

# The Changing Face of Lyme Disease—Rural to Urban

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Lyme disease is a multisystem, multistage disease caused by the spirochete *Borrelia burgdorferi*, which is named after Dr. Willy Burgdorfer who discovered this tick-borne spirochete in 1981.<sup>1</sup> *B. burgdorferi* is transmitted to humans by infected ticks of the *Ixodes* complex. The primary arthropod vector is *I. scapularis* in the northeastern and north central parts of United States and *I. pacificus* in the west.<sup>2</sup> Lyme disease is a rapidly emerging vector-borne infectious disease in the United States and currently accounts for one of the most commonly vector-borne diseases reported. The incidence increased 30-fold between 1982 and 1996 and continued rising rapidly each year.<sup>3</sup> The disease occurs in distinct and geographically limited areas. Most cases in the United States occur in the northeast, north central, mid-Atlantic, and western coastal regions where *Ixodes* ticks are prevalent.<sup>2-5</sup> The incidence in some of the highly endemic communities may reach 1% to 3% per year.<sup>5</sup> Although cases of Lyme disease have been reported from 49 states and the District of Columbia,<sup>5</sup> significant risk of infection was found in only 165 counties in which 91.6% of the cases occurred.<sup>2,3</sup>

The following case presentation is of a man residing in urban Michigan with no history of travel outside southeastern Michigan and no history of exposure to traditional vectors; however, similar presentations may arise in any US urban area. Incidence of Lyme disease is increasing in the urban setting because of many rodent and bird reservoir hosts for the deer tick, which help in the transmission of this disease to both urban and suburban populations.<sup>6</sup>

## CASE PRESENTATION

### Initial Presentation and History

A 41-year-old man presented with a rash on the anterior aspect of his right leg. The rash started as a small papule and, over a period of about 10 to 15 days, its diameter increased to 3 to 4 in with central clearing.

The rash was associated with marked pruritis initially and at the time of presentation had some burning. The patient noticed the rash a few days after he had worked on an outside masonry job. There was no history of a tick bite; however, he did remember being bitten by an insect while in the area. There was no history of travel for 3 years. The patient complained of flu-like symptoms associated with diffused body aches, sore throat, low-grade fever, and malaise accompanied with severe fatigue. He also complained of multiple joint pains for which he had been taking over-the-counter acetaminophen.

### Physical Examination and Laboratory Evaluation

On physical examination, the patient was an otherwise healthy man in no acute distress. He was afebrile with a pulse of 82 bpm, blood pressure of 125/72 mm Hg, and a respiratory rate of 12 breaths/min. The results of cardiac, abdominal, and respiratory systems were unremarkable; however, dermatologic examination revealed a circular, maculopapular, well-circumscribed 3 × 3 in area of erythema with central clearing on his right leg (Figure).

Initial laboratory work-up included complete blood count and erythrocyte sedimentation rate, which were normal. Lyme titer, which included enzyme immunoassay followed by Western blot, was also ordered. The patient's enzyme immunoassay and Western blot were positive for the 23 kD and 41 kD IgM bands, respectively.

### Treatment

The patient was diagnosed with Lyme disease because of the characteristic appearance of the rash,

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erythema migrans, and the positive IgM bands on Western blot. As he had no known drug allergies, he was treated with doxycycline 100 mg twice daily for a period of 14 days.

## DISCUSSION

Diagnosing Lyme disease can be very difficult because the symptoms vary widely and mimic those seen in other common diseases. The diagnosis of Lyme disease is based primarily on clinical manifestations, especially the characteristic rash, erythema migrans. In an urban setting, especially in areas of the United States where Lyme disease is not endemic, it is rarely included in the list of differential diagnoses, but with the changing reservoir hosts, this disease should also be considered by primary care physicians.

## Epidemiology

Lyme disease was first recognized in Old Lyme, Lyme, and East Haddam, CT when 51 residents were diagnosed with a distinct clinical illness involving a unique form of oligoarticular arthritis in 1975.<sup>7</sup> Since then, it has emerged as a significant threat to the public's health in the northeastern United States. According to the Centers of Disease Control and Prevention (CDC), more than 157,000 cases have been reported to health authorities in the United States since a systematic national surveillance was initiated in 1982.<sup>5</sup> In 2002, 23,763 cases of Lyme disease were reported to the CDC, which was a 40% increase over the number of cases reported in 2001 (17,029).<sup>4</sup> The overall incidence rate of reported cases in the United States is about 8.2 per 100,000 population,<sup>4</sup> but there is considerable underreporting.

## Etiology

*B. burgdorferi* is a spirochete that causes Lyme disease in humans. Typically, immature *I. scapularis* ticks acquire *B. burgdorferi* during their initial blood meal from an infected reservoir host, such as white-footed mice, birds, rodents, bats, armadillos, and other small mammals. The animal reservoir host is needed to perpetuate the cycle of *B. burgdorferi*. Lyme disease is then introduced into the human body via the bite of an infected tick. Infection occurs only if the tick has been feeding on the human host for 24 to 36 hours.<sup>8</sup> A blood meal is required to stimulate *B. burgdorferi* to migrate from the tick intestine to its salivary glands.

## Clinical Presentation

Lyme disease evolves in 3 stages, and all the 3 stages can have overlapping signs and symptoms. The stages



**Figure.** The case patient presented with a well-circumscribed 3 x 3 in area of erythema with central clearing on his right leg.

are early localized involvement, dissemination to multiple organ systems, and a chronic disseminated stage.<sup>9</sup>

The early localized stage is characterized by the "bull's-eye" rash or erythema chronicum migrans, which classically is a flat circular erythema, often in the form of a raised red swelling around the tick bite. As it expands radially, the edges remain red but there is central clearing, commonly called the bull's-eye or target lesion.<sup>8</sup> The incubation period from infection to onset of erythema migrans is typically 7 to 14 days. The rash may appear as early as 3 days and as late as 30 days to several months after the time of tick bite. This type of rash occurs in 60% to 80% of the patients and is diagnostic of Lyme disease.

The spirochetes disseminate from the site of the tick bite by cutaneous, lymphatic, and hematogenous routes. The signs of early disseminated infection usually occur days to weeks after the appearance of a solitary erythema migrans lesion, and they can have various manifestations during this stage. In fact, multiple erythema migrans lesions may be the only presentation in early disseminated disease. Patients also can experience headaches, lymphadenopathy, fever, and malaise. Musculoskeletal involvement may present as migratory joint and muscle pains with or without signs of joint swelling. Patients may develop mild hepatitis with associated upper right quadrant tenderness. Neurologic and/or cardiac involvement may occur. Bell's palsy, which is a peripheral neuritis, and other cranial nerve palsies along with radiculoneuritis are commonly seen. Cardiac manifestations are rare but may include myocarditis and transient atrioventricular blocks of varying degree.

Late stage Lyme disease is very diverse in its presentation and may present weeks to months after infection. The most common manifestation of late disseminated

Lyme disease is arthritis that presents as intermittent swelling and pain of 1 or more joints. Usually large, weight-bearing joints, such as the knee joints, are involved. Some patients develop chronic axonal polyneuropathy or encephalopathy, the latter usually manifested by cognitive disorders, sleep disturbance, fatigue, and personality changes. After the late disseminated stage of the disease occurs, 50% to 60% of patients may experience brief attacks of arthritis.

### Diagnosis

The diagnosis of Lyme disease can be made relatively easily in patients where the bull's-eye rash and/or tick bite is a known occurrence. In cases where the rash did not occur or the tick bite went unnoticed, the diagnosis can be facilitated by serologic tests.

As seen with the case patient, routine laboratory tests are usually normal in Lyme disease. Also, erythrocyte sedimentation rate usually is normal. The gold standard for laboratory confirmation of Lyme disease is cultivation and direct detection by polymerase chain reaction, but this method has limitations. Accuracy of the test is highly dependent on correct sample collection, storage of the sample, and the techniques used for the assay. *B. burgdorferi* can be cultivated from their arthropod vectors or vertebrate hosts in a Barbour-Stoener-Kelly medium. Culture of *B. burgdorferi* is possible early in the disease, usually from biopsy specimens of the erythema migrans rash.<sup>10</sup> Culture can be performed late in the disease but is difficult to grow.

Currently, the only available useful laboratory testing are the immunologically-based enzyme-linked immunosorbent assay (ELISA) and Western immunoblot assay.<sup>11</sup> The CDC recommended in 1994 to have a two-tiered testing system with a sensitive first test, either ELISA or an indirect fluorescent antibody test, followed by testing with the more specific Western blot test to corroborate equivocal or positive results obtained with the first test.<sup>10,12</sup> Dual testing is necessary as the ELISA gives false-positive results due to cross-reactions with other bacteria or in other conditions.<sup>13</sup> Western blot detects antibody to individual proteins of the *B. burgdorferi*. However, it is difficult to standardize Western blot for a positive result. It is recommended to test both IgM and IgG during the first 4 weeks of disease onset. IgM is considered positive if 2 of the 3 bands are present (ie, 23 kD, 39 kD, or 41 kD). There are 10 protein antigens classified by Dressler's criteria for IgG in a set (18 kD, 23 kD, 28 kD, 30 kD, 39 kD, 41 kD, 58 kD, 66 kD, and 93 kD).<sup>10,12</sup> The test is considered positive if the patient's blood serum has 5 or more out of the 10 proteins in the set.

The ELISA has been shown to be an unreliable test in many patients with Lyme disease in early and late disease. By Western blot analyses, the first immunologic reactions in Lyme disease at the time of erythema migrans rash are to the IgM 41 kD flagellar proteins and the 23 kD outer-surface protein C, but there are no IgG reactions. The laboratory report of Western blot should be reviewed in context with the clinical picture, taking into consideration early or late disease.

### Treatment

Antibiotics are the mainstay of therapy of Lyme disease. The choice of antibiotic depends upon the stage of the disease.<sup>14</sup> Patients with early Lyme disease (either early localized and early disseminated disease associated with erythema migrans in the absence of neurologic or cardiac involvement) should be treated with a 14- to 21-day course of doxycycline (100 mg twice daily) or amoxicillin (500 mg 3 times daily).<sup>15</sup> Cefuroxime should be reserved as an alternative agent for those allergic to doxycycline or amoxicillin and should be give 500 mg orally twice daily or 30 mg/kg divided into 2 doses for 14 to 21 days (**Table**). Macrolides are not recommended as first-line therapy.

Late manifestations include Lyme arthritis, neuropathy, and encephalopathy. The Infectious Diseases Society of America guidelines for treatment of Lyme arthritis without neurologic disease are with doxycycline 100 mg orally twice daily or amoxicillin 500 mg orally 3 times a day for 28 days along with symptomatic treatment with nonsteroidal anti-inflammatory drugs for the arthritis. Patients with neurologic disease should receive parenteral therapy with ceftriaxone (2 g intravenous [IV] once daily) for 14 to 28 days. Alternative parenteral agents include cefotaxime 2 g IV 3 times/day or penicillin G 18 to 24 million units IV/day divided into doses given every 4 hours (**Table**).<sup>15</sup> Doxycycline should not be used in pregnant women or children younger than 8 years; these patients should be treated with either amoxicillin or cefuroxime.

In terms of prophylaxis for Lyme disease, a recent study concluded that a single dose of 200 mg of doxycycline given within 72 hours of the tick bite can prevent the development of Lyme disease.<sup>16</sup>

### Prevention

The Infectious Diseases Society of America guidelines for Lyme disease state that prevention remains the best approach.<sup>15</sup> Avoiding exposure to ticks remains the best way to prevent infection; therefore, it is important for patients to be educated about areas of maximum risk, to take appropriate precautions prior to entering endemic

**Table.** Overview of Treatment of Lyme Disease

Stage of Disease	Treatment	
	Agent and Dosage	Duration
Early Lyme disease	Doxycycline 100 mg orally twice a day OR Amoxicillin 500 mg orally 3s times a day; In case of allergy to doxycycline or amoxicillin: cefuroxime 500 mg orally twice a day or 30 mg/kg divided in 2 doses	14–21 days
Late manifestations (neurologic manifestations)	Ceftriaxone 2 g IV once a day OR Cefotaxime 2 g IV 3 times a day OR Penicillin G 18–24 million units IV/day divided in doses given every 4 hours	14–28 days
Late manifestations (arthritis without neurologic disease)	Same as early Lyme disease Same as therapy for neurologic manifestation	28 days 14–21 days
Cardiac manifestations 1st or 2nd degree, heart block 3rd degree	Same as early Lyme disease Same as therapy for neurologic manifestations	14–21 days 14–21 days

IV = intravenous.

areas, and to know what to do in case of a bite.<sup>17</sup> If exposure to ticks is unavoidable, prevention can be achieved by wearing long-sleeved clothing, tucking trousers into shoes, and using tick repellents.<sup>18,19</sup> The most effective tick repellants are DEET (N,N-diethyl-3-methylbenzamide) and permethrin, which are helpful in reducing tick attachment.

The entire body should be inspected daily and ticks removed at once before transmission of *B. burgdorferi* can occur.<sup>20</sup> Patients who remove attached ticks should be monitored closely for signs of illness—particularly a rash at the site of the tick bite—for up to 30 days. Patients should be advised to save the tick for proper identification by their physician especially if they develop any symptoms.

A vaccine had been approved for the prevention of Lyme disease in 1999 and was recommended for people at high risk. In 2002, however, the manufacturer of the vaccine announced that it would no longer be commercially available.<sup>21</sup> The vaccine's manufacturer cited poor sales as the reason for pulling the vaccine off the market.

### Changing Reservoir Hosts

Recent studies have shown that certain birds may also contribute to the transmission of Lyme disease. Evidence of the reservoir competence of seabirds has been obtained in Arctic islands.<sup>22</sup> Another study examined the competency of American robins as reservoir hosts and suggested that robins might contribute to the emergence of Lyme disease in previously unaffected sites to the extent that the season of their migration overlaps with that of the activity of nymphal vector

ticks.<sup>23</sup> Tick-borne Lyme disease spirochetes may readily infect certain birds and other small rodents, and these animals and birds may subsequently infect numerous vector ticks. The result is that infected ticks, and, consequently, Lyme disease are appearing in patients from urban areas without a history of travel into an endemic area, as was the case with the patient presented here.

### CONCLUSION

Although the patient had no history of travel to a Lyme disease–endemic area, the diagnosis of Lyme disease was considered because of the clinical presentation. This case illustrates the importance of considering Lyme disease in urban populations. More research is needed on mechanisms of spread of disease, dynamics of vector spread, and new endemic foci. **HP**

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