Cryptosporidiosis in a patient with Crohn's disease under anti-TNF treatment

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To the Editor,

Ulcerative Colitis (UC) and Crohn's Disease CD), are chronic inflammatory bowel diseases (IBD) which may benefit from the treatment with biologic agents which target specific cytokines involved in inflammation (1). The anti-TNF therapy is the first biologic agent used in the treatment of complicated CD (2). Although the clinical efficacy of anti-TNF agents has been proven, their use may also be associated with an increased risk of opportunistic infections caused by bacteria, viruses and parasites (3). Cryptosporidiosis is a parasitic infection caused by *Cryptosporidium Spp*, clinically characterized by watery diarrhea, often profuse and prolonged, abdominal pain, nausea, vomiting, and fever. *Cryptosporidium* is an emerging protozoan parasite and it can be transmitted to humans from animals, from humans and from contaminated food or water. Disease severity varies according to the host general health: immunocompetent patients may develop a mild, self-limiting disease, while immunocompromised patients, may have severe and persistent symptoms, with gastrointestinal, biliary or respiratory manifestations (4).

Whether the use of biologic agents is associated to an increased risk of infection by *Cryptosporidium Spp* is not clear.

We report a case of a 23-year-old woman diagnosed with ileal CD, treated with steroids and mesalamine, who came to our observation because of a disease flare with abdominal pain and diarrhea. The patient underwent a colonoscopy with retrograde ileoscopy, which confirmed ileal location of the disease. Intestinal ultrasonography (US) as well as small intestine Magnetic Resonance (MR) confirmed small bowel involvement for an extension of approximately 30 cm. An upper GI endoscopy excluded upper GI CD. Patient reported azathioprine intolerance and therefore we started induction therapy with subcutaneous anti-TNF agent. Because of clinical response (no abdominal pain no diarrhea) associated to a decrease of inflammatory indices both in the serum (C Reactive Protein) and stools (fecal calprotectin), the patient was maintained on anti-TNF therapy. One year later, intestinal US and MRI showed a dramatic improvement with normal thickness of the affected ileum. A colonoscopy was repeated to assess mucosal healing and, at retrograde ileoscopy,

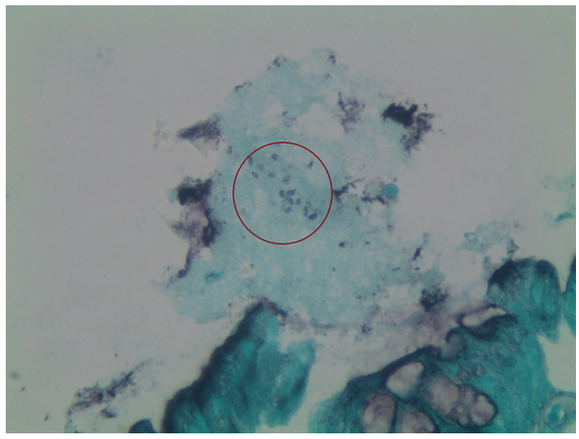

Figure 1. — Presence of *Cryptosporidium Spp* (circled) in colonic biopsies as assessed by Grocott staining.

ileal mucosa appeared normal with only chronic non-specific inflammation at histology. Also colonic mucosa appeared grossly normal. However, the pathology report on random biopsy specimens showed the presence of *Cryptosporidium Spp* (Fig. 1) which was confirmed at stool examination for parasites. Successively, patient was tested for HIV, which resulted negative, with a normal CD4+/CD8+ ratio. A course of albendazole was started for three weeks. Ten days after the end of therapy, three consecutive stool specimens did not show presence of *Cryprosporidium Spp*. The patient is still under anti-TNF therapy, and is doing well. Stool specimens have been retested for cryptosporidiosis every three months, and always resulted negative.

Despitec cryptosporidiosis is frequently associated with HIV infection (5), in the literature there are two reports of HIV-negative cryptosporidiosis one of which in an IBD patient who underwent orthotopic liver transplantion (OLT), who received anti-TNF therapy after OLT(6) (7).

Vismari et al. (8) suggest an association between

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stress and inefficient immune response to pathogens, which might facilitate the development of infections. Psychological stress may lead to dysfunction of neuronal transmission pathways, which in turn alters the immune response. This is under direct control of the hypothalamic-pituitary-adrenal axis, so that stressors may compromise the production of different cytokines or the correct migration of cells of immune system. On this basis, we hypothesize that in our case, anti-TNF immunosuppressive activity together with a stress-induced impaired immune response, contributed to the acquisition of the infection.

Based on our case, we suggest that stool specimens should be tested for parasitic infections in patients under biologic therapy for IBD.

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