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Case Report: Severe Colonic Crohn Disease Initiated after Liver Transplantation Requiring Surgery*

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Abstract

Introduction A patient using tacrolimus for hepatocyte transplantation (HT) was diagnosed with Crohn disease (CD) with mainly colonic involvement, despite drug immunosuppression due to the previous transplant. Upon routine colonoscopy, a lateral growth lesion was detected, which was endoscopically unresectable. Therefore, it was decided to perform a total colectomy with burial of the rectum and terminal ileostomy. During surgery, thickening of the terminal ileum and cecum was visualized, along with "fat-wrapping" and thickening of the entire mesocolon.

Discussion Immunosuppression in patients with HT should control the activity of autoimmune diseases. However, the literature shows evidence of some reports of inflammatory bowel disease (IBD) activity after liver transplantation (LT). A review article from 2015 highlighted 92 cases of IBD after LT in the literature, with only 14 being CD, demonstrating that this is a rare phenomenon. Among the hypotheses, cytomegalovirus infection is related to the increased disease activity in patients with IBD and HT. In addition, several studies show an association between the drugs used in immunosuppression after LT and relapsed IBD, important data in patients receiving tacrolimus.

Conclusion The occurrence of CD after LT is rare and seems to have a direct association with the immunosuppression used to prevent rejection of the transplanted organ.

Keywords
- inflammatory bowel disease
- Crohn disease
- liver transplantation
- total colectomy
- treatment surgical

Introduction

According to information based on the public system, inflammatory bowel diseases (IBDs) affect 100 cases per 100,000 inhabitants in Brazil. In 2020, the incidence reached 7 cases of ulcerative colitis and 3 cases of Crohn disease (CD) for every 100,000 inhabitants.[1]

It is understood that IBDs compromise genetically susceptible individuals, and it is hypothesized that they are a consequence of failures in the immune response to environmental stimuli and there may be interaction with infectious agents and psychological factors.[2–4]

Chronic IBD has a higher incidence in transplant recipients than in the general population (206 cases versus 20 cases per 100,000 person/year, respectively) and is more common after orthotopic liver transplantation (LT) than following other solid organ transplants.[5] This fact is paradoxical, since immunosuppression induced by medications

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after transplantation would tend to reduce disease activity.[5,6]

In the literature, Naito et al., in their 2015 review article, mentioned 92 previous cases of de novo IBD after orthotopic LT, with the majority presenting ulcerative colitis (69 cases of ulcerative colitis and only 14 of CD).[6] This seems to be associated with the fact that patients with primary sclerosing cholangitis, a common cause of the need for LT, also have ulcerative colitis. Thus, de novo CD after LT is a rare phenomenon.[6] Only one study, by Tinoco et al.,[5], indicates CD after LT, with cryptogenic cirrhosis being the cause of the surgery.

The development of IBD in transplant patients stands out, and this motivated the publication of the current case report and investigation of the literature on the subject.

Case Description

A 56-year-old male patient, who underwent LT for alcoholic cirrhosis in chronic immunosuppression via tacrolimus, was admitted reporting a change in bowel habits, weight loss, and asthenia.

After extensive investigation, he was diagnosed with CD with mainly colonic involvement. This drew attention because the patient presented with drug immunosuppression due to a previous transplant and, yet, such indications of IBD activity were identified. In addition, he underwent serology for cytomegalovirus, showing a negative polymerase chain reaction (PCR) for this microorganism.

In view of the clinical picture, sulfasalazine and azathioprine were initiated and clinical remission was achieved, but the patient still reported frequent abdominal cramps. However, in a routine colonoscopy in 2021, a mixed granular lateral spreading tumor (LST) was found in the descending colon, measuring ~ 35 mm in length. Upon magnification, the lesion was classified as Kudo pit pattern type IIIL, but it was endoscopically unresectable (►**Fig. 1A,B**). The anatomopathological result referring to LST indicated a tubular adenoma with low-grade dysplasia. Other examination findings were loss of haustration (tubular appearance), effacement of the vascular network, and numerous scar retractions in the cecum and the ascending, transverse, descending, and sigmoid colon.

Therefore, the patient was evaluated by the coloproctology team, and it was decided to perform a total colectomy with burial of the rectum and terminal ileostomy. Thus, in April 2022, the patient was admitted to undergo this procedure on an elective basis. Preoperative computed tomography (CT) showed parietal thickening with adipose proliferation of the submucosa, mainly in the terminal ileum, cecum, part of the ascending, descending, sigmoid, and rectum (►**Fig. 1**C,D), but no points of small bowel stenosis.

During the surgery performed by a conventional approach, the presence of thickening of the terminal ileum and cecum was visible, along with "fat-wrapping" (FW) in the ileal loops compared with the jejunal loops (►**Fig. 2A,B**), predictive of CD activity in the small intestine, which was not previously found in the patient's CT scan. Thickening of the entire mesocolon and adhesions, which were probably due to the previous LT surgery, were found in the hepatic flexure. The other findings observed in the surgical specimen include chronic inflammatory signs such as loss of haustration with colonic fat adipose proliferation, pseudopolyps and LST (►**Fig. 1E**,**F**).

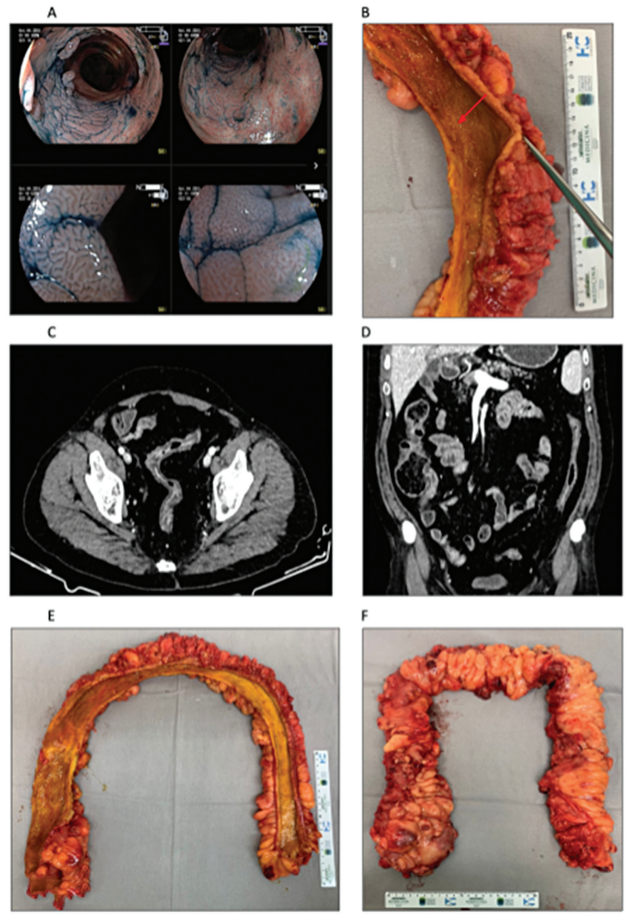

Fig. 1 (**A**) Colonoscopy with image magnification showing lateral spreading tumor (LST)with involvement of 90% of the descending colon, at magnification showing patterned elongated crypts with uniform arrangement (Kudo IIIL). (**B**) Surgical specimen at higher magnification showing LST in the descending colon (red arrow), which was endoscopically represented in the colonoscopy. (**C**) Preoperative contrast-enhanced tomography, axial section showing sigmoid "microcolon," in addition to parietal and submucosal thickening of this and the rectum. (**D**) Parietal thickening of the cecum and terminal ileum with adipose proliferation of the submucosa. (**E**) Open surgical specimen showing mucosa with chronic inflammatory signs, loss of haustrations, mucosal irregularity by pseudopolyps in the ascending and transverse colon regions and LST in the descending colon. (**F**) Surgical piece in anatomical position with parietal thickening, inflammatory signs, loss of haustrations, and adipose proliferation (*fat-wrapping)*.

The patient had a good postoperative evolution, spending 2 days in the ICU. As for intestinal transit, the ileostomy started to work on the second day with reintroduction and diet progression over 3 days. The abdominal drain was left in the buried rectal stump, which presented sero-hematic-to-serous output, being removed on the seventh day upon hospital discharge.

In the outpatient follow-up, currently in the fourth postoperative month, the patient is feeling a significant improvement in the abdominal cramps that were felt daily and significant improvement in the quality of life already.

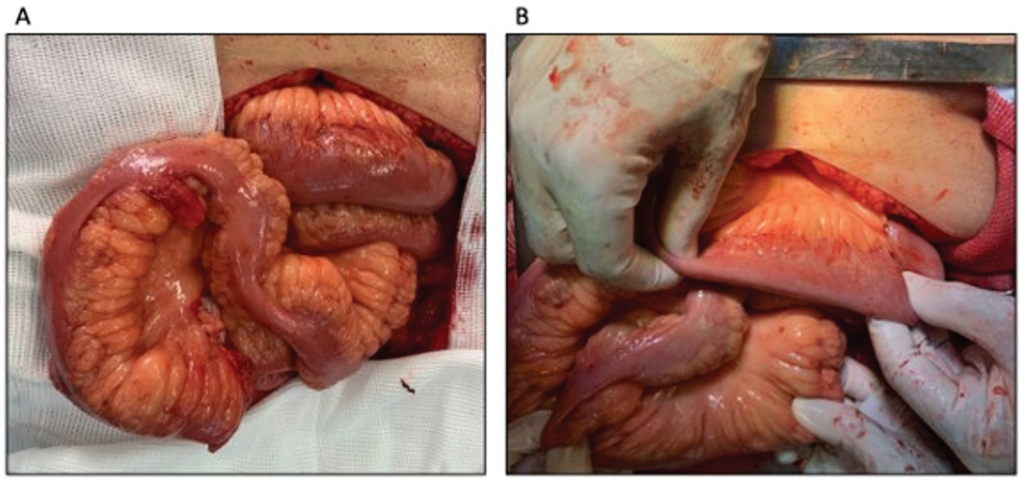

Fig. 2 (A) Intraoperative image showing fat wrapping in the distal ileum with intense mesenteric fatty proliferation. (B) Comparative demonstration of the mesenteric fat of the jejunum not involving the loop compared with the ileum.

Discussion

In the case herein described, the pancolitis due to CD and the LST were decisive to indicate a total colectomy. In this sense, it is important to emphasize that LSTs have an overall malignancy rate of 9.8%, according to the study by Kim et al.[8]

In addition, IBDs increase the incidence of malignant colonic lesions, a probability that is even more increased in immunosuppressed patients; this was highlighted by the study of Nicolaas et al.,[9] which was a meta-analysis of 29 studies and showed a relative risk (RR) of 2.59 (95% confidence interval, 1.65–4.05) for colorectal cancer in postliver transplant patients versus the general population. More specifically, Fabia et al.[10] compared the incidence of colorectal cancer in 1,085 liver transplant recipients and divided them into 2 groups: with and without IBD, finding incidence rates of 8% and 0.1%, respectively.[11]

During the colectomy, it was possible to identify disease activities in both the small intestine and the colon in the present case, mainly due to the presence of FW, thickening, and retraction of the mesocolon and colonic tubulization, despite using medication to continue the remission of symptoms and immunosuppression following the LT in 2012. The study by Dvorchik et al.[12] showed that immunosuppression combined with LT triples the rate of progression of IBD and increases the need for colectomy.

In the literature, the pathophysiology of IBD after solid organs transplantations is poorly understood and paradoxical.[13] There is a hypothesis that cytomegalovirus (CMV) infection can trigger disease activity after LT in patients with a previous diagnosis of IBD.[13,14] It is described that the presence of the virus in the donor's organ positively influences the occurrence of posttransplant intestinal pathology (RR = 4.5), which could be explained by the fact that CMV can lead to dysfunctions in the epithelial barrier and in the immune system, increased intestinal permeability, increased expression of vascular cell adhesion molecule 1 (VCAM-1), upregulation of major histocompatibility complex 1 (MHC-1), and the increased production of mucosal interleukin-6 (IL-6), favoring the emergence of IBDs.[15]

Another hypothesis is based on the relationship between the drugs used in immunosuppression after LT and relapsing IBD. This finding was particularly important in patients transplanted for autoimmune hepatitis or primary sclerosing cholangitis (PSC) receiving tacrolimus.[16] Although the case presented in this report was of a patient requiring LT due to alcoholic cirrhosis, he was using tacrolimus. Therefore, it is important to emphasize that the study by Verdonk et al.[15] pointed out that calcineurin inhibitors are not sufficient to prevent relapses and, if used for a long time, can contribute to IBD activity.[7,15]

The explanation for this is attributed to the action of the medication in inhibiting calcineurin, a cytoplasmic protein that, when activated, serves as a transcription factor for inflammatory interleukins such as IL-2. However, although IL-2 is essential as a clonal expansion factor for effective T cells, it is also essential for regulatory T cells, which are CD4+ T cells that have differentiated to develop suppressor activity. These are essential for preventing autoimmunity and play an important role in transplant tolerance. In parallel, IL-2 also triggers the secretion of negative modulation cytokines of the immune system, such as IL-10 and TGF-β. In addition, calcineurin inhibitors downregulate activation-induced cell death (AICD) of the remaining T cells, making them more resistant to apoptosis, which, in the context of autoimmune disease, is one of the factors that compromises the neutralization of expansion and excessive cloning.[15]

Patients using tacrolimus had IBD recurrence after 5 to 14.5 years, on average. However, this risk of recurrence after LT was not evidenced in the use of cyclosporin, due to its much lower potency compared with tacrolimus.[15] Studies showed that tacrolimus has not been so favorable to induce remission in CD.[7,17] Furthermore, the work by Verdonk et al.[15] and the study by Haagsma et al.,[16] showed the use of tacrolimus to be an independent risk factor for IBD after LT.

Conclusion

The occurrence of CD after LT is rare and seems to be directly associated with the immunosuppression used to avoid rejection of the transplanted organ. Despite presenting a high surgical risk, total colectomy may be the only way to control the progression of colonic disease and prevent advanced polyp malignancy.

Authors' Contributions

All authors contributed to the conception and design of the study. Material preparation, data collection and analysis were carried out by Gabriela Feres Sapienza, Rodrigo Ambar Pinto, Ítalo Beltrão Simões and Maria Clara Traldi. The first version of the manuscript was written by Gabriela Feres Sapienza, Rodrigo Ambar Pinto and Ítalo Beltrão Simões, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript. The anatomopathological material and images were performed by Felipe Lourenço Ledesma and Camilla Marchiolli. The material of the tomography images were performed by Manuel Rocha.

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Conflict of Interests

The authors have no conflict of interests to declare.

References

1 Gasparini RG, Sassaki LY, Saad-Hossne R. Inflammatory bowel disease epidemiology in São Paulo State, Brazil. Clin Exp Gastroenterol 2018;11:423–429
2 Castro LP, Savassi Rocha PR, Lacerda Filho ACA. Topics in Gastroenterology. Advances in Coloproctology. Rio de Janeiro: MEDSI; 2001
3 José Joaquim Ribeiro da Rocha. Coloproctology: principles and practices. Publisher Atheneu, editor. Sao Paulo; 2006
4 Hackstein H, Thomson AW. Dendritic cells: emerging pharmacological targets of immunosuppressive drugs. Nat Rev Immunol 2004;4(01):24–34
5 Tinoco R, García E, Ramírez F, Correro F, Vega V. [A case of de novo inflammatory bowel disease after liver transplantation for cryptogenic cirrhosis]. Gastroenterol Hepatol 2016;39(07):458–460
6 Naito T, Shiga H, Endo K, et al. De novo Crohn's disease following orthotopic liver transplantation: a case report and literature review. Intern Med 2015;54(02):199–204
7 Mogl MT, Baumgart DC, Fischer A, Pratschke J, Pascher A. Immunosuppression following liver transplantation and the course of inflammatory bowel disease - a case control study. Z Gastroenterol 2018;56(02):117–127
8 Kim KO, Jang BI, Jang WJ, Lee SH. Laterally spreading tumors of the colorectum: clinicopathologic features and malignant potential by macroscopic morphology. Int J Colorectal Dis 2013;28(12): 1661–1666
9 Nicolaas JS, De Jonge V, Steyerberg EW, Kuipers EJ, Van Leerdam ME, Veldhuyzen-van Zanten SJO. Risk of colorectal carcinoma in post-liver transplant patients: a systematic review and meta-analysis. Am J Transplant 2010;10(04):868–876
10 Fabia R, Levy MF, Testa G, et al. Colon carcinoma in patients undergoing liver transplantation. Am J Surg 1998;176(03):265–269
11 Rao BB, Lashner B, Kowdley KV. Reviewing the Risk of Colorectal Cancer in Inflammatory Bowel Disease After Liver Transplantation for Primary Sclerosing Cholangitis. Inflamm Bowel Dis 2018; 24(02):269–276
12 Dvorchik I, Subotin M, Demetris AJ, et al. Effect of liver transplantation on inflammatory bowel disease in patients with primary sclerosing cholangitis. Hepatology 2002;35(02):380–384
13 Filipec Kanizaj T, Mijic M. Inflammatory bowel disease in liver transplanted patients. World J Gastroenterol 2017;23(18): 3214–3227
14 Nannegari V, Roque S, Rubin DT, Quera R. A Review of Inflammatory Bowel Disease in the Setting of Liver Transplantation. Gastroenterol Hepatol (N Y) 2014;10(10):626–630
15 Verdonk RC, Dijkstra G, Haagsma EB, et al. Inflammatory bowel disease after liver transplantation: risk factors for recurrence and de novo disease. Am J Transplant 2006;6(06):1422–1429
16 Haagsma EB, Van Den Berg AP, Kleibeuker JH, Slooff MJ, Dijkstra G. Inflammatory bowel disease after liver transplantation: the effect of different immunosuppressive regimens. Aliment Pharmacol Ther 2003;18(01):33–44
17 Ogata H, Matsui T, Nakamura M, et al. A randomised dose finding study of oral tacrolimus (FK506) therapy in refractory ulcerative colitis. Gut 2006;55(09):1255–1262

