The Role of the Allergist in Lyme Disease

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ABSTRACT

The allergist may frequently be involved with cases of Lyme disease. There are at least three reasons for this. First, the major symptom is often a rash that brings into the differential diagnosis several diseases that the allergist is likely to have expertise in; therefore, the allergist's role as a diagnostician is very important. The second reason is that the Borrelia burgdorferi (Bb) infection is treated with antibiotics and the patients may frequently develop reactions that may be immune-mediated. The allergist's expertise in diagnosis and management of allergic reactions is important. The third reason is that there is no established laboratory diagnostic test so that the clinician must use the existing tests, most often serologic, with their limitations, in the context of a history and physical. The allergist as an immunologist can be very helpful in the proper interpretation of the test results. The differential of the rash and the immune response to the infecting agent is described. (Allergy and Asthma Proc 22:29–31, 2001)

Lyme disease is caused by infection with the spirochete *Borrelia burgdorferi* (Bb), which is transmitted by the deer tick *Ixodes scapularis.*[1–4] It is the most common tick-borne disease in the United States; frequently, it is a multisystem disease.[1,5–9] The almost pathognomonic initial clinical marker, erythema migrans (EM) occurs in almost two-thirds of cases. However, it may not be observed or may be atypical in its presentation. Antibiotic therapy is usually successful if initiated promptly. Oral antibiotics may suffice for localized infection, and even some systemic infections; intravenous medication is recommended for infection involving the central nervous system. Commonly used antibiotics include amoxicillin, ceftriaxone, doxycycline, and other related antibiotics. The allergist may frequently be called on to evaluate cutaneous lesions to provide a differential diagnosis of a hypersensitivity reaction versus an infection. Even after the diagnosis of Lyme disease is established, during antibiotic therapy the patient may develop reactions to the antibiotic. These reactions may be immune-mediated or due to other effects that may provide a challenge to the allergist. The allergist may also be in the position to reassess the diagnosis of Lyme disease. For these reasons we present some of the aspects of Lyme disease that may guide the allergist as a diagnostician.

As noted above, the most important diagnostic sign is the presence of the EM, an expanding nonpruritic erythematous annular skin lesion. It often has a clear center or several concentric rings, hence its term as a bull's eye lesion. On the average it appears 4–14 days after a tick bite. Dissemination can occur, producing multiple EM lesions. It can also disseminate to other organ systems, which may include the heart, affecting conduction; the joints, especially large joints such as the knee; and most frequently, after the skin, are neurologic manifestations.

EM may be confused with several other cutaneous pathologies (see Table I). Cellulitis is often characterized by a sudden onset, it can occur any time of the year, it is painful, the distal leg is a frequent site, and lymphangitis may accompany it. Erythema annulare centrifugum usually has a slow enlargement and is associated with an underlying disease. Erythema multiforme is pruritic, vividly red, affects the distal extensor limbs, back of hands, and dorsum of feet, including palms and soles. There are oral lesions and a toxic syndrome. A fixed drug reaction is associated with medi-

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TABLE I
EM: Differential Diagnosis
Cellulitis
Erythema annulare centrifugum
Erythema multiforme
Fixed drug reaction
Granuloma annulare
Insect or spider bite
Plant dermatitis
Serum sickness
Tick bite reaction
Tinea corporis
Urticaria

cation, often has a burning pain, and involves the face and genitals commonly. Granuloma annulare occurs year around, with dermal papules, involves the dorsum of the hands and feet, is often chronic, and subcutaneous lesions may be seen. An insect or spider bite very often occurs on exposed area, is painful and pruritic, and local ulcerations may be seen. A plant dermatitis is characterized by sudden onset, erythema and edema, and pruritis. Serum sickness is accompanied by severe arthralgias, fevers, and may wax and wane. A local reaction to a tick bite develops within 24 hours. Tinea corporis, which is scaly with thin raised borders, occurs year round. An urticarial lesion is raised, pruritic, and may be episodic.

The nervous system may be involved even before the appearance of the EM lesion, although most frequently the neurologic symptoms occur later. There may be early manifestations or late manifestations. There are characteristic neurologic syndromes that may occur in early Lyme disease which are a viral-like meningitis, a Bell's palsy, or a radiculitis.[5,8,10] Later characteristic manifestations that may occur are a mild encephalopathy, mild polyneuropathy, or encephalomyelitis. Clues that a patient has neurologic Lyme disease include EM, exposure in an endemic area, a prior tick bite, a prior flu-like illness, a suggestive neurologic syndrome, and other organ system involvement such as joints, muscles, or palpitations.

The complete spectrum of neurologic Lyme disease has not yet been described, but it is clear that some atypical syndromes do occur in the presence of convincing laboratory evidence of the disease. It should be noted that North American neurologic Lyme disease is frequently accompanied by the appearance of a noninflammatory cerebrospinal fluid (CSF) analysis. In contrast, the European cases regularly demonstrate a pleocytosis. In North American cases specific symptoms that would alert the clinician to neurologic involvement include headache, stiff neck, drooping of one side of the face, "foggy" thinking, poor concentration, severe fatigue, pins and needles, or shooting pains in arms, legs, or trunk. Uncommon neurologic syndromes that have been described are cerebrovascular disease, intracranial pressure, myositis/myopathy, unusual manifestations, psychiatric disorders, dementia, motor neuron disease, and movement disorders.

The tick responsible for transmitting Bb may also transmit other infections. Co-infections are common and have included Babesia species, human granulocytic ehrlichia (HGE) species, deer tick (flavi) virus, Rickettsia species, and Bartonella species. Therefore, even treating Lyme disease may leave HGE beyond.

Unlike most other infection diseases, the laboratory diagnosis of Lyme disease has been hampered by several factors. Microbiologic confirmation by cultures of the slow-growing organism are rarely achieved in clinical settings, and if so, take weeks to show positive results. Identification of Bb DNA by PCR has not been of clinical value because it is infrequently positive in blood or CSF. The best source has been the skin lesion EM. However, a classic EM lesion would prompt therapy without further tests. The commercially available existing clinical antibody (Ab) tests take weeks to become positive, and if positive, cannot distinguish active ongoing infection from historical infection. The Ab test results may be indeterminate, requiring further testing, and extend the period of indecision and anxiety.[1] In addition,[2;11–14] current and developing LD vaccines will negate the currently recommended, but limited, two-tier laboratory approach for diagnostics because all immunized people will be positive on the first-step ELISA to whole Bb. Thus the need for an active marker of infection is needed.

The majority of EM patients are seronegative at the time they are first evaluated, so the diagnosis is presumptive.[15,16] With early antibiotics, up to 30% do not seroconvert.[16]

We have developed an approach using Bb-specific immune complexes (BbIC), which can be performed on a single sample. Data from our, and recently two independent labs, support this contention.[17–25] The rationale for our approach is anchored to well-studied other infection-immune interactions: the general response to any infection is production of Ab, which will bind infectious antigens (Ag). Bound Ab and Ag form the immune complex (IC). The very earliest Ab after infection will thus be found within IC, before they reach threshold detection in conventional Ab assays.[26] Once infection is eliminated Ab production continues, but there is no longer infectious Ag to bind to, and thus pathogen-specific IC disappear.[27–30] Therefore, detection of complexed specific Ab indicates active infection, whereas detection of free Ab does not.[26]

In summary, the allergist may become involved with a diagnosis and management of a Lyme disease patient for a variety of reasons.

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