Recurrent erythema migrans despite extended antibiotic treatment with minocycline in a patient with persisting *Borrelia burgdorferi* infection

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Erythema migrans recurred in a patient 6 months after a course of treatment with minocycline for Lyme disease. Polymerase chain reaction on heparinized peripheral blood at that time demonstrated the presence of *Borrelia burgdorferi*–specific DNA. The patient was seronegative by Lyme enzyme-linked immunosorbent assay but showed suspicious bands on Western blot. Findings of a Warthin-Starry stain of a skin biopsy specimen of the eruption revealed a *Borrelia*-compatible structure. Reinfection was not believed to have occurred. Further treatment with minocycline led to resolution of the erythema migrans. (J AM ACAD DERMATOL 1993;28:312-4.)

Controversy exists about whether ongoing signs and symptoms in patients previously treated for Lyme disease are caused by persisting infection, immunologic sequelae in the absence of infection, or a combination of the two.[1] We report a case that we believe emphasizes the stubborn and persisting nature of *Borrelia burgdorferi* infection.

CASE REPORT

A 68-year-old woman developed typical erythema migrans (EM) on her right anterior thigh; the lesion eventually attained a diameter of 10 cm. The patient had no history of a tick bite, but she had gone hiking in Harriman State Park in Rockland County, New York, 3 weeks earlier. She developed arthralgias of the fingers of both hands and of the left knee, ankles, and tibias, and she also had myalgia of the left thigh. Headache and fever were absent. Before the development of the lesion on the thigh, a dime-sized eruption had been noted on her right forearm. This eruption lasted approximately 3 weeks. Its intensely red and indurated center eventually sloughed.

The patient was treated for Lyme disease with tetracycline for 10 days. Results of Lyme serologies were negative. Her joint symptoms resolved and the eruption faded, leaving a faint, red-purple ring. Physical examination 4 months later revealed the skin lesion, tenderness of the left first metacarpalphalangeal joint, and discomfort with internal and external rotation of the left hip. Results of Lyme serology, antinuclear antibody, rheumatoid factor, and syphilis serology were negative.

The patient was treated with minocycline, 100 mg, twice daily, for 3 months. The eruption faded. Fleeting polyarthralgias continued after completion of treatment but gradually subsided.

Two months later she began to experience migratory

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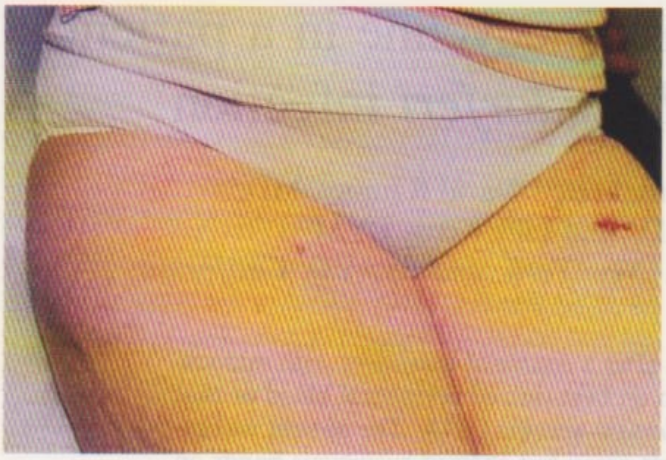

Fig. 1. EM lesions as they appeared November 1989, 17 months after onset of illness. Lesion on right thigh is remnant of original EM. Lesion on left thigh, which was biopsied, appeared in July 1989.

"pin jab"–like sensations in her right leg, right sole, left palm, and right great toe. These sensations resolved in 1 month. A repeat Lyme serology was negative.

Three months later a new annular erythematous eruption suggestive of EM developed on her left anterior thigh. In addition, the original lesion on the right thigh, which had never entirely disappeared, became more erythematous (Fig. 1), and arthralgia of the left thumb recurred. She had no opportunity for reexposure to deer ticks.

A specimen of heparinized whole blood tested by the polymerase chain reaction (PCR) technique for *B. burgdorferi*–specific DNA by the method of Rosa and Schwan was positive.[2] T-cell blastogenic response to *B. burgdorferi* was negative. A repeat specimen for PCR analysis was again positive. A skin biopsy specimen from the left thigh revealed a slightly thinned epidermis. Within the papillary and upper reticular dermis there was a moderately dense, perivascular infiltrate of lymphocytes that cuffed vessels. Occasional plasmacytoid lymphocytes were found. Mild edema was noted within the papillary dermis, and lymphocytes in small numbers were scattered between collagen bundles, occasional mast cells, and one small focus of exocytosis of lymphocytes (Fig. 2). A single *Borrelia*-compatible structure was identified within the epidermis by Warthin-Starry staining (Fig 3). A portion of the skin biopsy specimen, cultured for several months in Barbour-Stoenner-Kelly II medium, was negative. It had been shipped on dry ice and stored at −70° C before it was cultured.

Treatment with minocycline was resumed, and the eruptions faded gradually. After 3 months of treatment, PCR testing was negative.

After 10 continuous months of treatment with minocycline, the patient was completely well. Serum tested by Western blot for *B. burgdorferi* at that time showed the presence of weak bands at 31, 41, and 66 kd on IgG testing and a 31 kd band on IgM testing. Indirect fluorescent antibody and enzyme-linked immunosorbent assays for Lyme serology continued to be negative. When last seen 9 months later, the patient remained healthy with no reemergence of her skin lesions.

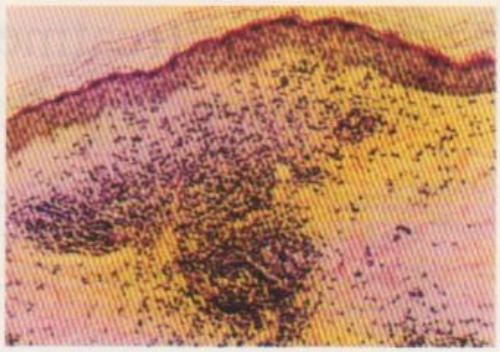

Fig. 2. Skin biopsy specimen shows a moderately dense perivascular infiltrate of lymphocytes cuffing vessels in papillary and upper reticular dermis. (Hematoxylin-eosin stain.)

Fig. 3. Skin biopsy specimen. *Borrelia*-compatible form. (Warthin-Starry stain.) (Courtesy Alan MacDonald, MD.)

DISCUSSION

We believe that this patient had Lyme disease. Seronegativity may have been the result of early treatment with tetracycline.[3]

The histologic findings of her skin biopsy specimen were compatible with EM. Similar late skin manifestations of Lyme disease that showed benign lymphocytic infiltration of the dermis have been described recently.[4] EM recurred without reexposure to deer ticks. Therefore, late-occurring skin lesions in patients previously treated for Lyme disease should not necessarily be interpreted as reinfection, but may signify persisting, recrudescent disease. It may be difficult to distinguish recrudescence from reinfection in patients who reside in Lyme-endemic areas. Our patient lived in New York City and had no opportunity for reexposure. Her original eruption intensified at the same time that a new lesion of EM appeared on the opposite thigh, which supports the likelihood that these phenomena represented recrudescent disease rather than reinfection.

B. burgdorferi has been cultured from patients after treatment with a variety of antibiotics. In one patient the living organism was cultured from the cerebrospinal fluid after a 10-day course of intravenous ceftriaxone.[5] How is *B. burgdorferi* able to evade destruction by antibiotics and the patient's immune response? Recent in vitro studies demonstrated intracellular localization of *B. burgdorferi* in human umbilical vein endothelial cells.[6] This may explain the frequent relapses clinically observed in patients who have Lyme disease after treatment, because infections caused by intracellular pathogens are notoriously difficult to cure.[7]

Although we were unable to unequivocally prove the persistence of *B. burgdorferi* by culturing the organism in this case, epidemiologic, clinical, serologic, histologic, and PCR evidence indicates that Lyme disease was the correct diagnosis and suggests the ability of this organism to survive despite 90 days of treatment with minocycline. The patient had no symptoms and was clinically healthy 9 months after completing a further 10-month course of treatment. Time will tell whether the infection has been entirely eradicated or whether it persists and will subsequently recrudesce. Our experience with this patient and others like her[8, 9] has convinced us of the need to treat some patients who have Lyme disease far longer than currently recommended regimens, which we believe are inadequate for such patients.

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