CASE STUDY OF LYME DISEASE

Kawabata M.
ICMR, Kobe University School of Medicine, Japan

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Contents

Summary

Lyme disease is an infectious disease transmitted by ticks, and distributed in North America and across a wide area of Eurasia. It is considered one of the major emerging diseases from a public health perspective. An outbreak of Lyme disease was first reported in the United States in the 1970s. The presence of *Borrelia burgdorferi*, its causative organism, in the skin results in the development of the characteristic expanding red skin lesion, erythema migrans (EM). The EM may be associated with cardiac and neurologic abnormalities. The arthritis, neurologic and skin manifestations may persist for several years and became chronic in a small percentage of patients. Studies on the classification of *B. burgdorferi* resulted in the identification of three closely related species, namely *B. burgdorferi sensu stricto*, *B. garinii* and *B. afzelii*, and different clinical manifestation of Lyme disease have been linked to the infecting species. The diagnosis of Lyme disease should be based primarily on the clinical manifestations, the epidemiological background and serological tests. Lyme disease serodiagnosis tests have been standardized, and a two-step approach is available which utilizes a sensitive first test followed by confirmatory western immunoblotting of serum samples with equivocal or positive first test results. Antimicrobials are effective in the treatment of Lyme disease in most patients. However, the primary or secondary preventions such as avoidance of tick infested area, early detection and removal of attacked ticks, and diagnosis and treatment of disease are recommended.

1. First Case Report of Lyme Disease in East Asia

In 1986, a 64-year-old man had an embedded tick on his abdomen after an excursion to a mountainous district of Nagano Prefecture, Japan. Two days later, he developed an enlarging pink rash at the site of the tick bite; the patient complained of a low-grade fever. As the rash expanded peripherally, he consulted a medical doctor four weeks

after onset of the skin lesion. When initially seen, the lesion measured 22x15cm with an erythematous margin and a central area induration. Laboratory tests including serum levels of circulating immune complexes, complement, and immunoglobulin concentration showed normal values, with the exception of a slightly increased level of serum aspartate aminotransferase and an elevated sedimentation rate. Physical examination revealed an axillar lymphadenopathy. A biopsy from the center of the lesion showed perivascular edema and inflammatory cell infiltration composed mostly of small lymphocytes and histiocytes, and a few plasma cells throughout the dermis. An ELISA for serological diagnosis of Lyme disease performed in the laboratory of the Centers for Disease Control (Atlanta, USA) gave a significantly elevated level of antibody to *Borrelia burgdorferi*. The rash expanded further, but decolorized in the central area, and then began to fade and disappear spontaneously by eight weeks after the onset of the lesion without any antibiotic therapy. Over the next five years, the patient remained asymptomatic and had no other cutaneous, musculosketal, cardiac, or neurologic abnormalities. The tick removed from the patient was identified as a female adult *Ixodes persulcatus* and is considered to be the possible vector in this case. In this case, the patient had only EM accompanied by regional lymphadenopathy, the antibody to *B. burgdorferi* was significantly elevated, and tests for syphilis were negative. Therefore, the authors made a diagnosis of Lyme disease. Thus this case suggested the existence of Lyme disease in Far East Asia.

The species of *I. persulcatus* was predominantly reported from northern Japan, namely Hokkaido and the northern part of Honshu, and infests a variety of mammalian hosts, including cattle, horse, wild rabbit, and deer. Cases of human infestation sporadically occur in the summer and correspond with the peak of its seasonal distribution. An increasing number of *Borrelia* isolates are being found in ticks and wild rodents in the far eastern countries, such as Russia, China, Korea as well as Japan. Using 5S-23S intergenic spacer restriction fragment length polymorphism analysis (RFLP), the isolates from Russia, China and Korea were identified as *B. garinii* and *B. afzelii*, and resembled those of *Borrelia* isolated from *I. persulcatus* in Japan. This finding clearly indicates that transmission of *Borrelia* occurred between the far eastern countries and Japan.

2. Epidemiology

Lyme disease is a zoonosis, and as a result of a complex sequence of events people have become frequent accidental hosts for ticks and the etiologic agents they carry. Lyme disease is endemic in areas where suitable mammalian reservoirs for *B. burgdorferi* and appropriate vertebrate hosts for the tick vector are present. Due to the ecological requirements of the ticks of the *Ixodes* genus, the distribution of infected ticks can vary greatly within an endemic area. Lyme disease is endemic in large areas of North America, Europe and East Asia. The white-footed mouse is the most important reservoir for *B.burgdorferi*, a causative agent in North America, but in Europe a variety of small mammals and birds has an important role in transmission, possibly reflecting the more varied and complex ecology of the *Ixodes* ticks in this region. In the western USA, low tick infection rates with *B. burgdorferi* have been attributed to the fact that *Ixodes* ticks in that location commonly feed on lizards, which are not thought to be competent reservoirs for *B. burgdorferi.* White-tailed deer, an important host for adult

Ixodes ticks, also do not serve as reservoirs for *B. burgdorferi* transmission. The disease has also been sporadically reported from Southeast Asia, South America, Africa and Australia based on serological evidence. Whether transmission of Lyme disease exists in the southern hemisphere remains under invetigation. Extensive studies in Australia have failed to detect the etiologic agent. Ticks of the *I.ricinus* complex having the potential to be a vector show a worldwide distribution, particularly north of the Tropic of Cancer. *I .persulcatus* inhabits in Asia and *I. ricinus* is found in Europe. In the United States, two species of ticks are responsible for transmitting *B.burgdorferi* to human hosts*: I. scapularis* in the East, and *I. pacificus* in the West.

The incidence of Lyme disease varies markedly among countries, as well as within countries. As Lyme disease is not a noticeable disease in any European or Asian country, only estimated annual averages of incidence rates are available. They range from 0.6 cases per 100 000 inhabitants in Ireland, to 300 cases per 100 000 inhabitants in Austria. A recent epidemiological study of Lyme disease in southern Sweden found this disease to be very common, with an overall incidence of 69 cases per 100 000 inhabitants. Japan has a relatively low incidence of Lyme disease with fewer than 100 confirmed cases since the first case was diagnosed in 1986. Lyme disease is reported from the United States. According to a report from the Centers for Disease Control and Prevention, a total of 13 083 cases were reported in 1994, and 16 461 cases in 1996. In the most endemic north-eastern states, rates ranging from 23 to 95 cases per 100 000 inhabitants were reported. The highest reported county-specific incidence was 1 247 per 100 000 in Nantucket County, Massachusetts.

3. Causation

Borrelia species, along with the *Leptospira* and *Treponema*, belong to the eubacterial phylum of spirochetes. Like all spirochetes, the *Borrelia* species have a protoplasmic cylinder that is surrounded first by a cell membrane, then by flagella, and finally by an outer membrane, that is only loosely associated with the underlying structures. The entire outer membrane can move to one end of the cylinder, a phenomenon called capping or patching that may be important in cell adherence. The *Borrelia* species are fastidious, microaerophilic bacteria that grow best at 33^{o}C in a complex, liquid medium called Barbour-Stoenner-Kelly (BSK) medium. It is relatively easy to obtain a primary isolate of this spirochete from ticks, but it is difficult to do so from patients. When compared with most bacteria, *Borrelia* grow quite slowly; each spirochete elongates for 12 to 24 hours and then divides into two cells. *B. burgdorferi* loses its pathogenicity in culture, usually after 10 to 15 passages, and after that time, the organisms are no longer infectious. Of the genus *Borrelia*, *B. burgdorferi* is the longest (20 to 30 um) and narrowest (0.2 to 0.3 um), and it has fewer flagella (7 to 11).

The *Borrelia* are unique among the spirochetes in their arrangement of DNA. *B. burgdorferi* has a linear chromosome and linear plasmids in addition to the typical supercoiled variety. Genes encoding for the outer membrane are located on linear plasmids, rather than on the bacterial chromosome, which may facilitate antigenic variation. Some plasmids may be lost after culture passages, with loss of infectivity for experimental animals. There are two major outer surface proteins, Osp A (30-32kd) and Osp B (34-36kd). Other antigens include a flagella 40kd protein, a 66kd polypeptide

located on the outer membrane and a range of heat shock proteins, including the common antigen protein, which are cross-reactive with a wide range of bacteria and other organisms.

Studies on the classification of *B. burgdorferi* resulted in the identification of three closely related species of *Borrelia* that are etiologic agents of Lyme disease. The species *B. burgdorferi sensu stricto* is the only agent of Lyme disease present in North America. It is also present in Europe but absent in Asia. *B. garinii* and *B. afzelii* are present in Europe and Asia. The greater genetic diversity among the species of *B. burgdorferi* present in Europe in combination with the broad spectrum of clinical manifestations observed, suggest that the Old World is the birthplace of the agents of Lyme disease. However, recent genetic studies indicate that European strains of *B. burgdorferi sensu stricto* are derived form American strains, and that its migration to Europe is a recent and probably continuing process. Different clinical manifestations of Lyme disease have been correlated with the infecting species, *B. afzelii* was associated with cutaneous manifestations, and infection with *B. garinii* was correlated with extra cutaneous symptoms. The frequency of arthritis associated with Lyme disease appears to be greater in the United States than in Europe.

However, the results of a one year, prospective population-based active surveillance of Lyme disease apparently caused by *B. afzelii* in southern Sweden revealed that the pattern of disease observed was similar to that caused by *B. burgdorferi sensu stricto* in the United States. The exceptions were a lower incidence of carditis and a higher incidence of acrodermatitis and lymphocytoma in southern Sweden, as compared to the United States. Although the frequency of arthritis in this study was similar to that occurring in the United States, this may be because most patients with early signs of the disease are now treated with antibiotic therapy, decreasing the number of patients who develop arthritis. If the incidence of arthritis is based on the observation of untreated patients with erythema migrans, *B. burgdorferi sensu stricto* appears to be more arthritogenic than *B. afzelii*.

4. Clinical Manifestations

Lyme disease is a multi-system infection that can have cutaneous, musculoskeletal, neurologic, cardiac, hepatica and ophthalmologic involvement. Lyme disease generally occurs in stages, with different clinical manifestations at each stage. Before the use of antibiotic therapy for this infection, the typical patients in Connecticut first had erythema migrans (erythema chronicum migrans; ECM) (stage 1), sometimes followed several weeks or months later by meningitis or Bell's malsy (stage 2), and often followed months or years later by arthritis (stage 3). The problem with this classification is that each system - skin, neurologic system, and joints - may be affected either early or late in the illness. Asbrink has proposed a modified plan, analogous to that used in classifying syphilis, in which Lyme disease is essentially divided into early and late infection. Early infection consists of stage 1 (localized erythema migrans), followed within days or weeks by stage 2 (disseminated infection) and within weeks or months by intermittent symptoms. Late infection, or stage 3 (persistent infection), usually begins a year or more after the onset of the disease. A patient may have one or all of the stages, and the infection may not become symptomatic until stage 2 or 3.

Although a wide variety of disease manifestations have been reported in Lyme disease, many have been based on case-reports, uncontrolled series of patients, or merely serological evidence, rather than on infection confirmed microbiologically (i.e., isolation of *B. burgdorferi* in culture). Early descriptions failed to consider the possibility of co-infection with other tick-borne pathogens or unknown agents, some of which were not recognized when the reports were published.

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