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Alemtuzumab-Induced Inflammatory Bowel Disease in a Multiple Sclerosis Patient

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Abstract

Introduction: Alemtuzumab produces a total depletion and posterior repopulation of T and B cells. Autoimmunity is an important adverse event of this drug. In recent years, other autoimmune diseases, different to thyroid, kidney and platelets alterations have been described.

Clinical Case: We present one case of alemtuzumab-treated multiple sclerosis patient who develops ulcerative colitis after two cycles of alemtuzumab.

Conclusion: To our knowledge, no cases have been published in the literature, which relate alemtuzumab with the development of ulcerative colitis. The different kinetics in B and T cells repopulations and the change in the gut microbiota induced by alemtuzumab or by changes in diet to prevent listeriosis, could increase the risk of developing this autoimmune phenomenon.

Keywords: Alemtuzumab • Autoimmunity • Gut microbiota • Inflammatory bowel disease • Multiple sclerosis • Ulcerative colitis

Abbreviations: CD: Cluster of Differentiation • EDSS: Expanded Disability Status Scale • IBD: Inflammatory Bowel Disease • MRI: Magnetic • Resonance Imaging • MS: Multiple Sclerosis • RRMS: Relapsing Remitting Multiple Sclerosis • UC: Ulcerative Colitis

Introduction

Alemtuzumab is a licensed drug for the treatment of relapsing-remitting multiple sclerosis (RRMS). It is a monoclonal antibody against the CD52 antigen that produces a total depletion of T and B cells and their subsequent repopulation. The main adverse events are perfusion reactions, opportunistic infections and autoimmune diseases [1].

Autoimmunity mainly affects to thyroid, platelets and kidney, which can appear in a long-term. However, other autoimmune diseases have been described as autoimmune hepatitis, hemophagocytic syndrome, autoimmune encephalitis, haemophilia A, autoimmune myositis, type 1 diabetes [2].

We describe a clinical case of alemtuzumab-induced ulcerative colitis (UC) in a woman with RRMS. To our knowledge, no cases have been published in the literature, which relate alemtuzumab with the development inflammatory bowel disease (IBD).

Case Presentation

A 27-year-old woman diagnosed with RRMS in 2017 after two episodes of myelitis in a period of 4 months. Magnetic resonance imaging (MRI) of the spinal cord showed multiple T2 hyperintense lesions in T2 sequences, mainly in the medullary cone. Subsequent brain MRI scan showed more than 50 T2-hyperintense white matter lesions with one gadolinium enhanced juxtacortical lesion. After methylprednisolone treatment, the patient improved to full recovery: expanded disability status scale (EDSS): 0. An aggressive RRMS was considered and the patient was treated with two cycles of alemtuzumab in December 2017 and 2018. During the first month after each infusion, patient followed a free diet fresh food to prevent listeria infections. No clinical or radiological activity was detected after alemtuzumab treatment and patient maintained a normal neurological status (EDSS 0).

In July 2019 the patient started with acute asthenia, fever, abdominal pain, vomiting and bloody diarrhoea. Blood samples showed microcytic anemia and elevated acute phase reactants. Antibiotics therapy was started without improvement. Due to poor evolution a colonoscopy was performed which showed inflammatory continuous involvement with loss of vascular pattern and superficial ulcer from the anal margin and extending to cecal fundus, without non affected areas. Some biopsies were taken and the macroscopic and microscopic study was compatible with UC. Finally, patient was diagnosed of IBD type UC and corticosteroids and mesalazine were prescribed. After treatment, the patient improved until complete recovery.

Discussion

We presented a RRMS patient who develops alemtuzumab-induced IBD type UC. In our knowledge there are no cases published in the literature showing relationship between IBD and alemtuzumab. Alemtuzumab could induce IBD by two mechanisms: autoimmune phenomenon [3] and gut microbiota disturbance [4]. Additionally, diet to prevent listeria infection changes the gut microbiota and may also increase de risk of IBD [5].

Alemtuzumab produces a total depletion of T and B cells. After treatment, the bone marrow generates new lymphocytes, phenomenon denominate repopulation. However, the kinetics of this repopulation is asymmetric, which could be the cause of autoimmunity. B cells return to baseline levels or exceed the lower limit of normal within 3-6 months of a treatment course; moreover,

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the first subpopulations to increase are immature and transitional B cells. T cells, mainly CD4, remain below the lower limit of normal at 12 months. The hyperpopulation of immature B cells, in absence of T cell regulation could be responsible for secondary B cell autoimmunity and intestinal mucosa attack. Delay between B cell hyperpopulation and development of autoimmunity is because, the autoimmunity of B cells requires T-cell involvement and that doesn't occur until CD4 T cell number regenerate to sufficient levels [3]. In our case, the time between the first dose of alemtuzumab and the development of the patient's symptoms is 1.5 years.

Although the pathogenesis of IBD is still unclear, the resulting bowel inflammation seems to be due to dysregulation of the immune system in response to changes in commensal (nonpathogenic) gut flora. The decrease of 25% in the bacterial species alters the diversity of intestinal microbioma (dysbiosis) and this plays a critical role in IBD pathogenesis [6]. Alemtuzumab produces significant lymphocytes depletion in peripheral blood; in addition, alemtuzumab also produces depletion of intestinal mucosal lymphocytes. The effect of these mucosal lymphocytes depletion in human has not been studied in the literature. However, alemtuzumab treatment in cynomolgus monkeys showed that the intestinal microbiota composition was perturbed after depletion of mucosal lymphocytes and were recovered following the repopulation [4]. Diet also plays a significant role in the configuration of the microbioma because dietary alterations can induce large, temporary microbial changes within 24 hours. The diet to prevent listeriosis during the first months after alemtuzumab treatment could alter the gut microbiota and increase the risk of IBD development [5].

Another important fact to consider is the observation of increased incidence of both IBD among multiple sclerosis (MS) patients and MS among IBD patients. A meta-analysis of 1.086.430 patients showed a 0.08% of them with concurrent IBD and MS and concluded that both IBD and MS patients seem to have a fifty-percent increase risk of MS or IBD comorbidity, with no apparent differences between Crohn's disease or ulcerative colitis) [7]. However, we thought that the temporal relationship between the starting of alemtuzumab and the development of IBD, support that the intestinal disease was an adverse events of alemtuzumab.

Conclusion

In conclusion, we present the first case of the literature of a patient with RRMS that develops IBD type UC after two cycles of alemtuzumab. Alemtuzumab-treated patients, who present with abdominal symptoms, especially bloody diarrhea, after discarding the possibility of infection disease, should be evaluated for IBD as an autoimmune complication of alemtuzumab. Further studies are required to improve the knowledge of autoimmune phenomenon induced by alemtuzumab.

Declaration of Interest

None.

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