Infectious Dermatoses, Venereology, Dermapathology

Cutaneous manifestations of Lyme borreliosis

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Summary
The cutaneous manifestations of Lyme disease have been known for more than 100 years and are specified as different diseases. All of them show similar pathophysiological mechanisms. After invasion of the borrelial pathogen, the cellular immune response leads to noticeable changes in the skin that usually proceed without epidermal involvement. In most cases, the manifestations in early local infection (erythema migrans, borrelial lymphocytoma) do not yet lead to a measurable antibody response, whereas acrodermatitis chronica atrophicans as a classical manifestation in late persistent infection regularly shows a massive increase in IgG antibody titers. All of these Borrelia-associated skin manifestations can be quickly diagnosed by clinical inspection. The therapy follows standardized schemes and in most cases, can cure the disease.

Historical development
Even before 1900 there were a number of reports on skin diseases that are now known as manifestations of borreliosis: Buchwald (1883, Fig. 1) described a “diffuse idiopathic skin atrophy”, Schwimmer (1883) referred to “atrophia cutis universalis”. Touton (1886) spoke of “acquired idiopathic atrophy of the skin”, Pospelow (1886; it was Pospelow who coined the often-quoted description of “cigarette paper-like wrinkling of the skin” in acrodermatitis chronica atrophicans) spoke of “atrophie idiopathique de la peau”, Judassohn (1891) of “atrophia maculosa cutis”, and Pick (1894) of “erythromyelia”.

Figure 1: Acrodermatitis chronica atrophicans in the original description by Buchwald from 1883
In the United States as well, there were also lesser known reports of the disease, such as by Bronson (1894) and Elliot (1895), which, based on the drawings which have been preserved, are without a doubt acrodermatitis chronica atrophicans. The patient described by Bronson was a 45-year-old man who was born in Germany. Elliot reported that his patient, also a 45-year-old man from Germany had “attacks of rheumatism”, which is easily explained today.

It was Herxheimer and Hartmann (1902) who finally defined the disease as acrodermatitis chronica atrophicans (ACA). Numerous publications followed, including a review by Jessner and Löwenstamm (1924) of 66 cases (alone at the Breslau Hospital dermatology unit) as well as a review by Sweitzer and Laymon (1935). The latter reported that not only immigrants, but also patients born in America were affected by the disease. Thus, far from appearing “out of the blue,” the disorder has already long been endemic in America.

The characteristic symptoms seen in ACA, such as neuropathy and osteopathy, had also long been observed (e.g., Hövelborn 1931), even though it was not possible with the means available at that time to identify the etiological cause.

Erythema (chronicum) migrans is also by no means a new disease. At the beginning of the nineteenth century, Afzelius (1910) described this chief symptom of borrelial infection, reporting erythema following a tick bite. Lipschütz (1913) already used the term “erythema chronicum migrans”.

The mosaic of knowledge was completed by publications on neurological symptoms of the disease; Garin and Bujadoux (1922) as well as Bannwarth (1941) described lymphocytic meningo-polyradiculitis, which we now call “Bannwarth syndrome”, a typical manifestation during the generalized stage of borrelial infection.

The development initially occurred on several fronts at the same time; individual disease presentations were initially described as separate disease entities since it was not yet possible to identify the common etiology of all of these symptoms. At that time, parallels to syphilis were also being considered. In his dissertation Kahle (Halle 1942, cited in Weber et al. 1984) investigated “Pallida reactions blood flow to the skin.”

The discovery of penicillin was followed by a period of widespread experimentation with the new substance. The wonder drug was administered to patients for all possible diseases to see if it would have a positive effect on the outcome.

It is therefore no surprise that Svartz (1946) and Thyresson (1949) reported that penicillin could be used to heal acrodermatitis. Bianchi (1950) then treated lymphocytomas, while Binder et al. (1953) and others also used penicillin to treat erythema migrans.

In the 1950s transmission of erythema migrans was established after heroic self-testing by Binder et al. (1955). Paschoud (1957) showed transmission of lymphadenosis cutis and Götz (1955) demonstrated transmission of acrodermatitis chronica atrophicans via skin transplantation.

Thus it has already been clear for decades that an infectious penicillin-sensitive agent must be the cause of this chronic disease with a broad range of symptoms as Weber (1974) correctly postulated without being able to prove it at the time. In Europe an intense search began for the cause. Yet, given the inadequacy of the methods available at that time, the search was doomed to fail.

Nevertheless, given the significance and widespread distribution of Lyme borreliosis in Central Europe today, it is indeed quite surprising that it took so long to identify the disease. There were many signs, but they could not be brought together.

After discovery of the pathogen by Willi Burgdorfer and colleagues (1982), a breakthrough finally came with the advent of serological testing (see also above). The wide availability – of initially highly unreliable – test methods brought new momentum to the research on borrelial infection.

**Pathogen and reservoirs**

Borrelial infection is transmitted by tick bites. In Europe the disease is transmitted by *Ixodes ricinus*, or deer tick. Serving as pathogen reservoirs are various rodents, especially mice. Although the mouse itself does not contract the disease, it enables lifelong bacteremia so that at every point in time and at every site of the infected mouse, *Borrelia* can be drawn.

*Ixodes* *Ixodes* needs two (for males) or three (for females) blood meals. In the first stage, the 0.8 mm to 1 mm large larvae, is infected transovarially with up to 1% *Borrelia*. The first blood meal is taken from the mouse, whereupon the larvae matures into a nymph which is up to 15% infected. The nymph then requires one blood meal before it can mature into an adult which contains 30% to 70% *Borrelia*. 
For reasons that are unknown, in humans up to 80% nymphs are found (Maiwald et al. 1998), while on dogs and cats adults dominate. Maiwald and colleagues reported that out of 5000 ticks found on patients, 15% were infected and in 4% of all tick bites transmission of the pathogen had occurred.

Clinical presentation and pathophysiology
_Borrelia-burgdorferi_ infections usually proceed in three phases (Hassler 2006; previously used “staging” methods are not useful because they were symptom-oriented and did not give enough weight to pathophysiology).

Phase 1: local infection of the skin
In the first phase of infection, the pathogen is deposited in the skin by means of a tick bite. Once in the skin it begins to reproduce. The pathogen has a long generation time, spanning 20 to 30 hours which is why it reproduces only slowly. Only after a latency period, which normally covers about ten days (even with reinfection it is at least seven days), there is a cellular and humoral immune response. All cutaneous manifestations of borreliosis, from erythema migrans to acrodermatitis, present with bluish-red areas of skin caused by the migration of lymphocytes and plasma cells, i.e., the cellular immune response of the skin.

Depending on the intensity of the cellular immune response, typical erythema migrans (EM) or borrelial lymphocytoma (BL) develops. The latter can occur alone or in combination with EM. In rare instances, there is also a concomitant reaction of the subcutaneous fatty tissue in the form of panniculitis.

Phase 2: generalization of disease
After the pathogen multiplies in the skin, it migrates peripherally from the site of the bite and at some point enters the blood or lymphatic vessels. Borreliosis organisms are thus carried in the bloodstream and the generalization phase, the second stage of disease, begins. Clinically, this stage is characterized by generalized flu-like symptoms, myalgia, headache, (sometimes) fever, night sweats, and palpitations. Initial organ manifestations (carditis, neuritis, ophthalmitis, etc. can also occur). Afterward there is a severe immune response and the pathogen count drops drastically. Only in collagen can Borrelia successfully evade the immune response. There they persist and can trigger later disease episodes after a secondary latency period of a variously long duration.

Phase 3: chronic phase
Clinically the third stage of disease is characterized by neuropathy, arthralgia, and myalgia, which are accompanied during disease episodes by generalized symptoms (mainly night sweats, occasionally fever). In general, any area of the body may be affected. Acrodermatitis chronica atrophicans may develop on the skin, often after a prolonged course of disease lasting several. It is first apparent during an inflammatory stage, and then after a longer period develops into "cigarette paper-like" atrophy. This is almost always accompanied by neuropathy and osteopathy. Occasionally there are also the pathognomonic fibroid nodules containing a high number of pathogens.

In all stages of disease, the pathogen can be cultivated from infected tissue which underscores the character of a chronic bacterial infection analogous to syphilis. In no phase of borreliosis infection does spontaneous healing occur. This also parallels syphilis. In the following we focus on disease manifestations involving the skin.

Erythema migrans
Classic variants
For about ten (7 to 20) days after a tick bite, the patient is symptom-free before the cellular immune response to _Borrelia burgdorferi_ commences. Erythema migrans becomes visible at the site of the tick bite and initially usually has a diameter of 5 cm to 6 cm. Over the course of several weeks or months the lesion gradually spreads peripherally. Maximal variants are possible with involvement of the entire extremity or the entire trunk. Given the dilution effect, it usually becomes increasingly lighter until it is barely visible.

Because the _Borrelia_ migrate peripherally, the immunocompetent cells of the body’s own defense system follow them. At the center of the lesion the EM usually becomes lighter but patches may remain (Fig. 2-6). The EM is usually painless, but there is occasionally pruritus. The epidermis remains intact and there is no eczema.
Polytopic variants
Sometimes polytopic EM can occur. In such instances, hematogenous embolization of the pathogen should be assumed. Satellite EMs are usually smaller.

Differential diagnosis
The most common misdiagnosis is black fly bite. Simuliiidae, the most important member of Simulium equinum, are stinging flies that measure about 4 mm in length. Their venom contains proteolytic enzymes and thus the sting reaction reaches its maximum after about two days. Simuliiidae stings are always marked by excessive warmth, with tough patches of infiltration and are pruritic or very painful (Fig. 7). The reaction usually subsides after three to seven days. Lymphangitis is common. In Central Europe, however, there are no reports of disease caused by black-flies.

7-day rule: erythema migrans never appears before seven days, and by the fifth day the initial sting reaction has almost always subsided!

Important note: Erythema migrans is diagnosed based on appearance. Given that there is no epidermal involvement, there are no eczematous changes. The disorder is purely erythematous!

Antibody detection methods should not be used for diagnosis as antibodies do not appear until at least two weeks after pathogen generalization has begun.

Therapy
The therapy options for adults and children are listed in Table 1.

Erythromycin and roxithromycin are not sufficiently effective and are not advised!

Table 1: Treatment of borreliosis in adults and children

<table>
<thead>
<tr>
<th></th>
<th>Antibiotic</th>
<th>Dosage*</th>
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<tbody>
<tr>
<td>Adults</td>
<td>Doxycycline</td>
<td>3x100 mg/20 days (ensure adequate sun protection!)</td>
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<tr>
<td></td>
<td>Azithromycin</td>
<td>500 mg, 1 x daily for at least 10 days</td>
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<td></td>
<td>Amoxicillin</td>
<td>4 x 1 g daily, 20 days</td>
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<tr>
<td></td>
<td>Cefuroxime-axetil</td>
<td>3 x 500 mg daily, 20 days</td>
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<tr>
<td>Children</td>
<td>Amoxicillin (cefuroxime or azithromycin are also options)</td>
<td>3 to 4 x 75 mg/kg body weight, 20 days</td>
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</tbody>
</table>

*The dosages used today are partly based on pragmatic considerations and are not generally proven by studies (overview in Hassler 2006). The lack of reliable and recent therapy studies is striking, but cannot be easily redressed. Since the introduction of higher dosages and longer treatment durations, based on a consensus finding from 1996 there have been no further reports of treatment failures (author’s note).
Follow-up care
Serological testing should be conducted three months after therapy. At this time, there may still be IgM antibodies, but no IgG antibodies. If IgG antibodies are detectable, i.e., if there is seroconversion, further clinical and serological controls should be performed every three months. The patient should be informed of possible delayed symptoms.

Borrelial lymphocytoma
The clinical presentation of borrelial lymphocytoma (BL, synonym: lymphadenosis cutis benigna Bäfverstädt, LABC) was first described by Biberstein in 1923 (lymphocytoma) and then by Bäfverstädt in 1943 and 1960 (LABC in monoligotopic form and in the miliary form). Paschoud demonstrated transmission of the disease in 1957/58.

Borrelial lymphocytoma is generally monotopic. Infiltrates occurring at the site of the bite contain immunocompetent cells (pathophysiologically a punctate rather than patchy svariant of EM). It is especially common in re-infection. This can be explained by the fact that in already immunized patients, the immune response begins more rapidly and the borrelial organisms are thus already attacked at the site of the bite. This causes the appearance of small infiltrates with thickening of the skin (EM is, on the contrary, at the level of the skin). BL is less common than EM.

Lesions can persist for months or years (in 1962 Bäfverstädt described a patient with disease lasting 20 years who finally healed under penicillin therapy).

According to most of the literature, predilection sites are the nipple and earlobe (Fig. 8). It is possible that lymphocytomas occur on other parts of the body but are not recognized as such (Fig. 9, 10). Occasionally, lymphocytomas are also found at the center of erythema migrans (Fig. 10), and sometimes over the course of disease EM can migrate from BL. Oligotopic lymphocytomas, as described by Bäfverstädt, are rather uncommon. In our example, there were about 15 lesions on the right arm and shoulder (Fig. 11).

Histology shows a dense, perivascular infiltrate consisting of lymphocytes and plasma cells. Immunohistological studies show polyclonal stimulation. In some cases the etiology can only be determined by cultivation of Borrelia from the lesion.

Figure 8: Typical borrelial lymphocytoma on the earlobe
Figure 9: “Atypical” borrelial lymphocytoma on the buttocks (original size: 2.5 x 1.5 cm)
Figure 10: Borrelial lymphocytoma at the center of erythema migrans. Borrelial lymphocytoma represents an increased cellular immune response in re-infection (hyperergic variant of a cellular immune response)
Figure 11: Shoulder of a patient with a three-year history of polytopic borrelial lymphocytoma. Lesions caused by scratching have led to superinfection with Staphylococcus aureus, visible on the yellow fibrin deposits in the ulcerations. The etiology was confirmed by culture. Complete remission after systemic cefotaxime therapy (2 x 3 g/14 days)

Monotopic form
The classic monotopic form of BL consists of a variously sharply-bordered lymphocytic infiltrate with a blue-red color and a rubbery feel on palpation.

Oligotopic form
This form arises from the monotopic form after spreading along a lymphatic pathway. The lesions can persist for years and gradually increase in size.

Miliary form
Originally described by Bäfverstädt (1960) as lymphadenosis cutis benigna dispersa. There are a very high number of lymphocytoma lesions, usually only about the size of the...
Miliary lymphocytomas are only possible if there is spread of the pathogen via the bloodstream, i.e., if there is systemic infection. Differentiation from reactive lymphoma of other causes is not easy, but sometimes culture can be helpful. Immunohistology shows polyclonal stimulation.

Malignant transformation
Continued immune stimulation over longer periods of time can lead to malignant transformation due to development of a monoclonal infiltrate, and there have been several reports of this happening (overview in Garbe et al. 1988). The definitive transition from benign lymphocytoma into malignant lymphoma has been observed by Shelley in 1981, Torres-Cortijo and Ortiz Medina in 1986, and by other authors as well.

Malignant transformations into other histological types are most often seen in lymphocytoma with acrodermatitis (see the respective section). In 1952 Herzberg reported a patient in whom reticulosarcomatous transformation of multiple subcutaneous lymphocytomas occurred with concomitant acrodermatitis.

Therapy
The monotypic form is treated like erythema migrans (see the respective section), the miliary form requires systemic intravenous therapy (cefotaxime 2 x 3 g or ceftriaxone 2 g for 15 to 20 days; reserve: doxycycline, penicillin G i.v.)

Acrodermatitis chronica atrophicans (ACA)
The earliest reports of ACA were by Buchwald in 1883, Pospelow in 1886, Pick in 1894, and Herxheimer in 1902. The earliest reports in America were published by Bronson in 1894 and by Elliot in 1895. The earliest reports on the use of penicillin in ACA appeared by Thyresson in 1949 and by Pirilä in 1951. Finally, in 1955 Götz 1955 showed transmission of disease. The first identification of Borrelia in culture was by Asbrink in 1984.

Figure 1 (see historical development) shows ACA from Buchwald’s first publication.

After borrelial infection, it takes several years for the development of acrodermatitis chronica atrophicans (at the earliest after two to three years, or even decades after infection). The disease course is characterized by an initially edematous inflammatory stage, in which the epidermis remains intact while the dermis becomes swollen and inflamed. The skin is blue-red and the borders usually merge. Surrounding the vessels there is a lymphocytic infiltrate with abundant plasma cells which often extend into the subcutis. As a result of chronic inflammation, collagen degeneration occurs with loss of elastic fibers and thus ultimately a “cigarette paper-like” atrophy of the skin (Pospelow 1886). Atrophy mainly affects the acral regions (Fig. 12, 13).

Figure 12: ACA on the hand of a 70-year-old woman with at least a 20-year-long history of disease. The patient also had sensory neuropathy.

Figure 13: ACA on about the ankle and foot of a 53-year-old woman three years after a tick bite and subsequent erythema migrans which was treated by homeopathic methods. At the time of ACA diagnosis, the patient complained of severe night sweats, extreme fatigue, a chronic cap-like headache, and arthralgia.

Fibroid nodules
ACA is occasionally related to fibroid nodules (Herxheimer 1910) which are often found on the extensor aspects of the extremities, but can also occur elsewhere such as on the soles of the feet (Fig. 14). On histology the nodules have an onion-skin-like appearance (Hardmeier 1968). There is also sponge-like degeneration of collagen with lymphocytic infiltration.

Borrelia are especially easy to cultivate from fibroid nodules in ACA. This is evidence that the lesions are in fact due to persistence of the infectious agent and not due to an autoimmune reaction.

Figure 14: Fibroid nodules on the sole of the foot in the same patient
Relationship between morphea and lymphocytoma

ACA lesions are frequently inhomogeneous and can occur simultaneously with sclerodermiform changes (morphea) (Asbrink in Weber and Burgdorfer 1993). The combination with lymphocytoma is also not uncommon which may be explained by polyclonal immune stimulation (see the respective section). Related symptoms include neuropathy and osteopathy.

ACA is almost always related to peripheral, sensory polyneuropathy (Hopf and Klingmüller 1966, 1975; Kristoferitsch 1989). As a result of vasculitis of the vasa nervorum, chronic borrelial infection leads to axonal degeneration of peripheral nerves (as demonstrated by Camponovo and Meier 1988 in sural nerve biopsies). Similar to ACA itself, the damage can only heal after antibiotic therapy if the atrophy is not too advanced. Progression of the inflammatory process can always be stopped, however.

Another typical complication in ACA is joint and bone damage around the ACA lesions (Hövelborn 1931; Gans and Landes 1952). Today these are also understood to be a result of borrelial-induced vascular processes that lead to trophic disorders. The bone defects are often visible on radiographs as moth-eaten defects. They can also resolve after antibiotic therapy (Hassler 1998).

Malignant transformation

Occasionally malignant transformation occurs in patients with ACA as a result of persistent inflammatory activity. The histological spectrum of malignancy ranges from malignant lymphoma (Goor and Ott 1971; Denzer-Fürst et al. 1987) to aleukemic or leukemic lymphadenosis (Schneider 1957) and from lymphosarcoma to immunocytoma and carcinoma (Braun-Falco et al. 1978).

Therapy

Some authors have suggested that ACA may be adequately treated with oral therapies such as doxycycline. In our opinion, ACA should be viewed instead as «the tip of the iceberg» in chronic borreliosis and one should reckon with additional lesions in less accessible connective tissue structures. Thus we prefer systemic therapy with third generation cephalosporins (cefotaxime 2 x 3 g/20 days or ceftriaxone 1 x 4 g/20 days).

Morphea: no borrelial manifestation

In older literature there are repeated references to a relationship between morphea and borreliosis. Yet a large study by Weide and Garbe (Tübingen Hospital Department of Dermatology) has ruled out any relationship between the two. Nevertheless, there are interesting questions surrounding morphea. On the assumption that morphea is a borrelial-induced disease, many patients have been treated intravenously in the same way as for borreliosis with a resulting response rate of 50% to 60%. Despite this fact, the pathogen still has not been not identified on either serology or culture. Thus the disorder could be due to another penicillin- or cephalosporin-sensitive bacterium that has yet to be discovered.

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Keywords

Lyme borreliosis, erythema migrans, borrelial lymphocytoma, acrodermatitis chronic atrophicans

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Conflict of interest
The author declares that there is no conflict of interest as defined by the International Committee of Medical Journal Editors (ICMJE; www.icmje.org).

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Skin manifestations of Lyme borreliosis

Question 1
The diagnosis of erythema migrans is:
a. By sight (visual examination)
b. By serology
c. At the earliest after eight weeks
d. Always uncertain
e. Dependent on age

Question 2
Erythema migrans:
a. May be expected after seven days at the earliest
b. Is less than 1 cm large at presentation
c. Is caused by erythrogenic toxins
d. Always is scaly
e. Is never larger than 20 cm

Question 3
A measurable development of antibodies may be expected:
a. Immediately following a tick bite
b. In every erythema migrans
c. About two weeks after generalized spread of the pathogen
d. Only in late stages of disease
e. Often not at all

Question 4
Borrelial lymphocytoma is:
a. Merely a variant of erythema migrans with palpable infiltration of the skin
b. A symptom of late-stage disease
c. Never found on the earlobe or nipple
d. Always a sign of malignant transformation
e. Never associated with erythema migrans

Question 5
Sweating and generalized flu-like symptoms are suggestive of the following:
a. Unusual disease course
b. Beginning pathogen generalization
c. Beginning of the late stage of disease
d. Other disease
e. Immune deficiency

Question 6
Acrodermatitis chronica atrophicans:
a. Is due to zinc deficiency of the skin
b. Arises from increased concentration of Borrelia on cooler parts of the skin
c. Is not related to neuropathies or osteopathies
d. Is an autoimmune disease without pathogen persistence
e. Is a collagen disorder

Question 7
Erythema migrans can be well managed with:
a. Quinolone
b. Erythromycin
c. Doxycycline, amoxicillin, or cefuroxime
d. Metronidazole
e. Topical corticosteroids

Question 8
Borrelial infections are transmitted:
a. From person-to-person contact
b. By flying insects
c. By house pets
d. Only by tick bites
e. None of the above

Question 9
Morphea is:
a. A variant of borreliosis
b. A separate disease entity that is not associated with borreliosis
c. Never affected by antibiotics
d. A chronic disease without chance of healing
e. A malignant skin disease

Question 10
After treatment of erythema migrans, serological control should be performed:
a. Immediately after ending therapy
b. After two weeks
c. After about three months
d. After one year at the earliest
e. Never, as it is unnecessary