

CLINICAL REPORT

Early Disseminated Borreliosis with Multiple Erythema Migrans and Elevated Liver Enzymes: Case Report and Literature Review

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A 69-year-old man presented with multiple livid maculae and infiltrated urticarial plaques, as well as elevated liver enzymes. Based on typical clinical picture, histopathology and positive PCR from a skin biopsy, we diagnosed an early disseminated infection with *Borrelia afzelii* presenting with multiple erythema migrans (*erythemata migrantia*) and a subclinical hepatitis. During antibiotic treatment with intravenous ceftriaxone, the maculae and plaques vanished almost completely and the liver enzymes decreased within 14 days. Dermatologists should keep in mind that early disseminated borreliosis can present with multiple erythema migrans and hepatitis. Key words: disseminated borreliosis, erythemata migrantia, Lyme borreliosis, multiple erythema migrans, non-specific hepatitis, parainfectious hepatitis

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An infection with *Borrelia burgdorferi* can lead to different clinical diseases, which are divided into three stages (Table I). The dermatological symptom that occurs most often during borreliosis is erythema migrans, which is

early localized disease. Early disseminated disease, presenting with multiple erythema migrans or *erythemata migrantia*, appears more often in the USA than Europe, probably because of different infectious genospecies. It was first described in Europe by Detmar et al. in 1989 (1). The observed number of lesions of erythemata migrantia is less in Europe (<6) than in the USA (>20).

We wish to report a patient presented with about 70 erythematous maculae and infiltrated urticarial plaques over the whole body. Furthermore, he showed elevated liver enzymes that accompany early disseminated borreliosis in about 66% of cases. Both the *erythemata migrantia* and the subclinical hepatitis are very important symptoms of early disseminated borreliosis.

CASE REPORT

A 69-year-old white man presented in July 2005 with mild itching and multiple livid maculae and plaques, which had started on his legs one week previously and generalized during the last 3–4 days. The patient did not have any accompanying symptoms. He could not remember having any tick bites, and did not have any pets. His hobby was gardening. He suffered from metabolic syndrome and alcohol abuse and had been taking numerous medications for years.

Skin examination showed approximately 70 disseminated, not sharply demarcated, erythematous maculae

Table I. Clinical stages of Lyme borreliosis

Organ	Early localized disease	Early disseminated disease	Chronic disease
Skin	Erythema migrans	Disseminated erythema migrans +/- subclinical hepatitis and other systemic symptoms Borreliolymphocytoma	Acrodermatitis chronica atrophicans
Nervous system		Meningopolyradiculoneuritis Cranial neuritis	Encephalopathy Encephalomyelitis
Musculoskeletal system		Arthritis Myositis	Chronic arthritis
Cardiovascular system		Carditis Tachycardia Atrioventricular block	Cardiomyopathy



Fig. 1. Widespread, poorly demarcated erythematous maculae and infiltrated urticarial plaques with central lividity covering the entire body.

and infiltrated urticarial plaques with central lividity over the entire body, sparing the head, palms and soles (Fig. 1). No lymphadenopathy was present. Physical examination, including cardiovascular and neurological evaluations, was normal.

Histopathology showed an epidermis with slight basal layer hyperpigmentation and, in the dermis, diffuse lymphohistiocytic infiltrate rich in plasma cells centred around vessels, some of which were dilated (Fig. 2). *Borrelia* PCR from two skin biopsies detected DNA amplification of the borrelial outer surface protein A (OspA) gene (Fig. 3). The amplicon was sequenced to further subtype the genotype and revealed a base sequence corresponding to *B. afzelii*; the methods have been previously described (2). *Borrelia* serology revealed borderline values for *B. burgdorferi* IgG (5 U ml^{-1} – limit $5\text{--}9 \text{ U ml}^{-1}$) and qualitative positive *B. burgdorferi* IgM. The immunoblot was positive for *B. burgdorferi sensu lato* IgG (VlsE; p41; OspC) and IgM (VlsE; p41; OspC; p41/intern; p41/intern)*.

Furthermore the liver enzymes were elevated (alanine transaminase 51 U l^{-1} , lactate dehydrogenase (LDH)

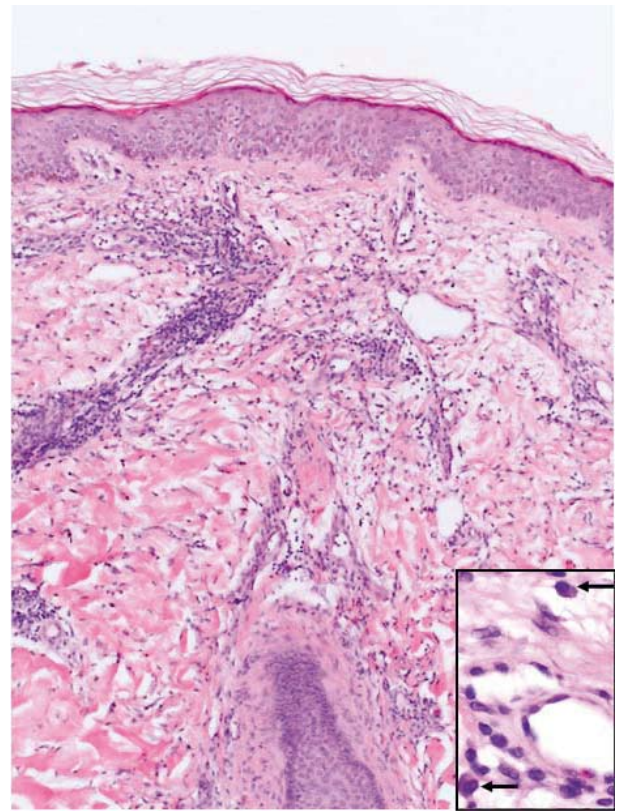


Fig. 2. Histopathology: in the upper dermis, diffuse lymphohistiocytic infiltrate with plasma cells (inset: arrows) centred around vessels, some of which are dilated (H&E $\times 100$).

274 U l^{-1} , gamma-glutamyl transaminase 367 U l^{-1}) as well as C-reactive protein (CRP) 2.13 mg dl^{-1} . Hepatitis serology showed slight positive anti-hepatitis A virus (HAV)-IgM and high positive HAV-IgG. Serology for hepatitis B and C was negative and a control serology after 8 months showed only positive anti-HAV IgG, but negative anti-HAV IgM.

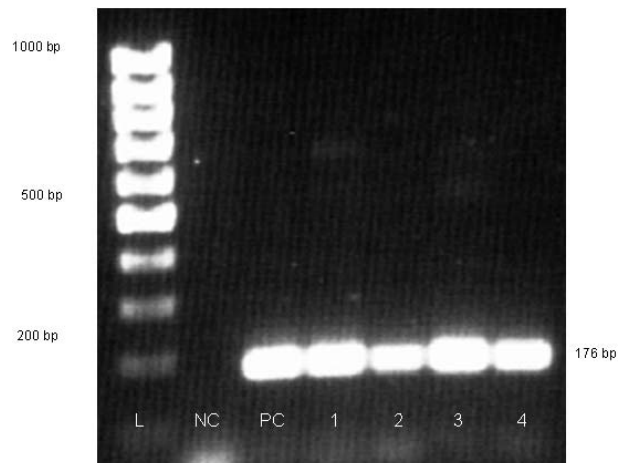


Fig. 3. DNA-amplification of the borrelial OspA gene in two skin biopsies. L, ladder; NC, negative control; PC, positive control; bp, base pairs; 1–4, patient samples (1: back; 2, back; 3: lower leg; 4: lower leg, diluted 1:10).

*VlsE protein encoded by the gene "variable major protein (VMP)-like sequence E".

The diagnosis of an early disseminated infection with *B. afzelii*, presenting with multiple erythema migrans was confirmed by PCR from skin biopsies and serology. During the antibiotic therapy with intravenous ceftriaxone (2 g/day) over 14 days the maculae and plaques blanched and decreased in number. Since complete remission was not achieved, the patient was treated for 7 more days with doxycycline (100 mg twice a day) leading to complete healing of the skin disease.

The elevated liver enzymes and the initially positive anti-HAV serology were both interpreted as an unspecific reaction during the generalized Borrelia infection. Abdominal ultrasound showed hepatomegaly (19 cm in the medioclavicular line). During antibiotic treatment, the liver enzymes decreased, suggesting a borrelial hepatitis superimposed on a pre-existing alcoholic hepatitis. However, the decrease in liver enzymes might also be due to the lower alcohol intake during the antibiotic treatment. There were no other findings suggesting disseminated borreliosis.

DISCUSSION

Lyme borreliosis is caused by infections with Borrelia species transmitted by ticks and is the most common vector-borne illness in the USA and Europe (3). The disease is endemic in the northeast and north-central states of the USA, Central Europe and Scandinavia, with an annual peak from May to September. The annual incidence rate in those countries ranges from 50–400 cases per 100,000 persons and is growing steadily. Lyme borreliosis affects both sexes and all age groups, but favours children and adults aged 30–50 years.

Up to now, 11 genome species have been characterized from the *B. burgdorferi* complex (*B. burgdorferi sensu lato*). Three of them are human pathogens: *B. burgdorferi sensu stricto* which occurs mainly in the USA, *B. garinii* and *B. afzelii* that are most often isolated in Europe (4, 5).

The clinical course is divided into three stages (Table I). Most (60–90%) Borrelia infections start with erythema migrans after an incubation time of 10–30 days. However, 27–79% of the patients do not remember a tick bite. Central clearing of the erythema migrans seems to depend on the duration of the lesion and not, as widely assumed, on the infectious species (6), and may be absent in >50% (7). Early cutaneous manifestations of Lyme borreliosis further include borrelial lymphocytoma. However, lymphocytoma and the chronic stage of acrodermatitis chronica atrophicans are extremely rare or non-existent in the USA (7).

Fifty-three percent of the patients with erythema migrans report itching, burning or pain due to local neuritis. Extracutaneous symptoms include fatigue, malaise, arthralgias, myalgias, headache, meningeal signs, lymphadenopathy, fever, chills, vertigo, nausea

and anorexia and can be found in 30–68% of patients. These symptoms occur more often in the USA than in Europe.

Through either haematogenous dissemination or several tick bites, up to 20% of the patients in the USA with Borrelia infections have multiple erythema migrans with up to 70 lesions (4, 8). Multiple erythema migrans are less often seen in Europe (5–10%) and the patients have fewer lesions (2–6 in Europe; >20 in the USA) (9, 10). This difference might be due to the higher occurrence of *B. burgdorferi sensu stricto* in the USA, as this genospecies is often isolated from patients with multiple erythema migrans there, while *B. afzelii* seems to be the most important genospecies causing multiple erythema migrans in Europe (11).

According to an investigation of 73 patients with early Lyme borreliosis, 27% had liver function abnormalities, with elevation of gamma-glutamyl transaminase being the most common finding (12). These results were confirmed in another study of 115 patients (13). Forty percent of the patients with erythema migrans had at least one generally mild liver function abnormality, with gamma-glutamyl transaminase and alanine transaminase being the most frequently affected enzymes. Patients with early disseminated Lyme borreliosis were more likely to have elevated liver function tests (66%) compared with patients with localized disease (34%).

Erythema migrans is a self-limiting disease, but antibiotic treatment is required because persisting *B. burgdorferi* might lead to dissemination and late manifestations of Lyme borreliosis. Oral doxycycline (2×100 mg/day), amoxicillin (3×500 mg/day) and cefuroxime axetil (2×500 mg/day) should be used as first-line antibiotics during a 2–3 week course. Doxycycline might cause photosensitivity, but has a superior penetration into the cerebrospinal. It is therefore also effective in neuroborreliosis at a dose of 200–400 mg/day for 2–3 weeks (14, 15). Erythema migrans can be treated with oral doxycycline over 21 days (range 10–21 days) as it is equally effective in preventing the late manifestations of Lyme borreliosis compared with parenterally administered ceftriaxone over 14 days (16). During the antibiotic treatment of erythema migrans an exacerbation of symptoms due to a Jarisch-Herxheimer reaction in a setting with high bacterial load has to be kept in mind. Normally the skin lesions dissolve over 1–4 weeks after the start of antibiotic treatment. As doxycycline, but not ceftriaxone, is contraindicated in liver dysfunction, and although our patient did not suffer from severe liver dysfunction, we decided to treat him with intravenous ceftriaxone. Our patient showed a decrease in transaminases under ceftriaxone and after discharge he was treated for a further 7 days with doxycycline. Dermatologists have to bear in mind that early disseminated borreliosis can present with multiple erythema migrans and sub-clinical hepatitis.

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