Prospective Clinical Evaluation of Patients from Missouri and New York with Erythema Migrans–Like Skin Lesions

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Background. The most common and most recognizable feature of *Borrelia burgdorferi* infection (Lyme disease) is the skin lesion erythema migrans (EM). An illness associated with an EM-like skin lesion, but which is not caused by *B. burgdorferi*, occurs in many southern states in the United States (southern tick–associated rash illness [STARI], also known as Masters disease).

Methods. Clinical features of 21 cases of EM-like skin lesions in 21 patients from Missouri were compared in a prospective study with those of 101 cases in 97 patients with EM-like skin lesions from New York.

Results. Among Missouri cases, the peak incidence of EM-like skin lesions occurred earlier in the year than it did among New York cases (P < .001). Case patients from Missouri were more likely to recall a tick bite than were New York case patients (85.7% and 19.8%, respectively; P < .001), and the time period from tick bite to onset of the skin lesion was shorter among Missouri case patients (6.1 ± 4.2 days and 10.4 ± 6.1 days, respectively; P = .01). Missouri case patients were less likely to be symptomatic than were New York case patients (19.0% and 76.2%, respectively; P < .011), and Missouri case patients were less likely to have multiple skin lesions (4.8% and 26.7%, respectively; P < .001). EM-like lesions in Missouri cases were smaller in size than those in New York cases (8.3 ± 2.2 cm and 16.4 ± 11.5 cm, respectively; P < .001), more circular in shape (P = .004), and more likely to have central clearing (76.2% and 21.6%, respectively; P < .001). After antibiotic treatment, Missouri case patients recovered more rapidly than did New York case patients (P < .037).

Conclusion. Cases of EM-like skin lesion in patients from Missouri and New York have distinct clinical presentations.

Lyme disease is the most prevalent tickborne disease in the United States [1]. The etiologic agent, *Borrelia burgdorferi*, is transmitted by *Ixodes* species ticks. The most common and most recognizable clinical feature is an annular erythematous skin lesion termed erythema migrans (EM). Cases of Lyme disease are predominantly reported from the Mid-Atlantic, Northeast, Midwest, and far West regions of the United States [1, 2].

Patients from the Southeast and South-Central United States may also develop an EM-like skin lesion [3–6]. Unlike patients with EM in other geographic locations, *B. burgdorferi* cannot be recovered from cultures of skin biopsy specimens obtained from such patients, and results of acute-phase and convalescent-phase serologic assays for antibodies to *B. burgdorferi* are almost always negative [3–5]. In addition, *Ixodes scapularis* ticks in the southern United States are rarely infected with *B. burgdorferi* (usually <0.5%) and infrequently bite humans [7–9]. Therefore, this rash illness is not Lyme disease and is preferably referred to as “southern tick–associated rash illness” (STARI) or as Masters disease.

Another hard tick, *Amblyomma americanum*, is found throughout the Southeast and South-Central
United States and is the most common tick parasitizing humans in these regions [4, 7, 10]. EM-like skin lesions in the South (as well as in New Jersey [11] and Maryland [12]) have followed the bite of this tick species [3–6]. This tick species has been shown experimentally not to be a competent vector for B. burgdorferi [13–16]. Approximately 2% of A. americanum ticks are infected with a spirochete different from both B. burgdorferi and the other Borrelia genospecies recognized as causes of Lyme disease in Eurasia [11, 17–21]. Barbour et al. [17] proposed the name B. lonestari species novum. This borrelial species appears to be closely related to B. theileri, the cause of bovine borreliosis [22].

B. lonestari has been associated with a single case of STARI [23]. A 74-year-old patient with a history of renal cell and prostatic carcinomas developed an EM-like lesion following the bite of an A. americanum tick during a trip to Maryland and North Carolina. By PCR amplification techniques, both the tick and the patient were found to be infected with B. lonestari or a closely related bacterium. The general significance of this observation is questionable, however, because extensive microbiologic testing of 30 patients with EM-like lesions from Missouri (who included the 21 patients in this report) failed to demonstrate any evidence of B. lonestari (or B. burgdorferi) infection [24], suggesting that there may be more than a single etiology for this condition.

In patients with EM-like lesions, differentiation of STARI from Lyme disease has important implications regarding diagnostic approach, case reporting, case management, and prevention strategies. For example, because STARI is not caused by B. burgdorferi [3–5, 24], serologic testing for antibodies to B. burgdorferi does not help to diagnose this condition. Although patients with STARI appear to improve coincident with the same antibiotic regimens commonly used to treat patients with Lyme disease [25], resolution of STARI has also occurred without antibiotic treatment [24, 26]. In contrast to Lyme disease [25], controlled treatment trials of patients with STARI are lacking.

In this article, we report the findings from a clinical evaluation of 21 patients with EM-like skin lesions from Missouri and compare these results with those for 101 cases of EM-like skin lesions in 97 patients from New York who were similarly evaluated during the same time period.

**EXPERIMENTAL DESIGN AND METHODS**

**Patient population.** Consecutive, untreated, consenting patients with potential tick exposures and annular erythematous skin lesions with a largest diameter of ≥5 cm were enrolled into this prospective study. This case definition is consistent with the surveillance case definition for Lyme disease provided by the Centers for Disease Control and Prevention (CDC) [27]. Three patients who had slightly smaller skin lesions with a largest diameter of at least 4 cm were also enrolled on the basis of the appearance of the lesions and the patients’ clinical histories. All 3 of these patients had reported a preceding tick bite at the lesion site. One of the 3 patients was from Missouri, and the other 2 patients were from New York. A culture of a skin biopsy specimen obtained from 1 of the 2 patients from New York grew B. burgdorferi.

The source of patient-referral for the Missouri patients with EM-like skin lesions was the office practice of Dr. Edwin Masters (Cape Girardeau, MO). Comparison cases consisted of adult patients with EM-like skin lesions enrolled at the Lyme Disease Practice of the Westchester Medical Center (Valhalla, NY). All patients at both sites were evaluated with the same data-collection instrument between the years 2001 and 2003, and all were treated for suspected Lyme disease with conventional antibiotic regimens (such as doxycycline for 14–21 days) at the baseline visit. Signs and symptoms were recorded as being present or absent. Defined symptoms were characterized by the patient with respect to severity by means of an 8-cm–long visual analogue scale [28].

**Patient research plan.** After obtaining written informed consent, a complete history was obtained, a physical examination was performed, and blood samples were obtained for determination of complete blood cell counts, erythrocyte sedimentation rates, and serum chemistries. A photograph of the skin lesion was taken. Patients were evaluated at the following time points: day 0 of the study, days 20–30, and 3 months. At each subsequent visit, clinical evaluation and physical examination were performed.

**Statistical analysis.** Fisher’s exact test was used to assess categorical comparisons between groups. Differences in mean values for continuous measurements between the groups were tested by the Student’s t test if normally distributed and by the Mann-Whitney U test if skewed. P < .05 was considered to be statistically significant, and all tests were 2-tailed. Statistical analyses were performed on a personal computer with the statistical package SPSS for Windows, version 11.5 (SPSS) and StatXact software, version 5.0.3 (Cytel Software).

**RESULTS**

Demographic features of the 21 Missouri case patients with EM-like skin lesions were similar to those of the 101 New York case patients, except for the inclusion of 4 children in the Missouri group (table 1). The temporal distribution of cases differed significantly (P < .001); in Missouri, the peak incidence during the 3-year study period occurred during the months of May and June, whereas cases in New York were most common in June and July (figure 1).

A tick bite at the skin-lesion site was reported significantly more frequently for Missouri cases than for New York cases (85.7% and 19.8%, respectively; P < .001) (table 1). In cases for
Table 1. Comparison of selected features of case patients from Missouri and New York with erythema migrans (EM)–like skin lesions.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Missouri case patients (n = 21)</th>
<th>New York case patients (n = 101)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult</td>
<td>17</td>
<td>101</td>
<td>...</td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>47.8 ± 16.7</td>
<td>47.6 ± 13.5</td>
<td>.967</td>
</tr>
<tr>
<td>Median (range)</td>
<td>47 (22–80)</td>
<td>48 (20–80)</td>
<td>...</td>
</tr>
<tr>
<td>Childa</td>
<td>4</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>13 (61.9)</td>
<td>72 (71.3)</td>
<td>.438</td>
</tr>
<tr>
<td>Tick bite at lesion site</td>
<td>18 (85.7)</td>
<td>20 (19.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No. of days from tick bite to lesion</td>
<td>6.1 ± 4.2</td>
<td>10.4 ± 6.1</td>
<td>.011</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>5 (2–16)</td>
<td>9 (3–28)</td>
<td></td>
</tr>
<tr>
<td>No. symptomatic</td>
<td>4 (19.0)</td>
<td>77 (76.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No. of symptoms</td>
<td>0.8 ± 1.8</td>
<td>3.4 ± 3.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>0 (0–6)</td>
<td>3 (0–11)</td>
<td></td>
</tr>
<tr>
<td>Cumulative symptom scorea</td>
<td>2.8 ± 7.2</td>
<td>12.0 ± 14.5</td>
<td>.005</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>0 (0–24.8)</td>
<td>6.93 (0–64.5)</td>
<td></td>
</tr>
<tr>
<td>Heart blocka</td>
<td>0 (0)</td>
<td>3 (3.0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Multiple lesions</td>
<td>1 (4.8)</td>
<td>27 (26.7)</td>
<td>.042</td>
</tr>
<tr>
<td>Temperature at time of presentation of ≥38.0°C C</td>
<td>1 (4.8)</td>
<td>5 (5.0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Regional lymphadenopathy</td>
<td>1 (4.8)</td>
<td>27 (26.7)</td>
<td>.042</td>
</tr>
<tr>
<td>Joint swelling</td>
<td>0 (0)</td>
<td>5 (5.0)</td>
<td>.586</td>
</tr>
<tr>
<td>Facial palsy</td>
<td>0 (0)</td>
<td>2 (2.0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Pain on neck flexion</td>
<td>0 (0)</td>
<td>10 (9.9)</td>
<td>.208</td>
</tr>
</tbody>
</table>

NOTE. Data are no. (%) cases, unless indicated otherwise.

a Ninety-seven patients with 101 cases of EM-like skin lesions were enrolled into this study, including 2 patients with 2 cases of EM-like skin lesions in different summers and 1 patient with 3 separate cases.

b Ages of children from Missouri were 8, 10, 11, and 12 years.

c For 20 Missouri case patients and 19 New York case patients.

d For 20 Missouri case patients. Based on a visual analogue scale with 0 being not present and 8 being the most severe. Symptom scores of 0 were included.

e For 20 Missouri case patients and 98 New York case patients. First degree atrio-ventricular block was present in 3 New York patients, but it reversed in no patient after receipt of antimicrobial therapy, making any relationship with Lyme disease unlikely.

which a tick bite was recalled, the time interval from tick detachment until onset of the skin lesion was shorter for Missouri cases, compared with New York cases (6.1 ± 4.2 days vs. 10.4 ± 6.1 days; P = .011). The 3 ticks that were saved by the Missouri patients were all identified as *A. americanum*. Missouri cases were less likely than were New York cases to be symptomatic (19.0% and 76.2%, respectively; P < .001); Missouri cases had fewer symptoms than did New York cases (mean number of symptoms, 0.8 and 3.4 per case, respectively; P < .001); and Missouri cases had a lower mean symptom score (mean score, 2.8 and 12.0, respectively; P = .005). Specifically, there were fewer reports of stiff neck in Missouri cases than in New York cases (0% and 34.7%, respectively; P < .001), as well as fewer reports of fatigue (19.0% and 57.4%, respectively; P = .002), concentration or memory problems (0% and 29.7%, respectively; P = .002), joint pain (4.8% and 33.7%, respectively; P = .007), dizziness (0% and 22.8%, respectively; P = .012), loss of appetite (0% and 23.8%, respectively; P = .013), and headache (9.5% and 36.6%, respectively; P = .019) (table 2). The most common symptom in cases in both groups was fatigue. On physical examination, Missouri case patients were less likely than New York case patients to have multiple skin lesions (4.8% and 26.7%, respectively; P = .042) or regional lymphadenopathy in proximity of the lesion (4.8% and 26.7%, respectively; P = .042) (table 1).

Both the largest (8.3 cm for Missouri cases and 16.4 cm for New York cases; P < .001) and smallest (6.5 cm for Missouri cases and 11.6 cm for New York cases; P = .002) mean di-
ameters of the skin lesion were significantly lower for Missouri cases than for New York cases (table 3). However, there was no significant difference in the estimated growth rate of the skin lesion (which was based on the largest diameter [measured in cm] of the skin lesion divided by the reported lesion duration [measured in days]) \( (P = .112) \). The difference in dimensions between the largest and smallest diameters of the skin lesion was less for Missouri cases than for New York cases, suggesting that the lesions were more circular in shape, a finding that is consistent with the impression obtained by visual inspection \((1.8 \pm 1.6\, \text{cm vs.} \ 4.8 \pm 4.6\, \text{cm}; \ P = .004) \). Skin lesions in Missouri cases, compared with New York cases, were more likely to be found on the patient’s trunk (61.9% and 36.5%, respectively; \( P = .047 \)) and were more likely to show central clearing (76.2% and 21.6%, respectively; \( P < .001 \)) (figure 2A). Skin lesions in New York cases, compared with Missouri cases, were more often uniform in color (40.5% and 4.8%, respectively; \( P = .001 \)) and more often tender (50.0% and 19.0%, respectively; \( P = .013 \)) or pruritic (50.0% and 19.0%, respectively; \( P = .013 \)). Unlike the appearance of EM-like lesions in Missouri cases, if clearing was present in EM-like lesions in New York cases, it often spared the exact center of the lesion (figure 2B). Skin lesions in Missouri cases often had irregular raised borders and a prominent punctum (presumed site of the preceding tick bite) (figure 2C); sometimes the entire lesion appeared patchy and irregular (figure 2D). The prevalence of leukopenia, lymphopenia, thrombocytopenia, or elevation of the aspartate aminotransferase level among Missouri cases was similar to the prevalence among New York cases \( (P > .20) \). However, the erythrocyte sedimentation rate was less often elevated in Missouri cases, compared with the rate in New York cases \((2 \ [13.3\%] \text{of} \ 15 \text{cases and} \ 40 \ [41.7\%] \text{of} \ 96 \text{cases, respectively}; \ P = .045) \).

After initiation of antibiotic therapy, the skin lesions completely resolved within 21 days in all Missouri cases and in all but 3 of the 92 evaluable New York cases. New York cases, however, were more likely to have subjective symptoms, such as...
as arthralgias and fatigue, at the 3-month follow-up visit than were Missouri cases (17 [21.3%] of 80 cases and 0 [0.0%] of 17 cases, respectively; \( P = .037 \)).

**DISCUSSION**

This prospective study demonstrates that there are several prominent clinical differences between Missouri and New York cases of EM-like skin lesions. The findings presented are consistent with the microbiologic and serologic results of our prior investigation, which showed that the etiology of EM-like skin lesions in patients in these same geographic locations is completely different [24]. For example, in our prior study, the 21 patients included in the present report were found to be uniformly seronegative for antibodies to *B. burgdorferi* by acute-phase and convalescent-phase serologic testing, in contrast to a 75% seropositivity rate for the 143 New York cases [24]. The cause (or causes) of STARI in patients from Missouri is undefined.

Missouri case patients with EM-like skin lesions were more likely to recall a tick bite than were New York case patients (85.7% and 19.8%, respectively). It is possible that *A. americanum* tick bites are more frequently noticed because the tick itself is larger than *I. scapularis* [29] or because *A. americanum* tick bites are more painful [30]. In addition, although a bite from either adult or nymphal stage *A. americanum* may precede the development of an EM-like skin lesion in a patient from Missouri [6], nymphal stage *I. scapularis* is the predominant vector for EM-like skin lesions among patients in New York [31]. The peak incidence of EM-like skin lesions among Missouri cases occurred during May and June, whereas the peak incidence among New York cases occurred during June and July. Factors that might contribute to this disparity include an earlier peak in the number of *A. americanum* ticks [30], compared with the number of nymphal *I. scapularis* ticks [32], and the shorter time period from tick bite to development of the skin lesion that was observed in this study.

Missouri patients with EM-like skin lesions had an illness with milder severity than that of New York patients. Missouri patients were less likely to be symptomatic, to have multiple skin lesions (the single patient from Missouri with multiple skin lesions appeared to have had 2 separate tick bites [figure 2C]), or to have regional lymphadenopathy found by physical examination. Although the skin lesions in patients in both geographic locations rapidly resolved coincident with a brief course of oral antibiotic therapy, patients with EM-like skin lesions in New York were more likely to be symptomatic at the third month of follow-up than were Missouri patients. Both the Missouri and New York study sites are well-known referral centers in their regions for patients with EM-like skin lesions, making an acquisition bias of less-ill patients for the Missouri study site unlikely.

Despite a short duration of illness (mean duration, 4.5 days), EM-like skin lesions in Missouri cases were more likely to show central clearing than were lesions in New York cases (76.2% and 21.6%, respectively), an appearance typically associated with much older skin lesions in patients with *B. burgdorferi* sensu lato infection [33–35]. EM-like lesions in Missouri patients were more circular in shape than were lesions in New York patients, and they often had a prominent punctum and raised, irregular borders (figure 2). An oval appearance of EM-like lesions in patients with Lyme disease has been previously noted, with orientation of the long axis along presumptive lines of skin tension [36]. This configuration might be attributable to invasion of type I collagen matrices by *B. burgdorferi* [37], because type I collagen is believed to be oriented along lines of skin tension [36]. Preliminary data from a separate study also suggest that the findings of a histologic analysis of EM-like lesions in Missouri patients differ from those of EM-like lesions in patients with Lyme disease, with a much lower frequency of plasma cell infiltration in Missouri patients with STARI [38].

A principal limitation of this study is that it was conducted in only 1 area of a single southern state. Therefore, it is unclear whether the findings would pertain to cases of STARI in other regions within Missouri or to other states in the South.
Lyme disease–like illnesses [3–5]. Certain of the observations made in this study, however, are comparable to those reported in other case studies from southern states. Similarities exist regarding temporal occurrence, high frequency of recollection of a preceding tick bite, and visual appearance of the skin lesion. Although the severity of disease has been uniformly described as mild in all case studies [3–6], the frequency of associated symptoms has been higher than we observed in some [4, 5] but not other [3] prior studies. When the cause or causes of this condition are better defined, it may be possible to categorize cases more precisely and to explain such disparities.

In conclusion, the EM-like illness known as STARI found in many southern states is not due to *B. burgdorferi* infection [3–5]. It is a milder illness than EM due to *B. burgdorferi* infection,
and the appearance of the skin lesion is often somewhat different. Awareness that this illness exists in states that are inhabited by *A. americanum* ticks outside areas where Lyme disease is endemic is important. Furthermore, spread of this tick to traditional areas where Lyme disease is endemic, along the east coast from New Jersey to Maine, has been documented [39], raising the concern that this illness may occur in these locations as well [11, 12]. Additional study of this condition is warranted.

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