

# Erythema Migrans: Course and Outcome in Patients Treated With Rituximab

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**Background.** Information on Lyme borreliosis (LB) in patients treated with rituximab is limited to individual case reports.

**Methods.** We reviewed data on adult patients diagnosed with typical erythema migrans (EM) at the LB outpatient clinic of the University Medical Center Ljubljana, Slovenia, in the 10-year period 2008–2017. For all patients, clinical and laboratory information was acquired prospectively using a standardized questionnaire.

**Results.** Among 4230 adult patients with a diagnosis of EM, 7 patients (0.17%), 5 women and 2 men with a median age of 65 years (range, 55–66 years), were receiving rituximab for an underlying medical condition. In these 7 patients, signs of disseminated LB (43%) and the isolation rates of borreliae from blood before antibiotic treatment (40%) were unusually high compared with corresponding findings in immunocompetent patients who had EM diagnosed at the same institution (8% vs <2%, respectively). The rates of LB-associated constitutional symptoms and borrelial antibodies in serum were lower than expected (14% and 29%, respectively, in patients receiving rituximab vs 25% and 65% in immunocompetent patients). One of the 7 patients (14%) experienced treatment failure; nevertheless, the outcome of early LB 1 year after antibiotic treatment, as used for immunocompetent patients with EM, was excellent in all 7 patients.

**Conclusions.** Findings in 7 patients with EM who were receiving rituximab for underlying disease suggest that although early LB in these patients is more often disseminated than in immunocompetent patients, the outcome 1 year after antibiotic treatment, as used for immunocompetent patients, is excellent.

**Keywords.** antibiotic treatment; *Borrelia*; erythema migrans; Lyme borreliosis; rituximab.

Although Lyme borreliosis (LB) has been recognized for >40 years, information on the course and outcome of the disease in certain groups, including immunocompromised patients, remains incomplete. Data on patients with LB treated with biologic therapy, such as rituximab, are very rare and are limited to individual case reports [1–4]. Rituximab is the anti-CD20 monoclonal antibody that influences B cells and consequently impairs secretion of antibodies, antigen presentation, and secretion of cytokines. It was first used in the treatment of non-Hodgkin lymphoma [5, 6] and later approved for the treatment of rheumatoid arthritis that does not respond adequately to conventional treatment or is dependent on high doses of corticosteroids [7]. Rituximab is also used for chronic lymphocytic leukemia, granulomatosis with polyangiitis (Wegener granulomatosis),

and microscopic polyangiitis, as well as for a variety of auto-immune diseases and conditions [8].

Erythema migrans (EM) is the most common manifestation of LB. It appears at the site of inoculation of *Borrelia burgdorferi* sensu lato into the skin by the bite of an infected tick. Borreliae may spread from the skin lesion, giving rise to subsequent manifestations of the early disseminated or late form of the disease [9]. There is a concern that impaired immunity might enhance the likelihood of dissemination and be associated with a different and more severe course of LB. The objectives of the present study were to assess the course and outcome of EM in adult patients treated with rituximab for underlying disease.

## PATIENTS AND METHODS

### Patients

We reviewed data on patients >15 years of age with typical EM diagnosed at the LB outpatient clinic, Department of Infectious Diseases of the University Medical Center Ljubljana, Slovenia, in the 10-year period 2008–2017. For all patients, clinical and laboratory information was acquired prospectively using a standardized questionnaire. The approach used in patients with EM was approved by the Medical Ethics Committee of the Republic of Slovenia (nos. 35/05/09 and 145/45/14). In the present article, we focus on patients who were receiving rituximab for their underlying disease.

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### Clinical Evaluation

A medical history was obtained and physical examination performed at the first visit, before the start of antibiotic therapy. EM was defined as an expanding red or bluish-red plaque, with or without central clearing, developing days to weeks after a tick bite or after exposure to ticks in an LB-endemic region. For a reliable diagnosis, the erythema had to reach >5 cm in diameter. If the diameter was smaller, a history of tick bite, a delay in appearance of  $\geq 2$  days, and expanding erythema at the site of the bite were required. Multiple EM was defined as the presence of  $\geq 2$  erythemas,  $\geq 1$  of which had to fulfill the size criterion for solitary EM [10]. Specific attention was paid to the characteristics of the EM lesion, the presence of associated constitutional symptoms (defined as symptoms that had newly developed or worsened since the onset of EM and which had no other known medical explanation), and other objective manifestations of LB. Patients were reevaluated at 2 weeks, 2 months, 6 months, and 1 year after enrollment.

### Laboratory Evaluation and Microbiologic Analysis

Basic laboratory tests (erythrocyte sedimentation rate, blood cell counts, liver function tests) were performed at baseline and at the 2-week follow-up visit. Patients with evident disseminated LB (multiple EM), and who gave their consent, underwent lumbar puncture for examination of cerebrospinal fluid (CSF).

Serologic tests for *B. burgdorferi* sensu lato were determined at baseline and at the 2-, 6-, and 12-month follow-up visits. Immunoglobulin M antibodies to outer surface protein C and variable membrane protein-like sequence, expressed borrelial antigens and immunoglobulin G antibodies to VlsE were determined using an indirect chemiluminescence immunoassay (LIAISON), according to the manufacturer's recommendations.

A 3-mm punch skin biopsy specimen obtained from the EM border and a whole-blood specimen (9 mL of citrated blood) were cultured for the presence of borreliae in modified Kelly-Pettenkofer medium [11]. In all patients with a positive skin culture result, a skin biopsy was repeated at the site of the previous procedure 2–3 months after the start of antibiotic treatment. Borrelial isolates were identified to the species level using pulsed-field gel electrophoresis after *Mlu*I restriction of genomic DNA or by polymerase chain reaction–based restriction fragment length polymorphism of the intergenic region [11, 12].

### Treatment

Patients receiving rituximab were treated with antibiotics in accordance with the then valid Slovenian treatment recommendations for EM in immunocompetent patients. Thus, patients with solitary EM were prescribed oral antibiotics: doxycycline (100 mg twice daily for 14 days), cefuroxime axetil (500 mg twice daily for 15 days), or azithromycin (500 mg twice daily on the first day followed by 500 mg once daily for 4

subsequent days). Patients with multiple EM were treated with ceftriaxone (2 g once daily intravenously for 14 days).

### Treatment Failure

For this study, treatment failure was defined as (1) the occurrence of objective extracutaneous manifestations of LB within 1 year after the start of antibiotic treatment, (2) the appearance/persistence of subjective symptoms or their increased intensity (at the 1-year follow-up visit) that could not be attributed to other causes, (3) persistence of a skin lesion (ie, still visible EM) at a follow-up visit 2–3 months after commencement of antibiotic treatment, or (4) demonstration of borreliae by skin culture at the site of previous EM 2–3 months after the start of antibiotic treatment (only patients with isolation of borreliae from skin before antibiotic treatment underwent repeated biopsy). Patients with treatment failure were treated again with an alternative antibiotic.

### Complicated Course of LB

Patients with clinical signs of borrelial dissemination (multiple EM, objective extracutaneous manifestations of LB) before treatment with antibiotics or those with treatment failure were interpreted as having a complicated course of LB.

### Statistical Methods

Numerical variables are summarized with medians (and ranges), and categorical variables with frequencies and percentages (with 95% confidence intervals). The number of patients treated with rituximab was too small to enable a reliable statistical comparison with immunocompetent patients who had EM diagnosed, and we therefore show the main findings in the group of immunocompromised patients and contrast them with published findings in a series encompassing >100 immunocompetent patients >15 years of age with EM diagnosed at our clinic during the same time period.

## RESULTS

Of 4230 adult patients diagnosed with typical EM at our LB outpatient clinic in the 10-year period, 7 (0.17%) were receiving rituximab: 3 had non-Hodgkin lymphoma, 2 had rheumatoid arthritis, 1 had anti-myelin-associated glycoprotein peripheral neuropathy, and 1 had neuromyelitis optica. Our patients were receiving rituximab for a median of 13 months (range, 3–24 months) before the diagnosis of EM; in all but 1 patient the drug was continued for  $\geq 1$  year after diagnosis and antibiotic treatment of EM.

The median dose of rituximab was 1000 mg (range, 500–1400 mg); it was given at a median of every 14 (4–24) weeks, and the last application was 6 (3–14) weeks before the diagnosis of EM. In 4 patients, rituximab was combined with another immunosuppressive drug: in 2 patients with corticosteroids, in 1 with methotrexate and corticosteroids, and in the fourth patient

**Table 1. Clinical and Epidemiologic Data in 7 Patients with Solitary Erythema Migrans During Rituximab Treatment for Underlying Disease**

Patient No./Age, /Sex	Underlying Diseases	Treatment with IC Drugs in Addition to Rituximab <sup>b</sup>	Tick bite/ Incubation, d/Duration of EM, d <sup>c</sup>	No. of EM/Size, cm/Appearance/ Other Findings	Local/ Constitutional Symptoms <sup>d</sup>	Antibiotic Regimen	EM After Therapy, d <sup>e</sup>	Laboratory Results/Antibodies to Borreliae (IgM/IgG)	Isolation of Borreliae from Skin/Blood/CSF
1/65/F	RA/15 y; 1 y/AH	Methotrexate + methylprednisolone	Yes/27/4	3/22 x 17/ homogeneous/ slight swelling of small joints in hands and feet	Itching, burning/ none	Ceftriaxone 2 g intravenously once daily for 14 d	4	Elevated liver enzymes, lymphopenia/serum: neg/neg; CSF: ND	<i>Borrelia burgdorferi</i> sensu stricto M1b8/B. burgdorferi sensu stricto M1b8/ND
2/65/M	NHL/8 mo; 8 mo/ DS	Bortezomib + methylprednisolone	No/NK/7	16/44 x 16/ Homogenous/ none	None/myalgia, arthralgia	Ceftriaxone 2 g intravenously once daily for 14 d	5	Elevated ESR and liver enzymes, lymphopenia, decreased serum IgA and serum IgG; CSF: normal findings/serum: neg/pos; CSF: neg/pos; intrathecal borrelial IgG synthesis: absent	<i>Borrelia afzelii</i> M1a1/neg/neg
3/65/M	AMPN/1 y; 3 mo/ none	None	Yes/31/5	1/15 x 10/ringlike/ none	None/none	Azithromycin 1 g on d 1, 500 mg d 2–d 5	12	Lymphopenia/serum: neg/neg; CSF: ND	ND/neg/ND
4/55/F	RA/25 y; 6 mo/HT	None	Yes/14/68	1/15 x 13/ homogenous/ none	Burning/none	Cefuroxime axetil 500 mg twice daily for 15 d	28	Lymphopenia/serum: neg/neg; CSF: ND	<i>B. afzelii</i> M1a1/neg/ND
5/57/F	NHL/1 y; 1 y/AH	Methylprednisolone	No/NK/7	12/16 x 6/ Homogenous/ none	Itching/none	Ceftriaxone 2 g intravenously once daily for 14 d	5	Elevated ESR and liver enzymes, lymphopenia, decreased serum IgM and serum IgA; CSF: Leukocytes 28 (ly 10, mo11, neutro 7) x 10 <sup>6</sup> /L; protein (0.50 g/L)/serum: neg/pos; CSF: neg/neg; intrathecal borrelial IgG synthesis: absent	<i>B. afzelii</i> M1a1/B. afzelii M1a1/neg
6/65/F	NMO/7 y; 1 y/none	Methylprednisolone	Yes/7/7	1/6 x 6/ Homogenous/ none	None/none	Doxycycline 100 mg twice daily for 10 d, and amoxicillin <sup>f</sup> 500 mg thrice daily for 15 d	72 (12 <sup>g</sup> )	Normal/serum: neg/neg; CSF: ND	ND/ND/ND
7/68/F	NHL/2 y; 2 y/AH	None	Yes/65/10	1/17 x 12/ Homogenous/ none	None/none	Doxycycline 100 mg twice daily for 14 d	18	Leukopenia/serum: neg/neg; CSF: ND	Neg/neg/ND

Abbreviations: AH, arterial hypertension; AMPN, anti-myelin-associated glycoprotein peripheral neuropathy; CSF, cerebrospinal fluid; DS, depressive syndrome; EM, erythema migrans; ESR, erythrocyte sedimentation rate; F, female; HT, hypothyroidism; IC, immunocompromising; M, male; NHL, non-Hodgkin lymphoma; ND, not done; neg, negative; NK, not known; NMO, neuromyelitis optica; pos, positive; RA, rheumatoid arthritis.

<sup>a</sup>Duration of underlying disease before EM diagnosis; duration of treatment with rituximab before EM diagnosis.

<sup>b</sup>Treatment of underlying disease at the time of EM.

<sup>c</sup>Incubation was defined as duration from tick bite to the onset of EM (as reported by patient); only tick bites at the site of later EM qualified. Duration of EM was defined as days from the reported onset of EM to diagnosis and the initiation of antibiotic treatment.

<sup>d</sup>Local symptoms were those at the site of the EM skin lesion. Symptoms that had newly developed or worsened since the onset of the EM and which had no other known medical explanation were regarded as Lyme borreliosis (LB)-associated constitutional symptoms at enrollment or post-LB symptoms at follow-up.

<sup>e</sup>Time from institution of the initial antibiotic treatment to complete resolution of EM, except where noted (patient 6).

<sup>f</sup>Retreatment because of persistence of EM for >2 months after therapy.

<sup>g</sup>Time from institution of the second antibiotic treatment to complete resolution of EM.

**Table 2. Demographic, Clinical, Laboratory, and Microbiologic Data in 7 Patients With Erythema Migrans (EM) Receiving Rituximab and in Nonimmunocompromised Patients with EM**

Characteristic or Finding/Outcome	Patients Receiving Rituximab, No. (%; 95% CI) <sup>a</sup> (n = 7)	Immunocompetent Patients <sup>b</sup> (n = 118–1109) [14–17]	
		Published Findings, Range	References
<b>Pretreatment demographic and clinical characteristics</b>			
Age, median (range), y	65 (55–66)	51–53	14–17
Male sex	2 (28.6; 3.7–71.0)	40.7%–44.7%	14–17
History of prior LB	4 (57.1; 18.4–90.1)	8.1%–15.5%	14, 17
Incubation, median (range), d <sup>c</sup>	27 (7–65)	16	14, 15
Duration of EM to diagnosis, median (range), d	7 (4–68)	7–13	14–17
Signs of disseminated early LB <sup>d</sup>	3 (42.9; 9.9–81.6)	3.6%–11.6%	14, 15
Homogenous EM	5 (71.4; 29.0–26.3)	39.1%–56.8%	14–17
Largest diameter of EM, cm	16 (6–44)	13–15	14–17
Local symptoms	3 (42.9; 9.9–81.6)	39.0%–51.9%	1, 15
Itching	1 (14.3; 0.4–57.9)	...	...
Burning	1 (14.3; 0.4–57.9)	...	...
Pain	2 (28.6; 3.7–71.0)	...	...
Constitutional symptoms <sup>e</sup>	1 (14.3; 0.4–57.9)	23.7%–29.1%	14–17
<b>Microbiologic findings</b>			
Borrelial serum IgM and/or IgG antibodies <sup>f</sup>	2 (28.6; 3.7–71.0)	62.7%–68.6%	14, 16, 17
Isolation of borreliae from skin	4 <sup>g</sup> (80; 28.4–99.5)	55.1%–62.8%	14–17
Isolation of borreliae from blood	2 <sup>h</sup> (40; 5.4–85.3)	1.9%	Unpublished data, LBOC 2008–2017
<b>Course and outcome of LB after treatment with antibiotics</b>			
Duration of EM, median (range), d <sup>i</sup>	12 (4–72)	7–10	14, 17, 18
Treatment failure <sup>j</sup>	1 <sup>k</sup> (14.3; 0.4–57.9)	7.5%–12.4%	14, 16, 17
Complicated course of LB <sup>l</sup>	4 <sup>m</sup> (57.1; 18.4–90.1)	NA	
Unfavorable outcome <sup>n</sup>	0 (0; 0–41.0)	6.3%–10.5%	14, 16, 17

Abbreviations: CI, confidence interval. EM, erythema migrans; IgA, IgG, and IgM, immunoglobulin A, G, and M; LB, Lyme borreliosis; LBOC, LB outpatient clinic; NA, not available.

<sup>a</sup>For patients receiving rituximab, data represent no. (%;95% CI) unless otherwise specified.

<sup>b</sup>Patients with EM diagnosed at the same LBOC and in the same time period as the patients treated with rituximab. Published findings are given as ranges of reported medians or percentages.

<sup>c</sup>Incubation data for patients who recalled a tick bite at the site of a later skin lesion (2 of the 7 patients receiving rituximab, 33% of the immunocompetent patients with multiple EM, and 54% of the immunocompetent patients with solitary EM [15, 18]).

<sup>d</sup>Three of the 7 patients treated with rituximab had multiple EM; 1 of them also had cerebrospinal fluid pleocytosis.

<sup>e</sup>Constitutional symptoms included fatigue, headache, arthralgia, myalgia, and dizziness.

<sup>f</sup>Presence of borrelial IgM and/or IgG antibodies in serum at the initial examination using protein C or VlsE as antigen; none of the patients receiving rituximab seroconverted during a 1-year follow-up.

<sup>g</sup>Skin cultures were performed in 5 patients, with positive results in 4; 3 isolates were identified as *Borrelia afzelii* and 1 as *Borrelia burgdorferi* sensu stricto.

<sup>h</sup>Blood cultures were performed in 5 patients, with positive results in 2; 1 isolate was identified as *B. afzelii* and 1 *B. burgdorferi* sensu stricto.

<sup>i</sup>Duration from the start of antibiotic treatment.

<sup>j</sup>Treatment failure was defined as the occurrence of objective extracutaneous manifestations of LB within 1 year after the start of antibiotic treatment, persistence of subjective symptoms or their increased intensity (at the 12-month follow-up visit) that could not be attributed to other causes, persistence of skin lesions at a follow-up visit 2–3 months after the start of antibiotic treatment, and/or demonstration of borreliae at the site of previous EM by skin culture 2–3 months after the start of antibiotic treatment.

<sup>k</sup>In this patient, treatment failure was defined as the persistence of EM 2.5 months after the start of doxycycline treatment.

<sup>l</sup>A complicated course was defined as the presence of clinical signs of borrelial dissemination and/or treatment failure.

<sup>m</sup>Three patients had multiple EM, and 1 had treatment failure (persistence of EM 2.5 months after the start of antibiotic treatment).

<sup>n</sup>Unfavorable outcome of LB 12 months after the start of antibiotic treatment.

with bortezomid and corticosteroids. One patient (patient 2 in Table 1) was included in a previous report on patients with hematologic cancer [13]. The group comprised 5 women and 2 men with a median age of 65 years (range, 55–66 years). Four patients (57%) had solitary EM, and 3 (43%) had multiple EM with a median of 12 skin lesions (range, 3–16) (Table 1).

In Table 2, basic demographic data and pretreatment clinical characteristics of early LB in the immunocompromised patients receiving rituximab are compared with published

findings for immunocompetent patients with EM diagnosed at our clinic in the same time period. The comparison suggests that immunocompromised patients treated with rituximab are more likely than anticipated to report having had prior LB, have a higher proportion of multiple EM and more skin lesions, have LB-associated constitutional symptoms unexpectedly rarely, are less often seropositive, and are more likely than those with normal immunity to have a positive result for borrelial blood culture.

Patients with solitary EM were treated with doxycycline (2 patients), cefuroxime axetil (1 patient), or azithromycin (1 patient). Patients with multiple EM received ceftriaxone (3 patients).

The course and outcome of the early LB were favorable. EM disappeared a median of 12 days (range, 4–72 days) after the beginning of antibiotic treatment. Treatment failure was documented in 1 of 7 patients (14%), a 65-year-old woman with solitary EM (patient 6 in Table 1); her skin lesion persisted for >2 months after the start of treatment with doxycycline; however, it disappeared after retreatment with amoxicillin and the subsequent clinical course was uneventful. Thus, a complicated course was found in 4 of 7 patients (57%) with impaired immunity who were receiving rituximab: 3 presented with multiple EM (1 also had CSF pleocytosis), and 1 had treatment failure (patients 1, 2, 5, and 6 in Table 1). At the examination 1 year after enrollment no (objective) findings that could be potentially associated with LB were documented in any of the 7 patients.

## DISCUSSION

Although the number of immunocompromised patients in past decades has increased substantially, information on the course and outcome of LB in this group of patients remains limited, particularly for those receiving biologic therapy such as rituximab. This biologic agent rapidly depletes CD20<sup>+</sup> B lymphocytes, directly influencing (auto)antibody production and indirectly impairing cellular immunity. CD20<sup>+</sup> B cells play an important role in maintaining a normal immune response; therefore, their depletion may lead to increased risk of infections, including serious bacterial infections (eg, sepsis and pneumonia), viral infections (eg, hepatitis B, cytomegalovirus, and varicella zoster), and fungal infections.

The increased incidence of infection in immunocompromised patients receiving rituximab has been reported in several but not in all studies; it seems that the increase is rather moderate [8, 19–22]. Relapses and treatment failures have also been described in some tick-borne diseases, such as babesiosis [23], but no corresponding clinical information has been available for infection with *B. burgdorferi* sensu lato; nevertheless, it is recognized that B cells are critical for control of the infection [24].

According to a PubMed literature search, only 4 reports have been published on patients in whom LB developed during treatment with rituximab. These comprise individual case reports, and in all 4 cases CSF pleocytosis was present. The diagnosis of Lyme neuroborreliosis was based on demonstration of borrelial antibodies in CSF in 1 patient [3] and the presence of borrelial DNA in CSF in the other 3 patients, using polymerase chain reaction [1, 2, 4]. It is of interest that *B. burgdorferi* sensu lato antibodies in serum were not detected in any of these 4 patients.

Herein we present findings in 7 patients with early LB (EM) who were receiving rituximab for an underlying hematologic,

rheumatic, or neurologic disease. These 7 patients represent 0.17% of the patients with EM diagnosed at our clinic. Physicians of different specialties who treat patients with immune defects, particularly physicians with a narrow professional orientation, may have limited knowledge of LB, and the small number of patients in our series and rare descriptions in the literature are probably not only a reflection of the small number of cases but may also reflect poor recognition of LB.

The number of patients in our series is too small to enable reliable statistical comparison with immunocompetent patients with a diagnosis of EM; therefore, we simply present the main findings in the immunocompromised patients and compare them with already published information in immunocompetent patients with EM diagnosed at our clinic during the same time period.

Several parameters, such as the duration of EM before diagnosis, the diameter of the skin lesion, and symptoms at the lesion site, were found to be similar to those reported for patients with EM without known immunosuppression. However, several findings suggested distinctions (Table 2), the majority of them not a surprise.

The median age of patients receiving rituximab was higher than that of the immunocompetent patients, which probably reflects the occurrence of the underlying illnesses at an older age. The chances of infection with *B. burgdorferi* sensu lato increase with increasing age, and older age might also be an explanation for the finding that immunocompromised patients treated with rituximab often reported having had prior LB. Laboratory abnormalities, such as elevated liver enzyme levels, lymphopenia, and lower levels of serum immunoglobulins, are probably associated with underlying illness and treatment with rituximab and other immunosuppressive drugs. Immune deficiency is a potential explanation also for several other differences.

When the patients receiving rituximab were compared with immunocompetent patients, those with impaired immune response resulting from rituximab treatment or from underlying illness showed a relatively high proportion with multiple EM and more numerous skin lesions, a high rate of isolation borreliae from skin, and more often a positive result for borrelial blood culture, as well as less frequent presence of borrelial antibodies in serum. A similar explanation may also be valid for the lower proportion of patients with LB-associated constitutional symptoms; namely, as *B. burgdorferi* sensu lato does not produce toxins or extracellular matrix-degrading proteases, most manifestations of human LB result from inflammation generated by host immune responses [24], so altered immune response may influence the severity and mode of clinical presentation.

Impaired immunity might be an explanation for the complicated course of LB (signs of disseminated LB or unfavorable outcome after antibiotic treatment) present in 57% of our patients



but rarely seen in immunocompetent adult patients with EM, of whom only about 8% have disseminated disease [15] and approximately 10% have treatment failure, most often the presence of LB-associated symptoms [14, 16, 17]. Nevertheless, the duration of EM after the start of antibiotic treatment in patients receiving rituximab was similar to that in the immunocompetent group, and the outcome of LB 1 year after antibiotic treatment was excellent in all patients.

Our study has several limitations. Our study is descriptive and the number of immunocompromised patients is too small to enable reliable statistical comparison with immunocompetent patients with EM. In addition, the patients had heterogeneous underlying illnesses, and in several patients rituximab was combined with other immunosuppressive drugs, making it more difficult to interpret the effects of rituximab. Moreover, because this is the only series of patients with early LB and concomitant rituximab treatment, we were not in a position to compare our findings with previously published data. Nevertheless, our results are probably applicable to European regions with similar ratios of borrelial genospecies causing EM but may not entirely apply to North America, where LB is nearly exclusively caused by *B. burgdorferi* sensu stricto [25].

In conclusion, in the 7 immunocompromised patients receiving rituximab to treat underlying illness, signs of disseminated LB (43%) and the isolation rate of borreliae from blood before antibiotic treatment (40%) were unusually high compared with corresponding findings in immunocompetent adult patients with EM diagnosed at the same institution (3%–8% vs about 1%, respectively). However, the outcome of early LB 1 year after antibiotic treatment, using a similar treatment approach as in immunocompetent patients with EM, was excellent.

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