Is really megacolon a contraindication to infliximab in Crohn's disease ?

Emanuele Sinagra[1], Ambrogio Orlando[1], Sara Renna[1], Valeria Criscuoli, Francesco La Seta[2], Mirko Olivo[1], Marco Ciofalo[1], Mario Cottone[3]

(1) DIBIMIS, Ospedali Riuniti Villa Sofia - Vincenzo Cervello, Division of Internal Medicine, and (2) Radiology Unit, Palermo ; (3) DIBIMEF, Sezione di Scienze Radiologiche, AOUP Paolo Giaccone, Palermo ; (4) Fondazione Istituto San Raffaele Giglio, Gastroenterology & Endoscopi Unit, Cefalù, Italy.

Abstract

Toxic megacolon (TM) is a rare complication of severe ulcerative colitis (UC) and colonic Crohn's disease (CD), defined as a clinical syndrome accompanied by radiographic evidence of colonic dilatation that in many cases must be treated aggressively with surgical intervention (1).

We report two cases of steroid and antibiotic-refractory fulminant Crohn's colitis, complicated by toxic megacolon, who were successfully treated with infliximab (IFX), thus avoiding surgical intervention.

Although there are no well defined recommendation about the correct timing of colectomy in CD-associated TM, and despite the fact that it may be imprudent to advocate delaying surgery in favour of anti-tumor necrosis (anti-TNF) factor therapy in these cases, we think that a medical "rescue therapy" can be considered in a subset of patients with stable clinical condition during corticosteroid treatment. (Acta gastroenterol. belg., **2013**, 76, **442-444**).

To the editor,

Toxic megacolon (TM) is a rare complication of severe ulcerative colitis (UC) and colonic Crohn's disease (CD). It is defined as a clinical syndrome accompanied by radiographic evidence of colonic dilatation that in many cases must be treated aggressively with surgical intervention (1).

The diagnostic criteria of TM are, according to Jalan and coworkers : the radiographic evidence of colonic dilation (> 6 cm at the level of the transverse colon) and 3 of the following : fever (> 101,5° F), tachycardia (> 120 beats/min), leucocytosis (> 10500 × mm^3) or anemia ; and 1 of the following : dehydration, altered mental status, electrolyte abnormality, or hypotension (1).

We report 2 cases of steroid and antibiotic-refractory Crohn's colitis, complicated by toxic megacolon, who were successfully treated with infliximab (IFX), thus avoiding surgical intervention.

A 18-year old woman with a recent diagnosis of colonic CD was admitted to our tertiary referral centre for a severe disease flare on February 2010. She had 8 bloody bowel movements per day, abdominal pain with tenderness and fever (38°C), a blood pressure of 95/65 mmHg and a pulse rate of 60 beats/min. The laboratory studies showed an erythrocyte sedimentation rate (ESR) of 120 mm/h, kaliemia of 3.2 mEq/L, leucocytosis (12.000 mm^3) and a C-reactive protein (CRP) of 18 mg/L ; blood and stools cultures showed no infection.

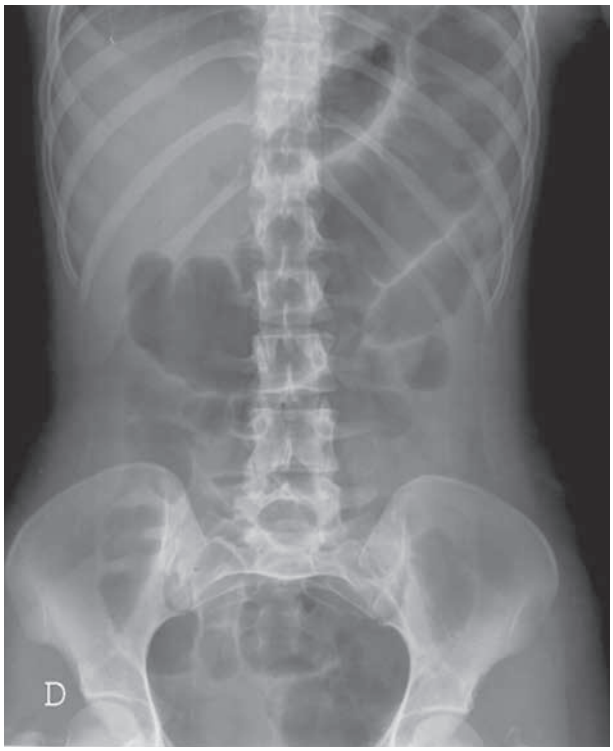

Fig. 1. — Plain abdomen x-ray showing a 7 cm colonic dilatation.

An endoscopically severe colonic CD was diagnosed two months before in a secondary referral centre, to which she was admitted for bloody diarrhoea, fever and abdominal pain. The patient was treated with methylprednisolone intravenously and empirical antibiotic therapy (metronidazole anc cyprofloxacine intravenously), and was discharged with prednisone per os and the same antibiotics per os.

At admission to our unit, therapy with steroid intravenously (methylprednisolone 1 mg/kg/day), antibiotics

Correspondence to : Emanuele Sinagra, via degli orti 41, 90143 Palermo - Italy.
E-mail : emanuelesinagra83@googlemail.com

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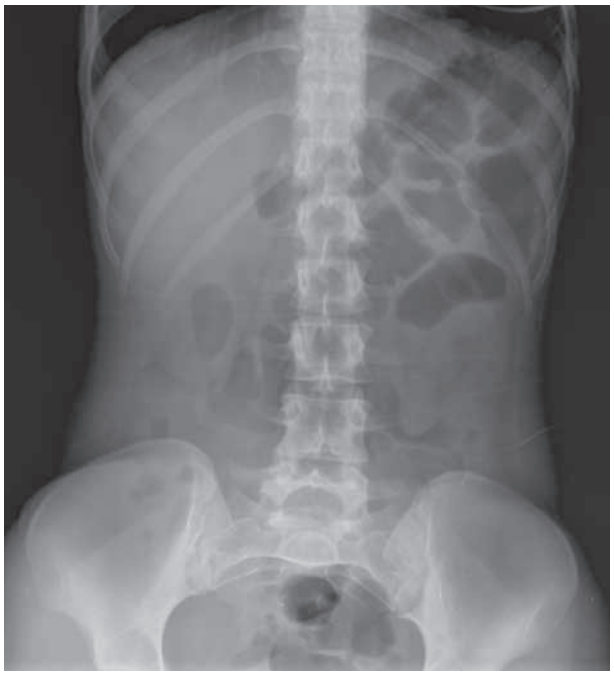

Fig. 2. — Plain abdomen x-ray showing a marked reduction of the colonic dilatation.

(ciprofloxacin 200 mg twice daily and metronidazole 500 mg, 3 × daily) and parenteral nutrition was started. The surgical consult at admission recommended a watchful approach with daily reevaluation. After 4 days the symptoms were stable but she developed colonic dilatation (7 cm) visible on plain abdomen x-ray (Fig. 1) and CT scan. Proctoscopy without air insufflation showed mild activity of the disease in the rectum ; rectal biopsies were negative for human cytomegalovirus (CMV) infection. Considering the absence of clinical improvement, the appearance of colonic distension, the presence of severe endoscopic and clinical activity of the disease, and the young age of the patient, who refused surgery, we started, at day 6 since admission, with IFX 5 mg/kg/IV after having secured a normal chest x-ray, negative Mantoux testing and Hepatitis B serology. Her abdominal pain and diarrhoea improved so that feeding was restarted two days after her first dose of IFX. Abdominal x-ray showed a marked improvements of the colonic distension 24 hours after IFX treatment (Fig. 2). The patient was discharged 5 days after initial IFX treatment with an abdominal x-ray showing a diameter of the transverse colon of 2,7 cm, and normal laboratory tests. Azathioprine 2 mg/kg/day was added to the IFX treatment that the patient continued until today. At the last outpatient's control, she was asymptomatic and the colonoscopy performed one years after the beginning of the biologic therapy showed endoscopical and histological healing of the colonic lesion.

A 21-year old man with a history of ileocolonic CD since 2011 was admitted to our centre, for a severe disease flare, in April 2012.

He had 12 bloody bowel movements per day, abdominal pain with tenderness and fever (38,5°C), a blood pressure of 100/60 mmHg and a pulse rate of 80 beats/min. The laboratory tests showed an ESR of 50 mm/h, a kaliemia of 3.7 mEq/L, leucocytosis of 11.300 × mm^3, an albuminaemia of 2,8 g/dl and a CRP of 16 mg/L ; blood and stools cultures showed no infection.

Because of ileal involvement, budesonide was started at diagnosis. However, one month before admission to our unit, he reported a flare and started prednisone 37,5 mg/day, without improvement.

At admission, therapy with intravenous steroid, antibiotics and parenteral nutrition was started and again surgeons proposed a daily reevaluation. After 4 days symptoms were stable but colonic dilatation (7 cm) developed (plain x-ray and CT scan). Proctoscopy showed a mild disease in the rectum ; rectal biopsies were negative for CMV infection. The patient refused a surgical intervention. Considering the stable clinical situation and the presence of a normal acid-base balance, we decided to start IFX, at day 6, after screening for infections and TBC . Abdominal pain and diarrhoea improved markedly two days after the fist dose of IFX. Abdominal x-ray showed a marked improvements of the colonic distension 24 hours after IFX treatment. The patient was discharged 7 days later, abdominal x-ray showing a diameter of the transverse colon of 2,8 cm and with normal laboratory tests. Because of an infusion reaction during the 3rd infusion, treatment was switched to Adalimumab subcutaneously every other week after induction therapy 160/80/40 mg. At the last outpatient's control, he was clinically asymptomatic.

The precise pathophysiology of TM is not fully understood. It is probably the spread of inflammation into the circular and longitudinal muscle layers that might induce neural injury and destruction of the myenteric and Auerbach plexus (2,3). Furthermore, inflammatory mediators have an inhibitory effect on the colonic muscle tonus, thus allowing the colonic distension (4). Hence, it would seem reasonable that potent anti-inflammatory treatment with anti-TNF agents might have an favourable effect.

Like in UC (5), only few case-reports suggested that infliximab and adalimumab might play a role in avoiding surgery in CD-associated TM (6,7). In the paper by Ng and Kamm (6), adalimumab was started in a patient with a colonic dilation of 9 cm, 3 days after the start of IV Hydrocortisone 100 mg 4 times daily, gaining an immediate clinical improvement (the patient started to eat 5 days after the 1st administration of adalimumab). Abdominal radiography returned to normal after ten days of treatment. In the paper by van Geenen and coworkers (7), IFX 5 mg/g was started in a patient with a colonic dilation of 9 cm, 7 days after introduction of IV prednisone 50 mg daily plus antibiotics, gaining a rapid clinical (he started to eat 12 hours after the administration of IFX) and radiological improvement (abdominal radiography normalised 5 days after IFX treatment).

Although there are no well defined recommendation about the correct timing of colectomy in CD-associated TM, and despite the fact that it may be imprudent to advocate delaying surgery in favour of anti-TNF therapy, we think that a medical "rescue therapy" can be considered in a subset of patients who do not present with a rapid deterioration of their clinical condition.

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