A 60-Year-Old Swiss Woman Presenting with Migratory Radicular Pain Diagnosed with Lyme Disease by Western Blot

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Patient: Female, 60-year-old
Final Diagnosis: Lyme disease
Symptoms: Migratory radicular pain
Medication: —
Clinical Procedure: —
Specialty: Infectious Diseases

Objective: Unusual clinical course

Background: Many diagnostic guidelines have been established to support the diagnosis of Lyme disease, but a recent meta-analysis did not find that 2-tier tests were better than individual tests. Here, we present the case of a patient who was diagnosed by immunoblot only, a second-line test that is usually not performed if the first-line test is negative.

Case Report: A 60-year-old Swiss woman, without relevant comorbidities, presented to our clinic with 1-week symptoms of migratory radiculitis in the L1, L2, and L5-S1 right dermatomes. Blood analysis and lumbar and brain MRI did not show any significant abnormalities. However, unexpected results were obtained after testing Lyme serologies. They were performed first with LIAISON® test (Diasorin, Italy) then with Borrelia VIRAstripe® immunoblot (Viramed, Germany) and a positive IgM result was only obtained with the latter. Consequently, doxycycline 100 mg 2×/day was initiated and the symptoms completely resolved after 6 weeks of treatment. Ever since, and more than 1 year after the initial presentation, the patient remains symptom-free.

Conclusions: As shown, it was possible to diagnose this patient and treat her successfully by testing all the available serologies. Furthermore, we were surprised to find out after a review of the literature that the IgM sensitivity in neuroborreliosis with the LIAISON® test is only 43.9-46% versus 90-100% with VIRAstripe®. Hence, clinicians need to understand the pitfalls of these tests before excluding Lyme disease.

Keywords: Blotting, Western • Enzyme-Linked Immunosorbent Assay • Fluorescent Antibody Technique, Indirect • Immunoblotting • Lyme Disease • Lyme Neuroborreliosis

Abbreviations: ELISA – enzyme-linked immunoassay; IFA – indirect immunofluorescence assay

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Background

Switzerland is known to be an endemic region for tick-borne diseases, particularly for Lyme disease, where up to 50% of ticks in certain Swiss regions are infected with *Borrelia* [1]. It is estimated that 10 000 Swiss get sick with Lyme disease every year and this number may increase in the future, as 2018 and 2020 had a record number of infected patients compared to the last 10 years [1,2].

Lyme disease is characterized by 3 stages [3]. The first stage is characterized by the pathognomonic cutaneous rash – the erythema migrans. The second stage leads to symptoms that frequently mimic influenza [3]. The third stage is associated with arthritis, heart disease, acrodermatitis chronica atrophicans, or neurological disease [3]. In Europe, the most frequent neurological presentation of *Borrelia* is peripheral radicular pain, which can progress to meningeoradiculitis, also known as the Bannwarth syndrome [3,4]. Interestingly, approximately 20% of Lyme disease patients do not develop erythema migrans [3] and this is one of the reasons why tick bites easily go unnoticed.

The diagnosis of Lyme disease is clinical, especially in stage 1, where no serological testing is usually necessary. However, in stages 2 and 3, serological testing may be useful to support its diagnosis. The first recommended serological test is usually the ELISA (enzyme-linked immunosassay) test or, less commonly, the IFA (indirect immunofluorescence assay) test [5]. Both detect antibodies to *Borrelia* in the patients’ serum [5]. They are considered to have an overall higher sensitivity than the western blot, which detects antibodies to specific *Borrelia* proteins, and this is the reason why they are usually performed first [5]. The western blot, with an overall higher specificity, is usually only performed if the ELISA or the IFA is positive in order to exclude any false-positive cases [5-7]. Nevertheless, a recent meta-analysis questioned these assumptions, as it was not able to verify that “ELISAs have a higher or lower accuracy than immunoblots” or that “2-tiered approaches have a better performance than single tests” [8].

Here, we report an unusual case of a patient who presented with peripheral radiculitis secondary to Lyme disease and who was diagnosed by western blot only.

Case Report

A 60-year-old Swiss woman, previously diagnosed with prediabetes and a mitral valve prolapse, without any regular medication, presented to our clinic on 3 June 2020 with symptoms of intermittent migratory polyneuropathy in the L1, L2, and L5-S1 right dermatomes. She reported a feeling like an electric current that started on her lumbar area and then radiated down her right lower limb over the right inguinal area, proximal antero-lateral region of the thigh, and the lateral part of the lower limb up to the foot. The symptoms had started 1 week earlier, manifested in an intermittent fashion, and the patient did not recall having been bitten by a tick or having had erythema migrans. There was also no history of chronic lumbar pain, recent lumbar traumatism, typical infectious symptoms, B symptoms, symptoms compatible with vasculitis, intermittent claudication, other neurological symptoms, or symptoms of psychological distress. The patient also denied having received a vaccine or any other medication before the start of the symptoms. She also denied having been exposed to toxic chemicals, having had a sexual risk behavior, or having traveled abroad. The patient has a high level of education, works as a magistrate and lives in a rural area of Switzerland.

The clinical examination was unremarkable during the initial and following visits to our clinic.

The blood analysis did not show any inflammatory syndrome, as the C-reactive protein was 0 mg/L and the erythrocyte sedimentation rate was 4 mm/h. There were no hematological disturbances. The kidney and the liver tests were normal. A protein electrophoresis was normal without any signs of paraproteinemia. There were also no signs of electrolytical imbalances and a urine test strip result was normal. Since Switzerland is an endemic region for Lyme disease, this disease was therefore screened and the results of the serological tests are presented in Table 1.

A lumbar and brain MRI did not show any signs for a demyelinating or an inflammatory disease and the lumbar MRI excluded significant discopathy. The lumbar MRI reported only a discrete discopathy in D12-L1, no anomaly at the level of L1-L2, a moderate discopathy with a diffuse disk hernia without signs of radicular compression at the level of L2-L3, a discrete discopathy in L3-L4, a lumbar canal stenosis at the level of L4-L5 associated with a diffuse herniated disk and foraminal stenosis of both sides and radicular irritation of L4 on both sides, and finally no abnormality of the L5-S1 disk. The brain MRI reported a little signal anomaly (FLAIR hypersignal) of 3 mm in the deep white matter of the left temporoparietal region, considered as totally unspecified. Of note, the MRI had to be performed without gadolinium because the patient was highly allergic to it.

As the results of the serology for Lyme disease came out positive on 4 June 2020, particularly the immunoblot (Table 1), the patient was started on doxycycline 100 mg 2×/day for 1 month, and the neuropathic symptoms progressively subsided and completely disappeared. On 1 July 2020, the patient reported another and unique episode of pain over the L1 and L2 right dermatomes. Therefore, the antibiotic doxycycline 100 mg...
Table 1. Patient’s serological results for Lyme disease.

|                          | Patient’s results | Reference ranges |
|--------------------------|-------------------|------------------|
| **LIAISON® test**        |                   |                  |
| (Diasorin, Saluggia, Italy) | <5.0              | <10 negative     |
|                          |                   | 10-15 threshold  |
|                          |                   | result           |
|                          |                   | >15 positive     |
| **Borrelia burgdorferi sensu lato IgG** | 9.4               | <18 negative     |
|                          |                   | 18-22 threshold  |
|                          |                   | result           |
|                          |                   | >22 positive     |
| **Borrelia VIRAstripe® immunoblot** |                 |                  |
| (Viramed, Biotech AG, Germany) |                |                  |
| **Borrelia burgdorferi sensu lato IgG** | Negative          |                  |
| VlsE                     | –                 |                  |
| 100/p83                  | –                 |                  |
| p58                      | –                 |                  |
| 45/p43                   | +/–               |                  |
| BmpA/P39                 | –                 |                  |
| p30                      | –                 |                  |
| OspC/p25                 | –                 |                  |
| 22/p21                   | –                 |                  |
| 21/Osp17                 | –                 |                  |
| DbpA                     | –                 |                  |
| 18/p14                   | –                 |                  |
| **Borrelia burgdorferi sensu lato IgM** | Positive         |                  |
| VlsE                     | –                 |                  |
| Fla/p41                  | +                 |                  |
| BmpA/p39                 | –                 |                  |
| OspC/p25                 | +                 |                  |
| 21/Osp17                 | –                 |                  |

These analyses were performed on 4 June 2020 by MCL® medical laboratories, Switzerland. The IgM in the immunoblot is considered positive if 2 out of 3 bands – OspC, BmpA (39 kDa), and Fla (41 kDa) – are detected [9].

2×/day was empirically continued for another 2 weeks and then stopped. It is also important to mention that the patient did not take any other medication during this period in addition to the antibiotic, and to date the patient is symptom-free.

Discussion

Here, we report a case of peripheral radiculitis secondary to Lyme disease, which is the most frequent neurological manifestation of this disease in Europe [3,4]. It is also known that peripheral radiculitis due to Lyme disease can be the result of a mononeuropathy multiplex, a plexopathy, or a radiculoneuropathy. But as an electromyographic study was not performed in our patient, and as the MRI did not show any inflammatory signs compatible with neuritis, we are not able to confirm which one of the 3 types of peripheral radiculitis described above our patient presented. However, not all Lyme patients with peripheral neuropathy have abnormal electromyograms, since there are cases reported with normal findings [10]. A spinal tap was not performed since, according to the recommendations of the Swiss Society for Infectious Diseases, a cerebrospinal analysis is not necessary in the case of a peripheral neuropathy secondary to Lyme disease [7]. A demyelinating disease could also be excluded since unenhanced MRI has similar accuracy as gadolinium-based contrast for the diagnosis of demyelinating diseases, including multiple sclerosis [11].

The authors are aware that the western blot test is usually not recommended in current guidelines as a first-line test and neither as a second-line test if the ELISA or the IFA is negative [5-7]. Nevertheless, during our search of the literature, we were surprised to find that the even though the overall sensitivities of those tests are quite good, the individual sensitivities of IgG and IgM according to the stage of Lyme disease are significantly different [12-14]. Moreover, the sensitivities also differ according to the technique employed by the laboratory that performs the tests, which could have a negative clinical impact [12-16]. For instance, the LIAISON® test (Diasorin, Saluggia, Italy), a type of indirect chemiluminescence immunoassay that has been shown to outperform IFA test in Lyme disease [13] and which was performed in our patient by the laboratory MCL®, medical laboratories in Switzerland, has an overall sensitivity of 98% in patients with neuroborreliosis, while IgM only has a sensitivity of 43.9-46% for neuroborreliosis [14,16]. Conversely, the sensitivity levels of the Borrelia VIRAstripe immunoblot (Viramed, Biotech AG, Germany), regularly used as a second-tier test by the laboratory MCL®, and also performed in our patient, has a sensitivity of 90-100% for IgM in neuroborreliosis [9]. Even among immunoblots there exist significant differences in the sensitivity and specificity according to stage of Lyme disease [9,12,15]. For example, the immunoblot performed by Euroimmun only has a 33% sensitivity for IgM in neuroborreliosis [9]. These considerations should alert the clinician that these serological tests, although helpful, may have misleading consequences in clinical practice.

The authors are also aware that positive IgM or IgG may be secondary to cross-reactivity to other circulating antibodies.
or may be a serological scar secondary to a previous infection with *Borrelia* [5-7]. However, we demonstrate that it was still possible to have a true-positive IgM result even in a second-tier test with a negative first-tier test since our patient did not present any evidence for another disease that could lead to a false-positive result. Although no serologies for viral or other bacterial infections were performed and no auto-immune panel or paraneoplastic investigations were conducted, this patient has been known to the clinic for many years and never presented any signs or symptoms as mentioned previously compatible with a chronic infection or an auto-immune or paraneoplastic condition. In addition, the fact that our patient has continued healthy up to this day and was able to completely recover after having received only an antibiotic as treatment, indicates that she had in fact Lyme disease. It could also be claimed that the patient presented a neuropathy secondary to an acute viral disease that could have been missed by the authors, but the clinical presentation, the positive IgM immunoblot for Lyme disease, and the clinical response to treatment argue against that hypothesis. Therefore, clinical judgment is paramount when interpreting the serological results from patients in order to avoid both missing Lyme disease and over-treating patients with false-positive results.

**Conclusions**

We demonstrate here that a second-tier test can also be helpful to diagnose Lyme disease even though the first-tier test was negative, particularly in a patient from an endemic region for this disease and in whom there is a high clinical suspicion. Clinicians therefore need to understand the pitfalls of Lyme serological tests, since they have different sensitivities and specificities according to the stage of the disease and to the type of test that is performed.

**Ethics Approval and Consent to Participate**

The patient has reviewed this document and consented to publication of the information herein.

**Acknowledgments**

We thank the patient for having accepted to be taken care by us and for having consented to share her experience with Lyme disease.

**Availability of Data and Materials**

The data can be obtained by contacting the corresponding author or the laboratory, MCL®, Switzerland.

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