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Case Report

Garin-Bujadoux-Bannwarth Meningoradiculoneuritis: A Case Report

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Abstract

Lyme disease is a tick-borne illness caused by Borrelia burgdorferi sensu lato and the nervous system involvement (e.g. meningitis, cranial neuropathies, radiculoneuritis, encephalitis) designates the Lyme disease (LNB) that may occur after infection as part of early disseminated Lyme disease (early LNB) or in untreated patients after at least 6 months (late LNB) after the infection. Herein we report a peculiar case of LNB as the patient, a 61-year-old man, developed meningoradiculoneuritis that relapsed after 9 months and to our knowledge very few cases of LNB relapse have been reported. Diagnosis of LNB was made, in both the episodes, according to EFNS criteria [1] on clinical and cerebrospinal and serum findings. We discussed whether the second episode of meningoradiculoneuritis was a relapse or a late LNB as well whether the second episode of meningoradiculoneuritis was due to a new infected tick bite occurred between the two episodes. Based on clinical and laboratory findings we believe that our patient developed a true relapse of LNB

Keywords: Lyme disease; Neuroborreliosis; Garin-Bujadoux-Bannwarth meningoradiculoneuritis; Relapse

Introduction

Lyme disease is a multi-systemic infectious disease caused by the spirochete Borrelia burgdorferi sensu lato (B. burgdorferi s.l.) and it is transmitted by Ixodes spp ticks. Based on the genospecies, the spirochete can infect several tissues, including skin, nervous and joint system and, although less frequently, Lyme disease can also affect eyes, heart, spleen, and other tissues [2]. The involvement of different Borrelia species contributes to the variability in the clinical manifestations of Lyme disease [3,4].

In North America, the Borrelia, associated with human disease is Borrelia burgdorferi sensu stricto (s.s.) [5] and Borrelia bissettii [6,7], whereas in Europe up to today, seven Borreliae Lyme (Borrelia garinii, Borrelia afzelii, Borrelia burgdorferi s.s, Borrelia spielmanii, Borrelia bavariensis, Borrelia lusitaniae and Borrelia valaisiana) are responsible of disease [8-10]. Lyme neuroborreliosis (LNB) designates the nervous system involvement and the predominant causative agents of LNB in European patients are Borrelia garinii, Borrelia bavarensis and Borrelia afzelii, more rarely Borrelia burgdorferi s.s. and only exceptionally Borrelia valaisiana, Borrelia bissettii or other Borrelia spp [11]. In Southern Italy Borrelia burgdorferi s.s. and Borrelia afzelii

were detected in tick pools belonging to Ixodes Ricinus [12]. Lyme disease may present in different stages. The early localized (stage 1) Lyme disease typically occurs within several days of a tick bite even though it can occur weeks or a few months after an infected tick bite and it includes fever, fatigue, and a rash, called the Erythema Migrans (EM) and affects around from two thirds [13] up to 90% [14] of people who develop Lyme disease. It may evolve into early disseminated (stage 2) Lyme disease, spreading to other areas of the body including the nervous system. In Europe, the most common neurological manifestation of early LNB is meningo-radiculoneuritis (Garin-Bujadoux-Bannwarth syndrome) often associated with cranial neuritis [15-18], while in United States, erythema migrans rash, arthritis, and carditis are historically the most common presentations [19]. However, a recent report described a cluster of Bannwarth Syndrome in the Midwest United States, suggesting that this syndrome may be more common than previously presumed [20]. If Lyme disease is not diagnosed in either of these early stages, and is not treated effectively, the Borrelia can spread throughout the body from the site of the tick bite, resulting in late disseminated Lyme disease. The late LNB is rare [21-22] and is primarily due to chronic meningitis, progressive encephalitis, acute transverse myelitis (ATM) [22] or encephalomyelitis and meningovascular central nervous system (CNS) involvement, while the peripheral nervous system (PNS) is not primarily affected. The onset of symptoms and complications of late disseminated Lyme disease occurs usually around 6-36 months after the original infection (stage 3). Herein we report a peculiar case of LNB as the patient developed meningoradiculoneuritis that relapsed after 9 months

Case Reports

A 61-year-old male, living in a rural area of Southern Italy in February 2021, following a febrile episode, developed marked balance disturbance with impairment of standing and autonomous walking, urinary incontinence. He also complained back pain that radiated into his legs, which worsened at night and during leg stretching. He was admitted to the internal medicine service. Neurological evaluation confirmed a marked gait ataxia, while no muscle weakness was recorded. Thoracic computed tomography (CT) scan was performed that showed a nodule with irregular margins of 9 mm. Brain and spinal cord magnetic resonance imaging (MRI) with gadolinium revealed a peri-medullary enhancement at cervical level (extending rostrally to the bulbar region) and at D11-L1 tract extending caudally to the medullary cone and the anterior roots of the cauda from L2 to S1 with sparing of brainstem and spinal cord parenchyma. In addition, cerebrospinal fluid (CSF) analysis showed many small lymphoid cells on cytological analysis, normal CSF cells [3 cells/μL (normal value <10)], normal CSF proteins [22 mg/dL (reference value 14-45)]. Multiplex PCR assay for detection of the 14 most common pathogens (E. coli K1, H. influenzae, Listeria monocytogenes, Neisseria meningitidis, S. pneumoniae, S. agalactiae, CMV, enterovirus, HSV 1-2, HPV 6, human parechovirus, VZV, and C. neoformans/C. gattii) responsible for community acquired meningitis or encephalitis from CSF specimens and culture for aerobes and anaerobes organisms of the CSF were negative. During stay in the Hospital, he worsened as he developed hypoesthesia and paresthesia in the left face and left peripheral facial nerve palsy, weakness of lower limb proximal muscles, disappearance of lower limb deep tendon reflexes and tactile and pinprick hypoesthesia at the lower limbs. Guillain-Barrè syndrome was suspected, and intravenous immunoglobulin (IVIg) and intravenous methylprednisolone were administrated without any benefit. Therefore, he was transferred to the Neurology Unit of Federico II University in Naples. On admission neurological examination showed hypoesthesia in the left face and left peripheral facial nerve palsy, severe proximal muscle weakness at lower limbs with inability to standing and autonomously walking, saddle anesthesia and bladder and bowel incontinence. The patient underwent neurophysiological examination that was consistent with a proximal involvement of peripheral nerve fibers at lower limbs as well as concomitant spinal cord involvement. A PET-CT performed to evaluate the hypothesis of a paraneoplastic syndrome, showed bilobed parenchymal nodulations (5 and 6 mm) with irregular margins in the dorsal segment of the right apical lobe of lung without significant contrast uptake. Oncological consultation did not consider appropriate further evaluation of the lesion. Brain and spinal cord MRI with gadolinium confirmed the peri-medullary enhancement at cervical and lumbosacral level with normal signal of the spinal cord parenchyma (Figure 1).

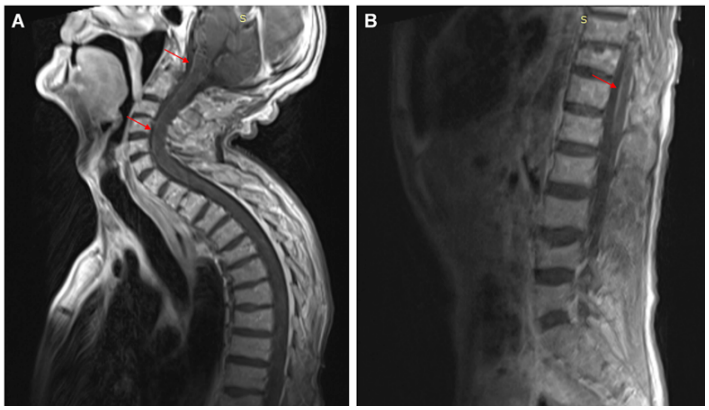

Figure 1: Spinal cord MRI.

Contrast-enhanced sagittal T1-weighted showed leptomeningeal contrast enhancement (red arrows) at cervical with extending rostral till the bulbar region (A), and lumbosacral (B) level with normal signal of the spinal cord parenchyma.

Lumbar puncture showed CSF pleocytosis characterized mainly by monomorphonuclear cells [244 leukocytes/µL (normal value <10)], slight increase of CSF proteins [66 mg/dL (reference value 14-45)]; we repeated a multiple-PCR array and culture of CSF that resulted negative. Infectious disease screening on serum was performed, including syphilis, Brucella, Bartonella, tuberculosis, CMV, VZV, EBV, and resulted negative. Enzyme-linked fluorescence assay [ELFA; VIDAS Lyme IgM and VIDAS Lyme IgG (Biomerieux); see supplementary material] screening, performed at 34th day from disease onset, resulted positive for serum IgM index (0.60, normal value <0.32) and IgG index (0.27, normal value <0.20) anti-borrelia antibodies. Anti-Borrelia antibodies, tested with an enzyme immunoassay (EIA), were not found in CSF. Serum and CSF Western blot [WB; VIROTECH Borrelia Europe +TpN17 IgG LINE Immunoblotand Borrelia Europe IgM LINE Immunobot, Virotech Diagnostics see supplementary material], after 36 days from disease onset, was positive for Borrelia. Moreover, WB was positive in serum for VisE-Mix, p39, DbpA-Mix, and Dbpa-PKO IgG bands, and p39 and VisE-Mix IgM bands while WB was positive in CSF for VisE-Mix and p39 IgG bands. Moreover, we tested for common co-infection in our region (Rickettsia conorii e Rickettsia tiphi) that resulted negative. According to the EFNS diagnostic criteria [1], Therefore, antibiotic therapy with intravenous ceftriaxone (2 gr for 14 days) was started. The patient did not refer recent tick bite, but he had memory of a single tick bite 10 years before that had not required any medical consultation neither antibiotics prophylaxis. However, he used to go to the countryside in a little village located in Cilento National Park. After 3 months from discharge gait was wide-based and possible with minimal support and muscle strength at lower limbs was normal apart from persistence of weakness of iliopsoas muscles. Fecal incontinence was resolved while bladder impairment persisted. After 9 months, the patient worsened again developing back lower pain, weakness at lower limbs and severe ataxic gait. Spinal cord MRI showed vertebral collapse of the L2 soma and a thin posterior linear enhancement of the spinal roots of the cauda equina. Vertebral collapse was treated with vertebroplasty. ELFA screening was negative for serum IgM and IgG anti-borrelia antibodies. However, lumbar puncture showed CSF pleocytosis (27 leukocytes/µL, normal value <10), and slight increase of CSF proteins (76 mg/dL, normal range 15-45) and WB was positive for Borrelia on serum (IgG and IgM positive) and doubtful on liquor (IgG positive, IgM uncertain). Moreover, WB was positive in serum for Ospc, VisE-Mix, p39, Dbpa-PKO and P58 IgG bands, and p39 and VisE-Mix IgM bands while WB was positive in CSF for Ospc, VisE-Mix and p39 IgG bands, and p39 IgM bands. In the suspicion of a relapse of LNB, he started again treatment with intravenous Ceftriaxone (2 gr/day) and Doxycycline (200 mg/day) for 21 days. At 3 month-follow up the gait was wide-based and possible with support and muscle strength in the lower limbs was recovered; neurological bladder impairment persisted

Materials and Methods

VIDAS Lyme IgM and VIDAS Lyme IgG (Biomerieux) assays are automated tests both intended for the detection of antibodies against Borrelia burgdorferi in human serum or plasma, VIDAS Lyme IgG assay is also intended for the detection of antibodies against B. burgdorferi in cerebrospinal fluid (CSF), in order to determine intrathecal antibody production. The assay principle combines a two-step enzyme immunoassay sandwich method with final fluorescent detection (Enzyme Linked Fluorescent Assay—ELFA). The tests were performed according to manufacturer's instructions. LINE Immunoblot kits are intended for qualitative detection of IgG (VIROTECH Borrelia Europe +TpN17 IgG LINE Immunoblot, Virotech Diagnostics) and IgM (VIROTECH Borrelia Europe IgM LINE Immunobot, Virotech Diagnostics) antibodies specific to B. burgdorferi sensu lato in human serum. In addition to its use in the serodiagnosis of Lyme borreliosis, the IgG/IgM LINE immunoblots are suitable for use in the diagnosis of cerebrospinal fluid for neuroborreliosis. The tests were performed according to manufacturer's instructions.

Discussion

Lyme disease is a tick-borne illness caused by Borrelia burgdorferi s.l. and nervous system involvement may occur after infection as part of early disseminated Lyme disease (early LNB) or in untreated patients after at least 6 months (late LNB) after the infection [15,24]. Our patient developed a meningoradiculoneuritis over two weeks with good neurological recovery after 14 days of intravenous ceftriaxone. The diagnosis was based on CSF pleocytosis, positivity for serum IgG ang IgM anti-Borrelia antibodies, and serum and CSF WB positivity for Borrelia. The clinical picture (lower limb weakness and sensory loss, with urinary incontinence) could resemble an acute transverse myelitis as well. However, radicular pain suggested the involvement of spinal root and MRI showed a peri-medullary enhancement, excluding the primary involvement of spinal cord as generally occurred in acute myelitis transverse. The characteristics of nervous system involvement (i.e. meningoradiculoneuritis) were consistent with an early LNB that typically occurs weeks or a few months after an infected tick bite and after EM. However, our patient had memory of a single tick bite 10 years earlier and he did not have a history of EM. Therefore, there probably was a more recent infected tick bite, since his habit to go to the countryside. Anyway, the most interesting feature of our case is the relapse of LNB that occurred after 9 months. Indeed, to our knowledge very few cases of LNB relapse have been reported [25-28]. Diagnosis of LNB during the relapse was again based on CSF pleocytosis, WB positivity for Borrelia on serum and WB positivity for specific IgG and IgM for

Borrelia both on serum and CSF. An interesting issue raised by this case is whether the second episode of meningoradiculoneuritis is a relapse or a late LNB. However, we believe that our case designates a relapse of LNB. First, the late LNB typically involves the CNS rather than the PNS (i.e. radiculoneuritis). Second, at first episode of LNB the patient was treated with an antibiotic and had a good clinical improvement, making unlikely a diagnosis of late LNB that typically occurs after 6 months in untreated or ineffectively treated patients. However, we cannot be sure about the clinical worsening was due to a relapse LNB. A point of discussion can be that the second episode could be due to an inadequate treatment. Although European guidelines recommend a single 14-day course of antibiotic [1] avoiding the long-term treatment [29], it is possible that the current therapeutic strategy is not definitely curative but maybe merely suppressive, as other infectious diseases have taught us [30]. We cannot exclude that the persistence of Borrelia in PNS could be responsible of the onset of the second clinical event, such as in chronic Lyme disease [31]. Interestingly, a recent study underlined that bacterium might upregulate genes that can serve as targets for developing new drugs for more effective treatment [32]. In the future we probably will have to re-consider the current drug modalities, in order to improve treatment strategies that must be tailored to individual patients, carefully followed over time and in response to treatment. Another issue raised by this case report is whether the second episode of meningoradiculoneuritis may be an early LNB due to a new infected tick bite occurred between the two episodes. Of course, such hypothesis, although exceptional, cannot be completely ruled out since Borrelia culture with OspC genotyping was not carried out from CSF samples to discriminate between relapse and reinfection from Borrelia as conversely is possible through culture from EM rashes [33]. Alternately, normal CSF findings between the two episodes and/or real-time PCR-analysis for Borrelia burgdorferi in CSF in both the episodes would have perhaps supported our hypothesis. However, patient between the two episodes did not report any rash neither refer new tick bite, since during this period he was first hospitalized in a rehabilitation center without open spaces and, coming back home, he was essentially home-bound and he did not have any pets that might have brought ticks in the home. Lastly, WB revealed on serum in the second episode the positivity for P58 IgG band that identifies a late antigen of Borrelia that thus suggest a relapse rather than a new infection.

Conclusion

Lyme neuroborreliosis is neurologic involvement secondary to systemic infection by the spirochete Borrelia burgdorferi and may occur as early or late complication after the infection. The diagnosis of LNB is based on clinical signs, CSF findings and serological testing. The present case report is characterized by a second episode of meningoradiculoneuritis occurred after 9 months apart from the first episode and after good response to therapy. Clinical and laboratory findings are consistent with a relapse of LNB that though very rare it should be considered during the follow-up of patients with LNB.

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