Borrelia burgdorferi Infections in the United States

[a]WARREN R. HEYMANN, MD; [b]DANA L. ELLIS, MD

[a]Professor of Medicine and Pediatrics, Head Division of Dermatology, Cooper Medical School of Rowan University, Camden, New Jersey;
[b]Tulane University School of Medicine, New Orleans, Louisiana

ABSTRACT

It is becoming increasingly evident that the clinical presentation of infection with *Borrelia burgdorferi* varies greatly between different parts of the world. A growing number of European and Asian isolates of Lyme borreliae, differing from the American strain of *Borrelia burgdorferi*, have been identified in several different disorders. In light of the increasing number of reports describing an association between various cutaneous disorders and infection with *Borrelia burgdorferi* and the controversy that still remains over where *Borrelia burgdorferi* is truly pathogenic in these diseases, this review of the literature assesses the significance of these reports in substantiating these hypotheses, as such associations are important both diagnostically and therapeutically. (*J Clin Aesthet Dermatol.* 2012;5(8):18–28.)

Lyme borreliosis first came to distinction approximately 30 years ago, following its emergence in Lyme, Connecticut. It has since become the most common vector-borne bacterial infection in temperate regions of the northern hemisphere. Lyme borreliosis is caused by several genospecies of *Borrelia burgdorferi*, a spirochete transmitted by Ixodes ticks.[1] Over the years, it has become increasingly evident that the clinical presentation of infection with *B. burgdorferi* varies greatly between different parts of the world. In addition, a growing number of European isolates of phenotypically heterogeneous Lyme borreliae, differing from the American strain of *B. burgdorferi*, have been identified in several different disorders.[2] Consequently, much controversy exists over where *B. burgdorferi* is truly pathogenic in these diseases. This manuscript will review and reflect on the nature of the association of *B. burgdorferi* with these lesions.

BORRELIA BURGDORFERI SENSU LATO COMPLEX AND ITS GEOGRAPHICAL DISTRIBUTION

Ten years after the discovery of spirochetes as etiological agents of Lyme disease, 18 genomic species have since diverged from the phenotypically heterogeneous strains of *B. burgdorferi*.[3] The three genospecies that cause most human disease are *B. burgdorferi* sensu stricto, *B. garinii*, and *B. afzelii*, although *B. spielmanii* has been detected in early skin disease, and *B. bissettii* and *B. valaisiana* have been detected in specimens from single cases of Lyme borreliosis.[3,4]

In North America, disease is caused exclusively by *B. burgdorferi* sensu stricto, whereas in Europe and parts of Asia, *B. garinii* and *B. afzelii* are implicated as well. *B. garinii* and *B. afzelii* are antigenically distinct from *B. burgdorferi* sensu stricto.[1] These differences may account for the broader range of European disease presentations. All pathogenic genospecies have the potential to cause erythema migrans. In general, *B. burgdorferi* sensu stricto appears to cause the most acute systemic infections, with musculoskeletal, neurological, and occasional cardiac manifestations resulting from hematogenous spread. *B. garinii* is particularly associated with neuroborreliosis, while *B. afzelii* is linked to many of the uncommon early and late skin manifestations, borrelial lymphocytoma and acrodermatitis chronica atrophicans.[1]

In Europe, Lyme borreliosis has a widespread distribution throughout forested and woodland areas from southern Scandinavia to some parts of northern Mediterranean countries, with an incidence trending upward from west to east. The most highly endemic regions are found in central and eastern Europe, where as many as 200,000 cases may occur annually.[1] It has recently been

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ADDRESS CORRESPONDENCE TO: Dana Ellis; E-mail: dellis1@tulane.edu

suggested that an ongoing northward shift in the geographic distribution of this infection may be taking place and that changes in climate may allow Ixodes ticks to survive in new areas of Canada and Scandinavia.[2]

More than 40,000 confirmed or probable cases of Lyme borreliosis were reported in the United States in 2010, with most disease occurring in the northeastern and north-central states.[1] Reported incidences have increased in most countries because of greater professional and public awareness, along with changing ecological and human behavioral factors leading to higher risk of tick exposure.[1]

MICROBIOLOGY OF *BORRELIA BURGDORFERI*

The genus Borrelia is a member of the family Spirochetaceae, which also includes Leptospira and Treponema.[4] *B. burgdorferi*, a Gram-negative spirochete, was first isolated in 1982, and its genomic sequencing was completed in 1997.[2] These genomes include a linear chromosome and multiple linear and circular plasmids. The number and size of plasmids vary among strains and species and encode many of the factors necessary for survival during the organism's life cycle.[4]

Spirochetes have a wavelike body and flagella enclosed between the outer and inner membranes.[1] These spirochetes have multiple antigenic surface lipoproteins in place of a typical lipopolysaccharide coat.[2] Marques[4] recently reviewed the microbiology of *B. burgdorferi* and explains how differential expression of surface proteins can confer virulence, capacity for antigenic variation, and the ability of *B. burgdorferi* to survive in a range of environments. Outer surface protein A (OspA) and outer surface protein B (OspB) are abundantly expressed in culture. OspA also is expressed in the tick gut, where it mediates spirochete attachment. As an infected tick begins to feed on a mammal, the synthesis of OspA is repressed and that of outer surface protein C (OspC) is induced. OspC is important in the transmission of the spirochete from tick to mammal, and it is required early in mammalian infection. Once inside the host, the spirochetes use the protein plasmin, found in tick saliva, to effectively hide from the immune system. Despite the production of anti-*B. burgdorferi* antibodies, the plasmin confounds the immune system's efforts, which is further obstructed by the spirochete's ability to reduce the expression of surface proteins that would normally be the target of such antibodies. The avoidance of detection involves alterations in the lipoprotein variable major protein-like sequence (VIsE). This effectively inactivates certain immune system components such as complement. Thus, VIsE is required for persistence of infection in the immunocompetent mammalian host and plays a vital role in immune evasion in Lyme disease.[2,4]

VECTORS AND RESERVOIRS OF *BORRELIA BURGDORFERI*

B. burgdorferi is transmitted to humans by Ixodes ticks.[1,2,4] This group of infective ticks varies by geographical region and is represented by *Ixodes scapularis* in the eastern half of the United States, *Ixodes pacificus* in California and the Pacific Northwest, *Ixodes ricinus* and *Ixodes persulcatus* in Europe, and *Ixodes persulcatus* and *Ixodes ovatus* in Asia.[2] These tiny black-legged ticks have a two-year life cycle consisting of four developmental stages: egg, larva, nymph, and adult. Eggs are laid in spring and hatch into larvae during the late summer. These larvae feed on small animals, such as mice, and can acquire *B. burgdorferi* infection at this stage. The larvae then transform into nymphs, which feed again the following spring or early summer and transmit the infection to a new host. Nymphs eventually develop into adult ticks during mid-fall to winter, after which the adult female ticks feed again, primarily on large animals. Small mammals like the white-footed mouse are important in the transmission cycle of *B. burgdorferi*, as many can remain infected yet asymptomatic, therefore serving as reservoirs for the organism.[4]

B. burgdorferi sensu stricto has two geographic groups of reservoirs. In the northeastern United States, white-footed mice, white-tailed deer, and raccoons are the primary reservoirs for infected *Ixodes scapularis*. In the western United States, the wood mouse and the western fence lizard may both serve as reservoirs for infected *Ixodes pacificus*. In Europe, reservoirs for *B. burgdorferi* consist of a variety of mammals, such as rodents, birds, squirrels, rabbits, hedgehogs, and bison.[2]

TRANSMISSION OF *BORRELIA BURGDORFERI*

Ixodes ticks carrying pathogenic strains of *B. burgdorferi* transmit infection while feeding on vertebrate hosts. Humans are the dead-end hosts in whom Lyme disease develops.[1,2,4] Tick bites often go unnoticed because of the small size of the tick in its nymphal stage, as well as tick secretions that prevent the host from feeling any itch or pain from the bite. However, transmission is quite rare, with only about one percent of recognized tick bites resulting in Lyme disease. This may be because an infected tick must be attached for at least a day for transmission to occur. The most effective transmission occurs 48 to 72 hours after the onset of tick attachment. Infection in humans is partly dependent on human behavior, such as time spent outdoors and lack of protective garments. Exposure to and risk of infection also depends on tick factors, such as geographic distribution, survival, and seasonal variations in infectivity.[2]

CLINICAL FEATURES OF INFECTION WITH *BORRELIA BURGDORFERI*

Approximately 80 percent of all Lyme borreliosis cases display cutaneous manifestations.[5] The three characteristic dermatoborrelioses include erythema migrans (EM), Borrelial lymphocytoma (BL), and acrodermatitis chronica atrophicans (ACA); each occurring at a different stage of the disease. EM manifests in early Lyme borreliosis, while ACA tends to be a feature of late Lyme borreliosis. BL is subacute in presentation and may be observed shortly after

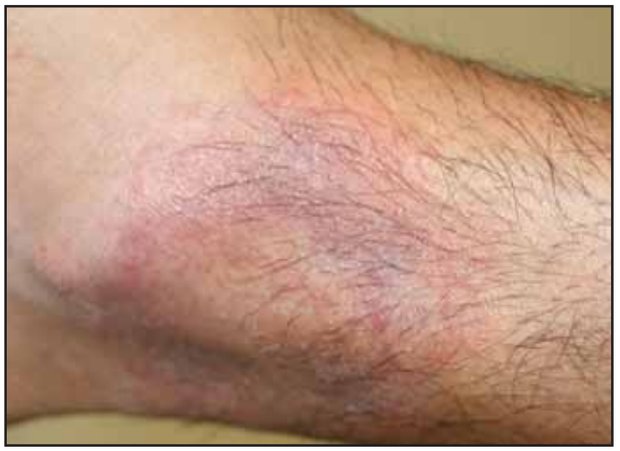

Figure 1. Classic annular lesion characteristic of erythema migrans

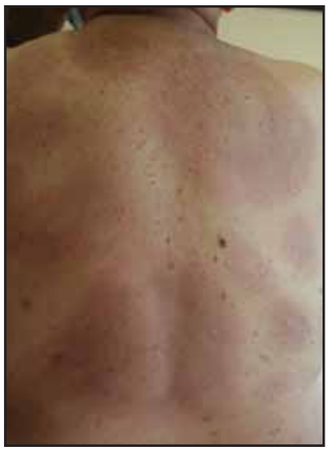

Figure 2. Multiple erythema migrans, representing disseminated infection with *Borrelia burgdorferi*

EM. Variations in the causative species have been noted among the three entities. Although all three prototypical species (*B. burgdorferi* sensu stricto, *B. garinii*, and *B. afzelii*) may very well be involved, *B. afzelii* is almost the exclusive cause of both BL and ACA and as such, both manifestations are more common in Europe than the United States.[6]

Erythema migrans. EM (previously known as erythema chronicum migrans [ECM]) is the most common objective symptom of Lyme disease and accounts for 90 percent of all cases.[6] The observation that EM arises within days to a few weeks at the exact site of the bite of certain Ixodes ticks is what initially led to the recognition of the tick vector for Lyme disease. The average incubation period after a tick bite is two weeks (range of 3–180 days), and only one- to two-thirds of patients in the United States who have EM actually recall the preceding tick bite that transmitted infection.[7]

EM begins as a small macule or papule at the bite site and subsequently transforms into a slowly enlarging erythematous patch. A depressed or raised area may remain at the center of the lesion at the site where the tick detached. The lesion expands over days to weeks, and central clearing may eventually occur, resulting in the formation of a target-like appearance (Figure 1). Size and central clearing are functions of infection duration.[6] Rashes present for a short time tend to have a more homogeneous appearance and may be misdiagnosed if too much emphasis is placed on central clearing as a diagnostic feature.[1] In the United States, the median diameter of most EM falls somewhere between 10 and 16cm, although some lesions may exceed 70cm.[6] EM lesions in the United States tend to be more inflammatory and faster growing than those in European countries. Pruritus or pain at the site of EM is uncommon, and if it exists, is usually mild. Some differential diagnoses of EM include tinea corporis, bacterial cellulitis, contact dermatitis, urticaria, fixed drug eruption, brown recluse spider bite, herpes simplex, herpes zoster, morphea, and granuloma annulare.[7]

In some patients, secondary EM lesions may occur as the result of hematogenous spread of spirochetes to other areas of skin and are strongly associated with *B. burgdorferi* sensu stricto infection, and as such, EM is more common in the United States than in Europe.[2,6,7] These secondary lesions are similar in morphology to the primary lesion, but slightly smaller, and because they are not directly associated with a tick bite, they lack a central punctum (Figure 2). The main differential diagnoses for disseminated EM are urticaria, multilple fixed drug eruption, erythema annulare centrifugum, and erythema infectiosum.[7] Patients presenting with multiple EM are usually systemically unwell and can have other objective manifestations including fatigue, malaise, arthralgias, myalgias, headache, lymphadenopathy, and fever in early disease (days to weeks), along with acute neuroborreliosis, arthritis, or carditis later in the disease course (months to years).[1,7]

Borrelial lymphocytoma. BL is a B-cell pseudolymphoma that occurs in response to the presence of *B. burgdorferi* antigens in the skin.[7] While this is a common lymphoproliferative reaction in endemic regions in Europe, BL is rarely, if ever, observed in the United States. It tends to appear as a subacute lesion, has a clear predominance in children, and accounts for approximately five percent of all dermatoborrelioses. The incubation period in positive cases is usually longer than with EM and tick bite history is more often negative (especially in children). In more cases than not, BL manifests as a solitary lesion and is typically found on the earlobe, in the areolar region, and less often on the scrotum or anterior axillary fold. It presents clinically as a soft, nontender, and sharply demarcated blue-red nodule or plaque that ranges in size from 1 to 5cm. Associated extracutaneous signs and symptoms are rare. Differential diagnoses for BL include arthropod bite reactions, cutaneous lymphoma, foreign body granuloma, sarcoidosis, cutaneous metastasis, keloid, perichondritis, granuloma

faciale, granulomatous contact dermatitis, and Paget's disease (if on the breast).[7]

Acrodermatitis chronica atrophicans. ACA is the cutaneous manifestation of late-stage Lyme borreliosis in Europe. Very few cases of ACA have been reported in the United States, most likely explained by the near-exclusive causation of ACA by *B. afzelii*—a borrelial genospecies that is not present in North America.

ACA is a disease of the elderly, and has a female predominance of 2 to 3:1. It often appears on the extensor surfaces of the distal extremities, such as the back of the hands and feet. Approximately 10 to 20 percent of all ACA patients had an EM lesion in the same body region months to years earlier. ACA develops slowly over many weeks to months, progressing from an early inflammatory phase to a chronic atrophic phase. In the early inflammatory stage, ACA lesions manifest a blue-red discoloration accompanied by ill-defined doughy swelling. In the chronic stage, gradual epidermal and dermal atrophy ensues with overlying telangiectasias. Up to 20 percent of patients will develop solitary or multiple flesh-colored to blue-red indurated nodules or pseudosclerodermatous bands over juxta-articular surfaces. Approximately two-thirds of patients with ACA will experience an associated peripheral neuropathy.[7]

The differential diagnoses of ACA include deep vein thrombosis, superficial thrombophlebitis, arterial occlusive vascular disease, acrocyanosis, livedo reticularis, lymph-edema, pernio (chilblains), erysipelas, bursitis/arthritis, and morphea.[7]

DIAGNOSTIC CONFIRMATION

Diagnosis of Lyme borreliosis should first be based on a thorough history and objective clinical findings, followed by the appropriate laboratory tests. Early and localized Lyme disease is best diagnosed by recognition of the EM skin lesion, and laboratory tests are generally not necessary, except in patients with more atypical skin lesions. For all other cutaneous manifestations of Lyme disease, such as BL and ACA, diagnostic confirmation is preferred. Serological analyses of immunoglobulin G (IgG) and immunoglobulin M (IgM) antibodies to *B. burgdorferi* are most often used in clinical practice, although they are not useful in the early stages of Lyme disease, as fewer than 50 percent of these patients will have positive serological results at presentation.[5]

The current recommendations for serodiagnosis of Lyme disease involves a two-tier approach: a sensitive enzyme-linked immunosorbent (ELISA) assay, followed by Western blotting (a more specific test than ELISA) when results are indeterminate or positive.[4,5] The ELISA provides a quantitative estimate of the concentration of antibodies against *B. burgdorferi*, while the Western blot provides information about the specificity of the antibodies—where positive bands indicate that antibodies against specific protein antigens of *B. burgdorferi* are present. The majority of authorities require the presence of antibodies against at least either two (for IgM) or five (for IgG) specific proteins of *B. burgdorferi* for the Western blot to be deemed positive.[8] Immunoassays used to detect anti-*B. burgdorferi* antibodies utilize either whole spirochete preparations or more often, a synthetic C6 peptide antigen (personal communication of DLE with Quest Diagnostics, January 20, 2012). The C6 peptide antigen is a 26-amino acid sequence derived from the VlsE membrane protein of Borrelia and can be used to detect infection from both American and European Borrelia species.[8]

IgM antibodies may present within a few weeks of disease onset, while IgG antibodies appear later. Thus, a positive IgM result as determined by two-tier testing, in conjunction with a negative IgG result, is evidence of early infection unless obtained on a specimen collected more than one month following symptom onset. In this instance, a positive IgM finding is more likely to represent a false-positive result, unless IgG is also positive. A positive IgG result by two-tier testing is required to confirm the diagnosis of disseminated disease.

The interpretation of Western blot assays is based on the number of positive bands: 2 of 3 bands (23, 39, 41 kDa) for IgM positivity and 5 of 10 bands (18, 23, 28, 30, 39, 41, 45, 58, 66, or 93 kDa) for IgG positivity,[8] where each band represents a Borrelial antigen. The 23 kDa band represents the Osp C; the 39 kDa band is an unknown antigen. However, based on research at the National Institutes of Health (NIH), it is the most specific antibody for borreliosis; the 41 kDa band represents flagella and is the most common Borrelial antibody; the 18 and 28 kDa bands correspond to outer surface proteins; the 30 kDa band is a variant of outer surface protein A; the 45 kDa band is a heat shock protein that helps the bacteria survive fever; the 66 kDa band is also a heat shock protein and is the second most common Borrelial antibody; and finally, the 93 kDa antigen is Borrelial deoxyribonucleic acid (DNA).[8]

False-positive serological test results may occur due to prior vaccination, infectious mononucleosis, systemic lupus erythematosus, or other diseases caused by spirochetes, such as syphilis, yaws, or leptospirosis. However, the Lyme disease C6 antibody test does not typically yield false-positive results in these conditions.[8] This said, a major shortcoming of current serological assays is that they do not distinguish between active and inactive infection.[4] There tends to be a background rate of seropositivity among patients in endemic regions, and previously symptomatic patients may continue to be seropositive for years, even after adequate antibiotic treatment. For this reason, there is no indication to recheck serology after therapy to determine the effectiveness of treatment.[4,8]

In addition to the aforementioned serological tests for Lyme disease, commercial laboratories may utilize the Lyme CD57 Test, which theoretically aids in determining the success of treatment. The Lyme spirochetal organisms suppress the number of CD57 natural killer cells, and as such, the CD57 count is used to indicate how active is the infection. Low CD57 counts occur in chronic Lyme disease or when the disorder has been active for more than one year. In such situations, CD57 counts are usually well below

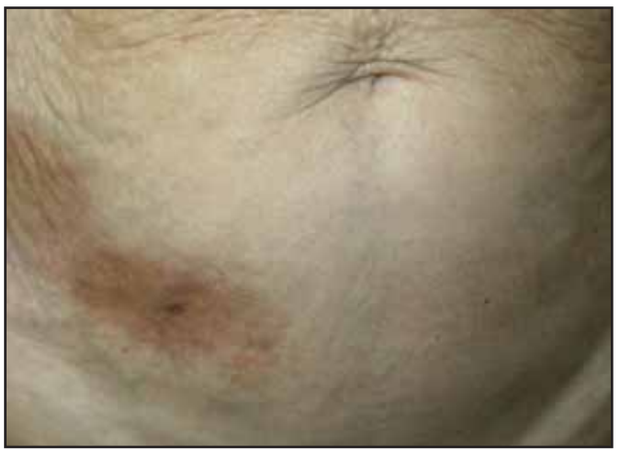

Figure 3. A characteristic lesion of morphea (well-defined indurated plaque) in an 86-year-old man

60 (normal >200). This test can be run at the start of therapy, then every several months to document the effectiveness of treatment (Personal communication of DLE with LabCorp, January 20, 2012).

Microbiological confirmation of *B. burgdorferi* infection includes spirochete culture and polymerase chain reaction (PCR) detection of its specific DNA. The use of spirochete cultivation in clinical practice is very limited primarily due its special requirements and the lack of sensitivity. Culture of *B. burgdorferi* requires special enriched media, such as Barbour-Stoenner-Kelly (BSK) or modified Kelly-Pettenkofer (MKP). In addition, due to the slow growth of the bacterium, a prolonged period of observation (up to 12 weeks) is often required. PCR has been used to amplify genomic DNA of *B. burgdorferi* in skin, blood, cerebrospinal fluid (CSF), and synovial fluid. Similar to cultivation, PCR is highly specific, but unsatisfactorily sensitive. In skin biopsies from EM lesions, PCR sensitivity varies from 25 to 90 percent and is similar to culture. The sensitivity of PCR for ACA lesions varies from 20 to 90 percent.[4]

The histopathological picture of the various manifestations of Lyme borreliosis is not absolutely diagnostic, but is a helpful adjunct to the clinical diagnosis, especially in cases of BL and ACA. A patchy perivascular mononuclear infiltrate in the superficial and deep dermis is histologically characteristic of EM. The infiltrate is primarily composed of lymphocytes and histiocytes with a variable amount of plasma cells. A few eosinophils may also be present in early lesions, which can make the distinction between EM and arthropod bite reactions difficult. There are two histopathological types of BL, with or without follicular structures (follicular type versus diffuse/nodular type, respectively). In some cases, BL may histologically simulate cutaneous lymphomas. ACA is characterized by a patchy to band-like mononuclear infiltrate within the entire dermis, with or without an increased number of fibroblasts and fibrosis, often present early in the disease process. In the later stages, degeneration and reduction of collagen and elastic fibers may be seen.[5]

The histopathological diagnosis of Lyme borreliosis may be aided by the direct detection of spirochetes by immunohistochemistry (using silver stains such as Steiner, Dieterle, and Warthin-Starry) and by the recently described technique of focus floating microscopy (FFM). The latter method is an advancement of older immunohistochemistry techniques by employing a polyclonal anti-borrelial antibody that recognizes all different borrelial strains. This diagnostic technique is more sensitive than PCR and ELISA-PCR, but results are largely operator-dependent, and as such, it is rarely used in clinical practice.[5]

SOUTHERN TICK-ASSOCIATED RASH ILLNESS

Southern tick-associated rash illness (STARI), or Masters disease, is associated with the bite of the Lone Star tick, *Amblyomma americanum*. These ticks are mainly found throughout southeastern and south-central states as well as along many coastal areas. STARI lesions generally occur 2 to 15 days after the tick bite and appear similar to EM, although they tend to be smaller with more prominent central clearing. Overall, there are fewer systemic complications in STARI than in EM and Lyme borreliosis.[2] The true etiology of STARI is unknown. Potential, yet unlikely agents include *Borrelia lonestari* and *Rickettsia amblyommi*. Cultures and serologies are negative for *B. burgdorferi* in all cases of STARI, but similar to Lyme borreliosis, STARI tends to respond well to doxycycline and other antibiotics.[4,7]

OTHER DISORDERS ASSOCIATED WITH *BORRELIA BURGDORFERI*

Morphea and lichen sclerosus et atrophicus. Since the first positive serological, immunohistochemical, and cultural studies in the 1980s, *B. burgdorferi* has been discussed as a causative agent of morphea and its variants (Figure 3, Table 1). Several case reports have implicated *B. burgdorferi* infection as a possible cause of many subtypes of morphea including (but not limited to) lichen sclerosus et atrophicus (LSA, Table 2), progressive facial hemiatrophy (Parry-Romberg), eosinophilic fasciitis (Shulman syndrome), morphea en plaque, guttate morphea, generalized morphea, bullous morphea, subcutaneous morphea, morphea profunda, linear scleroderma, and en coup de sabre. Conflicting results have been reported based on different diagnostic methods from variable geographic areas. With regard to the disparate findings in different geographic regions, it can be speculated that morphea may be caused in some cases by *B. burgdorferi* genotypes that are present in that area only.[5]

In addition, several authors have postulated a causative and/or triggering role of *B. burgdorferi* in other cutaneous manifestations—atrophic lesions, such as atrophoderma of Pasini and Pierini and anetoderma; annular lesions, such as granuloma annulare (Table 3), urticaria, erythema annulare, and pityriasis rosea; granulomatous diseases,

TABLE 1. Results of studies investigating *Borrelia burgdorferi* in patients with morphea (and variants)

AUTHOR	COUNTRY	N (TOTAL)	N (POSITIVE)	SEROLOGY	HISTOLOGY	IMMUNOHISTOCHEM	FFM	PCR	CULTURE
Aberer et al[9]	Austria	21	7 (33.3%)			X			
Aberer et al[10]	Austria	4	1 (25%)						X
Aberer et al[11]	Austria	9	3 (33.3%)			X			
Aberer et al[12]	Austria	11	1 (9.1%)						X
Breier et al[13]	Austria	1	1 (100%)						X
Weber et al[14]	Germany	2	1 (50%)						X
Schempp et al[15]	Germany	9	9 (100%)					X	
Schempp et al[16]	Germany	1	1 (100%)			X		X	
Weidenthaler et al[17]	Germany	1	1 (100%)					X	
Sommer et al[18]	Germany	12	0 (0%)	X					
Eisendle et al[19]	Germany/ Austria	30	1 (3.3%)					X	
		122	84 (68.9)				X		
Prinz et al[20]	Germany/ Hungary	90	20 (22.2%)	X					
Trevisan et al[21]	Italy	10	6 (60%)					X	
Hercogova[22]	Czech Republic	1	1 (100%)					X	
Goodlad et al[23]	Scotland	14	0 (0%)					X	
O'zkan et al[24]	Turkey	10	3 (30%)					X	
Fujiwara et al[25]	Japan	5	2 (40%)					X	
Santos et al[26]	Brazil	15	3 (20%)			X	X		
Ross et al[27]	United States	25	10 (40%)		X				
Granter et al[28]	United States	1	1 (100%)					X	
Fan et al[29]	United States	31	0 (0%)					X	

FFM=focus floating microscopy; PCR=polymerase chain reaction; N=number (of patients/samples)

TABLE 2. Results of studies investigating *Borrelia burgdorferi* in patients with lichen sclerosus

AUTHOR	COUNTRY	N (TOTAL)	N (POSITIVE)	SEROLOGY	HISTOLOGY	IMMUNOHISTOCHEM	FFM	PCR	CULTURE
Aberer et al[30]	Austria	13	6 (46.2%)			X			
Aberer et al[11]	Austria	2	1 (50%)			X			
Aberer et al[31]	Austria	19	13 (68.4%)					X	
Breier et al[32]	Austria	1	1 (100%)						X
Eisendle et al[33]	Austria	11	0 (0%)					X	
		60	38 (63.3%)				X		
Schempp et al[15]	Germany	6	6 (100%)					X	
Ranki et al[34]	Finland	1	0 (0%)					X	
Alonso et al[35]	Spain	8	0 (0%)						X
		1	0 (0%)						X
O'zkan et al[24]	Turkey	12	6 (50%)					X	
Fujiwara et al[25]	Japan	3	2 (66.7%)					X	
	Germany	10	1 (10%)						X
	United States	21	0 (0%)					X	
Ross et al[27]	United States	21	10 (47.6%)		X				
Dillon et al[36]	United States	10	0 (0%)					X	
De Vito et al[37]	United States	7	0 (0%)					X	
Colome-Grimmer et al[38]	United States	10	0 (0%)					X	

FFM=focus floating microscopy; PCR=polymerase chain reaction; N=number (of patientÏs/samples)

such as interstitial granulomatous dermatitis and necrobiotic xantho-granuloma; and other miscellaneous disorders, such as Gianotti-Crosti syndrome and septal panniculitis have been implicated. Many of these concepts are based solely on a minimal number of case reports and/or inconsistent serological data. The spectrum of cutaneous Lyme borreliosis is more narrow than is often suggested, and a link between these skin disorders and infection with *B. burgdorferi* has not been widely accepted.[5]

Urticaria. Svecova and Buchvald[39,40] looked at 57 patients with chronic urticaria using indirect immunofluorescence performed using endemic *B. burgdorferi* strains as antigens. Nineteen (33.3%) patients with chronic urticaria tested positive for high titer anti-*B. burgdorferi* (Bb) antibodies (above the cut-off value).

Annular erythemas. Goh et al[41] determined that Lyme

TABLE 3. *Borrelia burgdorferi* in patients with atrophoderma of Pasini and Pierini, anetoderma, and granuloma annulare

AUTHOR	COUNTRY	N (TOTAL)	N (POSITIVE)	SEROLOGY	HISTOLOGY	IMMUNOHISTOCHEM	FFM	PCR	CULTURE
ATROPHODERMA OF PASINI AND PIERINI									
Buechner et al[42]	Switzerland	26	10 (38.5%)	X					
Lee et al[43]	Korea	1	1 (100%)	X					
ANETODERMA									
Bauer et al[44]	Germany	1	1 (100%)	X				X	
Hofer et al[45]	Switzerland	2	2 (100%)	X				X	
Trevisan et al[46]	Italy	1	1 (100%)	X				X	X
GRANULOMA ANNULARE									
Strle et al[47]	Slovenia	1	1 (100%)	X					X
Gualco et al[48]	Italy	1	1 (100%)	X					
Fernandez-Flores et al[49]	Spain	8	5 (63%)					X	
Ziemer et al[50]	Germany	27	1 (4%)					X	
Zollinger et al[51]	Switzerland	48	1 (2.1%)					X	

FFM=focus floating microscopy; PCR=polymerase chain reaction; N=number (of patients/samples)

disease was not prevalent in patients presenting with annular erythema in Singapore. Serum samples from 72 patients presenting with annular erythema (at the National Skin Center) were tested for anti-*B. burgdorferi* antibodies using hemagglutination, indirect immunofluorescence, and ELISA. None (0%) of these patients tested positive for anti-Bb antibodies.[39]

Zeimer et al[39] performed a retrospective investigation of 90 cases of erythema annulare centrifugum (EAC). In 13 of 16 cases with a pseudolymphomatous reaction pattern on focus-floating microscopy, spirochetes stained positive, but were negative in other reaction patterns of EAC as well as in negative controls. These findings were confirmed by PCR.

Pityriasis rosea. Stinco et al[52] presented a case report of a 20-year-old man with *B. burgdorferi*-associated pityriasis rosea following a tick bite one week prior. Warthin-Starry stain technique did not detect any spirochetes within skin scrapings, although all PCR primer sets that recognized *B. afzelii* were positive. Specific serum IgM against *B. burgdorferi* was detected with chemiluminescence immunoassay and was confirmed by an immunoblot test.

Interstitial granulomatous dermatitis. Moreno et al[53] performed a case study on 11 patients with cutaneous manifestations resembling morphea and interstitial granuloma annulare. Results yielded PCR/PCR-ELISA proven detection of *B. burgdorferi* in all lesions with negative or inconclusive IgM and IgG serologies. Histopathological findings in 11 (100%) cases consisted of an interstitial inflammatory infiltrate, with focal areas of pseudorosette formation.

Necrobiosis xanthogranuloma (NXG). Zelger et al[54] investigated the skin biopsy specimens from seven patients with NXG for the presence of Borrelia by focus-floating microscopy. Borrelia was detected as single, paired, or clusters of spirochetes in 6 of 7 cases (86%).

Gianotti-Crosti syndrome. Baldari et al[55] reported two cases of an unusual association between infantile papular acrodermatitis and Lyme borreliosis, with *B. burgdorferi* serology positive in both cases.

Septal panniculitis. Kramer et al[56] reported a case of a

22-year-old woman who initially presented with EM and subsequently with tender, nodular skin lesions. Skin biopsy revealed acute septal panniculitis, and *B. burgdorferi* serology was positive.

DISCUSSION

In light of the increasing number of reports describing an association between various cutaneous disorders and infection with *B. burgdorferi*, the authors performed a thorough review of the literature in an attempt to assess whether these reports were large and/or significant enough to substantiate these hypotheses, as such associations are important both diagnostically and therapeutically.

In addition to the three characteristic dermatological manifestations of Lyme borreliosis, *B. burgdorferi*, fairly sustainable (yet incongruous) results have been generated about the role of *B. burgdorferi* in both morphea and LSA—two sclerosing and often overlapping skin diseases of unknown origin. Antibodies to *B. burgdorferi* have been found in one-third to one-half of Austrian and Swiss morphea patients. Serological studies in most other European countries, Asia, and the United States have reported negative results. Serological techniques (immunofluorescence, ELISA, and immunoblot) are often unsatisfying for the diagnosis of cutaneous borreliosis with false-negative or false-positive results (occasionally caused by cross-reactions with *Treponema pallidum* or more commonly in a positive endemic background of 20 to 50% in many parts of Europe). Direct detection of *B. burgdorferi* by culture from lesional skin has only succeeded occasionally in morphea and LSA patients in Austria and Germany.[27] Cultures with specified media, such as Barbour-Stoenner-Kelly medium, can detect Borrelia in all clinical forms, but these techniques are not generally available and unreliable with less than 50-percent sensitivity.[54] PCR studies were positive for borrelial DNA in the skin of approximately one-seventh to one-sixth morphea patients and two-fifths of LSA patients in Europe and Asia, but were consistently negative in the United States. Studies that failed to detect borrelial DNA usually included larger patient series and conducted analyses using more than one primer set. Positive results were often obtained using less reliable methods, such as immunohistology or silver staining of lesional tissue or by lymphoproliferative response assays. Comparability of PCR studies is limited due to different primers used in each case, and a possible explanation for the frequently observed negative or inconclusive PCR results could be the diversity of Borrelia organisms.[27] As opposed to PCR, FFM has proven to be a reliable and highly sensitive method to detect Borrelia in tissue sections of routinely formalin-fixed, paraffin-embedded biopsy samples. PCR uses primers highly specific for known human pathogenic strains, while FFM uses immunohistochemistry with a less specific polyclonal antibody that probably detects most different Borrelia species.[54]

In several case reports, *B. burgdorferi* has also been implicated in the causation of two additional sclerosing disorders: progressive facial hemiatrophy and eosinophilic fasciitis (Shulman's syndrome). These associations were based on silver staining, immunohistology, and/or PCR examinations. Negative serological results in recent case series have proved this theory doubtful.[27]

The role that *B. burgdorferi* sensu lato plays in the etiology of morphea (its variants and other cutaneous manifestations) remains controversial. However, a satisfactory explanation of causality does exist: *B. burgdorferi* bacteria are collagenotropic, whereas other spirochetes, such as *T. pallidium*, are epitheliotropic and endotheliotropic or mucotropic, such as *Helicobacter pylori*. *B. burgdorferi* organisms attach to glycosaminoglycans via fibronectin-binding proteins. While immune responses in EM cases tend to control borrelial organisms in a timely manner, the situation proves more complex in both ACA and morphea. In these cases, the observed low level of lesional organisms suggests that the disease is not only due to the effect of the infectious agent, but also due to the organism's effect on the immune system. It has been presumed that the presence of activated CD20+ may reflect the aggravated attempt of the immune system to defeat the borrelial infection and could be a key pathophysiological factor in the development of morphea. Thus, the role of *B. burgdorferi* in the onset of morphea is thought to be related to the inflammatory and immune processes elicited by the presence of the spiral organism within the patient's tissues.[26]

The detection of an infectious agent in diseased tissue is only one of several requirements for establishing a causative role of the agent in that disease. One additional important criterion for a causative link between Borrelia and morphea/LSA, as well as granuloma annulare, is clinical improvement or regression of these diseases following antibiotic treatment.[51] A bacterial etiology in these disorders is further supported by the fact that some cases respond very well to antibiotic therapy, such as doxycycline, minocycline, penicillin, and ceftriaxone. Not all patients treated exclusively with antibiotic regimens will evolve to clinical recovery and may require the addition of topical immunomodulatory drugs.[27] As a proportion of these patients appear to benefit from antimicrobial therapy directed against *B. burgdorferi*, appropriate antibacterials should be considered in Lyme borreliosis endemic areas as a viable therapeutic option.[27]

Utilization of antibiotics for the treatment of these disorders in nonendemic regions, however, would need to be rationalized on the basis of their anti-inflammatory properties rather than their ability to eradicate *B. burgdorferi*. Antibiotics have been reported to be of value in a solitary case report of linear morphea in a child (utilizing intravenous penicillin G in a 10-year-old girl with linear morphea and negative serological tests for *B. burdgorferi*).[57] Shelley et al[58] presented a series of 15 patients with lichen sclerosus, four of whom cleared with the use of either long-term oral penicllin (2 women, 1 man) or intramuscular ceftriaxone (1 man). Although the authors hypothesize that Borrelia (or other) species were

etiological for lichen sclerosus, there was no mention of testing these patients for the presence of these organisms in this report.[58] The authors agree with Zwischenberger and Jacobe[59] that there are no reported clinical trails utilizing antibiotics for morphea. Clearly, routine use of antibiotics for these conditions and other disorders that have putatively been associated with *B. burgdorferi* cannot be advocated without further clinical studies.

B. burgdorferi has also been both casually and causally linked to various other cutaneous disorders, such as GA, NXG, panniculitis, and numerous reactive and roseolar erythemas. These assumed associations are based on a minimal number of case reports and/or inconsistent serological data only. Thus, *B. burgdorferi* cannot be generally accepted as the causative agent in these conditions, and as such, no definitive treatment can be justly recommended.

CONCLUSION

The following general conclusions can be drawn from the authors' review of the literature on the possible dermatological manifestations associated with *B. burgdorferi* infection: 1) *B. burgdorferi* is genuinely associated with EM, BL, and ACA; 2) in the United States, any reports other than EM due to *B. burgdorferi* sensu stricto should be considered suspect; 3) perhaps in certain locales in Europe (Austria, Germany), *B. burgdorferi* may be responsible for certain cases of morphea and its variants; and 4) the relevance of *B. burgdorferi* found in all other disorders remains to be determined.

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