Intestinal Perforation as a Paradoxical Reaction to Antitubercular Therapy: A Case Report

Sung Hoon Kang¹, Hee Seok Moon¹, Jae Ho Park¹, Ju Seok Kim¹, Sun Hyung Kang¹, Eaum Seok Lee¹, Seok Hyun Kim¹, Byung Seok Lee¹, Jae Kyu Sung¹, Hyun Yong Jeong¹, Kyung Ha Lee²

¹Division of Gastroenterology, Department of Internal Medicine; ²Department of Surgery, Chungnam National University College of Medicine, Daejeon, Korea

Paradoxical reactions to tuberculosis (TB) treatment are characterized by an initial improvement of the clinical symptoms followed by clinical or radiological deterioration of existing tuberculous lesions, or by development of new lesions. Intestinal perforation in gastrointestinal TB can occur as a paradoxical reaction to antitubercular therapy. A 55-year-old man visited the outpatient department with lower abdominal pain and weight loss. He was diagnosed with intestinal TB and started antitubercular therapy. After 3 months of antitubercular therapy, a colonoscopy revealed improvement of the disease. Three days after the colonoscopy, the patient visited the emergency room complaining of abdominal pain. Abdominal computed tomography revealed extraluminal air-filled spaces in the pelvic cavity. We diagnosed a small bowel perforation and performed an emergency laparotomy and a right hemicolectomy with small bowel resection. This report describes the case of intestinal perforation presenting as a paradoxical reaction to antitubercular and provides a brief literature review.

Keywords: Intestinal perforation; Extrapulmonary tuberculosis; Paradoxical reaction; Small intestine; Antitubercular therapy

INTRODUCTION

In 2018, extrapulmonary tuberculosis (TB) accounted for approximately 15% of all TB cases. Gastrointestinal TB accounts for 3% to 19% of cases of extrapulmonary TB [1]. Complications of gastrointestinal TB include obstruction, fistula formation, and intestinal perforation [2]. The incidence of intestinal perforation due to gastrointestinal TB is 4% to 7.6%, while the associated mortality rate is 30%. While intestinal perforation can occur before or during antitubercular therapy [3], the latter presentation is rare and is suspected to be a possible paradoxical reaction.

Paradoxical reactions to TB treatment are characterized by an initial improvement of clinical symptoms followed by clinical or radiological deterioration of existing tuberculous lesions or by the development of new lesions [4, 5]. Paradoxical reaction is identified in 6% to 30% of patients receiving antitubercular therapy [5].

We report a case of intestinal perforation that occurred while a patient with normal immunity was being treated with antitubercular drugs for intestinal TB. This report was approved by the Institutional Review Board of Chungnam National University Hospital (CNUH 2020-01-017) and the written informed consent was received from the patient.

CASE REPORT

A 55-year-old man presented with a 2-month history of lower abdominal pain and diarrhea. He had lost 6 kg of weight since the symptoms started. Colonoscopy revealed transverse ulcerative lesions with clear borders and dirty exudates around the ileocecal valve (Fig. 1A). Histopathological examination revealed chronic granulomatous inflammation of the ileocecal mucosa with infiltration by histocytes and thin epithelioid cells (Fig. 1B). The TB polymerase chain reaction test was negative, but the interferon
gamma release assay was positive, which helped us to determine the diagnosis of intestinal TB. The patient's chest X-ray showed increased opacity of the right upper lobe (Fig. 2A), but he had no respiratory symptoms, such as cough or expectoration. He began antitubercular therapy with a once-daily regimen of isoniazid (400 mg), ethambutol (800 mg), and rifampin (600 mg) daily. The patient's symptoms of lower abdominal pain, diarrhea, cough, and expectoration were resolved, and he experienced no adverse effects apart from a mild rash.

A repeat colonoscopy was performed to evaluate treatment response after the patient completed 3 months of TB treatment. The ulcers, previously extending from the ileocecal valve till the cecum, had decreased in size. However, scars remained, associated with circular narrowing of the intestinal lumen. Localized inflammation had subsided (Fig. 3A). A microscopic examination of the ileocecal biopsy sample revealed chronic, nonspecific inflammation (Fig. 3B). We, therefore, decided to continue the patient on antitubercular drugs for a further 3 months as recommended.

Three days after the second colonoscopy, the patient came to the emergency room complaining of lower abdominal pain and constipation. On examination of his vital signs, his blood pressure, pulse rate, respiratory rate, and body temperature were 114/62 mmHg, 86 beats/min, 24 breaths/min, and 37.3°C, respectively. Signs of localized tenderness and rebound tenderness were elicited on lower abdominal palpation. Laboratory tests showed a white blood cell (WBC) count of 14,800/mm³ (with 90.3% segmented neutrophils), hemoglobin of 15.4 g/dL, platelet count of 321,000/mm³, and a C-reactive protein (CRP) of 0.7 mg/dL. Abdominal CT showed multisegmental wall thickening and luminal narrowing of the distal and terminal ileum, associated with partial small bowel obstruction, peritoneal inflammation, and complicated ascites (Fig. 4A). The patient was diagnosed with a small bowel obstruction with peritonitis. We performed bowel decompression using a Levin tube and administered antibiotics.

The patient did not report a lessening of lower abdominal pain,
even on the second day of hospitalization, and developed a fever of > 38°C. Blood tests revealed that his WBC count and CRP level had increased to 20,200/mm$^3$ and 31.3 mg/dL, respectively. A repeat abdominal CT revealed multiple, extraluminal, air-filled spaces in the pelvic cavity (Fig. 4B). We diagnosed small bowel perforation and performed an emergency laparotomy. Intraoperative examination revealed an ileal perforation at a distance of 100 cm, proximal to the ileocecal valve. Some stricturing lesions were observed from the perforation site to the ileocecal valve.

We performed an ileocecectomy (Fig. 5A); 100-cm-long distal ileum and an 11-cm-long colon, along with the IC valve, were excised. Postoperative histopathological examination of the resected bowel revealed a perforated ulcer with acute transmural supplicative inflammation (Fig. 5B).

Five days after the operation, the patient resumed oral feeding and was discharged on the 8th day after surgery. Antitubercular therapy was terminated after a further 3 months. The patient has been followed up for 2 years after the surgery and has remained asymptomatic. He has provided informed consent for the use of his medical information in this case report.

**DISCUSSION**

Extrapulmonary TB can affect lymph nodes, pleura, bones, the central nervous system, and the abdomen [2]. Gastrointestinal TB is the commonest presentation of abdominal TB and has been reported to account for 17% of all extrapulmonary cases.

Complications associated with gastrointestinal TB may include obstruction, perforation, fistula formation, and gastrointestinal bleeding. Risk factors for increased morbidity and mortality in patients with tuberculous intestinal perforation include delayed surgical treatment, multiple sites of perforation, concomitant cor-
sticosteroid therapy, anastomotic leaks, advanced age, and primary closure of the perforation [3, 4]. Considering the high mortality associated with intestinal TB, an operative resection of the affected portion of the intestine, followed by anastomosis, is preferred to primary closure [6]. Intestinal TB occurs mainly in the ileocecal region, with perforation commonly involving the ileal mucosa. Perforation can occur at single or multiple sites and may be associated with the formation of intestinal strictures or ulceration. As most perforations are stricture-related, small-intestinal perforations are more common than large-intestinal perforations. Perforation may occur before or after starting antitubercular therapy [3]. Intestinal perforation occurring during or after completion of antitubercular therapy can be a paradoxical reaction to treatment.

Paradoxical reactions have been observed in patients with TB affecting the nervous system, respiratory system, skin/soft tissue, lymph nodes, and the abdomen, in decreasing order of frequency. According to one report, approximately 75% of patients experience worsening of their primary lesions, and approximately 25% develop new lesions at other sites [5]. Risk factors for paradoxical reactions include extrapulmonary tuberculous lesions, a relatively low basal lymphocyte level in peripheral blood, and a sudden rise in the lymphocyte count during treatment [7].

The pathophysiological mechanism of paradoxical reaction to TB treatment is not fully understood. Increased exposure to mycobacterial antigens released from the bacilli, killed due to effective antitubercular therapy, strengthens delayed hypersensitivity of the host. Differential diagnoses of paradoxical reactions include diagnostic errors, inadequate response due to drug resistance, and poor adherence to therapy. Therefore, it is important to culture the affected tissue specimen at the time of the initial diagnosis to confirm the diagnosis and to determine the baseline level of drug resistance [2].

It is difficult to distinguish paradoxical reactions from treatment failures. When paradoxical reaction is suspected, continuing treatment is necessary. Surgeons may help determine appropriate surgical procedures for conditions such as intestinal TB, when paradoxical reactions require surgical treatment.

Our patient had 2 paradoxical reactions. The first was a paradoxical respiratory reaction. The initial chest X-ray had shown increased opacity of the right upper lobe, despite the absence of respiratory symptoms, such as cough and expectoration. He developed respiratory symptoms 4 weeks after starting antitubercular therapy, with findings of active TB on the chest CT. Some patients develop negative sputum AFB staining and culture results after completing 1 month of antitubercular therapy. Our patient experienced relief of his respiratory symptoms with concomitant improvement in his radiological findings after completing 6 weeks of treatment.

![Figure 5](image_url)

**Fig. 5.** (A) Intraoperative photograph showing suppurative inflammation on serosal surface of small bowel. (B) Luminal surface of the specimen. (C) Section of the resected bowel showing a perforated ulcer and acute, transmural, suppurative inflammation (H&E, ×40).
Table 1. Reported cases of intestinal perforation secondary to a paradoxical reaction in patients with intestinal tuberculosis (TB)

| Study       | Age (yr) | Sex  | HIV Status | Tuberculosis                          | TB agent used during treatment | Time to perforation | Perforation site | No. of perforations | Surgery               | Outcome         |
|-------------|----------|------|------------|--------------------------------------|---------------------------------|---------------------|------------------|-------------------|----------------------|-------------------|-----------------|
| Lee et al.  | 36       | Male | Negative   | Laryngeal, abdominal, miliary        | INH, RFP, EMB, PZA, MXF, CIP, AMK, STM | 6 Mo                | Ileum            | 1                 | Laparostomy          | Recovered         |
| Lee et al.  | 26       | Male | Negative   | Pulmonary, abdominal                | INH, RFP, EMB, PZA              | 6 Mo                | Jejunum          | 1                 | Segmental resection | Recovered         |
| Leung et al.| 63       | Male | Negative   | Pulmonary                            | INH, RFP, EMB, PZA, levofloxacin | 108 Day              | Terminal ileum   | 1                 | Right hemicolecotomy | Recovered         |
| Qureshi et al.| 14  | Male | Negative   | Abdominal                            | Unknown                         | 4 Mo                | Duodenum         | 1                 | Tube duodenoectomy | Death             |
| Liao et al. | 52       | Male | Negative   | Pulmonary                            | INH, RFP, EMB, PZA              | 1.20 Day, 2.71 Day, 3.146 Day | 1. Mid-jejunum, 2. Terminal ileum, 3. Ileocecal junction | 3                 | Segmental resection | Recovered         |
| Patel et al.| 26       | Male | Negative   | Pulmonary                            | Triple therapy                  | 6 Mo                | Jejunum          | 1                 | Segmental resection | Recovered         |
| Sherga et al.| 21     | Male | Negative   | Abdominal                            | Unknown                         | 2 Mo                | Distal ileum     | 1                 | Primary closure     | Recovered         |
| Naveen and Mukherjee | 54 | Male | Negative   | Pulmonary                            | INH, RFP, EMB, PZA              | 7 Mo                | Jejunum          | 1                 | Segmental resection | Recovered         |
| Saitou et al.| 61     | Male | Negative   | Pulmonary, intestinal, miliary       | INH, RFP, EMB, PZA              | 97 Day              | Ileocecal junction | 1                 | Right hemicolecotomy | Recovered         |
| Bellido Caparo et al. | 22 | Female | Negative | Pulmonary, abdominal, ganglionic    | INH, RFP, EMB, PZA              | 3 Mo                | Cecum            | 1                 | Right hemicolecotomy | Recovered         |
| Present case | 55      | Male | Negative, Abdominal, pulmonary       | INH, RFP, EMB, PZA              | 3 Mo                | Ileum            | 1                 | Ileocectomy          | Recovered         |

HIV, human immunodeficiency virus.  
*Anti-TB agents: INH, isoniazid; RFP, rifampicin; EMB, ethambutol; PZA, pyrazinamide; MXF, moxifloxacin; CIP, ciprofloxacin; AMK, amikacin; STM, streptomycin.  
†INH, STM, and para-aminosalicylic acid.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.
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