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CASE REPORT

Multiple sclerosis and inflammatory bowel disease: what implications in therapeutic decisions?

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Abstract

Introduction: Recent observations suggest an association between Multiple sclerosis (MS) and Inflammatory Bowel Disease (IBD). The anti-TNF-alpha antagonists such as infliximab are an effective therapeutic option in IBD, but may induce worsening of demyelinating diseases.

Case Report: A 33-year-old Caucasian male with a diagnosis of ulcerative colitis (UC) since 2007 and of relapse-remitting MS since 2004. After MS diagnosis, he started subcutaneous interferon beta-1a thrice a week. No relapses were observed. Six years after diagnosis, the patient developed injection-site reaction and had ulcerative colitis exacerbation. In spite of testing positive for anti-JC virus antibodies, he was medicated with natalizumab (Tysabri®) for two years. After this treatment, in the subsequent three years, by reason of UC worsening, he began azathioprine 150 mg daily. Patient persisted asymptomatic until 2013, when a significant aggravation of UC was detected. Consequently, he started anti-TNF-alpha agent (infliximab), maintaining azathioprine. He had no relapses until the one registered in May 2015. At that time high dose metilprednisolone pulse was initiated and anti-TNF-alpha was interrupted, azathioprine was augmented (200 mg/day) and, later on, the patient started daily subcutaneous glatiramer acetate (Copaxone®).

Discussion: Our report emphasizes the complexity of treating patients with MS and other autoimmune diseases such as IBD. Despite being very effective in controlling ulcerative colitis, infliximab may worsen MS. The authors discuss what should be the best treatment to control both conditions.

Keywords: Multiple sclerosis, Inflammatory bowel disease, Infliximab.

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Introduction

The association between multiple sclerosis (MS) and inflammatory bowel disease (IBD), namely ulcerative colitis (UC), has been reported in literature [1]. The incidence of IBD among MS patients is increased and both diseases have similar age of occurrence and clinical course. Tumor necrosis factor (TNF) alpha is an immunomodulatory cytokine that has been involved in the pathology of many inflammatory diseases, including ulcerative colitis. Anti-TNF-alpha agents, such as infliximab, are potent immunosupressive agents and are established therapies to treat these pathologies. However, in spite of being clinically effective, anti-TNF-alpha may have several neurological adverse events, such as peripheral and central nerve demyelination [2]. A challenging case of therapeutic management in a patient suffering from two autoimmune diseases, MS and UC, will be reported.

Case Report

A 33-year-old Caucasian male with a diagnosis of ulcerative colitis since 2007 and of relapse-remitting MS since 2004. After MS diagnosis, the patient started immunomodulatory treatment with subcutaneous injection of interferon beta-1a thrice a week, with regular outpatient department follow-up. No relapses were registered. Six years after diagnosis (2010), the patient developed injection-site reaction and symptoms consistent with ulcerative colitis exacerbation. Despite testing positive for anti-JC virus antibodies, he was treated with natalizumab (Tysabri®) for two years. After this treatment, in the following three years, due to serious ulcerative colitis worsening, he started azathioprine 150 mg daily. Patient remained clinically asymptomatic (Expanded Disability Status Scale 1.0) and his brain MRI showed no increase in lesion load. In 2013, a significant aggravation of ulcerative colitis was observed. Consequently, the patient started an anti-TNF-alpha agent (infliximab), maintaining azathioprine. He had no relapses until May 2015, when he began to show slow pseudoathetoid movements involving left superior limb, probably, due to severe left superficial and profound hemihypoesthesia. Neuroaxis MRI showed a new cervical demyelinating spinal lesion (**Figure 1**). At that time a high dose metilprednisolone pulse, 1g/day for five days, was started, anti-TNF-alpha was suspended, azathioprine was augmented (200 mg/day) and, later on, the patient began daily subcutaneous glatiramer acetate (Copaxone®).

Discussion

Our case report depicts a patient with an association of two different autoimmune diseases (MS and UC) that posed challenging and difficult therapeutic decisions.

The presence of two or more well-defined autoimmune conditions fulfilling validated classification criteria in one patient as such our case, is defined as polyautoimmune syndrome [3]. This syndrome is thought to be present in 0.4–0.5% of the worldwide population, more frequently in patients with MS, rheumatoid arthritis, autoimmune thyroid disease, type 1 diabetes, IBD and vitiligo [4]. This disease association, in one individual, may be explained since MS and UC are two autoimmune disorders that may develop in genetically susceptible individuals in whom their clinical expression is modified by permissive and protective environments occurring over time [3]. Indeed MS has

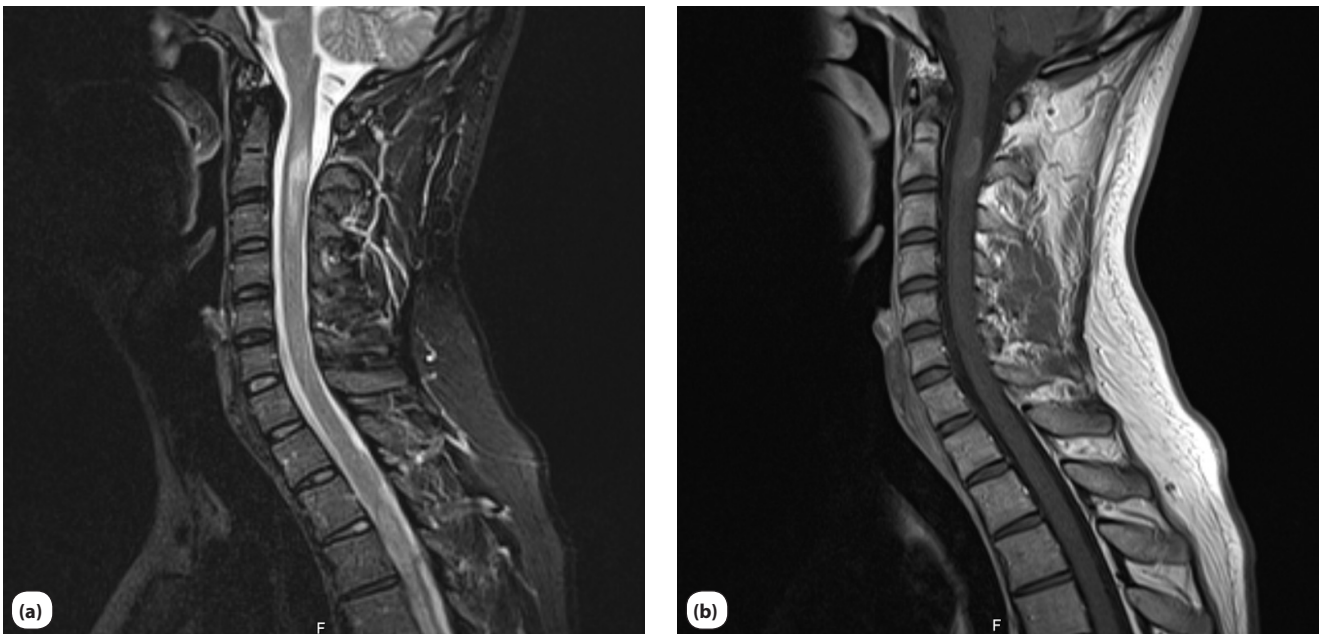

Figure 1. Spinal cord MRI. **(a)** Sagittal T2 showing a hyperintensity from C2 to C3, compatible with a demyelinating lesion. This lesion has gadolinium enhancement, reflecting inflammatory activity **(b)**.

been associated with environmental factors, for instance vitamin D deficiency, tobacco and Epstein–Barr virus and in large-scale genome-wide association studies with genes, many associated with immune function [5]. These MS environmental and genetic risk factors are in turn associated with a number of other autoimmune diseases [6], including UC. In addition, and recently, some authors [7, 8] think that a link between autoimmune diseases and gut microbiome may exist. This can be explained by the fact that gut microbiome influences gut-associated lymphoid tissue (GALT), which has the capacity to regulate systemic immunity, promoting an autoimmune reaction against CNS tissue [9]. Also, increased intestinal permeability, due to UC, could justify an autoimmune pathogenic response, considering molecular mimicry between intestinal antigens and self-antigens. On the other hand, this phenomenon called "leaky gut" observed in patients with MS could play a pathogenic role in the development of gastrointestinal disorders like IBD [2].

In the beginning, our patient had UC exacerbation when being treated with interferon (INF) Beta-1a. Type I interferons, such as IFN Beta-1a (INF-B1a), are a well established and effective relapse-remitting MS treatment [10]. INF-B1a has different anti-inflammatory mechanisms of action, such as: inhibiting expression of adhesion molecules leading to reduced adhesion of leukocytes and attenuation of inflammatory reactions, downregulation of matrix metalloproteinases, which are implicated in the immunopathogenesis of MS [11-15] and finally inhibiting Th17 cell differentiation known to be a pivotal cell in MS pathogenesis [16]. Conflicting data and paradoxical effects of INF-beta are described in the literature, since in spite of several clinical trials showing promising results in the treatment of UC with INF-B [13], there are various reports of development of UC in patients with MS treated with this drug [17-19]. Some authors think that the role of Type I IFN in controlling or exacerbating gut inflammation may be dependent upon factors intrinsic to the patients and this would explain spontaneous development of IBD in some patients receiving IFN-b therapy for MS or hepatitis [13]. Taking into account all these facts, natalizumab, a humanized monoclonal antibody against alfa 4 integrin, was started since this drug is effective in the treatment of either MS and IBD [20, 21]. Nevertheless because of the risk of progressive multifocal leukoencephalopathy (PML) due to activation of the John Cummingan virus this treatment was stopped [22]. Subsequently, azathioprine (150 mg/d) was initiated. This is an old drug that can be incorporated into DNA and can stop its replication. It also blocks the *de novo* pathway of purine synthesis. These mechanisms of action contribute not only to its relative specificity to lymphocytes but also to its potent immunosuppressor effect [23]. Therefore, it seemed, in our opinion at that time, the best option to treat our patient with two known autoimmune conditions. Latter on and due to UC exacerbation, we were forced to initiate anti-TNF-alpha treatment. TNF-alpha is an immunomodulatory cytokine that has been implicated in both diseases [24]. In fact, increased levels of TNF-alpha in UC patients are believed to promote inflammation and activation of immune response. Therefore, agents that inhibit activation or production of TNF-alpha are clinically effective in the treatment of this disorder. In MS, TNF-alpha also contributes to the demyelinating process [2] and has been associated with CNS demyelination and worsening of MS [24]. One possible explanation is that TNF-alpha blockers do not penetrate the blood–brain barrier, but they increase peripheral T-cell autoreactive cells, which can penetrate into CNS, causing demyelination. Therefore, patients on anti-TNF-alpha therapy with evidence of a demyelinating process should stop it [2]. Finally, we believe that the best therapeutic option, for now, was to increase azathioprine to a dose (3 mg/kg/day) that is effective in reducing MS new brain inflammatory lesions [25], to suspend infliximab and to start daily subcutaneous glatiramer acetate (GA) for MS treatment. GA binds to major histocompatibility complex molecules and competes with myelin antigens for their presentation to T cells. It also induces GA-specific CD4+ and CD8+ T cells that inhibit the inflammatory process in the brain [26]. Finally, in a mouse model of experimental colitis, GA relieved colitis symptoms and inhibited the production of TNF-alpha, an important mediator of inflammation in both MS and IBD [27]. These actions, altogether, were believed to be beneficial in our patient with evidence of progression of disease.

We have considered other agents used in MS treatment, namely rituximab (anti-CD20) or alemtuzumab. However they also may induce or aggravate UC [28].

This case describes a patient with a polyautoimmune syndrome, involving MS and UC. After treatment with anti-TNF-alpha agent to remit an exacerbation of UC, progression of MS was observed (a consequence previously reported). An adjustment of azathioprine dose and GA introduction were needed to control both conditions. Therefore, our report provides evidence that it may be a challenge to find the best therapeutic options for patients with many simultaneous autoimmune diseases since a drug that may alleviate one disease may also aggravate the other. In the future, more studies that explore several therapeutic solutions for this type of patient would be of great benefit.

Abbreviations

GA: Glatiramer acetate; GALT: Gut-associated lymphoid tissue; IBD: Inflammatory bowel disease; INF: Interferon; INF-B1a: Interferon Beta-1a; MS: multiple sclerosis; PML: Progressive multifocal leukoencephalopathy; TNF: Tumor necrosis factor; UC: Ulcerative colitis

Competing interests

The authors declare no conflict of interest.

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