Free Perforation in Crohn's Disease

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Key words: Crohn's disease, free perforation, peritonitis

Abstract

Background: Free bowel perforation is one of the indications for emergency surgery in Crohn's disease. It is generally accepted that 1–3% of patients with Crohn's disease will present with a free perforation initially or eventually in their disease course.

Objectives: To evaluate the incidence and treatment results of free perforation in patients with Crohn's disease and, based on our experience, to suggest recommendations.

Methods: Between 1987 and 1996, 160 patients with Crohn's disease were treated in our department and were followed for a mean period of 5 years.

Results: Of the 83 patients (52%) requiring surgical intervention, 13 (15.6%) were operated due to free perforation. The mean age of the perforated CD was 33 $\pm$ 12 years and the mean duration of symptoms prior to surgery was 6 years. The location of the free perforation was the terminal ileum in 10 patients, the mid-ileum in 2 patients, and the left colon in 1 patient. Surgical treatment included 10 ileocecectomies, 2 segmental resections of small bowel, and resection of left colon with transverse colostomy and mucus fistula in one patient. There was no operative mortality. Postoperative hospital stay was 21 $\pm$ 12 days (range 8–55 days). All patients were followed for 10–120 months (mean 58.0 $\pm$ 36.7). Six patients (42%) required a second operation during the follow-up period.

Conclusion: The incidence of free perforation in Crohn's disease in our experience was 15.6%. We raise the question whether surgery should be offered earlier to Crohn's disease patients in order to lower the incidence of free perforation.

IMAJ 2003;5:175–177

Crohn's disease is characterized by chronic transmural inflammation of the bowel. The accompanying fibrous reaction and adherence to adjacent organs appears to limit the complication of free perforation. It is generally accepted that 1–3% of patients with CD will present with a free perforation – initially or eventually in their disease course [1–6]. Some reports include secondary abscess perforation in their statistics, but this event is not a true free perforation. European and North American Jews are considered to be from three to five times more susceptible to Crohn's disease than non-Jews. Among Israeli Jews we have seen the prevalence of CD rise sharply from 7.08/10^5 in 1970 to 19.47/ 10^5 in 1980 and to 50.6/10^5 in 1992 [7–11].

Free bowel perforation is one of the indications for emergency surgery in Crohn's disease. Massive hemorrhage is rare [1], abscess formation can be treated non-surgically and is usually not an emergency procedure, bowel obstruction tends to resolve with appropriate medical treatment, and fistula tracts do not require emergency treatment.

Our clinical impression is that free perforation is not as rare as the published estimates of 1–3% and it now presents far more frequently than it did 20 years ago. We reviewed our data of 160 patients hospitalized during the last 10 years.

Materials and Methods

The records of 160 patients with Crohn's disease who were admitted to our department between 1987 and 1996 were obtained from the files of the hospital and were reviewed retrospectively. Free perforation due to CD was defined as a spontaneous perforation of the small or large bowel with flow of intestinal contents into the general peritoneal cavity. In this report, we excluded rupture of abscess that was defined as spontaneous rupture of an intraperitoneal abscess into the greater peritoneal cavity.

Of the 160 patients, 77 did not undergo any surgical procedure in our department; the remaining 83 patients required at least one operative procedure, and 13 them had free perforation of small or large bowel.

Results

Thirteen patients (6 men and 7 women) required surgical intervention for free perforation of Crohn's disease, and the incidence among all CD patients was 8.125 or 15.6% among the operated patients. Table 1 summarizes the patients' age, location, number of hospitalizations, and duration of disease.

In three patients the free perforation was the first sign of the disease and the diagnosis was made during operation and confirmed histologically. In the 10 patients who were diagnosed previously with CD, perforation occurred within 2 years of onset in 4 patients, within 5–10 years of onset in 4 patients, and within 15–20 years of onset in 2 patients. All patients with known CD had at least one visit to their gastroenterologist in the 4 week period prior to the perforation, and nine of them (90%) were treated with steroids.

All patients had generalized peritonitis on admission. Most perforations were in the terminal ileum (10/13 patients), two patients had a perforation of the mid-ileum, and one patient had perforation of the left colon. In all patients with terminal ileum or mid-ileum perforations, resections and primary anastomosis were performed; and in the patient with colon perforation, resection of the left colon with transverse colostomy and mucus fistula was done. There was no operative mortality. The histopathologic examination of all the resected specimens confirmed that the

CD = Crohn's disease

Table 1. Study population: free perforation of Crohn's disease

Age at hospitalization	33 ± 12 yrs (range 18–56)
Age at diagnosis (yrs)	
Under 20	6
20–50	7
⩾ 50	1
Duration of symptoms until surgery	6.2 ± 6 yrs (range 0–20)
No. of hospitalizations until surgery	3.3 ± 2
Age at first operation	
Under 20	3
20–50	9
> 50	2
Bowel involvement	
Small bowel only	8
Small and Large bowel	6
Site of free perforation	
Small bowel	12
Large bowel	1
Steroid therapy	
Yes	9
No	5

Table 2. Postoperative complications of free perforation of Crohn's disease

Complication	Patient
Anastomotic leak	2
Enterocutaneous fistula	1
Wound dehiscence	1
Wound infection	5
Prolonged ileus	2

perforation occurred in all cases within the diseased bowel segment.

Eight patients (61.5%) developed at least one postoperative complication [Table 2]. One patient had an enterocutaneous fistula that closed spontaneously. Two patients developed signs of generalized peritonitis between the 7th and 10th postoperative days. On exploration, partial disruption of the anastomosis with anastomotic leak was detected, and ileostomy and mucus fistula were performed. Postoperative hospital stay was 21 ± 12 days (range 8–55). All patients were followed for 10–120 months (mean 58.0 ± 36.7).

All patients with free perforation developed a recurrent disease diagnosed by recurrent symptoms and confirmed by small bowel passage, computed tomography, or endoscopies, while seven of them had mild symptoms that were managed conservatively. Six patients (46.1%) developed recurrent symptoms requiring re-operation in an interval of 5.1 ± 3.9 years (range 1–10 years). Recurrent operations were due to small bowel stricture (three patients), enterovesical fistula (one patient), and recurrent abdominal abscess (two patients).

Discussion

Crohn stated in a 1957 paper: "Free perforation of ileitis into the peritoneal cavity never occurs or at least I have not seen it" [12]. In 1965 however, he reported seven cases of free perforation [13]. In 1982 a case report from our department of surgery on one patient merited publication [14]. Holzheimer et al. [15] reports an incidence of 13% in 1995. In our current study, the incidence was 8.75% of all hospitalized CD patients who were treated in our surgical department and 15.6% of our operated patients. In a recent study, Nissan et al. [16], who advocated a more liberal approach to surgical treatment, found free perforation in only 3.8% of their study group.

During the study period, and in collaboration with the department of gastroenterology, a conservative non-surgical approach to Crohn's disease was adopted. Only patients with acute abdominal signs, multiple and frequent hospitalizations, and complicated fistulas underwent surgery. Disease severity as judged by quality of life, radiologic or endoscopic appearance, or the need for intensive medical treatment was usually not an indication for surgery. This resulted in a 6.2 year delay from diagnosis until surgery, in contrast to 3.3 years in the study by Greenstein and co-workers [6]. It is possible that a serious complication such as free perforation resulted from our conservative medical approach. Free perforation as a first sign of disease was seen in 23% of our patients with perforation, not far from the 30% published in a review by Greenstein et al. [2]. Steroids treatment probably contributed to the high rate of perforations in our series as a consequence of prolonged medical treatment.

Perforative Crohn's disease is accompanied by more post-operative complications, anastomotic healing is poor, and recurrent disease is more frequent in the short term (up to 5 years) follow-up than in obstructive Crohn's disease.

Can we define the nature of the disease in a given patient? Judging from the nature of presentation and the more fulminant course of disease, the answer is possibly yes. Should we be more liberal in our surgical treatment of all Crohn's disease patients? Nissan et al. [16] advocate this approach convincingly. Based on our results, we recommend considering earlier surgery in Crohn's disease patients depending on the clinical presentation, intensity and duration of medical treatment, and life quality impairment.

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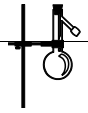

The role of the vascular endothelial cytoskeleton in NFkB and NFAT activation by physiologic and pathologic fluid shear stresses

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Vascular endothelium, a single cell layer lining the cardiovascular system, is constantly exposed to biomechanical forces derived by the pulsatile flow of the blood. This single cell layer, which serves as a selective barrier between the blood and other tissues and organs, is a dynamic surface undergoing structural and phenotypic changes in response to both humoral and cellular stimuli, changes that are relevant to the normal physiology and disease situations in the vessel wall. We have defined a promoter element – shear stress response element (SSRE) in the promoter of PDGF-B chain gene that is necessary and sufficient for the induction of this gene by shear stress. SSRE is present in the promoters of many other shear stress responsive genes and binds through a non-consensus site to both NFkB p65/p50 and NFAT (which are also activated by shear stress). The scope of the present proposal was to determine shear-stress-mediated signaling events, leading to the regulation of endothelial genes by both physiologic and pathologic shear stresses, using NFkB unique activation steps as a read-out. We hypothesize that shear stress, through membranal receptors, and cytoskeletal components lead to inefficient activation of NFkB resulting in the induction of SSRE but not NFkB-containing genes. In the course of our studies we have shown that NFkB activation steps differ under cytokine or shear stress stimulation. The late increase in binding of NFkB p65 to the DNA was attributed to tyrosine, rather than serine phosphorylation of the inhibitor IkB. P65 phosphorylation, which plays an important role in its binding to the DNA and to other transcription factors, occurred minutes after stimulating EC with cytokines and hours after exposing them to shear stress, also contributing to the failure of NFkB to bind to the DNA following shear stress exposure. Our results pointed for the first time at the cell-cell junction (adherens junction) and the VEGF receptor, VEGFR2 (Flk1), as a potential shear stress transducer. Endothelial cells lacking the gene for VE-cadherin, which forms the adherens junction, failed to phosphorylate Akt and P38 in response to shear stress, and to induce the transcription of a luciferase gene regulated by SSRE. Cells re-transfected with the gene mimicked the behavior of the wild-type endothelial cells. It is hoped that data accumulated in the current proposal will provide new insights regarding the signaling mechanism through which endothelial cells respond to hemodynamic forces and translate their response into genetic events. Ultimately, this knowledge may help in designing new diagnostic and therapeutic strategies for cardiovascular diseases.

Supported by the Office of the Chief Scientist, Ministry of Health, Jerusalem