

CASE REPORT

심한 협착이 동반된 크론병 환자에서 인플릭시맵 치료 후 발생한 소장 천공 1예

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A Rare Case of Free Bowel Perforation Associated with Infliximab Treatment for Stricturing Crohn's Disease

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Crohn's disease is characterized by chronic transmural inflammation of the bowel and is associated with serious complications, such as bowel strictures, abscesses, fistula formation, and perforation. As neither medical nor surgical therapy provides a cure for Crohn's disease, the primary goals of therapy are to induce and maintain remission and prevent complications. As a biologic agent, infliximab, a monoclonal antibody to tumor necrosis factor, is indicated for refractory luminal and fistulizing Crohn's disease that does not respond to other medical therapies or surgery. Infliximab has proven to be very effective for inducing and maintaining remission in Crohn's disease; however, infliximab treatment has several potential complications. Here, we report a case of free perforation following a therapeutic response after an initial dose of infliximab for Crohn's disease. This is the first case report describing a free perforation in a Crohn's disease patient after an initial dose of infliximab. (Korean J Gastroenterol 2013;62:169-173)

Key Words: Crohn's disease; Stricture; Infliximab; Perforation

INTRODUCTION

Crohn's disease is characterized by chronic transmural inflammation of the bowel. It can involve any portion of the gastrointestinal tract and is associated with serious complications, including bowel strictures, abscesses, fistula formation, and perforation. As neither medical nor surgical therapy provides a cure for Crohn's disease, the primary goals of therapy are to induce and maintain remission and prevent complications.

Treatment for Crohn's disease usually involves drug therapy or, in certain cases, surgery. Medical therapies include aminosalicylates, corticosteroids, immunosuppressants, and biologic agents.¹ As a biologic agent, infliximab, a monoclonal antibody to tumor necrosis factor (TNF), is indicated for refractory luminal and fistulizing Crohn's disease that does not respond to other medical therapies or surgery.^{2,3} Additionally, infliximab therapy increases mucosal healing and decreases the need for hospitalization and surgery. However, after one decade of experience with this potent anti-TNF ther-

Received November 8, 2012. Revised February 25, 2013. Accepted February 26, 2013.

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Financial support: None. Conflict of interest: None.

apy, it seems appropriate to evaluate the associated safety issues.^{4,5}

A retrospective observational study reported that infliximab may be a risk factor for free perforation in Crohn's disease;⁶ however, there was no specific case of this in the literature at that time. Here, we report a case of free perforation in Crohn's disease with strictures following infliximab treatment, despite effectiveness of the therapy. To our knowledge, there are no case reports describing free perforation in Crohn's disease following an initial dose of infliximab.

CASE REPORT

A 17-year-old Korean woman presented to the emergency room with an abrupt onset of severe abdominal pain of one hour's duration. She had been diagnosed with Crohn's disease (A2L3B2 Montreal Classification for Crohn's disease 2005: ileocolonic type and stricturing behavior) eight months prior. She had suffered from longstanding abdominal pain, diarrhea, and poor oral intake. Initial colonoscopy findings were compatible with Crohn's disease, including a cobblestone appearance and longitudinal ulcers (Fig. 1). A small bowel follow-through demonstrated multiple strictures with pseudosacculations in the distal ileum (Fig. 2). Her Crohn's Disease Activity Index (CDAI) was 198 points at diagnosis. She had been treated with 5-aminosalicylic acid and azathioprine (1.2 mg/kg/day). During treatment, her CDAI improved to 109 points and her hemoglobin, albumin, and BMI increased. Despite this improvement, she could not tolerate a full dose of azathioprine due to severe anorexia and generalized fatigue. She was admitted to the hospital twice due to poor oral intake. Her anorexia and poor oral intake

were attributed to azathioprine, with a contribution from the ileal strictures. Surgery was recommended, but her parents refused. Accordingly, intravenous infliximab (5 mg/kg) therapy was added to her previous azathioprine regimen, following a normal chest X-ray, negative Mantoux testing, QuantiFERON[®]-TB Gold (Cellestis Ltd., Victoria, Australia), and hepatitis B surface antigen. There were no immediate complications following the infliximab infusion. Seven days after the first infliximab infusion, her general condition and appetite rapidly and markedly improved. She was able to tolerate frequent high-fiber meals without difficulty. Before infliximab treatment, her height was 151 cm, she weighed 42 kg, and her BMI was 18.42 kg/m². Following treatment, her weight increased to 45 kg and her BMI increased to 19.74 kg/m².



Fig. 2. A small bowel follow-through at diagnosis demonstrating multiple strictures and pseudosacculations (arrowhead, stricture; arrow, pseudosacculum).

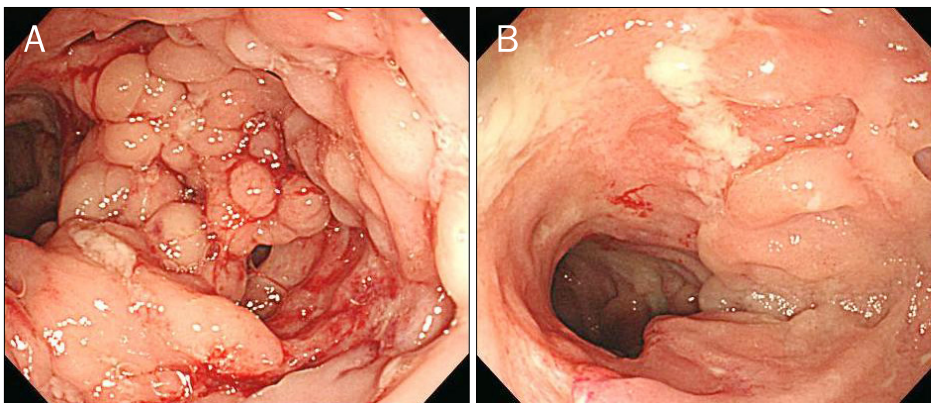


Fig. 1. Colonoscopic findings. (A) Cobble-stone appearance in the ascending colon consistent with Crohn's disease. (B) Longitudinal ulcers and luminal narrowing in the terminal ileum consistent with Crohn's disease.

However, thirteen days after the first infliximab treatment, she experienced a sudden onset of abdominal pain. On physical examination, blood pressure was 100/70 mmHg, pulse rate was 104/minute, and body temperature was 37.4°C. She was acutely ill-appearing and her abdomen displayed signs of generalized peritonitis. Initial blood work revealed a hemoglobin level of 9.4 g/dL and a total white blood cell count of 15,700/ μ L; her high-sensitive CRP (HS-CRP) was 0.06 mg/dL; all results were within the normal range (shortly before infliximab treatment, blood work revealed a total

white blood cell count of 7,900/ μ L and a HS-CRP level of 1.431 mg/dL). Chest and abdominal X-rays did not convincingly demonstrate the presence of free air. After 10 hours, follow-up blood work revealed a total white blood cell count of 16,900/ μ L and an elevated HS-CRP of 4.9 mg/dL. Computed tomography demonstrated a focal asymmetric wall defect in the distal ileum with extraluminal free fecal density in the peritoneal space (Fig. 3). Emergency small bowel segmental resection and ileostomy were performed. During the operation, a large perforation of the distal ileum was discovered and it was accompanied by the leakage of a large amount of pineapple-like, high-fiber, undigested food into the peritoneal cavity through the perforation. Surgical pathology demonstrated that a perforation was present in the distal ileum, at the prox-



Fig. 3. Abdominal CT at the time of the emergency room presentation demonstrating a focal, asymmetric wall defect in the distal ileum with extraluminal free fecal density in the peritoneal space. A stricture is noted in the distal part of the perforation lesion. The wall is relatively thin at the level of the distal ileum perforation (arrow, wall defect of the distal ileum; arrowheads, extraluminal free fecal density in the peritoneal space; open arrows, stricture).

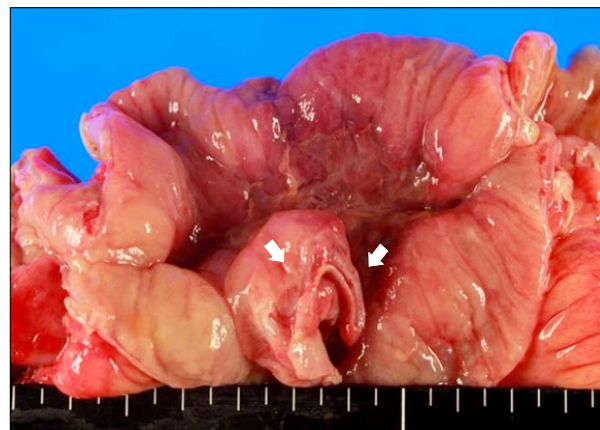


Fig. 4. Gross findings of the surgical specimen revealing a perforated lesion with a relatively thin ileal wall (arrows).

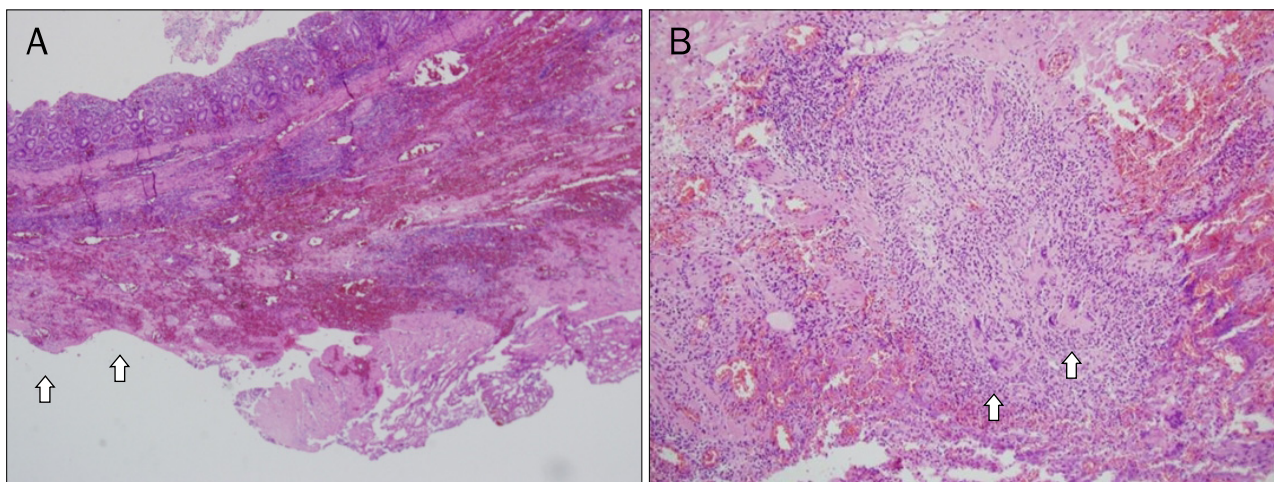


Fig. 5. Microscopic findings of the surgical specimen (H&E). (A) At the level of the perforation, only mild infiltration of inflammatory cells and fibrosis and a consequently thinned intestinal wall is noted (×40; arrows, perforated margin). (B) Non-caseating epithelioid granulomas are noted (×200; arrows, non-caseating epithelioid granulomas).

imal site of the stricture, without adhesions (Fig. 4). Microscopic findings at the level of the perforation demonstrated only mild infiltration of inflammatory cells and fibrosis with a resulting thinned intestinal wall (Fig. 5A) and several discrete non-caseating epithelioid granulomas (Fig. 5B). The post-operative course was uneventful and subsequent medical treatment of the underlying Crohn's disease proved successful, with clinical and biological parameters of inflammation returning to normal within several days. After surgery, she tolerated azathioprine treatment and is currently being treated with azathioprine 2.3 mg/kg/day without infliximab.

DISCUSSION

Burrill Bernard Crohn stated in a 1957 paper that "free perforation of ileitis into the peritoneal cavity never occurs or at least I have not seen it."⁷ In 1965 however, he reported seven cases of free perforation.⁸ Because Crohn's disease is a transmural inflammatory process, serosal adhesions develop that provide direct pathways for fistula formation and reduce the incidence of free perforation. Due to this, the etiology of free perforations is unknown. It is generally accepted that 1-3% of patients with Crohn's disease will present with a free perforation, either initially or later in their disease course.⁹⁻¹¹

Infliximab's mechanism of action is targeting TNF, which is responsible for the majority of the cases of inflammation associated with Crohn's disease. With the introduction of TNF alpha blockers, treatment options for Crohn's disease have improved significantly. Infliximab is very effective for the treatment of Crohn's disease, and is used to induce and maintain remission.¹² Unfortunately, infliximab treatment also has potential adverse events, including acute infusion reactions, severe serum sickness, and increased risk of infections, particularly reactivation of latent tuberculosis. Rarely, infliximab has been associated with optic neuritis, seizures, new onset or exacerbation of clinical symptoms, and radiographic evidence of central nervous system demyelinating disorders, including multiple sclerosis. It may also exacerbate symptoms in patients with New York Heart Association functional class III/IV heart failure.^{13,14}

Recently, Eshuis et al.⁶ reported that anti-TNF treatment for Crohn's disease was associated with a significantly higher rate of free perforation requiring surgery. Although there was

an attempt to equate the disease activity between cases and controls, it was quite clear that the disease activity comparison was poorly quantified. Therefore, the study demonstrated only a significant association between the occurrence of free perforation in Crohn's disease patients and the use of anti-TNF therapy, but did not prove a cause-and-effect relationship. However, the current report is the first case presentation describing free perforation in Crohn's disease patients after infliximab treatment and strongly suggests that infliximab may be a risk factor for free perforation in Crohn's disease, especially in cases with severe strictures.

Greenstein et al.¹⁰ suggested that increased intraluminal pressure proximal to the stricture and ischemia due to inflammation and abscesses caused by Crohn's disease may be potential causes of perforation. But, free perforations in Crohn's disease are relatively rare because adjacent organs and the omentum usually encapsulate the imminent perforation site by creating an inflammatory mass. In patients undergoing infliximab therapy, anti-TNF may block development of this protective inflammatory mass.⁶

In the current case, free perforation was likely caused by rapid and markedly increased intraluminal pressure proximal to the severe strictures, secondary to a large amount of food intake over a short time due to the therapeutic effectiveness of infliximab and relief of inflammation of the intestinal wall due to the effects of the drug. Previous studies have reported that cytokines, such as TNF- α , can influence human behavior during inflammatory conditions. Changes in behavior include decreased sexual drive, increased sleepiness, decreased appetite, and fatigue.^{15,16} Infliximab decreases the amount of circulating TNF- α , which is increased in Crohn's disease and, as a result, may influence behavior in Crohn's disease.¹⁷ Therefore, infliximab might contribute to overeating. In general, disease-associated fibrous reactions and adhesions to adjacent organs appear to be protective against free perforation. If a minimal perforation does occur, then either an abscess will develop within the inflammatory mass or a fistula to an adjacent organ will develop. But in the current case, infliximab blocked the inflammatory response as a "treatment" effect, and contributed to the occurrence of free perforation by preventing the formation of an inflammatory mass to seal off the imminent perforation.

This case report and discussion emphasize that during or after infliximab treatment for Crohn's disease accompanied

by severe strictures, a large food intake should be avoided. Although food tolerance is an important signal of treatment effectiveness, slow and incremental increases in intake are advised.

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