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Case Report

Disseminated Marginal Zone Lymphoma in a Patient with Lyme Neuroborreliosis: A Case Report

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Keywords
Marginal zone lymphoma · Lyme neuroborreliosis · Case report · *Borrelia burgdorferi* · B-cell lymphoma

Abstract
Introduction: Lyme borreliosis has been associated with lymphoma, particularly cutaneous lymphomas. The literature is conflicted regarding the effect of antibiotic therapy in cutaneous marginal zone lymphomas (MZLs) in individuals with Lyme borreliosis. We present a patient diagnosed with Lyme neuroborreliosis (LNB) and disseminated MZL. ***Case Presentation:*** A 67-year-old man was seen due to 6 weeks of neuropathic pain with nightly worsening, headache, and 5 kg weight loss. Two weeks prior to symptom debut, he had a tick bite in the left groin, no subsequent rash. A lumbar puncture revealed mononuclear pleocytosis and elevated CSF protein. The patient was admitted and started on ceftriaxone. The *Borrelia burgdorferi* intrathecal test showed intrathecally produced *Borrelia* antibodies, and treatment was changed to doxycycline with a total treatment duration of 21 days. A PET/CT revealed enlarged lymph nodes with increased FDG uptake. On pathological examination, the CSF showed 62% clonal B cells – compatible with low-grade B-cell lymphoma. Examination of bone marrow and an inguinal lymph node confirmed disseminated MZL. A control lumbar puncture 8 weeks later showed declining pleocytosis and clonal B cells. At last follow-up 20 months later, he was still asymptomatic and had not required antineoplastic treatment. ***Conclusion:*** To our knowledge, this is the first published case of LNB with non-cutaneous B-cell lymphoma treated and remitting on antibiotics alone. Antibiotic treatment for *Borrelia*-positive

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lymphomas has yet to be investigated with high-evidence study designs, so clinicians are encouraged to publish both positive and negative findings relevant to this. We believe this case brings new perspectives to future diagnosis and treatment of lymphomas in patients with verified Lyme borreliosis.

Introduction

Lyme borreliosis is caused by infection with spirochetes within the *Borrelia burgdorferi* sensu lato complex. Transmission occurs through tick bites from *Ixodes* spp. ticks. Infection can cause a broad spectrum of symptoms, e.g., erythema migrans, arthritis, and Lyme neuroborreliosis (LNB) [1].

Lyme borreliosis has previously been associated with lymphoma, particularly cutaneous lymphomas [2–4]. The suggested pathogenesis for this process is a chronic *Borrelia* antigen-driven B-cell stimulation leading to mutations and possible development into B-cell lymphomas through stages like the borrelial lymphocytoma and acrodermatitis chronica atrophicans [2, 5].

Several case reports have shown regression of cutaneous lymphomas in individuals with *B. burgdorferi* s.l. PCR or culture-positive tissue samples after treatment with antibiotic therapy [6, 7]. However, results are conflicting, with other cases showing no sign of regression [6, 8]. This has led some to recommend that cutaneous marginal zone lymphomas (MZLs) should first be treated with antibiotics before more aggressive treatments are used [2]. Others suggest this strategy for all low-grade cutaneous lymphomas in *B. burgdorferi* s.l. high endemic areas, while others recommend primarily testing for *B. burgdorferi* s.l. in skin biopsies and only provide antibiotic treatment if *Borrelia* DNA positive [4, 9].

The European Organization for Research and Treatment of Cancer and the International Society for Cutaneous Lymphoma concluded in their last consensus recommendations for management of cutaneous B-cell lymphomas that the evidence for antibiotic treatment of these patients was scarce and conflicting, and they encouraged the publication of cases of cutaneous MZL treated with antibiotics [10]. We here present a patient initially diagnosed with LNB and subsequently with MZL involving lymph nodes, bone marrow, and the central nervous system (CNS). Both conditions and the patient's symptoms remitted after antibiotic treatment without any immunotherapy.

Case Report

A 67-year-old man was seen in a neurologic outpatient clinic due to 5–6 weeks of neuropathic pain, headache, and a weight loss of 5 kg (Fig. 1). The burning pain had started in the lower back radiating down in both lower extremities and later spread to the neck and upper extremities. The pain worsened at nighttime severely affecting his sleep. Physical examination including a neurological exam revealed hyperalgesia on the feet and reduced sense of vibration on the first toe but was otherwise normal.

Besides hypercholesterolemia, he was previously fit, with frequent runs and bike rides. Two weeks before symptom debut, he had noted a tick bite in the left groin and removed the tick with no subsequent rash evolving. On the initial suspicion of LNB or a paraneoplastic

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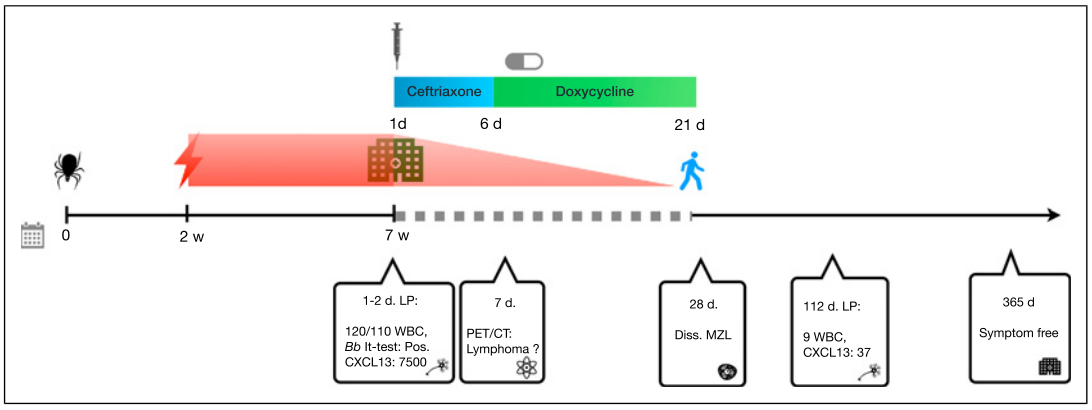

Fig. 1. Timeline of the patient's course of disease. LP, lumbar puncture; *Bb* It-test, *B. burgdorferi* intrathecal test; WBC, white blood cell; MZL, marginal zone lymphoma.

Table 1. Results from CSF and peripheral blood from a patient diagnosed with LNB and disseminated MZL

	Normal values	Day 1	Day 2	Day 21	Day 112
CSF					
Leukocytes, 10^6/L	0–5	120	110	83	9
Mononuclear		110	110	83	
Protein, g/L	0.40–0.70	1.40	1.17	0.64	0.55
Erythrocytes, 10^6/L	0	<300	<300	<300	<300
Glucose, mmol/L		2.1	2.3	3.0	3.0
CXCL13, ng/L	<10		7,500	258	37
B. burgdorferi intrathecal antibody test		Positive IgM		Positive IgM	
		Positive IgG		Positive IgG	
Flow cytometry, % clonal B cells			19%	62%	57%
Peripheral blood					
Hemoglobin, mmol/L	8.3–10.5	9.0			9.8
Leukocytes, 10^9/L	3.5–8.8	8.5			7.7
Platelets, 10^9/L		243			201
Lactate dehydrogenase, U/L	105–205				251
B. burgdorferi antibodies		Positive IgM		Positive IgM	
		Positive IgG		Positive IgG	

phenomenon, a lumbar puncture (LP) was performed the next day, revealing a mononuclear pleocytosis and elevated protein in the cerebrospinal fluid (CSF) (Table 1).

The patient was admitted to the neurological department and started on ceftriaxone 2 g once daily. The following day, a new LP was performed for additional diagnostics. An MRI of the brain showed no acute changes. Six days after the initial LP, the *B. burgdorferi* intrathecal test showed intrathecally produced *Borrelia* IgM and IgG antibodies. He was positive in *Borrelia* IgM and IgG serology in blood, but negative in *Rickettsia* spp., *Anaplasma phagocytophilum, Bartonella* spp., and tick-borne encephalitis virus serology. The treatment was changed to doxycycline 200 mg once daily with a total treatment duration of 21 days. The radicular pain subsided during treatment, but he remained fatigued.

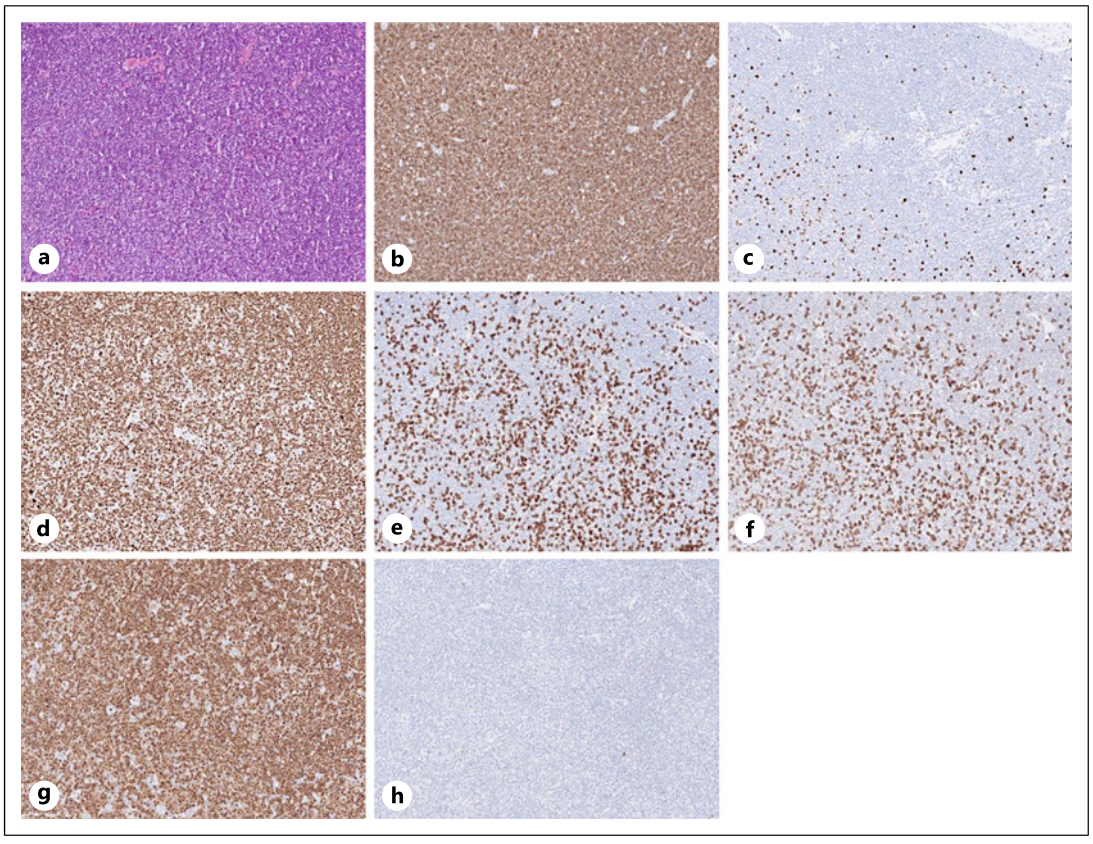

Fig. 2. Lymph node biopsy showing B cells with expression of CD20, PAX 5, and MNDA and low proliferation rate in Ki-67. The B cells do not express CD5 and CD10. Reactive background of T cells shown in CD3 and CD5. Further immune histochemistry with positive reaction in bcl-2 and Kappa. Negative reaction in CD23, cyclinD1, SOX11, LMO2, LEF1, p53 (not included in the figure). **a** HE stain (×10). **b** CD20 (×10). **c** Ki67 (×10). **d** MNDA (×10). **e** CD3 (×10). **f** CD5 (×10). **g** PAX5 (×10). **h** CD10 (×10).

Electroneurography showed prolonged f-waves when examining *n. peroneus* bilat., *n. ulnaris* bilat., and left *n. tibialis*, indicating multiple radiculopathies, compatible with the LNB diagnosis. A PET/CT revealed slightly enlarged lymph nodes with increased FDG uptake in the left groin and along the iliac external artery, compatible with a lymphoma.

After pathological examination, the initial LP turned out with mixed cells, dominated by T-lymphocytes but also 19% clonal B cells. This was interpreted as a likely reaction to LNB, but a new control LP was suggested.

After 8 days of hospitalization, the patient was discharged to outpatient follow-up. On day 21, a new LP was performed. This turned out with a lower total cell count but 40×10^3 clonal B cells/ml (62%) and was now interpreted as low-grade B-cell lymphoma, of an uncertain subtype.

Further diagnostic work-up included a bone marrow examination and excisional lymph node biopsy from the left groin. The bone marrow biopsy revealed 30% infiltration of a low-grade B-cell neoplasia, and based on results from the bone marrow and lymph node biopsies, a conclusive diagnosis of a CD20, PAX5, BCL-2, MNDA, and Kappa-positive MZL without evidence of histological transformation was established. The same Kappa clonality and immunophenotype were found by flow cytometry performed on CSF, clearly supporting a clonal relationship. No pathogenic lymphoma-relevant mutations were found (Fig. 2).

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A Hematological Multidisciplinary Team (MDT) conference concluded that the patient had a chronic low-grade B-cell lymphoma, probably primarily nodal MZL with bone marrow and CSF involvement. The MDT concluded that no further medical treatment, including antineoplastic treatment, was needed as all neurological symptoms reverted, but recommended a control LP 8 weeks later. This showed declining pleocytosis and clonal B cells (Table 1). The lymph node was later examined with PCR for *B. burgdorferi* DNA, but was found PCR negative.

All symptoms had remitted at the last follow-up at the Department of Infectious Diseases 12 months after antibiotic treatment. The patient is followed by hematologists every 6 months; at last follow-up 20 months after treatment, he was asymptomatic.

Discussion

Our case demonstrates a patient with LNB and MZL, the latter suspected developed secondary to the first. Both conditions and the patient's symptoms remitted after antibiotic treatment.

Although rare, MZL is a form of indolent lymphoma that can present with symptoms from the CNS [11]. There is a known association between several infectious agents and MZL. A correlation between *Helicobacter pylori* infection and the development of gastric mucosa-associated lymphoid tissue lymphomas has been established [2, 5, 11]. A correlation between infection with *Chlamydia psittaci* or *Campylobacter jejuni* and MZL has also been proposed [2, 5, 11]. MZLs have also been found with a significantly increased prevalence among patients with chronic viral hepatitis C [11, 12].

As for the association between Lyme borreliosis and MZL, the majority of published literature addresses cutaneous borreliosis and MZL. *B. burgdorferi* s.l. DNA has been found by PCR analysis in tissue samples from cutaneous lymphomas from several European countries: e.g., in 9/50 cases (18%) from a Borrelia-endemic area of Austria, in 3/16 cases (19%) from a non-endemic part of France, and in 7/20 cases (35%) in an endemic part of Scotland [7, 9, 13].

There are sparse data on an association between LNB and lymphoma. However, a Danish nationwide cohort study found a 4-fold increased risk of lymphomas among LNB patients compared with the background population [3]. To our knowledge, this case is the first published case of LNB with non-cutaneous B-cell lymphoma treated and remitting on antibiotics alone.

There are diagnostic challenges with both LNB and CNS lymphomas, where the symptomatology can be unspecific and multifaceted. There are several examples of patients with diagnostic and treatment delays due to suspicion of one of these diseases turning out to be the other [14, 15].

Due to the low positive predictive value of *Borrelia* serology in blood, the diagnosis of *Borrelia*-associated lymphoma should be based on additional diagnostic tests, e.g., PCR in tissue samples or evidence of intrathecally produced *Borrelia* antibodies when LNB is suspected [10, 16]. Additionally, the CSF of verified LNB patients should also be evaluated by flow cytometry.

Antibiotic treatment for *Borrelia*-positive lymphomas has yet to be investigated with high-evidence study designs, so clinicians should be encouraged to publish both positive and negative findings relevant to this. We believe this case brings new perspectives to future diagnosis and treatment of lymphomas in patients with verified Lyme borreliosis.

In conclusion, our case presents a patient initially diagnosed with LNB and subsequently with disseminated MZL, where the lymphoma regressed during antibiotic treatment without any immunotherapy. Our findings encourage more publications in this field to gain further

knowledge to support or challenge our findings. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000543348).

Statement of Ethics

The Danish Research Ethics Committee exempts case reports from requiring ethics approval. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Dorit Kraft Weisbjerg and Fredrikke Christie Knudtzen gathered information and wrote the case report. Sigurdur Skarphedinsson, Thomas Stauffer Larsen, and Louise Kristensen were involved in the patient treatment/examination and have provided input from their specific fields. Nanna Skaarup Andersen was responsible for the microbiological analysis. All authors read and approved the final manuscript.

Data Availability Statement

The data that support the findings in this study are not publicly available due to patient confidentiality and Danish data protection policies, but are available from the corresponding author upon reasonable request.

References

1 Stanek G, Wormser GP, Gray J, Strle F. Lyme borreliosis. Lancet. 2012;379(9814):461–73. https://doi.org/10.1016/S0140-6736(11)60103-7
2 Ferreri AJ, Govi S, Ponzoni M. Marginal zone lymphomas and infectious agents. Semin Cancer Biol. 2013;23(6):431–40. https://doi.org/10.1016/j.semcancer.2013.09.004
3 Obel N, Dessau RB, Krogfelt KA, Bodilsen J, Andersen NS, Møller JK, et al. Long term survival, health, social functioning, and education in patients with European Lyme neuroborreliosis: nationwide population based cohort study. BMJ Clin Res. 2018;361:k1998. https://doi.org/10.1136/bmj.k1998
4 Travaglino A, Varricchio S, Pace M, Russo D, Picardi M, Baldo A, et al. Borrelia burgdorferi in primary cutaneous lymphomas: a systematic review and meta-analysis. J Dtsch Dermatol Ges. 2020;18(12):1379–84. https://doi.org/10.1111/ddg.14289
5 Biernat MM, Wróbel T. Bacterial infection and non-hodgkin B-cell lymphoma: interactions between pathogen, host and the tumor environment. Int J Mol Sci. 2021;22(14):7372. https://doi.org/10.3390/ijms22147372

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DOI: 10.1159/000543348

6 Kütting B, Bonsmann G, Metze D, Luger TA, Cerroni L. Borrelia burgdorferi-associated primary cutaneous B cell lymphoma: complete clearing of skin lesions after antibiotic pulse therapy or intralesional injection of interferon alfa-2a. J Am Acad Dermatol. 1997;36(2 Pt 2):311–4. https://doi.org/10.1016/s0190-9622(97)80405-7
7 de la Fouchardiere A, Vandenesch F, Berger F. Borrelia-associated primary cutaneous MALT lymphoma in a nonendemic region. Am J Surg Pathol. 2003;27(5):702–3. https://doi.org/10.1097/00000478-200305000-00017
8 Monari P, Farisoglio C, Calzavara Pinton PG. Borrelia burgdorferi-associated primary cutaneous marginal-zone B-cell lymphoma: a case report. Dermatology. 2007;215(3):229–32. https://doi.org/10.1159/000106580
9 Cerroni L, Zöchling N, Pütz B, Kerl H. Infection by Borrelia burgdorferi and cutaneous B-cell lymphoma. J Cutan Pathol. 1997;24(8):457–61. https://doi.org/10.1111/j.1600-0560.1997.tb01318.x
10 Senff NJ, Noordijk EM, Kim YH, Bagot M, Berti E, Cerroni L, et al. European organization for Research and treatment of cancer and international society for cutaneous lymphoma consensus recommendations for the management of cutaneous B-cell lymphomas. Blood. 2008;112(5):1600–9. https://doi.org/10.1182/blood-2008-04-152850
11 Flospergher E, Marino F, Calimeri T, Cangi MG, Ferreri AJM, Ponzoni M, et al. Primary central nervous system marginal zone lymphoma. Br J Haematol. 2024;204(1):31–44. https://doi.org/10.1111/bjh.19238
12 Xiong W, Lv R, Li H, Li Z, Wang H, Liu W, et al. Prevalence of hepatitis B and hepatitis C viral infections in various subtypes of B-cell non-Hodgkin lymphoma: confirmation of the association with splenic marginal zone lymphoma. Blood Cancer J. 2017;7(3):e548. https://doi.org/10.1038/bcj.2017.28
13 Goodlad JR, Davidson MM, Hollowood K, Ling C, MacKenzie C, Christie I, et al. Primary cutaneous B-cell lymphoma and Borrelia burgdorferi infection in patients from the Highlands of Scotland. Am J Surg Pathol. 2000;24(9):1279–85. https://doi.org/10.1097/00000478-200009000-00012
14 Iriarte C, Vaitkevicius H, Marty FM, Miller AL, Loscalzo J. Missing the target. N Engl J Med. 2020;382(14):1353–9. https://doi.org/10.1056/NEJMcps1901669
15 Nijland M, Bakker M, Meijer K, Plattel W. Borrelia burgdorferi mimicking central nervous system relapse in diffuse large B cell lymphoma. Ann Hematol. 2020;99(12):2947–8. https://doi.org/10.1007/s00277-020-04022-5
16 Foster LH, Portell CA. The role of infectious agents, antibiotics, and antiviral therapy in the treatment of extranodal marginal zone lymphoma and other low-grade lymphomas. Curr Treat Options Oncol. 2015;16(6):28. https://doi.org/10.1007/s11864-015-0344-6