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Misdiagnosed Lyme: A Multidisciplinary Case Series from a Non-Endemic Region

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Lyme disease, caused by the spirochete *Borrelia burgdorferi* and transmitted through *Ixodes* tick bites, is the most prevalent vector-borne illness in North America and Europe. Early manifestations include erythema migrans and flu-like symptoms, which typically respond well to antibiotics.[1] However, non-specific symptoms such as fatigue and musculoskeletal pain often create diagnostic uncertainty and contribute to overdiagnosis.[2] Many patients referred for Lyme disease evaluation do not meet established diagnostic criteria and are ultimately found to have other medical or psychiatric conditions.[3] Overreliance on serologic testing, particularly in low-prevalence settings, may yield false positives and lead to inappropriate treatment.[4] In addition, some clinicians overdiagnose Lyme disease, occasionally bordering on quackery or fraud. Such practices result in unsupported diagnoses, further fueling overdiagnosis[5] and posing significant diagnostic and therapeutic challenges.[6] To illustrate this issue, we present a series of striking misdiagnosed cases from our clinical practice.

Between 2021 and 2024, we evaluated 37 patients who had been diagnosed with or suspected of having Lyme disease and were admitted to our two hospitals. Most were ultimately found to have alternative conditions-including infective endocarditis, Behçet's disease, and psoriatic arthritis-diagnoses made possible through systematic multidisciplinary evaluation.

Of the 37 patients, 32 carried a confirmed Lyme disease diagnosis from external centers, while 5 were suspected cases without diagnostic testing. The cohort consisted of 19 males and 18 females, ranging in age from 7 to 71 years. Only one patient recalled a tick bite, and two others reported travel abroad without known exposure.

Serologic testing yielded variable results. Three patients met the two-tier IgM-positive criteria via ELISA and Western blot. Five were IgM-positive on ELISA only, with negative Western blots. Two were IgG-positive on ELISA without Western blot confirmation. Seven tested negative for both IgM and IgG on ELISA. In some cases, the initial Lyme disease diagnosis was based on spirochete-like structures observed under dark-field microscopy. Twenty-two patients had received antimicrobial therapy for durations ranging from 3 weeks to 5 years, with some treated simultaneously with up to five antibiotic agents. Most had also been prescribed various supplemental therapies. Despite these extensive regimens, the majority experienced little or no clinical improvement.

Upon admission to our department, each case was re-evaluated through review of the patient's medical history, comprehensive physical examination, and targeted laboratory testing when indicated. This reassessment confirmed Lyme disease in only one patient. Twenty-two patients were determined not to be infected with *Borrelia* and were reassured without need for further investigation. The remaining 14 were referred to appropriate specialties based on their clinical history and findings; 10 of these patients accepted and completed specialist evaluations within our hospitals.

Specialist consultations established alternative diagnoses for all 10 patients, enabling revised treatment plans that resulted in symptom resolution or marked improvement. Most were diagnosed by rheumatologists with conditions such as fibromyalgia or inflammatory arthritis, including psoriatic arthritis and spondyloarthritis. One patient was diagnosed with Behçet's disease and another with familial Mediterranean fever, both representing autoinflammatory disorders.

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Neurological evaluation led to a diagnosis of multiple sclerosis (MS) in one patient, necessitating initiation of disease-modifying therapy. Another patient was diagnosed with subacute infective endocarditis by the infectious diseases team- a life-threatening condition requiring urgent antimicrobial and supportive management. Due to severe valvular damage at the time of diagnosis, this patient subsequently underwent heart valve replacement surgery. Clinical characteristics and final diagnoses of patients initially misdiagnosed with Lyme disease are summarized in Table 1.

TABLE 1. Clinical Characteristics, Initial Diagnostic Findings, and Final Diagnoses of Patients Initially Misdiagnosed with Lyme Disease.

Age, gender, and chief complaint	Initial Lyme diagnostic findings	Treatment for Lyme	Clinical clues leading to re-evaluation	Final diagnosis	Outcome
24 years, male, arthralgia	IgM positive, IgG negative; WB IgM positive; dark-field microscopy positive.	3 months of antibiotics	Recurring monoarthritis (knee, foot); recurrent oral aphthous ulcers; diffuse papulopustular eruption on the back; clubbing; pathergy test positive; HLA B51 positive.	Behçet disease	Symptoms resolved, in remission with treatment.
56 years, female, weakness in right arm and leg	IgM positive, IgG positive; WB IgG positive, WB IgM negative; dark-field microscopy positive.	3 weeks of antibiotics	Loss of vision 18 years ago (treated with steroids); numbness and weakness in left arm and leg 6 years ago (treated with steroids); multiple demyelinating plaques on cranial MRI with contrast.	Multiple sclerosis	Neurology follow-up at another hospital.
50 years, female, generalized myalgia	IgM negative, IgG negative; dark-field microscopy positive.	Antibiotics with supplements	Multiple hospital visits; normal laboratory results; normal skin biopsy; normal rheumatologic examination; depressive and anxious state with insomnia.	Generalized anxiety disorder/ fibromyalgia	Psychiatry follow-up at another hospital.
40 years, female, low back and hip pain; arthralgia	IgM negative, IgG negative; dark-field microscopy positive.	Antibiotics with supplements	Inflammatory hip, back, and ankle pain; active sacroiliitis on X-ray and MRI; psoriasis, spondylitis, and rheumatoid arthritis in family history.	Inflammatory spondylitis	Symptoms resolved, in remission with treatment.
71 years, female, head and neck pain; low back and hip pain; arthralgia	IgM negative, IgG negative; dark-field microscopy positive.	9 months of antibiotics with supplements	Long-term diffuse inflammatory arthritis; syndesmophytes on X-ray; psoriasis in medical and family history.	Psoriatic arthritis	Symptoms resolved, in remission with treatment.
32 years, male, recurrent fever with elevated acute-phase reactants	IgM negative, IgG positive; WB IgG positive.	3 weeks of doxycycline	Recurrent fever; recurrent chest, abdominal, leg, and knee pain; increased acute-phase reactants with leucocytosis.	Familial mediterranean fever	Stabilized patient with no recent attacks; acute-phase reactants normalized.
41 years, female, low back and hip pain; arthralgia	IgM negative, IgG negative; dark-field microscopy positive.	-	Inflammatory low back and hip pain for 6 years; ankle and Achilles pain for the last 4 months; plantar fasciitis; skin biopsy consistent with psoriasis; active sacroiliitis on MRI.	Psoriatic arthritis	Partial response with therapy, drug adjustment.
33 years, female, chronic fatigue; headache; Fainting	IgM positive, IgG negative; WB IgM positive.	-	-	Fibromyalgia	Psychiatry follow-up at another hospital.
51 years, male, fatigue	IgM negative, IgG negative; WB IgM and IgG negative.	-	-	Generalized anxiety disorder/ fibromyalgia	Psychiatry follow-up at another hospital.
65 years, male, fatigue; headache; leg pain; weight loss; elevated acute-phase reactants	IgM negative, IgG negative; dark-field microscopy positive.	6 weeks of ceftriaxone, doxycycline, and azithromycin	Increased CRP and WBC; heart murmur on auscultation; vegetation on native cardiac valve seen in TTE and TEE.	Infective endocarditis	Cured with antibiotics; heart valve replacement surgery.

WB, western blot; MRI, magnetic resonance imaging; CRP, C-reactive protein; WBC, white blood cells; TTE, transthoracic echocardiography; TEE, transoesophageal echocardiography; HLA, human leukocyte antigen.

The diagnosis of Lyme disease remains challenging due to variations in clinical presentation and differences in diagnostic criteria. A recent meta-analysis highlighted discrepancies between American and European guidelines, particularly in non-endemic regions such as Türkiye.[7] These inconsistencies, combined with physician misdiagnosis, contribute to inappropriate treatment, as illustrated by our case series.

A critical epidemiologic factor in diagnosing Lyme disease is a history of tick exposure, given that *Borrelia burgdorferi* is transmitted through *Ixodes* tick bites. In our series, however, only one patient reported a prior tick bite, and only two had traveled abroad. Although some individuals may not recall a tick bite because of the small size of nymphal *Ixodes* ticks, epidemiologic risk assessment remains an essential element of diagnosis.

Serologic testing was frequently positive but did not correlate with clinical improvement after antimicrobial therapy. False-positive serologic results may arise from cross-reactivity with other pathogens or non-specific antibody responses.[8,9] This highlights the importance of integrating clinical findings with laboratory results rather than relying solely on serology for diagnosis.

Dark-field microscopy was also used in some patients to identify structures resembling spirochetes. However, this method is not recommended for Lyme disease due to its low sensitivity and high false-positive rates. Artifacts and other microorganisms can easily be mistaken for *Borrelia* species, leading to misdiagnosis and unnecessary treatment. A narrative review concluded that dark-field microscopy has significant limitations and should not be employed as a diagnostic tool for Lyme disease.[10]

The misdiagnosis of Lyme disease in our patients resulted in prolonged and unnecessary antimicrobial treatments, lasting from 3 weeks to 5 years, without clinical improvement. Incorrect diagnoses also delayed identification and management of the true underlying conditions. In some cases, the consequences were severe-for example, the patient with subacute infective endocarditis, where timely recognition and treatment were critical to prevent life-threatening complications. Similarly, delays in diagnosing conditions such as MS and inflammatory arthritis led to extended symptom burden and potential disease progression. These findings underscore the importance of reconsidering a Lyme disease diagnosis in patients with persistent symptoms unresponsive to standard antimicrobial therapy. A multidisciplinary approach facilitated accurate diagnoses and effective treatment, as summarized in Table 1. Misdiagnosis not only prolonged inappropriate antimicrobial use but also allowed underlying conditions to progress unchecked. The most severe case involved a patient with undiagnosed infective endocarditis who required urgent antimicrobial therapy. By the time the correct diagnosis was established, irreversible cardiac damage had occurred, necessitating heart valve replacement surgery.

In conclusion, diagnosing Lyme disease requires caution, particularly in non-endemic regions. Overreliance on serologic testing-especially misinterpretation of Western blot results-and nonspecific methods such as dark-field microscopy can lead to misdiagnosis and inappropriate treatment. A multidisciplinary approach, strict adherence to established guidelines, and thorough clinical evaluation are essential for ensuring diagnostic accuracy and optimizing patient management.

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