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Short Communications

Management of Severe Gastrointestinal Tuberculosis with Injectable Antituberculous Drugs

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Abstract: Abdominal tuberculosis (TB) is generally responsive to medical treatment, and early diagnosis and management can prevent unnecessary surgical intervention. However, intravenous therapy is needed for severe forms of tuberculosis with extensive gastrointestinal involvement. The authors report an immunocompetent patient with gastrointestinal TB who was successfully managed with a combination of surgical intervention and anti-TB medications, and discuss the importance of injectable anti-TB medications in the management of severe gastrointestinal TB. The present case report provides a model for assessment and intervention in severe forms of gastrointestinal TB.
Key words: tuberculosis, gastrointesinal tuberculosis, *M. tuberculosis*, injectable antituberculous drugs, management

Introduction

Tuberculosis (TB) is one of the leading global causes of morbidity and mortality. The World Health Organization (WHO) has estimated an approximate annual incidence of 8.6 million cases of TB globally [1]. According to the WHO report, 1.3 million people died from the disease in 2012. Abdominal TB can be present in different clinical forms including peritoneal TB, tuberculous lymphadenopathy, gastrointestinal TB and visceral TB. This manifestation of TB, can be a source of significant morbidity and mortality and is usually diagnosed late due to its nonspecific clinical presentation [2]. Abdominal TB is generally responsive to medical treatment, and early diagnosis and management can prevent unnecessary surgical intervention. However, intravenous therapy is need for patients suffering from severe forms of TB with extensive gastrointestinal involvement, and difficulty taking and absorbing oral medications. Here, we report an immunocompetent patient with gastrointestinal TB who was successfully managed with a combination of surgical intervention and antituberculous (anti-TB) medications. The authors emphasize and discuss the importance of injectable anti-TB medications in the management of severe gastrointestinal TB.

Case Report

A 13-year-old female adolescent was referred to our hospital with bloody diarrhea, anemia and a 5-kg weight loss over approximately two months. Blood examination data revealed a hemoblobin count of 9.8 d/dL; hematocrit of 35%; white blood cell of 7.2×10^9/L, and platelets of 189×10^9/L. After admission, she was treated initially with corticosteroids for seven days following a colonoscopy suggestive of Crohn's disease. The symptoms had progressively worsened during the last week and she showed massive rectal bleeding upon arrival at ICU. She underwent repeated blood transfusions and a further colonoscopy showed fragile mucosa with multinodular appearance, circumferential deep ulcers, and hemorrhagic lesions predominantly in the cecum (Fig. 1). Histology of a biopsy fragment of the cecum showed the presence of acid alcohol fast bacilli. Laboratory tests revealed increased white blood cells as well as an increased erythrocyte sedimentation rate and C-reactive protein levels. Chest X-ray showed

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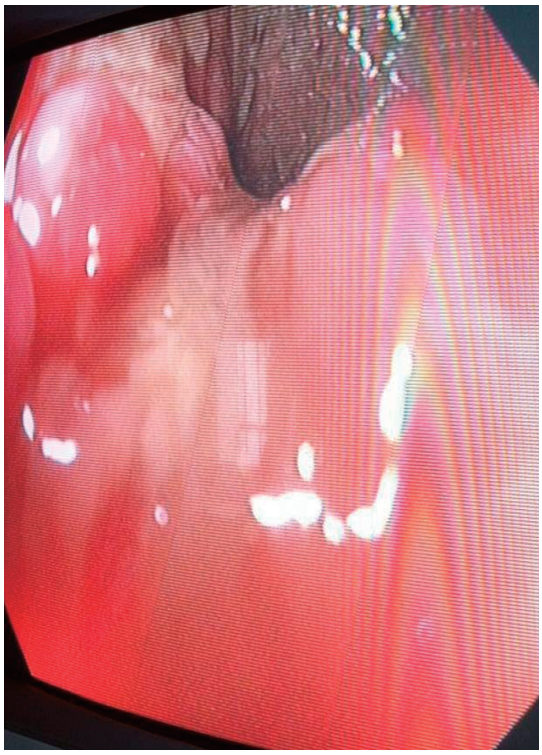

Fig. 1. Colonoscopy revealing deep ulcerated lesions in the cecum

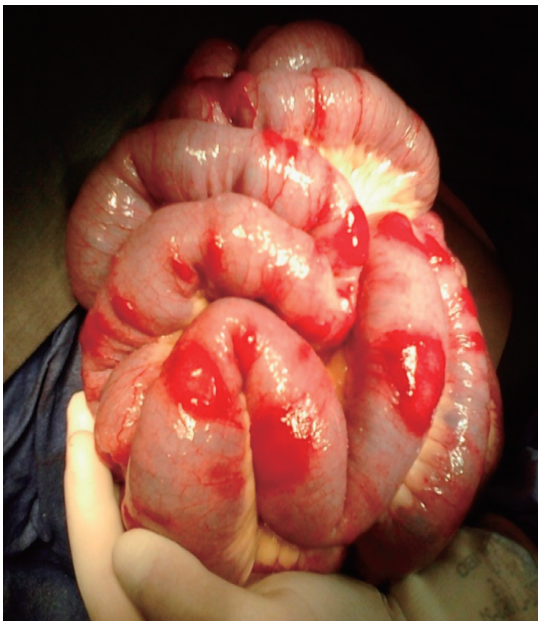

Fig. 2. Laparotomy showing extensive hemorrhagic areas of the intestine.

a small circumferential lesion in the upper left lobe. She had a positive history of non-treated pulmonary tuberculosis in the family, with an uncle as the index case. She was not vaccinated with BCG. Gastric lavage fluid showed acid alcohol fast bacilli. Anti-HIV serology (ELISA) was negative and serum imunoglobulins were normal. Tuberculin skin test was negative. Physical examination revealed a marked skin pallor and abdominal distension with marked pain in all the abdominal quadrants. Corticosteroid was withdrawn, and, since the conventional oral treatment with rifampin, isoniazid and pyrazinamide was precluded by massive rectal bleeding, the patient was started on intravenous regimen of levofloxacin (500 mg once a day), linezolid (600 mg every 12 hours), and streptomycin (750 mg once day). After 10 days, a second colonoscopy showed active bleeding from the upper small bowel through the distal ileum with no active bleeding in the colon. The first laparotomy performed the following day showed friability and bleeding throughout the small bowel. No resection was done, but lymph nodes were collected for culture. Histology showed no granuloma. Culture of the mesenteric lymph node produced *Mycobacterium tuberculosis*. *M. tuberculosis* was sensitive to all four first line anti-TB drugs (isoniazid, rifampin, streptomycin and pyrazinamide). While on the IV treatment for tuberculosis, she did not recover from the rectal bleeding, and an abdominal angiotomography showed a bleeding site at the distal ileum. She underwent a second laparotomy five days after the first laporatomy, and 30 cm of distal ileum, cecum and ascending colon were resected (Fig. 2). Histology of the resected intestine showed the presence of loose granulomas with acid alcohol bacilli (Fig. 3). The lower gastrointestinal bleeding stopped after the surgery, the patient completed 40 days of IV anti-TB treatment. Enteral feeding was started, and the intravenous regimen of streptomycin (750 mg/day), (linezolid 600 mg every 12 hours) and levofloxacin (500 mg/day) were replaced with an oral regimen of isoniazid (300 mg/day), rifampicin (600mg/day) and pyrazinamide (1000 mg/day). The patient successfully completed a full nine-month course of oral anti-TB drugs without any additional intervention after two years of follow-up.

Discussion

The most common site of gastrointestinal involvement in tuberculosis is the ileocecal segment, which is implicated in approximately 64% of cases [3]. In particular, the terminal ileum is commonly involved because of various contributing factors like stasis, presence of abundant lymphoid tissue, increased rate of absorption at this site and closer contact of the bacilli with the mucosa [4]. Concomitant jejunal involvement may be seen in the form of

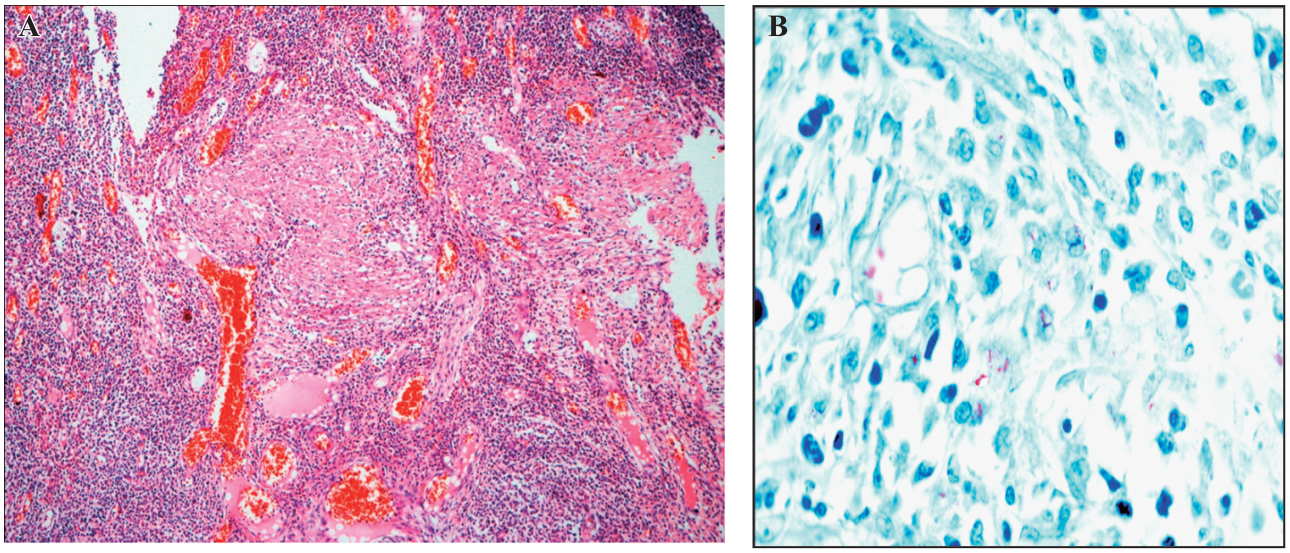

Fig. 3. (A) Histology of resected colon fragment showing loose granulomatous lesions (HE stain) with the presence of acid alcohol fast bacilli (ZN stain) (B).

single or multiple short or long segment strictures. Isolated jejunal involvement is rare, and if present may mimic Crohn's disease. Isolated involvement of the colon was reported to be 10.8% [5]. The incidence increases in immunocompromised patients and patients with AIDS. The cecum is the most common site of involvement of the colon but it is usually implicated in contiguous involvement with the terminal ileum and ileocecal junction [6].

Our patient was successfully managed, as in a a previous report describing an HIV-infected patient who presented severe disseminated tuberculosis with extensive intestinal involvement [7]. Although our patient did not have any detectable underlying immunosuppression, the presence of numerous acid alcohol fast bacilli with loose granulomatous lesions reflects the immunocompromised status of the host. In addition to surgery, this patient was successfully treated with an initial combinedregimen of injectable and oral anti-TB agents. With the advent of anti-TB therapy, surgery is usually reserved for in situations which it is absolutely indicated, such as cases of non- resolving intestinal obstruction, gastrointestinal bleeding, perforation and abscess fistula formation [8].

Injectable anti-TB drugs is essential for treating different categories of TB patients, including those with severe disseminated and gastrointestinal TB for whom oral anti-TB agents alone might not be effective. In some cases, this is caused by quick decomposition of the drugs during their relatively slow intake from the gastrointestinal tract and, in others, by the impossibility of increasing the dose. In the case of intravenous administration, the drugs are easily absorbed, which leads to the creation of higher concentrations in the infected tissues [9]. Unfortunately, current guidelines for the management of tuberculosis have not addressed this issue.

Fluorquinolones including levofloxacin are injectable anti-TB drugs that have been shown to have early/extended bactericidal activity and are well tolerated. They are concentrated in macrophages and other phagocytic cells, bronchial mucosa and epithelial lining fluid where levels are higher than those found in the serum [10]. Linezolid also has an injectable formulation which demonstrates good activity against drug-susceptible and drug-resistant *M. tuberculosis* strains in *in vitro* studies and animal models [11]. Interestingly, we did not observe the reported toxicities of linezolid in our patient, including myelosuppression and neuropathy. Aminoglycosides have excellent bactericidal activity and a long-post-antibiotic effect that has proved valuable after once-a-day administration [12, 13]. Additional potential antituberculous drugs such as Imipenem, meropenem and ampicillin-sulbactam are active against *M. tuberculosis* considering that resistance can be overcome by inhibiting the β-lactamase or by use of an antibiotic that is not a substrate for this enzyme [14].

Few TB guidelines address the use of injectable anti-TB drugs in patients with severe forms of tuberculosis who are unable to take oral medications. In many countries such as Brazil, first line injectable anti-TB drugs such as rifampim and isoniazid are not available. Considering that clinical trials are difficult to perform in this type of clinical setting, further case reports and case series addressing the

efficacy of adjunctive injectable anti-TB drugs have an important function in providing models for assessment and intervention and describing new clinical challenges and phenomena for the management of severe forms of gastrointestinal TB.

Conflict of Interest

The authors declare no conflict of interest.

References

1. WHO. Global tuberculosis report 2013. Geneva: WHO; 23 Oct, 2013.
2. Debi U, Ravisankar V, Prasad KK, et al. Abdominal tuberculosis of the gastrointestinal tract: revisited. World J Gastroenterol 2014; 20: 14831–14840.
3. Shah S, Thomas V, Mathan M, et al. Colonoscopic study of 50 patients with colonic tuberculosis. Gut 1992; 33: 347–351.
4. Horvath KD, Whelan RL. Intestinal tuberculosis: return of an old disease. Am J Gastroenterol 1998; 93: 692–696.
5. Sood A, Midha V, Singh A. Differential diagnosis of Crohn's disease versus ileal tuberculosis. Curr Gastroenterol Rep 2014; 16: 418.
6. Mukewar S, Mukewar S, Ravi R, et al. Colon tuberculosis: endoscopic features and prospective endoscopic follow-up after anti-tuberculosis treatment. Clin Transl Gastroenterol 2012; 3: e24.
7. Boff DF, Goldani LZ. Initial combination of injectable and oral anti-tuberculosis agents for the treatment of severe disseminated tuberculosis. Tropical Doctor 2013; 43: 148–150.
8. Uzunkoy A, Harma M, Harma M. Diagnosis of abdominal tuberculosis: experience from 11 cases and review of the literature. World J Gastroenterol 2004; 10: 3647–3649.
9. Peloquin CA. Therapeutic drug monitoring in the treatment of tuberculosis. Drugs 2002; 62: 2169–2183.
10. Johnson JL, Hadad DJ, Boom WH, et al. Early and extended early bactericidal activity of levofloxacin, gatifloxacin, and moxifloxacin in pulmonary tuberculosis. Int J Tuberc Lung Dis 2006; 10: 605–612.
11. Fortun J, Martin-Davila P, Navas E, et al. Linezolid for the treatment of multidrug-resistant tuberculosis. J Antimicrob Chemother 2005; 56: 180–185.
12. Zhu M, Burman WJ, Jaresko GS, et al. Population pharmacokinetics of intravenous and intramuscular streptomycin in patients with tuberculosis. Pharmacotherapy 2001; 21: 1037–1045.
13. Dickinson JM, Aber VR, Mitchison DA. Bactericidal activity of streptomycin, isoniazid, rifampicin, ethambutol and pyrazinamide and in combination against *Mycobacterium tuberculosis*. Am Rev Resp Dis 1977; 116: 627–635.
14. Segura C, Salvado M, Collado I, et al. Contribution of beta-lactamases to beta-lactam susceptibilities of susceptible and multidrug-resistant *Mycobacterium tuberculosis*. Antimicrob Agents Chemother 1998; 41: 1524–1526.