# SKIN MANIFESTATIONS IN LYME BORRELIOSIS*

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## SUMMARY

The dermatological manifestations of Lyme borreliosis, erythema (chronicum) migrans, lymphadenosis benigna cutis and acrodermatitis chronica atrophicans, have been well known tick borne skin diseases in Europe since more than 100 years. Association with neurological symptoms and arthritis has been described. After detection of the causative agent, *Borrelia burgdorferi*, by Willy Burgdorfer in 1981 these diseases were seen in a new context. Thereafter new diagnostic methods and therapeutic regimes were developed. It was possible to integrate atypical clinical manifestations into the new entity. The knowledge about the different clinical forms, the ultrastructure of the microorganism, and the epidemiology increased rapidly. In the course of the infection, skin symptoms appear usually at first. As serodiagnostic methods are not very reliable in the early stages, it is necessary to know about the skin manifestations of Lyme borreliosis in order to establish the correct diagnosis as early as possible, and to avoid serious systemic disease by early treatment.



## KEY WORDS

*Lyme borreliosis, skin manifestations, differential diagnosis*


Lyme borreliosis is a multisystem disorder involving skin, joints, central nervous system and heart (1).

Erythema migrans has been a well-known disease for the European dermatologist for a long time. It is the most frequent arthropode-transmitted infection. Its importance for early diagnosis of a serious systemic infectious disease has been realized since the detection of the etiologic agent by Willy Burgdorfer in 1981.

Diffuse skin atrophies following tick bites (acrodermatitis chronica atrophicans) were already described in 1883 by Buchwald (2) and in 1902 by Herxheimer

* *Dedicated to Prof. Dr. med. Dr. phil. S. Borelli on the ooccasion of his 70th birthday.*

(3). In 1909 Afzelius (Sweden) (4,5) and in 1913 Lipschütz (Austria) (6) discovered the association of erythema chronicum migrans with tick bites. Hellerström in 1930 referred to the correlation between erythema migrans and lymphocytic meningitis after tick bites. In 1950 (7,8) he supposed spirochetes to be the causative agents. For about 40 years these skin diseases have been treated successfully with penicillin (9). In 1952, Kahle and Grüneberg described a positive pallida reaction in sera of patients with acrodermatitis without having had syphilis (10).

Because of the responsibility to penicillin treatment, the positive pallida reaction and the histology with an abundance of plasmacells, they supposed spirochetes other than *Treponema pallidum* were cause of infection. In 1948, Lennhoff (11) detected spirochetes in a silver staining of an erythema migrans lesion. In 1955-1957, the infectious transmission of erythema migrans, acrodermatitis chronica atrophicans and lymphadenosis benigna cutis could be proven by German groups by skin transplantation experiments between humans (Götz (12), Binder (13), Paschoud (14)).

In spite of these observations, it was not possible to isolate the infectious agent. In the USA these dermatological diseases were largely unknown. Erythema migrans was first described in 1970 (15).

In 1977, Steere recognized an epidemic outbreak of an arthritis in children in the small town Lyme in Connecticut. In the following years, he discovered the fact, that it was an arthropode borne infectious disease. He called it Lyme disease (16,17,18). Long-known diseases were then seen in a new context.

## ISOLATION OF THE INFECTIOUS AGENT.

In 1981, Burgdorfer and Benach analysed ticks *(Ixodes dammini)* on Shelter-Island (New York) for rickettsiae. Instead of rickettsiae, in 60% of the ticks they isolated spirochetes which caused erythema migrans like skin lesions in rabbits (19).

Burgdorfer remembered the reports by Hellerström and the disease, observed in Lyme, and he suspected, that he might have found the infectious agent of the erythema migrans disease. In serological analyses of patients with Lyme disease high antibody titers against this organism were detected. In 1983, Barbour and Burgdorfer were able to isolate and cultivate the spirochetes in a modified Kelly medium (20,21).

According to morphology, molecular analysis and DNA-homologies the spirochetes were related to the Genus *Borrelia* and, in honour of Burgdorfer, named *Borrelia burgdorferi* (22, 23).

In Europe, antibodies against *Borrelia burgdorferi* in patients with meningopolyneuritis were found by Ackermann in 1983 (24,25). In 1984, *Borrelia burgdorferi* was isolated from *Ixodes ricinus* (26), from skin lesions as erythema migrans and acrodermatitis chronica atrophicans (Åsbrink (27)), and from liquor (Preac-Mursic (28)). Hovmark isolated *Borrelia burgdorferi* from a lymphadenosis cutis benigna lesion in 1986 (29). Aberer cultivated *Borrelia burgdorferi* from morphea (30) and Schlesinger described a connatal infection (31).

Morphologic and antigenetic heterogenities between European and American strains have been described (32,33,34). In spite of some differences in the clinical manifestations in European and American patients, the members of the 2nd International Conference in Vienna 1985 decided to call the disease "Lyme borreliosis", according to the first reports in the USA (35,36).

## SKIN MANIFESTATIONS IN LYME BORRELIOSIS.

### I EARLY LB WITHOUT DISSEMINATION.

**Erythema migrans (EM) and erythema chronicum migrans (ECM).**

Erythema migrans is the most common early manifestation of Lyme borreliosis. It develops after a symptom free interval within a few days to three

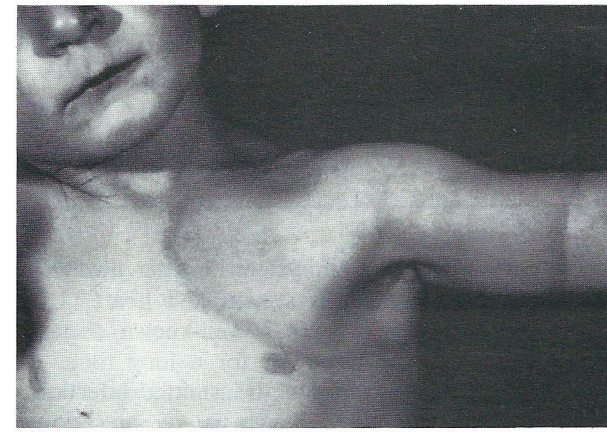

*Fig. 1: Typical EM lesions: Centrifugally spreading anular erythemas with a central reddish patch representing the tick bite.*

months (two weeks in the mean) after an infectious tick bite, in the surroundings of the primary maculopapulous lesion. For infection it is necessary that the tick feeds for at least 4 to 6 hours (37).

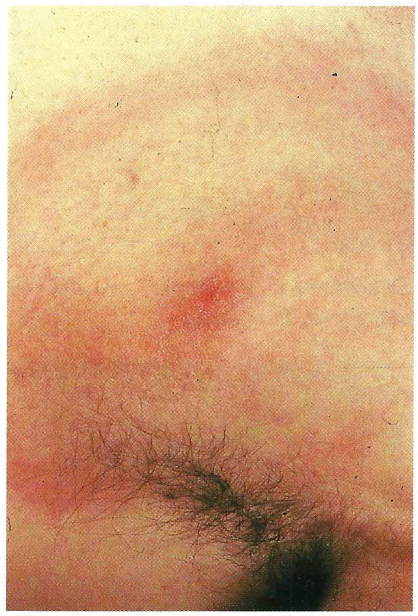

*Fig. 2: Typical EM lesions: Centrifugally spreading anular erythemas with a central reddish patch representing the tick bite.*

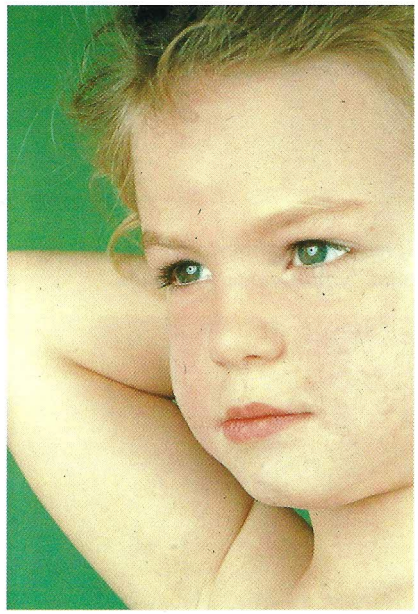

*Fig. 3: EM in the face of a child imposing as a diffuse, irregular erythema without visible tick bite.*

*Borrelia burgdorferi* spreads locally in the skin. That results in erythema migrans, which characteristically is a circular red lesion that migrates centrifugally. It shows accentuated red-violaceous margins and heals centrally. There are also homogeneous erythemas with slight infiltration. The lesion may be warmer than the surroundings, normal appearing skin (fig. 1 and 2).

Recently variations of the typical lesion could be

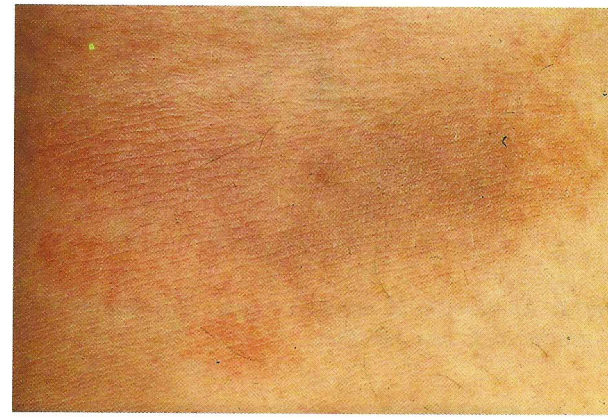

*Fig. 4: Speckled and patchy irregular EM lesions with a central tick bite reaction.*

observed: diffuse, spotted, homogeneous and vesiculous (fig. 3-7). In some cases the erythema is only visible after warming up the skin (i. e. after a hot shower or after sunbathing).

Besides light itching, usually neither the erythema, nor the tick bite cause any pain. Therefore in many cases it is not even recognized by the patient. If the

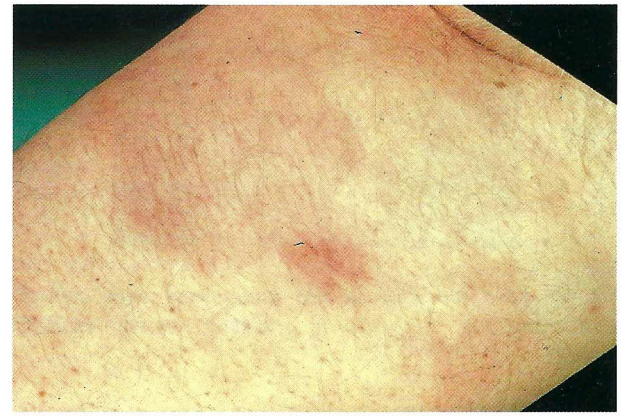

*Fig. 5: Speckled and patchy irregular EM lesions with a central tick bite reaction.*

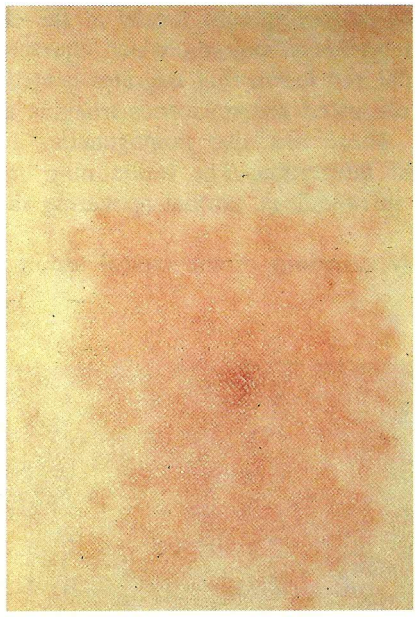

*Fig. 6: Speckled and patchy irregular EM lesions with a central tick bite reaction.*

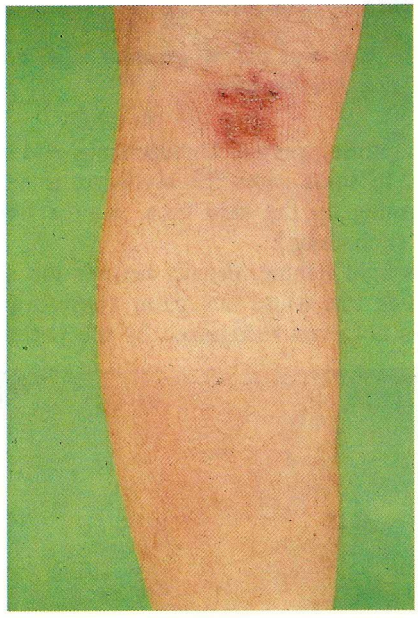

*Fig. 7: Pale red EM in the knee bend with central hemorrhageous, herpetiform arranged, mostly eroded, vesicles.*

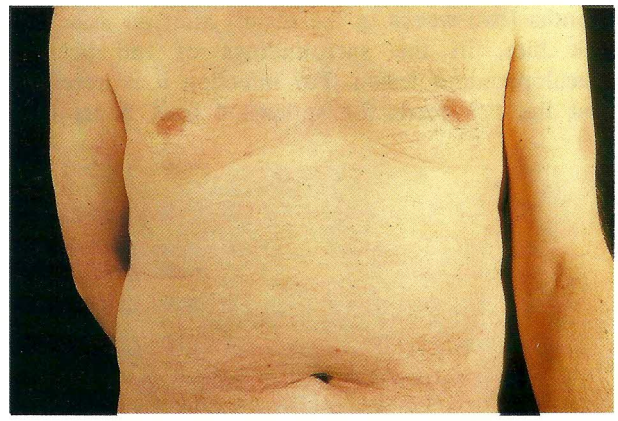

*Fig. 8: Disseminated erythemas on the trunk of a patient with Lyme borreliosis.*

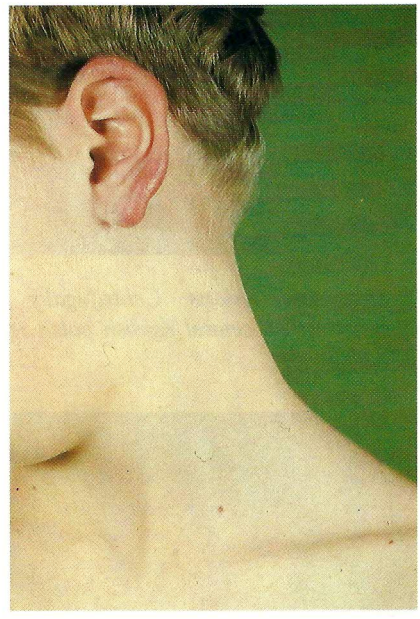

*Fig. 9: Borrelial lymphocytoma of the right ear lobe with regional lymph node swellings.*

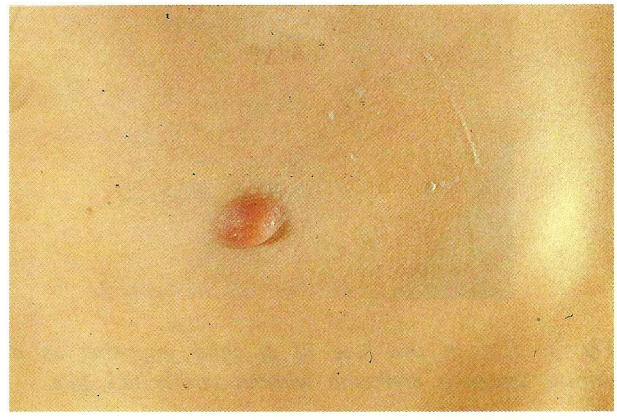

*Fig 10: Borrelial lymphocytoma of the right nipple.*

organisms spread through the vascular system, some patients suffer from a flu-like syndrome, reflected by fatigue, fever, headache, vomiting, joint aches, myalgia and lymphadenopathy, and in some rare cases they suffer from meningism, presumably provoked by spirochetemia. The appearance of multiple erythemas always indicates a disseminated disease (fig 8).

The development of the erythema is being explained by the effect of Interleukin I. Lipopolysaccharides of the borrelial membrane stimulate production of Interleukin I in macrophages of the skin (38). Borreliae are difficult to demonstrate directly in the tissue. Cultivation of Borreliae may be successful from the deeply red margin of the erythema migrans. There is no specific histological pattern, it shows perivascular infiltrates of plasmacells, lymphocytes, macrophages and rarely mast cells (39).

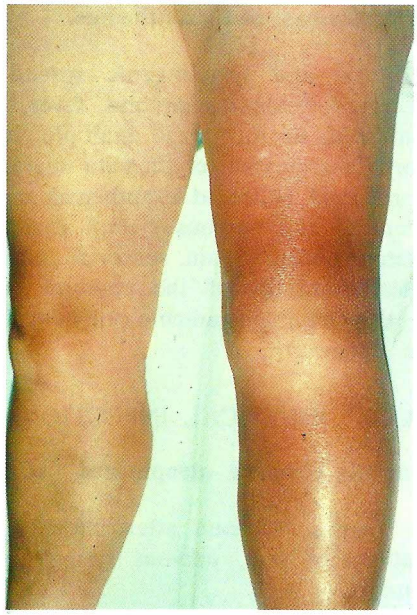

*Fig. 11: Inflammatory edematous stage of ACA. The skin is deeply red. In this case erysipelas is important differential diagnosis.*

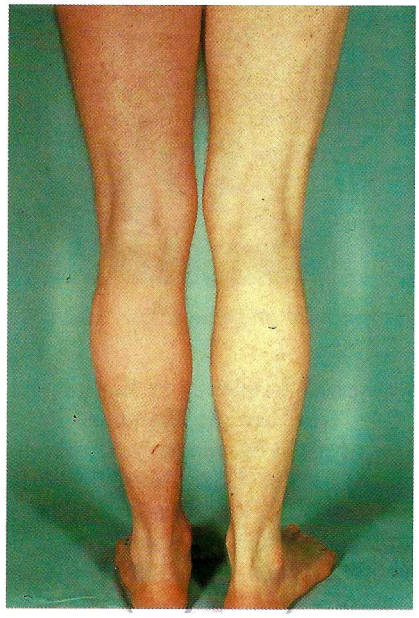

*Fig. 12: ACA with violaceous discoloration of the left leg.*

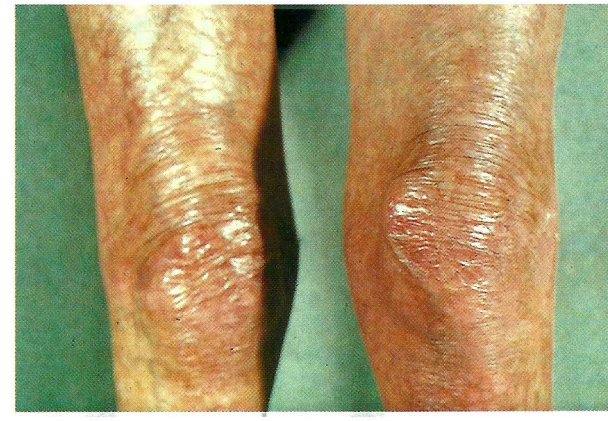

*Fig. 14: Atrophy of the skin over both knees with brown discoloration, cigarette-like skin. The vessels are clearly visible through the atrophic skin.*

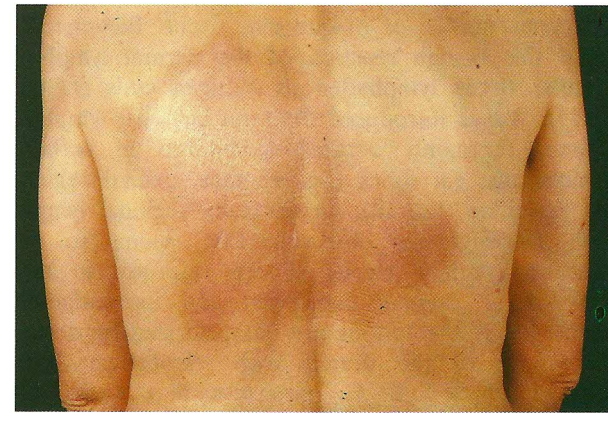

*Fig. 17: Scleroderma like lesions in patients with Lyme borreliosis.*

Erythema migrans may heal spontaneously within weeks or months, but it may also spread. Lesions remaining more than four weeks are called erythema chronicum migrans. According to the short incubation times, erythema migrans shows seasonal peaks from June to September (40).

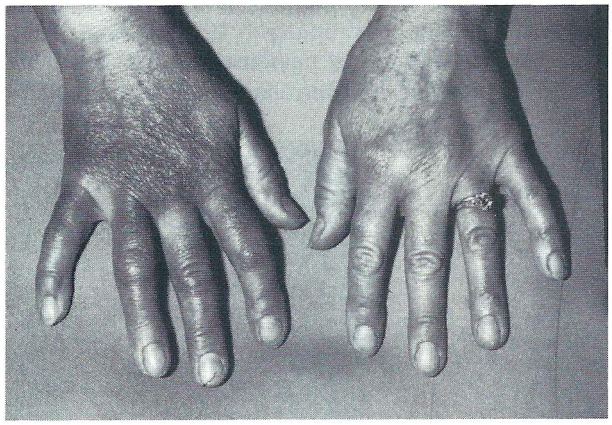

*Fig. 13: ACA of the right hand. The skin shows brown discoloration and atrophy.*

There are numerous differential diagnoses to erythema migrans: hyperergic insect bite reactions, initial erysipelas, erysipeloid, fixed drug eruption, granuloma anulare. Misdiagnoses: dermatomycoses (epidermal involvement obligatory), urticaria (transitory edema).

**Lymphadenosis benigna cutis (LBC).**

A typical but rare (1.3%) (41) lesion is the lymphadenosis benigna cutis. As first manifestation of Lyme borreliosis a solitary, soft, erythematous or violaceous nodule or plaque may occur. Bäfverstedt called this benign reaction of the dermal lymphoreticular tissue lymphadenosis benigna cutis (LBC) (42,43). Weber introduced the term borrelial lymphocytoma. It mainly occurs in children in certain localizations: ear lobes (fig. 9), face, genital region and mamillae (fig. 10). Occasionally regional lymph node swellings are observed. LBC seems to be associated with a strong B cell response to the presence of *Borrelia burgdorferi* and its antigens. Histologically the lesions are characterized by dense infiltrations of the dermis with lymphocytes and histiocytes in a follicular pattern, similar to that of a lymphoid follicle.

In rare cases disseminated forms in the face and at the trunk were described (44). Lymphadenosis benigna cutis and erythema migrans may occur together.

## DISSEMINATED EARLY MANIFESTATIONS.

**Multiple erythemas and exanthemas.**

Hematogenic and lymphogenic spread of the Borreliae cause systemic symptoms, fever, headache and arthralgias. In this stage multiple erythemas, often sharply marginated (erythemata migrantia) (fig. 8), urticarial and lichenoid exanthemas may occur. Involvement of the nervous system causes vertigo and migratory radicular pain, sensorial and motorical deficiencies, especially of the cerebral nerves, as well as the meningo-radiculo-polyneuritis Garin Bujadoux Bannwarth.

## LATE AND CHRONICAL INFECTION.

**Acrodermatitis chronica atrophicans (ACA).**

Within months to years after infection, chronic manifestations of skin, nervous system and joints may occur.

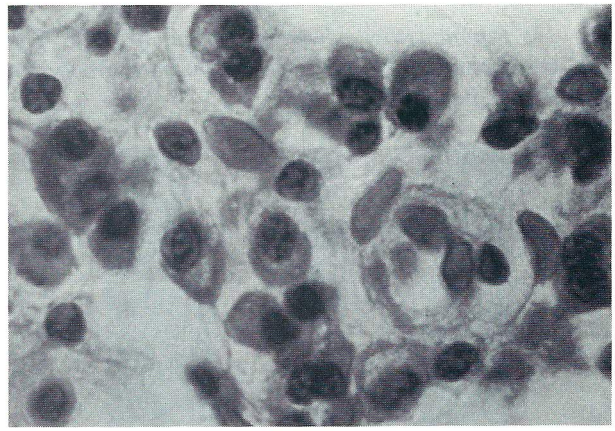

*Fig. 15: Perivascular plasmacells in ACA.*

ACA is observed frequently in Europe, very seldom in the USA; This can be explained by a special genospecies of *Borrelia burgdorferi*, which has not yet been isolated in the USA, called *Borrelia burgdorferi* group VS461 (45). It is characterized by a chronic progressive course, which consists of an inflammatory and an atrophic stage. The skin of the acral parts of limbs, mostly unilaterally and over the extensor surfaces of the joints, turns deeply red to violaceous and becomes pasty swollen (fig. 11, 12). This is the inflammatory infiltrative stage of the ACA. Forearms

and lower legs often show reddish brown stripping - the ulnar and tibial stripes. Subsequently the inflammatory infiltration decreases, epidermis and corium, sebaceous glands and hair follicles become atrophic, the subcutaneous fatty tissue is reduced or disappears completely. Vessels and tendons become clearly visible through the atrophic dermis, the skin appears like cigarette paper (fig. 13, 14). Even in this atrophic stage it is possible to detect Borreliae in biopsies. Histologically below the thin epidermis the corium shows dilated vessels, partially also swollen endothelia and edema, combined with patchy perivascular infiltrations of lymphohistiocytes. The most characteristic finding is the occurrence of moderate to abundant plasmacells in the dermis (fig. 15). The infiltrate may reach into the septa of the fatty tissue.

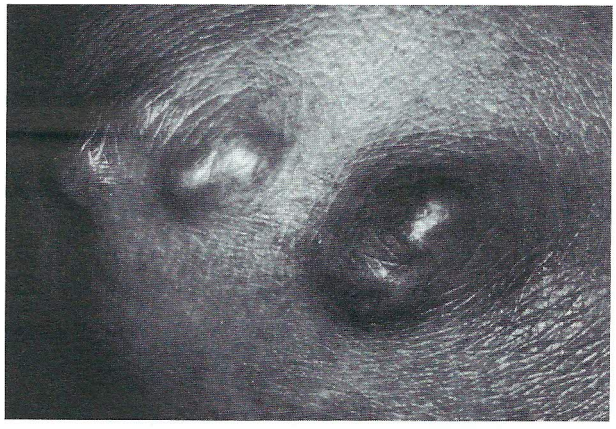

*Fig. 16: Fibroid nodules over the elbow in ACA.*

In single cases periarticular cutaneous to subcutaneous fibroid nodules or fibrous bands may develop (fig. 16). In those nodules it is possible to detect Borreliae, even after years. Numerous authors mentioned joint and neurologic symptoms in ACA. By careful neurologic examinations it is possible to detect in 40-50% of the patients with ACA an associated polyneuropathy (46,47). The patients complain of fatigue, disturbed sensitivity, paresthesias and twinges in the involved limb. ACA in females is twice as common as in males.

Differential diagnosis includes peripheral vascular disorders, venous insufficiency, disturbed venous circulation, acral cyanosis, thrombophlebitis, congelatio, autoimmune disease or an age related atrophy. Fibrinoid nodules often are misinterpreted as rheumatoid nodes or as gout tophi, especially if patients complain about arthralgias.

**Scleroderma-like lesions.**

Acrodermatitis chronica atrophicans is often associated with circumscribed sclerosing areas, clinically and histologically similar to circumscribed scleroderma or lichen sclerosus et atrophicus (LSA) (fig. (17).

In some of the patients with circumscribed scleroderma (morphea), after therapy with penicillin, the marginal violaceous erythema disappears, and

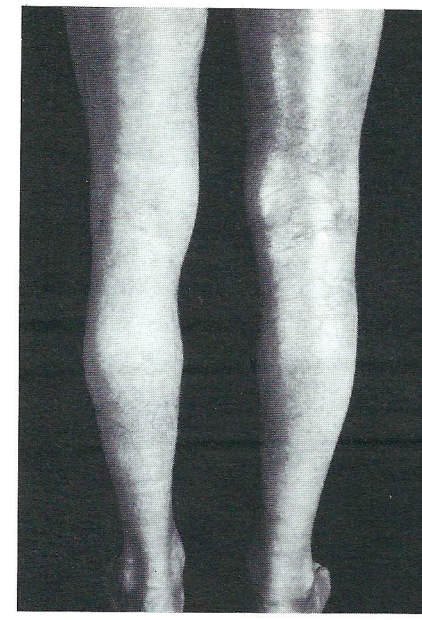

*Fig. 18: ACA of the left leg with intense sclerosis of the dermis.*

regression, or at least stagnation of the sclerosing lesions can be observed. Initial forms of these localized sclerodermas are histologically very similar to the perivascular infiltrates in ACA. Due to the increasing collagen the dermis is thickened (fig. 18). The role of Borreliae in localized scleroderma is still controversial. Some authors were able to detect antibodies against Borreliae in the serum in 20-40% of the patients with morphea (35). In our survey we found elevated IgG-titers in 7-28%, depending on specificity of the method (48). It is not yet certain, wether the detected antibodies are specific to *Borrelia burgdorferi.* In 1987, Aberer and Stanek were successful in cultivating *Borrelia burgdorferi* from a skin biopsy taken from an inflammatory margin of a lesion at the lower leg of a patient with disseminated morphea (30). Histologically they found an initial morphea.

With an avidin-biotin-immunoperoxidase staining they detected spirochetes in patients with morphea and LSA (49). The changes in the collagen structure in scleroderma are explained by persistent Interleukin-I-production by macrophages. In cooperation with the Max von Pettenkofer-Institute, Munich (Dr. Preac-Mursic) we were able to isolate *Borrelia burgdorferi* from a patient who had been suffering from an extensive symmetrical atrophodermia of the Pasini and Pierini type for twelve years (50). With different serological tests it was not possible to detect any

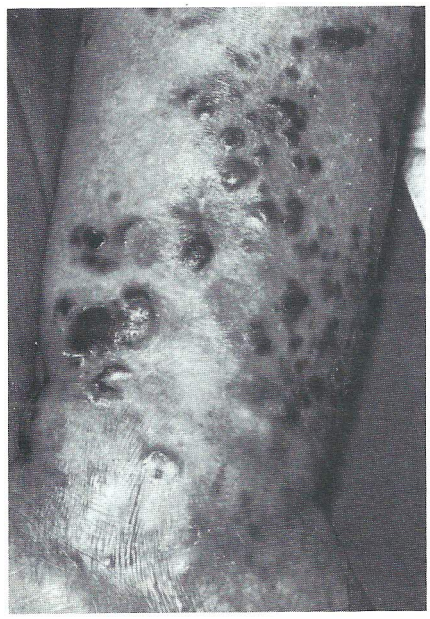

*Fig. 19: Malignant lymphoma on ACA.*

antibodies against *Borrelia burgdorferi*. Similar to the findings in ACA Aberer et al. (51) reported also on neurological findings in patients with morphea: facial palsy, muscular atrophy, myalgias, hyperesthesia, paresthesia and weakness.

**New dermatological manifestations.**

By means of serological tests and cultivation of *Borrelia burgdorferi* the detection of new clinical manifestations of Borreliosis is possible. Detmar et al. (52) described a disseminated borrelial infection with lichenoid papules and dermatomyositis-like skin lesions, joint swellings and muscular weakness. Elevated antibody titers were also observed in anetoderma and granuloma anulare. Miliary dissemination of benign lymphocytomas and malignant B cell-lymphomas have been described (44,53) (fig. 19).

Figure 20 shows a patient with extensive flat brown-red firm infiltrates at upper and lower limbs and at the trunk. The histological changes were equivalent to acrodermatitis and the inflammatory stage of a scleroderma.

It was not possible to cultivate Borreliae. High antibody titers (IgM and IgG) were found in IFT-abs as well as in the ELISAs with purified flagellum

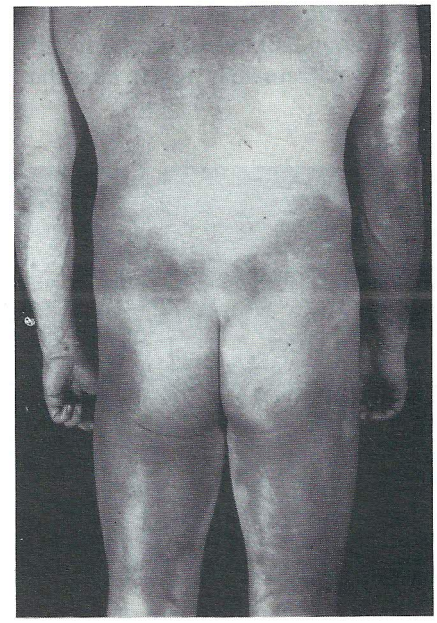

*Fig. 20: Generalized patchy acrodermatitis with intense sclerosis.*

antigen as well as in the immunoblot with recombinant borrelia proteins.

## REINFECTION.

After a successfully treated borrelial infection there is no immunity. Reinfections can often be observed and have repeatedly been described (54).

## DIAGNOSIS.

**Direct demonstration of *Borrelia burgdorferi*.**

Because of paucity of microorganisms in the tissue it is very difficult to detect Borreliae in histological sections.

Cultivation of *Borrelia burgdorferi* in the Barbour-Stoenner-Kelly medium is expensive, complicated and not very sensitive because the specimen is often contaminated (55,28).

Polymerase chain reaction, based on in vitro amplification of targeted gene sequences is a promising method for detection of *Borrelia burgdorferi* specific DNA (56,57).

**Antibody detection.**

The most important diagnostic instrument is the detection of specific IgM- and IgG-antibodies against *Borrelia burgdorferi* in the serum and in the cerebrospinal fluid. Sensitivity and reliability are best in disseminated or chronic forms. Unfortunately, the antibodies are often not detected in the early course of the disease. In some singular cases it is, even in the later course, not possible to demonstrate the humoral immunoresponse by todays methods (58, 59,60,61,62).

Dattwyler et al. (63) demonstrated a T-cell response to *Borrelia burgdorferi* in seronegative patients with persisting symptoms who were treated with oral antibiotics in the early course. It is not yet clear, whether this indicates a persisting infection, or whether it is a sign of a hyperergic immune reaction.

Serological tests at present are full of pitfalls concerning specificity, sensitivity, prevalence of antibodies, cross-reactivity and appropriateness of test antigen. As a consequence, it is to say, that an early infection is not excluded by a negative serological test. A positive IgG reaction is not necessarily an indicator of an infection that needs to be treated, it also may be an expression of cross-reactivity with other bacteriae (64), or residue of a sufficiently treated borreliosis in the past.

In any case, for setting the diagnosis, history, clinical and laboratory findings must be considered.

## Therapy.

The effectiveness of penicillin therapy in patients with ACA was described by Svartz (65) already in 1946. Since then the oral therapy of ECM, LBC, ACA and morphea with penicillin has been established. Since the detection of the causative agent and its classification as spirochete, it seems doubtful, whether sufficiently high levels in the tissue can be reached with oral penicillin therapy (66). In vitro susceptibility investigations by Preac-Mursic (67) showed, that the minimal inhibitory concentration of 4µg/ml for penicillin is relatively high. However, these results may be due to degradation of penicillin in the culture medium as shown by Hansen (68). So far no definite recommendations for therapy exist.

The current therapy regimes are summarized in table II, Oral tetracyclines and erythromycin are recommended in early infection (36). Penicillin, because of too low tissue levels, should no longer be used orally. In children under 12 amoxycillin or erythromycin is recommended.

In cases of disseminated disease, especially in neurological manifestations, antibiotics should be applied parenterally. High levels in CSF and tissue can be reached with cephalosporines of the third generation (ceftriaxon and cefotaxim) (69).

Hitherto, there exist no controlled studies to determine, whether it is possible to avoid persisting infections or late manifestations. For security reasons, the patients should stick to the high dosage and to the long duration of therapy in order to prevent irreversible defects of heart, joints and nervous system, as well as intrauterine infections.

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