# DERMATOLOGICAL MANIFESTATIONS OF LYME BORRELIOSIS

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## ABSTRACT

Lyme Borreliosis is a multisystemic infection involving skin, joints, the nervous system, the heart and eyes. As of yet four different genospecies of *Borrelia burgdorferi* have been identified: *Borrelia burgdorferi* sensu stricto, *Borrelia garinii, Borrelia afzelii,* and *Borrelia japonica*. Different strains of borreliae have been associated with different clinical manifestations of Lyme Borreliosis. Lyme Borreliosis is classically described as having three clinical stages or, similar to syphilis, an early phase and a late one. The early infection corresponds to the first stage, the late infection includes the second and the third stages. Skin manifestations of Lyme Borreliosis could be classified into five categories. The first one is characterized by skin manifestations proven to be caused by *Borrelia burgdorferi* infection, including erythema migrans, lymphadenosis benigna cutis and acrodermatitis chronica atrophicans. The second category covers controversial Lyme Borreliosis manifestations, such as lichen sclerosus et athrophicus, morphea, scleroderma, Scleredema of Buschke, atrophoderma of Pasini and Pierini, Parry-Romberg syndrome (facial hemiatrophy) and Shulman's fasciitis. The third category encompasses granuloma annulare, atypical persistent pityriasis rosea and pityriasis lichenoides which are skin lesions occasionally related to Lyme Borreliosis. Urticaria, erythema nodosum and papular acrodermatitis (Giannotti Crosti syndrome) have been classified as reactive Lyme Borreliosis skin manifestations. The last category of diseases includes exceptional skin manifestations during Lyme Borreliosis such as nodular panniculitis (Weber-Christian), B-cell cutaneous lymphoma and juvenile chronic myeloid leukemia.

*KEY WORDS*

*Lyme borreliosis, skin manifestations, Borrelia burgdorferi*

## INTRODUCTION

In recent years there have been numerous and important advances in the field of Lyme Borreliosis (LB). However, many questions concerning this disease still remain unanswered. The spirochetal behaviour is not clear after *Borrelia burgdorferi* (*Bb*) has infected the human body. These organisms can produce pathognomonic lesions, skin manifestations mimicking other diseases or clinical pictures that can also be induced by other causative agents.

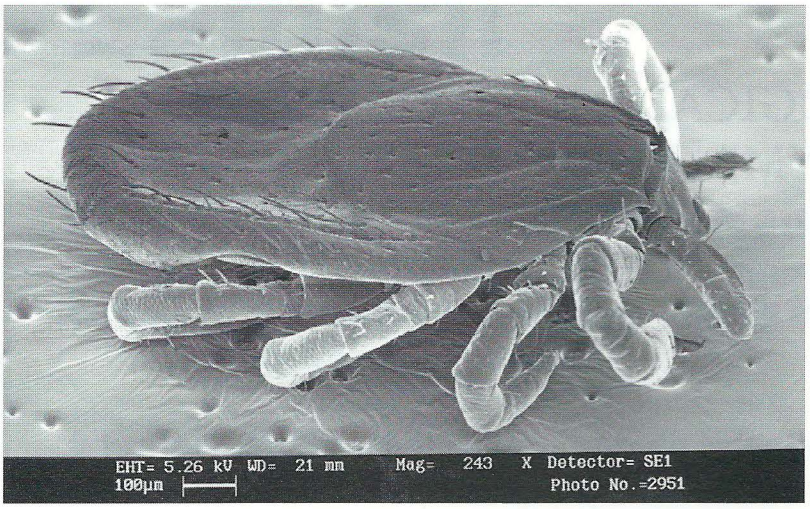


*Fig. 1: Ixodes ricinus*

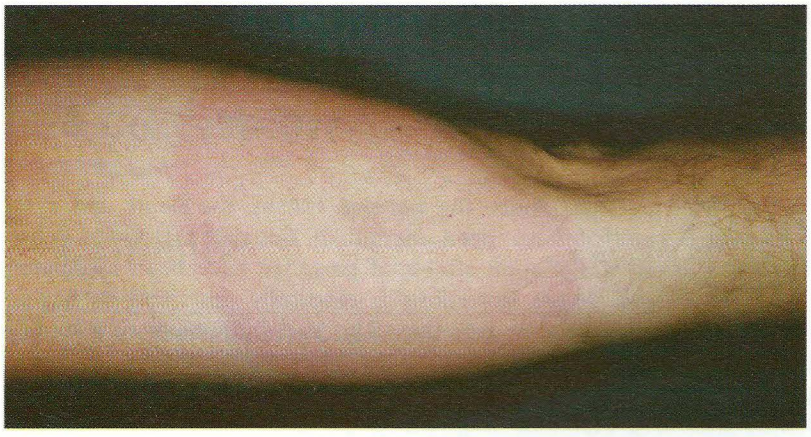

*Fig. 2. Erythema (chronicum) migrans*

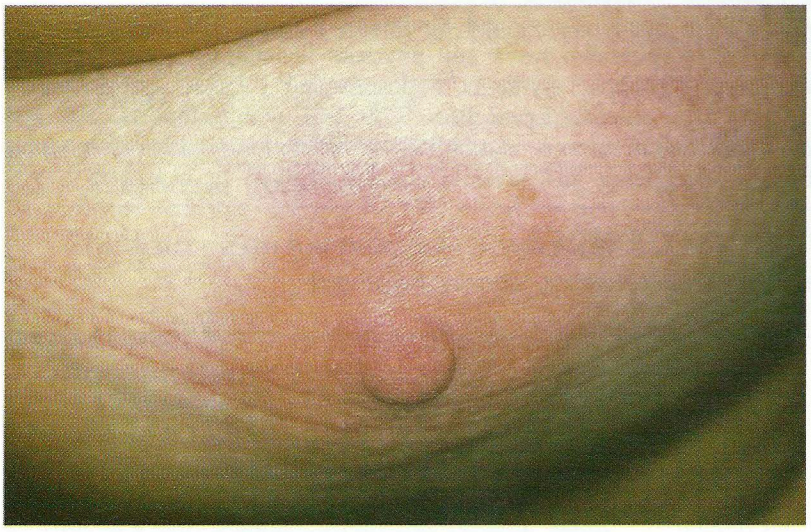

*Fig. 3. Lymphadenosis benigna cutis of areola mammae*

We have also become aware of the complexity of this disease since genetic studies were able to identify different species of *Bb* sensu lato responsible for human infections: *Bb* sensu stricto, *B. garinii* and *B. afzelii* (1). In Japan a new species was recently described, *B. japonica*, which does not appear to be a human pathogen (2). In the future additional species of *Bb* will most likely be recognized. The *Bb* infection is mostly transmitted by a hard tick of the genus *Ixodes* (Fig. 1). Different *Bb* strains appear to have a distinct organotropism and can induce various clinical manifestations. A possible follicular hair tropism of *Bb* may explain the erythema migrans (ECM) with hair loss. *B. afzelii* has been found in patients with acrodermatitis chronica atrophicans (ACA), whereas *Bb* sensu stricto has been found in patients with arthritis and *B. garinii* in patients with neuroborreliosis (3).

The presence of an infected tick, a persistent attachment to the skin for about one or two days and the appearance of an enlarging erythema after an incubation period of at least 4 - 5 days indicate the diagnosis of LB. Therefore, the clinical diagnosis of LB is confirmed when the vector is identified and ECM appears. On the other hand, a tick bite can often go unnoticed because skin reaction can be limited and asymptomatic. Sometimes a papule, an angiomatoid patch, a pseudo-lymphomatous or granulomatous nodule or a persistent oedematous-papular dermatitis appear on the tick bite site (4). These unspecific lesions indicate a chemical reaction to the anticoagulant saliva introduced by the tick and are not *Bb* infection-correlated.

LB skin manifestations could be classified into the following categories: i) proven LB skin manifestations, ii) controversial LB skin manifestations, iii) skin manifestations

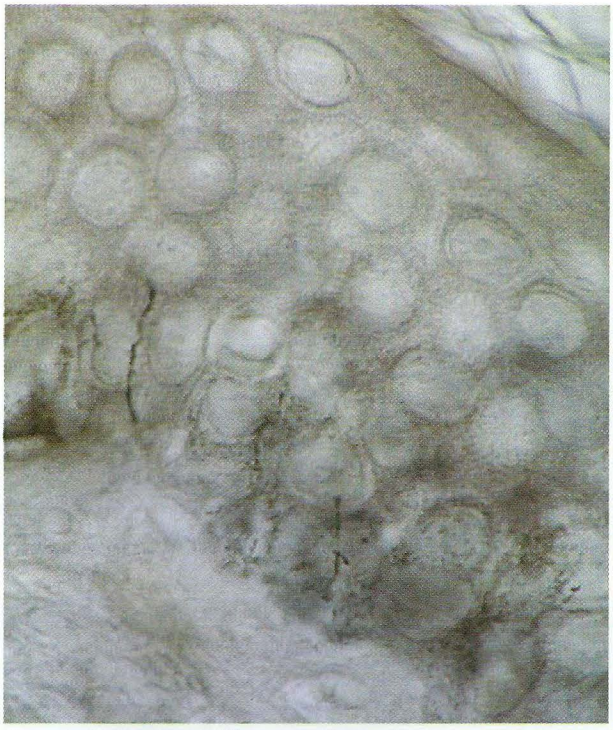

*Fig. 4. Spirochetal-like organisms in the epidermis of lymphadenosis benigna cutis (Warthin-Starry stain)*

occasionally related to LB, iv) reactive LB skin manifestations, v) exceptional skin manifestations during LB.

## PROVEN LYME BORRELIOSIS SKIN MANIFESTATIONS

These consist of erythema (chronicum) migrans, lymphadenosis benigna cutis (LABC) and acrodermatitis chronica atrophicans.

The old abbreviation ECM is still used, because EM alone may be confused with another skin disease, erythema multiforme. ECM is the most common and typical manifestation of LB (Fig. 2). It is an annular-shaped erythema rapidly extending centrifugally with a diameter of at least 5 cm and, over a period of 3 - 4 months, ECM can even reach a size of 50 cm (5). ECM appears about 4 - 30 days after a tick bite, usually at the same site. ECM is the only skin manifestation in the first stage of LB. It occurs as the first lesion in about 50% of LB cases (5). All of the *Bb* species are able to cause ECM. Any site on the human body can be affected. In children ECM is more often localized on the head because

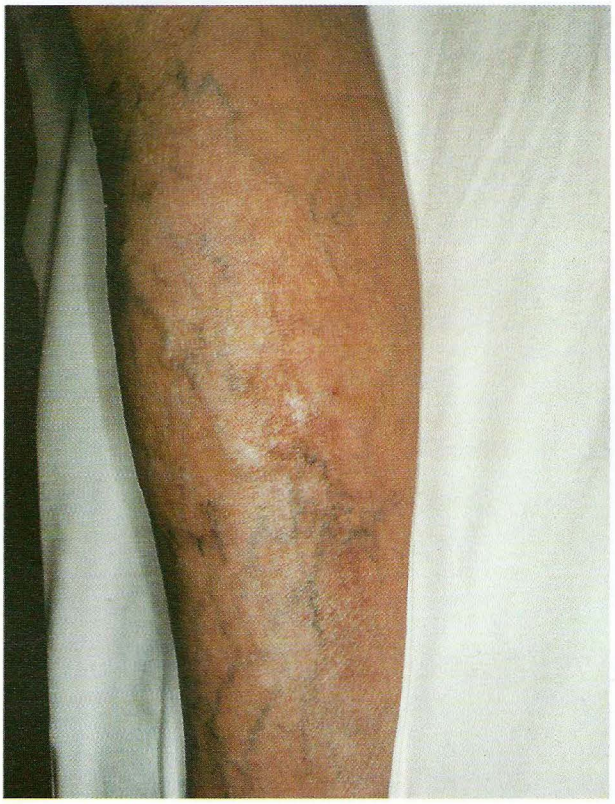

*Fig. 5. Acrodermatitis chronica atrophicans*

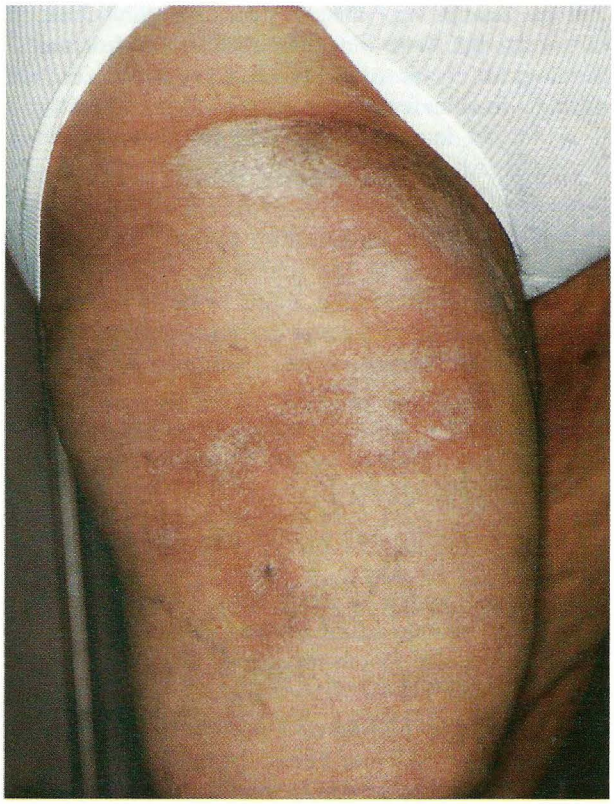

*Fig. 6. Lichen sclerosus et atrophicus*

of their small stature (6). There is considerable variation in the appearance of this lesion, including erysipeloid, purpuric, nodular and atrophic aspects (7,8). Hair loss on the site of ECM is also reported (9). Atypical ECM may be induced by different *Bb*, certain individual host reactivity, immunological mechanisms or lengthy *Bb* persistence in the skin.

This early skin lesion is sometimes associated with constitutional signs and symptoms including fever, chills, lymphadenopathy, headache, and myoarticular pain (7).

Untreated ECM can resolve spontaneously, but sometimes it persists longer, producing a central atrophy (10).

The criteria for the clinical diagnosis of ECM are the presence of an annular-shaped erythema with more than 5 cm of diameter and its appearance at least 4 - 5 days after a tick bite. These criteria are particularly important in case of atypical ECM. In cases when the diagnosis is uncertain, spirochetal organisms may be detected in involved skin by silver stain (Warthin-Starry), uranil stain (Steiner-Steiner), monoclonal antibodies, cultivation in BSK medium or by polymerase chain reaction. Positive culture results are able to confirm the clinical diagnosis, but false negative results are frequent. Serological assays often produce negative results during the first few weeks of the illness, therefore it is not an important criterion for diagnosis.

Multiple annular erythemas (MAE) are a consequence of the rapid blood dissemination of *Bb*. This justifies their classification at the early second stage, rather than at the first stage. MAE lesions are similar to ECM, but there is no evidence of a tick bite. MAE are more frequently observed in children (6).

In rare cases *Bb* infection may lead to roseolar manifestations. In one case we were able to cultivate *Bb* from the affected skin (11) which was later identified as *B. garinii*.

LABC is the typical second stage manifestation of LB (Fig. 3). There is a plain form (Jessner-Kanof type) and a nodular form (Spiegler-Fendt type). The Jessner-Kanof lymphocytoma consists of a port wine-like patch of more than 10 cm in diameter (12).

T-lymphocytic infiltration is present in histological samples. The Spiegler-Fendt lymphocytoma may appear in a solitary or disseminated form. Solitary lesions are often localized on the ear lobe or on

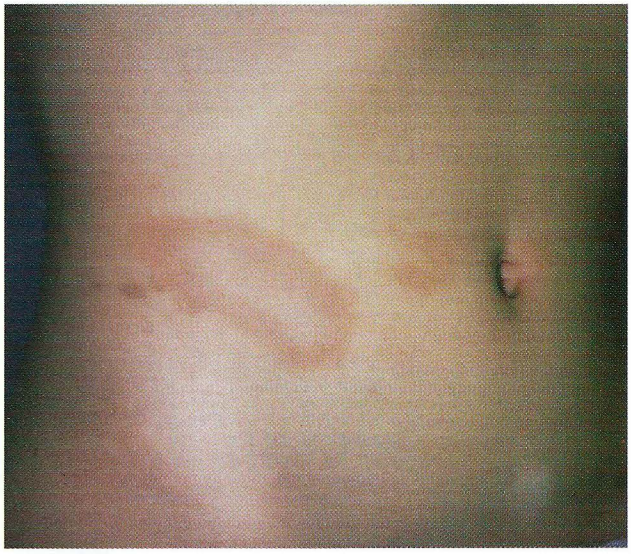

*Fig. 7. Morphea*

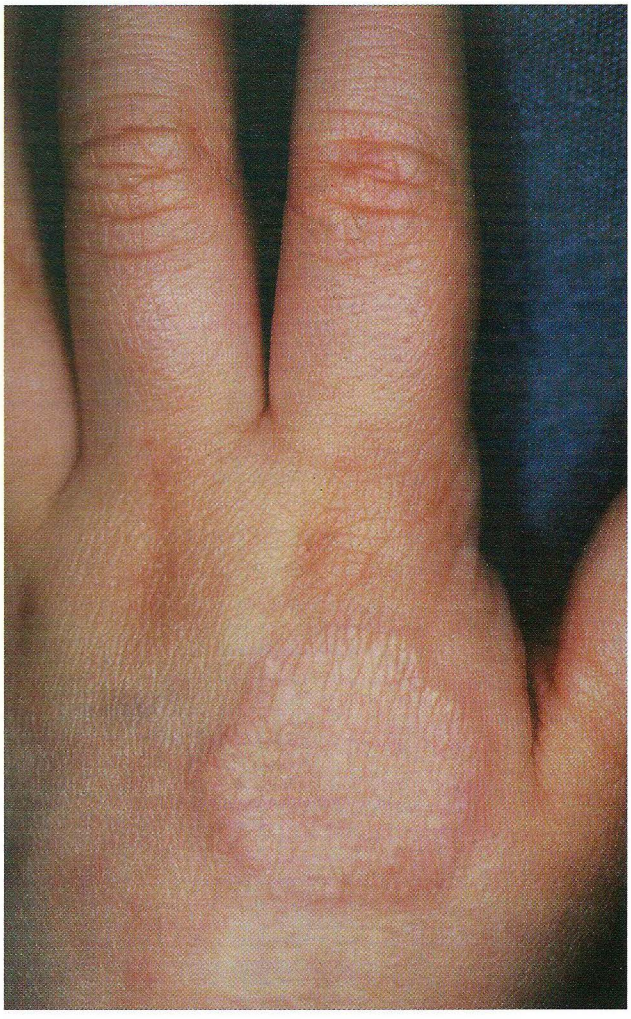

*Fig. 8. Granuloma annulare*

areola mammae (13), whereas disseminated lesions are localized on the back. The infiltrate consists mainly of B-lymphocytes.

Warthin-Starry stained biopsy specimens of LABC examined by light microscopy demonstrate spirochetes in the epidermis where these organisms cannot be confused with other cutaneous structures (14) (Fig. 4).

Sometimes LABC is caused by *Bb* infection (borrelial lymphocytoma), but it can also have a different etiology.

LABC resolves spontaneously within months to years but is cured more rapidly with antibiotics (10).

ACA is a typical late skin manifestation of LB (Fig. 5). It is caused only by *B. afzelii*; in the USA only few cases have been reported (15), probably because *B. afzelii* is not present in this country.

ACA is a chronic progressive dermatitis, characterized by an early inflammatory and a late atrophic stage (16). The inflammatory stage begins on one extremity, most common at an acral site, such as the hand or foot, with bluish-red discoloration and doughy swelling.

The atrophic stage involves not only the skin but also the subcutaneous tissue and the muscle underneath. The atrophy appears as extremely thin, transparent skin (cigarette paper-like) with clearly visible veins and a loss of hair follicles and sebaceous glands.

Sometimes fibrous nodules may occur adjacent to the joints. In these lesions it is possible to identify *Bb* by staining techniques or culture (17). Pain, pruritus, hyperesthesias or paresthesias are usually associated with it.

In our regions the observation of cases of inflammatory ACA is frequent, whereas atrophic ACA is very rare (18). The cause is unknown. It is conceivable that either a different strain of *B. afzelii* is present in Italy, climatic conditions or the Italian immunogenetic type is responsible for that fact.

*Table 1. Controversial skin manifestations of Lyme Borreliosis.*

| **Controversial skin manifestations of Lyme Borreliosis** |
|---|
| Lichen sclerosus et atrophicus |
| Morphea |
| Scleroderma with generalized plaque lesions |
| Linear scleroderma |
| Atrophoderma of Pasini and Pierini |
| Parry-Romberg syndrome (facial hemiatrophy) |
| Shulman's syndrome (eosinophilic fasciitis) |
| Scleredema of Buschke |

## CONTROVERSIAL LYME BORRELIOSIS SKIN MANIFESTATIONS

The possible relationship between LB and sclero-atrophic skin manifestations has been suggested by some clinical, immunological and microbiological evidence. However, numerous authors were not able to demonstrate *Bb* infection in such patients and have cast doubts on an etiological role of *Bb* in scleroatrophic skin lesions. *Bb* may be an etiological agent of lichen sclerosus et atrophicus (LSA) (Fig. 6), although this affection must be considered a multifactorial disease. LSA related to *Bb* infection has been first reported by Åsbrink (19) who noticed the frequent association between LSA and ACA. Aberer et al. demonstrated the presence of *Bb* in LSA (20). Further evidence for *Bb* infection in morphea and LSA has been recently shown by PCR. We observed a specific amplification in three children living in Trieste (Friuli-Venezia Giulia), an Italian area endemic for LB. However, we were not able to detect *Bb*-specific DNA in four patients with LSA living in a non-endemic area (Milan) (21) (Table 1).

Since 1985 when Aberer et al. claimed that morphea (Fig. 7) might be a late manifestation of LB (22), numerous conflicting reports have followed and this hypothesis is still debatable (23-26). In some cases morphea might be caused by *B. afzelii*.

The possible relationship between *Bb* infection and LSA or morphea, respectively, is suggested by the following evidence: i) clinical and histological similarities between morphea, LSA and ACA and the coexistence of ACA, LSA and/or morphea in the same patient, ii) the presence of antibodies against *Bb* in some patients with LSA and morphea, iii) the identification of borrelial organisms or genoma in histologic sections, iv) a response to antimicrobial therapy in many cases of LSA and morphea.

## SKIN MANIFESTATIONS OCCASIONALLY RELATED TO LYME BORRELIOSIS

Granuloma annulare (GA), atypical persistent pityriasis rosea and pityriasis lichenoides are skin

lesions occasionally related to LB. The association between GA (Fig. 8) and *Bb* infection has been reported by Strle et al. (27). The correlation has been suggested by serological evidence or by identification of spirochetal organisms in the affected skin by silver staining. Based on our experience, GA is rarely related to LB. We could detect *Bb* in affected skin by PCR in only three patients with an unusual clinical course.

An atypical persistent pityriasis rosea, lasting longer than 4 - 5 months, could also be suspected to be related to LB (28).

We are presently studying some children who developed papular dermatitis with perifolliculitis, mimicking pityriasis lichenoides. In one case we were able to cultivate *Borrelia sp.* from the affected skin (BSK medium) (29).

Further studies are necessary to define the clinical aspects of this form of dermatitis to confirm the correlation to LB.

## REACTIVE LYME BORRELIOSIS SKIN MANIFESTATIONS

Reactive LB skin manifestations are nonspecific lesions that usually also occur during other infectious diseases. They are immunologic responses to spirochetal antigens. None of these manifestations has been found to contain spirochetes.

Diffuse urticaria is more frequent in early LB, whereas the localized form is more frequent in late LB; the last one usually occurs in the skin adjacent to the affected joints during articular attacks (30,31).

Erythema nodosum has also been observed during LB.

We have recently reported two children who developed papular acrodermatitis (Gianotti-Crosti syndrome) after *Bb* infection.

## EXCEPTIONAL SKIN MANIFESTATIONS DURING LYME BORRELIOSIS

Nodular panniculitis (Weber-Christian), B-cell cutaneous lymphoma and juvenile chronic myeloid leukemia are exceptional skin manifestations during LB.

Two patients suffering from nodular panniculitis associated with *Bb* infection have been reported (32). In one case *Bb* was repeatedly isolated from the skin and subcutaneous tissue even after antibiotic treatment.

The correlation between LB and cutaneous B-cell lymphoma is still debated. The evolution from borrelial lymphocytoma to malignancy has been suggested (33), nevertheless this hypothesis needs to be further investigated.

Only one case of association between LB and juvenile chronic myeloid leukemia was described (34).

## CONCLUSION

The subject of cutaneous LB manifestations is not fully understood up to now. Further studies may reveal that some other skin disorders of actually unknown etiology are induced by *Bb* infection.

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