

Clinical aspects and diagnosis of erythema migrans and borrelial lymphocytoma

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SUMMARY

There are three distinct cutaneous manifestations of Lyme borreliosis (LB), erythema migrans (EM), borrelial lymphocytoma (BL), and acrodermatitis chronica atrophicans. EM, the hallmark of early LB, is the most frequent manifestation of LB and develops within 4-180 days (median, 14 days) after an infectious tick bite. There are five different clinical types of EM.

Solitary macular and solitary annular EM comprise more than 80% of all EM lesions. Less frequent variants are the bull's eye type, the minimal size EM, the combined BL and EM, and the multilocular EM. EM in children is most frequently located in the head-neck region and often displays an atypical morphology. It may be associated with an ipsilateral peripheral facial palsy. Extracutaneous, usually mild and transient, signs and symptoms occur in up to 40% of all EM patients (major form of EM). They must not be confused with features of human granulocytic ehrlichiosis that is found in about 20% of LB patients in Austria. The diagnosis of EM is primarily made on clinical grounds. Serologic test results are often false negative or positive. Histopathology from lesional skin is a helpful adjunct to the diagnosis. Direct detection of *B. burgdorferi* (DNA) by cultivation or PCR can prove the diagnosis.

BL is a subacute cutaneous manifestation of LB that has been defined as a stage 2 (early disseminated infection) manifestation, but may also occur during early localized infection. It usually represents a solitary lesion in stereotypical locations (ear, nipple) and represents a B cell pseudolymphoma.

KEY WORDS

Lyme borreliosis, *Borrelia burgdorferi*, erythema migrans, borrelial lymphocytoma

Introduction

Lyme borreliosis (LB) is a multisystemic infectious disease that is caused by the arthropod-borne spirochete *Borrelia burgdorferi* sensu lato (*Bb*). In Europe, about 80% of all cases of LB represent skin manifestations, all together named dermatoborrelioses (DB). There are three characteristic manifestations of DB, in which the

etiopathogenic role of *Bb*, most often the subtype *Borrelia afzelii* (1,2), is proven by cultivation of the spirochete from lesional skin. These manifestations are erythema migrans (EM), borrelial lymphocytoma (BL), and acrodermatitis chronica atrophicans. In this article, clinical and diagnostic aspects of EM and BL will be

discussed, based on our experience with more than 1,000 DB patients, seen at the Department of Dermatology in Graz, Austria between 1993 and 2000.

Erythema migrans

*Epidemiology and transmission of *Borrelia burgdorferi**

EM, the hallmark of early LB, is the most frequent manifestation of LB at all. It is found in endemic areas (clusters) all over the northern hemisphere, including the Alpe-Adria-region (3). The incidence of EM in Styria, the southeastern-most state of Austria is estimated to be 50/100.000 per year. EM affects both sexes and all age groups equally and shows seasonal variations with a peak incidence between May and September, although several cases also occur regularly during the winter months. EM develops at the site of an infectious tick bite in most cases, but in a small percentage of patients EM lesions develop distantly to a tick bite. In accordance with the most frequent sites of tick bites (higher body temperature), the location of EM is usually the calf/popliteal fossa region, or the thigh/groin/buttock region, or the armpit/shoulder region. A tenet in the etiopathogenesis of EM has been that an attachment period of at least 24 hours is necessary for the tick to transmit enough spirochetes into the human skin to produce EM. In our patients, the average attachment period is between 12 and 72 hours, but many patients also give a reliable history of a shorter attachment period. EM develops after an incubation period of 4-180 days (median, 14 days) following the tick bite. A still debatable question is, whether or not arthropods other than ticks are able to transmit *Bb*. Over the last eight years, about 10% of our patients, who could specifically recall an arthropod bite at the site where EM developed later, were sure that this arthropod was a flying insect.

Clinical types of erythema migrans

There are different clinical types of EM:

(i) Solitary macular and

(ii) solitary annular EM comprise 43% and 38% of all EM lesions, respectively, and are round to oval, sharply demarcated, red to bluish-red erythemas with a diameter of at least 5 cm (4,5). The difference between these two types is that annular lesions are ring-like (Fig. 1), whereas macular lesions show no central clearing, but remain homogenous. The latter is characterized by a pronounced inflammatory edge in most cases (Fig. 2).



Figure 1. Solitary annular type of erythema migrans.



Figure 2. Solitary macular type of erythema migrans.



Figure 3. Bull's eye type of erythema migrans.



Figure 4. Atypical variant of solitary erythema migrans. Note that the erythematous ring is incomplete.

EM usually lacks epidermal changes, although vesicles or minimal scaling have been observed in a few patients. EM lesions on the calf tend to develop a hemorrhagic component due to stasis. Local symptoms are generally mild (itching or burning sensations) or absent.

(iii) The bull's eye type (2%) is a variant of solitary annular EM that is characterized by a target-like morphology with a peripheral bright red rim that is separated from a central bluish-red patch by a ring of normally appearing skin (Fig. 3).

(iv) Another type of EM is the minimal size EM, which is defined as EM lesion with a diameter of less than 5 cm on presentation (6). We have observed 52 patients with such lesions in a series of 957 consecutive EM patients. In 21 of these patients, EM remained in this size also 7-10 days after the first visit without antibiotic treatment, whereas EM expanded beyond a diameter of 5 cm over time in the other 31 patients. Thus, in around 3% of patients, EM is smaller than 5 cm ("true minimal size EM"). In our 21 patients, the sex ratio m:f was 10:11 and the median age of the patients was 45 years. Twelve of the lesions were macular, nine annular. Of interest, 66% of all these EM lesions were located on the lower extremities. The mean disease duration before start of antibiotic treatment was 13.6 days (range, 6-50 days). Extracutaneous signs and symptoms, in particular fatigue, were present in 5/21 (24%) patients. Serum anti-*Bb* IgG and/or IgM antibodies were found in 16/21 (76%) patients by a standard ELISA test.

(v) Five percent of EM lesions are atypical (Fig. 4). Among these lesions there are the combined BL and EM lesions, which we have defined as the occurrence of the two manifestations of DB together at the same site of the body (7). We scrutinized our patients files for bluish-red nodules or plaques in the center of an EM and found such combined lesions in 15/1,007 (1.5%) patients. The sex ratio of m:f was 8:7 and a median age of 51 years. Twelve of the 15 (73%) combined lesions were localized on the upper part of the body. Interestingly, Borrelial lymphocytoma (BL) preceded EM in all 15 patients by 2-8 weeks. Extracutaneous signs and symptoms were present in 3/15 (20%) of patients and occurred simultaneously with the beginning of EM, indicating that the development of EM around BL may represent the transition from a primarily localized into a disseminated manifestation of DB.

Figure 5. Disseminated erythema migrans.

Figure 6. Borrelial lymphocytoma on the earlobe.

(vi) The development of more than one EM lesions in one patient (multifocal EM) has been observed in 9% of our patients. The mean total number of lesions per patient was four, with a range from 2-36. The underlying pathogenic mechanism in many patients is hematogenous dissemination of the spirochete, in which case there is a primary EM with a typical clinical aspect, followed by a median of six secondary lesions all over the body after a latency period of a few days. Secondary lesions are generally smaller and less inflammatory (Fig. 5). These patients are affected more often by extracutaneous signs and symptoms than patients with solitary lesions and are more often seropositive. This kind of disseminated EM is less frequent in Europe than in the USA (8), and the number of lesions per patient is smaller in European patients. Besides this disseminated form of EM, there are also patients in whom the occurrence of multiple lesions is due to more than one infectious arthropod bites or to local spread of *Bb*.

Erythema migrans in children

EM in children is most frequently located in the head-neck region and often displays an atypical (band-like or gyrate) morphology. These lesions are very transient (few days) and variable in intensity over time. Neuropediatricians sometimes see children who are suffering from an ipsilateral peripheral facial palsy along with an EM lesion on the face, which may point to a neurotropic spread of *Bb*. Disseminated EM is found more often in children than in adults.

Extracutaneous signs and symptoms

Extracutaneous signs and symptoms occur in up to 40% of all EM patients, in which case the disease has to be classified as major form of EM. These signs and symptoms are unspecific and usually mild. The most common features associated with EM are elevated temperature, headache, arthralgias, myalgias, fatigue, malaise, regional or generalized lymphadenopathy, and sore throat. These signs and symptoms occur along with EM and are usually transient, generally lasting for a few days only. In many cases, they have already disappeared before initiation of antibiotic treatment, but may indicate that (hematogenous) dissemination of *Bb* has taken place. It must be clear that these signs and symptoms



are not due to another etiology or primary disease. They must also be distinguished from signs and symptoms indicating another organ manifestation of LB (e.g., neuroborreliosis, cardioborreliosis) on the one hand and from features of ehrlichiosis on the other hand. Ehrlichiosis, in Europe usually human granulocytic ehrlichiosis, is caused by the HGE agent that is transmitted by the same ticks as *Bb*. Co-infection with *Bb* and the HGE agent is found in about 20% of borreliosis patients in Austria (9).

Differential diagnoses

The differential diagnoses of solitary EM comprise unspecific insect bite reactions, which develop more rapidly and will clear from the periphery within a few days without antibiotic therapy, erysipelas, which is usually accompanied by high fever and chills, morphea, which has an ivory-like whitish center that is surrounded by a lilac ring and has an increased consistency on palpation. Granuloma annulare, which may also be caused by *Bb* infection, has a small elevated border consisting of multiple confluent papules. Tinea lesions are scaling and erysipeloid is located on the hand or fingers in most cases. The most important differential diagnoses for multilocular EM are urticaria, multilocular fixed drug eruption, erythema annulare centrifugum, and erythema infectiosum.

Diagnosis

The diagnosis of EM is primarily made on clinical grounds, which may be supported by the history of an arthropod bite. Analysis of IgG and IgM antibodies to *Bb* in the serum of patients should be performed using an ELISA; an additional immunoblot test (two-test approach) should be carried out to prove the specificity of a positive or undetermined ELISA result in clinically difficult situations. It must be kept in mind that neither a positive result can prove the diagnosis of EM unequivocally, nor does a negative result exclude EM, because of seroprevalence, cross-reactions etc. Interpretation of positive test results must include the following possibilities: acute EM, EM during or shortly after antibiotic therapy, seroprevalence (15-20% in Styria), persistent titer after appropriate antibiotic treatment that may result from a polyclonal B-cell activation and does not require further treatment when the patient is disease-free, cross reaction with other antigens (e.g., EBV, mumps (12), varicella zoster virus, etc.). Vaccination titers are currently no problem in Europe, as there is no vaccination available so far, but need already to be considered in the USA.

Interpretation of negative test results must include

the following possibilities: false clinical diagnosis (skin lesion does not represent EM), no seroconversion (analysis too early in the course of the disease), antibiotic pre-treatment. Histopathology from lesional skin is a very helpful adjunct to the diagnosis of EM. In a biopsy specimen from the edge of the lesion, the most important finding will be a superficial (and deep), perivascular (and interstitial) mononuclear infiltrate composed mostly of lymphocytes and histiocytes with a variable admixture of plasma cells (13).

The gold standard for diagnosing EM is the direct detection of the infectious agent from the rash by cultivation. A 3 mm punch biopsy specimen must be obtained from the leading edge of EM under sterile conditions and has to be directly transferred into a tube with BSK-H medium. Cultivation has to be carried out at 34°C in an incubator. Assessment of spirochete growth is performed weekly with a dark field microscope. Under optimal conditions, sensitivity of this method may reach 80%. However, the procedure is laborious and it may take several weeks for *Bb* to grow in the medium. Because of this delay of culture results, it is not a suitable method, when therapeutic decisions have to be made. Moreover, cultivation of *Bb* is only available in specialized laboratories. Polymerase chain reaction (PCR) is able to detect *Bb* specific DNA in biopsy samples from lesional skin. As LB is a "paucibacillary" disease, which means that only few spirochetes are present at the site of infection/inflammation.

PCR is a very advantageous technique, because it amplifies the (small amounts of) DNA present in the skin lesion. It should be kept in mind, however, that in contrast to cultivation, no viable spirochetes but only DNA is detected. The advantages of PCR are high sensitivity as well as specificity and that the results are available very quickly. Also, it may be used with archival (formalin-fixed, paraffin-embedded) samples (14). The sensitivity is 70-90% depending on the sample source (archival versus frozen tissue). False positive results due to contamination may be a problem. PCR from serum or urine are also feasible, but currently not used as routine diagnostic procedures.

Borrelial lymphocytoma

BL is a subacute cutaneous manifestation of LB that has been defined as a stage 2 (early disseminated infection) manifestation, but may also occur directly at the site of a tick bite (15). Thus, BL can also represent a stage 1 (early localized infection) manifestation of LB. BL is the least common manifestation of LB (5%) and occurs more often in children than in adults. Extracutaneous signs and symptoms are very infrequent. BL is a solitary lesion in most patients. It is a bluish-red nodule or plaque with a size between 1-5cm, sharply demarcated, and often with a slightly atrophic surface.

On palpation, BL is a soft and non-tender lesion. BL is located typically on the earlobe (Fig. 6), breast (nipple, areola), and less frequently on the scrotum or the (anterior) axillary fold.

The diagnosis is based primarily on the clinical aspect, but histopathology, which reveals a B-cell pseudolymphoma, is mandatory for the definite diagnosis of BL, in particular to rule out B-cell lymphoma of the skin. For this differentiation, it is sometimes necessary to perform additional immunohistochemical and PCR studies

to exclude monoclonality. Although some patients with BL may be seronegative, Bb IgG and/or IgM antibodies are found in the serum of 80% of all BL patients. Direct detection of Bb or Bbspecific DNA in lesional skin by culture or PCR are helpful addition to the diagnosis.

Differential diagnoses of BL include insect bite reactions, cutaneous lymphoma, foreign body granuloma, sarcoidosis, cutaneous metastasis, keloid, perichondritis, and granulomatous contact dermatitis due to golden earrings.

REFERENCES

1. Zöchling N, Müllegger RR, Schläpfer EM, Stumpfenhausen G, Soyer HP, Wienecke R, Hödl S, Volkenandt M, Kerl H. Molecular subtyping of *Borrelia burgdorferi* (Bb) in lesional skin from Styrian (Austrian) patients with various manifestations of dermatoborreliosis (DB). *J Invest Dermatol* 1995;104: 687.
2. Picken RN, Strle F, Picken MM, Ruzic-Sabljic E, Maraspin V, Lotric-Furlan S, Cimperman J. Identification of three species of *Borrelia burgdorferi* sensu lato (*B. burgdorferi* sensu stricto, *B. garinii*, and *B. afzelii*) among isolates from acrodermatitis chronica atrophicans lesions. *J Invest Dermatol* 1998;110: 211-4.
3. Stanek G. Lyme Borreliosis. *Wien Med Wschr* 1995;145: 155-61.
4. Wharton M, Chorba TL, Vogt RL, Morse DL, Bühler JW. Case definitions for public health surveillance. *MMWR* 1990;39: 1-43.
5. Stanek G, O'Connell S, Cimmino M, Aberer E, Kristoferitsch W, Granström M, Guy E, Gray J. European Union concerted action on risk assessment in Lyme borreliosis: clinical case definitions for Lyme borreliosis. *Wien Klin Wochenschr* 1996;108: 741-7.
6. Weber K, Neubert U, Büchner SA. Erythema migrans and early signs and symptoms. In: Weber K, Burgdorfer W (editors). *Aspects of Lyme borreliosis*. Berlin: Springer, 1993; 105-21.
7. Müllegger RR, Weger W, Binder B, Kerl H. Combined borreliac lymphocytoma with erythema migrans. Retrospective study of a rare manifestation of dermatoborreliosis in 15 patients. *J Eur Acad Dermatol Venereol* 2000;14(Suppl.1): 48-9.
8. Müllegger RR, Brunner-Köhler G, Zöchling N, Reiter H, Hödl S, Soyer HP, Kerl H. Erythema migrans multiloculare in Styria (Austria). *Acta dermatovenerologica APA* 1996;5: 13-6.
9. Müllegger RR, Weger W, Sixl W, Binder B, Aberer E, Marth E, Kerl H, Stünzner D. Serologischer Nachweis von humaner granulozytärer Ehrlichiose (HGE) bei 19% von Patienten mit Dermatoborreliose (DB). *Z Hautkr* 2001; 76(Suppl.1): S6.
10. Åsbrink E. Cutaneous manifestations of Lyme borreliosis. Clinical definitions and differential diagnoses. *Scand J Infect Dis* 1991; Suppl.77: 44-50.
11. Hansen K. Laboratory diagnostic methods in Lyme borreliosis. *Clin Dermatol* 1993;11: 407-14.
12. Millner MM, Schimek MG, Müllegger RR, Stanek G. *Borrelia burgdorferi* ELISA titres in children with recent mumps meningitis. *Lancet* 1990; 336: 125-6.
13. Hödl S, Soyer HP, Müllegger RR. Dermatopathologic diagnosis of Lyme borreliosis. *Acta dermatovenerologica APA* 1996; 5: 123-9.
14. Wienecke R, Neubert U, Volkenandt R. Molecular detection of *Borrelia burgdorferi* in formalin-fixed, paraffin-embedded lesions of Lyme disease. *J Cutan Pathol* 1993; 20: 385-8.
15. Åsbrink E, Hovmark A, Olsson I. Lymphadenosis benigna cutis solitaria -borrelia lymphocytoma in Sweden. *Zbl Bakt Hyg* 1989; Suppl 18: 156-63.

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