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CASE REPORT

Enterocutaneous fistula in severely active Crohn's disease: preoperative anti-TNF alpha treatment to limit bowel resection—report of a case

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Abstract

Purpose Strategies for limiting the extent of bowel resection in cases of enterocutaneous or interenteric fistulas in severely active Crohn's disease are urgently necessary. Anti-inflammatory therapy with tumor necrosis factor alpha (anti-TNF alpha) inhibitors has positive impact on fistulizing Crohn's disease. We describe a case of a 32-year-old male suffering from enterocutaneous fistula in severely active Crohn's disease.

Methods The patient's clinical course and data of therapy monitoring before bowel resection were reviewed and compared to the pretherapeutic findings. In addition, the reports of surgery and histopathological workup were evaluated and a clinical follow-up was performed. The literature on anti-TNF alpha treatment in fistulizing Crohn's disease was surveyed.

Results A 32-year-old male with an 8-year history of Crohn's disease and condition after previous ileocecal and sigmoid resection at the age of 28 presented with increasing pain in the middle-right abdomen. Laboratory and radiologic assessment detected elevated C-reactive protein and presence of a conglomerate of inflammatory thickened and narrowed small intestine involving the neoterminal ileum and enteroenteric fistulas. Ileocolonoscopy showed a stenosing inflammation of the neoterminal ileum. After initial anti-infective therapy, as a result of an interdisciplinary decision, preoperative anti-TNF alpha treatment was performed to achieve limited bowel resection. After declining of inflammation, limited bowel resection was carried out successfully.

Conclusions Preoperative therapy with anti-TNF alpha might potentially reduce inflammation to subsequently limit the extent of bowel resection in selected cases of enterocutaneous or interenteric fistulas in severely active Crohn's disease. We describe an impressive case in which such therapeutic approach was carried out.

Keywords Surgery in Crohn's disease · Inflammatory bowel disease · IBD · Enterocutaneous fistula · Anti-TNF therapy

Introduction

The risk for surgery in patients suffering from Crohn's disease (CD) increases up to 45% 10 years after diagnosis [1]. In particular, interenteric or enterocutaneous fistulas are serious complications of CD [2]. They can occur spontaneously or postoperatively and show a high morbidity and even mortality [3]. Extended or repeated intestinal resections may result in a

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short bowel syndrome even with the need for intestinal transplantation [4, 5]. Previous studies showed a positive effect based on an anti-inflammatory therapy with tumor necrosis factor alpha (anti-TNF alpha) inhibitors in fistulizing CD [6, 7]. By analogy with multimodal therapy concepts in oncological therapy, we hypothesize that in selected cases, preoperative therapy with anti-TNF alpha might reduce inflammation and subsequently limit the extend of resection. To the best of our knowledge, data on this are not available.

We present the case of a 32-year-old male suffering from enterocutaneous fistulas and severely active Crohn's disease, in which preoperative anti-TNF alpha treatment was performed as a result of an interdisciplinary decision. After declining of inflammation, limited bowel resection was carried out successfully. The patient's consent for publication of the case is available to the authors.

Case report

A 32-year-old male (body mass index 28.6 kg/m^2) with an 8-year history of Crohn's disease presented at the Department of Internal Medicine of the University Hospital of Tuebingen because of increasing pain in the middle-right abdomen for 4 weeks. Formerly been under medical attendance of a hospital close to his place of residence, contact with our hospital represented the patient's first connection with a high-volume inflammatory bowel disease center. At the time of presentation, he was treated with azathioprine monotherapy. Apart from mesalazine, which was discharged because of hepatotoxicity, no other drugs have been administered earlier until presentation to our hospital. During the patient's previous disease course, enteroenteric fistulas necessitated an ileocecal and sigmoid resection 4 years after first diagnosis at the age of 28 years. While still anastomosed at this time, 6 months after, Hartmann's procedure combined with the excision of a new ileoneosigmoidal fistula was performed. Hereafter, descendorectostomy and protective loop ileostomy, as well as the closure of the ileostomy, were done consecutively. In addition to recurrent enteroenteric fistulas, the patient also suffers from perianal fistulas and an enteropathic spondyloarthritis as an extraintestinal manifestation. The patient has a history of cigarette smoking and a subclinical thrombophilia in terms of a factor V Leiden mutation (heterozygous).

During initial presentation at our hospital, physical examination revealed a painful palpation in the middle-right abdomen without rebound tenderness. Laboratory findings showed an elevated C-reactive protein (CRP) (14 mg/dl [reference range ≦ 0.50 mg/dl]) and a normal white blood cell count. By sonography, a small intestinal wall thickening in the middle-right abdomen was shown (4.5 mm). The subsequent computed tomography confirmed the presence of a conglomerate of inflammatory thickened and narrowed small intestine involving the neoterminal ileum and enteroenteric fistulas as shown in Fig. 1a, b. A prestenotic distention of the small intestine became evident too. The initial emergency diagnosis was supplemented by an MRI (Sellink) and ileocolonoscopy. The MRI also revealed an inflammatory conglomerate of the small intestine adjacent to the abdominal wall in the middle-right abdomen with long segment lumen constriction and a prestenotic bowel distention up to 6 cm as well as multiple fistulas in contact to the abdominal wall and enteroenteric fistula (Fig. 1c, d). By ileocolonoscopy, a stenosing inflammation of the neoterminal ileum and normal mucosa in the colon was shown (Fig. 2). The histopathological findings of biopsies taken in the neoterminal ileum showed ulceration and atrophia of the neoterminal ileum. No dysplasia, malignancy, or granulomas were detected.

Due to the patient's fear of losing his job again, he was discharged and an antibiotic therapy (ciprofloxacin 500 mg p.o. twice daily and metronidazole 400 mg p.o. three times daily) in an outpatient setting was started. At the agreed restoration 1 week after, the patient complained of intermittent strongest abdominal cramps and nausea. The white blood cell count was still in the normal range but the CRP increased up to 19.6 mg/dl. At this time, the patient was examined by a visceral surgeon for the first time, and the further therapy was discussed in our multidisciplinary inflammatory bowel disease (IBD) board. Based on the cross-sectional imaging carried out 1 week earlier, surgery at this time would be associated with a high risk of losing a long segment of the small intestine, possibly ending in a functional short bowel syndrome. Thus, to achieve limited bowel resection, anti-TNF alpha therapy (in addition to the already established azathioprine therapy; adalimumab 160 mg week 0, 80 mg week 2, then 40 mg every 2 weeks s.c.) for declining inflammation as first stage in treatment and delayed surgery was decided by the IBD board, individualized for this special case. A close monitoring of the patient by the Department of Gastroenterology was agreed with the patient. The patient reported a rapid improvement of symptoms by telephone interviews and outpatient visits within the first few weeks. After 1 month, the patient presented to the surgical outpatient department due to sanious and enteral secretion from the former ostomy location as well as previous abdominal cramps. The clinical findings were correlative to an enterocutaneous fistula. A mild leukocytosis (10,730 1/μl [reference range 3800–10,300 1/μl]) and a progressive CRP elevation (26.5 mg/dl) were found. The patient described an immediate relief of pain after cutaneous perforation; nausea was denied. The computed tomography [8] at readmission showed an extensive phlegmon of the abdominal wall with an adjacent abscess as well as fistulas.

Anti-TNF alpha therapy was stopped. Azathioprine and ciprofloxacin/metronidazole as well as regular surgical

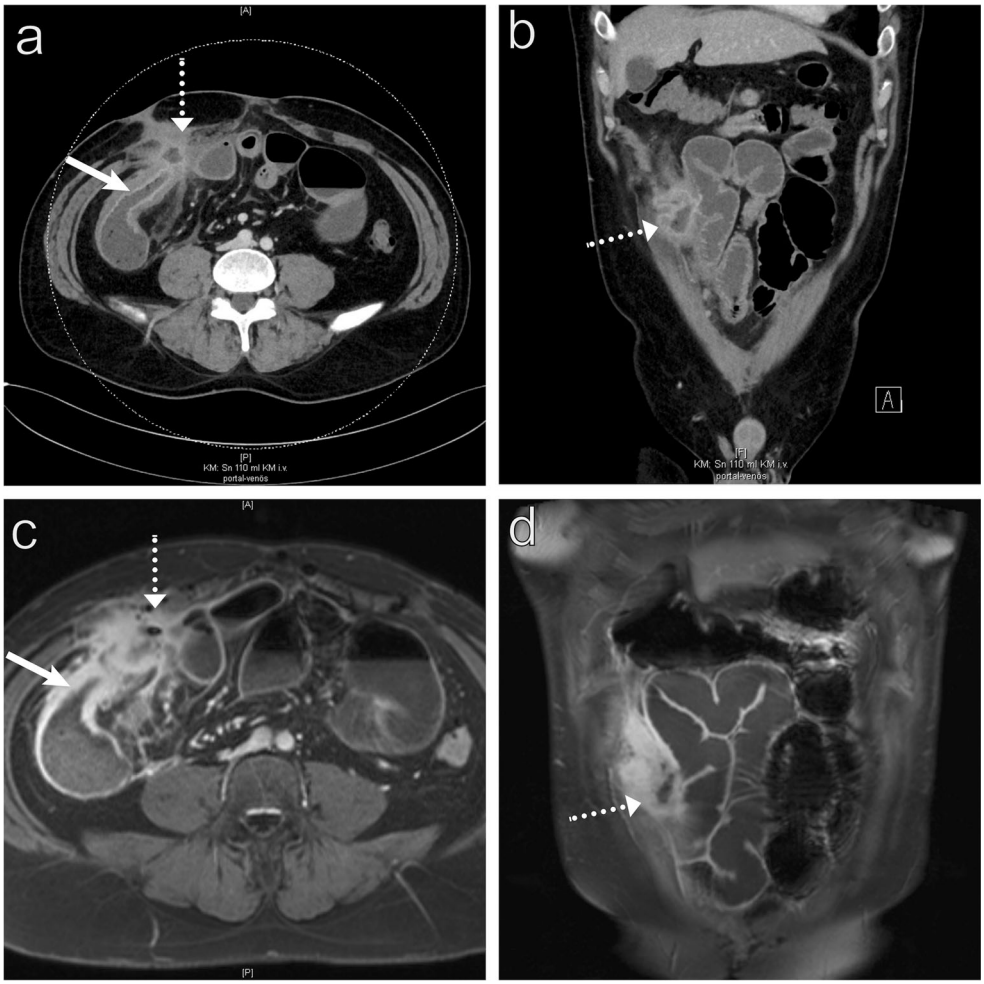

Fig. 1 Contrast-enhanced computed tomography in axial and coronal orientation and contrast-enhanced MR Sellink at 1,5 Tesla after administration of Mannitol p.o. were performed to estimate the extension of inflammation before therapy. CT (**a**, **b**) and MRI (**c**, **d**) showed an advanced inflammation of the mesenteric fatty tissue and massively thickened intestinal walls in the right lower abdomen corresponding to the neoterminal ileum (arrow), as well as fistula tracts (dotted arrow). A demarcation of the intestinal wall in relation to the fistula tracts is not given. A prestenotic distention of the small intestine is also depicted

controls were continued. In the following weeks, CRP values varied between 5.6 and 11 mg/dl and the patient reported an increasing improvement of physical well-being. Approximately 8 weeks after skin perforation and manifestation of enterocutaneous fistula, CT scan was carried out again. The CT scan showed a regression of the interenteric fluid, but still fluid combined with gas in the subcutaneous tissue corresponding to an enterocutaneous fistula, possibly sourced by the ileum (Fig. 3).

Based on the CT findings and remaining low symptoms, adalimumab administration was restarted (40 mg s.c. every 2 weeks) as decision of our interdisciplinary board.

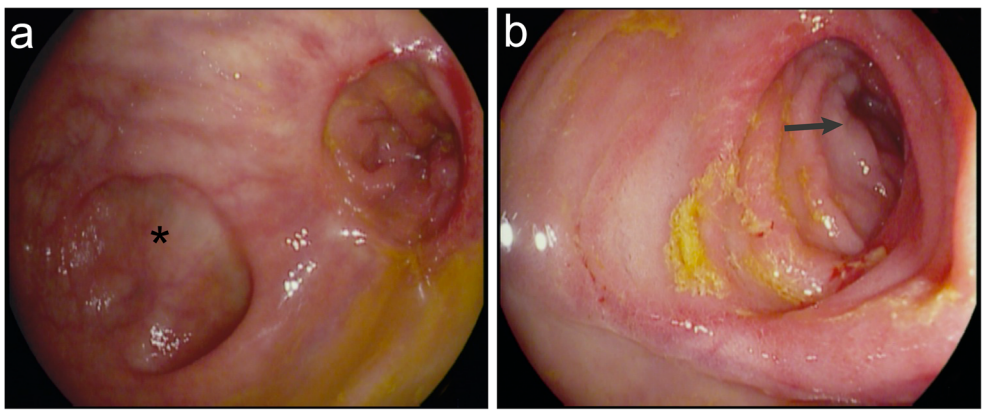

Fig. 2 Ileocolonoscopy (Video Colonoscope, Pentax EC-3870 LK) was performed for initial mucosal evaluation and sampling. The side-to-side ileoascendostomy with an inflammation-free short colonic blind sac (asterisk) and an inflamed neoterminal ileum is displayed (**a**). The neoterminal ileum could only be intubated for a short distance due to the massive stenotic inflammation (arrow) (**b**)

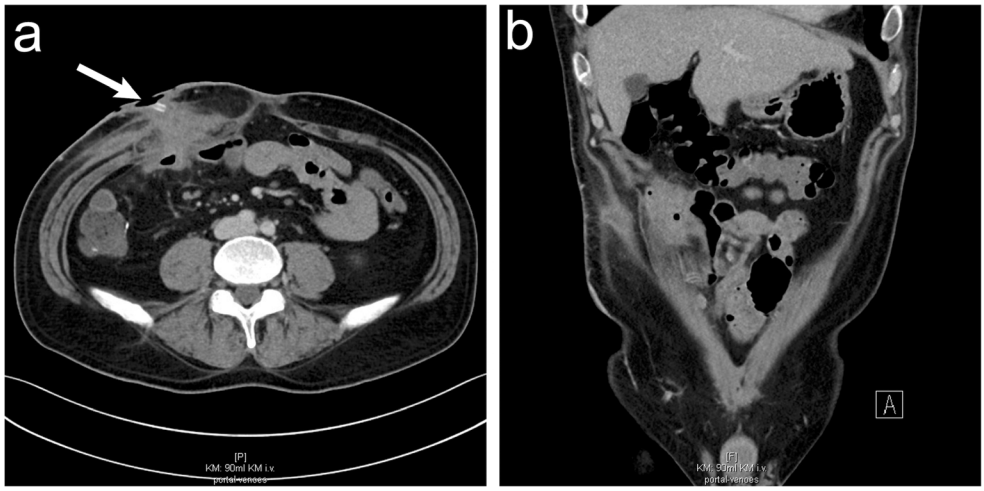

Fig. 3 Contrast-enhanced computed tomography in axial and coronal orientation 8 weeks after skin perforation and manifestation of an enterocutaneous fistula. The axial (**a**) as well as the coronal plane (**b**) shows a regression of the interenteric fluid. Compared to the initial CT imaging, fluid in the subcutaneous tissue increases and inclusion of gas is detectable (arrow). This corresponds to enterocutaneous fistulas, possibly sourced by the ileum. In the meantime, no disturbance of the intestinal passage is seen any more. Thereafter, the therapy with anti-TNF alpha was continued

Thereafter, the symptoms improved steadily, fistula output decreased, and CRP values reached a serum level of 3 mg/dl. Meanwhile, the indication for surgery was decided interdisciplinary, which was performed 6.5 weeks after re-administration of adalimumab. The last adalimumab dose was administered 2 weeks prior to surgery.

On the elected date, laparotomy was performed for adhesiolysis of two fistulating loops of the small bowel to the abdominal wall, resection of the former ileoascendostomy (50 cm of ileum and 5 cm of colon) and primary ileoascendostomy (side by side). Remaining length of jejunum and ileum was intraoperatively measured to be 250 cm. The resected specimen consisted of a 31.8-cm-long fistulating ileum (3.3 cm in diameter) and a 6.7-cm-long ascending colon (4.5 cm in diameter) and cutis-subcutis with a centrally located, transcutaneous fistula tract showing florid and chronic granulating as well as fibrosing inflammation. The histopathological examination revealed the oral and aboral resection margin as inflammation-free except for a purulent peritonitis (oral). The finding was consistent with the clinically known Crohn's disease.

No major postoperative complications occurred. A local surgical site infection at the former fistula opening site was observed without necessity for further intervention. The patient was discharged from the hospital by personal request on the third postoperative day with metronidazole and adalimumab administration every 4 weeks as an individual decision.

At the follow-up 10 weeks postoperatively, the patient reported no symptoms and best well-being. He stopped smoking. Anti-TNF alpha therapy was continued at 4-week intervals.

Discussion

Treatment of enterocutaneous fistulas in Crohn's disease still represents a major challenge to gastroenterologists and surgeons. The therapy highly depends on the fistula's characteristics. In selected low-to-moderate output fistulas, a conservative treatment can be the first therapeutic option due to the chance of spontaneous closure even in Crohn's disease [8]. A conservative strategy includes sepsis control, access to long-term enteral and parenteral nutrition support, output control, wound care, and skin protection [9]. Nonetheless, the large majority of patients are at high risk for surgery [10]. Extended or repeated small bowel resections may result in a short bowel, which may even require intestinal transplantation [4, 5].

Therefore, strategies for limiting the extent of resection are urgently necessary. Studies already showed anti-inflammatory therapy with tumor necrosis factor alpha inhibitors had positive effects on fistulizing Crohn's disease [6, 7]. Even though anti-TNF alpha treatment is associated with potential infectious complications, *Ibanez-Samaniego* et al. were able to show favorable results for the use of anti-TNF agents in patients with Crohn's disease–associated enteric abscesses and enterocutaneous fistulas [11]. However, whether a preoperative anti-TNF alpha treatment is associated with a higher rate of postoperative complications or not has not been conclusively clarified. Current studies on a French cohort with ileocolonic resection due to Crohn's disease stated anti-TNF therapy within 3 months prior to surgery as a risk factor for postoperative morbidity [12]. In contrary, the REMIND Group did not find anti-TNF therapy to be associated with an elevated risk of postoperative complications [13].

The case presented shows that a multimodal treatment strategy with anti-TNF alpha (adalimumab) administered preoperatively as anti-inflammatory therapy and surgery performed consecutively could be a future possibility to limit the extent of bowel resection in highly selected cases. As the course showed, it seems to be important that an abscess should be excluded, removed, or closely monitored (as in our case) prior to anti-TNF alpha therapy. And even though no major complications occurred in the presented case, the increased risk for opportunistic infections and aggravation of preexistent infections under anti-TNF alpha therapy associated with impaired immune response in sepsis demonstrate the importance of an intensified patient monitoring. At present, scarce evidence for effect of preoperative anti-TNF alpha treatment on internal and blind fistulas is at hand. Based on a critical review concerning an intentional use of preoperative anti-TNF alpha treatment in abdominal Crohn's disease, *Kotze* et al. stated that indication for preoperative treatment could be considered in patients with high inflammatory burden, clear indication for surgery, without abscesses but with internal fistulas present. As intended in our case, the authors conclude that a reduction of specimen size as well as a less complicated procedure could result [14].

We therefore advise that a highly individual therapy as described in this case should be restricted to high-volume centers with particular experience in inflammatory bowel disease management as well as anti-TNF alpha therapy monitoring. Interdisciplinary gastroenterological-surgical therapy planning is of paramount importance in these lines [15].

Compliance with ethical standards

Conflict of interest Thomas Klag received speaker's honorary from Abbvie. Jan Wehkamp received speaker's honorary from Abbvie, MSD, Biogen, and Hexal. All remaining authors declare that they have no conflict of interest.

Research involving human participants and/or animals This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent The patient's written consent was obtained for publication of this case report.

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