Erythema Migrans in Solid-Organ Transplant Recipients

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Six adult solid-organ transplant recipients who had chronic drug-induced immunosuppression and who presented with solitary erythema migrans were treated with antibiotics administered at the same dosage and for the same duration used for the treatment of early, localized Lyme borreliosis in immunocompetent patients. The patients had a smooth course of illness and a favorable outcome but did not develop a measurable borrelial serum antibody response.

Lyme borreliosis (LB) is caused by Borrelia burgdorferi sensu lato. The typical manifestation of the illness is the skin lesion erythema migrans (EM), which develops within days to weeks after an infected tick has bitten an individual. Borreliae may disseminate from the skin lesion, leading to subsequent skin, neurological, joint, cardiac, or other manifestations [1]. Although LB has been recognized for >30 years, knowledge of the course and outcome of the illness in certain groups, including immunocompromised patients, is limited.

In Slovenia, a small central European country with a population of ~2 million, LB has been reportable since 1986. In the past few years, the incidence of LB exceeded 150 cases/100,000 individuals; >80% of patients with LB were diagnosed with EM [2]. Because a substantial number of Slovenian patients with LB have been referred to and examined at the Lyme Borreliosis Outpatients’ Clinic of the Department of Infectious Diseases at our institution (University Medical Centre Ljubljana, Ljubljana, Slovenia), we had the opportunity to create a prospectively acquired database of information on patients with LB. Recently published information on the first case of LB in a transplant recipient in the United States [3] was a stimulus for us to review our records for patients with EM to identify patients who had chronic drug-induced immunosuppression after undergoing solid-organ transplantation.

Patients and methods. We reviewed data for adult patients with typical EM that was diagnosed at the Lyme Borreliosis Outpatients’ Clinic from 1993 through 2003. We also analyzed data on transplant recipients treated with immunosuppressive drugs.

We have been using a single approach for patients with EM for nearly 20 years, including the period from 1993 to 2003. The approach was approved by the Medical Ethics Committee at the Ministry of Health of the Republic of Slovenia. The diagnosis of EM is made clinically, on the basis of slightly modified criteria of the Centers for Disease Control and Prevention [4]. Clinical and laboratory data are acquired prospectively by means of standardized questionnaire. At the time of a patient’s initial visit to our institution, a medical history is obtained, a physical examination is performed, and basic laboratory tests (liver function tests and determinations of the erythrocyte sedimentation rate and blood cell counts) are done. The presence of serum antibodies against B. burgdorferi sensu lato is determined (in the time period of the present study, an immunofluorescence assay was used; serum antibody titer of \( \geq 1:256 \) were considered to denote a positive finding) [5]. For the majority of patients not previously treated with antibiotics, biopsy of a skin specimen is proposed. A skin biopsy specimen obtained from the border of the EM and a 5-mL whole-blood specimen are obtained and cultured for the presence of borreliae in modified Kelly-Pettenkofer medium, as described elsewhere [6]. Isolated strains are typed using PCR or PFGE [6]. Patients are followed up clinically and serologically for 1 year. As a rule, patients are examined 2 weeks, 2 months, 6 months, and 12 months after their first visit to our institution. In addition, 2–3 months after the initial examination (after initiation of antibiotic treatment), patients with positive skin culture results have biopsy repeated using skin specimens obtained from the vicinity of the site where specimens were obtained for the previous procedure, with the aim of assessing the potential persistence of B. burgdorferi sensu lato in skin.

Results. Six (0.1%) of 7208 adult patients who had typical EM diagnosed at our institution during 1993–2003 were receiving immunosuppressive treatment (a combination of methylprednisolone and either cyclosporine or azathioprine) for solid-organ transplantation. Four patients underwent kidney transplantation, and 2 patients underwent liver transplantation. Table 1 presents data on the basic demographic characteristics.
Table 1. Clinical and epidemiological data for 6 solid-organ transplant recipients with erythema migrans (EM).

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age in years, sex</th>
<th>Presence of tick bite</th>
<th>Time from tick bite to EM, days</th>
<th>Duration of EM, days</th>
<th>Maximal diameter of EM, cm</th>
<th>Symptom(s) present</th>
<th>Skin culture result</th>
<th>Therapy received</th>
<th>Duration of EM, days</th>
<th>Transplanted organ (time span)</th>
<th>Immunosuppressive therapy (daily dosage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>47, M</td>
<td>Yes</td>
<td>90</td>
<td>33</td>
<td>60 × 50</td>
<td>No, No</td>
<td>+</td>
<td>Azm</td>
<td>3</td>
<td>Kidney (3 years)</td>
<td>Cysp (60 mg + 60 mg) and MP (8 mg)</td>
</tr>
<tr>
<td>2</td>
<td>46, M</td>
<td>No</td>
<td>NA^g</td>
<td>2</td>
<td>8 × 8</td>
<td>No, No</td>
<td>+</td>
<td>Amox</td>
<td>5</td>
<td>Kidney (12 years)</td>
<td>Cysp (50 mg + 75 mg) and MP (10 mg)</td>
</tr>
<tr>
<td>3</td>
<td>63, F</td>
<td>Yes</td>
<td>23</td>
<td>7</td>
<td>8 × 7</td>
<td>Yes, No</td>
<td>+</td>
<td>Azm</td>
<td>90^h</td>
<td>Kidney (23 years)</td>
<td>Aza (50 mg + 25 mg) and MP (12 mg)</td>
</tr>
<tr>
<td>4</td>
<td>56, M</td>
<td>Yes</td>
<td>3</td>
<td>4</td>
<td>10 × 6</td>
<td>No, No</td>
<td>−</td>
<td>Ctri</td>
<td>7</td>
<td>Liver (1 year)</td>
<td>Cysp (50 mg + 75 mg) and MP (4 mg)</td>
</tr>
<tr>
<td>5</td>
<td>52, F</td>
<td>Yes</td>
<td>4</td>
<td>16</td>
<td>13 × 8</td>
<td>Yes, No</td>
<td>−</td>
<td>Azm</td>
<td>14</td>
<td>Liver (6 months)</td>
<td>Cysp (75 mg + 75 mg) and MP (4 mg)</td>
</tr>
<tr>
<td>6</td>
<td>54, M</td>
<td>Yes</td>
<td>14</td>
<td>5</td>
<td>9 × 6</td>
<td>No, No</td>
<td>+</td>
<td>Cxm</td>
<td>5</td>
<td>Kidney (5 years)</td>
<td>Cysp (75 mg + 50 mg) and MP (6 mg)</td>
</tr>
</tbody>
</table>

NOTE. Amox, amoxicillin; Aza, azathioprine; Azm, azithromycin; Ctri, ceftriaxone; Cxm, cefuroxime axetil; Cysp, cyclosporine; MP, methylprednisolone; o.d., once daily.

^a Tick bite noted at the site where EM later developed.
^b No. of days from the time that the tick bite occurred to the onset of EM (as indicated by the patient).
^c No. of days from the onset of EM (as indicated by the patient) to diagnosis and initiation of antibiotic treatment.
^d No. of days from the initiation of antibiotic treatment to complete resolution of EM.
^e The time from transplantation to enrollment in the study.
^f For *Borrelia afzelii*.
^g No tick bite was recalled by the patient, so no data are available.
^h The lesion faded substantially after 3 weeks of treatment but disappeared completely only after 3 months.
^i For *Borrelia garinii*.
of these 6 patients and the clinical characteristics of their cases of borrelial infection. All patients had solitary EM, the maximum diameter of which was 9 cm (range, 8–60 cm). They were referred to our Lyme Borreliosis Outpatients’ Clinic a median of 6 days (range, 2–33 days) after they appreciated skin lesions. None of the patients had systemic symptoms, and only 2 reported mild local itching. With the exception of a slightly elevated erythrocyte sedimentation rate noted in 2 patients, the results of all laboratory tests were within the range considered to be normal. At the initial examination, all 6 patients had negative results of immunofluorescence assay performed for the detection of serum antibodies against B. burgdorferi sensu lato, and the patients continued to have negative immunofluorescence assay results during the entire period of observation. For 4 of 6 patients, cultures of skin lesion biopsy specimens were positive for Borrelia organisms, whereas, for 5 of 5 patients, blood cultures remained negative for Borrelia organisms. For immunocompetent patients with solitary EM, the corresponding isolation rates during this period were 56% for skin specimens and 1.2% for blood samples.

Three patients were treated with azithromycin, 1 received amoxicillin, 1 was given cefuroxime axetil, and 1 received ceftriaxone (table 1). No significant adverse effects of therapy were noted. The median time to complete resolution of skin lesions after initiation of antibiotic treatment was 6 days (range, 3–90 days). The clinical course was smooth. None of the 6 patients developed any clinical sign or symptom that indicated progression of the illness during 1 year of follow-up, and all patients remained Borrelia seronegative. In addition, none of the 4 patients who had positive skin culture results and who had successive skin biopsies performed 2–3 months after the initiation of antibiotic treatment had borreliae recovered from skin specimens.

Discussion. Successful transplantations of various organs enable prolonged and higher-quality life for several patients with end-stage organ failure but are somehow compromised by chronic immunodeficiency due to the immunosuppressive agents that are prescribed to prevent rejection of the transplanted organs. As a rule, cytotoxic drugs and corticosteroids are used, influencing both humoral and cellular immunity [7].

Immunocompromised patients have bacterial infections that are, in general, more frequent and more severe than bacterial infections in persons who have normal immune function. Knowledge of the behavior of borrelial infection in immunocompromised persons, including transplant recipients, is very limited. In Europe, 2 single cases of LB in transplant recipients have been reported: neurologic manifestation of LB developed in one patient 7 years after kidney transplantation was performed, and Lyme carditis developed in another patient 11 years after heart transplantation was performed [8, 9]. In addition, a study comparing the course and the outcome of EM in immunocompromised and immunocompetent patients in Europe has been published [10]; of the 67 immunocompromised patients who were included in the study, only 1 was receiving immunosuppressive treatment as a result of transplantation. However, this patient (known as “patient 1” in the present report) was only mentioned in one of the tables in the original article and was not described in any detail [10]. Recently, the development of Lyme meningoradiculitis and myositis after allogeneic hematopoietic stem cell transplantation was reported in a patient in the United States [3].

In the present report, we described the course and outcome of LB in 6 solid-organ transplant recipients who had chronic drug-induced immunosuppression and who had EM diagnosed at the Department of Infectious Diseases at our institution during an 11-year period. There was no surprise concerning the etiology of EM: of 4 skin culture–positive patients, 3 were infected with Borrelia afzelii, the most common species causing skin manifestation of LB in Europe [1, 6]. All 6 patients had solitary skin lesions with basic clinical characteristics comparable to those of the skin lesions of our immunocompetent patients [11]. In contrast to presumptions of a more severe and complicated course of LB occurring in organ transplant recipients, the findings were reassuring. No clinical signs or symptoms suggesting Borrelia dissemination were present or were reported either during the initial course of the illness or during the 1-year follow-up period after antibiotic treatment, the duration of EM after initiation of antibiotic treatment was short (median duration, 6 days), persistence of Borrelia organisms in the skin after treatment was not established, and additional antibiotic treatment was not needed. This smooth course of illness and favorable outcome were achieved using oral antibiotic treatment (for all but 1 patient) administered at the same dosage and for the same duration usually used for immunocompetent patients in Slovenia. For our organ transplant recipients, the choice of antibiotic for the treatment of EM was not the consequence of an analytic approach but, rather, of the fact that several patients were included in different studies of EM treatment performed during 1993 and 2003; however, the choice of antibiotic was based on the assumption that patients with transplanted organs and immunocompetent patients with solitary EM could be treated similarly.

It is of interest that, in all 6 transplant recipients, serum antibodies to B. burgdorferi sensu lato were absent not only at first examination but, also, throughout the 1-year follow-up period, indicating limited diagnostic value of serological testing for this and similar groups of patients. Nevertheless, negative serological findings are not uncommon, even in immunocompetent European patients with EM [1, 12].

Conclusions. Our solid-organ transplant recipients who had chronic drug-induced immunosuppression and who presented with solitary EM seemed to have only localized infection
of the skin, even though they were immunosuppressed. All patients had a mild and smooth course of illness, as well as a favorable outcome of the illness after treatment with antibiotics administered at the same dosage and for the same duration used for the treatment of EM in immunocompetent patients. We would like to stress that the number of patients in the present study is too small to enable safe and valid generalization of the findings. Potential application of the observations might have been appropriate for European patients with solitary EM caused by *B. afzelii*, but the observations may not apply to US patients with *B. burgdorferi* infection (localized infection of the skin is more commonly associated with *B. afzelii* infection in Europe than with *B. burgdorferi* infection in the United States [12]) or to patients in whom *Borrelia* causes disseminated infection.

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**References**