Course and Outcome of Early Lyme Borreliosis in Patients With Hematological Malignancies

Vera Maraspin,1 Eva Ružič-Sabljic,2 Lara Lusa,3 and Franc Strle1

1Department of Infectious Diseases, University Medical Center Ljubljana, 2Institute of Microbiology and Immunology, and 3Institute for Biostatistics and Medical Informatics, Medical Faculty, University of Ljubljana, Slovenia

Patients with erythema migrans and underlying hematological malignancy more often had signs of disseminated Lyme borreliosis and more frequently needed antibiotic retreatment than sex-, age-, and antibiotic treatment–matched immunocompetent persons with erythema migrans. However, the outcome was excellent in both groups.

Keywords. Lyme borreliosis; erythema migrans; outcome; hematological malignancies; lymphoid neoplasms.

Data on Lyme borreliosis (LB) in immunocompromised patients are limited. However, the high incidence (337/100 000 in 2013) of LB in Slovenia [1] and the large number of patients referred to our institution, including those with impaired immunity, gave us the opportunity to analyze the course and outcome of patients with erythema migrans (EM) and underlying hematological malignancy (HM).

METHODS

Selection of Patients

Information was obtained from the database on adult patients diagnosed with EM at the LB outpatient clinic of the University Medical Center Ljubljana, Slovenia, from 1992 to 2013. Data on these patients had been collected prospectively using a structured questionnaire.

To qualify for inclusion in the study, the presence of typical EM, defined according to published criteria [2], and the existence of HM were required. For each patient with HM and EM, 2 sex-, age-, and antibiotic treatment–matched immunocompetent patients diagnosed with EM at our institution in the same year were selected. The only mismatch was in 4 patients with HM who received ceftriaxone for disseminated LB, whereas their controls were treated with doxycycline.

Clinical and Laboratory Evaluation

Patients and controls were evaluated clinically before the start of antibiotic therapy and then at 2 weeks, 2 months, 6 months, and 1 year after the first visit. Serum immunoglobulin (Ig)M and IgG antibodies to Lyme borreliae were determined using an indirect chemiluminescence immunoassay (LIAISON), with antigens OspC and VlsE for detection of IgM antibodies and VlsE for IgG antibodies, or an indirect immunofluorescent test, using as antigen a local isolate of Borrelia afzelii.

In patients who gave consent, a skin biopsy was taken from the border of the EM lesion. Specimens were cultivated in a modified Kelly–Pettenkofer medium and checked for the presence of Borreliae for up to 9 weeks [3]. In patients with positive skin culture results, the procedure was repeated 2–3 months later at the site of the first biopsy. In the majority of patients, a sample of citrated blood was taken for cultivation in the same medium as for skin culture; the procedure was as reported elsewhere [4].

Isolates were identified to the species/strain level using pulsed-field gel electrophoresis after MluI restriction of genomic DNA or by polymerase chain reaction–based restriction fragment length polymorphism of the intergenic region [3, 5].

Treatment

At the first visit, patients with HM were treated with doxycycline 100 mg bid for 15 days (14 patients), amoxicillin 500 mg tid for 15 days (13 patients), cefuroxime–axetil 500 mg bid for 15 days (12 patients), azithromycin 500 mg twice on the first day followed by 500 mg od for 4 days (10 patients), or ceftriaxone 2 g od intravenous for 14 days (4 patients with signs indicating disseminated LB).

Complicated Course of LB

Patients with signs of disseminated LB (multiple EM, objective extracutaneous manifestations of LB) and/or those with treatment failure were interpreted as having a complicated course of LB.

Treatment failure was defined as follows: (i) appearance of objective extracutaneous manifestations of LB, (ii) appearance/persistence of subjective symptoms or their increased intensity that
could not be attributed to other causes, (iii) persistence of EM (visible EM at visit 2–3 months after the start of antibiotic treatment), or (iv) demonstration of Borreliae by skin culture at the site of previous EM 2–3 months after antibiotic treatment. These patients were retreated with ceftriaxone (i, ii) or an alternative oral antibiotic (iii, iv).

Statistical Methods
Pretreatment characteristics of early LB as well as the course and outcome of the disease after antibiotic therapy in patients with HM were compared with the corresponding findings in a control group of previously healthy persons with EM. The categorical variables were compared using the χ² test with Yates continuity correction; numerical variables were compared using the Mann–Whitney test. The percentage or median differences and their 95% confidence intervals (CIs) were reported. CIs for the difference of the medians were based on 10,000 bootstrap samples and on the bias-corrected and accelerated method. The CIs for single proportions were based on the binomial distribution. The statistical language R was used for the analyses [6].

RESULTS
During the 22-year period analyzed, 53/12,518 (0.4%; 95% CI, .3–5) patients with EM and underlying HM were diagnosed. Seven of the 53 patients (13.2%) had been reported previously [7].

The group comprised 25 females and 28 males aged 17 to 75 (median 61) years. Solitary EM was diagnosed in 52 (98.1%) patients, and 1 (1.9%) patient presented with multiple skin lesions. Among the 53 patients, 11 had myeloid neoplasms and 42 had lymphoid (B-cell) neoplasms; 16 (30.2%) were receiving antineoplastic treatment (Supplementary Table 1).

Characteristics of Early Lyme Borreliosis Before Treatment With Antibiotics
Basic demographic data and pretreatment clinical characteristics of early LB in patients with impaired and normal immunity were analogous for the majority of parameters, including the proportions of patients with serum antibodies to Borreliae, the ratio of patients with positive culture results, and the proportions of the isolated Borreliae according to species (Supplementary Table 2). However, at the first visit, signs of early disseminated LB were found in 4/53 (7.6%; 95% CI, 2.1–18.2) patients with HM but in 0/106 immunocompetent patients (0%; 95% CI, 0–3.4; difference in the proportion: 7.6%; 95% CI, 0–16.1; P = .02). All 4 suffered from lymphoid malignancy; 3 had extracutaneous manifestations of LB associated with solitary EM (2 meningocerebritis, 1 lymphocytic meningitis and peripheral facial palsy), and 1 had multiple EM accompanied by pronounced constitutional symptoms (Table 1). Patient 1 has already been presented [7].

Clinical Course and Outcome After Treatment
Duration of EM after the beginning of antibiotic treatment was similar in patients with HM (median, 7; interquartile range, 5–16 days) and their controls (10; interquartile range 7–18 days; P = .24).

The subsequent course and outcome of LB in 4 patients with symptoms and signs of disseminated borrelial infection at presentation and treated with ceftriaxone were favorable. However, 3 (5.7%; 95% CI, 1.2–15.7) other patients with HM (all had underly- ing lymphoid malignancy) but none in the immunocompetent group (95% CI for the difference: −2 to 13; P = .06) needed additional antibiotic therapy: 1 patient because of development of pronounced subjective symptoms and 1 patient because of persistence of EM; the third patient developed multiple EM (Table 1). In all 3 patients, the clinical course was uneventful after retreatment with antibiotics.

The course of EM in patients with HM was more often complicated than in patients with normal immunity. Disseminated early LB or treatment failure was diagnosed in 7/53 (13.2%; 95% CI, 5.5–25.3) patients with HM but in 0/106 immunocompetent patients (95% CI, 0–3.4; 95% CI for the difference: 2.7–23.7; P < .0001). The complications were limited to patients with underlying lymphoid neoplasm (complications present in 7/42 patients with lymphoid neoplasm and in 0/11 with underlying myeloid neoplasia; P = .34) and were associated with receiving immunosuppressive drugs. Five of 7 (71.4%, 95% CI, 29.0–96.3) patients with complications vs 11/46 (23.9%; 95% CI, 12.6–38.8) with HM who had an uncomplicated course (P = .03) were receiving therapy against cancer; the corresponding findings for the subgroup of patients with lymphoid malignancy were 5/7 vs 8/35 (23%; 95% CI, 10–40; difference: 48%, 95% CI, 4–93, P = .04). Humoral response to B. burgdorferi sensu lato was established in only 2/7 (28.6%; 95% CI, 3.7–71.0) patients with complications, that is, less often than in patients without complications (25/46; 54.3%; 95% CI, 39–69), though this difference was not statistically significant (P = .39).

At the examination 1 year after the first visit, no objective findings that could have been potentially associated with LB were documented in any patient, including those with and without HM.

DISCUSSION
Results of the present study, based on prospectively collected data at a single European center during a 22-year period, revealed that patients with EM and underlying HM more often had signs of disseminated LB and more frequently needed antibiotic retreatment than sex-, age-, and antibiotic treatment–matched immunocompetent persons with EM. However, the outcome was excellent in both groups. The results are similar to those suggested for the course and outcome of early LB in patients with miscellaneous causes of immunodeficiency.
<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age</th>
<th>Sex</th>
<th>Year of EM Diagnosis</th>
<th>HM</th>
<th>Duration of Treatment</th>
<th>Tick Bite</th>
<th>EM Location/Duration</th>
<th>Main Symptoms Associated With EM/Duration</th>
<th>Abnormal Laboratory Results/ Anti-borreliae Blood and CSF Antibodies (IgM, IgG)</th>
<th>Culture of Borreliae Skin/Blood/CSF</th>
<th>Duration of Signs and Symptoms* After the Onset of Treatment With Ceftriaxone</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>65 y F</td>
<td>1994</td>
<td>CLL</td>
<td>No</td>
<td>16 y</td>
<td>Yes玛</td>
<td>Head/40 d</td>
<td>Fatigue, cephalea/5 d</td>
<td>EM (20 × 20 cm), PFP</td>
<td>Thrombocytopenia, ↑ liver enzymes, CSF pleocytosis: Le 26 (ly 26) × 10^6/L/ Negative</td>
<td>EM (8 d); PFP (60 d); Symptoms (8 d)</td>
<td>Early disseminated Lyme borreliosis before treatment with antibiotics</td>
</tr>
<tr>
<td>2</td>
<td>70 y F</td>
<td>1999</td>
<td>MCL</td>
<td>Yes (CHOP)</td>
<td>2 m o</td>
<td>Yes</td>
<td>Thorax/7 d</td>
<td>Radicular pain, headache, tiredness, myalgia, insomnia/7 d</td>
<td>EM (60 × 50 cm), enlarged liver and spleen</td>
<td>↑ ESR, leukopenia, CSF pleocytosis: Le 36 (ly 24) × 10^6/L/Negative</td>
<td>EM (7 d); Symptoms (10 d)</td>
<td>In 1999/2000 the patient received 8 cycles of chemotherapy; her death in 2000 (16 mo after the onset of EM) was due to progression of HM.</td>
</tr>
<tr>
<td>3</td>
<td>62 y F</td>
<td>2008</td>
<td>CLL stage IV</td>
<td>5 y Yes (chlorambucil, MP)</td>
<td>39 d</td>
<td>No</td>
<td>Pelvic region and thighs/39 d</td>
<td>Intensive local burning, pains, myalgia, low fever/7 d</td>
<td>EM (90 × 78 cm)</td>
<td>CSF pleocytosis: Le 10 (ly 6) × 10^6/L, ↑ CSF protein concentration (0.52 g/L)/ Serum: IgM neg, IgG pos, CSF: IgM neg, IgG pos, Intrathecal borrelial IgG synthesis: present</td>
<td>EM (4 d); Symptoms (7 d)</td>
<td>Successfully cured of invasive ductal breast cancer in 1996 (7 y before the onset of CLL and 12 y before EM); the patient’s death in 2010 was due to acute myeloid leukemia diagnosed a few months earlier.</td>
</tr>
<tr>
<td>4</td>
<td>65 y M</td>
<td>2013</td>
<td>WM</td>
<td>Yes (bortezomib, rituximab, MP)</td>
<td>8 mo</td>
<td>No</td>
<td>Trunk and extremities/7 d</td>
<td>Myalgia, arthralgia/7 d</td>
<td>↑ ESR, ↑ liver enzymes CSF: normal findings/Serum: IgM neg, IgG pos, CSF: IgM neg, IgG pos, Intrathecal borrelial IgG synthesis: absent</td>
<td>EM (5 d); Symptoms (7 d)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Duration of Signs and Symptoms**: After the onset of treatment with Ceftriaxone.
Table 1 continued.

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Age</th>
<th>Sex</th>
<th>Year of EM</th>
<th>Diagnosis</th>
<th>Duration of HM a</th>
<th>Treatment b</th>
<th>Tick c</th>
<th>EM Location/ Duration d</th>
<th>Main Symptoms Associated With EM</th>
<th>Main Clinical Findings at Initial Visit</th>
<th>Abnormal Laboratory Results/ Borrelia Culture Skin/Blood/CSF</th>
<th>Initial Therapy for EM</th>
<th>Duration of LB Signs and Symptoms e</th>
<th>Reason for Re-treatment</th>
<th>Re-treatment: Antibiotic/time f</th>
<th>Duration of Signs and Symptoms After the Onset of Initial Antibiotic Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>49</td>
<td>y</td>
<td>1992</td>
<td>MCBCL</td>
<td>6 y</td>
<td>No</td>
<td>Yes</td>
<td>Left arm/21 d</td>
<td>Fatigue, myalgia, arthralgia/10 d</td>
<td>EM (25 × 20 cm) No/Negative/ND/ND/ND</td>
<td>AZM 1 g 1st day, 500 mg 2nd-5th day</td>
<td>EM (32 d), Symptoms (6 d)</td>
<td>Severe myalgia, arthralgia, fatigue (onset 6 mo after the initial treatment)</td>
<td>CRO 2 g intravenous, od, 14 d/8 mo</td>
<td>Severe symptoms (2 mo)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>58</td>
<td>y</td>
<td>1995</td>
<td>CLL stage IV</td>
<td>2 wk</td>
<td>No</td>
<td>No</td>
<td>Right leg/14 d</td>
<td>EM (70 × 50 cm), enlarged liver and spleen</td>
<td>↑ ESR, leukocytosis, ↑ liver enzymes/Negative/BA/NEG/ND</td>
<td>AMX 500 mg tid 10 d, AZM g</td>
<td>EM (62 d)</td>
<td>Persistence of EM &gt;2 mo after therapy</td>
<td>AZM 1 g 1st day, 500 mg 2nd-5th day/ 8 wk EM (13 d)</td>
<td>EM (5 d)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>33</td>
<td>M</td>
<td>2006</td>
<td>Hodgkin lymphoma</td>
<td>1 mo</td>
<td>Yes h</td>
<td>Yes h</td>
<td>Back/7 d</td>
<td>EM (9 × 6 cm) Leukopenia, ↑ liver enzymes, CSF: normal/Negative/NEG/Neg/ND</td>
<td>CEF-AX h 500 mg bid 15 d</td>
<td>EM (30 d)</td>
<td>Re-appearance of primary EM (42 d) and occurrence of 2 additional EM (49 d after the initial treatment). Diameters (cm) of EM at re-treatment: 9 × 8; 7 × 4; 3 × 3</td>
<td>CRO 2 g intravenous, od, 14 d/7 wk l</td>
<td>Multiple EM (14 d)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ↑, elevated; AMX, amoxicillin; AZM, azithromycin; Ba, Borrelia afzelii; Bg, Borrelia garinii; CEF-AX, cefuroxime-axetil; CHOP, cyclophosphamide, hydroxydaunorubicin, Oncovin, prednisone; CLL, chronic lymphocytic leukemia; CRO, ceftriaxone; CSF, cerebrospinal fluid; EM, erythema migrans; ESR, erythrocyte sedimentation rate; F, female; HM, hematological malignancy; Ig, immunoglobulin; LB, Lyme borreliosis; Le, leukocytes; Ly, lymphocytes; M, male; MCBCL, marginal zone B-cell lymphoma; MCL, mantle cell lymphoma; MP, methylprednisolone; ND, not done; neg, negative; PFP, peripheral facial palsy; pos, positive; WM, Waldenström’s macroglobulinemia.

a Duration of HM prior to diagnosis of EM.
b Treatment of HM at the time of EM.
c Tick bite at the site of later EM skin lesion.
d Duration of EM (as appreciated by patients) prior to diagnosis.
e Interpretation to be associated with Lyme borreliosis.
f Time from the start of the initial treatment to the onset of retreatment.
g Therapy with AMX was suspended after 10 days because of generalized rash. Treatment was continued with AZM (total dose of 3 g).
h Between the second and third cycle of chemotherapy.
i During treatment with CEF-AX, the patient received the third cycle of chemotherapy.
j In the 7-week period, the patient received 3 cycles of chemotherapy.
A MEDLINE literature search revealed individual case reports on patients with LB and various underlying illnesses associated with immunodeficiency, including a few patients with HM [8–12] and 3 series of patients with EM in immunocompromised hosts [7, 13, 14]. In 2 of the 3 series, patients with HM (7/67 and 9/33, respectively) were also included [7, 13]. However, heterogeneous causes and different levels of immunodeficiency did not enable a reliable assessment of the course and outcome of the LB.

Our study showed that the antibiotic treatment approach as used in immunocompetent patients with EM is effective in patients with underlying HM. The results apply to European regions with similar ratios of *Borrelia* genospecies causing EM, as in Slovenia (80%–90% *B. afzelii*, 5%–15% *B. garinii*, <5% other *Borrelia* species), but may not entirely pertain to North America where LB is caused by *B. burgdorferi* sensu stricto [15].

**Supplementary Data**

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyrighted. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

**Notes**

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**References**


