ERYTHEMA MIGRANS MULTILOCULARE IN STYRIA (AUSTRIA)

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ABSTRACT

To characterize clinical, serologic, and histopathologic features of patients with erythema migrans multiloculare from Styria (Austria), an European area well known to be endemic for Lyme Borreliosis, 270 consecutive patients (m:f = 128:142, mean age = 54 years) with erythema migrans were studied at the Department of Dermatology in Graz, Austria between March 1993 and October 1995. 17/270 patients (m:f = 9:8, mean age = 37 years) (6.3%) presented with a multifocal form of the disease. Several findings in these 17 patients were remarkable. Anamnestic data/clinical findings: History of tick or insect bite(s): 10/17 patients (4 singular, 6 multiple); mean total number of lesions/patient = 4 (ranging 2-18); latency of 1 - 14 days (mean 7 days) in 9/17 patients (53%) between primary erythema migrans and secondary lesions; in these 9 patients the secondary lesions showed a different morphologic aspect in comparison to the primary erythema migrans; extracutaneous signs and symptoms: 7/17 patients (41%). Serologic findings: *Borrelia burgdorferi* serum ELISA IgG-antibodies: 9/17 patients (53%), IgM: 9/17 patients (53%). Histopathologic findings: Complete lack of epidermal changes and milder inflammatory dermal infiltrate in all secondary lesions (4 biopsy specimens) in comparison to primary erythemata migrantia (5 biopsy specimens).

Our clinical and serologic findings are largely in accordance with the scarce literature on this condition from Europe where erythema migrans multiloculare is much rarer than in the USA. The pathogenesis of erythema migrans multiloculare which is currently defined to be a disseminated form of Lyme Borreliosis due to haematogenous spread of *Borrelia burgdorferi* will be discussed in consideration of our observations.

KEY WORDS

Lyme borreliosis, Borrelia burgdorferi, erythema migrans multiloculare, early disseminated disease

INTRODUCTION

Erythema migrans (EM) usually occurs as a single lesion. However, multiple (secondary) erythemas in one patient (erythema migrans multiloculare (EMM)) are quite frequent in the USA (25 - 50% of all EM patients) (1), whereas EMM is rarely seen in Europe (4 - 10% of all EM patients) (2). In the USA up to 100 erythematous lesions may appear in one patient with EMM (1). On the contrary, EMM patients in Europe normally present with only few

erythemas (up to 10) (3). Differences between the primary EM and the secondary lesions concerning morphology, predilection sites, dynamics, and local symptoms can be observed (4,5). Extracutaneous signs and symptoms are described to be found more often in EMM than in patients with solitary EM (4,5). Elevated serum antibody titres against *Borrelia burgdorferi* (*Bb*) are more common in EMM than in singular EM (6). *Bb* could be cultivated from single/ primary lesions as well as from secondary lesions (1). EMM is currently classified as manifestation of the secondary stage (early disseminated stage) of Lyme Borreliosis (LB) (7).

The present study has been undertaken to assess the characteristics of EMM patients in Styria the southernmost province of Austria which is known to be highly endemic for LB.

PATIENTS AND METHODS

270 consecutive patients (m:f = 128:142, mean age = 54 years) with EM were seen at the Department of Dermatology in Graz, Austria between March 1993 and October 1995. The diagnosis was made on clinical and partly histopathologic (167/270 patients) grounds. All patients resided in Styria (Austria) a LB endemic area. 17/270 patients (m:f = 9:8, mean age = 37 years) (6.3%) presented with multiple EM lesions. 10/17 patients could recall an arthropod bite 18 days before the occurrence of EM on the average (ranging 4 - 73 days). 4/10 patients had singular, 6/10 multiple arthropod bites.

Analysis for IgG and IgM antibodies to *Bb* was performed in 252/270 patients including all patients with multiple lesions. Purified native flagella of *Bb*, strain DK-1, isolated from a human EM lesion (DAKOPATTS ELISA Kit, DAKO Diagnostica, Glostrup, Denmark) was used as a test antigen.

In 167/270 patients punch biopsies (4 mm) were taken for routine histopathologic examination. After formalin-fixation and paraffin-embedding, specimens were haematoxylin-eosin stained. 7/167 patients had EMM. In these 7 patients punch biopsies were taken either from the primary lesion (3/7), or secondary lesion (2/7) or primary and secondary lesion (2/7).

RESULTS

The mean disease duration before hospital visit was 18 days in solitary EM (ranging 4 - 55 days) compared to 15 days in EMM (ranging 2 - 28 days). The mean total number of erythemas in one patient with EMM was 4 (ranging 2 - 18). In 9/17 EMM patients (53%) a primary erythema occurred on the average of 7 days before secondary lesions (ranging 1 - 14 days). In all these 9 patients primary EM showed the same morphology as a typical solitary EM, whereas the secondary erythemas were characterized by a smaller size and milder inflammatory reaction. All secondary erythemas showed a quite similar morphology and had no predilection sites. They lacked the typical peripheral expansion of solitary lesions. In the other 8/17 EMM patients (47%) erythemas developed more or less simultaneously and there were no differences in the clinical appearance between the lesions. 108/253 EM patients (43%) suffered from extracutaneous signs and symptoms of LB in comparison to 7/17 EMM patients (41%). A positive *Bb* serum ELISA IgG antibody titre was found in 71/235 EM patients (31%) and in 9/17 EMM patients (53%), respectively. 91/235 EM patients (39%) had a positive *Bb* serum ELISA IgM antibody result, whereas 9/17 EMM patients (53%) were IgM reactive. The histopathologic examination of the 4 biopsy specimens from secondary lesions in EMM revealed a mild to moderate (in comparison to solitary or primary erythemas) perivascular infiltrate with very sparse interstitial extension throughout the dermis. The infiltrate was mainly composed of lymphocytes intermingled with some plasma cells. Epidermal changes were not observed in secondary lesions, whereas slight atrophy of the epidermis and few spongiotic foci could be found in primary EM.

DISCUSSION

Within a period of 31 months only 17 from a total of 270 patients with EM (6.3%) seen at the Department of Dermatology in Graz, Austria presented with a multifocal form of the disease. A similar low incidence of EMM as in Styria is also reported from other European areas (2), whereas EMM is quite frequent in the USA (1). The low average number of 4 erythemas in one EMM patient in our series is also consistent with former publications from Europe (3). In contrast to these observations, a high number of lesions usually occurs in EMM patients in North America (1). A latent period between primary and secondary erythemas with differences concerning their morphology were present in 9 of our 17 patients (53%). On the other hand we were not able to find an interval or clinical

variations between erythemas in the other 8 patients (47%). Berger noted morphological differences of the lesions in EMM patients „in some instances" (4) and Melski described this diversity in a very distinct manner (5). Weber and coworkers discovered secondary EM lesions to „resemble" the primary EM (8). However, no clear and comprehensive data on the time course of multiple erythemas exist in the literature. Additional signs and symptoms were not found more often in our EMM patients (41%) than in patients with singular EM (43%). This contradicts the more frequent and severe constitutional symptoms in EMM patients known from the European as well as from the American literature (4,5,7). The percentage of increased serum ELISA IgG and IgM antibodies to *Bb* in our EMM series was far above the sensitivity for patients with solitary EM as in former reports (6). All 4 secondary EM lesions from which a punch biopsy was obtained in our EMM patients clearly differed clinically from the primary EM. Thus, the milder dermal infiltrate found in these lesions on histopathologic examination reflects the distinct clinical aspect of the erythemas.

EMM is defined at present as secondary stage manifestation of LB (early disseminated disease) due to a haematogenous spread of *Bb* after primary infection (7). On the other hand it is conceivable that EMM is caused by multiple bites of infected vectors in some cases. The current definition is supported by some characteristics of EMM patients in comparison to patients with solitary EM in the literature: (i) Delayed occurrence of secondary erythemas with distinct morphological features (4,5,8). (ii) A more frequent appearance of extracutaneous signs and symptoms (4,5). (iii) Elevated *Bb* specific antibody titres are more common (6). (iv) A higher rate of positive *Bb* serum PCR reactions (9). Features (i) and (iii) were also seen in our EMM patients, but not feature (ii). However, our data are not sufficient enough to decide which pathogenetic mechanism underlies EMM.

In case the postulate of a haematogenous spread of *Bb* in EMM is correct, one crucial question seems to have been addressed insufficiently so far: What are the prerequisites for a single patient to acquire either solitary EM or EMM? On the one hand, infection with a specific *Bb* subtype is conceivable. Associations between the existence of distinct *Bb* subtypes, different clinical manifestations of LB and various geographic regions were shown (10). As *Bb sensu stricto* is mainly found in the USA, whereas very rarely in Europe (11), and the incidence of EMM is much higher in the USA (1), one might suspect a relation between EMM and *Bb sensu stricto*. In lesional skin from 19 of our solitary EM patients in 1993, only *B. afzelii* (74%) and *B. garinii* (26%) could be detected (unpublished), although all three *Bb* subtypes were isolated from the Styrian tick population (Pierer K., et al., unpublished). However, neither results from the literature nor own investigations are available so far to answer whether *Bb sensu stricto* might be the exclusive pathogen in EMM. On the other hand, a certain precondition of the patient (e.g. immunological status) could be responsible for the development of EMM. For example, a German patient receiving radiation therapy because of cancer developed around 70 lesions (12).

More studies on the subject of EMM are necessary to better characterize this peculiar variant of EM. If the assumption will be further corroborated that EMM is a disseminated form of LB it appears to be a good model to study several pathogenetic aspects of LB (relation between *Bb* and the patient).

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