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Atypical Erythema Migrans in Patients with PCR-Positive Lyme Disease

To the Editor: The best diagnostic sign in patients with early Lyme disease is a skin lesion, erythema migrans (EM). However this sign may not occur or be recognized in 30% of cases (*1*). Furthermore, the EM rash may not display a classic bull's-eye (ring-within-a-ring) appearance, a fact that may be underappreciated (*2,3*). Some studies noted uncharacteristic variants of EM in 25%–30% of cases (*4*–*7*). One study reported the rash to be uniformly red in 60% of cases (*6*). Other atypical variants of EM are a blue-red appearance and, occasionally, a vesicular central region (*4,5*). We describe the occurrence of atypical EM in patients with microbiologically proven *Borrelia burgdorferi* infection.

During spring and summer 2009, a total of 29 patients with classic or possible EM and suspected Lyme disease were referred by primary care physicians for an ongoing prospective study. Laboratory methods have been described (*8*). The patients were >18 years of age and lived in suburban Baltimore, Maryland, USA, where Lyme disease is endemic. All patients had extracutaneous manifestations (e.g., virus-like symptoms). Fourteen patients met laboratory criteria for study analysis: 1) positive PCR at the initial study visit, detected by a *B. burgdorferi*–specific nucleic acid–enhancing PCR method on a 1.25-mL whole blood sample (*8*), and 2) evidence of *B. burgdorferi* exposure by the 2-tiered antibody test at the initial or posttreatment visit. Other entry criteria were a rash >5 cm and symptoms compatible with early Lyme disease (*1*); exclusion criteria were certain preexisting medical conditions (*8*).

A panel of experienced specialists, including dermatologists, were shown photographs of the patients' skin lesions and asked if they would expect the average primary care physician to diagnose the lesions as EM. To avoid bias, PCR and serologic test results were withheld from the specialists and they were asked to categorize lesions by characteristics common to target-like and non–target-like lesions. Lesions with the classic bull's-eye appearance, with central clearing and peripheral erythema, were classified as classic EM; those with uniform red or red-blue or other appearance and lacking central clearing were classified as possible atypical EM. If any lesion of a multiple lesion set was classic in appearance, we categorized the rash as classic EM. Of the 14 patients with positive PCR, 10 had nonclassic EM (Figure) and 4 had classic, target-like EM. Atypical rashes varied from those close to classic EM to those resembling

Figure. Atypical erythema migrans lesion on a patient with PCR-positive result for *Borrelia burgdorferi* infection. The rash was not considered typical because it lacked central clearing and peripheral erythema. The differential diagnosis included a contact dermatitis and arthropod bite. At the initial examination, this patient was seronegative for *B. burgdorferi* by 2-tiered criteria. Three weeks after therapy, the patient had positive results for ELISA and IgM Western blot and negative results for IgG Western blot, providing evidence of seroevolution (i.e., increasing antibody titer and/or increase in band intensity or appearance of new antigen bands to *B. burgdorferi*).

lesions more common in other conditions (e.g., insect or spider bites) and, consequently, prone to misdiagnosis.

Depending on the appearance of an atypical rash, the differential diagnosis could include contact dermatitis, arthropod bite, or, in cases with annular lesions, fixed drug eruptions, granuloma annulare, cellulitis, dermatophytosis, or systemic lupus erythematosus (*5*). In addition, a diagnosis can be more challenging when there are multiple skin lesions rather than a single lesion and in a pattern unfamiliar to a general practitioner.

Multiple textbooks and websites have featured pictures of EM as a bull's-eye lesion (online Technical Appendix, wwwnc.cdc.gov/EID/pdfs/12-0796-Techapp.pdf). This emphasis on target-like lesions may have inadvertently contributed to an underappreciation for atypical skin lesions caused by Lyme disease. Nevertheless, physician recognition of Lyme disease–associated EM is essential because current approved laboratory tests may not identify *B. burgdorferi* in the first few weeks of infection (*8*), when an accurate diagnosis can lead to early curative therapy.

Separate studies found different percentages of atypical Lyme disease–associated rashes (*3,4,9*); each was lower than the percentage found in our study. Our study has several limitations: it encompassed only 1 recruitment season, 1 geographic site, and a small number of patients. The sensitivity of PCR for blood specimens is improving (*8*); however, PCR may have missed some acute cases in our study for reasons cited below. Therefore, these patients should not obligatorily be considered as representative of all acute Lyme disease patients.

Our study results serve as an impetus for studying more patients with systemic and nonsystemic signs and symptoms over multiple seasons and geographic areas and for including PCR analysis of skin lesions in future studies. PCR of skin biopsy samples may provide insight as to whether a negative blood PCR is the result of infection with a skin-restricted strain (*10*) in patients in whom bacterial dissemination is not expected or a result of low copy number of *B. burgdorferi* in the blood sample.

Our results serve as a reminder that patients with early Lyme disease may have an atypical rash, not the classic (textbook) bull's-eye lesion. Close observation and a detailed history of whether the rash is enlarging, has enlarged, or is spreading should be part of the consideration of the diagnosis. Observation for extracutaneous signs of early infection, such as cranial seventh nerve palsy (Bell's palsy) or meningitis, is also essential.

In summary, the EM rash of Lyme disease can have an atypical appearance. Thus, clinicians should consider Lyme disease in the differential diagnosis of patients who have a rash that may not be classic EM and who have been in areas where Lyme disease occurs.

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Brucellosis in Guangdong Province, People's Republic of China, 2005–2010

To the Editor: Brucellosis is one of the most prevalent zoonotic diseases in the world. It is principally an animal disease, but globally, >500,000 human cases are reported each year (*1*). Transmission to humans occurs primarily through contact with infected animals and consumption of contaminated food (*2*,*3*). Persons with occupational exposure are at highest risk for brucellosis, in particular those performing husbandry activities, butchering, and livestock trading (*4*,*5*).

Although brucellosis has been eradicated from many industrialized countries, new foci of disease continually appear, particularly in parts of Asia (*6*–*8*). In China, 160,214 brucellosis cases were reported during 2005–2010; 90% of them occurred in 6 northern agricultural provinces: Neimenggu, Shanxi, Heilongjiang, Hebei, Jilin, and Shaanxi. Livestock, such as goats, cattle, and pigs, are the main infectious source. However, factors such as the rapid movement of people from northern to southern China, increased livestock trading, and lack of livestock quarantine mean that infected livestock or their products readily traverse provincial borders and transmit disease to persons who have no direct contact with livestock.

With an illness rate of <0.01 cases/100,000 population, Guangdong Province in southern China is one of the areas in China with the lowest incidence of brucellosis (*9*), but incidence is increasing. During 1955–2004, Guangdong Province recorded 51 confirmed cases of brucellosis; however, during 2005–2010, 112 cases were reported. All reported cases had typical clinical characteristics, including undulant fever, night sweats, chills, and weakness; some cases were associated with encephalitis, meningitis, and arthritis. Of the 112 reported cases during 2005–2010, 105 were laboratory confirmed: 61 by culture (55 from blood culture, 3 from bone marrow, and 1 each from joint fluid, cerebrospinal fluid, and a vertebrae disc abscess); and 44 by serum agglutination test (SAT; single titer >400). The male:female ratio among these patients was 66:46. The age ranges were similar by sex; male patients were 18–71 (median 47) years of age, and female patients were 20–70 (median 43) years of age.

The first 3 cases of brucellosis in 2005 were reported in Shenzhen in Guangdong Province. One case was culture confirmed by clinical laboratory, and the isolate was identified as *Brucella melitensis* biovar 3 by SAT and phage biotyping. The other 2 cases were in dairy farm workers; their infections were laboratory confirmed by SAT but could not be identified by biovar. Since 2005, more cities in Guangdong have reported brucellosis cases (Figure, Appendix, wwwnc.cdc.gov/EID/article/19/5/12-0146-F1.htm). The Pearl River Delta region reported 100 cases: 48 in Guangzhou, 27 in Shenzhen, 7 in Zhongshan, 6 in Foshan, 6 in Jiangmen, 4 in Zhuhai, and 2 in Dongguan. Only 12 cases were reported from undeveloped rural areas in Guangdong: 5 in Zhaoqing, 2 in Yangjiang, and 1 each in Huizhou, Qingyuan, Meizhou, Maoming, and Yunfu.

A total of 42 *Brucella* isolates were cultured during 2005–2009, and all were identified as *B. melitensis* biovar 3. However, of 19 *Brucella* isolates cultured during 2010, a total of 13 were identified as *B. melitensis* biovar 3, 4 as *B. melitensis* biovar 1, and 2 as *B. suis* biovar 3. These results indicate a shift in species and biovar for *Brucella* spp. circulating in China.

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Technical Appendix

Figure. Classic bull's-eye (ring-within-a-ring) erythema migrans lesion (5 cm). Whole blood PCRs of samples obtained at the patient's initial medical visit were positive for *Borrelia burgdorferi*, and results of 2-tiered serologic testing were negative. The patient seroconverted after a 3-week course of antimicrobial drug treatment.