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Case report

Case report: First case of *Borrelia miyamotoi* meningitis in an immunocompromised patient in Norway

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ABSTRACT

Background: Tick-borne disease caused by *B. miyamotoi* (BMD) usually manifest as a febrile illness in humans. Complications include relapsing fever and in rare occasions involvement of the central nervous system. Only a few cases of meningoencephalitis have been described, mostly in immunosuppressed patients.
Case presentation: A 70-year-old female receiving immunosuppressive rituximab therapy presented with frontal headache, dizziness, nausea, vomiting and chills. Clinical laboratory blood analyses were normal. Cerebrospinal fluid (CSF) was translucent and analysis showed increased leucocyte count (187 10^6/L) and elevated level of protein (1056 mg/L). Empiric antibiotic treatment was initiated. The patient showed an early symptomatic relief and 24 h after admission she was discharged from the hospital and antibiotic treatment was discontinued. Two weeks after hospitalisation the *B. miyamotoi* specific PCR turned out positive in both CSF and serum. At the time, the patient was recovered with mild residual headache. She was treated with high dose doxycycline and her subtle symptoms disappeared.
Conclusions: To our knowledge, we present the first patient with BMD-associated meningitis in Norway, one of eight cases reported worldwide. The patient had mild symptoms and received an early diagnosis. A more severe progression or relapse of disease may have been prevented by antibiotic treatment. BMD should be considered as causes of aseptic meningitis, especially in immunosuppressed patients living in endemic areas.

Background

Borrelia miyamotoi is a relapsing fever spirochaete globally distributed in *Ixodes* ticks. Human disease caused by *B. miyamotoi* (BMD) manifesting with symptoms as fever, headache and myalgia, was first diagnosed in Russia in 2009 [1]. Most cases present with a single febrile episode whereas approximately a tenth has relapsing symptoms [2]. Meningoencephalitis caused by *B. miyamotoi* has been described in seven patients only, four from Europe [3–5], and three from the USA [6–8]. All, except two immunocompetent patients [5,6], were undergoing B-cell depleting rituximab therapy. BMD patients with infections of the central nervous system (CNS) had a wide variety of symptoms including dizziness, vomiting, anorexia, weight loss, headache, neck stiffness, and decline of sensorimotor and cognitive functions [2]. The impact of BMD on public health, including CNS involvement, is unknown. The disease is likely to be underreported due to clinicians' lack of experience with clinical manifestations and limited diagnostic services.

Case presentation

In Autumn 2021, a 70-year-old female was admitted to hospital with a one-week history of frontal headache, nausea and chills, including vomiting and dizziness in the last 24 h. She did not reported a fever. Cerebral magnetic resonance imaging ordered by her general practitioner a few days prior admission was normal. Her medical history revealed anti-cyclic citrullinated peptide-positive rheumatoid arthritis and fibrosing interstitial pulmonary disease, for which she received the immunosuppressive therapy methylprednisolone (4 mg/24 h) and rituximab (1000 mg/6 month). The last rituximab injection was administered five months' prior disease onset. Despite her comorbidities, age and medical treatment, the patient was active and working part-time.

During physical examination, she was in good general condition,

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afebrile, well oriented and did not have neck stiffness. Apart from elevated blood pressure of 184/83 mmHg, the vital parameters were normal. Laboratory blood tests were normal; C-reactive protein 8 mg/L, leucocytes 7.5 10^9/L, haemoglobin 13.0 g/dL, platelets 270 10^9/L, creatinine 59 μmol/L, and glucose 6.3 mmol/L. Analysis of cerebrospinal fluid (CSF) showed increased total leukocyte count 187 10^6/L (normal range < 4 10^6/L) with predominance of mononuclear cells 133 10^6/L, glucose level 3.0 mmol/L (reference > 50 % of s-level), glucose CSF/serum ratio 0.47 (reference > 0.5), and elevated level of protein 1056 mg/L (normal range 0–449 mg/L). Polymerase chain reaction (PCR) analyses for detection of herpes simplex 1 and 2 and varicella zoster viruses were negative in CSF. Culture and microscopy of CSF and blood revealed no signs of bacteria. Empiric treatment for potential bacterial meningitis with ceftriaxone (4 g/24 h), ampicillin (3 g/6 h) and dexamethasone (10 mg/24 h) was initiated few hours after hospital admission. The patient reported no recent history of travelling abroad or intake of unpasteurised dietary products. However, three months prior to hospitalisation she had been bitten by ticks three times on the lower extremities. Despite early removal (within 24 h) of the attached ticks without signs of rashes, a tick-borne infection caused by *Borrelia burgdorferi* sensu lato was considered likely, and *B. burgdorferi* antibody tests were requested.

Within 24 h ward observation, the patient improved and was discharged from the hospital. Antimicrobial treatment was discontinued due to a suspicion of aseptic meningitis. At follow-up, the *B. burgdorferi*-antibody tests from the local laboratory came back inconclusive due to low levels of IgG in serum and IgM in serum and CSF. Lyme neuroborreliosis was therefore not excluded, and serum and CSF samples taken at hospital admission (hereafter designated day 0) were sent to the Norwegian reference laboratory for additional *Borrelia* diagnostics. In the reference laboratory, the *B. burgdorferi*-specific PCR was negative in CSF, whereas the *B. miyamotoi* specific PCR turned out to be positive in both CSF and serum.

At the time of these test outcomes, the patient had been without treatment for two weeks and her condition had improved. However, she still experienced intermittent headaches. Due to detection of *B. miyamotoi* in serum and CSF, the patient underwent an additional medical examination 16 days after hospitalisation. General laboratory tests were still normal, HIV serology was negative, and immunoglobulin A, G, and M, as well as CD3 and CD8 lymphocytes were within normal range. The lymphocyte counts of CD4 (281 cell/μL; normal range 500–1000 cell/μL) and CD19 (< 5 cell/μL; normal range 100–500 cell/μL) were low, consistent with the immunosuppressive status of the patient caused by rituximab therapy. She was started on doxycycline (200 mg/12 h) treatment for two weeks, in line with the treatment of reference cases in literature [5]. In the following months, the patient fully recovered, and rituximab therapy was resumed eight months after the meningitis, by her rheumatologist. Follow-up after one year showed that the patient was in good condition, despite experiencing Covid-19 disease and a PCR-proven erythema migrans Lyme borreliosis (LB) after an unrelated tick-bite.

Microbiological analysis and follow-up testing

At the Norwegian reference laboratory for *Borrelia* diagnostics, DNA for PCR analysis was isolated by MagNAPure 96 DNA or viral NA small volume kit (Roche, Mannheim, Germany), from 200 μL CSF, serum, whole blood, and plasma/buffy coat fraction. The plasma/buffy coat fractions were collected after centrifugation of whole blood at 1000 × *g* for 12 min and concentrated to 200 μL by centrifugation at 10,000 × *g* for 2 min. Nucleic acid eluates were tested by specific PCR analyses for the *B. burgdorferi ospA* and 16S rRNA genes, and the *B. miyamotoi* 16S rRNA gene [9]. Further, Serion ELISA Classic IgG and IgM (serum or CFS) antibody tests (Wurzburg, Germany) and Euroline Anti-borrelia IgG and IgM immunoblot serum tests (Lübeck, Germany) were used for detection of *B. burgdorferi*-antibodies. Tests were performed using the manufacturers' cut-off levels and interpretation criteria.

The day 0 CSF sample was tested by the *B. burgdorferi*-specific *ospA* and 16S rRNA PCR analyses. The *ospA* PCR was negative, and an uncommon amplification curve barely above threshold was observed for the 16S rRNA PCR, indicating an unspecific result. Furthermore, the CSF sample tested positive by the *B. miyamotoi*-specific 16S rRNA PCR (Table 1). *B. miyamotoi* was also detected in serum (day 0). Due to limited amount of sample material from the patient's admission date, CSF was the only material tested by *B. burgdorferi* ELISA, and IgG was detected although IgM was not.

For follow up testing, serum and EDTA whole blood samples were obtained before (day 16) and after (day 36) doxycycline treatment (Table 1). *B. miyamotoi* was neither detected in the whole blood or plasma/buffy coat fraction in samples taken before nor after antibiotic treatment by PCR. *B. burgdorferi*- ELISA antibody testing of serum (day 36) taken after treatment was IgM positive whereas the IgG was intermediate. A serum sample drawn more than three months before the diagnosing of the *B. miyamotoi* infection was available. Similar results were seen in the *B. burgdorferi*- ELISA serum test for the prior-infection and the post-treatment (day 36) serum. Testing the same two samples by the *B. burgdorferi* immunoblot assay indicated the same IgM band pattern. However, additional bands were detected by the IgG blot after infection (Table 1).

Patient samples were analysed at the Amsterdam University Medical Centers to confirm the findings. Molecular affirmation was obtained on the serum and CSF samples at day 0, specifically targeting the *Borrelia* genus (*flagellin* gene), relapsing fever *Borrelia* genus (16S rDNA), and *B. miyamotoi* (*flagellin* gene) [3]. In addition, the experimental *B. miyamotoi* serology was performed through IgM and IgG protein array (targeting GlpQ, Vmps and flagellin) [10], and Western blot (targeting a whole cell lysate of a European *B. miyamotoi* isolate) [5,11,12]. This resulted in IgM and IgG reactivity against multiple Vmps (Vsp-1, Vlp-5 and Vlp-15/16), but an overall negative test algorithm in the protein array, and weak positive IgM and IgG Western blot tests.

Discussion

In this report, the first case of meningitis caused by the emerging tick-borne pathogen *B. miyamotoi* in Norway is described. The patient was immunocompromised due to rituximab therapy and presented with mild symptoms and short duration of disease. At this time, only seven BMD-associated meningoencephalitis cases have been reported worldwide [2,6]. Six of the now eight meningoencephalitis patients described, have been on immunosuppressive treatment of rituximab [3–5,7,8]. This highlights the potential opportunistic nature of the disease and the role of the humoral immune response in controlling the infection.

The Norwegian patient experienced a rapid improvement of symptoms after admission to hospital. It is not known if the patient spontaneously recovered from infection or if improvement was aided by the empiric antibiotic treatment that was withdrawn after 24 h. Despite feeling healthy, with only a few residual symptoms after the acute disease phase, the patient still may have been at risk of disease relapse prevented by the doxycycline treatment received 16 days after hospitalisation. A Swedish BMD-associated meningitis patient not treated with antibiotics in the first symptomatic phase, due to suspicion of a viral cause, spontaneously improved for a week until her condition worsened again [5]. Relapse and further progression of the infection may be critical. Patients having a delayed diagnosis appear to be at risk of a more serious presentation of neurological disease, given that BMD-associated meningoencephalitis cases with disease duration ongoing for months displayed symptoms such as impaired sensor and cognitive functions [3,5,7,8].

The risk of being bitten by a *B. miyamotoi*-infected tick is 10–30 times lower than a tick harbouring *B. burgdorferi* in Norway [13,14]. However, *B. miyamotoi* may transmit to the host during the first day of attachment, while *B. burgdorferi* need longer attachment for transmission [15,16].

Table 1
Confirmatory analyses performed on samples from the Norwegian patient with meningitis caused by *Borrelia miyamotoi*.

	The time of sample collection				
	>3 months before infection	Day 0 Hospitalization		Day 16 Recovery and pre- treatment	Day 36 Post- treatment
	Serum	**Serum**	**CSF**	**Serum**	**Serum**
Borrelia miyamotoi-specific PCR*	Negative	**Positive**	**Positive**	(Negative in whole blood**)	(Negative in whole blood**)
Borrelia miyamotoi- protein array	IgM- IgG -	IgM- IgG -	NA	IgM - IgG -	IgM - IgG -
Borrelia miyamotoi- crude lysate Western blot	IgM - IgG -	IgM - IgG -	NA	IgM + IgG +	IgM + IgG +
Borrelia burgdorferi- ELISA antibody test	IgM + IgG intermediate	NA	IgM - IgG +	NA	IgM + IgG intermediate
Borrelia burgdorferi- antibody test Immunoblot	IgM: ospC +, VlsE - IgG: VlsE garinii +, Flagellin +	NA	NA	NA	IgM ospC +, VlsE - IgG: VlsE afz/garinii + Flagellin +, ospC +

*The day 0 serum and CSF samples tested positive by *B. miyamotoi* (two tests, two laboratories), relapsing fever *Borrelia* genus and *Borrelia* genus specific PCR, other samples were tested with *B. miyamotoi* specific PCR assay only.
**Tested in both the whole blood and plasma/buffy coat fraction
Abbreviations: CSF, cerebrospinal fluid; PCR, polymerase chain reaction; Ig Immunoglobulin; NA, not analyzed; ELISA, enzyme-linked immunosorbent assay; ospC, outer surface protein C; VlsE, variable major protein-like sequence, expressed; afz, *Borrelia afzelii*; garinii, *Borrelia garinii*; +, positive; -, negative.

Because *B. miyamotoi* and not *B. burgdorferi,* is transovarially transmitted from infected parent ticks to their offspring, humans are at risk of contracting BMD and not LB when bitten by tick larvae [17]. The Norwegian patient removed her noticed ticks within 24 h, which might prevent *B. burgdorferi,* but not *B. miyamotoi* transmission. Her recognised tick bites occurred three months before hospitalisation, indicating a longer disease incubation time compared to what is observed for immunocompetent patients with febrile BMD [18]. This might be explained by a longer incubation period, gradual onset of disease, or the pathogen may have been transmitted by an unnoticed later-occurring tick bite.

B. miyamotoi antibodies may induce false positive *B. burgdorferi* tests, as a result of *B. miyamotoi* Vmp antibodies cross-reacting with the C6 consensus of the *B. burgdorferi* VlsE antibodies. Vice versa, in LB patients VlsE antibodies cross-react with Vmp antibody tests [19,20]. Even if not caused by a *B. miyamotoi* infection, reactivity in *B. burgdorferi* tests is likely to be misinterpreted for patient with signs of a neurological infection as an atypical Lyme neuroborreliosis [4,5]. No difference in reactivity of *B. burgdorferi* ELISA tests used in this study due to cross-reactivity was observed when comparing serum taken some months before and after the infection. Although, two extra bands appeared after *B. miyamotoi* infection in a *B. burgdorferi* IgG immunoblot assay. Specific but weak antibody responses were detected in the *B. miyamotoi* Western blot. The antibody responses of the Norwegian patient may have been hampered by the B-cell depleting rituximab therapy. The therapy may have influenced both the assumed cross-reactivity in the *B. burgdorferi*- and the level of specific response in the *B. miyamotoi*- antibody tests.

Most BMD-associated meningoencephalitis cases are likely overlooked, often misinterpreted as viral infection, and only a few cases have been diagnosed in early phase of disease. Improved awareness of BMD and available diagnostic methods is needed for early diagnosis and treatment of disease to reduce patients with critical complications such as impaired cognitive functions.

Ethical approval

Authors are complying with the requirements of the author's institutions for publishing case reports.

Consent

Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent is available for review by the Editor of this journal.

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CRediT authorship contribution statement

Thomas Schwartz: Patient treatment and clinical diagnosis, Writing – original draft. **Dieuwertje Hoornstra:** Methodology, Writing – original draft. **Erik Øie:** Patient treatment and clinical diagnosis, Writing – review & editing. **Joppe Hovius:** Supervision, Writing – review & editing. **Hanne Quarsten:** Conceptualization, Methodology, Project administration, Writing – original draft. The authors declare that they have read the reviewers' remarks and have taken them into account.

Conflicts of interest

None.

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