Differential Diagnosis of Leprosy [1]

Contributing Authors

- Samuel L Moschella [2]
  - MD
  - Senior Consultant
  - Lahey Clinic
  - 41 Mall Road
  - Burlington, MA 01850 USA
  - Clinical Professor, Emeritus
  - Harvard Medical School

- Victoria Garcia-Albea [3]
  - NP, MSN, BSN, PNP, DCNP
  - Dermatology Certified Nurse Practitioner, Pediatric Nurse Practitioner
  - Leprosy Clinic
  - Lahey Clinic
Introduction

In an endemic area of leprosy, a practitioner confronted with a patient with an acute or chronic atypical rash that is not diagnostic and/or fails to respond to treatment would generally have leprosy in his differential diagnosis. In a non-endemic area, leprosy would not be considered in the differential diagnosis because practitioners have no familiarity with the disease in either medical practice or education. In endemic areas, practitioners not only have diagnosed the disease in practice, but also have been educated about the disease and its management. The only danger that occurs in endemic areas is that leprosy may be over diagnosed, since the organism is not found in cultures, skin scrapings, or skin biopsies in patients with pure neural leprosy, tuberculoid leprosy (TT), and, possibly, borderline tuberculoid leprosy (BT). If a physician is to improve his diagnostic acumen, he has to know what to look for and how to integrate the clinical signs to arrive at a diagnosis of leprosy. Fortunately, the diagnosis is more easily established by utilizing the following approach:

1. Investigate for potential exposure. Are any members of the family a source of infection? Has the patient ever lived or spent significant time in the military service, scientific research, business, or some exploratory capacity in an endemic area?
2. Does the patient clinically have a localized or disseminated eruption, asymmetric or symmetric eruption, or diffuse infiltration of the skin? Does the patient have lesions of the upper respiratory tract or the exposed part of the ears, or acropathic changes of the hands, feet, and face? Is there evidence of any neurologic or ocular changes, acral edema, testicular swelling or tenderness, mastitis, dactylitis, synovitis, or arthritis?
3. Do scrapings of skin lesions and the cooler sites of the skin such as ears, chin, elbows, and knees reveal the presence of the acid-fast bacilli? Does a biopsy of such sites show the presence of the mycobacteria with Fite-Faraco stain, especially in the nerves and arrector pilaris muscles, and a distinctive histologic distribution of the granulomatous infiltrate?
Dermatologic Diseases Simulating Leprosy

To identify the dermatologic diseases that simulate leprosy, one must recognize the nature of cutaneous manifestations of both the non-reactive and reactive presentations of leprosy, as seen in Tables 1, 2, and 3. In non-endemic areas, these dermatologic simulants can be more easily differentiated from leprosy by their clinical presentations and especially by their histopathology.

Ordinarily, cutaneous medical diagnoses are verifiable by distinctive symptoms, signs, test results, histopathology, or a combination of these. The dermatologic simulants of leprosy based solely on clinical grounds with no objective proof are "educated guesses."

There are patients with systemic diseases who have skin eruptions that suggest leprosy, without ocular or neurologic changes (see Table 1). There are patients with systemic disease who present with ocular and/or neurologic changes without the appreciated skin eruptions of leprosy. Among these diseases are sarcoidosis, syphilis, tuberculosis, Lyme disease, Behcet's disease, inflammatory bowel disease, polyarteritis nodosa, periodic Mediterranean fever, and lymphomatoid granulomatosis.

TABLE 1 Clinical characteristics of cutaneous manifestations of nonreactive leprosy

<table>
<thead>
<tr>
<th>Dyssmorphia</th>
<th>Plaque lesions</th>
<th>Dyschromia</th>
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</thead>
<tbody>
<tr>
<td>Asteatosis</td>
<td></td>
<td>Diffuse infiltration of the skin (deposition of mucin, amyloid, leukemia and lymphomas)</td>
</tr>
<tr>
<td>Alopecia</td>
<td></td>
<td>Mutilatory acropathy of hands and feet</td>
</tr>
<tr>
<td>Macular lesions</td>
<td></td>
<td>Auricular and nasal lesions</td>
</tr>
<tr>
<td>Annular lesions</td>
<td></td>
<td>Mutilatory rhinopathy</td>
</tr>
</tbody>
</table>

When one reviews the literature for acceptable leprosy simulants, some of these "mistakenly" diagnosed cases were treated with immunosuppressive drugs, which resulted in the worsening of symptoms and the appearance of...
new lesions. When biopsied, these lesions revealed not only the histologic features consistent with leprosy but also the presence of *M. leprae* on Fite-Faraco stain. "The clinician backed into the diagnosis."

Among the non-infectious, non-granulomatous dermatitic conditions that may simulate the lesions seen in non-reactive leprosy are non-scarring alopecias, hypopigmented lesions (vitiligo, acquired post-inflammatory hypopigmented lesions with or without scaling), contact dermatitis, nummular eczema, psoriasiform eruptions (psoriasis, parapsoriasis, Reiter's syndrome, drug eruptions), lichenoid dermatitides (lichen planus, drug eruptions), and gyrate erythema.

Among the superficial non-granulomatous skin infections that cause arcuate inflammatory lesions are tinea corporis ("ringworm"), tinea versicolor, impetigo circinatum, and erythema migrans (Lyme borreliosis).

Among the non-infectious plaque and nodular diseases, with or without systemic involvement, that may be included in a differential diagnosis of leprosy are sarcoidosis, palisading granulomas (granuloma annulare, necrobiosis lipoidica, necrobiotic xanthogranuloma, granuloma multiforme [Makars disease]), histiocytic diseases (histiocytosis X and multicentric reticulocytosis, Rosai Dorfman disease), mastocytosis, granuloma faciale, appendageal hamartomas (trichoepitheliomas, eruptive syringoma, steatocystoma multiplex), Kaposi's sarcoma, drug reactions, von Recklinghausen's disease, and lymphoproliferative disorders. Skin lesions of histoid lepromatous leprosy can resemble either dermatofibromas or nodular-like keloids both clinically and histologically.

Among the cutaneous infectious granulomas that may be considered in the differential diagnosis of leprosy are tuberculosis (lupus vulgaris, tuberculosis verrucosa cutis, erythema induratum of Bazin), atypical mycobacterial infection (e.g., *mycobacterium chelonae*), leishmaniasis skin infections (lupoid, recidive, disseminatum, mucocutaneous, diffuse cutaneous anergic and postkalazar), syphilis (secondary, late secondary, and tertiary), chromoblastomycosis, South American blastomycosis, African histoplasmosis, and blastomycosis keloidalis (Lobo's disease).

There are systemic disorders with diffuse cutaneous infiltration such as systemic sclerosis, scleromyxedema, amyloidosis, and mycosis fungoides, which can simulate the diffuse cutaneous infiltration of lepromatous leprosy.

There are non-reactive and reactive leprosy lesions that can mutilate the nose and the ears. Among the non-leprous diseases that can cause mutilatory rhinopathy are bacterial infections (tuberculosis, rhinoscleroma), spirochaetal infections (syphilis, yaws, endemic syphilis), protozoal infections (mucocutaneous leishmaniasis), deep fungal infections (South American blastomycosis, rhinophycomycosis), malignancy (basal cell carcinoma, lymphoma), relapsing polychondritis, arthropod infestations (nasal myiasis, rhinoestrus), granulomatous diseases (granulomatosis with polyarteritis [formerly called Wegener's granulomatosis], sarcoidosis), and sterile neutrophilic disorders (Sweet's disease and pyoderma gangrenosum).

The diseases that can mutilate the ear in ways that are similar to the destruction seen in leprosy are lupus vulgaris, leishmaniasis, lupus erythematosus, Lobo's disease, sarcoidosis, relapsing polychondritis, lymphoproliferative diseases, and keloids (see Table 2).

The skin changes resulting from the underlying superficial sensory autonomic and motor neuropathy are anhidrosis, resulting in dryness and fissuring of hands and feet; ichthyosiform changes of the arms and legs; dysmorphea of the body secondary to muscular palsies and paralysis; malum perforans; and charcot joints of the ankles. Other clinical signs are alopecia due to the diffuse lepromatous infiltration, especially of the eyebrows; gynecomastia due to testicular involvement; and dystrophic nail changes due to the disease or, secondarily, due to complicating dermatophyte infection.

The cutaneous reactions (see Chapter 2.2 [8]) that a patient may develop depend on the type of leprosy. Type I reversal reactions are seen in TT, BT, and BL and are lymphocyte driven. Type II erythema nodosum leprosum
(ENL) spectrum reactions are seen in BL and LL and are neutrophil driven. Lucio’s phenomenon is an endotheliitis of unknown origin (see Table 2).

**TABLE 2 Clinical characteristics of cutaneous manifestations of reactive leprosy**

<table>
<thead>
<tr>
<th>Localized edema and/or ulceration</th>
<th>Vasculopathy</th>
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<tr>
<td>Polymorphous erythema</td>
<td>Connective tissue-like syndrome</td>
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<tr>
<td>Vesiculo-bullous-pustular eruptions</td>
<td>Panniculitis (suppurativa or non-suppurative)</td>
</tr>
<tr>
<td>Nodular suppurative or non-suppurative lesions</td>
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</table>

The skin changes in Type I reversal reactions are characterized by keratosis spinulosa; edema and ulcerations of existing lesions; edema of the face, hands and feet; the appearance of new lesions; and tender swelling of involved nerves. Among the cutaneous disease simulants of reversal reactions are urticaria; angioedema; erysipelas; gyrate erythema; Well’s syndrome (eosinophilic cellulitis); erythema multiforme; tumid, subacute and acute lupus erythematosus; and drug eruptions (including fixed drug eruptions).

The clinical spectrum of Type II ENL lesions usually presents as inflammatory, tender nodules and plaques, and occasionally vesiculopustular eruptions, which are characterized histologically by a diffuse non-vasculitic neutrophilic infiltrate. The inflammatory plaque or an annular lesion seen in acute cutaneous lupus erythematosus, with or without systemic involvement, can resemble the ENL lesions seen in lepromatous or borderline lepromatous leprosy. These eruptions are basically inflammatory non-infectious, non-granulomatous, non-vasculitic infiltrates with specific histologic features.

Among the diseases that can resemble those of the spectrum of ENL are the neutrophilic dermatoses (Sweet’s disease and pyoderma gangrenosum) because of their clinical appearance; histopathologic sterile non-vasculitic neutrophilic infiltrate; subcorneal pustular dermatosis (Sneddon-Wilkinson disease); pityriasis lichenoides et varioliformis (PLEVA); and varicella or disseminated herpes zoster. A rare presentation of ENL is characterized by a necrotic ulceration of the penis, which must be differentiated from venereal disease or a non-infectious neutrophilic ulceration such as Behcet’s disease or Crohn’s disease.

When borderline and lepromatous leprosy present with erythema nodosum-like lesions, one might consider systemic non-infectious and infectious granulomatous diseases that have cutaneous plaques or nodules plus erythema nodosum, such as sarcoidosis, coccidiomycosis, histoplasmosis, South and North American blastomycosis, and tuberculosis, in the differential diagnosis.

Among the non-leprous conditions simulating the leprous panniculitis of ENL are erythema nodosum, erythema induratum, alpha-1 antitrypsin deficiency, pancreatic disease and pancreatic carcinoma, vasculitides such as cutaneous polyarteritis, lupus profundus, typical and atypical mycobacterial infections, calcific arteriopathy (calciphylaxis), cholesterol embolus, and lymphoproliferative disorders (lymphomatoid granulomatosis, B-cell lymphoma, and cutaneous T-cell lymphomas).

Ulcereative conditions that can simulate the lesions of Lucio’s phenomenon are the leukocytoclastic vasculitides and the vasculopathy associated with cryoglobulinemia, macroglobulinemia, and fibrinogenia, and calciphylaxis, cholesterol embolism, coumadin necrosis, and factitial dermatitis (see Table 3).

**TABLE 3 Ulcerative lesions seen in type II reactions**
Erythema nodosum leprosum | Sweet’s disease-like tissue neutrophilia – presenting as varicelliform eruptions, dermal cellulitis, or suppurative panniculitis

Venular or arteriolar necrotizing vasculitis | With or without cryoglobulinemia or positive ANCA

Lucio’s phenomenon | Endothelium loaded with bacilli (endotheliatis) and intraluminal thrombosis

Patients with nonreactive and reactive leprosy especially can have arthritis and tendonitis, which can simulate clinically, symptomatically, and serologically those seen in autoimmune disease such as rheumatoid arthritis and systemic lupus erythematosus, and may be inadvertently treated with immunosuppression or biologic drugs, which can unmask the presence of leprosy and/or type I or type II leprous reactions.

Although studies have shown that HIV-1 infection is not a risk factor, cases of borderline tuberculoid leprosy with type I reversal reaction have been reported and attributed to the induction of the immune reconstitution inflammatory syndrome associated with highly active antiretroviral therapy (HAART).

Finally, the systemic drugs used to treat leprosy (see Chapter 2.6 [9]) can cause adverse hypersensitivity reactions, which can simulate the skin eruptions seen in type I and type II lepra reactions. Dapsone, rifampin, and ofloxacin can cause skin lesions such as urticaria and angioedema, which can simulate lesions seen in type I reversal reactions. Dapsone and ofloxacin can cause hypersensitive adverse skin eruptions such as blistering and ulcerative necrotic ulcers, as seen in vasculitis, erythema multiforme, and pustular, plaque, and nodose skin lesions as seen in so called neutrophilic dermatoses, and erythema nodosum, which can be seen in type II (ENL) reactions. Minocycline has caused a lupus erythematosus syndrome resembling that seen in erythema nodosum leprosum. The anti-TNF biologics have caused, as a complication of therapy, non-infectious and infectious granulomatous dermatoses characterized by plaque and nodular lesions simulating these seen in tuberculoid and borderline tuberculoid and lepromatous disease. [1]

Figures
Leprosy

Borderline Reversal Reactions

Psorasisform Borderline Leprosy

Simulants

Contact Dermatitis due to after shave lotion

Allergic Angioedema (Penicillin reaction)

Psoriasis vulgaris (with classic distribution of eruptions)
Leprosy

Lichenoid Papular
Lepromatous Leprosy

Ichthyosiform
Cutaneous Leprosy
with saber shins due to periostitis

Borderline Lepromatous
Leprosy

Simulants

Lichen Planus

Ichthyosis vulgaris

Parapsoriasis
(patch-type area of dermatitis favoring bathing suit distribution)
Leprosy

Simulants

Subacute Lupus Erythematosus

Churg-Strauss Granulomatosis
(eosinophilic granulomatosis with polyangiitis)

Late Syphalid

Borderline Lepromatous

Necrobiotic xanthogranuloma
(in a patient with a mavelupus monoclonal gammopathy)

Well's Syndrome
(in a patient with neurocysticercosis)
Leprosy

- Hypo-pigmented Borderline Tuberculoid
- Borderline Lepromatous

Simulants

- Morphea (localized cutaneous scleroderma)
- Necrobiosis Lipoidica (in a diabetic)
- Late Syphalid
- Sweet’s Disease (associated with a viral infection)
- Mastocytosis (urticaria pigmentosus; in an adult with no systemic involvement)
Other Plaque Simulants

Sarcoidosis
(non-infectious granuloma)

Mycosis Fungoides
(T-cell lymphoma of skin)

Disseminated Anergic Cutaneous Leishmaniasis
(infectious granuloma)

Disseminated anergic cutaneous Leishmaniasis

Post-Kalazar dermal Leishmaniasis
(relapse of Kalazar infection)

Post-Kalazar dermal Leishmaniasis
(relapse of Kalazar infection)
Leprosy

Simulants
Granuloma faciale
(Non-infectious granuloma)

Xanthoma tuberosum
(skin and tendon involvement)

Histoid type

Mycosis Fungoides

Leukemia cutis
Leprosy
Diffuse Lepromatous
Leprosy with saddle nose
(secondary to destruction of cartilage)

Simulants
Systemic Amyloidosis
with macroglossia and carpal tunnel syndrome

Mycosis Fungoides
(diffuse induration of skin by a T-cell lymphoma)

Scleredema Diabeticorum
(wooden, non-pitting infarction of skin)
Leprosy

Lepromatous Leprosy
(diffuse infiltration of skin by granulomatous process)

Simulants

Systemic Scleroderma
(with diffuse thickening and hardening of skin)

Mycosis Fungoides
(Leonine facies of patient with mycosis fungoides)
Footnotes

1. See the Additional Resources [10] tab for a list of references that may assist in making a differential diagnosis of leprosy.

borderline lepromatous leprosy
borderline tuberculoid leprosy
erythema nodosum leprosum
tuberculoid leprosy
lepromatous leprosy
reversal reaction
lepra reactions
neural leprosy
ENL
RR