

Mini Erythema Migrans – A Sign of Early Lyme Borreliosis

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Key Words

Borrelia burgdorferi · Erythema migrans · Lyme borreliosis · Mini erythema migrans

Abstract

Background: An erythema migrans (EM) remaining smaller than 5 cm in diameter, called mini EM by us, has not been addressed in detail. **Objective:** To study the significance of the mini EM as a sign of Lyme borreliosis. **Methods:** Patients with suspected mini EM were retrospectively selected out of 257 consecutive patients with EM. The diagnosis of mini EM rested on the cultivation of *Borrelia burgdorferi*. Species and subtype analysis of culture isolates was performed using outer surface protein A (OspA) polymerase chain reaction followed by restriction fragment length polymorphism and sequencing of the OspA gene. **Results:** There was one patient with definite (0.4%) and another patient with a questionable mini EM. *Borrelia garinii* OspA type 6 was identified in the patient with the definite and *B. burgdorferi* sensu lato in the patient with the questionable mini EM. **Conclusion:** The mini EM represents an important and apparently uncommon sign of early Lyme borreliosis.

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Introduction

Erythema migrans (EM) is the hallmark of Lyme borreliosis. The typical primary EM is a ring-shaped or homogeneous erythematous and usually peripherally expanding skin lesion caused by *Borrelia burgdorferi* sensu lato [1, 2]. In Europe [1, 3–6] and in the USA [7–9], the median or mean maximum diameter of the primary EM varies between 10 and 20 cm with a range of 1–85 cm.

EM lesions with a size of less than 5 cm had previously been noted [1, 3–9]. This is not in agreement with the US case definition stating that an EM should have a size of at least 5 cm [10]. In Europe, a case definition allows for the diagnosis of an EM if its size is less than 5 cm [11], but diagnostic criteria for such small lesions have not been discussed. In another European study, however, the isolation of *B. burgdorferi* sensu lato from 3 EM lesions with a size of 2–4 cm has been reported [1]. In this study, we present more details about the clinical and laboratory investigations of our patients with what we call mini EM.

Patients and Methods

Definition and Diagnosis

We defined a mini EM to be a cutaneous erythema with a maximum diameter of 2 up to less than 5 cm, remaining smaller than 5 cm and being due to *B. burgdorferi* sensu lato. The essential cri-

terion for the diagnosis of the mini EM was the identification of *B. burgdorferi sensu lato* by culture and/or PCR within the erythema.

Patients, Study Design, Follow-Up and Treatment

We carried out a retrospective study of 257 consecutive patients with the objective to study patients with mini EM in more detail. The 257 patients came from several German dermatological centers in which they were seen between 1978 and 1991 [3, 4, 12–14]. After the first visit, the patients were usually followed for 3–12 months, sometimes for years. All patients with established EM received systemic antibiotic treatment [4, 12–15].

Cultivation and Subtype Analysis of B. burgdorferi sensu lato

Up to 1991, an attempt had been made to culture borreliae from fresh biopsy material of the suspected mini EM lesions in the laboratory of Prof. Vera Preac-Mursic [16, 17].

In 2003, the *Borrelia* isolates from patient 1 and from a patient with a typical expanding EM could be re-cultivated and subjected to subtype analysis using outer surface protein A (OspA) PCR with subsequent analysis by sequencing [18] and restriction fragment length polymorphism [19] of the amplicons.

Serology

The sera of our patients were tested for the presence of IgM and IgG antibodies against *B. burgdorferi* by ELISA according to Wilske et al. [20] and by immunoblot according to Schulte-Spechtel et al. [21].

Results

Patients with a Small EM at the First Visit

Five patients (2%) had a small EM with a size of less than 5 cm at the first visit. Three of these patients (1.2%) developed typical ring-shaped peripherally expanding EM lesions with a size of 10, 20 and 21 cm in diameter, respectively, within the next 4 weeks.

B. afzelii was identified in 1 of these 3 patients.

Patients with Mini EM

The remaining 2 patients were found to have a definite (patient 1) and a questionable (patient 2) mini EM. The erythema in these patients was bright red, homogeneous, nonindurated, nonraised and nonscaling. From both mini EM lesions, *B. burgdorferi sensu lato* could be cultivated. Species and subtype analysis from the isolate of patient 1 yielded *B. garinii* OspA type 6. The isolate of patient 2 could not be re-cultivated for typing. None of the patients with mini EM had elevated antibody titers against *B. burgdorferi* (confirmed by repeated serological testing performed in 2002).

Case Report of the Patient with Definite Mini EM.

Patient 1, a 26-year old woman, presented with an asymptomatic erythema with a size of 2 by 2.5 cm at the first



Fig. 1. EM of 3 days' duration on the right lower leg, 2.5 × 4 cm in diameter, in patient 2; from Weber et al. [1, colorplate 1].

visit. She had observed the lesion on the left thigh for 1 week. A tick bite had not been noted. She complained of fatigue and abdominal pain. A biopsy from the erythema to culture borreliae was done at the first visit. The lesion did not change in size until it subsided spontaneously 6 weeks after the first visit. The patient was seen by one of us (K.W.) at the first visit and after 2, 4 and 7 weeks. At the follow-up after 7 weeks, she received amoxicillin 500 mg with clavulanic acid 3 times daily for 2 weeks because the culture had revealed growth of *B. burgdorferi sensu lato*. Fatigue and abdominal pain subsided within a few weeks after therapy. There were no signs and symptoms related to Lyme borreliosis during the next 12 months.

Case Report of the Patient with Questionable Mini EM.

Patient 2, a 43-year old man, presented with an asymptomatic erythema with a size of 2.5 by 4 cm at the first visit. The lesion had been noted on the right lower leg for 3 days (fig. 1). A tick bite had not been observed. He suffered from fatigue. A biopsy from the erythema to culture borreliae was performed 4 days after the first visit. The patient decided to start taking doxycycline 200 mg daily for 2 weeks after the second visit although at that time the result of the culture was not yet available. As ascertained by his wife, a physician, several times during the 3-week period and by one of us (K.W.) after 2 weeks, the EM did not change in size until it disappeared within 2 weeks after therapy. The fatigue subsided within a few days of therapy. Follow-up for 3 more years showed that he developed no later signs or symptoms related to Lyme borreliosis.

Discussion

Our observations on 257 consecutive patients have revealed that a small EM with a size of less than 5 cm seen at the first visit can develop into two directions. First, the small EM may peripherally expand into a typical EM. Secondly, the small EM may not reach a size of 5 cm in diameter at any time to represent a mini EM.

One of our patients with mini EM could be observed for 7 weeks without treatment. This time period appears to be sufficiently long to assure that the patient did not develop a typical expanding EM. However, early antibiotic treatment could have prevented the development of a typical expanding EM in our patient 2 so that this case appears to be questionable.

EM lesions can strongly vary in size. The mini EM apparently represents an EM which stops to expand after some time, expands so slowly or disappears so soon that it does not reach a size of 5 cm. The other extreme variant is an EM which spreads over large parts of the skin [1–9] and rarely even over the entire skin within about 4 months as reported in a single patient [22].

Early European Lyme borreliosis is occasionally associated with another erythematous lesion which is usually smaller than 5 cm in diameter, borrelial lymphocytoma. However, borrelial lymphocytoma is a raised, indurated, tumor-like lesion preferentially occurring at certain sites such as the ear lobe or nipple [23, 24].

Contrary to a typical EM, a mini EM represents a considerable diagnostic problem [1, 25]. A couple of other dermatoses such as a nonspecific tick bite reaction, ec-

zema, granuloma anulare, tinea corporis, fixed allergic drug reaction, the initial lesion of pityriasis rosea or erysipelas might be considered. On the other side, an erythema following a tick bite and not expanding to more than 1 cm in diameter most likely indicates a nonspecific tick bite reaction rather than a mini EM.

The diagnosis of a mini EM rests on the identification of *B. burgdorferi* sensu lato within lesional skin. In Europe, most EM lesions are now known to be associated with *B. afzelii* [2, 6, 18, 25–28]. Yet, *B. garinii* OspA type 6 was identified in one of our patients with mini EM. This was somewhat surprising considering the recent findings of Logar et al. [6], who obtained hints that EM lesions due to *B. garinii* expand more rapidly than EM lesions due to *B. afzelii*. In their study however, the subtype (OspA type) has not been determined. For example, OspA type 4 is more often found among isolates from cerebrospinal fluid than among isolates from ticks [17] indicating differences of pathogenicity regarding different OspA types of *B. garinii*. Further work appears to be necessary to determine which species or subtype of *B. burgdorferi* sensu lato predominates in association with the mini EM.

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