

Early Dermatological Manifestations of Lyme Disease

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ABSTRACT

In the past 15 years, Lyme Borreliosis has emerged as a significant challenge within endemic regions and previously unaffected areas. Consequently, during periods of heightened infection risk, such as spring and summer, individuals should remain vigilant and be capable of identifying risky behaviors to mitigate the risk of infection. Given that the skin is the primary organ affected, with erythema migrans being a hallmark symptom, recognizing this characteristic rash is paramount. In cases where the condition remains undiagnosed, it can involve various organ systems, including the neural, cardiovascular, or musculoskeletal systems. Therefore, the accurate recognition of this rash by both patients and healthcare providers plays a pivotal role in enabling early diagnosis and initiating appropriate treatment. This article presents two cases of Lyme Borreliosis observed in Georgia and underscores the significance of a thorough evaluation of cutaneous manifestations for early diagnosis within a scientific research context.

Keywords: Erythema migrans, Lyme borreliosis, Lyme disease.

INTRODUCTION

Lyme borreliosis (LB), or Lyme disease, is a bacterial infection induced by spirochetes belonging to the *Borrelia burgdorferi sensu lato* complex. These spirochetes invade human skin approximately 48 hours post-exposure to ticks infected with the bacteria, and after 72 hours, the risk of spirochete infection reaches 100%. The probability of human infection within an endemic region is influenced by vector ticks' local abundance and infection rate, along with human behaviors, occupations, and recreational activities that increase tick exposure (e.g., forestry workers, hunters, and hikers).^{1,2}

The onset of the infection typically manifests as an enlarging skin lesion known as erythema migrans (EM). The interval between the tick bite and the appearance of erythema varies between 3 to 30 days. EM is characterized by its round or oval shape, red coloring, and centrifugal expansion, often exceeding a diameter of 5 cm. EM occurs in approximately 70–80% of cases. In acute Lyme disease, EM may or may not be accompanied by flu-like symptoms, including fever, fatigue, myalgia, and arthralgia.

Untreated Lyme disease can affect multiple body systems and present many symptoms. These may include the development of acute Lyme neuroborreliosis, Lyme carditis within weeks of infection, or Lyme arthritis within months of infection. Therefore, the precise recognition of EM by both patients and healthcare providers is essential for ensuring early diagnosis and appropriate treatment.^{3,4}

CASE REPORT 1

A 42-year-old male, employed as a forestry worker in the vicinity of Kiketi forest, which is geographically proximate to

Tbilisi, presented with a rash on the lateral surface of his left forearm. The patient could not recall the precise tick bite incident but noted his frequent forays into the forest due to work requirements. The rash became increasingly conspicuous over a few days, and a week following its initial appearance (during the first decade of August), he sought medical consultation with a dermatologist at "Health Center" Ltd, Tbilisi, Georgia. He reported no joint swelling, vomiting, or abdominal or chest pain history. Physical examination unveiled clinical features consistent with Lyme disease, notably the presence of a characteristic skin rash: a single, well-defined, oval erythema measuring 10 cm in diameter, with a centrally located dark red papule, corresponding to the site of a tick bite (Fig.1).

FIGURE 1. Early localized erythema migrans with typical characteristics



The patient's history, the manifestation of classic localized status, and the increased susceptibility of individuals spending extended periods in wooded areas raised concerns regarding Lyme borreliosis. The serology was made on the 20th day after the onset of the rash, and Lyme disease was confirmed. An infectious disease specialist was engaged in the treatment process, resulting in the patient's complete recovery.

CASE REPORT 2

A 54-year-old female was referred to the dermatology department at Health Center, Ltd., reporting the presence of multiple rashes on the dorsal surface of her right tibia, accompanied by fatigue and malaise. According to the patient, she had recently been on a summer vacation in Tskneti, a geographical area near Tbilisi. During a forest walk, she observed an insect crawling on her leg, which she removed. On the third day post-incident, she noticed a medium-sized red spot on her skin, along with itching in the affected area. Over the subsequent days, the spot failed to regress and expanded and gave rise to multiple foci. The patient sought medical attention 15 days after the tick bite. Clinical evaluation revealed an erythematous rash consistent with the characteristic presentation of Lyme borreliosis. Notably, two nearly identical round erythemas, each measuring 6 cm in diameter, displayed dark red and indurated central papules, indicative of tick bites. The surrounding ring exhibited more intense pink coloring and perifocal signs of inflammation (Fig.2).

FIGURE 2. Multiple erythema migrans lesions in the early disseminated stage of Lyme disease



This presentation included two distinct rash types: a red-colored lesion, deviating from the classical Bull's Eye Erythema Migrans pattern and a target-like lesion. The skin surface remained smooth, and the patient reported no associated burning or painful sensations. In early disseminated Lyme disease, many cutaneous manifestations of Erythema Migrans may emerge, such as erythematous rings with central clearing, erythematous plaques, or

purpura.⁵ Considering the patient's medical history, clinical presentation, and heightened tick activity during the relevant period, a diagnosis of the Early Disseminated Stage of borreliosis was established. Serological confirmation was obtained three weeks after the incident, with the involvement of an infectious disease specialist, ultimately leading to the patient's full recovery.

DISCUSSION

The typical presentation of an erythema migrans (EM) rash manifests after the third day of infection, primarily occurring at the tick bite site and expanding outward as the condition progresses. EM rash typically lacks characteristics such as heat, itching, or elevation and does not typically respond to antihistamines or antifungal creams. The rash may take on circular or oval shapes but can also exhibit a blotchy appearance, varying in coloration from red, blue, and/or purple, with occasional yellowing.⁵ A classic manifestation is a "ring-within-a-ring" or a "bull's eye" lesion. The first case described a single classical skin lesion (resembling a "Bull's eye").

When a patient presents with a slowly expanding, annular, erythematous skin lesion during the summer months, along with a potential risk of Lyme borreliosis due to exposure to ixodid ticks, current guidelines advise clinicians to make a clinical diagnosis of EM rather than immediately pursuing Lyme borreliosis diagnostic tests. This approach is preferred due to the lower sensitivity of antibody-based blood tests in the acute phase of the illness. Direct detection through culture or PCR necessitates a skin biopsy and specialized laboratory procedures, typically only available in research settings. Serological testing carries a high risk of producing false-negative results, especially within the first week of infection, while false-positive results are more commonly associated with IgM antibodies, which can also appear in individuals suffering from other bacterial or non-infectious diseases.^{6,7}

In diagnosing early Lyme disease, the primary criteria rely on visual identification of EM, associated symptoms, the patient's history of tick exposure, and the epidemiologic risk. The absence of a standardized appearance may lead to misdiagnosis. Distinguishing erythema migrans from conditions like cellulitis, herpes simplex or herpes zoster, mycosis fungoides, granuloma annulare, interstitial granulomatous dermatitis (IGD), tinea corporis (mini-EM), discoid (nummular) eczema, urticaria, erythema multiforme, and erythema necroticans migrants is reliant on the expertise of clinicians.⁸

Numerous erythema migrans lesions are relatively uncommon but suggest infection dissemination. The second case described such a presentation. Multiple erythema migrans lesions are smaller than the original ones and exhibit uniform discoloration. Skin changes associated with erythema migrans can be accompanied by systemic symptoms, including fever, muscle and joint pain, headache,

and, occasionally, meningeal signs and lymph node enlargement.

The fields of molecular biology and biochemistry significantly contribute to our understanding of the structure and function of micro and macro-organisms and intracellular regulatory processes. This knowledge of the molecular mechanisms of disease development is crucial for accurate diagnosis and the effective targeting of new therapeutic agents.

The pathogenicity of *Borrelia burgdorferi* hinges on several factors, including the spirochete's motility, cytotoxicity, antigenic variability, lymphocyte stimulation, and the spirochetes' resistance to complement activation in the absence of specific antibodies.¹ The interaction of spirochetes with glycosaminoglycans, such as heparin, heparan sulfate (facilitating endothelial cell fusion), and dermatan sulfate (enabling fusion with glial cells), plays a pivotal role. Bacterial lipoproteins located on the membrane recognize host skin proteoglycan decorin. The outer membrane contains high-density outer-surface lipoproteins (Osp) and low-density β -barrel outer-membrane-spanning proteins like Bama. The inner membrane consists of integral membrane proteins, many of which function as transporters. Researchers have recently identified tick salivary proteins that contribute to pathogen transmission. This inflammatory response results in the hallmark skin lesion, erythema migrans, during the initial days of infection, characterized by papillary dermal edema and a mixed infiltrate predominantly consisting of T cells, neutrophils, dendritic cells, and monocytes or macrophages. Cytokine expression during this stage is predominantly pro-inflammatory, marked by elevated tumor necrosis factor (TNF), IL-2, IL-6, and type I interferons (IFNs). Chemokines attracting neutrophils (e.g., CXCL1), macrophages (e.g., CC-chemokine ligand 3, CCL3, and CCL4), and T cells (e.g., CXCL9, CXCL10, and CXCL11) are also increased in erythema migrans lesions.⁹

Borrelia burgdorferi inhibits phagocytosis, and phagocytosed spirochetes are removed from the host through oxygen-dependent and independent processes. Oxygen-dependent processes involve reactive oxygen and nitrogen species, such as hydrogen peroxide (H₂O₂), singlet oxygen, and halogenated derivatives. In contrast, oxygen-independent processes rely on hydrolases like proteases and glycosidases located in the lysosomes of phagocytes.¹

CONCLUSIONS

Accurate interpretation of dermatological manifestations plays a pivotal role in facilitating the diagnosis of Lyme Borreliosis. The prompt confirmation of the disease and the timely initiation of antibiotic therapy are critical factors in ensuring a favorable disease course and preventing the development of multisystem complications. As such, the assessment of dermatological presentations is recognized as

the primary tool in managing Lyme borreliosis within scientific research.

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