The diagnostic challenges in a child with intestinal tuberculosis

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Abstract
Introduction: Romania is one of the European countries with a significant burden of tuberculosis (TB). Although pulmonary TB is still highly prevalent, intestinal TB is very rare and remains a diagnosis of exclusion, especially in children. The authors aimed to raise the awareness on this pathology by discussing the challenges faced in the management of one difficult case. Case presentation: A 3-year-old boy was hospitalized in the Pediatrics Department of Grigore Alexandrescu Emergency Children’s Hospital, Bucharest, Romania, for abdominal pain and melena. On clinical examination, he was malnourished, with generalized edema and marked abdominal distension. Laboratory tests revealed iron-deficiency anemia, low plasma proteins, inflammatory syndrome and high fecal calprotectin. The abdominal ultrasound showed bowel wall thickening and diffuse edematous mesentery; the colonoscopy described multiple ulcers with edematous margins. Parenteral nutrition and complex antibiotic treatment were initiated with no effect. During the hospital stay, the medical staff observed how the mother chewed the patient’s food. The child’s pulmonary X-ray was normal, but the mother’s was suggestive for pulmonary TB. The QuantiFERON® test was positive. Biopsy of the bowel mucosa revealed numerous granulomas; the Auramine O/Rhodamine B staining of the specimen was positive. Specific TB treatment was started with good results: the patient resumed growth, abdominal pain and distention disappeared.

Conclusions: Intestinal TB poses a diagnostic challenge, especially in the absence of pulmonary disease. It may mimic many other intestinal pathologies. Since correct treatment depends on making the correct diagnosis, a high index of suspicion must be kept when facing atypical abdominal symptoms.

Keywords: intestinal tuberculosis, child, diagnosis.

Introduction
Tuberculosis (TB) is a chronic granulomatous inflammatory disease and remains till date a major public health issue due to a worldwide distribution and special affiliation for underdeveloped countries [1]. It is a life-threatening disease, which can virtually affect any organ or system. According to World Health Organization (WHO) Global TB Report, the TB load is high, affecting 10 million individuals in 2019 [2].

Pediatric TB remains an important epidemiological problem in high prevalence areas, with children shouldering 20% of all disease burden. Although pulmonary disease is the leading form, up to 40% of infection may be extra-pulmonary. Abdominal TB refers to involvement of the gastrointestinal (GI) tract, the mesentery, lymph nodes, peritoneum and related solid organs. There is a broad clinical spectrum depending on the site of involvement. Any presenting picture is possible, from mild, nonspecific symptoms to severe disease mimicking Crohn’s disease. In the pediatric population, TB most frequently affects the peritoneum and lymph nodes. Intestinal TB is very rare in children, thus representing a great challenge for the clinician.

There are several ways by which TB can affect the abdomen. First of all, it is transmitted by ingestion of infected food and milk (primary intestinal TB, caused mainly by Mycobacterium bovis) or by ingestion of infected sputum (secondary intestinal TB). In recent years, with boiling of milk, pasteurization and eradication of infected cattle, incidence of M. bovis infection is decreasing. It is close to be eradicated in industrialized countries, but still present in low-income countries [3–5]. Spread can occur if a patient with pulmonary TB is always swallowing his sputum. Another pathway is hematogenous spread from distant tubercular focus to abdominal solid organs, such as peritoneum, kidneys, and lymph nodes. The third way consists in contagious spread to peritoneum from infected adjacent foci. Lastly, TB can spread from infected nodes through the lymphatic channels [3, 4].

Aim
The authors describe the steps taken up to the diagnosis of intestinal TB in the case of a small boy hospitalized for diarrhea and failure to thrive, to increase awareness on this rare pediatric condition among physicians.

Case presentation
ML is a 3-year-old boy hospitalized in the Pediatrics
Level was mildly increased [4 mg/dL, normal value (NV) <0.5 mg/dL]. Presenting C-reactive protein (CRP) (negative specific serology). Viral hepatitis B and C, also in the differential diagnosis. Celiac disease was excluded.

Persistent diarrhea, several pathologies were considered with a layered appearance, enlarged appendix (8 mm), except for a thickening of the large bowel wall (up to 7.6 mm), anemia (hemoglobin 7.6 g/dL), low serum iron (6 μg/dL), very high levels of fecal calprotectin, protein-losing enteropathy and lymphoma were now under consideration.

The patient had low inflammatory syndrome, but the fecal calprotectin was high (2600 mg/g). Food protein-induced allergic proctocolitis (cow’s milk protein allergy – positive specific immunoglobulin E), inflammatory bowel disease (IBD) (elevated anti-Saccharomyces cerevisiae antibodies, very high levels of fecal calprotectin), protein-losing enteropathy and lymphoma were now under consideration.

The patient received poorly the oral feeds, lost weight (1 kg/two weeks). Partial parenteral nutrition was decided (Kabiven) with improvement of the weight curve.

During the hospital stay, the medical staff observed how the mother chewed the patient’s food in her mouth. The QuantiFERON® test was performed and came back positive (2.58 IU/mL, NV <0.35 IU/mL). The child’s pulmonary X-ray was normal (Figure 2a), but the mother’s showed round opacity in the superior quarter of the left lung, suggestive for pulmonary TB (Figure 2b).

The patient showed no improvement (persistent low appetite, diarrhea and marked abdominal distention). Repeated surgical consults were needed to exclude acute surgical abdomen.

The abdominal computed tomography (CT) with contrast revealed: diffuse thickening of the colic wall up to 7 mm, with high contrast uptake in the mucosa of the ascending, transverse and descending colon, sigmoid wall up to 2 mm; diffusely densified intraperitoneal adipose tissue; mesenteric adenopathy maximum diameter 10/6 mm, portocaval adenopathy 9/6 mm; medium ascites, 7 mm recto-vesical, 8 mm in the iliac fossa, 4 mm in the Morison’s pouch, 5 mm perihepatic (Figure 1b).

An endoscopic examination was decided. Upper endoscopy showed no lesions of the mucosa and no signs of bleeding. The colonoscopy revealed multiple ulcers with edematous margins and clean bottom lining of mucosa of the sigmoid, descending, and transverse colon (Figure 1a); seriated biopsies were taken.

The patient received extensively hydrolyzed formula feeds, parenteral rehydration, complex antibiotic treatment (Ceftazidime, Meropenem, Ciprofloxacin, Rifaximin) and antifungal medication for 14 days. Oral Mesalazine treatment is initiated after colonoscopy. In two weeks time, the patient showed no improvement (persistent low appetite, diarrhea and marked abdominal distention). Repeated surgical consults were needed to exclude acute surgical abdomen.

The pathology results came back at this point, revealing an erosive granulomatous colitis: colonic mucosa with focal architectural distortion, chronic active inflammation with erosions and numerous large mucosal and submucosal granulomas, frequently confluent, with epithelioid macrophages, Langerhans giant cells, lymphoid cuff around and central necrosis (Figure 3a).
Differential diagnosis included Crohn’s disease, sarcoidosis, chronic granulomatous disease, Behçet’s disease, other infectious granulomatous colitis: *Yersinia enterocolitica, Mycobacterium spp.*, *Chlamydia spp.*, *Treponema spp.*, *Campylobacter spp.*, *Salmonella spp.*.

Auramine O/Rhodamine B fluorochrome staining (Figure 3b) for acid-fast organisms was performed with a positive result and revealed the presence of reddish-orange bacteria on a background of necrotic granulomatous tissue – Centers for Disease Control and Prevention (CDC) score 4+ (>90 bacilli/microscopic field – 200×; >36 bacilli/microscopic field – 400×).

![Figure 3](image3)

**Figure 3** – (a) Pathology on colonic biopsy: numerous large mucosal and submucosal granulomas; (b) Positive Auramine O/Rhodamine B staining (CDC score 4+). CDC: Centers for Disease Control and Prevention.

The diagnosis set was intestinal TB. Malabsorption syndrome. Severe failure to thrive. Cow’s milk protein allergy.

The patient was transferred to a TB Clinic and the specific treatment regimen was started. He received six months of anti-TB therapy (ATT), which includes initial two months of therapy with Isoniazid, Rifampicin, Pyrazinamide and Ethambutol thrice weekly, followed by Rifampicin with isoniazid for another four months. He resumed growth, the stool normalized, and the abdominal distension and pain disappeared.

**Discussion**

Abdominal TB is a disease with an insidious course without disease-specific clinical and laboratory signs. This localization of the bacillary infection, should be included in the differential diagnosis in regions with a high incidence of TB when there is abdominal pain, weight loss or lack of weight gain, history of contact with infected patients and positive tuberculin skin test or equivalents. *Kiliki** et al. (2015) reported that 4.3% of the pediatric cases with TB had abdominal TB. Male children were more commonly affected [6].

The most common site of intestinal TB is ileocecal region (in around 85% of the cases), followed by jejunum and colon; duodenal involvement is seen in less than 3% of all GI TB cases [4, 7]. Our patient had involvement of the colon, and probably of the appendix. We were unable to evaluate the small bowel, as he did not meet criteria for capsule endoscopy and intestinal magnetic resonance imaging (MRI) was not an option (it is not available in our hospital and the family’s financial situation did not allow them to bear the costs of the investigation in a private setting).

Establishing a definite diagnosis of intestinal TB is often elusive, as in the case presented as well. The symptoms are polymorphic and non-specific, the diagnostic resources still limited, which often leads to diagnostic delays and development of severe complications [3, 4, 8, 9]. Increasingly, differentiating TB from IBD has assumed importance for pediatric specialists from both developed and developing countries [10].

One of the most important diagnostic clues in our case was observing the feeding habits of the family (the mother was chewing her son’s meals). As we found no signs of pulmonary TB in our patient, the most likely mean of contamination was through infected saliva/sputum from his mother. She underwent investigations for TB due to our suspicion of intestinal TB in her child. She was diagnosed with active pulmonary TB. Debi et al. (2014), Akhan & Pringot (2002) reported that only 15–25% of cases with abdominal TB have concomitant pulmonary TB [4, 11].

As the literature states, the patient with intestinal TB may present with acute or subacute/chronic disease. Intestinal obstruction, intestinal perforation and peritonitis are usually found in the acute type. In case of chronic presentation, the onset is insidious, most patients having symptoms for a few weeks to months, sometimes years. The most frequent symptom is abdominal pain (51.2–90% of the cases); other events include: fatigue (81%), fever (73–75%), weight loss (46.9–81%), diarrhea or constipation, nausea, vomiting and poor absorption. Low digestive hemorrhage is rare. Physical examination may show palpable abdominal mass [1, 3, 5, 7, 12–16]. Our patient was repeatedly seen by the surgeon as the main presentation was persistent, important abdominal distension and pain. We would regard this case as a chronic presentation with insidious onset (loss of appetite, poor weight gain), evolving with recurrent abdominal pain, persistent, protein losing diarrhea, failure to thrive and edema.

Diagnosis of intestinal TB includes various molecular, immunological and imaging investigations. Mantoux test may have its pitfalls. Positive purified protein derivative (PPD) tuberculosis tests only mean infection, not disease, so a TB diagnosis may not be based on a positive skin test. Polymerase chain reaction (PCR) detection of *Mycobacterium* deoxyribonucleic acid (DNA) may provide a fast diagnosis of extrapulmonary TB, with specificity of 100% and sensitivity ranging from 64% to 86% [1, 7]. Despite rigorous investigations, bacterial isolation is only possible in about half the cases, as the literature states. It seems that the advances in investigative modalities have not been translated into higher microbiological yields in abdominal TB [10].

Abdominal US is a noninvasive method of detecting abdominal fluid and lymphadenopathy, also peritoneal or omental thickening and bowel wall thickening in some cases [4]. It can be used as a first step investigation method for intestinal TB. The most common sonographic findings are ascites and lymphadenopathy with hypoechogenic centers, which indicate caseating necrosis [3, 4, 7]. Abdominal US was the first investigation to raise major concerns in our case. Colonic wall thickening, high diameter appendix, pericecal, interileal, sub hepatic ascites, diffusely edematous mesentery, these were persistent findings in repeated scans.

We did not perform Barium studies. These may be used for ileocecal and colonic lesions. Findings may include
shortened ascending colon, deformed cecum, incompetent ileocecal valve or dilated ileum. Barium studies are still “gold standard” in diagnosing strictures, fistulae, erosions [1, 4].

Colonoscopy combined with biopsy is the diagnostic procedure of choice because it allows the direct visualization of the lesions. Colorectal TB is found in almost 11% of the cases, with the cecum being the most common site of involvement (usually associated with lesions in the terminal ileum and ileocecal junction); isolated or segmental colon disease affects primarily the transverse colon, followed by rectum and ascending colon involvement. It consists mainly of linear/fissured, transverse or circumferential ulcers, which is why Crohn’s disease is the first differential diagnosis to be considered. Colonic lesions are often indistinguishable from those of IBD [4, 17]. In the case presented the colonoscopy revealed extensive lesions of the sigmoid, descending and transverse colon, mostly numerous ulcers, early onset Crohn’s disease being at that point our first suspected diagnosis. Apart from Crohn’s disease and lymphomas, other pathologies that we also considered for differential diagnosis were infections of the GI tract, such as *Yersinia, Campylobacter, Clostridium difficile* and *Cytomegalovirus* infection [3, 7].

CT scan is frequently used and seems to be the imaging modality of choice in detection and assessment of abdominal TB, as it shows bowel wall thickening (up to 3 cm in the cecum and terminal ileum) with associated mesenteric lymphadenopathy [4, 18], at sites that correlate with pathological findings at colonoscopy. The CT scan in our case was informative towards the extent of the intestinal involvement.

Exploratory laparoscopy is a rewarding investigation tool in children with relevant history; it has a high rate in histological diagnosis, and it can also be extended for therapeutic purposes, such as stricturoplasty and adhesiolysis [3, 7]. We managed to avoid this step in the management of our patient as the pathology results shed light upon the diagnosis.

Granulomas are demonstrated in 18% to 48% of colonic biopsies in different studies, while specific acid-fast bacilli staining confirmation varies between 0 and 40% of cases [10, 19, 20]. The caseation necrosis in granulomas is the histological hallmark of TB. In intestinal TB granulomas are multiple, large, and coalescent in mucosa and submucosa. A positive culture is seen in only 20% of cases as reported by Debi et al. (2014) [4]. Confluent granulomas, presence of caseation necrosis, presence of granulomas in lymph nodes in the absence of granulomatous lesions in the intestine, absence of transmural cracks and fissures serve to distinguish intestinal TB from Crohn’s disease [4]. In our case, the pathology set the diagnosis as numerous granulomas with epithelioid macrophages and central necrosis were described.

Fluorescent staining consisting of a mixture of Auramine O and Rhodamine B dyes binds to the nucleic acids within acid-fast organisms. Conventional Ziehl–Neelsen will most probably be replaced by Auramine O/Rhodamine B staining soon [21]. Intensely positive Auramine O/Rhodamine B staining confirmed intestinal TB for the patient presented.

In terms of medical therapy, all diagnosed cases of GI TB should receive at least six months of ATT with the classical four-drug chemotherapy: Isoniazid, Rifampicin, Pyrazinamide and Ethambutol [4]. Balasubramanian et al. (1997) found no difference in effectiveness between the six months short course therapy regimen with Rifampicin, Isoniazid and Pyrazinamide for two months, followed by Rifampicin with Isoniazid for another four months (6R series) and 12 months standard regimen of Ethambutol and Isoniazid with Streptomycin supplemented for two weeks [22]. The patient and his mother both received the classical regimen with good clinical results.

**Conclusions**

A high index of suspicion is essential to set the diagnosis of intestinal TB in children. This condition is regarded as a great mimicker of other abdominal pathology. The disease should be considered in children presenting with vague abdominal pain, abdominal distension, weight loss and low-grade fever. Setting the diagnosis is often very difficult and furthermore this is just the first challenge the clinician will face while managing an intestinal TB case. Various molecular and immunological techniques alongside radiological studies are highly recommended for rapid diagnosis in suspected cases. As the diagnosis might be easily omitted, severe complication may occur, such as strictures or fistulas. Management of GI TB is generally done with medical therapy; surgery remains a conservative therapeutic method, used only if absolutely indicated.

**Conflict of interests**

The authors declare that they have no conflict of interests. The authors declare they have no financial relationships to disclose concerning the content of this work, nor any other conflict of interests.

**Ethics statement**

The original work presented complies with the Helsinki Declaration. Informed consent was obtained from the parents.

**References**

[1] Mirza B, Ijaz L, Saleem M, Sheikh A. Surgical aspects of intestinal tuberculosis in children: our experience. Afr J Paediatr Surg. 2011, 8(2):185–189. https://doi.org/10.4103/0189-6725.86059 PMID: 22005362

[2] World Health Organization (WHO) Team. WHO guidelines on tuberculosis infection prevention and control: 2019 update. *Global Tuberculosis Programme, Water, Sanitation, Hygiene and Health, WHO/CDS/TB/2019.1*, Geneva, Switzerland, accessed: March 10, 2020. https://www.who.int/publications/i/item/9789241550512

[3] Tinsa F, Essaddam L, Filouni Z, Brini I, Douira W, Ben Becher S, Boussetta K, Bousnina S. Abdominal tuberculosis in children. J Pediatr Gastroenterol Nutr. 2010, 50(6):634–638. https://doi.org/10.1097/MPG.0b013e3181b6a57b PMID: 20386326

[4] Debi U, Ravisanankar V, Prasad KK, Sinha SK, Sharma AK. Abdominal tuberculosis of the gastrointestinal tract: revisited. *World J Gastroenterol*, 2014, 20(40):14831–14840. https://doi.org/10.3748/wjg.v20.i40.14831 PMID: 25356043 PMCID: PMC4209546

[5] Shah I, Uppuluri R. Clinical profile of abdominal tuberculosis in children. *Indian J Med Sci*, 2010, 64(5):204–209. PMID: 22842319

[6] Kılıç Ö, Sömer A, Hançeri Törcün S, Kesen Emirgö M, Salman N, Salman T, Çelik A, Yekeler E, Uzun M. Assessment of 35 children with abdominal tuberculosis. Turk J Gastroenterol, 2015, 26(2):128–132. https://doi.org/10.5152/tjg.2015.6123 PMID: 25835110
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Brambilla E, Dal Ponte M, Ruschel LG, Da Silva PG. Intestinal tuberculosis in immunocompetent/HIV negative patients: case report of two patients. J Coloproctol, 2012, 32(3):304–307. https://doi.org/10.1590/S0103-23492012000300015 https://www.scielo.br/j/jcol/a/MZ6cVTPh8fK5zqzB8KB9j/?lang=en

Thapa BR, Yachha SK, Mehta S. Abdominal tuberculosis. Indian Pediatr, 1991, 28(9):1093–1100. PMID: 1802856

Basu S, Ganguly S, Chandra PK, Basu S. Clinical profile and outcome of abdominal tuberculosis in Indian children. Singapore Med J, 2007, 48(10):900–905. PMID: 17909673

Malik R, Srivastava A, Yachha SK, Poddar U, Lal R. Childhood abdominal tuberculosis: disease patterns, diagnosis, and drug resistance. Indian J Gastroenterol, 2015, 34(6):418–425. https://doi.org/10.1007/s12664-015-0582-3 PMID: 2667893

Akhan O, Pringot J. Imaging of abdominal tuberculosis. Eur Radiol, 2002, 12(2):312–323. https://doi.org/10.1007/s00330-0100994 PMID: 11870428

Khan R, Abid S, Jafri W, Abbas Z, Haqee K, Ahmad Z. Diagnostic dilemma of abdominal tuberculosis in non-HIV patients: an ongoing challenge for physicians. World J Gastroenterol, 2006, 12(39):6371–6375. https://doi.org/10.3748/wjg.v12.i39.6371 PMID: 17072964 PMCID: PMC4088149

Hu ML, Lee CH, Kuo CM, Huang CC, Tai WC, Chang KC, Lee CM, Chuah SK. Abdominal tuberculosis: analysis of clinical features and outcome of adult patients in southern Taiwan. Chang Gung Med J, 2009, 32(5):509–516. PMID: 19840508

Uygur-Bayramicli O, Dabak G, Dabak R. A clinical dilemma: abdominal tuberculosis. World J Gastroenterol, 2003, 9(5):1098–1101. https://doi.org/10.3748/wjg.v9.i5.1098 PMID: 12717865 PMCID: PMC4611381

Muneef MA, Memish Z, Mahmoud SA, Sadoon SA, Bannatyne R, Khan Y. Tuberculosis in the belly: a review of forty-six cases involving the gastrointestinal tract and peritoneum. Scand J Gastroenterol, 2001, 36(5):528–532. https://doi.org/10.1080/0300565001750153412 PMID: 11346208

Uzunkoy A, Harma M, Harma M. Diagnosis of abdominal tuberculosis: experience from 11 cases and review of the literature. World J Gastroenterol, 2004, 10(24):3647–3649. https://doi.org/10.3748/wjg.v10.i24.3647 PMID: 15534923 PMCID: PMC4612009

Misra SP, Misra V, Dwivedi M, Gupta SC. Colonic tuberculosis: clinical features, endoscopic appearance and management. J Gastroenterol Hepatol, 1999, 14(7):723–729. https://doi.org/10.1046/j.1440-1746.1999.01940.x PMID: 10440219

Nagi B, Kocchar R, Bhasin DK, Singh K. Colorectal tuberculosis. Eur Radiol, 2003, 13(8):1907–1912. https://doi.org/10.1007/s00330-002-1409-z PMID: 12942293

Singh V, Kumar P, Kamal J, Prakash V, Vaiphei K, Singh K. Clinicocolonoscopic profile of colonic tuberculosis. Am J Gastroenterol, 1996, 91(3):565–568. PMID: 8633510

Mukewar S, Mukewar S, Ravi R, Prasad A, Dua KS. Colon tuberculosis: endoscopic features and prospective endoscopic follow-up after anti-tuberculosis treatment. Clin Transl Gastroenterol, 2012, 3(10):e24. https://doi.org/10.1038/ctg.2012.19 PMID: 23238066 PMCID: PMC3491534

Hänscheid T, Ribeiro CM, Shapiro HM, Perlmutter NG. Fluorescence microscopy for tuberculosis diagnosis. Lancet Infect Dis, 2007, 7(4):236–237. https://doi.org/10.1016/S1473-3099(07)70058-0 PMID: 17376374

Balasubramanian R, Nagarajan M, Balambal R, Tripathy SP, Sundararaman R, Venkatesan P, Paramasivam CN, Rajasambandam P, Rangabashyam N, Prabhakar R. Randomised controlled clinical trial of short course chemotherapy in abdominal tuberculosis: a five-year report. Int J Tuberc Lung Dis, 1997, 1(1):41–51. PMID: 9441058

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