INTRODUCTION

The venereal and nonvenereal treponemal diseases are caused by motile bacteria of the family Spirochaetaceae, which also includes the genera Borrelia and Leptospira. Accurate recognition of spirochetal infection requires correlation of a given patient's travel and medical histories with a detailed knowledge of the clinical and histologic expression of each pathogen. The pathogenic treponemes resemble each other in dark-field and biopsy preparations, being coiled, silver-staining organisms 6 to 20 μm by 0.10 to 0.18 μm, and have a high degree of DNA sequence homology (1,2). A single genetic difference in the 5' and 3' flanking regions of the 15-kD lipoprotein gene tpp15 was described for venereal and nonvenereal treponematoses in one study (3), evidence that suggests that these organisms evolved from a common ancestor to cause different diseases (4,5). Size and sequence heterogeneity is demonstrated by other treponeme genes, such as those controlling the expression of the TprK antigen, a target of opsonizing antibodies that is important to host immune protection, variance in which may play a role in evasion of the host response (6,7). The uncultivable pathogenic nonvenereal Treponema pallidum subspecies include T. pallidum subsp. pertenue, T. pallidum subsp. endemicum, and T. careatum, which cause yaws, bejel, and pinta, respectively. Oral treponemes may be important in the causation of periodontitis (8–10).

VENERAL SYphilIS

Clinical Summary. Acquired syphilis, caused by T. pallidum, has afflicted humanity since at least the 15th century (11). Although it was a major cause of morbidity and mortality in the early 20th century, public health programs and the advent of penicillin so reduced its incidence in First World countries by mid-century that many physicians became unfamiliar with its signs and symptoms (1). The incidence of acquired syphilis has since increased; in 1990, the incidence was 20 per 100,000 in the United States and 360 per 100,000 in areas of Africa, in part reflecting the epidemic of human immunodeficiency virus (HIV) infection, with which acquired syphilis is linked epidemiologically and with which coinfection is common (12,13). New diagnoses of syphilis increased eightfold in the United Kingdom between 1997 and 2002 (14). In 2003, greater than 60% of all reported cases of syphilis occurred in men who had sex with men (15,16); data from one venereal and HIV testing center in Thailand showed a prevalence of HIV infection of 28% and of syphilis of 10% in this population. African Americans, particularly those in lower income groups, have higher incidence rates of syphilis (17).

T. pallidum, of which there are three antigenically similar subspecies (18), is generally spread through contact between infectious lesions and disrupted epithelium at sites of minor trauma incurred during sexual intercourse. The transmission rate is between 10% and 60%. Early lesions reflect a delayed-hypersensitivity response to the organism, although some bacteria escape, in part due to integral outer membrane proteins that may render the treponeme invisible to the immune system (19). The result in the untreated host is persistent infectivity over the course of decades.

Primary syphilis is defined by a skin lesion, or chancre, in which organisms are identified; it typically arises 21 days after exposure at the inoculation site and is classically a painless, brown-red, indurated, round papule, nodule, or plaque 1 to 2 cm in diameter. Lesions may be multiple or ulcerative, and the regional lymph nodes may be enlarged.

Secondary syphilis results from the hematogenous dissemination of organisms, yielding widespread clinical signs accompanied by constitutional symptoms inclusive of fever, malaise, and generalized lymphadenopathy. A generalized eruption comprises brown-red macules and papules, papulosquamous lesions resembling guttate psoriasis, and, rarely, pustules (20). Lesions may be follicular based, annular, or serpiginous, particularly in recurrent attacks of secondary syphilis. Other skin signs include alopecia and condylomata lata, the latter comprising broad, raised, gray, confluent papular lesions arising in anogenital areas, pitted hyperkeratotic palmoplantar papules termed “syphilis cornee,” and, in rare severe cases, ulcerating lesions that define “lues maligna.” Some patients develop shallow, painless ulcers in the mucosae.

Meningovascular syphilis is usually seen in tertiary syphilis after 7 to 12 years of disease (21) but can occur in the secondary stage and be symptomatic; usually, it...
manifests as basilar meningitis and can be associated with cranial nerve palsy (22). Acute transverse myelitis (23), glomerulonephritis, and self-limited hepatitis are other uncommon manifestations.

Primary- and secondary-stage lesions may resolve without therapy or go unnoticed by the patient, who then passes into a latent phase. This may be subdivided into early and late stages, an arbitrary distinction that may help to guide the therapeutic approach. The Centers for Disease Control base the distinction of the early (infectious) latent stage from the late (noninfectious) latent stage on whether the duration of the infection is less or more than 1 year, respectively. The World Health Organization uses a 2-year period to make this distinction. After a variable latent period, the patient enters the tertiary stage.

Tertiary syphilis comprises gummatous skin and mucosal lesions ("benign tertiary syphilis"), cardiovascular manifestations, and neurologic manifestations. The skin lesions may be solitary or multiple and can be divided into superficial nodular and deep gummatous types. The nodular type has a smooth, atrophic center with a raised, serpiginous border. The gummatous lesions present as subcutaneous swellings that ulcerate (24).

Congenital syphilis, on the rise since the mid-1980s (25), is a diagnosis rendered when organisms are identified in dark-field, immunofluorescent, or conventionally stained tissues or smears of lesions of skin, placenta, or umbilical cord (26). A presumptive case is an infant born to a mother with inadequately treated syphilis at the time of delivery, or when an infant or child with a reactive treponemal test for syphilis exhibits evidence of congenital syphilis by virtue of physical or long-bone radiologic examination, a reactive cerebrospinal fluid (CSF), Venereal Disease Research Laboratory test, an elevated CSF protein or white blood cell count of unknown cause, or quantitative treponemal titers four times higher than the mother's at the time of birth (26). Clinical signs include rhinitis, chancres, or a maculopapular desquamative rash (25). Transplacental infection occurs in more than 50% of infants born to mothers with primary or secondary syphilis, roughly 40% of those born to mothers in the early latent stage, and only 10% of those born to mothers with late latent infections (26).

Histopathology. The two fundamental pathologic changes in syphilis are (a) swelling and proliferation of endothelial cells and (b) a perivascular infiltrate of lymphoid cells and often of plasma cells. In late secondary and tertiary syphilis, there are also granulomatous infiltrates comprising epithelioid histiocytes and giant cells. Newborns with congenital syphilis have shown at autopsy multiorgan involvement by an angioinvasive CD68⁺ mononuclear cell infiltrate that imparts an "onion-skin" morphology to involved vessels with numerous demonstrable spirochetes (27).

**Primary Syphilis**

The epidermis at the periphery of the syphilitic chancre reveals changes comparable to those observed in lesions of secondary syphilis, namely, acanthosis, spongiosis, and exocytosis of lymphocytes and neutrophils. Toward the center, the epidermis becomes thinned, edematous, and permeated by inflammatory cells. In the center, the epidermis may be absent. The papillary dermis is edematous. A dense perivascular and interstitial lymphohistiocytic and plasmacellular infiltrate spans the entire thickness of the dermis (Fig. 22-1); the lymphocytes are principally of T-helper phenotype. Neutrophils are often admixed. Endarteritis obliterans characterized by endothelial swelling and mural edema is observed (Fig. 22-2).

By silver staining with the Levaditi stain or the Warthin–Starry stain and by immunofluorescent techniques, spirochetes are usually identified along the dermal–epidermal junction and within and around blood vessels. If seen in their full length, which is rare, spirochetes generally show 8 to 12 spiral convolutions, each

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**Figure 22-1 Primary syphilitic chancre.** The epithelium is eroded, and the corium contains a dense, plasma-cell-rich infiltrate. There is neovascularization, with secondary necrotizing vasculitic changes manifested by mural fibrin deposition.

**Figure 22-2 Primary syphilitic chancre.** There is endarteritis obliterans manifested by endothelial cell swelling, endothelial hyperplasia, and expansion of vessel walls by edema and a lymphohistiocytic infiltrate with resultant lumenal attenuation. A diffuse extravascular plasma-cell-rich infiltrate is present.
The cytoplasm of plasma cells. Ultrastructurally, the organism is 8 to 16 μm in length with regular spirals, a wavelength of 0.9 μm with an amplitude of 0.2 μm, and a cytoplasmic body 0.13 μm in diameter with tapering ends, all enveloped by a 7 nm trilaminar cytoplasmic membrane (38). The organisms attach to host cells by means of acorn-shaped nosepieces. The contractile motility of the spirochete is mediated by three or four axial filaments that course the length of the cytoplasmic body (39). A paraplastic membrane surrounds these axial filaments in young organisms but is replaced by an electron-dense amorphous substance produced by the host cell as an immunologic response in older spirochetes (36).

**Differential Diagnosis.** Lesions of chancroid are the most difficult to differentiate clinically from a syphilitic chancre. The characteristic histopathology of chancroid is one of dense lymphohistiocytic infiltrates with a paucity of plasma cells and a granulomatous vasculitis. An epidermal reaction pattern similar to the syphilitic chancre is observed, namely, psoriasiform epidermal hyperplasia and spongiform pustulation. A Giemsa or Alcian blue stain reveals coccobacillary forms between keratinocytes and along the dermal–epidermal junction. The infiltrate is composed mainly of T-helper lymphocytes and histiocytes including Langerhans cells (40).

**Secondary Syphilis**

**Clinical Summary.** There is considerable histologic overlap among the various clinical forms of secondary syphilis, such as the macular, papular, and papulosquamous types (41). Nevertheless, epidermal changes are least pronounced in the macular type and most pronounced in papulosquamous lesions.

Biopsies generally reveal psoriasiform hyperplasia, often with spongiosis and basilar vacuolar alteration, often measuring from 1 to 1.2 μm in length (Fig. 22-3A). It should be remembered that silver also stains melanin and reticulum fibers. Differentiation may cause some difficulties but should be possible based on the fact that the melanin in the dendritic processes of melanocytes has a granular appearance, the granules being thicker and more heavily stained than *T. pallidum* (28). Reticulin fibers, although wavy, do not exhibit a spiral appearance. Immunohistochemistry with antibodies to treponemal antigens are now available in paraffin-embedded applications (Fig 22-3B). Correlation with serology is prudent; in addition to conventional serology, emerging point-of-care tests for rapid screening for syphilis on serum samples have a sensitivity of 75% to 90% and a specificity of 90% to 99%, while those for whole blood are both less sensitive and less specific (29).

Histologic examination of enlarged regional lymph nodes in primary syphilis most commonly reveals a chronic inflammatory infiltrate containing many plasma cells with endothelial hyperplasia and follicular hyperplasia. Spirochetes are numerous and can nearly always be identified with the Warthin–Starry stain. In some cases, nonnecrotizing granulomas resembling those of sarcoidosis are found in the lymph nodes (30).

**Histogenesis.** *T. pallidum* can be demonstrated by histochemistry or by immunohistochemistry. The latter comprises immunofluorescent methods in frozen (31) or fresh specimens and immunoperoxidase methods employable in fixed tissues (32). By electron microscopy, the organism can be seen in both intra- and extracellular dispositions in the epidermis and dermis (33) and within keratinocyte nuclei (34), fibroblasts (34,35), nerve fibers (36), blood vessel endothelia, and the lumina of lymphatic channels (34). Phagocytic vacuoles of macrophages and neutrophils may contain organisms (37), as may the cytoplasm of plasma cells. Ultrastructurally, the organism is 8 to 16 μm in length with regular spirals, a wavelength of 0.9 μm with an amplitude of 0.2 μm, and a cytoplasmic body 0.13 μm in diameter with tapering ends, all enveloped by a 7 nm trilaminar cytoplasmic membrane (38). The organisms attach to host cells by means of acorn-shaped nosepieces. The contractile motility of the spirochete is mediated by three or four axial filaments that course the length of the cytoplasmic body (39). A paraplastic membrane surrounds these axial filaments in young organisms but is replaced by an electron-dense amorphous substance produced by the host cell as an immunologic response in older spirochetes (36).
with edema of the papillary dermis (Fig. 22-4). Exocytosis of lymphocytes, spongiform pustulation, and parakeratosis also may be observed (28,41). The parakeratosis may be patchy or broad, with or without intracorneal neutrophilic abscesses. Although lesions may mimic psoriasis, attenuation of the suprapapillary plate is uncommon. Scattered necrotic keratinocytes may be observed. Ulceration is not a feature of macular, papular, or papulosquamous lesions of secondary syphilis. The dermal changes include marked papillary dermal edema and a perivascular and/or periadnexal infiltrate that may be lymphocyte predominant, lymphohistiocytic, histiocytic predominant, or frankly granulomatous and is of greatest intensity in the papillary dermis and extends as loose perivascular aggregates into the reticular dermis. Obscuration of the superficial vasculature and lichenoid morphology is observed in some cases, and a cell-poor infiltrate is seen in others. In a few cases, when the infiltrate is heavy, atypical nuclei may be present and may then suggest the possibility of mycosis fungoides (42) or non-Hodgkin lymphoma. Neutrophils may permeate the eccrine coil to produce a neutrophilic eccrine hidradenitis or manifest as a neutrophil-imbed scale crust (Fig. 22-5) (28). Granulomatous inflammation is almost invariable in lesions of greater than 4 months' duration and may be present in some cases of early syphilis (43). A plasma cell component is usually present but is inconspicuous or absent in 25% of the cases (Fig. 22-6) (41). Eosinophils are not usually observed. Vascular changes such as endothelial swelling and mural edema accompany the angiocentric infiltrates in half of the cases (41). Necrotizing vascular injury is distinctly unusual. A confirmatory stain is recommended in all cases that are suspected of being secondary syphilis. A silver stain may show spirochetes in about one third of the cases of secondary syphilis, mainly within the epidermis and less commonly around the blood vessels of the superficial plexus. In some instances, the silver stain is positive even when dark-field examination of the patient's lesions is negative (28). By the immunofluorescent technique, essentially all cases are positive. Phenotypic analysis of the infiltrate reveals a lymphoid populace composed mainly of T cells, with an equal proportion of cytotoxic and T-helper cells.

There are several histologic variants of secondary syphilis—namely, condylomata lata, syphilitic alopecia, pustular lesions (Fig. 22-5), syphilis cornee, and lues maligna. Lesions of condylomata lata show all of the aforementioned changes observed in macular, papular, and papulosquamous lesions, but more florid epithelial hyperplasia and intraepithelial microabscess formation are

Figure 22-4 Secondary syphilis. There is striking psoriasiform hyperplasia of an epidermis surmounted by an ortho-hyperkeratotic and parakeratotic scale. There is prominent papillary dermal edema.

Figure 22-5 Secondary syphilis. There is psoriasiform epidermal hyperplasia with basilar vacuolopathy and lymphocytic interface dermatitis. The epidermis is surmounted by a parakeratotic scale rich in neutrophils. Plasma cells may be inconspicuous, as in this example.

Figure 22-6 Secondary syphilis. A dense, lymphocytic, and often plasma-cell-rich infiltrate surrounds the cutaneous vessels of the dermis.
observed (28). A Warthin–Starry stain shows numerous treponemes (36).

Biopsies of syphilitic alopecia may demonstrate a superficial and deep perivascular and perifollicular lymphocytic and plasmacellular infiltrate that permeates the outer root sheath epithelium with a concomitant perifollicular fibrosing reaction (28). An involutional tendency characterized by increased numbers of telogen hairs is observed. A concomitant necrotizing pustular follicular reaction may also be seen (20).

An unusual variant of secondary syphilis is rupial syphilis (44,45), an ulcerative form characterized by severe thrombotic endarteritis obliterans involving vessels at the dermal–subcutaneous junction with resultant ischemic necrosis. A concomitant dense plasmacellular infiltrate with a variable admixture of histiocytes may be observed. Defective cell-mediated immunity may play an integral role in the pathogenesis of lues maligna, particularly in cases in which vascular alterations are minimal (46,47). Several cases of lues maligna arising in the setting of HIV disease have been described, with involvement of the oral cavity as the principal manifestation. A case of secondary syphilis resembling bullous pemphigoid by both light microscopy and immunofluorescent studies has been described (48).

Syphilis cornee/keratoderma punctatum associated with secondary syphilis manifests an epidermal invagination containing a horny plug composed of laminated layers of parakeratotic cells with loss of the granular cell layer and thinning of the stratum spinosum (49). A moderately dense perivascular plasmacellular infiltrate with concomitant capillary wall thickening involves the cutaneous vasculature.

In the rare pustular lesions of secondary syphilis, a necrotizing pustular follicular reaction accompanied by noncaseating granulomata and a perivascular lymphoplasmacellular infiltrate typically characterizes the histopathology (20). A pustular psoriasiform process with an absent granular cell layer and a strikingly thickened cornified layer laced with neutrophils may be seen (Fig. 22-5); if the clinical correlate is rugose or elephantine skin thickening, the designation rupial syphilis may be applied (20).

In addition to small, sarcoideal granulomata in papular lesions of early secondary syphilis, late secondary syphilis may show extensive lymphoplasmacellular and histiocytic infiltrates resembling nodular tertiary syphilis (50). Conversely, lesions of early tertiary syphilis may lack granulomata (51).

Although often nonspecific, the hepatitis of secondary syphilis may produce a granulomatosus or cholestatic morphologic pattern on liver biopsy; hepatic necrosis and spirochetes may also be observed (52). Syphilis is a cause of reversible nephritic syndrome (53); kidney lesions of secondary syphilis show proliferative changes in the glomeruli (54).

Histogenesis. The renal changes in secondary syphilis relate to immune complexes containing treponemal antigen. Not only has direct immunofluorescence shown granular deposits of immunoglobulin and complement along the glomerular basement membrane (54,55), but indirect immunofluorescence antibody studies using rabbit treponemal antibody and sheep antirabbit globulin conjugate have demonstrated treponemal antigen in the glomerular deposits (54).

Differential Diagnosis. The differential diagnosis of lesions of secondary syphilis includes other causes of lichenoid dermatitis, including lichen planus, a lichenoid hypersensitivity reaction, pityriasis lichenoides and connective tissue disease, sarcoidosis, psoriasis, and psoriasiform drug eruptions (28). Prominent spongiosis, suprabasal dyskeratosis, a mid and deep perivascular component, and the presence of plasma cells are not histologic features of lichen planus or psoriasis (56). Although a mid-dermal perivascular infiltrate, keratinocyte necrosis, and prominent lymphocytic exocytosis are present in pityriasis lichenoides, the infiltrate is purely mononuclear in nature, and neither spongiform pustulation nor plasmacellular infiltration is observed (57). Although lichenoid hypersensitivity reactions and psoriasiform drug reactions may also demonstrate a perivascular infiltrate of plasma cells, tissue eosinophilia is typically observed as well.

Tertiary Syphilis

Tertiary syphilis is categorized into nodular tertiary syphilis confined to the skin; benign gummatous syphilis principally affecting skin, bone, and liver; cardiovascular syphilis; syphilitic hepatic cirrhosis; and neurosyphilis. In the first variant, the granulomas are small and may be absent in rare cases (51). The granulomatous process is limited to the dermis, with scattered islands of epithelioid cells admixed with a few multinucleated giant cells, lymphocytes, and plasma cells. As a rule, necrosis is not conspicuous. The vessels may show endothelial swelling (47).

In benign gummatous syphilis, the main pathology, irrespective of the organ involved, is one of granulomatous inflammation with central zones of acellular necrosis. In cutaneous lesions, the blood vessels throughout the dermis and subcutaneous fat exhibit endarteritis obliterans along with angiocentric plasmacellular infiltrates of variable density involving the dermis and subcutaneous fat.

In cardiovascular syphilis, elastic tissue fragmentation and reduplication with neovascularization and fibrosis of main arteries occurs. Neurosyphilis includes an asymptomatic form—meningovascular syphilis—and parenchymatous syphilis, which is divided into generalized paresis of the insane and tabes dorsalis (58). In meningovascular syphilis, an inflammatory endarteritis involves the leptomeningeal vessels. In generalized paresis of the insane, gliosis with ventricular dilation is observed; spirochetes are identified in the cortex in 50% of the cases. In tabes dorsalis there is demyelination of the posterior columns of the spinal cord, atrophy of the posterior spinal roots, and lymphoplasmacellular leptomeningitis (21,58).
Principles of Management. Antibiotic therapy is the mainstay of management.

NONVENEREAL TREPONEMATOSES

Yaws (Frambesia Tropica)

Clinical Summary. Yaws is caused by *T. pallidum* subsp. *pertenue*, which is indistinguishable microscopically from *T. pallidum* subsp. *pallidum* but has been shown to be distinctive by virtue of the substitution of a single nucleotide coding for a 19-kD polypeptide demonstrable by Southern blot analysis (59). Other molecular methodologies confirm distinctive DNA sequences (2,4). Yaws is spread by casual contact between primary or secondary lesions and abraded skin and is most prevalent in warm, moist, tropical climates; 95% of the studied population in one province of Ecuador proved seropositive in one series (60). Some 40% of children proved seropositive in two districts of the Congo in 2012 (61). However, if a patient were treated by antibiotics for infection(s) of another type or types, they might be seropositive but disease-free (62). It is estimated that 2.5 million people globally are affected (63), and in some locations the disease appears resurgent (64). Children are particularly afflicted (65). Sites of involvement include buttocks, legs, and feet. Unlike syphilis, yaws does not manifest transplacental spread to neonates (4). A positive side effect of yaws infection may be the production of antiphosphorylcholine antibodies that may be cardioprotective as they inhibit atherogenesis (66).

Primary Yaws

The initial primary-stage lesion, or “mother yaw,” begins as an erythematous papule roughly 21 days postinoculation, which enlarges peripherally to form a 1- to 5-cm nodule surrounded by satellite pustules covered by an amber crust. A red crusted appearance prompted German physicians to give the appellation “frambesia” to the disease. Lesions may heal as pitted, hypopigmented scars. Fever, arthralgia, and lymphadenopathy may coexist.

Secondary Yaws

Roughly 10% of cases progress to tertiary yaws, the skin manifestations of which comprise subcutaneous abscesses, ulcers that may coalesce to form serpiginous tracts, keloids, keratoderma, and palmoplantar hyperkeratosis. The bone and joint lesions of this stage include osteomyelitis, hypertrophic or gummatous periostitis, and chronic tibial osteitis, which may lead to “saber shin” deformities. Bilateral hypertrophy of the nasal processes of the maxilla produces the rare but characteristic “goundou,” which obstructs the nasal passages and, if not treated with early antibiotic therapy, may require surgery. Another otorhinolaryngologic complication is “gangosa,” characterized by nasal septal or palatal perforation. Although neurologic and ophthalmologic involvement is not a universally accepted phenomenon, reports of macular atrophy and culture-positive aqueous humor suggest that yaws may exhibit neuroophthalmologic manifestations similar to those of venereal syphilis. A less virulent form of the disease, observed in lower-prevalence areas, is termed “attenuated yaws,” the cutaneous manifestations of which comprise greasy gray lesions in the skin folds.

Histopathology. Primary lesions show acanthosis, papillomatosis, spongiosis, and neutrophilic exocytosis with intraepidermal microabscess formation. A heavy, diffuse dermal infiltrate of plasma cells, lymphocytes, histiocytes, and granulocytes is observed; unlike the case in syphilis, blood vessels manifest little or no endothelial proliferation (Figs. 22.7 and 22.8) (67). Secondary lesions show the same histologic appearance, resembling condylomatata lata in their epidermal changes but differing by virtue of the dermal infiltrate being in a diffuse, as opposed to a perivascular, disposition. The ulcerative lesions of tertiary yaws greatly resemble those observed in late syphilis in histologic appearance (67). The spirochetes can be demonstrated in primary and secondary lesions by dark-field examination. Silver stains demonstrate numerous organisms between keratinocytes. Unlike *T. pallidum*, which is found in both epidermis and dermis, *T. pertenue* is almost entirely epidermotropic (67).

Differential Diagnosis. The distinction between yaws and syphilis is based on clinical features; although the location of the organism in a skin biopsy may be helpful, no histologic feature or laboratory test absolutely distinguishes the two diseases (68).

Principles of Management. Antibiotics are the mainstay of therapy for yaws. Widespread use of azithromycin in endemic areas has been proposed to control yaws with an...
affects no age group preferentially and is the mildest of the treponematoses, with hypopigmentation being the only significant sequela. The incidence of pinta is declining precipitously for unknown reasons. Transmission appears to be from lesion to skin, classically between family members; the ritualistic whipping of diseased adults and unaffected youths is the putative mode of transmission in one aboriginal tribe in the Amazon Basin (72).

The primary lesion is characterized by an erythematous papule surrounded by a halo and occurs 1 to 8 weeks postinoculation. By direct extension or through fusion of satellite lesions, the primary site may grow to a diameter of 12 cm, forming an ill-defined erythematous plaque on the legs or other exposed sites. In infants, the primary lesion classically occurs at the sites where the baby was held most closely to the affected mother. The secondary lesions, or “pintids,” manifest months after inoculation as small, erythematous, scaly papules that coalesce to form psoriasiform plaques. Both primary and secondary lesions are highly infectious. In the tertiary stage, hypopigmented macules are present over bony prominences such as wrists, ankles, and elbows. Symmetric areas of achromia alternating with areas of normal or hyperpigmented skin may result in a mottled appearance. Atrophy and/or hyperkeratosis may be present. An attenuated variant is not described.

Histopathology. Primary and secondary lesions show a similar morphology—namely, acanthosis with spongiosis and a sparse dermal infiltrate of lymphocytes, plasma cells, and neutrophils disposed about dilated blood vessels (73). Endothelial swelling in the dermal vasculature is inconspicuous (74). Lichenoid inflammation may be present, accompanied by hyperkeratosis, hypergranulosis, basal layer vascuolopathy, and pigmentary incontinence. Increased numbers of Langerhans cells are present in the epidermis (75). Lesions of the tertiary stage are hyperpigmented, characterized by a large number of melanophages within the dermis, or depigmented, manifesting complete absence of epidermal melanin. Both lesions show epidermal atrophy and perivascular lymphocytic infiltrates. Organisms are present in all but late, longstanding lesions.

Histogenesis. Electron microscopy reveals absent melanocytes in depigmented lesions of tertiary or late pinta (75).

**Endemic Syphilis (Bejel)**

Clinical Summary. Primary-stage skin lesions are rare and are characterized by erythematous papules or ulcers of the oropharyngeal mucosa or the skin of the nipple of an uninfected mother nursing an infected infant. Unlike yaws, endemic syphilis, caused by *T. pallidum* subsp. *endemica*, is largely confined to the arid climates of the Arabian peninsula and the southern border of the Sahara Desert (72), whose seminomadic populations term the disease “bejel.” Children 2 to 15 years of age constitute the principal reservoir. Infection occurs by skin-to-skin contact or by means of fomites such as communal pipes or drinking vessels.
Primary-stage skin lesions are rare and are characterized by erythematous papules or ulcers of the oropharyngeal mucosa or the skin of the nipple of an uninfected mother nursing an infected infant.

More commonly, the initial manifestation is the presence of secondary-stage lesions, characteristically multiple, shallow, rather painless ulcers involving lips, buccal mucosa, tongue, faucets, or tonsils. Such lesions may be accompanied by hoarseness due to supenor laryngitis and/or regional lymphadenopathy. Condylomata lata involving the axillae and anogenital regions are also observed. Rarely, the secondary stage manifests as erythematous, crusted papules, macules, or an annular papulosquamous eruption, which may be accompanied by generalized lymphadenopathy or periostitis.

The tertiary stage comprises gummatous lesions of nasopharynx, larynx, skin, and bone, which may progress to ulcers that heal as depigmented, sometimes geographic scars with peripheral hyperpigmentation. Bone and joint involvement may manifest as tibial periostitis, which mimics that of yaws, or as mutilating lesions involving the nasal septum and palate. Ophthalmologic involvement comprises uveitis, chorioretinitis, choroiditis, and optic atrophy; T. pallidum has been cultured from intraocular fluid.

Histopathology. Although the pathology of early lesions of endemic syphilis is not well characterized, late lesions are said to show parakeratosis, acanthosis, spongiosis, pigmented incontinence, and a dermal lymphohistiocytic and plasma cell infiltrate.

Lyme Disease

Clinical Summary. First described in patients from Lyme, Connecticut, in 1975 (76), Lyme disease, transmitted by Ixodes ticks, is a systemic spirochetosis caused by Borrelia burgdorferi sensu stricto, B. afzelii, B. garinii, and, in some cases in Europe, by B. lusitanae, B. bissetti and B. spielmanii (77). Mice, rabbits, and lizards serve as principal reservoirs in the United States, with other animals including birds serving this role in Europe. Anywhere from 10% to 70% of Ixodes ticks in endemic areas carry the spirochete (77). Although the disease in the index cases manifested as inflammatory arthritis and central nervous system and cardiac symptoms (78) preceded by cutaneous erythema, manifestations may be protean and perplexing to the clinician. Lyme disease is the most common vector-borne disease in the United States, with roughly 20,000 new cases in 2005 (79). The incidence and geographic distribution of Lyme disease is increasing due to human travel habits and changing habitats of the vector (80), which may partly be explained by climate change (77). Males are predominantly affected, with a bimodal age peak: children aged 5 to 14 years and adults aged 60 to 65 years; most cases occur between June and August (79). Recurrences after appropriate antimicrobial therapy have been reported; it appears that most represent second tick bite inoculations as opposed to relapses (81).

Although the tick Ixodes dammini is the prototypic vector (82), other species of ticks from the genus Ixodes can also be infected—namely, I. ricinus (83), I. pacificus, and I. scapularis (84–86). Lyme disease has been reported in 43 states, Europe, Canada, Africa, and Asia (84). Infection by multiple different bacterial species transmitted by the same infected tick may occur. Coinfection of ticks and of humans by Ehrlichia chaffeensis, the etiologic agent of human granulocytic ehrlichiosis, and by B. burgdorferi is demonstrable in areas where the two diseases are endemic (87–91). Babesiosis is another tick-borne infection that can coexpress with Lyme disease (89,92). Although it seems counterintuitive, one model suggests that certain animals, such as the lizard Eumeces fasciatus (the five-lined skink), can act as a dilutional host, whereby reservoir incompetence can act to reduce vector infection prevalence and the associated risk of human infection (93).

There are three phases of Lyme disease. In stage I disease, hematogenous dissemination from lesions of erythema chronicum migrans to other organs may occur, the effects of which are usually self-limited (94) and include orchitis, splenomegaly, lymphadenopathy, and mild pneumonitis. The two main systems involved in stage II are neural and cardiac (94). The triad of meningitis, cranial neuritis, and radiculoneuritis is characteristic for neural involvement (95); Lyme cerebritis may also occur, and alteration of mental status may be the only initial clinical manifestation (96). Cardiac involvement manifests mainly as tachycardia and heart blocks, the basis of which is epi- and transmyocarditis. A biopsy of myocardium may show interstitial lymphoplasmacellular infiltrates, with a bandlike endocardial disposition said to be characteristic. A nonneutrophilic myocardial vasculitis has been described. Chronic disease at organ sites where spirochetes persist, most commonly the skin and nervous system in Europe and the musculoskeletal system in North America, constitutes stage III. Lyme arthritis and synovitis are characterized by a migratory oligoarthritis usually involving the knee joint, with the shoulder, wrist, temporomandibular, and ankle joints involved in some cases. Rarely reported is involvement of other sites such as metatarsal heads with edema and soft tissue swelling (97).

Erythema Chronicum Migrans

Clinical Summary. Erythema chronicum migrans (84) is the distinctive, albeit not pathognomonic, gyrate erythema that manifests at the site of a primary tick inoculation (98) and appears to occur in only roughly half of cases of Lyme disease (79). In the absence of a rash, the diagnosis depends on the demonstration of an antibody response to B. burgdorferi in an appropriate clinical setting (99). Unfortunately, patients who are immunosuppressed, such as those with underlying lymphoproliferative diseases, may never mount a detectable antibody response (100). Patients are
frequently unaware of the often painless tick bite (101). The lesion starts as an area of scaly erythema or a distinct red papule within 3 to 30 days after the tick bite, before spreading centrifugally with central clearing after a few weeks, occasionally reaching a diameter of 25 cm (102). The clinical presentation may be atypical by virtue of purpuric, vesicular, or linear lesions. Average lesional duration is 10 weeks in the European variant and 4 weeks in the American variant; in some cases, lesions persist for as long as 12 months. Females are affected more frequently in the European variant than in the American variant. The lesions may be solitary or multiple, the latter reflecting hematogenous dissemination of the spirochete, which may be accompanied by fever, fatigue, headaches, cough, and arthralgias. Distinguishing erythema migrans from the rash of Southern tick-associated rash illness (STARI), or Master disease, vectored by the lone star tick, is challenging (103,104).

**Histopathology.** An intense superficial and deep angiocentric, neurotropic, and eccrinotropic infiltrate predominated by lymphocytes with a variable admixture of plasma cells and eosinophils is the principal histopathology (Fig. 22-9). Plasma cells have been identified most frequently in the peripheries of lesions of erythema chronicum migrans, whereas eosinophils are identified in the centers of the lesions (105). Not infrequently, these florid dermal alterations are accompanied by eczematous epithelial alterations or an interface injury pattern (98), and some cases exhibit edema of blood vessels with transmural migration of lymphocytes, histiocytes and occasionally plasma cells (Fig. 22-9), granulomatous neuritis or vasculitis with luminal thrombosis (personal observation), and interstitial infiltration of the reticular dermis with a concomitant incipient sclerosing reaction. Interstitial granulomatous dermatitis mimicking granuloma annulare is described (106). A Warthin–Starry stain may be positive; one study demonstrated spirochetes by this technique in 41% of the cases, with approximately one to two spirochetes, measuring 10 to 25 μm by 0.2 to 0.3 μm, per section (105). Spirochetes have been identified primarily from the advancing border of the lesion. Most patients have elevated immunoglobulin M antibody titers (101).

**Differential Diagnosis.** The differential diagnosis includes other causes of delayed hypersensitivity in which potential antigenic stimuli include other forms of arthropod assaults, drugs, and contactants. A similar distribution of the dermal infiltrate is observed in connective tissue disease; however, the presence of tissue eosinophilia along with concomitant eczematous changes is not a feature of the latter. Differentiation from erythema annulare centrifugum may be impossible.

**Dermal Atrophying and Sclerosing Lesions as Manifestations of Lyme Disease: Acrodermatitis Chronica Atrophicans**

**Clinical Summary.** First described in 1883 in Germany and subsequently named by Herxheimer in 1902 (107), acrodermatitis chronica atrophicans usually begins as a diffuse or localized erythema on one extremity with the underlying dermis having a doughy consistency. After several months, the lesions become atrophic. The skin is frequently so thin that vessels and subcutaneous tissue can be easily visualized (108). Appendageal structures disappear, resulting in hair loss and decreased sweat and sebum production. The lesions are located mainly on the upper and lower extremities, frequently around joints, and spare the palms, soles, face, and trunk (108). Sclerosis may predominate in late-stage lesions and take several distinct forms: pseudosclerodermatous plaques over the dorsa of the feet; dense, fibrotic linear bands over ulnar and tibial areas; or localized fibromas overlying joint surfaces (107). Antibodies against *B. burgdorferi* are present in 100% of cases. Patients frequently have an elevated erythrocyte sedimentation rate and hypergammaglobulinemia. Either at the peripheries of lesions or distant from them, anetoderma, lymphocytoma, and morphea have also been described (108).

**Histopathology.** Within a few months to a year, the epidermis appears atrophic with loss of the rete ridges. There is granular layer diminution, and the epidermis is surmounted by a hyperkeratotic scale. In one study, a sparse interface dermatitis characterized by lymphocyte tagging along the dermal–epidermal junction, as well as basal layer cytolysis, was seen in 41% of cases (Fig. 22-10) (109), resulting in variable postinflammatory pigmentary alterations ranging from leukoderma to hyperpigmentation (107). The papillary dermis appears...
edematous, with a grenz zone of collagen fibers oriented parallel to the epidermis ranging from a few strands to a wide zone (110), with subsequent cosinophilic homogenization. A bandlike lymphocytic infiltrate is found in the mid and upper dermis and in some cases may produce a lichenoid morphology, obscuring the dermal–epidermal junction. Occasionally it extends throughout the cutis and subcutis (109). The infiltrate is predominantly in an angiocentric, eccrinotropic, and folliculotropic disposition and comprises mainly lymphocytes

and histiocytes with scattered eosinophils, neutrophils, and plasma cells. The vessels amid the superficial infiltrate appear destroyed (109). Within the infiltrate, there is piecemeal fragmentation of collagen, and elastic tissue is lacking. Beneath the infiltrate, disorganization and destruction of the collagen, along with hyperplasia, fragmentation, and basophilia of the elastic fibers, are observed. An end-stage lesion exhibits a characteristic constellation of epidermal atrophy, large dilated dermal vessels, and an attenuated dermis composed of damaged and degenerated collagen and elastic fibers with fatty atrophy (lipoid phanerosis). The collagen may appear homogenized and hypereosinophilic and may resemble morphea (Fig. 22-11). There is ultimately marked atrophy of adnexae with periannexal fibrosis.

**Histogenesis.** Acrodermatitis chronica atrophicans is mainly a stage III (late) cutaneous manifestation of the European variant of Lyme disease; the major vector is *I. ricinus* (107), and hence the distribution of the lesion is worldwide, with Middle Europe being the epicenter. Most North American cases occur in European immigrants; *I. ricinus* is not an inhabitant of North America (107). Immunophenotyping reveals that most of the lymphocytes are of T cell phenotype and that the elastic fibers express HLA-DR (109), suggesting a role for cell-mediated immunity in lesional development.

### Other Atrophying and Sclerosing Disorders Associated with Lyme Disease

**Clinical Summary.** Atrophoderma of Pasini and Pierini, facial hemiatrophy of Parry–Romberg, lichen sclerosus et atrophicus, eosinophilic fasciitis, and morphea (Fig. 22-11) are among the atrophying and sclerosing disorders of connective tissue that have been associated with *B. burgdorferi* infection based on the positive serology for *B. burgdorferi* in patients with these conditions, the isolation of spirochetal organisms in cultures of the respective skin lesions, and/or their identification in histologic sections (84,85,110,111).

In addition, acrodermatitis chronica atrophicans and morphea may coexist in the same patient. A possible etiologic basis of the sclerosis in all five entities—either as the inciting event (in morphea and eosinophilic fasciitis) or as an end-stage phenomenon (in atrophoderma, facial hemiatrophy, and lichen sclerosus)—may relate to increased production of interleukin 1 mediated by the *B. burgdorferi* spirochete, resulting in enhanced fibroblast production. Only progressive facial hemiatrophy will be considered further; all of the conditions are covered elsewhere in this book (see Chapter 10).

Facial hemiatrophy is an apposite term for an atrophying condition of the skin, subcutaneous fat, muscle, and bone involving either one division of the trigeminal nerve or half of the face. Occasionally the entire ipsilateral side of the body may be affected, or the atrophy may first manifest on the trunk or extremities.
Histopathology. A sclerodermoid tissue reaction mimicking morphea is observed, including the presence of adnexal atrophy and subcutaneous fibrosis. The muscles are atrophic, with loss of striations, edema, and vacuolation. Ocular and neurologic complications including iritis, keratitis, optic nerve atrophy, trigeminal neuralgia, and facial palsy may occur (84).

Principles of Management. The mainstay of therapy remains doxycycline, amoxicillin, cefuroxime, or ceftriaxone (112). When neuroborreliosis supervenes, doxycycline is less likely to be used and alternative antibiotics gain prominence (112).

Borrelial Lymphocytoma Cutis

Clinical Summary. Lymphocytoma cutis is a benign cutaneous lymphoid hyperplasia first described by Spiegel later the end of the 19th century and subsequently named lymphocytoma cutis in 1921 by Kaufmann-Wolff. Various triggering factors have been isolated, such as drugs, contactants, and infections, suggesting that an excessive immune response to antigen may be its etiologic basis. The B. burgdorferi spirochete transmitted by I. ricinus has been implicated among the infectious agents. Evidence supportive of a spirochetal etiology of some cases of lymphocytoma cutis includes the identification of spirochete-like structures in mercury- and silver-stained sections of skin biopsies from patients with lymphocytoma cutis in whom increased serum titers of antibodies against Borrelia spirochetes are observed (113). The term borrelioma has been coined to describe such lesions. Lymphocytoma cutis in association with B. burgdorferi infection has the same clinical appearance as lesions arising in other settings—namely, as isolated or multiple violaceous, firm nodules and infiltrative plaques (84). Sites of predilection for the solitary lesions are the earlobes, nipples, and areolae mammae. Lesions of lymphocytoma cutis may occur at sites of erythema chronicum migrans or in patients with stage II Lyme disease. Jessner lymphocytic infiltrate of skin is considered by some authors to be a form of lymphocytoma cutis and was reported in one patient whose biopsy showed spirochetes (84).

Histopathology. Skin biopsies show superficial and deep angiocentric, neurotropic, and eccrinotropic lymphocytic infiltrates, often accompanied by plasma cells and eosinophils, the former at the periphery and the latter in the center of lesions (105). The dermal alterations may be accompanied by epidermal spongiosis, and some cases show edema of blood vessels, transmural migration of lymphocytes and plasma cells, granulomatous vasculitis with luminal thrombosis, lymphohistiocytic neuritis, and interstitial reticulal dermal infiltrates with a sclerosing reaction. Germinal centers may be observed. A florid inflammatory cell infiltrate with granulomatous vasculitis and neuritis is seen at the tick bite punctum, whereas a biopsy taken within 1 cm of the edge shows a pauci-inflammatory process with only sparse mononuclear cells, no eosinophils or plasma cells, and a vasculopathy comprising endothelial swelling and hyperplasia and mural edema accompanied by mucinosis (114). Biopsies taken between the center and edge show superficial and deep perivascular lymphocytic, plasmacellular, and eosinophilic infiltrates with variable eczematous alterations. Although spirochetes have been identified in the lesional border in only 40% of cases (105), most patients manifest elevated immunoglobulin M antibody titers (85), and we therefore rely heavily on serology to make the diagnosis. Others hold that the diagnosis at this stage is largely a clinical one due to the incidence of false-positive and false-negative results (113); the sensitivity and specificity of confirmatory molecular tests are not optimal, and culture is insensitive (116). The background high seropositivity rates in healthy patients in endemic and nonendemic areas have prompted a two-tiered approach through which seropositive patients undergo a subsequent and more specific Western blot analysis (117,118). Meta-analysis of molecular methods shows that assays of skin and synovial fluid have the highest sensitivities and specificities; plasma and CSF assays are less accurate (116). Quantitative polymerase chain reaction of erythema chronicum migrans lesions shows positivity in up to 80% of cases, with the mean number of spirochetes in a 2-mm biopsy specimen ranging from 10 to 11,000; larger numbers of spirochetes correlate with smaller lesions and shorter duration of skin symptomatology (119). Molecular tests for Lyme disease should be reserved as confirmatory tools for cases in which the index of suspicion is high (116,120).

Differential Diagnosis. The clinical differential diagnosis encompasses other forms of annular erythema (121). Other causes of lymphocytoma cutis should be considered, such as drug therapy (122) or other infections (e.g., herpetic or mycobacterial). Well-differentiated lymphocytic lymphoma and chronic lymphocytic leukemia (CLL) should be excluded because both may mimic the diffuse type of lymphocytoma cutis; as the immune response mounted to the spirochetes in patients with underlying CLL comprises CD5/CD20+ lymphocytes, the phenotype and histology may mimic cutaneous marginal zone B-cell leukemia (123). When eosinophils and plasma cells are present and when there are germinal centers, the distinction from other forms of lymphoma is less challenging.

Other arthropod assaults, drug hypersensitivity, contact reactions, and connective tissue diseases such as lupus erythematosus, scleroderma, morphea, Sjögren syndrome, mixed connective tissue disease, and relapsing polychondritis can mimic Lyme disease. Tissue eosinophilia and epidermal changes help to discriminate Lyme disease from connective tissue disease, but differentiation from erythema annulare centrifugum is more problematic. Tissue necrosis at the primary inoculation site of Lyme disease can mimic a brown recluse spider bite (124).

Histogenesis. Most ticks become infected with B. burgdorferi by feeding on small animals such as the white-footed
mouse. B. burgdorferi is a long, narrow spirochete with flagella (125). It has at least 30 different proteins, including two major outer-surface proteins—Osp A and Osp B—which elicit antibody responses late in the course of the disease (125). It has been suggested that phagocytosis of the spirochete by macrophages leads to two different mechanisms of degradation: a phagolysosomal process, which may lead to major histocompatibility complex (MHC) class II-restricted antigen processing, and cytosolic degradation, which leads to MHC class I-restricted antigen presentation. This disparity may in part explain the variable immunologic aspects of Lyme disease (126).

Principles of Management. Antibiotic therapy is the mainstay of treatment, in particular, oral doxycycline, although other first-line antibiotics include amoxicillin and cefuroxime axetil (127).

REFERENCES


