Lyme borreliosis (LB) is a multisystem infection caused by the tick-borne spirochete *Borrelia burgdorferi* (1). Diagnosis of LB is primarily based on history and clinical evidence; however, the characteristic skin lesion, erythema chronicum migrans, may not always develop, and it is possible to confuse the long-term neurological, rheumatological and cardiac manifestations of LB with other diseases (2-4). Serologic testing is the preferred technique for laboratory confirmation of this infection because direct visualization of *B. burgdorferi* in patient specimens is difficult, and cultivation is a low-yielding process (4,5). Currently, the most common serologic tests used in LB diagnosis are indirect immunofluorescence assay (IFA), enzyme-linked immunosorbent assay (ELISA) (6,7), enzyme-linked fluorescent immunoassay (ELFA) (8), and Western blotting (WB) (9,10). The test results must be interpreted with caution because false-positive and false-negative results are common with them.

Erythema induratum of Bazin (EIB) is a form of nodular vasculitis associated with *Mycobacterium tuberculosis* (11). Clinically, it is characterized by recurrent, tender nodules subcutaneous usually seen on the legs (12). We describe a patient with EIB whose serology was false-positive for *B. burgdorferi*. An association of tuberculosis with LB has not been reported in the English language literature to date. To our knowledge, this is the first reported case of EIB to feature false-positive *B. burgdorferi* serology.

**Summary**

Lyme borreliosis is a multisystem disorder that is diagnosed on the bases of characteristic clinical picture and laboratory confirmation. Although serologic analysis is generally considered the best laboratory method for detecting the disease, false-positive and false-negative results are common with the tests currently in use. We report a case of false-positive *Borrelia burgdorferi* serology associated with erythema induratum of Bazin.

**Key Words:** Lyme Disease, Erythema Induratum, Serodiagnosis, Borrelia Burgdorferi

**Özet**


**Anahtar Kelimeler:** Lyme Hastalığı, Eritema Induratum, Serolojik Tanı, Borrelia Burgdorferi

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CASE REPORT

In September 1997, a 52-year-old man presented with recurrent, painful, nonulcerative erythematous nodules on the anterior aspect of his right thigh and calf over the last three months (Fig. 1). Two months prior to admission, serum testing with ELFA at another hospital indicated the patient was positive for *B. burgdorferi* (total Lyme Ig M and Ig G). The lesions seemed to clear after a 2-week course of oral amoxicillin (1g/day) but a relapse was encountered 1 week after completing therapy. We repeated the serology for *B. burgdorferi* by ELFA, and again found a positive result, with an index value of 1.67. ELFA was carried out using an automated VIDAS instrument (bioMerieux Vitek, Inc., Hazelwood, Missouri, USA). The index value is obtained by dividing the relative fluorescent value of the sample by the standard value. An index ≥ 1.00 is considered positive. Although there was no history of a tick bite, we pursued further treatment based on the tentative diagnosis of LB. Considering his first antibiotic therapy as inadequate for LB, we prescribed 3 weeks of oral doxycycline (200 mg/day). However, when the patient did not respond to this course of antibiotic therapy, we eliminated LB as a possible diagnosis.

Histopathology of an incisional biopsy specimen from one of the lesions on the patient’s right thigh revealed granulomatous panniculitis compatible with nodular vasculitis. A positive purified protein derivative test (PPD) (induration area of 15mm x 15mm in 48 hours) and detection of mycobacterial DNA in the lesional skin by polymerase chain reaction (PCR) supported the diagnosis of EIB. The patient was given triple-drug antituberculous chemotherapy (isoniazid 300 mg/day, rifampicin 600 mg/day, pyrazinamide 2 g/day) and was free of lesions after the first week of treatment. The pyrazinamide was discontinued after 2 months of therapy, and the patient continued to take isoniazid and rifampicin for another 7 months. One week after completion of therapy, his lesions reappeared. Since this was an indication of potentially insufficient therapy, the same triple-drug regimen was started again; however, the patient’s lesions persisted. Thinking this might be due to drug resistance, we added ethambutol (1.5 g/day) and ciprofloxacin (1g/day) in the third month of treatment, and also added prednisolone (1mg/kg/day) 1 month later. After five months of therapy, he was lost to follow up.

DISCUSSION

Our patient had no history of a tick bite or any of the classic clinical findings for LB. However, his subcutaneous nodules, one of the cutaneous findings in early LB(13), and the positive serology for *B. burgdorferi* supported the tentative diagnosis of LB. Unfortunately, we were unable to complete a two-test protocol, which would have been a more solid basis for diagnosis. We ruled out LB when the patient did not respond to appropriate antibiotic therapy. Histopathological and clinical findings, a positive PPD test and detection of mycobacterial DNA in the lesional skin by PCR led to the final diagnosis of EIB.

Figure 1. Erythematous nodules on the anterior aspect of the patient’s right thigh.
Because there are some proteins of *B. burgdorferi* common with the other bacteria(14) the patient’s positive serology result for *B. burgdorferi* may reflect immunologic cross-reactivity. Nonetheless, one can not exclude the other causes of false-positivity completely. The English literature contains no reports of immunologic cross-reactivity of *B. burgdorferi* with *M. tuberculosis*.

The diagnosis of LB is based on history, clinical findings and laboratory data. Clinical diagnosis of LB can be challenging. The presence of erythema migrans, a skin lesion unique to this condition, is the best marker during the initial stage of the infection, but it does not always develop or may manifest atypically(2-4) Other cutaneous lesions may also be encountered (13). Later stages of the disease may include severe arthritic, neurologic and cardiac manifestations that can easily be confused with several other disorders(2-4).

Since culturing the organism or visualizing *B. burgdorferi* in specimens from LB patients tends to be difficult, serologic testing is the main diagnostic aid(4,5). ELISA and IFA are the most common serologic techniques used, and both measure the binding of circulating serum antibody to antigen. These tests are not completely sensitive and specific for LB(15). Comparing the two, a number of studies have shown ELISA to be more accurate than IFA(6,7). ELFA is a type of enzyme immunoassay in which the intensity of fluorescence is measured by optical scanner (fluorometer)(8). Western blotting is a technique that is more sensitive and specific than ELISA (9). In WB, spirochete antigens are separated by electrophoresis, and antibodies in the serum to any of these antigens can be characterized. The disadvantages are that this method is time-consuming, nonquantitative and difficult to standardize as the results are observer-dependent. WB is usually favored as the test to confirm ELISA results, and thus improve specificity(9,10). In 1995, Centers for Disease Control and Prevention recommended the use of a two-test protocol for serodiagnosis of LB(16). In this protocol, suspected LB patients are screened with an ELISA test and any positive cases are confirmed with WB. While some reports(10,17) have deemed this approach useful, Goossens and colleagues(18) found that WB did not increase the specificity of ELISA testing for LB.

The specificity of serology for detecting *B. burgdorferi* is limited by a number of issues and circumstances. The main problems are lack of standardization between laboratories, immunologic cross-reactivity, asymptomatic subclinical or previously treated LB(15). Inconsistency between laboratories has produced significant variation in LB test results. Laboratories may use different test methods e.g. ELISA or IFA, different methods of antigen preparation, different cut-off values to define positivity(19) and different techniques in the adsorption step that blocks antibodies that cross-react to other treponemes(20) Borrelia genus shares certain antigens, such as flagellin, with each other and with the treponemes (21), and this explains the false-positive reactions for Borrelia that occasionally occur in other spirochetal infections, such as syphilis, yaws, pinta and relapsing fever(6,7). Hansen and coworkers(14) showed that *B. burgdorferi* has a 60-kilodalton antigen that is common to a wide range of remotely related bacteria. This may explain the false-positive LB serology in our case, and in other bacterial infectious diseases. To our knowledge, *M. tuberculosis* has not been reported to lead to false-positive LB serology. Patients with infectious mononucleosis(20), Rocky Mountain spotted fever(22), mumps meningitis(23), human granulocytic ehrlichiosis (24), and varicella zoster infection(25) have also been reported to have false-positive LB serology. Immunologic cross-reactivity to LB antigen also occurs in systemic lupus erythematosus and rheumatoid arthritis (26), diseases that feature elevated levels of immune complexes. In these diseases, false-positivity may occur due to nonspecific cross-reactive antibodies, or high concentrations of antinuclear antibody, or both(15,27). Once a mature humoral response is mounted in LB, antibodies can be detected for
years, whether or not the patient has received appropriate treatment (6). Therefore, previous infections that have been treated can confound testing and yield false-positive results (15).

We conclude that LB diagnosis should be established primarily on clinical findings. All of the serologic tests currently available for LB must always be interpreted with caution, and in the context of the patient’s clinical picture. If accurate laboratory diagnosis of LB is to be achieved in future, advances in laboratory technology and standardization of the methods should be accomplished.
REFERENCES


