



Free intestinal perforation in children with Crohn's disease

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ABSTRACT

Background: Free intestinal perforation in children with Crohn's disease (CD) is a rare, but serious complication that requires urgent surgical management. The incidence, contributing risk factors, diagnostic workup, and management strategies for these complex pediatric patients are not well established.

Methods: We present a recent case of free intestinal perforation in a patient with CD. In addition, a systematic review of the literature was conducted by searching the PubMed, Embase, Ovid, Scopus and Cochrane databases. Two authors independently extracted data, reviewed the abstracts, and assessed them for inclusion in the review.

Results: The literature review identified 21 pediatric patients documented in 14 publications; including our case, there are a total of 22 pediatric patients reported. The majority of patients presented with features of peritonitis. Perforation occurred early in the disease course (median 6.5 months), and was most commonly a single perforation in the ileum with active Crohn's disease (82%). Colonic perforation occurred in 18% of patients. All patients underwent urgent surgical management. Surgical approaches included resection of the diseased bowel segment with proximal diversion in eleven patients (50%), resection with primary anastomosis in 9 (41%) or direct suture repair in two (9%). Both patients who underwent simple primary repair developed post-operative complications.

Conclusions: Free intestinal perforation may occur at any age and stage of Crohn's disease. Three-dimensional imaging may be required to confirm the diagnosis. The management of free intestinal perforation in CD is surgical. This should involve resection of the involved segment with proximal diversion or resection with primary anastomosis in selected cases. Primary suture closure of the perforation is discouraged.

1. Introduction

The natural course and presentation of Crohn's disease (CD) in children are variable and often unpredictable. This includes the disease activity, risk of recurrence, frequency and severity of complications, need for surgery, severity of growth impairment, and quality of life. Some children require early surgical intervention to manage complications or to alleviate symptoms of the disease, while others remain in remission for years with medical therapy only [1–3].

Although medical management of Crohn's disease has evolved, there are still many clinical situations that warrant consideration of elective, urgent or emergent surgical management. The majority of surgical indications are non-emergent. The most common indication for surgery in children with Crohn's remains failure or intolerance of medical management (50%), intestinal obstruction, abscesses, fistulas and other non-emergent indications [1,4–6]. The timing of surgery can be

carefully planned by interdisciplinary teams, including the surgeon, radiologist and gastroenterologist, to achieve control of the inflammatory process while minimizing the adverse effects from medications. Surgical emergencies in children with Crohn's disease are rare, but may carry substantial morbidity. Typical indications for urgent surgery include free intestinal perforation with diffuse peritonitis, acute abscesses with sepsis, and toxic colitis. The primary goal of emergency surgery in these circumstances is to control sepsis or provide bowel decompression [4,7].

Free intestinal perforation with diffuse peritonitis and free air on imaging is a very rare but potentially life-threatening complication of Crohn's disease that necessitates urgent surgical management [7]. The incidence of Crohn's-related free perforation in adults ranges between 1 and 2% [7,8]. Due to the rarity of this presentation in children with CD, the pediatric literature on this subject is scarce and the incidence is unknown. Although free bowel perforation is an exceedingly rare in

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children with CD, pediatric surgeons should be familiar with this serious and potentially life threatening complication. The clinician's high index of suspicion for complicated CD, and a low threshold for appropriate imaging are of great importance to facilitate prompt diagnosis and intervention for free bowel perforation.

This case report and systematic literature review are intended to assist pediatric surgeons in the early recognition of symptoms of free perforation in children, in addition to assessment of potential risks leading to the occurrence, and to define the most appropriate imaging choices and surgical management options.

2. Material and methods

Our case report was approved by the institutional ethics board TRAQ#6022476. A systematic search of the literature was performed to identify relevant articles documenting cases of free intestinal perforation in children with Crohn's disease. The PubMed, Ovid, Scopus and Cochrane databases were searched using the combination of the following search terms: free bowel perforation in children with Crohn's disease, free intestinal perforation in Crohn's disease, colonic free perforation in Crohn's disease, pneumoperitoneum in Crohn's disease, free air and peritonitis in Crohn's disease. The search was limited to patients up to 18 years of age. Two authors (MK and MP) independently extracted data, reviewed the abstracts, and assessed them for inclusion in the review.

The fourteen articles matching the search terms were identified. Most of the retrieved studies were single case reports describing pediatric CD patients with free bowel perforation. The extracted data consisted of: author names, patient age and gender, clinical presentation, preoperative duration of disease, extent of the disease, site of perforation, number of perforations, presence of bowel stenosis, preoperative use of corticosteroids, biologics or immunomodulators, previous surgeries or percutaneous abscess drainage, imaging used to confirm free abdominal air, and medical/surgical management. Extracted data are presented in Table 1.

3. Case report

A previously healthy 14-year-old boy was referred to a pediatric gastroenterologist with an approximately six-week history of recurrent abdominal pain, diarrhea, loss of appetite, fatigue, and weight loss. He took no medications and his social history was non-contributory. He had no family history of inflammatory bowel disease. Physical examination was normal aside from a BMI of 14.9 (less than 1st %ile for age). Blood work revealed a microcytic anemia (HGB 97 g/L), low albumin (23 g/L), normal WBC, elevated CRP (82.8 mg/L) and increased ESR (54 mm/h). He underwent an esophagogastroduodenoscopy that was normal. Colonoscopy and ileoscopy revealed a stenotic ileocecal valve and an approximately 10 cm long segment of terminal ileum with severe ileitis. Histopathology of the biopsy specimens from the terminal ileum and cecum confirmed the diagnosis of Crohn's disease. Following this diagnostic confirmation, he was started on oral Prednisone 40 mg BID daily.

Four days after initiation of therapy he presented to the emergency department with abdominal pain and diarrhea. He was afebrile and his vital signs were otherwise normal. The patient's abdomen was soft, mildly tender to palpation in the right lower quadrant, with no guarding and no rebound tenderness. Blood work revealed a mild increase in his WBC to 15.4 and ESR 51 mm/h. An ultrasound of the abdomen revealed extensive circumferential thickening of the distal ileum and a 3 cm by 3 cm adjacent complex collection. The patient was admitted to the hospital and started on broad spectrum I.V. antibiotics. His oral steroids were continued. The next morning his pain resolved and he was tolerating oral intake. Routine follow-up abdominal ultrasound four days later showed free fluid in the lower quadrants of the abdomen. He remained asymptomatic with a normal abdominal exam.



Fig. 1. Free intraperitoneal air seen on abdominal CT.

However, over the next 24 h, he refused to eat, was severely fatigued and slept most of the day. That evening, he reported sudden onset of severe abdominal pain. He was tachycardic, with diffuse abdominal tenderness, but no peritoneal signs. The patient's WBC rose to 35 with marked shift to the left, and CRP increased to 125 mg/L. An urgent abdominal CT was obtained, and revealed extensive inflammatory bowel changes, free fluid and substantial intra-abdominal free air (Figs. 1–3).

The patient was taken for an emergent exploratory laparotomy. At laparotomy, a large amount of turbid yellow fluid was found throughout the peritoneal cavity. Thorough exploration demonstrated a thickened terminal ileum covered with the omentum, and a single perforation on the antimesenteric side of the diseased terminal ileum approximately 9–10 cm proximal to the ileocecal valve. There was no evidence of bowel stricture. Ileocecectomy was performed, involving resection of approximately 15 cm of the terminal ileum, followed by abdominal irrigation and end ileostomy with colonic mucous fistula. Diversion was necessitated given the patient's clinical intraoperative instability requiring vasopressor support. Corticosteroid therapy was discontinued postoperatively. Histopathology of the resected specimen demonstrated transmural inflammation with extensive mucosal ulceration, with one fistulous tract leading to the area of perforation. Pathology review was not consistent with iatrogenic perforation associated with the preceding ileoscopy.

The patient made a gradual but satisfactory recovery. Stoma closure was performed 6 months postoperatively. The patient is well at two-year follow-up, in remission and off medications.



Fig. 2. Free intraperitoneal air seen on abdominal CT.



Fig. 3. Axial CT slice demonstrates wall thickening of multiple bowel loops as depicted with three bold arrows. Small gas collections are evident within adjacent free fluid collection as well as within further fluid collections within left lower quadrant (thin arrow).

4. Results

Systematic review of the literature on free bowel perforation in children with Crohn's disease (1967–2017) identified 22 patients including our case report. The majority of publications are single case reports (55%). The findings are summarized in Table 1.

The review identified 13 males (59%) and 9 females (41%). Patients' age ranged from 9 to 18 years, with a mean age of 15 years (SD 2.7). The disease duration prior to presentation of free perforation ranged from 1 day to 4 years with a median length of 6.5 months.

Details on clinical symptoms of free intestinal perforation were documented in only 11 patients (50%). Symptoms are nonspecific and include abdominal pain, nausea, vomiting, diarrhea, fatigue, tachycardia and fever. Peritonitis was reported in 64% of these children.

The most common site of perforation was the terminal ileum in 18 patients (82%), with only 4 colonic perforations (18%). All perforations were single and all were found within a diseased bowel segment. Toxic dilation of the colon was found in two patients (9%). One patient (4%) had an iatrogenic colonic perforation during diagnostic biopsy (4%), and one developed a perforation after mild blunt abdominal trauma (4%). Free bowel perforation was the presenting clinical manifestation of previously undiagnosed Crohn's disease in four patients (18%). Twelve patients (55%) were on steroid treatment prior to the free perforation, and one (4%) was on infliximab. Coexisting risk factors prior to perforation were identified in 32% of patients (obstruction/stricturing disease, use of steroids, biologics or toxic colitis). Evaluation of disease extent showed that 59% of children had isolated ileal disease, and 41% had combine ileal and colonic disease.

In the majority of cases findings on imaging were not documented (81%). Pneumoperitoneum was found on plain abdominal radiographs in one patient (4%). CT abdomen was done in 14% of patients and was diagnostic for free air. Abdominal ultrasound was done in one patient and was not diagnostic for free air.

All patients underwent urgent surgical management. Primary resection with proximal ostomy was the most frequent procedure (50%). Resection of the diseased bowel segment with primary anastomosis was done in 9 patients (41%), and direct suture repair of the perforation was performed in two patients (9%). There were no reported complications following resection with proximal diversion. Following resection and primary bowel anastomosis one patient developed an abdominal collection that resolved after percutaneous drainage. Both patients who underwent direct suture repair of the perforation developed complications (1 fistula and 1 intra-abdominal collection). A 96% of cases were done as open procedures. There have been no reported mortalities. Recurrent free perforation was reported in one patient (4%).

5. Discussion

Free intestinal perforation in CD is characterized by free abdominal air on imaging with or without peritonitis, and a focal intestinal defect noted intraoperatively. Since the first description of Crohn's disease in 1932, about 100 cases of free intestinal perforation have been reported in adults [8,16,22]. The incidence in Western countries ranges between 1 and 2% [7,8], while in Asia it has been reported to be as high as 6.5–9.4% [21,23]. Little is known about Crohn's-related pediatric free intestinal perforations due the rarity of it's occurrence.

The paucity of reported free intestinal perforations can be explained by the chronic nature of the transmural inflammatory process in Crohn's disease. The resulting bowel wall exudation favors the development of fibrous adhesions between affected bowel loops and adjacent abdominal structures. This process usually leads to walled-off, rather than free perforation into the peritoneal cavity. In the setting of acute or fulminant Crohn's inflammation, rapidly formed tracks between bowel mucosa and serosa may fail to contain full-thickness ulceration due to the lack of the adhesions, thus leading to free intestinal perforation and generalized peritonitis [2,7,11,24–26].

In adults, free intestinal perforation tends to occur in patients in their third to fourth decade after a mean disease duration of 6 years [17,23,27]. In children the median age of perforation was 15 years, and disease course was much shorter, with a median duration of 6.5 months. Free perforation constituted the first presentation of Crohn's disease in 18% of children.

Several risk factors are recognized to precipitate free perforation in adults including distal intestinal obstruction, use of corticosteroids and biologics, ischemia, toxic dilatation of colon, blunt abdominal trauma and malnutrition [20,22,25,28]. Increased intraluminal pressure, due to distal obstruction or stricturing disease, is an established risk factor documented in 34.1% of adults with free perforation [22]. In our series of pediatric patients, a distal obstruction was identified in 23%.

The relationship between preoperative use of corticosteroids and free perforation is controversial. One hypothesis is that corticosteroids may promote the development of free peritonitis by decreasing the inflammatory response and impairing the ability of a resulting phlegmon to seal off imminent perforation [24]. However, the majority of early studies were not able to confirm this theory [16,17,22]. Twelve of the included 22 pediatric patients in our series were on steroids (55%) but it is difficult to establish causation versus association with active disease. Only one included patient was on infliximab at time of perforation.

Blunt and iatrogenic trauma have both been associated with free perforation in Crohn's disease. In addition, patients with active inflammation and on steroids are at higher risk for iatrogenic perforation during endoscopic evaluation compared to the general population [29]. One included pediatric patient suffered mild blunt abdominal trauma resulting in intestinal free perforation at a site of active Crohn's [20]; blunt force that may not otherwise injure healthy pliable bowel can cause more significant damage when the bowel is inflamed and thickened.

In adults with Crohn's disease, although perforation may occur in any involved bowel segment, terminal ileum is the most common site of free perforation (90%), while colonic perforations are rare [2,7,8,11,17,23,25,27]. In children, the ileum was also found to be the most common site of free perforation (82%), whereas the incidence of colonic perforation (18%) was higher than in adults. All perforations occurred in areas of active Crohn's disease. Toxic colitis was identified in 9% of children, while colonic perforation occurred in 18%. This finding in pediatric patients is consistent with Roy's observation in adults, that although colonic perforation is mostly found in association with toxic colitis, it can also occur in the absence of toxic dilatation [25]. One of pediatric patients with toxic colitis developed ileal perforation [16], identifying consideration for this possible presentation.

The number of free perforations in adults ranged from 1 to 5 [24].

Table 1
Free perforation in patients with Crohn's disease (1967–2017).

Publication	Age/ gender	Disease duration/Extent/Symptoms of perforation	Pre-op medications	Prior surgery	Imaging	Site of perforation	Surgical procedure	Complications & Follow up
Tolins [9] et al., 1967	15, F	Not documented	Steroids	Resection of anal ulcer	Not documented	Descending colon	Ostomy.	Ileitis of stoma.
Graham [10] et al., 1969	17, M	3-day history of increasing lower abdominal pain.	None	None	Not documented	Terminal ileum	No other data documented. Ileocectomy with primary anastomosis.	Follow-up not documented. None. 2-month follow-up
Nasr [11], 1969	11, F	Peritonitis. 2-year history of CD involving distal ileum, sigmoid colon and rectum. Recurrent episodes of partial obstruction with sudden onset of severe abdominal pain.	Steroids	None	Not documented	Terminal ileum	Ileocectomy with ileo-colostomy. Stoma closure 2 months later	None. 2-year follow-up
Menguy [12], 1972	11, F	3-month history of CD. Small bowel obstruction with sudden onset of abdominal pain and peritonitis.	Steroids	None	Not documented	Terminal ileum	Ileocectomy, double barrel ileostomy. Stoma closure 2 months later	None. 2-year follow-up
18, M		2-month history of CD. Sudden onset lower abdominal pain and peritonitis.	Steroids	None	Not documented	Terminal ileum	Ileocectomy with ileocolostomy. Stoma closure 5 weeks later.	None. Follow-up not documented
Steinberg [13] et al., 1973	17, M	3-month history. No other information documented.	None	None	Not documented	Ileum	Primary closure of perforation.	Developed fistula that has resolved. Further follow-up not documented.
Fischer [14] et al., 1976	17, M	11-month history of CD. Sudden onset of severe abdominal pain and peritonitis.	Steroids	Ileocectomy and anastomosis	Pneumoperitoneum on x-ray	Colon	Resection of the involved segment and primary ileocolonic anastomosis.	None. 11-month follow-up, active CD despite intensive therapy.
Abascal [15], 1982	17, M	1-month history of intermittent fever, diarrhea, and anemia. Onset of severe abdominal pain in right iliac fossa, peritonitis.	None	None	Not documented	Terminal ileum	Pre-op presumed appendicitis. Ileocectomy with end to end anastomosis. Drainage.	None. 1-year follow-up
Katz [16], 1986	16, M	2-year history, ileal and colonic involvement with prior toxic megacolon.	Steroids	None	Not documented	Ileum	Resection and diverting ostomy	Re-perforation 6 years later
14, M		7-month history. Ileal involvement.	Steroids	None	Not documented	Ileum	Resection and diverting ostomy	None
13, F		4 year history.	None	None	Not documented	Ileum	Resection and diverting ostomy	Follow-up not documented.
15, F		Ileal and colonic involvement	Steroids	None	Not documented	Ileum	Resection and drainage	None
18, M		4-month history, ileal involvement.	Steroids	None	Not documented	Ileum	Resection and diverting ostomy	Follow-up not documented.
17, F		2 year history.	Steroids	None	Not documented	Ileum	Resection and diverting ostomy	None
18, M		Ileal involvement.	Steroids	None	Not documented	Ileum	Resection and diverting ostomy	Follow-up not documented.
17, F		One-month history. Ileal involvement.	Steroids	None	Not documented	Ileum	Resection and diverting ostomy.	None
Freeman [8], 2002	18, M	3 year history of CD. Ileal involvement.	None	None	Not documented	Ileum	Ileocectomy and anastomosis.	Follow-up not documented.
17, M		1-year history of CD. Ileal and colonic involvement.	None	None	Not documented	Ileum	Ileo-colectomy and anastomosis.	15-year follow-up
Ikeuchi [17], 2002	16, M	1-year history of CD. Ileal and colonic involvement.	None	None	Not documented	Ileum	Ileo-colectomy and anastomosis.	None. 24-year follow-up
Gasparrato [18], 2012	9, F	6-month history of abdominal pain, fatigue and weight loss. Diagnostic endoscopy complicated by iatrogenic colonic perforation.	None	None	Not documented.	Ileum	Resection and anastomosis.	None. Follow-up not documented
Tra [19] et al., 2013	10, F	2.5-year history of ileal and stricturing anorectal disease. Sudden onset of fever/tachycardia. Toxic colitis and peritonitis.	Steroids	None	Not documented.	Colon, splenic flexure	Laparoscopic suture of the colonic perforation.	Perisplenic collection that resolved on nonsurgical management. Well on follow up.
				X-ray: colonic dilatation, no free air. CT abdomen: copious free air		Transverse colon	Total abdominal colectomy and end ileostomy	Prolonged postoperative recovery. No complications. Follow-up not documented.

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Table 1 (continued)

Publication	Age/ gender	Disease duration/Extent/Symptoms of perforation	Pre-op medications	Prior surgery	Imaging	Site of perforation	Surgical procedure	Complications & Follow up
Onwubiko [20], 2015	13, F	Peritonitis following minor blunt abdominal injury. Past medical history of anemia.	None	None	CT abdomen: thickened ileum and free air.	Terminal ileum	Ileocectomy with primary anastomosis	Abdominal collection that resolved with percutaneous drainage. Follow-up not documented.
Kim [21] et al., 2017	15,M	8-month history of stricturing CD. Ileal and colonic involvement.	Infliximab	None	Not documented.	Ileum	Small bowel resection and anastomosis.	None. Follow-up not documented.
Kolar et al., 2017 (Current report)	14,M	1.5-month history of CD. Sudden onset of abdominal pain.	Steroids	None	US abdomen: no free air. CT abdomen: free air.	Ileum	Ileocectomy with ileo colostomy. Stoma closure 6 months later.	None. None. 2-year follow-up.

The majority of perforations in adult patients are single 88.6% [21], while all reported pediatric cases have been single perforation.

Histopathological review has identified both evidence of perforation at the site of chronic disease activity and acute fulminant disease [14]. This may contribute to the variability of clinical presentations.

Free bowel perforation in adults is usually marked by sudden onset of symptoms including severe abdominal pain, nausea, vomiting, abdominal distention, fever and signs of diffuse peritonitis. In our series, symptoms and signs of free perforation in children were similar to those in adults. Administration of large doses of steroids may obscure the clinical picture and cause delay in diagnosis [22,27,30,31]. High index of suspicion and low threshold for appropriate imaging play a significant role in timely diagnosis [32].

The importance of serial clinical examination and appropriate use of imaging were important in our case as his initial presentation initially suggested a much more benign course before the rapid development of peritonitis and sepsis. The main initial complaint was the sudden onset of severe fatigue. Data on whether fatigue severity is proportional to disease activity and severity is sparse and conflicting [33,34]. Given the ability of steroids to mask clinical exam findings, early imaging in patients who develop excessive fatigue should be considered.

The hallmark of free bowel perforation is the presence of free air in the abdominal cavity. Plain abdominal radiography is sensitive in only 50–75% of cases [35,36]. Although ultrasound may aid in diagnosis in pediatric patients and its utility in pediatric patients has been espoused [37], in our patient was not diagnostic. The lack of free air on ultrasound may have been due to the fact that bowel hadn't perforated yet, or because amount of free air was still small. CT scan may be accurate in identifying the location of small bowel perforation in 80% of cases [38].

The management of free intestinal perforation is surgical, following adequate resuscitation and administration of antibiotics. The necessity for pre-operative stress-dose steroids is controversial [7,39]. Resection of the affected bowel with diversion is typically required with primary anastomosis utilized in select cases [31]. Careful attention must be paid to small bowel length preservation, resecting only macroscopically affected bowel [4,6]. Early reports have advocated against simple suture repair of Crohn's-related small bowel perforation [22] and this was borne-out in the reported pediatric cohort, with both patients who underwent suture repair developing subsequent complications. In the presence of minimal contamination, hemodynamic stability, and adequate nutritional reserve, resection of the diseased segment with a primary intestinal anastomosis can be considered [17,22,40] otherwise proximal diversion should be utilized. There were no reported pediatric mortality, but surgical emergencies in adult Crohn's patients are associated with substantial morbidity and mortality [5,7]. Restoration of the intestinal continuity should be delayed until the patient's health and nutritional status have been optimized [41].

6. Conclusion

Free bowel perforation in children with Crohn's disease is exceedingly rare. It may occur as a first presentation of the disease or at any point during the course of the disease. Symptoms of free perforation are variable and may be nonspecific, particularly in patients on steroid therapy. Physicians and surgeons must maintain a high index of suspicion, especially in patents with risk factors. Three-dimensional imaging may be required to confirm the diagnosis.

Free bowel perforation in Crohn's disease is a surgical emergency and patients will require resuscitation and resection of the involved segment. Proximal diversion versus primary anastomosis should be determined on a case-by-case basis. Primary closure of perforation is discouraged.

Disclosure statement

The authors report no conflicts of interest.

References

- [1] Patel HI, Leichtner AM, Colodny AH, Schamberger RC. Surgery for Crohn's disease in infants and children. *J Ped Surg* 1997;32(7):1063–8.
- [2] Leal RF, Ward M, Ayrizono MLS, Paiva NM, Bellaguarda E, Rossi DBG, et al. Free peritoneal perforation in a patient with Crohn's disease – report of a case. *Int J Surg Case Rep* 2013;4(3):322–4.
- [3] Markowitz JF. The Natural history of Crohn's disease in children. In: Mamula P, Markowitz JE, Baldassano RN, editors. *Inflammatory bowel disease*. 2013. p. 65–71 chapter 7.
- [4] Von Allmen D. Surgical management of Crohn's disease in children Chapter 37. 406–415 In: Mamula P, Markowitz JE, Baldassano RN, editors. *Pediatric inflammatory bowel disease*New York: Springer; 2013.
- [5] McLeod RS. Surgery for inflammatory bowel diseases. *Dig Dis* 2003;21(2):168–79.
- [6] Lightner AL, Pemberton JH, Dozois EJ, Larson DW, Cima RR, Mathis KL, et al. The surgical management of inflammatory bowel disease. *Curr Probl Surg* 2017;54:172–250.
- [7] Berg DF, Bahadursingh AM, Kaminski DL, Longo WE. Acute surgical emergencies in inflammatory bowel disease. *Am J Surg* 2002;184(1):45–51.
- [8] Freeman HJ. Spontaneous free perforation of the small intestine in Crohn's disease. *Can J Gastroenterol* 2002;16(1):23–7.
- [9] Tolins PG, Cornell A. Free and contained perforations occurring in granulomatous ileo-colitis. *Recent Adv Gastroenterol* 1967;2:434–7.
- [10] Graham PA, Baugh J. Perforation and peritonitis in regional enteritis. *Am J Surg* 1968;115(6):856–60.
- [11] Nasr K, Morowitz DA, Anderson JGD, Kirsner JB. Free Perforation in regional enteritis. *Gut* 1969;10:206–8.
- [12] Menguy R. Surgical management of free perforation of the small intestine complicating regional enteritis. *Ann Surg* 1972;175:178–89.
- [13] Steinberg DM, Cooke TW, Alexander-Williams J. Free perforation in Crohn's disease. *Gut* 1973;14:187–90.
- [14] Fischer J, Mantz F, Calkins WG. Colonic perforation in Crohn's disease. *Gastroenterology* 1976;71:835–8.
- [15] Abascal J, Rojas-Diaz F, Jorge J, Sanchez-Vagazo I, Escartin P, Abreu L, et al. Free perforation of the small bowel in Crohn's disease. *World J Surg* 1982;6:216–20.
- [16] Katz S, Schulman N, Levin L. A report 33 cases and review of literature. *Am J Gastroenterol* 1986;81:38–43.
- [17] Ikeuchi H, Yamamura T. Free perforation in Crohn's disease: review of the Japanese literature. *J Gastroenterol* 2002;37:1020–7.
- [18] Gasparetto M, Giorgi B, Kleon W, Al Bunni F, Guariso G. Colonic perforation in a child with Crohn's disease: successful medical treatment rescues from colectomy Case report Hindawi Publishing Corporation; 2012:152414
- [19] Traa MT, Orkin BA, Flores A, Popowich DA. Toxic colitis in a 10 year old girl with Crohn's disease. *J PedSurg Case Rep* 2013;1:284–7.
- [20] Onwubiko C, Pennington EC, Mooney DP, Jennings. Intestinal perforation due to minor blunt abdominal trauma – a harbinger on underlying disease pathology. *J PedSurg Case Rep* 2015;3(1):35–7.
- [21] Kim JW, Lee H, Ye BD, Yang SK, Hwang SW, Park SH, et al. Incidence and risk factors for free bowel perforation in patients with Crohn's disease. *Dig Dis Sci* 2017;62:1607–14.
- [22] Greenstein AJ, Mann D, Sachar DB, Aufses AH. Free perforation in Crohn's disease: a survey of 99. *Am J Gastroenterol* 1985;80(9):682–9.
- [23] Werbin N, Haddad R, Greenberg R, Karin E, Skornick Y. Free perforation in Crohn's disease. *Isr Med Assoc J* 2003;5(3):175–7.
- [24] Orda R, Goldwasser B, Wiznitzer T. Free perforation of the colon in Crohn's disease: report of a case and review of the literature. *Am Soc Colon Rectal Surg* 1982;25(2):145–7.
- [25] Roy MK, Delica RJ, Carey PD. Crohn's disease presenting with acute colonic perforation. *Postgrad Med J* 1997;73(864):645–6.
- [26] Bellolio F, Cohen Z, Macrae HM, O'Connor B, Huang H, Victor JC, et al. Outcomes following surgery for perforating Crohn's disease. *Br J Surg* 2013;100(10):1344–8.
- [27] Chirantan B, Niladri S, Madhumita M, Sabyasachi S, Sibaji D, Jay K. Crohn's perforation: not so uncommon in the Indian population. *Indian J Surg* 2013;75(1):28–30.
- [28] Makowiec F, Jehle EC, Köveker G, Becker HD, Starlinger M. Intestinal and perforating complications in Crohn's disease.
- [29] Navaneethan U, Kochhar G, Phull H, Venkatesh PG, Remzi FH, Kiran RP, et al. Severe disease on endoscopy and steroid use increase risk for bowel perforation during colonoscopy in inflammatory bowel disease. *J Crohn's Colitis* 2012;6(4):470–5.
- [30] Leal RF, Ward M, Ayrizono MLS, Paiva NM, Bellaguarda E, Rossi DHG, et al. Free peritoneal perforation in a patient with Crohn's disease – report of a case. *Int J Surg Case Rep* 2013;4:322–4.
- [31] Patil SA, Cross RK. Medical versus surgical management of penetrating Crohn's disease: the current situation and future perspectives. *Expert Rev Gastroenterol Hepatol* 2017;11(9):843–8.
- [32] Faggian A, Berrito D, Iacobellis F, Alfonso R, Cappabianca S, Grassi R. Imaging patients with alimentary tract perforation: literature review. *Semin Ultrasound CT MRI* 2016;37:66–9.
- [33] vanLangenberg DR, Gibson PR. Systemic review: fatigue in inflammatory bowel disease. *Aliment Pharmacol Therapeut* 2010;32(2):131–43.
- [34] Bager P, Befrits R, Lindgrens S, Moum B, Hjortswang H, Hyollund NH, et al. Fatigue in out-patients with inflammatory bowel disease is common and multifactorial. *Aliment Pharmacol Ther* 2012;35(1):133–41.
- [35] Levin MS, Scheiner JD, Rubesin SE, Kaufer I, Herling H. Diagnosis of pneumoperitoneum on supine abdominal radiographs. *Am J Roentgenol* 1991;156:731–5.
- [36] Miller RE, Nelson SW. The roentgenologic demonstration of tiny amounts of free intraperitoneal gas: experimental and clinical studies. *Am J Roentgenol Radium Ther Nucl Med* 1971:574–85.
- [37] Nazerian P, Tazzetti C, Vanni S, Bartolucci M, Goltieri S, Trausi F, et al. Accuracy of abdominal ultrasound for the diagnosis of pneumoperitoneum in patients with acute abdominal pain: a pilot study. *Crit Ultrasound J* 2015;7:15.
- [38] Zissin R. Abdominal CT findings in small bowel perforation. *Br J Radiol* 2009;162–71.
- [39] Sharma A, Chinn BT. Preoperative optimization of Crohn's disease. *Clin Colon Rectal Surg* 2013;26(2):75–9.
- [40] Henry JN, Tesfaye B, Tammanna VS, Tyson C, Sanderson A. Jejunal perforation: an unusual presentation of Crohn's disease. *Int J Case Rep Images* 2013;7(7):349–52.
- [41] Komidis C, Anthimidis G. Emergency and elective surgery for small bowel Crohn's disease. *Tech Coloproctol* 2011;15(1):S1–4.