Can We Kill an Extra Bird with the Same Stone?

To the Editor:

We read with interest the case report by Remy Phan-Ba et al[1] about a patient with celiac disease who transiently improved after treatment with natalizumab for concurrent multiple sclerosis (MS). Here we report the case of an Italian gentleman affected by MS, celiac disease, and Crohn's disease (CD) who was treated with natalizumab for MS for a year and a half with benefit.

The patient started complaining of malabsorptive symptoms at the age of 18. This pathological condition resolved spontaneously before achieving a specific diagnosis. At the age of 40 he developed a severe malabsorption syndrome with diarrhea and remarkable weight loss and for this reason he was admitted to a gastroenterology unit. An esophagogastroduodenoscopy and duodenal biopsy supported the diagnosis of celiac disease both by macroscopic and histological analysis, despite the lack of anti-transglutaminase and anti-endomisial antibodies. Moreover, an abdominal computed tomography (CT) scan revealed thickening of the distal ileal tract. Based on the diagnosis of seronegative celiac disease, the patient started a gluten-free diet and oral treatment with prednisone. However, a few months later the ileal stenosis worsened and had to be surgically removed. Histological findings were suggestive of CD. The patient was diagnosed with ''Crohn's disease and possible celiac disease.'' Six months later, long-term treatment with azathioprine treatment was started. In the subsequent years the patient's clinical conditions partially improved. At the age of 43 he presented with mild weakness of the right limbs. He underwent brain and spinal magnetic resonance imaging (MRI) revealing multiple T2-weighted MRI abnormalities of the white matter suggestive of a demyelinating disease of the central nervous system; subsequently, he underwent lumbar puncture, with cerebrospinal fluid (CSF) examination showing the presence of CSF IgG oligoclonal bands, suggestive of intrathecal IgG synthesis. He was treated with a pulse of intravenous methylprednisolone with some benefit and azathioprine treatment was carried on. After a few months the hemiparesis worsened: he was again treated with intravenous steroids with benefit and the diagnosis of MS was made. At this time azathioprine was stopped and the patient started treatment with natalizumab. Following a year and a half of therapy, the patient did not show relapses of MS and brain MRI was unchanged. From a gastroenterological point of view, he presented with an improvement of symptoms despite the stop of azathioprine therapy, with absence of abdominal pain and reduction of stool frequency (from 2–3 soft stools/day to 1–2 evacuations/day of normal or slightly soft stools).

Natalizumab binds to the alpha4 integrin on the surface of lymphocytes, blocking their adhesion to the vascular endothelium of the brain and the gut and the consequent extravasation to the target organs. It is approved by U.S. Food and Drug Administration (FDA) and by European Medicines Agency (EMA) as a treatment for MS on the basis of the results of the AFFIRM clinical trial.[2] Regardless of the demonstrated clinical effect in CD (clinical trials ENACT-2[3] and ENCORE[4]) and in contrast to what happened with MS, EMA has not approved natalizumab as a treatment for CD due to concerns on maintenance of the effect and on side effects, particularly due to the risk of progressive multifocal leukoencephalopathy (PML) caused by the JC virus.[5] No clinical trials exist on the use of natalizumab for celiac disease; however, Phan-Ba et al[1] reported a transient improvement of celiac disease during natalizumab treatment; this is conceivable, as there are reports that the interaction between alpha-4beta7 integrin, expressed on the lymphocyte surface and its ligand mucosal addressin cell adhesion molecule-1 (MAdCam1), expressed on gut endothelial cells, could play a role in the pathophysiology of celiac disease.[6]

Recently, research on natalizumab-associated PML has moved forward and the presence of anti-JCV antibodies, evaluated with a newly developed assay, has been found to be a strong risk factor for the development of PML in MS patients.[7] Specifically, seronegative patients appear to be at very low risk of developing this possibly lethal complication, while, in the presence of anti-JCV antibodies, the risk depends on the previous exposure to immunosuppressants and on the duration of therapy with natalizumab.[8]

The patient we describe here had some residual gastroenteric symptoms, despite ongoing azathioprine treatment, which improved markedly after starting natalizumab; these symptoms are likely to be caused by an insufficient activity of azathioprine therapy on CD as well as by an occult gluten intake.

In our opinion, this case report should further confirm the efficacy of natalizumab both in MS and inflammatory bowel diseases and should prompt regulatory authorities to reevaluate the possible use of natalizumab for CD, based on the novel safety data obtained from the cohort of MS patients exposed to the drug.[8]

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