be used to assess viability,[95,96] but these assays are still only available in research settings. MDT for leprosy was recommended by a WHO committee in 1981, but has not been studied in a randomized, controlled trial.[97] The clinical efficacy of MDT has been demonstrated by clinical experience in patients in the United States[98] and in hundreds of thousands of patients globally over the last 3 decades.[97]

Lesions of Hansen's disease respond slowly to treatment, and the primary means of evaluation is clinical observation. In the early decades of treatment, slit skin smears were often performed. The minute amount of fluid obtained from the dermis was smeared onto slides and stained for AFB, and the number of bacteria was estimated by manual counting. This method was promoted as a means to demonstrate the decline in the bacterial load. The difficulty of standardizing this technique clinically, as well as the variability of staining quality and of counting accuracy in different laboratories, has resulted in the discontinuation of this method in most clinics and national programs. A more complete and accurate assessment can be obtained by annual biopsy of skin lesions.

Even after *M leprae* have been killed by MDT, dead organisms remain in tissues for months or years (**Fig. 19**), their numbers declining very slowly, to the great consternation of many physicians unfamiliar with the management of leprosy. The removal of dead bacilli by physiologic processes is not enhanced by extending MDT; continuing to treat until no organisms can be seen in biopsies or skin smears was recommended in the early days of dapsone monotherapy, but with MDT this is unnecessary and costly and risks long-term side effects of the medications.

Drug resistance in *M leprae* occurs but is rare.[99] Mutations associated with resistance to dapsone, rifampin, and fluoroquinolones are the same as those seen in *M tuberculosis.*[100] These mutations can be identified in *M leprae* DNA extracted from formalin-fixed, paraffin-embedded biopsies if the bacterial load is great enough to provide sufficient DNA.

Relapses or reinfection with *M leprae* is possible but is also rare[101] and usually occurs more than 10 years after completion of treatment. The development of "new" lesions during or after treatment is not unusual and is almost always due to leprosy reactions, not relapse.

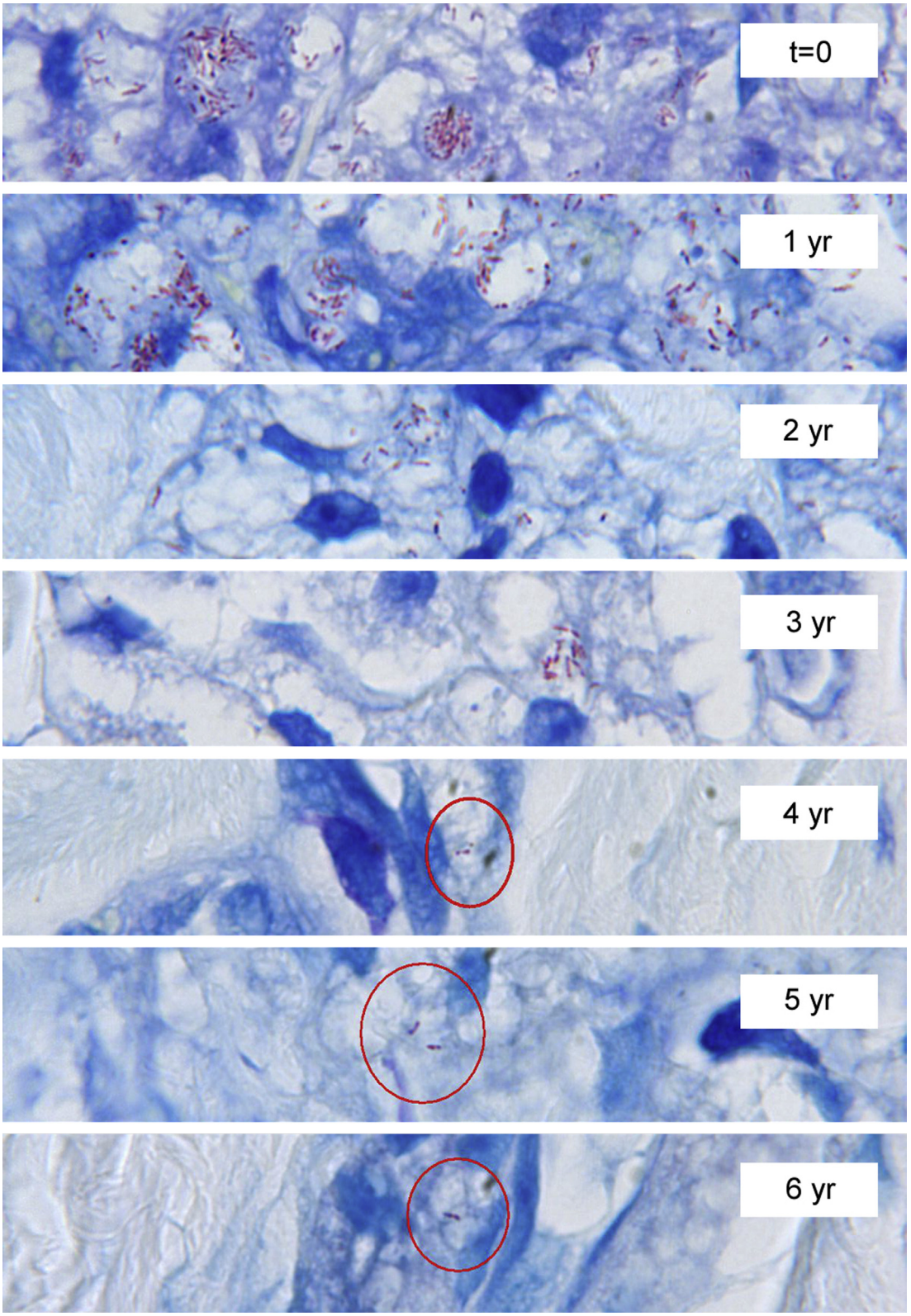

Fig. 19. Decline of *M leprae* in skin during and after treatment. Representative portions of sequential, annual biopsies of skin lesions from one lepromatous patient are shown, starting with the initial, pretreatment biopsy (t = 0). The patient was treated with the NHDP-recommended MDT regimen of daily rifampin, dapsone, and clofazimine for 2 years. At 1 year, organisms are still numerous but show evidence of degeneration. Treatment was discontinued at the time of the biopsy taken at 2 years. The bacterial load continued to decline slowly after MDT was discontinued, but rare organisms could still be observed after 6 years. Circles locate rare bacilli. Clinically, the cutaneous lesions resolved and did not relapse (Fite stains, ×1000). (*From* Scollard DM, Stryjewska B, MD, Leprosy. In: Rose BD, editor. UpToDate. Wellesley (MA): UpToDate; 2013; Graphic 74309, with permission.)

Coinfection with *M tuberculosis* and *M leprae* was common before the availability of good antimycobacterial treatment, but is uncommon today.[102] Coinfection is usually seen in immunocompromised or immunosuppressed patients.

Summary

Leprosy remains an important disease worldwide and, although rare, continues to be seen in the United States. Globally, untreated persons constitute the main reservoir of infection; in North America, leprosy is also a zoonotic infection among 9-banded armadillos, and people can acquire the infection from them. Uncomplicated infections appear as chronic, indolent lesions that not are painful, but systemic immunologic reactions occurring during the course of the disease may be so severe as to suggest sepsis, with fever, prostration, and an elevated leukocyte count. Reactions are common; relapse is rare. *M leprae* infection is curable, requiring 1 to 2 years of MDT. Neuropathy resulting from the infection may be permanent and disabling if the disease is not diagnosed and treated early. An extraordinarily broad spectrum of cellular immunity and granuloma formation in leprosy results in a wide range of clinical appearances. Hypoesthesia in or near lesions, or concomitant nerve enlargement or tenderness, aids in differentiating leprosy from superficial fungal infection, sarcoidosis, granuloma annulare, cutaneous lymphoma, and histiocytosis. Skin biopsies of suspicious lesions, diffuse histiocytic processes, or granulomas of uncertain cause should be evaluated for AFB using a Fite stain. The finding of AFB within cutaneous nerves is pathognomonic of leprosy. *M leprae* can also be identified by PCR in biopsies; this is highly specific but is not significantly more sensitive than a Fite stain and careful histologic examination.

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