

Bowel Perforation Associated With Infliximab Use in a Pediatrics Patient

Aditya Joshi, MD; Raza Bajwa, MD; Nandita Bhattacharjee, MD; Rajasekhar Bodicharla, MD

ABSTRACT

Crohn's disease (CD) is an idiopathic inflammatory disease of the gastrointestinal tract and typically causes inflammation with granuloma formation. Biologic agents like infliximab (IFX) that target tumor necrosis factor alpha (TNF- α), have emerged as important medications for treating refractory CD. With increasing use, there also are reports of rare but potentially fatal complications associated with exposure to TNF- α , such as bowel perforation. We present a case report of spontaneous bowel perforation in a child with Crohn's while on IFX therapy, and a review of the current literature. The purpose of this report is to alert physicians to this rare association, especially in pediatric patients with intestinal strictures.

INTRODUCTION

Crohn's disease (CD) is an idiopathic inflammatory disease of the gastrointestinal tract. It is believed to result from environmental triggers in a genetically susceptible patient and may involve any site of the gastrointestinal tract in a segmental or focal distribution. Classic CD typically causes transmural inflammation with granuloma formation. Biologic agents like infliximab (IFX) that target the inflammatory cytokine, tumor necrosis factor alpha (TNF- α), have emerged as important medications for treating refractory CD. With increasing use, there also are reports of several rare adverse events associated with exposure to the medication. We present a case report of spontaneous bowel perforation in a child with CD while on IFX therapy.

• • •

Author Affiliations: Department of Pediatrics, Marshfield Clinic, Marshfield, Wis (Joshi); Department of Pediatrics-Hospitalist, Marshfield Clinic, Marshfield, Wis (Bajwa); Department of Radiology, Marshfield Clinic, Marshfield, Wis (Bhattacharjee); Department of Pediatrics-Gastroenterology, Marshfield Clinic, Marshfield, Wis (Bodicharla).

Corresponding Author: Rajasekhar Bodicharla, MD, Department of Pediatrics-Gastroenterology, Marshfield Clinic, 1000 N Oak Ave, Marshfield, WI 54449; phone 715.387.5251; e-mail bodicharla.rajasekhar@marshfield-clinic.org.

CASE PRESENTATION

An 11-year-old boy with a 4-year history of CD presented with sudden onset of abdominal pain and nonbloody, nonbilious emesis, 1 week after completing a third dose of IFX. The patient had been treated with 100 mg of azathioprine daily for the previous 2 years. He had further received several courses of steroids during intermittent flares. His weight-to-height ratio declined from the 50th percentile when he was first diagnosed to the 10th percentile before initiation of IFX. Magnetic resonance enterography (MRE) of the abdomen before the start of IFX therapy revealed moderate contiguous wall thickening and abnormal enhancement along a long segment of distal ileum indicating active CD.

The patient's symptoms improved considerably following IFX, with improvement in height-to-weight ratio as well. One week after completing his third dose of IFX, the patient had acute abdominal pain, nausea, and vomiting. Physical examination was significant for abdominal rigidity and guarding. Abdominal radiograph revealed air fluid levels with possible colitis and ileus consistent with intestinal obstruction. A computed tomography scan of the abdomen and pelvis (Figure 1) revealed a long segment of abnormally dilated and thickened distal ileum with multiple tiny interloop abscesses, as well as a significant amount of free fluid in the pelvis. Complete blood count was remarkable for leukocytosis ($21.2 \times 10^3/\mu\text{L}$; range $4.5\text{--}13.5 \times 10^3/\mu\text{L}$), with leftward shift. C-reactive protein was slightly elevated at 1.8 mg/dL (range 0-1.0 mg/dL) on admission, which further increased to 24.2 mg/dL in 48 hours. Liver function tests and blood electrolytes were within normal limits. Blood culture was obtained, which was negative after 5 days.

The patient was started on metronidazole and piperacillin/tazobactam along with supportive care. A nasogastric tube was placed to achieve gastric decompression, and total parenteral nutrition was started. This resulted in significant symptomatic improvement; however, he continued to have high nasogastric output, suggesting ongoing intestinal obstruction. An MRE after

1 week of antibiotics revealed persistent terminal ileal stricture (Figure 2). The bowel inflammation and interloop abscesses showed interval resolution.

A consult with pediatric surgery was obtained because of persistent intestinal obstruction. The patient underwent laparoscopic-assisted ileocectomy with primary staple anastomoses to repair the bowel perforation. He recovered well postoperatively without further complications.

DISCUSSION

TNF- α is a potent pro-inflammatory cytokine with a prominent role in inducing inflammation in CD. TNF- α stimulates recruitment of inflammatory cells to local tissue sites of inflammation, induces edema, and activates coagulation and granuloma formation.¹ Stool and serum TNF- α concentrations were found to be significantly increased in children with active CD.^{2,3} IFX is effective in mediating mucosal healing, induction and maintenance of remission, improvement in extra-intestinal manifestation, and growth in children.⁴ Currently there are 3 anti-TNF therapies approved for treatment of CD in the United States: IFX, adalimumab, and certolizumab pegol. Compared to the other 2 agents, IFX has demonstrated greatest efficacy for induction of remission.⁵

Several adverse effects have been reported in association with IFX therapy. A retrospective cohort study conducted by Vermeire et al⁴ evaluated the safety of IFX in patients with inflammatory bowel disease over a 14-year period and reported an increased risk for malignancies and serious infections. In another study,⁶ serious infections, infusion reaction, autoimmune phenomenon like arthritis, drug-induced lupus, autoimmune hemolytic anemia, optic neuritis, skin eruptions were noted, with 15 malignancies and 8 nonmelanoma skin cancers reported. Bowel perforation was not reported in any of these patients.

In a case control study by Eshuis et al,⁷ higher occurrence of free perforation, defined as intestinal perforations necessitating emergency surgical intervention, in CD patients was revealed with anti-TNF therapy compared with those without anti-TNF therapy (OR 4.1, 95% CI, 1.1-16.).⁷ The study population did not include pediatric patients. Since a larger number adults are reported with perforation after anti-TNF therapy, it raises an important question of whether cases are being underreported in the pediatric population.⁷

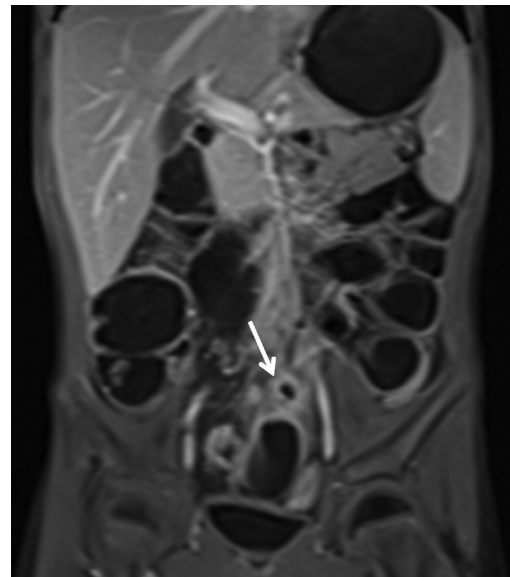
The first case of ileal perforation was reported in a 30-year-old heart transplant patient who presented with an ileal perforation after IFX treatment for CD. This patient also received other medications including corticosteroids, mycophenolate mofetil, and cyclosporine A.⁸ An elderly smoker diagnosed with ankylosing spondylitis developed lung cancer during treatment, further complicated by perforation of a metastasis to the sigmoid colon.⁹ Among the pediatric population, free perforation 13 days after an

Figure 1. Computed Tomography of the Abdomen and Pelvis With Oral and Intravenous Contrast



The coronal image shows thickened and dilated distal small bowel loops. The arrow indicates the site of a small bowel wall defect and an adjacent small contained abscess.

Figure 2. Magnetic Resonance Enterography



Six days after the computed tomography, a magnetic resonance enterography was performed. T1 VIBE fat-saturated coronal 50sec after gadolinium-based intravenous contrast administration, the small bowel remains dilated, but there is less thickening. The small abscess collection with wall enhancement is still present, as indicated by the arrow.

initial dose of IFX for CD was reported in a 17-year-old girl.¹⁰ To our knowledge, ours is the second case of spontaneous perforation reported in a pediatric patient.

While the mechanism associated with bowel perforation and IFX therapy remains largely unclear, it is postulated that IFX prevents activation of the inflammatory cascade and recruitment of neutrophils in the bowel wall, physiological pathways very important to sealing of the perforation. Since TNF- α also acts as a growth factor, neutralization by IFX may reduce the inflammatory mass formation that usually encapsulates imminent perforations.¹¹ It is also postulated that increase in oral intake after IFX therapy results in further dilation and increase in the pressure inside the bowel segment proximal to the stricture. A combination of decreased inflammatory cascade and increased pressure and dilation of proximal bowel may lead to perforation.¹²

Most CD patients develop a mild chronic disease pattern. The relapsing nature of the disease leads to bowel occlusion, fistula, and abscess formation. A significant number of patients will require surgical treatment within a 10-year time frame.¹³ Syed et al⁴ analyzed a cohort of CD patient to compare postoperative complications following intra-abdominal surgery in patients exposed and unexposed to anti-TNF agents. It was observed that use of TNF- α therapy less than 8 weeks before abdominal surgery was independently associated with an increase in infectious and surgical complications. However, this association might be biased, since TNF- α is used in sicker patients who are more likely to have postoperative complications. Prevention of postsurgical recurrence of CD is an important task. However, there is data that IFX administration after surgery prevents recurrence. Low dose IFX post surgically seems to be a safe and cost-effective strategy in the long term management of CD patients.¹⁵

CONCLUSION

Spontaneous bowel perforation is a rare but potentially fatal complication associated with IFX therapy in patients with CD. The purpose of this case report is to alert physicians to this rare association, especially in pediatric patients with intestinal strictures. Severe abdominal pain, protracted emesis, and abdominal distension in patients on IFX therapy with intestinal strictures should raise suspicion.

Acknowledgments: The authors thank the Marshfield Clinic Research Foundation's Office of Scientific Writing and Publication for assistance in preparing this manuscript.

Funding/Support: None declared.

Financial Disclosures: None declared.

REFERENCES

1. Stronkhorst A, Tytgat GN, van Deventer SJ. CD4 antibody treatment in Crohn's disease. *Scand J Gastroenterol Suppl.* 1992;194:61-65.
2. Braegger CP, Nicholls S, Murch SH, Stephens S, MacDonald TT. Tumor necrosis factor alpha in stool as a marker of intestinal inflammation. *Lancet.* 1992;339(8785):89-91.
3. Komatsu M, Kobayashi D, Saito K, et al. Tumor necrosis factor alpha in serum of patients with inflammatory bowel disease as measured by a highly sensitive immuno-PCR. *Clin Chem.* 2001;47(7):1297-1301.
4. Vermeire S, van Assche G, Rutgeerts P. Review article: Altering the natural history of Crohn's disease—evidence for and against current therapies. *Aliment Pharmacol Ther.* 2007;25(1):3-12.
5. Osterman MT, Haynes K, Delzell E, et al. Comparative effectiveness of infliximab and adalimumab for Crohn's disease. *Clin Gastroenterol Hepatol.* 2014;12(5):811-817.
6. Fidder H, Schnitzler F, Ferrante M, et al. Long term safety of infliximab for the treatment of inflammatory bowel disease: a single-centre cohort study. *Gut.* 2009;58(4):501-508.
7. Eshuis EJ, Griffioen GH, Stokkers PC, Ubbink DT, Bemelman WA. Anti tumor necrosis factor as risk factor for free perforations in Crohn's disease? A case-control study. *Colorectal Dis.* 2012;14(5):578-584.
8. Yamashita K, Oka Y, Okumura H, et al. An ileal perforation after infliximab treatment for Crohn's disease in a heart transplant patient : a case report. *Kawasaki Med J.* 2009;35(1):63-65.
9. Sifuentes Giraldo WA, González García A, Chamorro Tojeiro S, Sánchez Sánchez O, Pian H, Vázquez Díaz M. Colonic perforation secondary to metastatic lung adenocarcinoma during anti-TNF treatment for ankylosing spondylitis. *Acta Reumatol Port.* 2014;39(1):72-76.
10. Lim CS, Moon W, Park SJ, et al. A rare case of free bowel perforation associated with infliximab treatment for stricturing Crohn's disease. *Korean J Gastroenterol.* 2013;62(3):169-173.
11. Walters TD, Kim MO, Denson LA, et al. Increased effectiveness of early therapy with anti-tumor necrosis factor- α vs an immunomodulator in children with Crohn's disease. *Gastroenterology.* 2014;146(2):383-391.
12. Mowat C, Cole A, Windsor A, et al. Guidelines for the management of inflammatory bowel disease in adults. *Gut.* 2011;60(5):571-607.
13. de Buck van Overstraeten A, Wolthuis A, D'Hoore A. Surgery for Crohn's disease in the era of biologics: a reduced need or delayed verdict? *World J Gastroenterol.* 2012;18(29):3828-3832.
14. Syed A, Cross RK, Flasar MH. Anti-tumor necrosis factor therapy is associated with infections after abdominal surgery in Crohn's Disease patient. *Am J Gastroenterol.* 2013;108(4):583-593.
15. Sorrentino D, Paviotti A, Terrosu G, Avellini C, Geraci M, Zarifi D. Low-dose maintenance therapy with infliximab prevents postsurgical recurrence of Crohn's disease. *Clin Gastroenterol Hepatol.* 2010;8(7):591-599.

advancing the art & science of medicine in the midwest

WMJ

WMJ (ISSN 1098-1861) is published through a collaboration between The Medical College of Wisconsin and The University of Wisconsin School of Medicine and Public Health. The mission of *WMJ* is to provide an opportunity to publish original research, case reports, review articles, and essays about current medical and public health issues.

© 2016 Board of Regents of the University of Wisconsin System and The Medical College of Wisconsin, Inc.

Visit www.wmjonline.org to learn more.