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CASE REPORT

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Selective effect of infliximab on the inflammatory component of a colonic stricture in Crohn's disease

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Abstract Although infliximab has been shown to improve the clinical course of Crohn's disease, its effect on intestinal strictures is controversial. We describe the case of a woman with steroid-resistant colonic Crohn's disease presenting with intermittent obstruction because of a tight stricture in the splenic flexure. Compared with uninvolved areas, biopsies showed intense edema and inflammatory cell infiltration and immunohistochemistry revealed an excess of TNF-α. Her symptoms responded promptly (CDAI went from 444 to 168) to an infliximab infusion (10 mg kg^{-1} BW), which also had a dramatic effect on the stricture, now presenting radiologically as a moderate residual, apparently fibrotic, narrowing of the lumen. Endoscopy and histology confirmed the resolution of inflammation and TNF-α virtually disappeared. The patient refused additional infusions and after a few months the disease recurred with features identical to the pre-treatment phase. She then opted for surgery. Histology of the resected strictured colon revealed edema, inflammation, and fibrosis, with TNF-α back to pre-treatment levels. This case indicates that, in the colon, infliximab specifically relieves the TNF-α-mediated inflammatory component of the stricture while having no effect on fibrosis and suggests that the response to infliximab treatment may depend on the nature of the, stricture itself.

Keywords Crohn's disease · Colonic strictures · Infliximab

Abbreviations TNF: tumor necrosis factor · CDAI: Crohn's disease activity index

Introduction

Strictures, both in the small intestine and colon, are one of the most common complications of Crohn's disease and a leading indication for surgery. Indeed, without strictures many patients with inflammatory (i.e. non-fistulizing) Crohn's disease could be probably managed conservatively. Pathologically, two types of strictures have been described in Crohn's disease [1]: a stricture resulting from florid inflammation due to edema and cell accumulation in the mucosa and a more chronic type of stricture characterized by muscular hyperplasia and irreversible scarring. It is not clear whether the stricturing pattern in Crohn's disease can be associated with gene mutations [2, 3] or, rather, to disease location and environmental factors [4]. Both types of stricture may result in obstruction. Furthermore, cell infiltration and fibrosis may coexist in the same stricture and be part of the same inflammatory process [5]. A clinical distinction between the two types of stricture would, however, be highly desirable to address

the issue of medical versus surgical management of the disease in the individual patient [1]. Although some radiological features may help in this regard [1] there are no firm criteria for pre-operative differential diagnosis [6]. As such, it is not clear whether medical treatment is capable of avoiding or postponing surgery [6, 7], except perhaps when steroids are given as a local injection combined with endoscopic dilation in the small intestine [8], an effective alternative to surgery almost exclusively in patients with anastomotic strictures [9].

Infliximab, an anti-TNF monoclonal antibody, has been shown to improve the clinical course of Crohn's disease [10]. With this therapy, clinical improvement is accompanied by significant healing of endoscopic lesions and disappearance of the mucosal inflammatory infiltrate by downregulation of inflammatory mediators [11–13] without significant side effects [14]. Yet it has been reported that after infliximab treatment strictures may develop in some patients [15], although other studies have not found an increased risk of such complications [16]. However, it is unknown which type of stricture was predominant among the patients studied.

We describe here a case that may shed light on the effect of infliximab on colonic strictures. A young woman with Crohn's disease of the colon had an important narrowing of the splenic flexure and part of the transverse colon. The stricture was responsible for her obstructive symptoms which had not fully responded to oral steroids. Infliximab treatment brought about a dramatic improvement in her symptoms and a resolution of the inflammatory component of the stricture, which recurred several months after the end of the treatment.

Case report

In June 2001, E.C., an 18-year-old white woman, was admitted to our ward with abdominal pain, fever, diarrhea, and weight loss. A sigmoidscopy with biopies performed the previous year was diagnostic for Crohn's disease of the colon but a cycle of steroids and mesalazine had been only partially successful. On physical examination, her abdomen was tender. Her blood count revealed iron-deficiency anemia (Hb, 10.6 g dL^{-1}), serum albumin was also low (2.8 g dL^{-1}) and ESR and CRP were markedly increased (116 mm h^{-1} and 87 mg dL^{-1}, respectively). A sigmoidoscopy (the patient did not tolerate a full colonoscopy), showed a classic cobblestone appearance of the mucosa with diffuse ulcerations starting 25 cm from the IAS. The endoscopic and histologic pictures were compatible with active Crohn's disease. A double contrast barium enema showed a disease extended to the mid-transverse colon. The splenic flexure and the left transverse colon appeared scarcely distensible. A small intestine double contrast enteroclysis and an abdominal ultrasound were virtually normal. The patient was restarted on prednisone 50 mg day^{-1} for 4 weeks which, as in previous occasions, was only marginally effective. Shortly, the patient complained of symptoms suggesting an initial obstruction. Indeed, a repeat double contrast barium enema in January 2002 revealed a frank stenosis in the splenic flexure and part of the left transverse colon (Fig. 1a).

She was then re-admitted to our ward. As on previous occasions, she was mildly anemic, ESR and CRP were increased, an erythema nodosum was present in her left leg, and her abdomen was diffusely tender. A repeat endoscopy

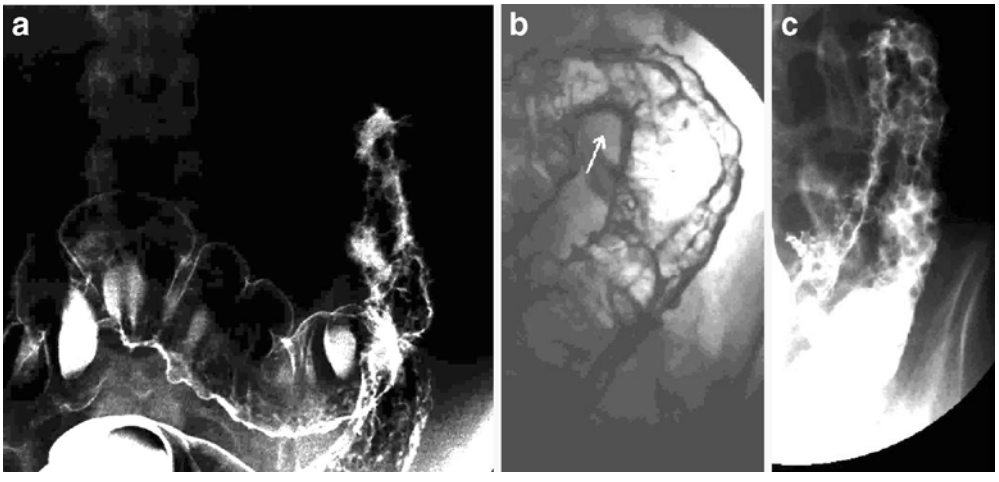

Fig. 1 Double contrast barium enema. **a** (01/2002) In the proximity of the splenic flexure and part of the transverse colon the lumen is stenotic, a finding confirmed by colonoscopy. The patient was clinically ill with symptoms of intermittent obstruction. **b** (05/2002) Approximately 6 weeks after a single infliximab infusion (10 mg kg^{-1}, BW), there is almost complete disappearance of the stricture. However, note (*arrow*) a residual, moderate narrowing of the splenic flexure. At this time the patient was feeling well and her blood routine was normal. **c** (09/2002) Approximately 6 months after the infusion the radiogram shows a recurrence of the stricture in the same location. The patient, again, had abdominal pain and signs of intermittent obstruction

confirmed an ulcerated stricture (which precluded passage of the instrument; not shown) observed at the barium enema. The biopsies of the stricture showed edema and an intense inflammatory infiltrate (Fig. 2a).

Immunohistochemistry for TNF-α, performed with a specific monoclonal antibody (1:10, Innogenetics, Gent, Belgium), as recently described by Baert et al. [12], revealed an excess of this cytokine in the affected tissue

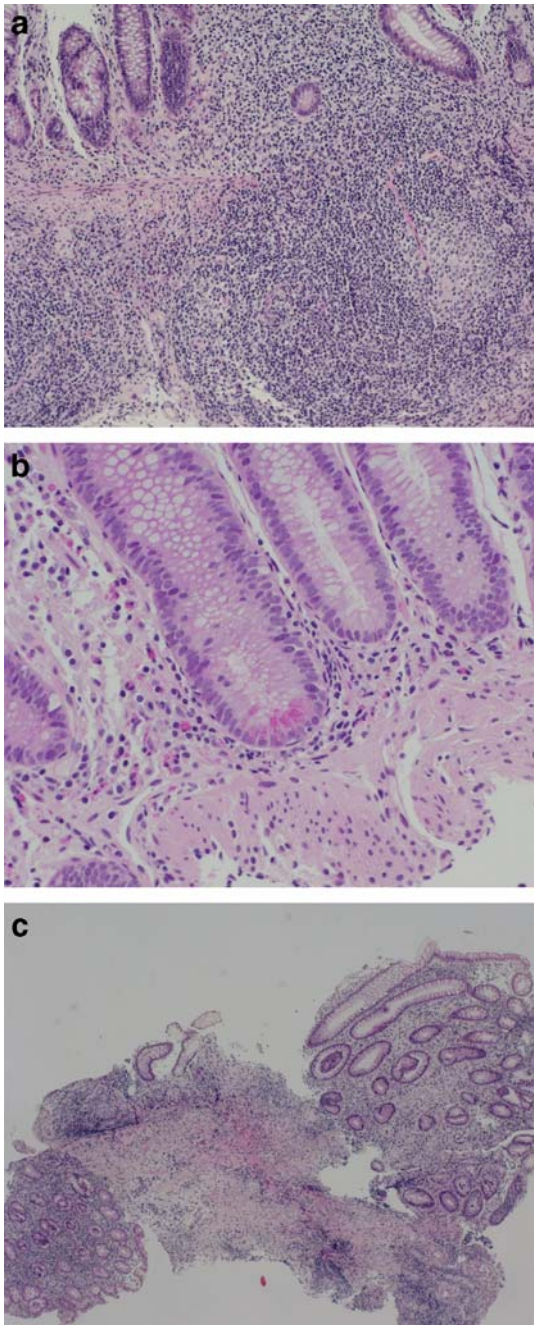

Fig. 2 H & E stain of colon mucosa. **a** Edema and intense inflammatory infiltrate in a biopsy from the stricture depicted in Fig. 1a. Note a follicle in the *right lower corner*. **b** Virtual resolution of inflammation 6 weeks after infliximab infusion in a tissue sample from the splenic flexure. **c** Tissue sample from the resected strictured splenic flexure depicted in Fig. 1c showing fibrosis (*pink area in the center*) and edema and inflammation (magnification 200×, 400× and 100×, respectively)

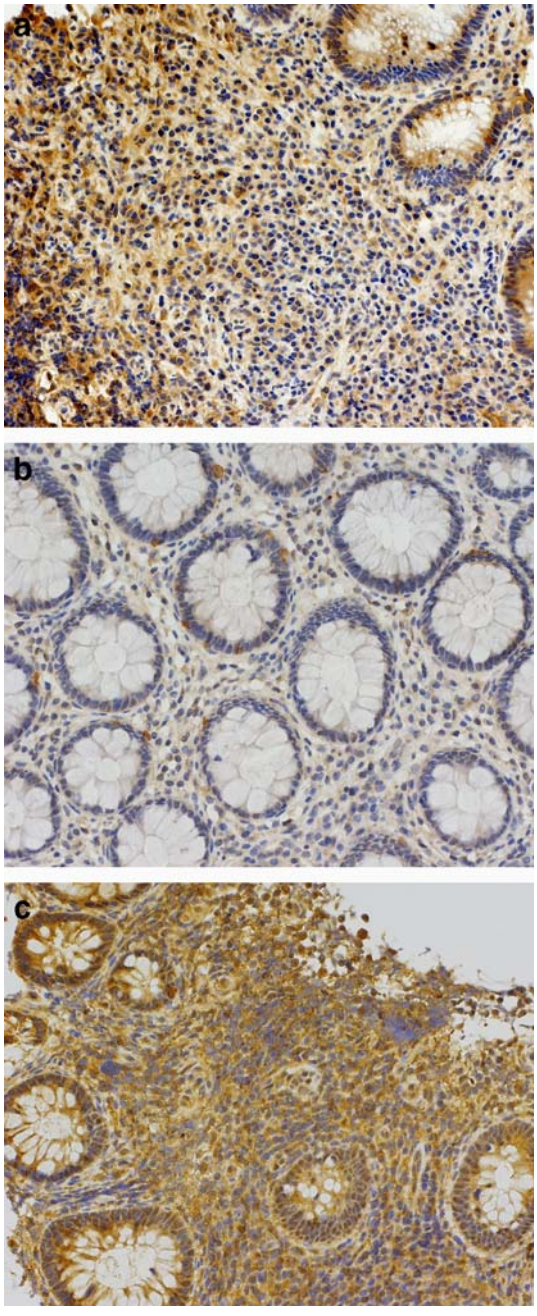

Fig. 3 Immunohistochemistry for TNF-α in colon mucosa. Panels **a**, **b**, and **c** were obtained from the same tissue samples depicted in Figs. 2a, b, and c, respectively. **a** Intense positive staining of cells before infliximab treatment. **b** Virtual disappearance of TNF 6 weeks after the infusion. **c** TNF density returns to pretreatment levels in the resected strictured splenic flexure approximately 6 months after infusion of infliximab (for methods, see text; magnification 200×)

(Fig. 3a) with levels far higher than those in unaffected or in non strictured tissue (not shown).

At this point, the patient was offered a trial with infliximab, which she accepted. After a single i.v. infusion (10 mg kg^{-1}, BW) she reported an almost immediate symptomatic benefit, especially with regard to pain and to bowel movements (which became regular). Despite our recommendations, and the virtual absence of any side effect, the patient refused additional infusions of infliximab or other medications except for mesalazine. She was kept on mesalazine at the dose of 4 g day^{-1}. Two months after the infusion, in May, the patient still felt well, had gained weight, had no diarrhea, and her blood tests (including ESR and CRP) were within limits. Crohn's disease activity index (CDAI)—calculated 1 week before and 7 weeks after the infusion as recently recommended [5]—had fallen from 444 to 168. At 6 weeks, a double contrast barium enema showed an almost complete resolution of the previous stricture (Fig. 1b).

In fact, the radiogram also showed a moderate residual, apparently fibrotic, narrowing of the splenic flexure (Fig. 1b, arrow). The mucosal surface on colonoscopy appeared virtually healed (not shown) while biopsies at the flexure confirmed the resolution of inflammation (Fig. 2b). TNF-α had returned to background levels in the previously affected mucosa (Fig. 3b).

The patient presented approximately 6 months after the infusion of infliximab with abdominal pain, alternating diarrhea and constipation, weight loss, and elevation of ESR and CRP. A double contrast barium enema showed a recurrence of the original stricture in the splenic flexure and transverse colon (Fig. 1c).

The patient refused another infliximab infusion and opted, instead, for surgical resection of the affected colon. Macroscopic examination of the latter confirmed the stenosis and histology of the strictured segment revealed edema, inflammation as well as fibrosis (Fig. 2c). At this site TNF-α had returned to pretreatment levels (Fig. 3c).

Discussion

Intestinal strictures are among the most common complications of Crohn's disease, one of the main indications for surgery in these patients. Strictures tend to affect the small intestine more often than the colon [17]. However, when present in the latter, they may also lead to obstruction and may be difficult to differentiate from neoplasia [18]. Of the two types of stricture described in Crohn's disease, inflammatory strictures are due to mucosal inflammation and edema; by contrast, fibrosis and muscle cell accumulation in the submucosa are the hallmarks of the scarring type of stricture [1]. The latter process is the result of an intense proliferation and migration of smooth muscle cells in the muscolaris mucosae and the accumulation of collagen type V in the submucosa [19]. These changes may be mediated by inflammatory target cells (monocytes and lymphocytes) which, through cytokines and growth factors [20], may promote the differentiation of smooth muscle cells into a fibrogenic phenotype [5, 9, 21]. Among the cytokines, IGF-I seems to play a pivotal role, because it is capable of stimulating smooth muscle cell proliferation and fibrosis [22]. IGF-I expression is, in turn, increased by various other mediators, for example interleukin 1 and TNF-α, which are present in large amounts in the injured bowel of Crohn's disease patients [23]. The anti-TNF antibody, infliximab, seems to interfere with soluble and membrane-bound TNF, a process which may promote the apoptosis of the target cells and block/delay the entire inflammatory process [24]. Whether infliximab, via this or other mechanisms, may also prevent initiation and progression of fibrosis is unknown [13].

Although this drug has been shown to improve the clinical course of Crohn's disease [10], its effect on intestinal strictures is still unclear [9, 15, 16]. This may, in part, be because of the often heterogeneous and unknown nature of the treated strictures.

In the case study reported here, after a single infusion of infliximab, most—but not all—of the colonic obstruction due to a stricture in the splenic flexure and left transverse colon resolved and so did the patient's signs and symptoms of active disease. Paradoxically, the treatment was so effective that it may have induced in the patient a false sense of a definite cure because she refused other infusions of infliximab and in a few months her conditions deteriorated. Strikingly, the stricture recurred in the same area of the colon. At this point, still hoping for a definite cure, the patient opted for surgery. Various cycles of steroids had only a modest effect on her symptoms and they probably did not affect the development of the stricture [7].

Thus, this case report indicates that infliximab has a beneficial effect on colonic strictures. The effect seems to be limited to the inflammatory component of the disease and to be the result of local neutralization of TNF, as shown here by immunohistochemistry. Indeed, after the infusion, the previously involved area showed a resolution of inflammation (as assessed by endoscopy and histology) and the disappearance of TNF (Figs. 2b, 3b) while the contrast study showed a residual and fixed narrowing—evidently fibrotic—which had not responded to infliximab (Fig. 1b). That acute and chronic aspects coexisted in the stricture was confirmed by histologic examination of the resected splenic flexure, which revealed acute inflammatory aspects with an excess of TNF, and fibrosis of the submucosa (Fig. 2c, 3c). Hence, the concomitant presence of the two components in the stricture of our patient and the opportunity to distinguish them with a combined radiologic, endoscopic, and histologic approach (including the timely examination of the resected colon) gave us a unique insight into the mechanism of action of infliximab.

Thus, our study suggests that benign, TNF-positive, inflammatory colonic strictures in Crohn's disease could be

included among the indications of a therapeutic trial with infliximab [25]. Whether this drug, given as a maintenance treatment [26, 27], would also prevent the fibrotic evolution of inflammatory strictures is not clarified by our case. It is evident, however, that persistent suppression of inflammation may require continuous, rather than episodic, treatment [28]. A large study focusing on these issues would clearly be needed.

Our observation could also account for the reported apparent variability in the clinical effect of infliximab on strictures [15, 16]. Indeed, it has been reported that after infliximab treatment strictures may develop in some patients [15] although other studies have not found an increased risk of such complications [16]. It is important to point out that it is unknown which type of stricture (i.e. inflammatory or fibrotic) was predominant among the patients studied in previous reports. Thus, although it is possible that the healing process initiated by infliximab may facilitate scarring as suggested by some authors [15], it is also possible that scarring is already the major component of the strictures in unresponsive patients before the treatment. Alternatively, if inflammation does invariably lead to scarring, there may be a point of no return during the evolution of the process (such as cell phenotype change [20, 21, 29]) beyond which the administration of infliximab may not be able to prevent scarring. At the moment, there is not enough data to clarify this important issue.

In conclusion, we have shown that infliximab, given as a single infusion, had a dramatic beneficial effect on a tight stricture of the colon in Crohn's disease, by specifically relieving its TNF-mediated inflammatory component. This observation indicates that the response to infliximab treatment of a given stricture may depend on the nature of the stricture itself.

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