



“Making Lemonade” out of Lyme

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Practitioners often encounter peculiar round/oval rashes in pediatric patients, particularly during the warm-weather months. Most of these rashes are benign, and most are insect-related; but certain ones may be more ominous.

In some regions of the country, tick bites are a year-round issue, but cases have been reported elsewhere in colder months, due to the frequent number of warm spells during the winter in which ticks may emerge. Besides, soon enough the warm months of “lemonade-time” and tick bites will be upon much of the rest of us. Thus I thought this presentation “refreshing” some aspects of particularly benign-looking rashes — with especially problematic outcomes if left untreated — would be worthwhile. As usual, these cases show that the synthesis of the history with the physical findings is critical.

CASE ONE

A previously healthy, white, 3-month-old girl presents to your office with a

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Figure 1. A 3-cm, faint, oval, maculopapular annular concentric lesion with some clearing in posterior axilla of 3-month-old girl. The small central papule, or “punctum,” was the site of tick bite.

faint, concentric 3-cm ovoid rash in the posterior axillary area (see Figure 1) that started yesterday. During a 3-day family camping trip at a Kentucky state park the previous weekend, the mother noticed a small black dot under the baby’s axilla, which she scraped off with much difficulty. The baby’s immunizations are up to date, she has been healthy, and is growing well. There are no other symptoms such as pruritus, fever, cough, rhinorrhea, or fussiness. Her physical examination is otherwise unremarkable; there is no fever and the range of motion in her neck and joints is normal. The mother remarked that the day after the camping trip, she removed a lot of “tiny little dark ticks” from her 4-year-old son. Could a 3-month-old child develop an arthropod-borne illness?

CASE TWO

A previously healthy, white, 4-year-old boy from central Kentucky comes to your office with a rash that has slowly progressed across his back since having a “tiny” tick removed. His mother reports the boy constantly plays outside on his family’s farm and that the tick was on the boy’s back for 7 days before it was removed 3 days prior to the office visit. Since the removal of the tick, the annular rash has enlarged to 5 cm in diameter with central clearing, a maculopapular border, and a central punctum bite (see Figure 2, page 58). The boy has been healthy recently and is fully vaccinated. He has no complaints of pruritus or pain with the rash, and also denies sore throat, other rashes, headache, fever, arthralgias, and gastrointestinal symptoms.

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The mother demands that her son be tested for Lyme disease. Is this rash alone significant enough to be diagnostic of an arthropod-borne illness?

CASE THREE

A previously healthy, white, 3-year-old boy from central Kentucky sustained a deer tick bite 8 days before coming to your office. When removed, the tiny tick was noted to be engorged and still barely visible. Six days later, an oval rash started on his left anterior chest region, which has now enlarged to 3 cm by 6 cm over 2 days (see Figure 3). The punctum area of the tick bite now has some mild papular urticaria as well. The rash has a mostly flat border, some central clearing, and has recently developed a tail of lymphangitis spreading posterior-laterally. The rash is not painful and only slightly pruritic. The boy has been fully vaccinated. He denies any sore throat, arthralgias, headaches, neck stiffness, fever, other rash, or gastrointestinal symptoms. His physical examination is otherwise unremarkable.

Does an arthropod-borne rash ever develop a mild lymphangitis? Could there be two concomitant bacterial infections, such as a lymphangitis from a concomitant staphylococcal infection?

CASE FOUR

A previously healthy, white, 16-year-old girl from central Kentucky frequently walks outside in the woods of her family's land. Twelve days earlier, she removed a deer tick from her left bicep area. Five days later she noticed the start of a small, red, slightly raised rash that was initially somewhat pruritic but never painful. It grew to about 5 cm by 5 cm by the time she presented to your office 2 days later. You prescribed amoxicillin 1 g twice daily for 14 days.

Five days later, however, the rash had doubled in size (see Figure 4, page 59), and she now complained of arthralgias of her knees, elbows, and neck, along with mild headaches, malaise, and feel-

ing slightly feverish. Although her initial physical examination 5 days earlier was normal, she now has some slight stiffness of her knees but no pain or redness of any joints. She is afebrile, her neck is supple, her retinal fundoscopic examination reveals no papilledema nor any blunting of the spontaneous venous pulsations, and the remainder of the examination is normal.

You were not aware of any report of antibiotic resistance to amoxicillin for *Borrelia*, but you do know that doxycycline is the preferred antibiotic for patients aged older than 8 years because it may have a higher noncomparative cure rate than amoxicillin in adults (100% vs. 92%, respectively) and it covers anaplasmosis.¹ Because she has now developed some mild systemic symptoms but no true arthritis, you surmise that switching to doxycycline 100 mg twice daily for 14 days would be prudent. Within 48 hours, she is remarkably better, and her arthralgias and subjective fever had abated.

LYME DISEASE

Epidemiology

Lyme disease, a zoonosis transmitted by the common deer tick (*Ixodes scapularis* in the East and Midwest, and *Ixodes pacificus* in the West), is caused by the bacterial spirochete, *Borrelia burgdorferi*.

When ticks attach, they appear as a tiny, black or dark dot, similar to an elevated freckle on the skin. Of the 15,000 cases reported annually,¹ the mid-Atlantic, northeastern, and north central areas of the United States account for 93% of all reports of Lyme disease.² Interestingly, Lyme disease is rarely reported south of Virginia because ticks in southeastern states and southwestern states feed mostly on reptiles rather than small mammals and deer.²

Reptile blood is bacteriostatic for *Borrelia*, thus explaining the rare incidence of Lyme disease in the southern US.^{1,3} However, the different species



Figure 2. A white, 4-year-old boy with a 5-cm rash with concentric round rim of raised maculopapules surrounding a central punctum deer tick bite from 10 days earlier.



Figure 3. A white 3-year-old boy with a 3-cm by 6-cm, oval, 2-day rash with slightly raised rim surrounding small raised papular-urticarial punctum deer tick bite from 8 days earlier. Note the faint 6-cm long, flat tail of redness spreading posterior-laterally from rim of lesion. Slightly pruritic directly over the tick bite, the rash was not painful.

of tick, *Amblyomma americanum*, can transmit a “look-a-like” spirochetal infection that can cause a similar solitary erythema migrans rash and a self-limited infection, known as southern tick-associated rash illness (STARI).^{2,3} The etiology of this lesion is unknown. Kentucky is located on the same geographic latitude as Virginia, so in my opinion, all cases of solitary erythema migrans must unfortunately be considered as early Lyme disease in our region. Just like the other rarer arthropod-borne diseases, Rocky Mountain spotted fever and ehrlichiosis, the primary season for Lyme disease is April through October, with the peak during the summer months.

The incubation period for Lyme disease is from 1 to 32 days, with a median of 11 days. Persons of any age can be infected, as we shall see in our discussion of Case One.

Stages of Lyme Disease

There are three distinct stages of Lyme disease. It is notable that these stages are similar to those of another rarer spirochetal infection, syphilis.¹

Stage one: early localized disease

Early localized Lyme disease presents with a solitary lesion, erythema migrans, in 80% to 90% of cases. It usually starts as a central small “punctum,” or papule, where the tick bite originated. It then spreads centrifugally to form a large annular or sometimes ovoid lesion usually 5 cm or larger, often accompanied by central clearing. This lesion is usually painless and nonpruritic but not always.

Erythema migrans can be differentiated from tick bite hypersensitivity. This usually occurs either while the tick is still attached or within 48 hours of detachment. The hypersensitivity rash typically begins to disappear within 1 to 2 days; is usually pruritic; and can sometimes become secondarily infected with *Staphylococcus* or *Streptococcus* bacteria, causing an abscess, cellulitis, lymphangitis, or reactive lymphadenitis. Case Three is characteristic of a typical lymphangitis from a tick bite. Lyme disease does not cause these types of skin manifestations by itself. The solitary erythema migrans rash of Lyme will typically begin to spread about 5 to 7 days after tick detachment or removal, and the untreated rash will last about 3 weeks.

But be aware that about 65% of patients will also develop nonspecific virus-like symptoms, such as malaise, fatigue, neck pains, headache, migratory arthralgias, chills, and fever.³ However, objective physical findings of frank arthritis are not present during stage one, when a diagnosis is made on clinical



Figure 4. A rapidly spreading 10-cm, concentric, nonpruritic, round rash with raised maculopapular rash border, clearing around the punctum in a white, 16-year-old girl. The patient sustained a tick bite 12 days earlier. Despite amoxicillin therapy, the rash enlarged and the patient developed some systemic symptoms and arthralgias.

grounds alone. Early treatment nearly always aborts the development of later stages of Lyme disease.

Stage two: early disseminated disease

If early Lyme disease is left untreated, as it is in about 10% to 20% of children, it will evolve into the secondary disseminated stage.^{2,3} This stage most commonly manifests several weeks, or occasionally several days, after the tick bite as multiple lesions of smaller erythema migrans. Other rare findings during this stage include carditis manifested as mild to severe atrioventricular block, cranial nerve palsies (particularly of the 7th cranial nerve—facial palsy), ophthalmic conditions, and a subacute lymphocytic meningitis. Systemic symptoms are also much more prevalent and intense at this stage, and include fever, headache, myalgia, arthralgia, and fatigue.^{2,3}

Stage three: late disease

This very rarely observed stage is characterized most commonly by a

large-joint, pauci-articular arthritis, usually in the knees. Peripheral neuropathy and central nervous system manifestations are rarely ever seen in children.²

DIAGNOSTIC TESTS

The early stage of Lyme disease is diagnosed strictly on the clinical observation of a solitary erythema migrans lesion of at least 5 cm, with or without a history of a deer tick attachment. *Borrelia* antibody titers are not detectable in most people within the first 4 weeks following the appearance of erythema migrans.⁴ Once treated appropriately, most patients will never develop antibodies. The development of antibodies after the treatment of early stage Lyme disease, however, does not indicate therapy has failed.⁵

The biopsy and culture of the skin lesion is not recommended due to the difficulty with growing the culture from the specimen.

The diagnoses of early disseminated disease and late disease should be made on the basis of both clinical appearance

and serologic confirmation. Nearly all patients with later stage Lyme disease will have detectable antibodies. This requires a two-step process for most laboratories.^{1,2} The first test consists of either an enzyme immunoassay or an immunofluorescent antibody assay. Only if this test is positive or equivocal should a Western immunoblot test be performed for confirmation.

TREATMENT OF EARLY STAGE LYME DISEASE

Early Localized Disease

According to the American Academy of Pediatrics (AAP) 2012 Red Book, "Antimicrobial therapy for nonspecific symptoms or for asymptomatic seropositivity is discouraged."² Doxycycline is the preferred antibiotic for those older than 8 years; whereas amoxicillin is recommended for younger patients. Cefuroxime is recommended for those allergic to penicillin; note that first-generation cephalosporins are not effective for *B. burgdorferi*. Azithromycin is less effective and is not recommended as first-line therapy. Duration of beta-lactam and doxycycline therapy should be for at least 14 to 21 days.

Erythema migrans usually resolves within a few days of antibiotic therapy, but other low-grade signs and symptoms may persist for weeks to months despite successful therapy. In fact, fatigue and arthralgias may persist for up to 3 months in 25% of adequately treated patients; 10% of adults do not respond to therapy.³ For further specific antibiotic dosing regimens and for management of early disseminated disease and late disease, refer to the 2012 AAP Red Book.²

DISCUSSION OF CASES

Each of the four cases presented a peculiar diagnostic aspect of Lyme disease. All four cases were treated with appropriate doses (50 mg/kg/day to 90 mg/kg/day, with a maximum dose of 1 g) of amoxicillin twice daily, and each patient responded rapidly and unevent-

fully to therapy except for Case Four.

Case One

You were perplexed by the very young age of this patient with an early erythema migrans lesion. But all other indicators pointed to the Lyme diagnosis, including the deer tick removal, the timing of the rash's appearance several days later and not immediately (tick hypersensitivity), the punctum, the central clearing, and the raised border. The down-side of non-treatment was too consequential because of high morbidity, and the risk of antibiotic treatment was miniscule.

Case Two

Despite your objections and clear explanations to the child's mother that serologic titers were unnecessary for early localized Lyme disease, at her insistence, you obtained the serology. The acute *Borrelia* titer results were negative, and the child did fine, with total resolution of the rash in a few days.

Case Three

Despite a fairly typical solitary ovoid erythema migrans lesion, this child most likely had a secondary bacterial infection of the tick bite with a mild ascending lymphangitis from either a staphylococcal or streptococcal infection. In hindsight, amoxicillin clavulanate or cefuroxime may have been better choices because of their methicillin-sensitive *Staphylococcus aureus* coverage. The most important factor in atypical cases is the careful follow-up over the next several days.

Case Four

You initially thought that the continued spread and new onset of systemic symptoms 5 days into therapy most likely indicated a failure while on amoxicillin therapy. Up to 10% of adults do not respond to initial antibiotic therapy. However, one caveat: Could she have possibly experienced a Jarisch-Herxheimer-like immunologic reaction from

the lysis of the spirochetes treated with penicillin? This reaction is reported in 15% of patients. It typically consists of fever and chills within 24 hours of antibiotic therapy, and is associated with more intense systemic symptoms and an increase in size and intensity of erythema of the skin lesion. The rash will eventually resolve in 7 to 14 days.² Thus, in this case, a 10% antibiotic failure rate must be contrasted with a 15% Jarisch-Herxheimer reaction rate. Because this rash worsened despite 5 days of amoxicillin therapy, you surmise this patient was an antibiotic failure.

For initial antibiotic failures with early stages of Lyme, a repeat course of a different appropriate oral antibiotic for 14 to 21 days is recommended. Finally, for early disseminated Lyme disease, appropriate oral antibiotics are still considered first-line therapy. Oral doxycycline for 21 days has been shown to be as comparably effective as intravenous ceftriaxone for the same duration. Hospitalization and intravenous therapy with ceftriaxone is only indicated for symptomatic patients with meningitis, carditis, second- or third-degree atrioventricular (AV) block, or first-degree AV block with a very prolonged PR interval (≥ 300 milliseconds). ■

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