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Case Report

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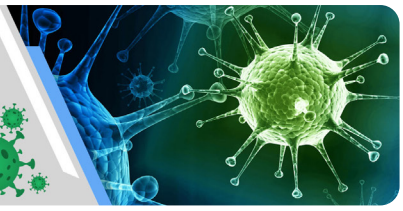

Patient with Chronic Lyme Disease and Recurrent Relapses, Maintained in Complete Remission by Low Doses of Metronidazole

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Abstract

We report herein the case of a patient presenting with a chronic form of Lyme disease. The statement of the chronic form of Lyme disease is definitely corroborated by known and published biological mechanisms and by the report of cases of successive remissions and relapses on the introduction and cessation of antibiotics. In the present case, prolonged clinical remission was achieved with very low doses of metronidazole (500 mg once a week)

Keywords: Lyme ; *Borrelia*; SPPT; Chronic Lyme disease

Background

Borrelia burgdorferi sensu lato (including *B. burgdorferi sensu stricto, B. afzelii, B. garinii* and *B. hermsii*) is the bacterium responsible for Lyme's disease and is transmitted by tick bites. This bacterium can be the cause of a particular type of Lyme's disease that recurs when treatment is stopped, known as chronic Lyme's disease. The real chronicity of the clinical symptoms of this disease, is now being recognized by the CDC in Atlanta, and is illustrated by various clinical observations and explained by numerous scientific publications.

History of the Disease

A 55-year-old patient, an artisan roofer had been suffering from an unexplained disabling syndrome since 2006. He had had type 2 diabetes mellitus for 15 years. Initially, he had experienced numbness in one leg, thereafter in the contralateral one, and in his hands, combined with severe asthenia. This was followed by anaesthesia and burning in the legs. He also complained of tinnitus. He was said to have been bitten by a tick in the 1990s but had no notion of erythema migrans. He had reported taking antibiotics for another reason than suspected Lyme disease, in this case biliary pancreatitis, with a marked improvement of the clinical symptoms described above. His general practitioner had ordered various tests including: MRI of the spinal cord, MRI and CT scan of the lumbar spine and multiple electromyograms of the upper and lower limbs, all of them had failed to find any precise cause for all his symptoms. There was moderate stenosis of the lumbar canal at L4-L5 anatomical level, and cervical osteoarthritis mainly at C5-C6 and C6-C7 levels. The spinal cord feature appeared normal on MRI. Electromyograms were normal. Chest X-ray was normal. A cardiology consultation revealed no abnormalities. A neurologist finally diagnosed diabetic neuropathy and prescribed analgesics and duloxetine. After several months of treatment, however, the pain intensified.

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Duloxetine doses were then increased to 30 mg 3 times a day, without efficacy. An ENT doctor concluded that there was a link between tinnitus and the neuropathy. Walking distances became shorter and shorter, and the pain more and more severe. The patient underwent multiple peri-neural infiltrations of the lower limbs, and upper limbs (ulnar nerves) without efficacy. A novel neurology consultation concluded in peripheral neuropathy, and amitriptyline drops were added to the patient's prescription without efficacy. This patient was finding it increasingly difficult to work as a self-employed roofer at height. This was followed by urinary and erectile dysfunction, for which a urologist concluded that neurological damage was the cause of the symptoms.

Clinical Presentation

On examination, the patient reported intense pain, cramps at night and at rest, impatience of the lower limbs at night and when sitting, paresthesias, palpitations, orthostatic hypotension, headaches, tinnitus, and a sensation of shortness of breath. Fatigue was intense and incapacitating, accompanied by anxiety, difficulty concentrating, mental fogginess and sleep disturbances. Physical examination showed no abnormalities. Standard laboratory tests were normal. A prolactin assay was also normal. There was no biological inflammatory syndrome. Infections were investigated, with negative Lyme serology by Western blot (IgM and IgG), and negative *Borrelia* enzyme-linked immunospot. *Chlamydia pneumoniae* IgG and IgA, *Mycoplasma pneumoniae*, *Coxiella*, *Babesia divergens and Anaplasma phagocytophilum* serologies were negative. 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). SPPT is defined by (a) a possible tick bite (b) the clinical triad associating several times a week, for more than 6 months: a polyalgic syndrome (musculoskeletal and/or neuropathic pain and/or headaches), persistent fatigue with reduced physical capacity, and cognitive complaints (concentration and/or attention problems, memory problems, slowness of ideation); (c) with or without a history of erythema migrans.

Treatment was initiated at the end of June 2017, under clinical and biological monitoring, with pyrantel (1250 mg repeated 15 days after the first dose), followed by doxycycline (200 mg per day) and hydroxychloroquine (200 mg per day) for one month. An ampoule of 80,000 IU of vitamin D was also prescribed. Due to intercurrent acute sigmoiditis, her general practitioner interrupted this treatment and prescribed a treatment with ceftriaxone (2 g per day) combined with metronidazole. At the end of this treatment, all signs had disappeared except for some residual intermittent leg pain. Duoxetine was further reduced to 30 mg daily. In February 2021, a chest CT scan performed in the setting of a cough and a history of smoking, revealed a 2 cm invasive squamous cell carcinoma of the right lung (pT4 with vascular emboli, but without lymph node metastasis). Treatment consisted of a combination of chemotherapy, complete right pneumonectomy and mediastinal radiotherapy. Three years later, the patient was in complete remission. A recurrence of his symptoms linked to a possible SPPT recurred every two to three months after the patient had stopped cancer treatment. Each episode of relapse had been treated with complete success by antibiotic therapy, most often with doxycycline or azithromycin, sometimes combined with low doses of hydroxychloroquine. A few courses of tinidazole had been prescribed, with the aim of treating any persistent forms of *Borrelia*, such as biofilms or round forms, on which this antibiotic is reputed to be active. In view of these recurrent and seemingly inescapable recurrences, long-term treatment was initiated in the hope of maintaining a prolonged remission with the minimum antibiotic as possible: metronidazole 500 mg once a week. For the past year, the patient had been free of recurrence and is currently in complete remission of his neurological disease.

Discussion

This case perfectly illustrates the existence of a chronic form of Lyme disease, as the patient relapsed numerous times (every two to three months for several years), and always went into remission after reintroducing antibiotics, usually for a short course. In this case, hydroxychloroquine was used, as this molecule has many interesting properties: anti-inflammatory, anti-infectious against *Borrelia* and other germs [2] and potentiates the action of other antibiotics by alkalinizing the phagolysosome. Tinidazole and metronidazole are also effective antibiotics against all forms of *Borrelia*, that display mobile and round-body forms [3, 4]. The disease was not microbiologically documented. Nevertheless, serology is probably not very sensitive, for a number of reasons, including historically opaque calibration, and an arbitrary antibody detection threshold, so that less than 5% of patients can be positive [5, 6]. Some PCR-positive patients (not tested in this case) are indeed serologically negative [7]. Empiric antibiotic treatment may be required for hidden infections which are known as crypto-infections, i.e. infections that are difficult to document [8]. For example, PCRs may be positive one day and negative the next, and vice versa [9, 10]. Moreover, this possibility has been endorsed by the HAS 2018 report defining a new entity, the so-called "SPTT" [1]. The Centers for Disease Control and Prevention (CDC) which is the national public health agency of the United States under the Department of Health and Human Services in Atlanta now recognizes the existence of chronic manifestations of Lyme disease [11]. Therefore, there should no longer be any scientific controversy on this subject.

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Chronicity can be explained by multiple factors, many of which are scientifically established (a) persistence forms of *Borrelia* that are not sensitive to antibiotics: biofilms, round forms [3, 4, 12-15], (b) sanctuaries in the body such as collagen fibers [16], (c) association of the infection with other germs with which *Borrelia* may cooperate: parasites for example [17], (d) *Borrelia*'s immunosuppressive effect, (e) the presence of co-infections which do not induce a real chronicity but are to be taken into account and treated (*Babesia* for example) [9, 10, 18, 19]. This chronicity is particularly well illustrated in the case reported by Sapi et al.: a patient whose autopsy confirmed the presence of *Borrelia* despite several courses of antibiotics over several months [20]. There are other examples in both human and veterinary medicine [21-25]. Chronicity has probably other factors than microbial persistence, explaining the possible relapse after effective anti-infective treatments. Among causes, dysimmune phenomena seem to play a major role [27-30]. Most chronicity mechanisms are observed both in vitro and in vivo (biofilms, round forms) [31, 32]. Lyme disease is a great mimicker, as syphilis was in the last century. It can thus resemble many autoimmune diseases (in this case, an undetermined neuropathy or one linked to diabetes), for which expensive biotherapies prescribed for years or even for life, with deleterious consequences on immunity: cancers, infections. In such cases, appropriate antibiotic therapy can lead to a cure, or at least prolonged remission. Recurrences are usually amenable to a new, shorter course of antibiotics. Antibiotic treatment has sometimes to be long [33]. In our case, long-term, inexpensive treatment with minimal doses of antibiotics (500 mg metronidazole per week) was successfully introduced: the patient has not relapsed since then, leads a normal life and has even returned to work.

Conclusion

In conclusion, this clinical observation corroborates the existence of chronic Lyme's disease (or a related infection) and the interest of tailored maintenance treatments (in this case, treatment with 500 mg metronidazole per week) to achieve complete and persistent remission.

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