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Case presentation

Vesicular erythema migrans: an atypical and easily misdiagnosed form of Lyme disease

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Abstract

Erythema migrans is the initial sign in the majority of patients infected with *Borrelia*, the genus of spirochetes that causes Lyme disease. Early identification and treatment decrease the risk of progression to later stages of disease. Although a "bull's eye" appearance owing to lesional clearing is considered classic for erythema migrans, this feature is surprisingly often lacking among patients in the United States. Furthermore, cutaneous Lyme disease can exhibit a wide range of morphologic variability in a minority of patients. Herein, we describe the case of a patient with Lyme disease in which the presence of atypical vesicular features, in conjunction with the initial absence of clearing, resulted in multiple misdiagnoses and delayed treatment. We also review the literature on the epidemiology and management of erythema migrans for cases in which the diagnosis may pose a challenge.

Keywords: arthropods; Borreliosis; doxycycline; erythema migrans; Lyme borreliosis; Lyme disease; tick bite; vesicles

Introduction

Erythema migrans (EM) is the presenting sign of Lyme disease in over 70% of patients [1]. Classically, the lesion begins as an erythematous macule or papule at the site of a *Borrelia*-infected *Ixodes* tick bite. Over days to weeks, it expands centrifugally to a diameter of at least 5 centimeters while developing paracentral or central clearing [2, 3]. The resulting "bull's eye" or annular appearance has become the *sine qua non* of erythema migrans, yet the most common presentation in the United States is actually a uniformly erythematous patch or plaque [4]. In addition, several morphologic variants of EM have been described, including vesiculobullous, urticarial, and linear eruptions [2, 5, 6]. As demonstrated by the following case report and review of the literature, overreliance on the "bull's eye" pattern of erythema migrans and under-appreciation of its morphologic spectrum can delay accurate diagnosis and appropriate treatment.

Case synopsis

A healthy 36-year-old woman presented to the emergency department (ED) in June with a painful eruption of the left popliteal fossa. Fourteen days prior, she first noticed a firm, asymptomatic nodule developing in the left popliteal fossa. She presented to her primary medical doctor (PMD) seven days later; no overlying skin changes were noted and the doctor suspected that she had a Baker's cyst. Over the next three days, the patient developed painful, non-pruritic papulovesicles across the skin folds of the left popliteal fossa. Repeat visits to her PMD led to a diagnosis of allergic contact dermatitis (ACD) secondary to poison ivy and the patient was given a mild topical corticosteroid. She continued to develop vesicles and went to a walk-in urgent care clinic one day prior to ED presentation, where she was diagnosed with superimposed cellulitis and was started on oral trimethoprim-sulfamethoxazole and topical triple antibiotic ointment. On the day of ED presentation, the skin of the left popliteal fossa became increasingly edematous, erythematous, and painful, limiting the patient's mobility and interfering with sleep. As she had experienced no improvement after one day of trimethoprim-sulfamethoxazole, she decided to present to the ED. She denied fevers, chills, night sweats, arthralgias, prior localized varicella-zoster virus (VZV) infection (she recalled a childhood history of chickenpox), prior herpes simplex virus (HSV) infection, or recent tick or other arthropod bites. She did report that she spent weekends in a wooded area of Long Island, New York during the months of May and June. She otherwise had no relevant travel history.

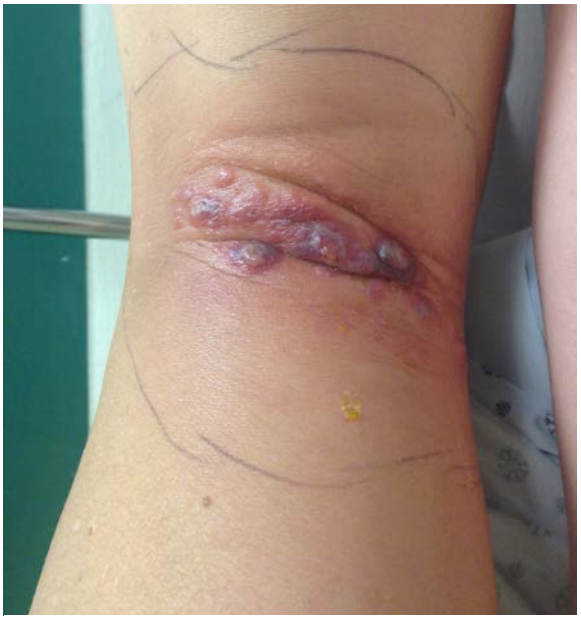
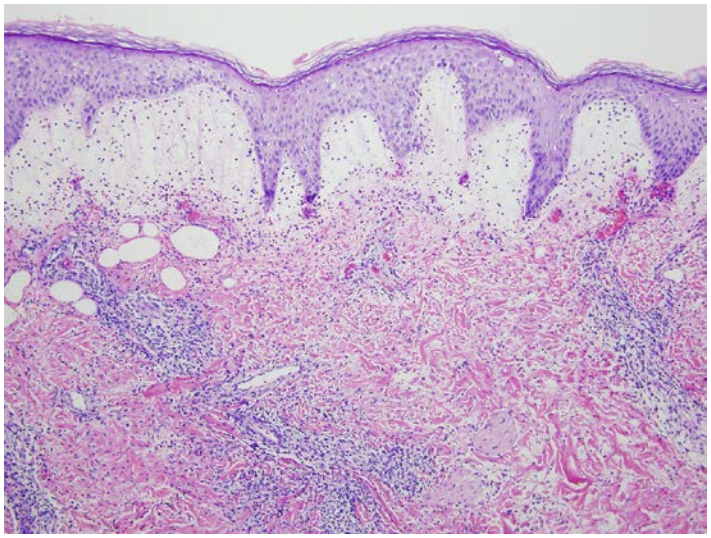


Figure 1. Left popliteal fossa with an oblique linear array of erythematous, edematous papulovesicles containing hemorrhagic fluid and surrounded by a 10-centimeter, uniformly erythematous plaque.

Physical examination of the left popliteal fossa demonstrated an oblique linear array of erythematous, edematous papulovesicles, some of which contained hemorrhagic fluid. The area was tender to palpation and was surrounded by a well-demarcated uniformly erythematous plaque approximately 10 cm in diameter (Figure 1). The patient was afebrile and had a white blood cell count of 7.3 x 10^9/L (normal 4.8-10.8 x 10^9/L). The remainder of the skin examination was unremarkable.

The differential diagnosis in the ED included an exuberant reaction to an arthropod bite, ACD secondary to poison ivy and/or triple antibiotic ointment, VZV infection, HSV infection, and superimposed cellulitis. The patient was discharged from the ED on empiric valacyclovir and topical mupirocin ointment and was instructed to complete the full 10-day course of trimethoprim-sulfamethoxazole.

A Tzanck preparation of a papulovesicle was negative for multinucleated giant cells and showed many neutrophils, erythrocytes, and some keratinocytes without nuclear atypia. Gram stain identified a few white blood cells and no organisms. Bacterial and viral cultures were negative. Biopsy of a papulovesicle revealed a perivascular and interstitial mixed cell dermatitis with prominent papillary dermal edema and lymphocytic vasculitis (Figure 2). No viral cytopathic changes were present.



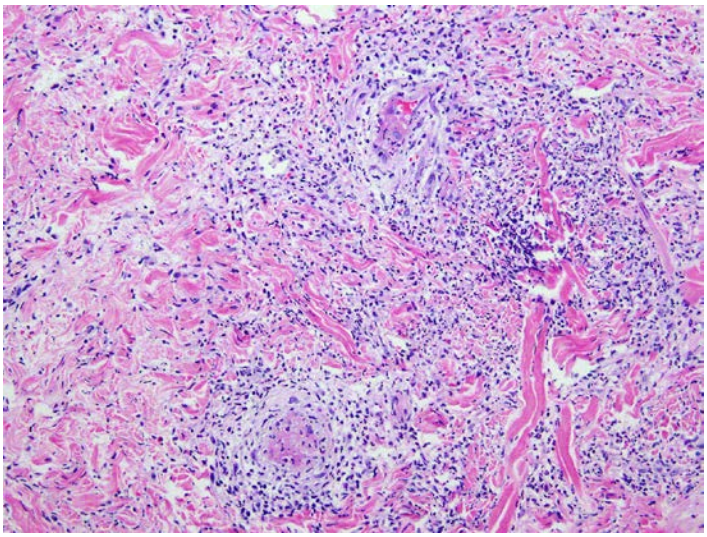


Figure 2. Histopathologic images of a skin biopsy from the left popliteal fossa (hematoxylin-eosin). (A) 100X, Prominent papillary dermal edema, and an infiltrate composed of lymphocytes, histiocytes, and neutrophils. (B) 200X, Lymphocytes within the walls of blood vessels, and fibrin within vessel walls and lumens.

On follow-up four days after discharge from the ED and 18 days from initial nodule development, the patient reported malaise, continued pain, and new vesicles despite strict adherence to antibacterial and antiviral therapy. Physical examination revealed that the erythematous plaque surrounding the central cluster of papulovesicles had developed paracentral clearing or a "bull's eye" pattern (Figure 3). Because the patient had not improved with therapy, erythema migrans was considered and trimethoprim-sulfamethoxazole was switched to oral doxycycline. Serological testing for Lyme disease was performed 22 days after the initial nodule was noted and 15 days after the papulovesicular eruption started. Enzyme-linked immunosorbent assay (ELISA) was positive; Western blot was IgM positive (bands 23, 39, and 41) and IgG negative. Steiner silver staining of the papulovesicle biopsied at the patient's original ED visit did not reveal spirochetes.

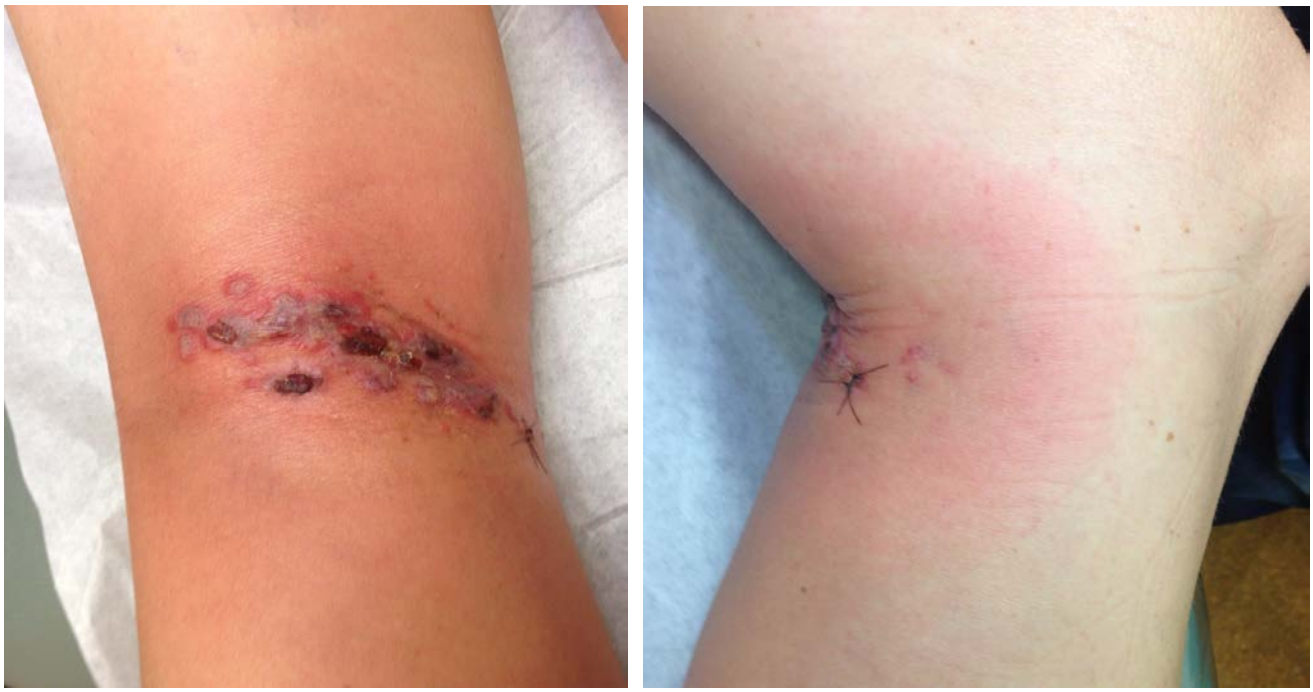


Figure 3. Frontal (A) and lateral (B) views of the paracentral clearing, or "bull's eye" pattern, that developed in the erythematous plaque surrounding a central cluster of papulovesicles 18 days after initial lesion onset.

During the first 24 hours on doxycycline, the patient reported intensified systemic malaise and backaches. On day two of doxycycline, she noted dramatic improvement with resolution of her systemic symptoms and healing of the cutaneous lesions of the left popliteal fossa. Physical examination 25 days after initial nodule onset demonstrated postinflammatory hyperpigmentation, residual crust, and no tenderness to palpation. The patient completed a two-week course of doxycycline 100 mg twice daily, after which she reported full resolution of the lesions and return to her normal state of health.

Discussion

As underscored by this case, the classic features of erythema migrans are relatively uncommon among patients with Lyme disease in the United States. According to a recent meta-analysis, only 26% of patients in the United States with Lyme disease-associated erythema migrans recalled a tick bite and only 19% had central clearing, compared with 64% and 79% of patients in Europe, respectively. In addition, patients in the United States more often presented with systemic symptoms such as fatigue, headache, myalgias, and arthralgias [4]. This difference has been suggested to reflect the greater virulence of *Borrelia burgdorferi*, the spirochete responsible for Lyme disease in the United States, compared with *Borrelia afzelii* and *Borrelia garinii* in Europe [7, 8]. It is therefore not surprising that patients in the United Sates present for medical attention sooner and with less lesional central clearing, which occurs, in part, as a function of time [7].

Among the morphologic variants of erythema migrans, the vesiculobullous form may be more prevalent than previously thought. In prospective studies of U.S. patients with Lyme disease-associated erythema migrans, 3.7% to 8% had central vesicles and/or bullae containing clear, cloudy, or hemorrhagic fluid [8, 9, 10, 11, 12]. The observation that the vesicles and bullae occur exclusively in the center of erythema migrans has prompted the hypothesis that they may represent a reaction to the tick bite [11]. This is supported by our patient's histology showing a tick bite reaction with edema and localized lymphocytic vasculitis. This

theory is further supported by the lack of vesiculation in patients with multiple erythema migrans lesions, which do not result directly from a tick bite but rather the hematogenous or lymphatic spread of *Borrelia* from the inoculation site [8]. In addition, it has been proposed that vesiculobullous erythema migrans may reflect an enhanced host immune response to *Borrelia* inherently or to a greater spirochetal load [11]. Similarly, an enhanced immune response to antigens released from dying spirochetes is believed to underlie the Jarisch-Herxheimer reaction, a temporary worsening of symptoms within the first 24 hours of treatment of a spirochetal infection. Eight to 19% of patients with Lyme disease-associated erythema migrans have developed the Jarisch-Herxheimer reaction [13, 14, 15, 16, 17], including our patient and another patient reported to have vesicular erythema migrans [18].

As exemplified by our patient's multiple misdiagnoses, vesiculobullous erythema migrans can be challenging to diagnose because it is often confused for cellulitis, herpes zoster, an arthropod bite, or ACD secondary to allergens like poison ivy [11, 19, 20, 21]. Furthermore, because erythema migrans tends to be more painful when vesicles or bullae are present, patients may present sooner after onset and thus before clearing develops [8]. These factors have contributed to delays in treatment of up to three weeks in reported cases [11, 19, 20], which is critical given that recovery is less likely if therapy is initiated after four weeks of symptom onset [22]. To help prevent this delay, the diagnosis of erythema migrans should be considered based on a patient's epidemiologic context, affected skin surface, and report of systemic symptoms, irrespective of a lesion's morphology. Patients at risk have resided in, or traveled to, an area endemic for Lyme disease. In the United States, New York and 13 other states, mostly in the Northeast, accounted for 95% of the country's confirmed Lyme disease cases in 2013 [23]. The peak months of onset are June and July, when ticks in the nymphal stage most actively seek blood meals from vertebrate hosts [24, 25]. Erythema migrans favors areas of the body where tick movement is impeded, such as the popliteal fossae and other intertriginous zones, sites of clothing straps, and the hairline [2, 9].

When erythema migrans has an atypical morphology or is absent altogether, two-tiered serologic testing for anti-*Borrelia* antibodies can be helpful diagnostically. In most cases, the Centers for Disease Control and Prevention and the Infectious Diseases Society of America (IDSA) recommend that erythema migrans be diagnosed and treated exclusively based on compatible clinical findings [26, 27]. Serologic testing should not be performed, as it is not sensitive within the first two weeks of erythema migrans onset (only a minority of patients has been found to be seropositive as early as the first week) [27, 28]. However, in those few cases of diagnostic uncertainty, the IDSA makes an exception and recommends serologic testing during both the acute phase and convalescent phase (two to four weeks after the acute phase) [27]. Other features that may support the erythema migrans diagnosis include the development of a Jarisch-Herxheimer reaction and, when vesicles are present, the absence of significant pruritus (in contrast to the pruritic vesicles of ACD or VZV infection) [27]. In addition, a Tzanck preparation, viral culture, viral polymerase chain reaction, and/or routine histology can help to exclude VZV or HSV infection. Other laboratory tests, such as Steiner staining and *Borrelia* culture, have limited value because they are too insensitive or not routinely available [5]. In cases in which erythema migrans cannot be differentiated from cellulitis, treatment for both conditions can be considered with amoxicillin-clavulanate, oral cefuroxime, or the combination of oral doxycycline and cephalexin [18, 19, 29].

Conclusion

This case report and review of the literature highlight the paradox of EM in the United States: the classic "bull's eye" pattern is often lacking and atypical features—especially painful, non-pruritic vesicles—may occur more frequently than expected. As a result, regardless of a lesion's morphology, erythema migrans should be considered in the differential diagnosis of all patients with a compatible clinical and epidemiologic history.

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