Widespread localized areas of annular patches, plaques, and erythema

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Abstract

Without prompt diagnosis and treatment, patients with Lyme disease may develop life threatening multi-organ system complications. As such, we discuss the key diagnostic features of the condition along with patient-specific suggested treatment protocols. Additionally, Lyme disease is reportedly expanding to regions that were previously not impacted, key epidemiological features are outlined. We discuss a patient with severe Lyme disease who presented with widespread cutaneous involvement and atypical pathologic findings within an uncharacteristic geographic region. Erythematous, annular patches and plaques with dusky-to-clear centers were initially observed on the right thigh and later extended to the trunk and bilateral lower extremities. The diagnosis of Lyme disease was made clinically and confirmed with western blot testing that was positive for IgM antibodies. The patient additionally had a history of rheumatoid arthritis, for which he discontinued treatment prior to the current presentation with Lyme disease. During follow up visits, the patient noted lower extremity joint pain. Due to the overlapping clinical features of post-Lyme arthritis and rheumatoid arthritis, key differences are outlined to prevent misdiagnosis. Data revealing trends in the geographic distribution of the disease and possible need for increased surveillance and prevention strategies within previously unaffected areas are discussed.

Keywords: Borrelia burgdorferi, chronicum migrans, erythema, infectious, Lyme disease

Introduction

We present a patient with early disseminated Lyme disease observed in North Carolina with erythema chronicum migrans widely distributed on the trunk and bilateral lower extremities. Lyme disease is the most common vector-borne disease in the United States and occurs secondary to an infection with *Borrelia burgdorferi*, a bacterial species transmitted to humans by the *Ixodes* tick. The clinical manifestations present in three major stages termed early localized, early disseminated, and late disseminated. Progression to later stages, typically due to a lack of prompt recognition and treatment, leads to increased risk of complications and multi-organ dysfunction. The diagnosis can be confirmed with two-tiered testing with either enzyme-linked immunosorbent assays or indirect immunofluorescence assays, followed by a Western blot testing. A biopsy of a dermatologic site of involvement can also be taken, which typically reveals a dense superficial and deep perivascular and interstitial mixed inflammatory infiltrate. Treatment typically includes oral antibiotics (doxycycline or amoxicillin) on an outpatient basis for mild presentations caught early or more intensive treatment (ceftriaxone) with hospitalization for more severe, disseminated cases.

Case Synopsis

A 68-year-old man was referred to the dermatology clinic with a 10-day history of fatigue and

hypotension as well as newer onset diffuse rash. Past medical history was significant for hepatitis C (post-treatment), hypertension, and rheumatoid arthritis (RA). Patient interview revealed a recent work-related trip to a remote area in northeastern North Carolina and frequent outdoor gardening in a wooded area but he recalled no tick or bug bites. The patient discontinued adalimumab, prednisone, and sulfasalazine 1-2 months prior to the current presentation following RA remission. He also reported recent addition of a mushroom supplement to his diet.

The rash first appeared exclusively on the right thigh and progressed during the week to involve his trunk and bilateral lower extremities. Examination revealed widespread erythematous patches and plaques, some being annular with dusky or clear centers on the bilateral lower extremities (**Figure 1A**), chest (**Figure 1B**), and back (**Figure 1C**). Vital signs were notable for hypotension and fever. Complete blood count revealed leukocytosis, normocytic anemia (most likely anemia of chronic disease per iron profile results), and an elevated absolute neutrophil count. Blood and urine cultures were unremarkable. Serology was positive for Lyme disease. Western blot testing revealed positive IgM antibodies and negative IgG antibodies. Additionally, antibody testing for *Anaplasma phagocyophilum*, *Ehrlichia chaffeensis,* HIV, hepatitis (A, B, and C), cANCA, and pANCA were negative.

A 4mm punch biopsy was obtained which demonstrated spongiotic dermatitis with perivascular inflammation and eosinophils (**Figure 2**). The patient was administered intravenous fluids, broad-spectrum antibiotics including intravenous cefepime (1g in sodium chloride 0.9% 100ml), vancomycin (1,250mg/282.5ml NS), and doxycycline (100mg in 100ml sodium chloride 0.9%) with 90% improvement in the rash, resolution of fever, and normalization of leukocyte count. With respect to the erythema migrans, the trunk and arm skin findings cleared and faint annular erythematous plaques were observed with central hyperpigmentation on the lower extremities bilaterally. Following this clinical improvement, the patient was administered a 14-day course of 100mg oral doxycycline on an outpatient basis.

Three weeks after the completion of the outpatient treatment course, the patient presented for a follow-up appointment. During the visit, there were no dermatologic abnormalities and complete resolution of previous erythema migrans was observed. The patient reported new onset achiness in bilateral hips and lower extremities, which he attributed to strenuous outdoor physical activity and described it as being distinct from previously experienced RA-related pain. On physical examination, no lower extremity synovitis, tenderness, swelling, or erythema was observed. Serologies were positive for Lyme disease; Western

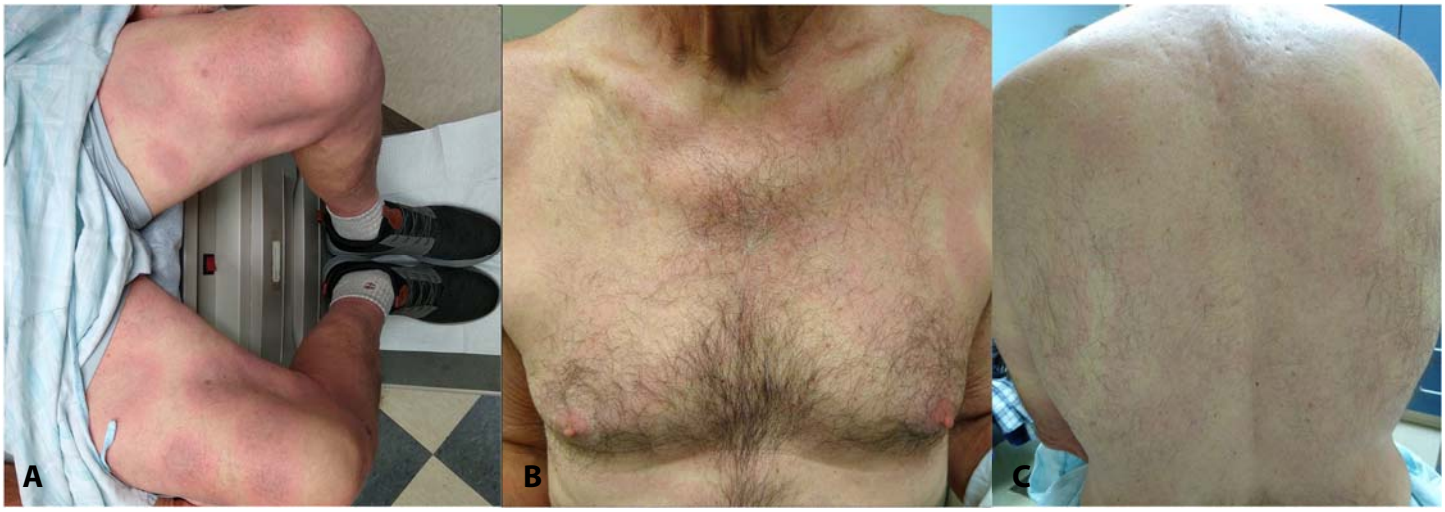

Figure 1. ***A)*** *Annular patches and plaques with poorly demarcated rings of erythema surrounding a dusky center on the bilateral lower extremities.* ***B)*** *Coalescing, erythematous targetoid patches and plaques on the chest and upper abdomen.* ***C)*** *Faint, coalescing erythematous targetoid patches and plaques on the back.*

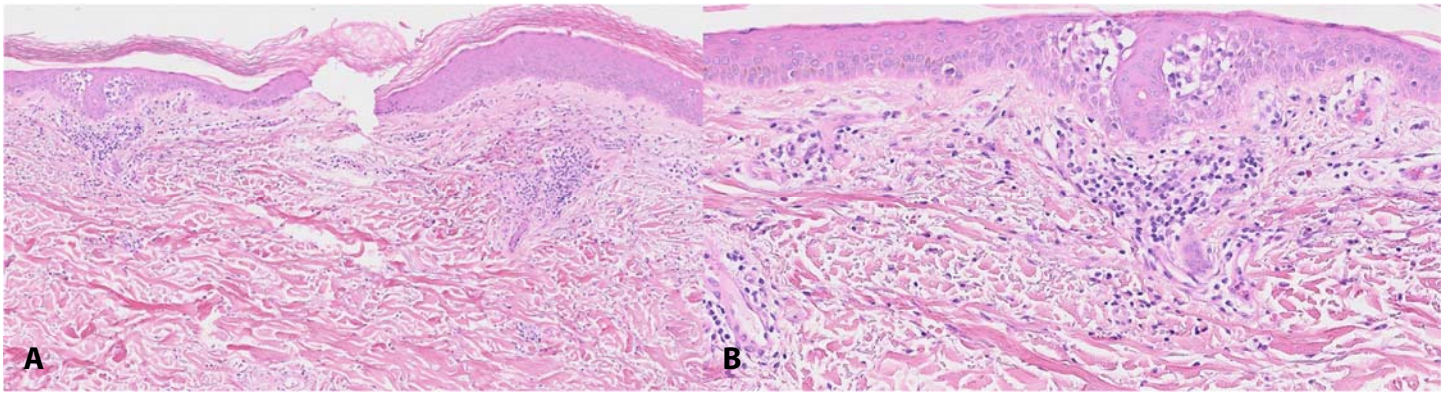

Figure 2. *H&E histopathology. A 4mm punch biopsy was performed, revealing orthokeratosis, mild spongiosis and rare dyskeratotic keratinocytes with a superficial perivascular lymphocytic infiltrate with eosinophils and occasional neutrophils.* ***A)*** *40×;* ***B)*** *100×.*

blot analysis revealed positive IgM Lyme disease antibodies, negative IgG Lyme disease antibodies, and elevated inflammatory markers (ESR: 42mm/hr; CRP: 12.8mg/l). Two months afterwards, the patient described progressive improvement of the bilateral lower extremity achiness, noted intermittent lower extremity pruritus, and reported no fever or rash. Although serology and IgM Western blot analysis for Lyme disease remained positive, inflammatory marker levels normalized. Finally, during the most recent follow-up visit three months afterwards, the patient reported an acute episode of bilateral lower extremity pruritus followed by feeling off-balance. Subsequent pain in the region was also noted and this lasted several days and self-resolved. Although occasional bilateral lower extremity pain is endorsed the patient reports the symptoms continued to improve in intensity over time.

Case Discussion

Lyme disease is caused by bacterial infection with *Borrelia burgdorferi* and is transmitted through *Ixodes* tick bites. The clinical presentation consists of three major stages, with the first termed *early localized*. It is characterized by an isolated rash, fatigue, headache, myalgias, and arthralgias. The rash is classically referred to as erythema migrans and initially presents with localized erythema at the site of the tick bite within two weeks. Later, it expands outward and creates a central area of clearing with a ring of surrounding erythema [1]. The next stage is termed *early disseminated* and presents with subsequent areas of multiple erythema migrans, cranial nerve palsy, meningitis, carditis, and migratory arthralgias. Finally, without treatment, Lyme disease can progress to the *late stage* with complications including arthritis, encephalitis, and peripheral neuropathy. Of note, the initial dermatologic manifestation of Lyme disease, classically termed the "bulls-eye rash," can appear differently in patients in skin of color which can lead to a delayed diagnosis and increased risk for life-threatening complications from untreated disease progression. For example, in a study investigating the clinical manifestations of Lyme disease in Black and White patients, a greater proportion of Black patients were observed with neurological complications of Lyme disease compared to White patients (34% versus 8%, $P<0.001$), [2]. Increased awareness, training, and representation within clinical resources of the differences in skin findings observed among patients with darker skin types with dermatologic conditions may reduce late diagnoses and misdiagnosis.

The patient was diagnosed with RA (rheumatoid factor negative) in 2019 that was effectively managed with adalimumab, sulfasalazine, and prednisone. Treatment was discontinued following remission 1-2 months prior to the current presentation, during which he endorsed no RA-related symptoms and continued to be in remission. As a result of potentially overlapping symptoms between Lyme arthritis and systemic autoimmune conditions that are reported to occur following Lyme disease including rheumatoid arthritis (RA) and psoriatic arthritis (PsA), careful history taking, evaluation, and testing are essential in preventing misdiagnoses and ensuring proper treatment

administration [3]. Of note, post-Lyme RA and PsA are more likely to present with polyarticular joint involvement, experience a longer duration of arthritis, and show equivocal or low levels of Anti-Borrelia burgdorferi IgG antibody levels compared to Lyme arthritis [3]. Additionally, although Lyme disease is a reported risk factor for RA development, there is limited information regarding susceptibility for patients with previously diagnosed RA to experience flares following Lyme disease. Within the present case over the follow-up period of three months, the patient has not experienced an RA flare following treatment and resolution of Lyme disease.

The diagnosis of Lyme disease is clinical and treatment does not require specific laboratory testing techniques. Punch biopsies of patients with erythema migrans are routinely performed in cases of suspected Lyme disease. Histology typically demonstrates a dense superficial-to-deep perivascular and mixed interstitial inflammatory infiltrate mixed with eosinophils and plasma cells [4]. Histopathologic variations are also possible, including epidermal spongiosis, interface changes, and/or lymphocytic infiltrate in the perineurial or periadnexal regions [4]. Confirmatory testing involves quantitative serum measurement of *B. burgdorferi* antibodies by way of a 2-tiered testing comprised of immunoblotting. More specifically, ELISA or immunofluorescence assays are utilized initially and if positive, a Western blot is performed [5]. Per guidelines, a Western blot test requires two of three and 5 of 10 bands for positive IgM and IgG blots, respectively [6]. Of note, serologies may reveal persistence of IgG and/or IgM antibodies for up to 10-20 years after antibiotic treatment and are not indicative of an active infection [7]. Additionally, serological testing is not recommended for monitoring antibiotic treatment response because levels of both IgM and IgG antibodies can be extremely low or undetectable during early stages of the disease [8]. The inability to detect IgG antibodies specifically following antibiotic treatment may be a result of antibiotic-mediated prevention of IgM-to-IgG isotype switching [9]. As such, serological testing should be performed after clinical evaluation reveals a suspected case of Lyme disease rather than for isolated diagnostic or treatment monitoring purposes [9].

Treatment is typically determined by the extent of the disease and observed organ system involvement. Generally, the early localized and early disseminated stages of Lyme disease can be successfully treated with oral doxycycline, amoxicillin, or cefuroxime in adults and children, oral amoxicillin or cefuroxime in pregnant and lactating women, and azithromycin in patients allergic to amoxicillin. In contrast, the treatment of choice in adults and children with late disseminated disease is dependent on the presenting organ-system complications [10]. For example, with respect to neurological Lyme disease, adults and children with facial palsy are treated with oral doxycycline, whereas adults and children with Lyme meningitis or radiculoneuritis can be treated with oral doxycycline or intravenous ceftriaxone [10]. Patients with evidence of Lyme carditis are treated based on the severity, with mild cases of atrioventricular block in children and adults treated with oral doxycycline, amoxicillin, or cefuroxime, whereas intravenous ceftriaxone is recommended for severe, symptomatic cases. Finally, adults and children ≥8 years of age with Lyme arthritis are treated with oral doxycycline, amoxicillin, or cefuroxime and children <8 years of age are treated with oral amoxicillin or cefuroxime [10]. In cases of Lyme arthritis unresponsive to the oral antibiotic treatment options intravenous ceftriaxone is recommended [10].

Lyme disease is the most common vector-borne disease in the United States, with 275,589 reported cases during 2008-2015 [11]. States experiencing the highest incidence of Lyme have typically been localized within the Northeast, mid-Atlantic, and Midwest regions, with the highest three-year average incidence reported in Maine, Vermont, and New Hampshire [12]. Interestingly, however, reported cases within regions where the disease has been historically predominant have remained stable or decreased, while neighboring states have reported an increase in incidence [11]. For example, the map of reported cases from 2001 display only the northern-most area of Virginia affected with

extension through the state in subsequent years. By 2018-2019, however, a greater proportion of reported cases were observed in the previously unaffected northwestern region of North Carolina [12]. Additionally, the number of counties reporting an incidence of ≥10 cases per 100,000 individuals increased from 324 in 2008 to 432 in 2019 [13].

Conclusion

Lyme disease should be considered as a diagnosis in patients presenting with the appropriate clinical signs and/or symptoms in the neighboring states of regions with a high historical incidence [11]. Additionally, careful patient history gathering and diagnostic testing are recommended in addition to efforts to distinguish Lyme arthritis from post-Lyme RA and PsA. Further, this case highlights the need for increased public awareness and healthcare provider surveillance in prompt recognition and treatment of Lyme disease for the prevention of potentially life-threatening complications. With over 2,000 reported yearly hospitalizations and 26-million-dollars in healthcare expenditures annually in the United States, efforts focused on improving detection and promoting prevention are essential in reducing overall disease burden [13]. Adoption of previously successful measures employed in historically high-incidence regions observing disease stabilization into neighboring states with increasing case numbers may be beneficial.

Potential conflicts of interest

The authors declare no conflicts of interest.

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