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CLINICAL NOTE

Adenocarcinoma of the rectum and anus in a patient with Crohn's disease treated with infliximab

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ABSTRACT

In the present paper, we report the case of a patient with long-standing Crohn's disease and multiple complications that, after receiving treatment with infliximab, was diagnosed with an adenocarcinoma of the rectum and anus that required radical surgery, later presenting multiple metastases. In the discussion, characteristics and major risk factors for colorectal cancer in patients with inflammatory bowel disease will be largely reviewed, and current studies will be analyzed in connection with the appearance of neoplasms in patients being treated with biologics.

Key words: Crohn's disease. Colorectal cancer. Infliximab.

RESUMEN

Presentamos el caso de un paciente con enfermedad de Crohn de larga evolución y con múltiples complicaciones de su enfermedad que, tras recibir tratamiento con infliximab, es diagnosticado de un adenocarcinoma de recto y ano que precisa cirugía radical, presentando posteriormente metástasis múltiples. Se repasarán durante la discusión las características y los factores de riesgo más importantes del cáncer colorrectal en pacientes con enfermedad inflamatoria intestinal, y se analizarán los trabajos existentes hasta la fecha en relación con la aparición de neoplasias en pacientes tratados con fármacos biológicos.

Palabras clave: Enfermedad de Crohn. Cáncer colorrectal. Infliximab.

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INTRODUCTION

Crohn's disease (CD) is associated with a higher incidence of colorectal cancer (CRC), especially in patients with a long-standing disease and significant perianal involvement. Risk, incidence, characteristics of the tumor and prognosis do not differ substantially from those of patients with ulcerative colitis (UC).

Infliximab, a monoclonal antibody against tumor necrosis factor alpha, is an effective tool in the treatment of CD, being now indicated and widely used for inflammatory bowel disease (IBD). However, *de novo* malignancies have been reported in patients undergoing this therapy, currently representing a major concern among gastroenterologists and researchers.

CASE REPORT

A 54 year old male, diagnosed in 1991 (at 35 years of age) with stenosing/fistulizing CD. Throughout his evolution, he was admitted multiple times due to severe outbreaks and various surgical complications of his disease.

The first years after diagnosis, he responded well to treatment with steroids and 5-ASA. In 1995, a stenosis at the descending colon was observed, yet no surgery was performed at that time. In early 1999, the patient presented an abdominal wall abscess that required surgical intervention. Later that same year, he was diagnosed with fibrous anal stenosis for which endoscopic dilatation was performed, along with double stenosis of the sigmoid colon for which therapeutic intervention was again rejected. In May 2000 he was admitted again due to anoth-

er wall abscess that required intervention. An enterocutaneous fistula appeared as a late complication, which also required surgery some months later. In late 2001, patchy inflammatory stenoses are revealed in the terminal ileum, along with the previously discovered strictures in the descending colon. One of them fistulized in the left lumbar region and required segmental resection of descending and sigmoid colon, followed by colorectal anastomosis.

In 2004, treatment with azathioprine was started but had to be suspended twice and permanently removed later on, since the patient showed several adverse effects after its administration, such as stiffness, joint pain, loss of strength in his lower limbs and paresthesias.

In 2007, he had to be readmitted due to significant rectal bleeding, both clinically and analytically. A severe fistulizing perianal involvement was observed this time, with no involvement of the colorectal anastomosis and with inflammatory activity present at the terminal ileum.

In February 2008, treatment with infliximab was started and the patient received his first dose after 17 years of CD evolution. He showed a partial initial response, so it was decided that the dosing interval should be shortened. Nevertheless, in late April that year there was an obvious clinical worsening that required admission. A new colonoscopy was performed, showing a large rectal ulceration and stenosis of the colorectal anastomosis. Radiologic study evidenced stenosis at the terminal ileum level and proximal dilatation of bowel loops. He was discharged with tapering steroid therapy, mesalazine, antibiotics and Infliximab (5 mg/kg every 6 weeks), remained asymptomatic and his evolution was good for several months.

He required admission once again in early 2009 due to rectal bleeding and anal pain. Endoscopically, a significant proctitis was found along with a large ulcer at this level and an almost complete stenosis at the transverse colon level. A barium intestinal transit showed a slender terminal ileum with reduced lumen size and no apparent fistulae.

Some months later, in early June 2009, the patient returns to hospital due to several weeks suffering from a significant worsening of his perianal involvement, disabling pain and the onset of incontinence. Exploration was performed under sedation, for the pain prevented us from normally inspecting the affected area, and the rectal mucosa was found to be severely affected with multiple irregular ulcerations showing spontaneous bleeding and bleeding on contact with the endoscope, as well as several fistulae (Figs. 1 and 2). At that moment multiple specimens were taken for histological study to rule out superinfection or cytomegalovirus. Histopathologic examination ruled out infection but found an invasive moderately differentiated adenocarcinoma in all the samples received from the rectum and anus. A staging study was then performed and the results were negative, so the neoplastic disease was confirmed to be confined to rectum and anus. Surgery was scheduled and the patient underwent abdominoperineal amputation with a permanent colostomy. Four months later, the patient was readmitted for bilateral pulmonary and femoral embolism that required the placement of a temporary cava filter and anticoagulation with low molecular weight Heparins, with several episodes of rectal bleeding that forced the removal of anticoagulation. During that same admission,

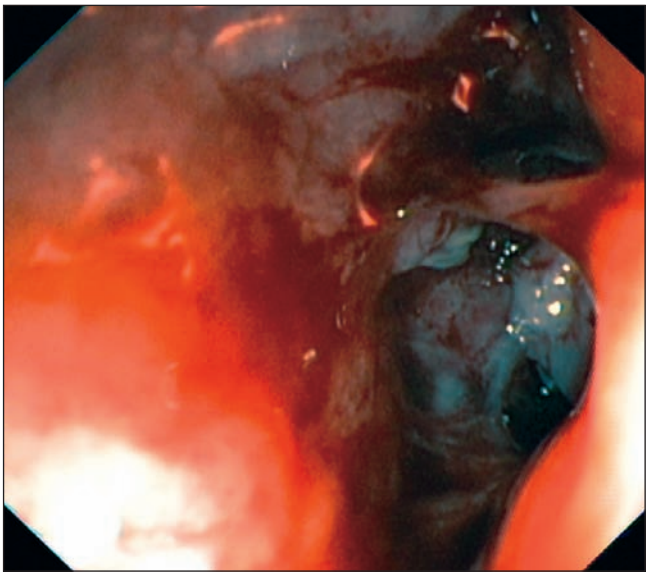

Fig. 1. Endoscopic image showing multiple ulcers and fistulae in the rectal ampulla of the patient, along with active bleeding at the time of exploration.

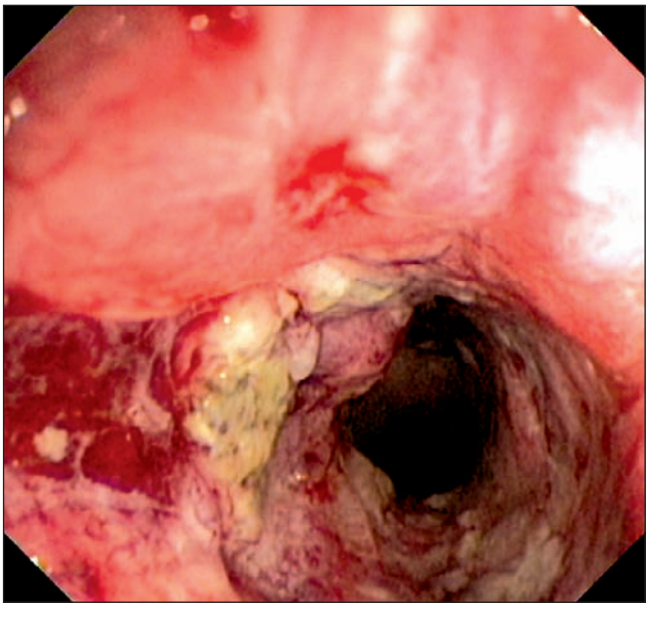

Fig. 2. Sigmoidoscopy performed under deep sedation revealing significant mucosal involvement and infiltration.

an ileal intestinal perforation occurred that required an emergency surgical resection, all with normal imaging tests and good subsequent evolution. Fifteen days later, he is readmitted due to fever and two space-occupying lesions are evidenced in the liver. The study showed recurrence of stage IV rectal adenocarcinoma and the presence of bone, liver, mesenteric and pelvic metastases, currently treated with chemotherapy.

DISCUSSION

The association between IBD and CRC has been widely described. Although it was classically assumed that UC was more oncogenic than CD, it is now accepted that the incidence, characteristics and prognosis of CRC as a complication of CD are similar to those of distal digestive tract neoplasms found in UC, including early age of onset, the possible occurrence of multiple synchronous neoplasms and a long evolution of the underlying inflammatory disease.

In these patients, the risk is directly related to the extent of the disease and the time course and severity of perianal involvement. In the specific case of CD, most authors agree on a cumulative risk estimate of around 30% to develop CRC 25 years after diagnosis, and an even greater risk for patients diagnosed before age 30. It has also been stated that since the tumor is widespread in many cases at diagnosis, prognosis is worse in these patients than in those suffering from sporadic CRC. Some studies largely disagree with these general conclusions, although it is true that these are only a few and are based on small sample sizes. In any case, the number of patients included in this risk group is tight, and IBD-related CRC are quantitatively exceptional when compared with sporadic CRC.

Considering the case under discussion, it is also important to note that it is often impossible to distinguish between anal and rectal carcinomas, especially in patients with severe proctitis and fistula formation. So much so that both types of tumour are grouped together in most classifications, and final treatment is usually the same. It is also noteworthy that the tumor rarely appears in the fistulous tracts, even those chronic with a very poor outcome, and despite the fact that, as already stated, chronicity and severity like these are risk factors for cancer development.

Infliximab, a monoclonal antibody against tumor necrosis factor-alpha (TNF-α), has recently become an extremely important therapeutic tool for the treatment of CD. Although its effectiveness has been thoroughly proved, its safety margins remain uncertain, in particular on infectious complications and especially as regards the occurrence of malignancies in patients undergoing this treatment. Even though they are only a few, mostly either in isolation or in short series of cases, some reports have described the incidence of various types of malignancies such as lymphomas (seemingly the most common of all), lung cancer, Kaposi's sarcoma, lymphoblastic leukemia, squamous cell carcinoma and hepatocellular carcinoma, among others. Interestingly enough, in most of these cases the diagnosis was reached a few weeks after initiation of therapy with infliximab.

Although TNF-α can stimulate tumor growth and the fact that different lines of research have been developed with anti TNF-α as antineoplastic therapy or treatment of graft *versus* host disease in allogeneic bone marrow transplantation, there are experimental studies on mice indicating that suppression of TNF-α may contribute to tumor progression. In spite of these studies, data available are often contradictory and can not establish a relationship beyond any doubt between the use of these immunomodulators and the development of neoplasia. On the one hand, the spectrum of tumors reported in patients treated with Infliximab is very similar to that found in other types of immunocompromised patients. On the other hand, several multicenter studies have shown that the frequency of tumors in patients with CD being treated with infliximab is not greater than in those who have never received this therapy, thus concluding that the former is not a group with an increased risk of malignancy. Some authors suggest that a possible increased incidence of tumors in these patients would only respond to a greater number of diagnoses due to the close monitoring they currently undergo.

Reports of CRC in patients with CD treated with infliximab are even rarer. The few cases reported in the literature are those of patients with long standing disease (20 years at least) who had received Infliximab for a relatively short time. These are generally patients with an increased risk of CRC due to the severity, extent and time course of their disease, who also have received immunosuppressive therapy for many years. The fact that the tumor diagnosis was reached in most cases shortly after starting treatment with Infliximab along with the aggressiveness of tumors suggest that blocking TNF-α might contribute to tumor progression and extension in particularly susceptible individuals.

In the case presented, the patient suffers from a CD of very long evolution, with multiple medical and surgical complications and many changes and adjustments in his immunosuppressive medication throughout these years. Perianal involvement was fairly striking and very difficult to control, an additional point in common with the general characteristics of patients at risk covered in this discussion. Other characteristics shared with published cases are tumor aggressiveness and poor prognosis, despite a seemingly early diagnosis. Unlike in other cases reported in the literature, the patient had been receiving infliximab for several months when the tumor was diagnosed, which represents a higher duration of treatment compared to other cases.

CONCLUSIONS

The risk of CRC for patients with long standing colonic CD is comparable to those with UC. Therefore, a protocol validated strategy must be established for the screening and early diagnosis of CRC in patients with long standing CD.

In recent years, there has been widespread use of biological therapies for the treatment of IBD, being infliximab the most important medication of the group and the most commonly used. Regardless of indication, its use has been associated with the diagnosis of different types of tumor and thus has been described in some isolated cases and small series of cases. While it is not possible to definitively establish a direct relationship between drug administration and the appearance of these neoplasms, and given that its usefulness has been thoroughly demonstrated and its use should be recommended in cases where indicated, it is necessary to closely monitor these patients and continue with the relevant lines of research in order to clarify the possible relationship between anti TNF-α and carcinogenesis or mechanisms of tumor growth and progression.

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