REVISTA DO INSTITUTO DE MEDICINA TROPICAL DE SÃO PAULO
JOURNAL OF THE SÃO PAULO INSTITUTE OF TROPICAL MEDICINE

CASE REPORT
http://doi.org/10.1590/S1678-9946202062078

Severe gastrintestinal bleeding as an unusual presentation of pediatric tuberculosis: a situation for injectable antituberculous drugs use?

Ana Carolina Etrusco Zaroni Santos[1], **Jaques Sztajnbok**[2], **Amaro Nunes Duarte-Neto**[3], **Amanda Freire Tamburini Sousa**[1], **Alessandra Geisler Daud Lopes**[1], **Anna Carlota Mott Barrientos**[4]

ABSTRACT

Disseminated tuberculosis is a severe disease with high-mortality that requires early diagnosis and treatment. Intestinal tuberculosis accounts for only 2% of tuberculosis cases worldwide and is extremely rare in children. We report a case of a 4-year-old girl admitted due to disseminated tuberculosis with extensive intestinal involvement characterized by massive intestinal bleeding and hemorrhagic shock. The severity of the intestinal involvement precluded the exclusive use of oral anti-tuberculosis drugs and the patient was successfully treated with a combination of injectable and oral anti-tuberculosis agents. We discuss the importance of a regimen with injectable drugs for treating severe forms of tuberculosis in which the intestinal involvement impaired the use of oral drugs.

KEYWORDS: Gastrintestinal tuberculosis. Bleeding. Pediatric. Injectable antituberculous drugs.

INTRODUCTION

Pediatric tuberculosis remains an important health issue in high burden areas. According to WHO, at least 1 million children fall ill with tuberculosis (TB) each year. In 2018, 205,000 children died due to TB. It is estimated that 67 million children are infected by *Mycobacterium tuberculosis* (latent tuberculosis infection - LTBI) and are therefore at risk of developing disease in the future. Brazil is one of the 30 countries with the highest TB burden, with an estimated annual incidence of approximately 90,000 cases, 10% among children under 14 years-old[1,2].

Childhood deaths from TB are usually caused by tuberculous meningitis or disseminated disease[2]. The management with first-line drugs is crucial for the patient's survival. Oral medications are the first choice. However, severe cases require the use of injectable drugs, thus guaranteeing optimal serum concentrations to achieve the desired therapeutic effect.

We report herein an immunocompetent child with disseminated TB who was successfully treated with a combination of oral and injectable anti-TB medications. The legally responsible for the patient has provided an informed consent for publication of the case.

CASE REPORT

A 4-year-old malnourished girl (11 kg, < 3rd percentile) was admitted to the

[1]Hospital Municipal Infantil Menino Jesus, Unidade de Terapia Intensiva Pediátrica, São Paulo, São Paulo, Brazil

[2]Instituto de Infectologia Emílio Ribas, São Paulo, São Paulo, Brazil

[3]Universidade de São Paulo, Faculdade de Medicina, Hospital das Clínicas, Departamento de Patologia, São Paulo, São Paulo, Brazil

[4]Hospital Municipal Infantil Menino Jesus, Departamento de Infectologia Pediátrica, São Paulo, São Paulo, Brazil

Correspondence to: Ana Carolina Etrusco Zaroni Santos
Hospital Municipal Infantil Menino Jesus, Unidade de Terapia Intensiva Pediátrica, Rua dos Franceses, 250, Bela Vista, CEP 01329-010, São Paulo, SP, Brazil
Tel: +55 11 95080-9383,
+55 11 3016-0500,
Fax: +55 11 3016-0500

E-mail: anazaroni@gmail.com

Received: 11 May 2020

Accepted: 30 September 2020

Hospital Infantil Menino Jesus, Sao Paulo State, Brazil, with a history of intermittent fever for 20 days, diarrhea without blood, night sweats, weight loss and dry cough. The patient had no comorbidities, no history of contact with a patient with pulmonary tuberculosis and received BCG vaccination. Laboratory exams revealed anemia (hemoglobin 8.8 g/dL), leukocytosis 21,600/mm^3 (1% band, 79% segmented neutrophils, 15% lymphocytes and 10% monocyte), platelets 269,000/mm^3, INR 1,25, urea 18 mg/dL (normal range 7-18), creatinine 0.2 mg/dL (normal range 0.66-1.25), alanine transaminase 22 U/L (normal range < 35) and aspartate transaminase 29 U/L (normal range 15-50). Chest radiography presented a miliary pattern (Figure 1). Ceftriaxone and first-line oral anti-tuberculosis agents (RHZ: rifampicin, isoniazid and pyrazinamide) were introduced after the diagnosis of disseminated tuberculosis confirmed by gastric washing that identified a rifampicin-sensitive *Mycobacterium tuberculosis* (X-pert MTB/RIF assay). The patient evolved with respiratory distress, septic shock, melena and hematochezia with massive bleeding requiring red blood cell transfusion of about 80 mL/kg six days after starting the enteral anti-tuberculous therapy. Upper digestive endoscopy, colonoscopy and angiography failed to identify the bleeding source. The macroscopic findings of endoscopy revealed no abnormalities in the esophagus and stomach. In the duodenum, there was a shallow ulceration in the second portion with no sign of active bleeding. A duodenal biopsy showed chronic duodenitis and a positive acid-fast bacilli test (Figure 2), confirming the diagnosis of disseminated tuberculosis. The abdominal tomography revealed lymphadenopathy, jejunal loops clusters with difficult identification of their contours, distal ileal and sigmoid wall thickening (Figure 3). The patient did not receive any medications that could increase the risk of bleeding, except for hydrocortisone due to the refractory septic shock. The severity of the case and the intestinal involvement cast doubt on the expected response of the

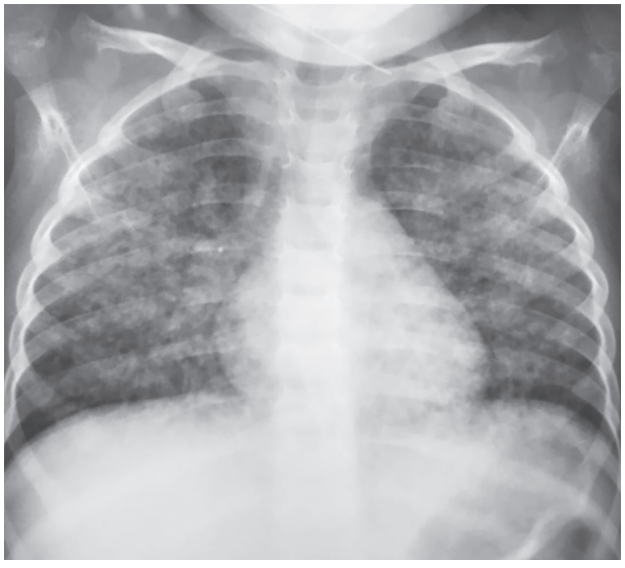

Figure 1 - Chest radiograph showing a miliary pattern on the admission to the hospital.

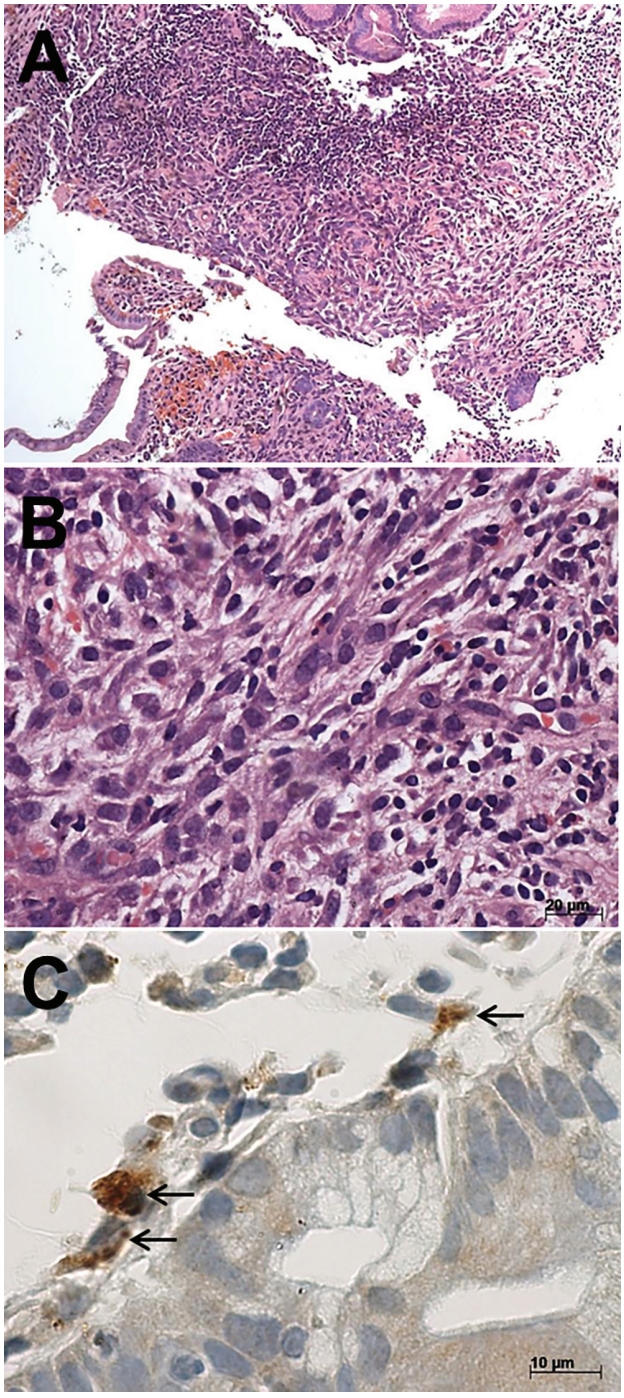

Figure 2 - Intestinal tuberculosis in a 4 year old child: A) Granulomatous reaction in the intestinal lamina propria (HE, 100 x); B) Epithelioid histiocytes, lymphocytes and few eosinophils forming the intestinal granulomatous reaction (HE, 400 x); C) Positive detection of BCG antigen in the cytoplasm of some histiocytes (arrows, Immunohistochemistry, 1000 x).

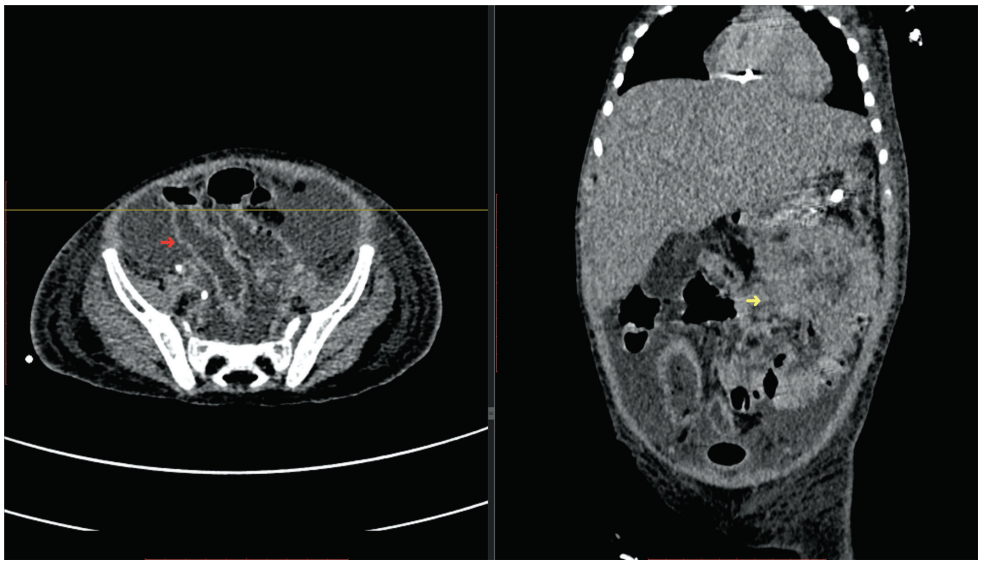

Figure 3 - Abdominal tomography showing parietal thickening of the sigmoid (red arrow). Jejunal loops present clusters with difficult identification of their contours (yellow arrow).

enteral absorption of oral drugs. Thereafter, an intravenous second line drug therapy was associated: linezolid (10 mg/kg/day), amikacin (15 mg/kg/day), meropenem (120 mg/kg/day) and ciprofloxacin (20 mg/kg/day). After seven days of combined therapy there was no more bleeding. Linezolid was suspended after 14 days of treatment, amikacin after 7 days, meropenem after 12 days and ciprofloxacin after 14 days. She was discharged after 35 days of hospitalization with RHZ regimen. The patient's parents had neither respiratory symptoms nor abnormalities on their chest radiographs.

DISCUSSION

Disseminated tuberculosis is a severe disease with high-mortality that requires early diagnosis and treatment. Pulmonary disease is the leading form but 40% of infections are extrapulmonary[3]. Intestinal tuberculosis (ITB) accounts for 2% of TB cases worldwide. The most common intestinal site is the ileocecal segment, usually presenting with multiple ulcerated lesions that are implicated in approximately 90% of cases. There are several factors that explain the frequent ileal involvement: stasis of gut contents, abundance of lymphoid tissue and close contact of bacilli with the mucosa[4-6].

ITB presents a diagnostic challenge, given its non-specific clinical presentation and tendency to mimic other abdominal diseases. In a retrospective study with 61 adult ITB patients, the most common CT findings were bowel wall thickening, intra-abdominal lymphadenopathy, intra-abdominal collection and peritoneal thickening. The gold standard for ITB diagnosis is the endoscopy, even though upper endoscopy failed to show any findings associated with ITB. Colonoscopy helped to confirm the diagnosis in 77% of patients. The most common findings were ileocecal inflammation, ileocecal ulceration and ileal strictures[5,7]. Gastroduodenal tuberculosis constitutes 1% of all abdominal diseases and may present with gastric or duodenal obstruction mostly due to periduodenal lymphadenopathy. Duodenal perforation occurs due to a tuberculous ulcer or erosion from adjacent lymph nodes. Rarely, patients may present with large volume of bleeding per rectum due to ileocecal or colonic disease, or infrequently, an isolated ileal disease[3]. As far as we know, only two cases were described in children involving massive intestinal bleeding, one with superior mesenteric artery aneurysm and the second case requiring resection of distal ileum, cecum and ascending colon (Table 1)[4,8].

The intradermal BCG vaccine was introduced in Brazil in the 1960s and provides protection against severe and disseminated forms of tuberculosis (mainly meningitis and military tuberculosis). Despite receiving BCG vaccination, this child presented with a rare and potentially fatal form of tuberculosis[9].

RHZ is crucial for the management of tuberculosis. According to the Brazilian Ministry of Health Manual published in 2019, the standardized treatment comprises two phases: intensive (aiming at the rapid reduction of the bacillary population) and maintenance (aiming at the reduction of persistent bacilli). For a new TB case in children under 10 (except meningoencephalic and osteoarticular tuberculosis), rifampicin, isoniazid and pyrazinamide are used for 2 months followed by rifampicin and isoniazid for another 4 months[10]. However, due to the possibility of

Table 1 - Cases of pediatric intestinal tuberculosis with massive gastrointestinal bleeding presentation.

Reference	Clinical presentation	Treatment	Outcome
Kahan *et al.*[8] (2006, USA, case report)	Massive intestinal bleeding with superior mesenteric artery aneurism	Oral regimen (RHZE); vascular embolization	Discharge; RHZE (time course not described)
Goldani *et al.*[4] (2015, Brazil, case report)	Massive rectal bleeding	Intravenous regimen (levofloxacin, linezolid and streptomycin); resection of distal ileum, cecum and ascending colon	Discharge; RHZ (9 months)

R = rifampicin; H = isoniazid; Z = pyrazinamide; E = ethambutol

malabsorption and a slow onset of the action, it is important to highlight the correct use of intracellular agents with rapid action and adequate infection site penetration in critically ill patients. In this case report, the combined treatment included linezolid, amikacin, meropenem and ciprofloxacin.

Linezolid has a dose-dependent protein synthesis inhibitory action with a good lung tissue penetration. It has a synergistic effect with rifampicin. There are few studies on linezolid in children with tuberculosis. A few published reports described its use in multi-resistant mycobacteria therapy. In these cases, all had negative cultures in a period of 1 to 3 months of treatment and more than 80% of linezolid-treated children had a favorable outcome. Linezolid has serious time and dose-dependent side effects mainly reported in adults than in children: myelosuppression, neurotoxicity, hepatotoxicity, nephrotoxicity and pancreatitis[11-13]. During the treatment of the reported case, there was a mild and transient elevation of hepatic enzymes, with no need to suspend the therapy. The child did not present granulocytopenia or needed bone marrow analysis, as well. Because of the high cost, considerable toxicity, and good outcomes with current treatment regimens, the existing evidence does not support the routine use of linezolid in children. However, considering its high concentration in lung parenchyma, rapid onset of action and lower risk of side effects in short use regimens, this drug was chosen for our treatment regimen[11-13].

Meropenem acts by inhibiting the synthesis of bacterial cell lines. The association meropenem-clavulanate potentiates the bactericidal action, as the clavulanate prevents the rapid breaking of the beta-lactam ring and the potential consequent action loss. However, clavulanate is not commercially available alone. Therefore, amoxicillin-clavulanate is a possibility of association with carbapenems. Nonetheless, amoxicillin has gastrointestinal effects, which could complicate and prolong the treatment. In our patient, we chose not to associate carbapenem-clavulanate. Adverse events due to carbapenems were mild and include hypersensitivity reactions, seizures, renal and hepatic dysfunction[14,15].

Fluoroquinolones are well tolerated protein synthesis inhibitors with excellent and fast bactericidal action. Moxifloxacin is the most potent quinolone against TB, however, this drug was not available in our institution. When they are compared, ciprofloxacin, moxifloxacin and levofloxacin showed the same efficacy against *M. tuberculosis* sensitive to anti-TB drugs. However, in the multiresistant group, ciprofloxacin presented the highest resistance among the quinolones, reaching 15%. This group of antibiotics rarely cause serious side effects when compared to other classes of anti-tuberculosis drugs. A concern is especially present in the pediatric population regarding the potential musculoskeletal toxicity related to quinolones. Since the 1960s, several studies have been published associating the use of quinolones with musculoskeletal disorders (arthritis, arthralgia, tendinopathy and gait changes). In an extensive review published in 2017, adverse effects reported in children were rare or absent. Arthralgia was the most described event, usually transient. In some cases, there is no need to discontinue the medication. There was no report of long-term growth impairment. In addition, fluoroquinolones exhibit excellent intracellular action and high bioavailability in tissues[15-17].

Amikacin is an aminoglycoside with protein synthesis inhibitory action. It is an excellent bactericidal anti-TB medication and has a long-term effect that has proved valuable for administration once a day. The main reported side effects are ototoxicity and nephrotoxicity. In a previous published survey, hearing impairment was reported in 21% of children after prolonged therapy (5.9 ± 2.9 months). The aminoglycosides-induced ototoxicity is permanent, as the cochlear cells are destroyed and they are incapable of regeneration. Nephrotoxicity has been reported in 15% of patients on prolonged therapy (9 ± 4 months). Serum creatinine was normalized after the dose reduction[15,18].

In addition to extrapulmonary disease, our patient had other risk factors associated with worse outcomes, such as: age under five years, malnutrition and gastrointestinal involvement[4,10,19,20]. These findings, the unfavorable evolution and the low reliability of gastrointestinal tract

drugs absorption justified the use of oral and injectable drugs. Although they were drugs of choice in multiresistant tuberculosis cases, the decision to use them was not based on the bacillary profile, but on the route of administration by which we would obtain an adequate drug concentration in infected tissues[14].

In summary, attending physicians should be aware of the eventual impossibility to rely upon oral drugs to treat disseminated tuberculosis with severe gastrointestinal involvement, such as the one presented here. In these cases, the combined IV and oral therapy should be considered in order to guarantee a timely and appropriate treatment.

ACKNOWLEDGMENTS

The authors thank Dr. Adriano Salgado for performing, processing and analyzing the computed tomography images and InRad – Instituto de Radiologia HCFMUSP for performing the angiography.

CONFLICT OF INTERESTS

None was declared.

FUNDING

None was declared.

REFERENCES

1. World Health Organization. Global tuberculosis report 2019. Geneva: WHO, 2019 [cited 2020 Sep 30]. Available from: https://www.who.int/tb/publications/global_report/en/
2. Lamb GS, Starke JR. Tuberculosis in infants and children. Microbiol Spectr. 2017;5:TNMI7-0037-2016.
3. Malik R, Srivastava A, Yachha SK, Poddar U, Lal R. Childhood abdominal tuberculosis: disease patterns, diagnosis, and drug resistance. Indian J Gastroenterol. 2015;34:418-25.
4. Goldani LZ, Spessatto CO, Nunes DL, Oliveira JG, Takamatu E, Cerski CT, et al. Management of severe gastrointestinal tuberculosis with injectable antituberculous drugs. Trop Med Health. 2015;43:191-4.
5. Chincha O, Cáceres J, Seas C. Tuberculosis gastrointestinal como causa de hemorragia digestiva masiva en un paciente con infección por VIH. Rev Chilena Infectol. 2017;34:393-6.
6. Liu J, Bai G, Qiu J, Chi Y, Hu X, Huang Y, et al. Atypical serious hematochezia and rare imaging feature in gastrointestinal tuberculosis. Clin J Gastroenterol. 2019;12:182-8.
7. Kentley J, Ooi JL, Potter J, Tiberi S, O'Shaughnessy T, Langmead L, et al. Intestinal tuberculosis: a diagnostic challenge. Trop Med Int Health. 2017;22:994-9.
8. Kahn SA, Kirshner BS. Massive intestinal bleeding in a child with superior mesenteric artery aneurysm and gastrointestinal tuberculosis. J Pediatr Gastroenterol Nutr. 2006;43:256-9.
9. Barreto ML, Pereira SM, Ferreira AA. BCG vaccine: efficacy and indications for vaccination and revaccination. J Pediatr (Rio J). 2006;82 Suppl 3:S45-54.
10. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Vigilância das Doenças Transmissíveis. Manual de recomendações para o controle da tuberculose no Brasil. 2ª ed. atual. Brasília: Ministério da Saúde; 2019. [cited 2020 Sep 30]. Available from: http://www.aids.gov.br/pt-br/pub/2019/manual-de-recomendacoes-para-o-controle-da-tuberculose-no-brasil
11. Garcia-Prats AJ, Rose PC, Hesseling AC, Schaaf HS. Linezolid for the treatment of drug-resistant tuberculosis in children: a review and recommendations. Tuberculosis (Edinb). 2014;94:93-104.
12. Srivastava S, Deshpande D, Pasipanodya J, Nuermberger E, Swaminathan S, Gumbo T. Optimal clinical doses of faropenem, linezolid, and moxifloxacin in children with disseminated tuberculosis: goldilocks. Clin Infect Dis. 2016;63 Suppl 3:S102-9.
13. Deshpande D, Srivastava S, Pasipanodya JG, Bush SJ, Nuermberger E, Swaminathan S, et al. Linezolid for infants and toddlers with disseminated tuberculosis: first steps. Clin Infect Dis. 2016;63 Suppl 3:S80-7.
14. Van Rijn SP, Zuur MA, Anthony R, Wilffert B, van Altena R, Akkerman OW, et al. Evaluation of carbapenems for treatment of multi- and extensively drug-resistant Mycobacterium tuberculosis. Antimicrob Agents Chemother. 2019;63:e01489-18.
15. Boff DF, Goldani LZ. Initial combination of injectable and oral anti-tuberculosis agents for the treatment of severe disseminated tuberculosis. Trop Doct. 2013;43:148-50.
16. Yilmaz FF, Eraç B, Ermertcan S, Cavusoglu C, Biçmen C, Aktogu Ozkan, et al. In vitro effects of ciprofloxacin, levofloxacin and moxifloxacin on Mycobacterium tuberculosis isolates. Tuberk Toraks. 2018;66:32-6.
17. Patel K, Goldman JL. Safety concerns surrounding quinolone use in children. J Clin Pharmacol. 2016;56:1060-75.
18. Shah I, Goyal A, Shetty NS. Adverse effects of aminoglycosides in children with drug resistant tuberculosis. Infect Dis (Lond). 2019;51:230-3.
19. Drobac PC, Shin SS, Huamani P, Atwood S, Furin J, Franke MF, et al. Risk factors for in-hospital mortality among children with tuberculosis: the 25-year experience in Peru. Pediatrics. 2012;130:e373-9.
20. Jaganath D, Mupere E. Childhood tuberculosis and malnutrition. J Infect Dis. 2012;206:1809-15.