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Case Report

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Prolonged Treatment with Ceftriaxone Cures A Patient with Chronic Lyme Disease

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Abstract

This is the case of a 40-year-old immunocompetent, female patient presenting with a "polymorphic persistent syndrome after a possible tick bite" (SPPT), a syndrome officially recognized by the French High Authority for Health (HAS). This patient presented with polymorphic symptoms and was unable to walk without a walker. Only ceftriaxone was effective. She experienced several episodes of remission and relapse, when treatments were started and stopped. Finally, it was possible to achieve a prolonged final remission, persisting for 3 years after the last anti-infective treatments had been stopped.

Keywords: High Authority for Health (HAS), PTLDS (post-treatment Lyme disease syndrome), DAPI, SPPT

History of the Disease

A 40-year-old female patient presented with "polymorphic persistent syndrome after a possible tick bite" (SPPT) with polymorphic symptoms and, above all, weakness of the lower limbs, evolving since January 2017 and worsening more significantly in August 2017. Her history included severe depression several years ago, weaned alcoholism and smoking, and inguinal hernia surgery. This patient had been bitten by a tick six years earlier and presented with a series of symptoms, including profuse sweating, headaches with vomiting, and neck and back pain. No treatment was initiated. Symptoms returned five years later with progressive worsening: intense asthenia, walking difficulties, and pain, leading to a loss of employment. Abdominopelvic and cervical ultrasonography were normal, and brain MRI showed only a few non-specific FLAIR white matter hypersignals, which were stable at one-year follow-up. A spinal cord MRI with contrast injection was normal. Lyme disease serology was negative (presence of IgM below the significant threshold: p41 (0.2) and p39 (0.2) in Western blot). PCRs were performed for *Borrelia (B. burgdorferi s.l., B. miyamotoi, B. hermsii), Bartonella (Bartonella spp., B. quintana, B. henselae), Babesia spp., Coxiella burnetii, Theileria spp., Rickettsia spp., Ehrlichia spp., Anaplasma spp., Francisella tularensis, Brucella spp., Candidatus neoehrlichia, and Candida spp.*, in blood, urine, and saliva. PCR for *Coxiella* was positive in the urine.

Despite a negative Lyme serology, several anti-infectious treatments were implemented without success. In August 2018, amoxicillin was prescribed at a dose of 3 g per day for 3 weeks, followed by a course of doxycycline (200 mg per day) for 2 months. Due to the ineffectiveness of these antibiotics, an anti-*Babesia* treatment combining azithromycin (250 mg), one tablet per day, and atovaquone (250 mg) and proguanil (100 mg), three tablets per day, was

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instituted for one week. The patient showed no exacerbation reaction under treatment (Jarisch-Herxheimer type) nor any improvement. It was against this background that she presented for consultation.

Clinical Presentation

On examination, the patient was found to have abnormal, incapacitating asthenia with no depressive syndrome. The patient was anxious and presented with spatial disorientation, brain fog, concentration and memory problems, and speech disorders with a lack of words. Sleep was altered, with difficulty falling asleep once lying down and, above all, being non-restorative. She presented with muscle fasciculations and tremors, palpitations, lipothymia, hot flushes, excessive chilliness, chills, sensations of cold extremities, and abnormal sweating. Dyspnea, hyperacusis, photophobia, and, to a lesser degree, moments of very blurred vision were noted, as well as diffuse and disabling pain in the joints, muscles, spine, and abdomen, and paresthesia, especially of the right leg. The patient also had amenorrhea for several months and urinary discomfort. In the foreground, there were neurological disorders with weakness of the lower limbs and impossible walking except with the use of a walker.

Overall, her quality of life was severely affected by her condition, and she was no longer able to work. The presence of a third party was indispensable for her daily life. A diagnosis of "polymorphic persistent syndrome after a possible tick bite" (“syndrome polymorphe après possible piqûre de tique”, SPPT), a syndrome officially recognized by the French High Authority for Health (Haute Autorité de Santé, HAS), was mentioned. This syndrome is rather similar to PTLDS (post-treatment Lyme disease syndrome) [1, 2]. The usual laboratory workup was normal. There was no iron, folate, or vitamin B12 deficiency. TSH was normal. There was no abnormality in the blood protein electrophoresis. There was no biological inflammatory syndrome. The electrocardiogram was normal. The chest X-ray was normal. In early 2019, serologies for *Borrelia* (Lyme disease), *Chlamydia pneumoniae*, *Coxiella burnetti, Babesia divergens, Anaplasma phagocytophilum*, herpes virus, EBV, and CMV were negative. There were a few traces of anti-*Mycoplasma pneumoniae* IgG, but no IgM. EBV was nevertheless found by PCR on a swab of the buccal mucosa (5730 copies/ml). Four months later, *Babesia divergens* serology was performed again and was weakly positive.

Despite her negative Lyme serology and the failure of previous empiric treatments, and given her history of tick bites and severe neurological impairment with the inability to walk, this patient was treated with intravenous ceftriaxone (2 g/day) from late November 2018 for one month, then renewed every 15 days, for a total course of two and a half months. After one month, hydroxychloroquine was added at a dose of 200 mg per day. An ampoule of 80,000 IU of vitamin D was also prescribed. At the beginning of January 2019, the patient's general condition improved markedly, with better balance, reduced paresthesias, the disappearance of functional urinary signs, the return of menstruation, and a 1.5-kilometer walk in a walker. However, the course of the disease fluctuated, with periods of symptom exacerbation and episodes of marked improvement. Finally, deterioration was observed, with amenorrhea, an inability to walk, pain, an intense headache, visual blurring, hot flushes, and chills. A one-week course of tapering corticosteroids was instituted under the hypothesis of a Jarisch-Herxheimer reaction, resulting in an improvement in symptoms but without any improvement in walking. Subsequently, other anti-infectives were tested: azithromycin (250 mg/day) for 6 days, tinidazole (500 mg/day) for 8 days, and doxycycline (200 mg/day) for one month, all of which were ineffective.

In view of the latter failure, with the inability to walk having a major impact on the patient's quality of life, the partial success of ceftriaxone alone, and the absence of a differential diagnosis or other proposed solution, it was decided to reintroduce treatment with ceftriaxone (2 g/day) combined with hydroxychloroquine (200 mg/day). This therapeutic protocol was implemented for a few weeks, with biological monitoring and precise, regular evaluation of the treatment's effects. At the end of the treatment, in early August 2019, the headaches had disappeared, and the dyspnea and asthenia had diminished significantly. Above all, the patient had completely recovered the ability to walk without any assistance. However, some tingling, areflexia of the right lower limb, and paresthesia persisted. At the end of August, however, a relapse occurred, making it impossible to walk. The only effective treatment, ceftriaxone 2 g daily, twice weekly, was reintroduced with the aim of achieving a new remission; this treatment was continued for a few weeks. The menstrual periods that had disappeared reappeared, and the patient was walking normally again at the beginning of September, one month after the start of treatment.

However, in February 2020, there was again a marked deterioration in the patient's general condition, with walking again impossible, menses disappearing, and symptoms so intense as to require hospitalization. When the patient was discharged from the hospital, the only treatment that had proved effective in the past—ceftriaxone at a dose of 2 g per day for a month—was again introduced, resulting in a rapid remission with the return of menses and the ability to walk normally. Maintenance treatment was instituted with the aim of maintaining remission and the possibility of independent living while using as little ceftriaxone as possible. Ceftriaxone was then administered at a tapering dose, with the aim of maintaining the patient's ability to walk while hoping for long-term weaning, at a dose of 2 g per day, twice a week,

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then once a week until discontinuation, which was not possible until early October 2020. The patient then remained in remission, allowing treatment to be discontinued. The patient has been asymptomatic for years and has not relapsed. The patient was recalled recently, in November 2023, and orally confirmed that she was still walking well and that her general condition was continuing to improve, with no need for further treatment.

Discussion

This case report is the result of an analysis of the files of colleagues treating Lyme disease. The patient has been contacted to attest to the complete veracity of the elements reported. The authors of the article, who have seen similar cases, are suspending judgment on this case and the protocols used and are reporting it in order to contribute to the scientific debate, albeit with caution. This is an exceptional case of a patient with a condition compatible with PTLDS, in which walking was impossible other than in a walker, with remarkable efficacy of ceftriaxone and dependence on this drug, which was the only effective. The choice of ceftriaxone, after the failure of other treatments, was justified by the presence of severe neurological impairment. During treatment, discontinuation of this drug always resulted in a rapid relapse; conversely, resumption of antibiotic treatment resulted in almost complete remission, with a return to normal walking. Strangely, other anti-infectives failed to improve this patient's condition. In the end, it was only possible to work by observation and empiricism to preserve her quality of life by avoiding relapses while trying to reduce ceftriaxone infusions as much as possible, both in dose and time. However, it was impossible to treat this patient in any other way, as she recovered her motor functions each time ceftriaxone was administered. It was therefore unthinkable to stop taking this antibiotic and see her walking with a walker, if at all. A one-month course of antibiotics may not be enough to bring about clinical improvement, as clinical signs continue to fluctuate and, in some patients, Jarish-Herxheimer-type reactions can exacerbate the condition, particularly pain [3]. Indeed, despite antibiotic treatment, the bacterium is able to persist, as described in vivo and in vitro in the medical literature: biofilms (a shell of protein material under which the bacterium protects itself), antibiotic-resistant round forms that the bacterium can take, and body sanctuaries where antibiotics penetrate little or not at all (e.g., tendons). This ability to persist explains the existence of a chronic form of the disease [4–8]. A long course of antibiotics may therefore sometimes be essential, as has already been described in the literature [9]. Finally, our patient is currently in remission, almost 3 years after the end of the anti-infective protocols.

We do not know precisely why ceftriaxone was particularly effective. The efficacy of this antibiotic may be related to its bactericidal rather than bacteriostatic activity and its better diffusion across the blood-brain barrier. Doxycycline, for example, has low diffusion [10, 11]. The question also arises as to which microorganism is responsible. As a matter of fact, ticks carry numerous bacteria, parasites, viruses, and probably as yet unknown germs [12, 13]. The efficacy of ceftriaxone would suggest a diagnosis of borreliosis despite negative serology and PCR. Ceftriaxone is usually very effective against *Borrelia.* Nonetheless, the treatment could have failed, as some *Borrelia* can produce a rare extended-spectrum beta-lactamase, which was not the case here [14]. It could also be an unknown micro-organism in the context of what is now called a crypto-infection [15], or possibly a non-anti-infectious pleiotropic effect of ceftriaxone. We know, for example, that ceftriaxone inhibits neuronal secretions of glutamate, a toxic compound in Lou Gherig's disease. Hydroxychloroquine is a drug of interest for its various effects in Lyme disease. This drug has an anti-inflammatory effect of its own, an anti-infectious effect of its own, notably on *Borrelia;* it is anti-parasitic; and moreover, it potentiates the action of antibiotics by alkalinizing the phagolysosome [16–20]. With regard to the possibility of borreliosis, we would point out that serology is controversial, between those who believe that its sensitivity is excellent in the late phase and those who have voiced criticisms and questioned the scientific consensus. Indeed, it would appear that Lyme serology is imperfect, fraught with numerous false negatives, for the following reasons: Firstly, anti-*Borrelia* antibodies may be produced slowly and absent in the early stages of the disease; moreover, there are several different *Borrelia* serotypes, some of which may not be detected by current tests. False-negative results may also be explained by antibiotic therapy, the sequestration of antibodies within immune complexes, and the presence of quiescent metabolic forms of *Borrelia*, the so-called round forms [21, 22].

The "predicate" is the performance of the previously validated test, and the clinical picture chosen by all manufacturers is that of erythema migrans and chronic atrophic acrodermatitis or Pick-Herxheimer disease. These expressions of Lyme disease are however just one of the many manifestations of Lyme disease. It should be noted, however, that the chronic form of the disease is perfectly integrated into the validation of ELISA kits, whereas the majority of infectiologists deny this chronic form outright while referring to the ELISA kit. If we go back to the ELISA kits validated on the basis of an earlier kit itself validated, we arrive in 1989 at the leaflet for the MarDx *Borrelia burgdorferi* EIA IgG + IgM kit, whose diagnostic performance is a comparison with that of an "in-house" kit, i.e., manufactured in-house by a "referent" laboratory; neither the name of the kit nor that of the "referent" laboratory is mentioned in the leaflet. This method of validation based on a previously validated

test is questioning, provided that there is no dispute over the initial kit; however, this MarDx *Borrelia burgdorferi* EIA IgG + IgM kit is indisputably a serological test based on the antigens of *Borrelia burgdorferi* sensu stricto (s.s.), discovered by Willy Burgdorfer in the early 80's in the USA, and due to its constitution, recognizes only the antigens of *Borrelia burgdorferi* (s.s.); subsequently, and due to the genomic proximity between *Borrelia burgdorferi* and some fifteen *Borrelia* species, it will be referred to as *Borrelia burgdorferi* sensu lato (s.l.). What's more, we don't know how the antibody detection threshold was determined. Given the validation of a kit based on a previously validated kit and the absence of a reference test, it is impossible for manufacturers to impose a new serological kit enabling, for example, the detection and discrimination of all or some of the other tick-borne pathogens.

The ELISA test was in fact calibrated with an arbitrary threshold so that no more than 5% of patients could be positive. In ELISA, the threshold is determined by adding, according to the authors, two or three standard deviations to the mean of the optical densities of the controls. The recommendations of the "European Concerted Action on Lyme Borreliosis" are to test at least 100 negative controls from the normal population of the same geographical area and to verify that no more than 5% of these controls are positive at the chosen threshold" [23]. In our series, among 9 patients who were tested positive for *Borrelia* by PCR, 1 patient had a positive *Borrelia* serology [24]. Other detection methods could be of interest: PCR on several matrices (blood, capillary blood, urine, and saliva) [12, 13, 24] and light microscopy of "live" (i.e., unfixed) fresh blood, using various combined techniques: phase contrast, darkfield, and Köhler illumination. Giemsa staining without alcohol or glycerine and at a neutral pH to avoid alteration will clearly identify the pathogens of interest. Fluorescence techniques (DAPI) can also be used to highlight DNA. A magnification of x2500 can be obtained with an oil lens and the right eyepiece/camera combination, enabling the identification of spirochetes and mycoplasmas, for example. Comparative analyses can also be carried out on the same slide, with a thick control drop under neutral Giemsa to observe circulating blood in its normal state and another drop from the same sample, also under neutral Giemsa, to which a product has been added to express the intracellular parasite load.

Conclusion

Lyme disease may be an extremely difficult disease to diagnose, not least because of the imperfection of serological diagnosis. In addition, there are numerous co-infections to take into account, and perhaps other germs yet to be discovered. In most cases, therefore, we should be talking about "crypto-infections." In our case, the patient was put into complete remission by means of prolonged antibiotic therapy with ceftriaxone, which was the only effective antibiotic treatment. This case also perfectly illustrates the chronicity of SPPT and Lyme disease, with its succession of remissions and relapses when effective treatments are started and stopped. This chronicity is perfectly established, as the mechanisms of persistence, the presence of biofilms, and quiescent round forms have been demonstrated in vitro and in vivo.

Conflict of Interest: Michel Franck is CEO of ADNucleis.

The others authors do not declare any conflict of interest

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