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DOI: 10.17235/reed.2020.7228/2020
Link: PubMed (Epub ahead of print)

Please cite this article as:

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OR 7228

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Received: 09/05/2020
Accepted: 6/8/2020

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Requirements for the authors: The case presented has not been approved by an ethics committee. All identifying information and all data related to the patient have been thoroughly eliminated. Written informed consent was obtained and documented.

Conflicts of interest: the authors declare no conflicts of interest.

ABSTRACT

Toxic megacolon is most commonly considered as a complication of inflammatory bowel disease, especially ulcerative colitis and colonic Crohn’s disease to a lesser extent. It appears in the context of moderate-to-severe disease and often requires colectomy. Currently, after an inadequate response to conventional therapy with systemic corticosteroids, the use of cyclosporine or infliximab is considered as an alternative option, prior to surgical intervention.

We present a case report of toxic megacolon in a patient with a severe refractory colonic Crohn’s disease, where anti-tumor necrosis factor (anti-TNF) therapies were contraindicated. Consequently, we decided to use ustekinumab as a rescue therapy,
despite insufficient evidence to provide recommendations for this indication.

**Keywords:** Toxic megacolon. Crohn’s disease. Ustekinumab.

**INTRODUCTION**
The development of toxic megacolon in the setting of moderate-to-severe ulcerative colitis (UC) or colonic Crohn’s disease (CD) is a potentially lethal complication (1). Currently, its incidence has decreased as well as the need for colectomy as a rescue therapy, due to the incorporation of immunomodulator therapies and monoclonal antibodies into inflammatory bowel disease (IBD).

The objective of this study was to report our experience of using ustekinumab as a rescue therapy in a patient with severe refractory colonic CD. The clinical and endoscopic outcomes after a 24-week follow-up period were also assessed.

**CASE REPORT**
We present the case of a 57-year-old female patient followed-up in our outpatient clinic since the age of 47 (2011), with colonic Crohn’s disease with perianal involvement (A3 L2 B1p). At the time of initial diagnosis in 2011, she presented a moderate colonic Crohn’s disease and received systemic steroids (oral prednisolone 0.75 mg/kg) for the induction of clinical response. After maintenance treatment with mesalazine and azathioprine, azathioprine was suspended in 2013 due to intolerance. She remained in clinical remission until October 2019 (Crohn’s Disease Activity Index [CDAI] score < 150).

In July 2019, after presenting arthralgia and facial erythema in a malar distribution, the patient was referred to the Rheumatology Unit. The study was completed with laboratory testing, including ANA positive to 1/10,240 in a homogeneous pattern, anti-dsDNA and anti-nucleosome positive. She was diagnosed with systemic lupus erythematosus (SLE).

In December 2019, she presented diffuse abdominal pain, diarrhea with stool frequency of 7-8 stools/day and obvious blood in the stool most of the time, which was mainly nocturnal. She also reported urgency and a significant weight loss. Due to the
diagnosis of moderate-to-severe Crohn’s disease (CDAI > 220), hospital admission was decided.

On the first day of admission, intravenous methylprednisolone (1 mg/kg) was started and stool samples were obtained for microbiological analysis with negative results. Within 24 hours of hospital admission, a flexible sigmoidoscopy (without bowel preparation) was performed and extensive and deep ulcerations were observed (Fig. 1). The histopathology combined with immunohistochemistry was negative. However, the detection of cytomegalovirus (CMV) DNA through C-reactive protein (CRP) in tissue biopsies was positive and treatment with intravenous ganciclovir was started.

On the 5th day of admission, the stool frequency decreased, along with increased abdominal pain. The physical examination showed a blood pressure of 96/63 mmHg, heart rate of 125 bpm and a body temperature of 37.3 °C (99.1 °F). The abdomen was distended with decreased bowel sounds. The laboratory study showed hemoglobin at 78 g/l, leukocytosis with neutrophilia (WBC of 11,800/µl) and CRP at 115 mg/l.

According to the Jalan diagnostic criteria, there was a high clinical suspicion of toxic megacolon (2). Stool testing was repeated, ruling out infection by *Clostridium difficile* and an abdominal x-ray showed colon dilation of up to 8.5 cm at the level of the transverse colon and wall thickening in relation to inflammatory changes (Fig. 2). An abdominal computed tomography (CT) scan confirmed these findings and excluded the presence of free fluid and/or complications.

As the clinical picture was confirmed, close monitoring by a multidisciplinary team was decided including a colorectal surgeon, and the therapeutic options were evaluated. Infliximab was contraindicated because of SLE and cyclosporine was ruled out due to the patient’s intolerance to thiopurines. Consequently, ustekinumab was chosen. A single infusion of intravenous ustekinumab (6 mg/kg) was administered. At the same time, the “rolling technique” was used for medical decompression, consisting of frequent rolling of the patient to the prone position (15 minutes every 1-2 hours) in order to redistribute colonic gas (3).

The evolution was favorable, with a significant clinical response at 24-48 hours, and the patient was discharged from hospital two weeks after ustekinumab infusion. After discharge, she continued in clinical remission with a normal number of stools (1-2/day).
and normalized analytical parameters. Six weeks after the first infusion, she presented diarrhea with an increase of frequency of 5-6 stools/day, some with blood. At this time, we decided to administer a 2nd dose of intravenous ustekinumab (6 mg/kg), again achieving clinical response within 48 hours.

Currently, after 24 weeks of follow-up, the patient has achieved clinical remission (CDAI < 150) and is now receiving ustekinumab 90 mg subcutaneously every four weeks as a maintenance treatment. At week 24, a new colonoscopy was performed, showing endoscopic improvement with no signs of acute activity and mucosal healing. However, numerous pseudo-polyps and scar tracts were present (Fig. 3).

**DISCUSSION**

Megacolon is defined as the segmental or total dilation of the colon with a diameter greater than 5.5 cm in the absence of an obstructive mechanical cause. The association of systemic toxicity is more important than the dilation itself and is most commonly observed as a complication of IBD (1). Megacolon is also observed in any serious inflammatory process in the colon, with special attention to infections. In particular, *Clostridium difficile* can simulate or coexist with IBD, conditioning the disease response to various treatments. Special mention should be made to CMV, which was detected by PCR in the colonic mucosa of our patient. We decided to perform this treatment, since it was a severe refractory colonic Crohn’s disease (4). However, there is considerable controversy in the literature regarding the indication for antiviral treatment, and the lack of consensus in its diagnostic process.

The diagnosis and early treatment of toxic megacolon are essential for its evolution and to avoid the development of complications, especially bowel perforation, which is the main factor related to mortality. The management of patients with toxic megacolon must be multidisciplinary. Patients usually should be placed on complete bowel rest with total parenteral nutrition and correction of the electrolyte deficits. Antithrombotic prophylaxis must be administered, and broad-spectrum antibiotics are recommended to reduce septic complications as well as intravenous corticosteroids, especially in patients with IBD-related toxic megacolon (5). Regarding decompressive
techniques, there is no strong scientific evidence to support a favorable prognosis for their use, and they should in no way replace appropriate medical or surgical treatment (3,6).

It has been reported in the medical literature that 50 to 75% of cases of toxic megacolon treated medically do not require a surgical intervention (5,7). However, it is important to remark that early surgery may lead to a lower mortality (8,9). Surgery is indicated for bowel perforation, clinical signs of peritonitis, progressive colonic dilation, bleeding and deterioration of the general condition, despite appropriate medical treatment.

The specific therapy for toxic megacolon must target the underlying etiology. The management of moderate-to-severe ulcerative colitis/colonic Crohn’s disease which have not responded to conventional therapy with systemic corticosteroids (refractory disease) should be closely monitored by a multidisciplinary team, including a gastroenterologist and colorectal surgeon (10). If an alternative option is considered prior to surgery, two medical treatments are currently recognized, cyclosporine or infliximab (monoclonal antibodies directed against TNF-α). These therapies have been compared in some cases in the literature, although the results do not allow for a strong recommendation. Therefore, the decision is at the discretion of the specialist, depending on the characteristics of the patient and the experience of the center (11).

Regarding megacolon, the scientific community seems to have leaned slightly towards the use of infliximab in this situation, especially in recent years. The response rate without surgery is around 75%, although the quality of the evidence is very low (12,13).

With regard to the patient in this case report, the choice of expanded access to ustekinumab as a rescue therapy was first due to the absence of other alternatives and second, to its well-known pharmacokinetics in terms of speed of response. In the medical literature, there is no previous reference to the use of ustekinumab in patients who have contraindication to anti-TNF therapies and present a moderate-to-severe refractory ulcerative colitis/colonic Crohn’s disease. Thus, we aimed to report the results of this experience and to open the debate about the administration of ustekinumab as an effective alternative in the formerly referred patients. Further
studies in a larger number of patients will be required to assess our results and to provide stronger scientific evidence.

AUTHOR’S CONTRIBUTIONS
M. I.: clinical management of the patient in the Gastroenterology clinic and paper writing.
J.O.Z., N.H.A., S.D., N.I.: clinical consultation and critical revision of the manuscript for important intellectual content.
All contributors included in the IBD study group thoroughly revised the manuscript, were involved in the conception of the study and have approved the final manuscript.

ACKNOWLEDGMENTS
Martín Irabien wants to thank the Inflammatory Bowel Disease Unit of the Hospital Universitario de Basurto for the training received.

REFERENCES


Fig. 1. Sigmoidoscopy: several mucosa inflammation with extent of the ulcerated surface.
Fig. 2. Abdominal x-ray: colon dilation of up to 8.5 cm at the level of the transverse colon and wall thickening in relation to inflammatory changes.
Fig. 3. Twenty-four weeks follow-up endoscopy: mucosal healing with numerous pseudo-polyps and scar tracts.