Intestinal perforation due to paradoxical reaction during treatment for miliary tuberculosis

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Abstract
A 61-year-old man was being treated for poor nutritional status. He had been on weekly methotrexate 6 mg and daily tacrolimus 1 mg and prednisolone 18 mg for 8 years due to dermatomyositis. On further workup, he was initially detected to have ileocecal ulcer with subsequent development of diffuse miliary shadows on chest radiograph. He was diagnosed as having ileocecal with miliary tuberculosis (TB). While receiving anti-tuberculous therapy, there was initial improvement of TB-related symptoms and he had no conditions that interfered with the efficiency of the anti-tuberculous therapy. However, he developed intestinal perforation. Emergency surgery for resection of the ileocecal ulcer and ileocolostomy led to improvement and he was finally discharged. Recently, cases of intestinal TB have been rare and perforation due to TB is extraordinary. In this case, paradoxical reaction and poor nutritional status may have contributed to the intestinal perforation.

Introduction
Intestinal tuberculosis (ITB) was previously recognized during the tuberculosis (TB) epidemic period as a frequent and most common complication of active pulmonary TB. Nowadays, ITB has become a rare disease. In Japan, the incidence of TB was 16.7 per 100,000 population in 2012, and the incidence of ITB was 1.61% of total TB [1]. Especially, intestinal perforation due to ITB is extremely uncommon [2].

Paradoxical reaction (PR) in TB is defined by a clinical or radiological worsening of pre-existing TB lesions or the development of new lesions, in patients receiving anti-tuberculous medication who had initially improved on treatment [3]. Although PR is generally recognized as initial aggravation which is progression of chest radiograph infiltrates, intestinal perforation during effective anti-TB therapy can be ascribed to PR.

Case Report
A 61-year-old man was admitted with a diagnosis of miliary TB. He was an engineer of metal analysis, and mainly worked at his office. At another hospital, he was prescribed and had been taking weekly doses of methotrexate 6 mg, and daily doses of tacrolimus 1 mg and prednisolone 18 mg for the past 8 years for dermatomyositis. Seven months prior to admission, he complained of gastrointestinal discomfort, but neither abdominal pain, intermittent diarrhoea, nor constipation was reported. It was then followed by loss of appetite and 15-kg weight loss in the last 2 months. Medical examination performed 6 weeks prior to admission found no abnormality in laboratory data and chest radiograph, and no exacerbation of dermatomyositis was also found. However, immunoassay test for faecal occult blood was positive. Colonoscopy revealed ulcers and nodules in the ileocecal region. Two weeks prior to admission, he developed dry cough and fever. Chest radiograph (Fig. 1A) and computed tomography at this time revealed diffuse bilateral miliary shadows. His sputum and stool specimens were positive for TB. Therefore, he was admitted to our hospital for further management of miliary TB.

On physical examination, he had muscle weakness on both legs and arms; his body mass index was 13.8. Human immunodeficiency virus antigen was not detected. Moderate liver dysfunction and leucocytosis were seen due to
miliary TB, but no renal dysfunction or hyperglycaemia was observed. Urine and bone marrow specimens were positive for acid-fast bacilli. Subsequently, medications were started for a diagnosis of miliary TB. The patient was treated with once daily regimen of isoniazid 300 mg, rifampicin 450 mg, ethambutol hydrochloride 750 mg, and pyrazinamide 1.2 g. Isoniazid and rifampicin were for 9 months, whereas ethambutol and pyrazinamide were for first 2 months only. For the first three days, methylprednisolone was given for respiratory failure due to exacerbation of miliary TB. Administration of anti-TB medications was supervised for 9 months to ensure compliance. Oral steroids and immunosuppressants were continued during TB therapy after admission. After 90 days of TB therapy, his general condition had improved, but constipation was a new complaint. His body weight increased by about 4 kg, peripheral blood lymphocytes increased from 130/μL in white blood cell count of 25,850 to 640/μL in white blood cell count of 8770. Serum albumin also increased from 1.4 to 2.6 g/dL. During this time, he had no side effects from intake of anti-TB drugs; his chest radiograph improved (Fig. 1B), and acid-fast bacilli were both smear- and culture-negative in sputum and stool. In addition, his initial cultured *Mycobacterium tuberculosis* did not show multidrug resistance. On day 97, he suddenly complained of acute abdominal pain. Physical examination revealed abdominal tenderness and rigidity; abdominal computed tomography showed a small amount of free air, suggesting bowel perforation. Upon emergency surgery, a looped terminal ileum adherent to the caecum and an ulcer in the ileocecal region were detected (Fig. 2). The involved segment was resected and ileocolostomy was performed. Histopathological examination showed a non-caseating granuloma that was positive for acid-fast bacilli. However, resected tissue specimen was culture-negative for miliary TB.

After admission, the ileocecal lesion that was detected at the previous hospital was revealed to be of TB aetiology. After the operation, his condition improved and he was discharged on day 113 of hospitalization.

**Discussion**

ITB was recognized as one of the most common complications of active pulmonary TB in the 20th century. It is estimated that intestinal perforations occur in 1–15% of all intestinal TB patients [4]. There are two types of ITB, namely primary and secondary. The latter is disseminated from elsewhere in the body [5]. Our case was classified as primary ITB because he was first detected to have an ileocecal lesion without tuberculous lesions in other sites, especially the lungs, at that time. Histopathological examination that was taken with previous colonoscopy also showed non-caseating granuloma and positive for acid-fast bacilli.

In various studies, several patients with ITB have been reported to show no evidence of pulmonary TB [5]. In this regard, ITB may frequently occur with minimal or no radiographic evidence of pulmonary TB. The possibility that acid-fast bacilli may infect the intestine directly should be considered.
With the advent of effective anti-TB therapy, enteric TB is now decreased and is an uncommon complication of pulmonary TB in Japan, as mentioned before [1]. Symptoms of ITB are non-specific as abdominal pain, diarrhoea, constipation, body weight loss, and so on.

There are actually some cases of ITB perforation, despite of receiving or completed TB therapy. According to a recent report, 3.3% of patients with ITB perforation were receiving or had completed anti-tuberculous therapy before developing perforation [4].

Intestinal perforation during effective anti-TB therapy can be ascribed to PR. PR is defined as paradoxical worsening or recurrence of pre-existing tuberculous lesions or development of new lesions in patients receiving adequate anti-TB therapy [2,6]. Previous reports described that PR usually developed within 1–6 months of starting anti-TB therapy [7]; in our case, intestinal perforation occurred 97 days after initiation of anti-TB therapy. Additionally, it was reported that poor nutritional status may contribute to intestinal perforation. Intestinal perforation, which is an uncommon complication of ITB, is due to a reactive thickening of the peritoneum and subsequent formation of adhesions within the surrounding tissues. In our case, the long-term intake of prednisolone and immunosuppressant may have predisposed the development of TB and accelerated the poor nutritional status, which caused intestinal perforation due to PR.

In our case, the patient had constipation after 90 days of TB treatment. It might be a symptom of PR of ITB leading to perforation. Intestinal perforation complicating TB has a severe prognosis, with a high mortality rate of 30% [2]. Although intestinal perforation due to PR is rare and unexpected, knowledge of this pathophysiological state may contribute to earlier diagnosis and successful management of ensuing complications.

Disclosure Statements
No conflict of interest declared.
Appropriate written informed consent was obtained for publication of this case report and accompanying images.
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