Research Article

When Two Mimics Coexist: Simultaneous Crohn's Disease and Intestinal Tuberculosis in An Adolescent

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Abstract

Background: Crohn's disease and intestinal tuberculosis are usually exclusion diagnoses in children, but coexisting Crohn's disease and intestinal tuberculosis have been reported. Hazards of missing diagnoses of Crohn's disease and intestinal tuberculosis in children include disseminated tuberculosis in an immunocompromised person and failure to diagnose and treat Crohn's disease in a country with high rates of tuberculosis, such as Indonesia.

Case summary: A 14-year-old girl with two months of abdominal pain, blood in the stool, and 10 kg weight loss, as well as pallor and ascites and bilateral leg edema. Hemoglobin 8.2 g/dL, albumin 2.1 g/dL, erythrocyte sedimentation rate 78 mm/h, and C-reactive protein 45 mg/L. Colonoscopy and ileoscopy showed deep ulcers and cobblestoning and skip lesions in the cecum and ascending colon. Biopsy histology showed widespread chronic active colitis with cryptitis and noncaseating granulomas but no acid-fast bacilli. Stool testing for Mycobacterium tuberculosis using the Xpert MTB/RIF assay detected rifampicin-susceptible M. tuberculosis. Diagnosis of CD and ITB made. Anti-tuberculosis therapy and nutritional support started.

Conclusion: Concurrent CD and intestinal TB should be considered in children living in or born in regions with a high prevalence of active TB. Stool and tissue Xpert testing can help confirm a diagnosis of intestinal TB in addition to histopathologic testing. Antituberculosis therapy should be given before immunosuppressive therapy for CD. Endoscopy to reassess CD can be performed after antituberculosis therapy.

Keywords: Crohn disease; intestinal tuberculosis; child; Xpert MTB/RIF; feces; granuloma.

Introduction

Tuberculosis is one of the leading infectious causes of death worldwide, and Indonesia has the second-highest number of estimated tuberculosis cases, after India [1]. The number of pediatric IBD cases in newly industrialized Asian countries is rising [2]. Pediatric gastroenterologists in newly industrialized Asian countries commonly see cases of Crohn's disease and intestinal tuberculosis among children.

The two conditions share symptoms of chronic diarrhea, bloody stools, abdominal pain, and growth impairment in children or weight loss in adults. Both conditions involve ulcers and granulomas at the ileocecal junction [3,4]. Clinical scoring tools and other tests can help differentiate the two conditions, but no test or scoring tool has been fully validated for use in individual patients to make this differentiation [5,6]. Other shared clinical features and findings in children living in areas where either condition is endemic include fever and other exposures and skip lesions and perianal disease [7,8].

Most published studies report on CD and ITB independently. Few studies have examined the effects of CD and ITB occurring together in patients. Patients with CD receiving corticosteroids, thiopurines, or anti-TNF agents for CD treatment have developed active or disseminated TB if they also have localized TB [9,10]. Failure to treat CD in patients with tuberculosis can lead to malnutrition and growth problems in children with CD.

We describe an adolescent female patient with CD and ITB, tested positive for TB by fecal Xpert MTB/RIF and negative for acid-fast bacteria testing. We discuss clinical considerations when treating patients with CD and ITB according to the literature. This case report adheres to the CARE guidelines [11].

Case Presentation

History and examination

A 14-year-old female patient was referred for evaluation of two months of abdominal pain, bloody stools, and weight loss of 10 kg. Stool frequency was one to two daily episodes, plus multiple nocturnal bowel movements, and the patient has low-grade fever, no night sweats or evidence of cough, and no contacts with patients with tuberculosis. Parents say the patient had a BCG vaccination, but no BCG scar was visible. There are no other family members with IBD or perianal diseases. The patient was pale, had ascites, and bilateral leg edema but no palpable lymphadenopathy. The patient was assessed as severely malnourished based on body weight of 33 kg, height of 157 cm, BMI of 13.4, and BMI z-score below -3SD according to WHO growth charts. No perianal abnormalities were identified on examination.

Laboratory findings

Studies showed anemia (hemoglobin 8.2 g/dL), leukocytosis (13.730 103/µL), low albumin (albumin 2.1 g/dL), and elevated acute-phase reactants (erythrocyte sedimentation rate 78 mm/h; C-reactive protein 45 mg/L). X-ray examination of the chest was normal. Diagnostic tests are shown in Table 1.

Endoscopy

Ileocolonoscopy revealed deep, irregular ulcerations and nodular mucosa, with skip areas, in the cecum and ascending colon (Figure 1). Deep ulcers, nodularity, and involvement of the ileocecum on ileocolonoscopy suggested a diagnosis of Crohn's disease or intestinal TB. Nodular mucosal lesions were present at the ileocecal valve, but endoscopic examination of the terminal ileum was incomplete due to bleeding.

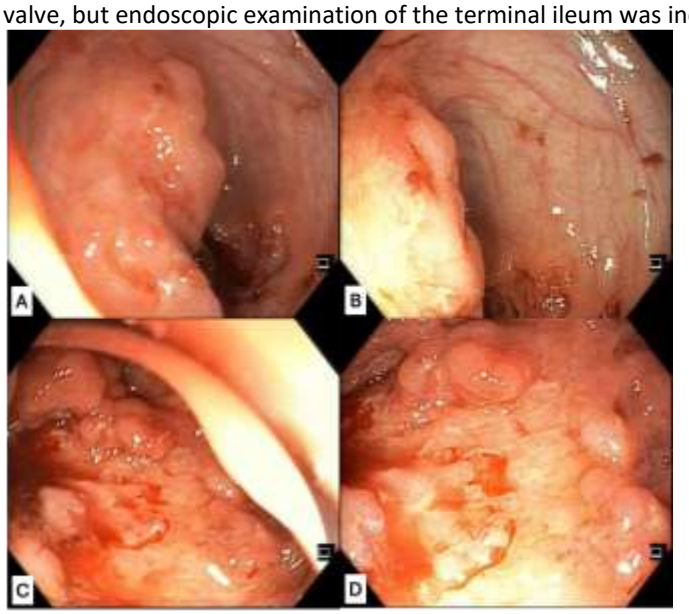


Figure 1. Ileocolonoscopy showing multiple mucosal nodules and deep, irregular ulcers with exudate in the cecum (A, B) and ascending colon (C, D). Differential diagnosis included CD and ITB.

Histopathology

Colonic biopsy specimens showed severe active chronic colitis, characterized by infiltration of the lamina propria by inflammatory cells and cryptitis and neutrophil infiltration of the reactive crypt epithelium (Figure 2). Noncaseating granulomas were present, and no acid-fast bacilli were detected by Ziehl-Neelsen stain. The biopsy results were most suggestive of IBD.

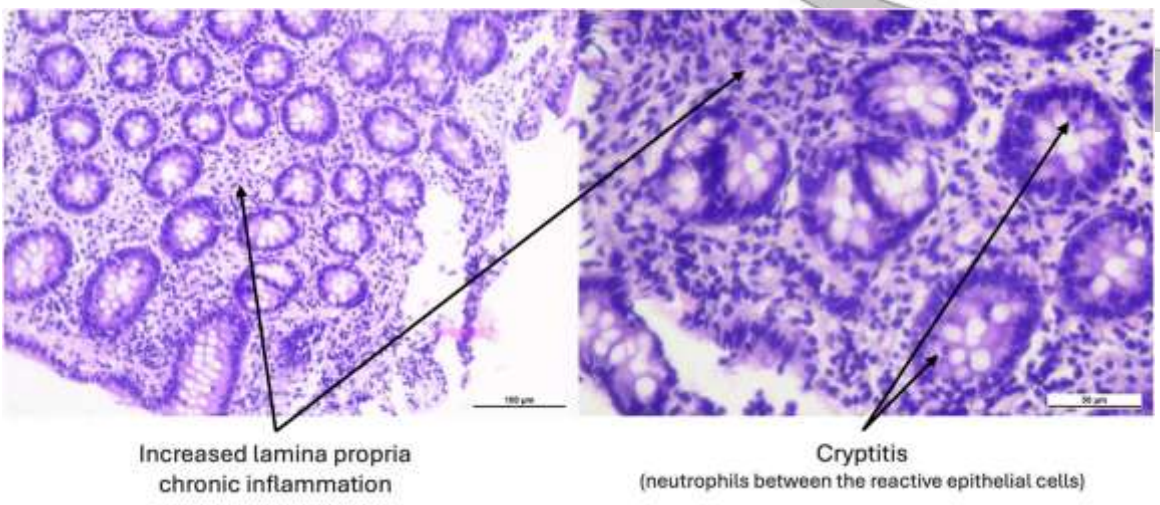


Figure 2. Colonic biopsy (hematoxylin and eosin). Left (scale bar 100 µm): increased chronic inflammation of the lamina propria. Right (scale bar 50 µm): cryptitis with neutrophils between reactive epithelial cells. Acid-fast bacilli staining was negative.

Molecular diagnosis

Because tuberculosis was not excluded in an endemic location, the stool was tested for M. tuberculosis complex using Xpert MTB/RIF. Molecular testing of the stool was positive for M. tuberculosis complex but negative for rifampicin resistance. A diagnosis of CD and ITB was made at the same time, based on endoscopic and histopathologic evidence of CD and molecular evidence of tuberculosis.

Table 1. Diagnostic work-up at presentation

Domain	Finding	Interpretation
Clinical	2 months of abdominal pain, bloody stools; 10 kg weight loss; pallor, ascites, bilateral edema	Severe chronic inflammatory enteropathy with protein-losing state
Hematology	Hemoglobin 8.2 g/dL	Severe anemia
Biochemistry	Albumin 2.1 g/dL	Hypoalbuminemia
Inflammation	ESR 78 mm/h; CRP 45 mg/L	Marked systemic inflammation
Ileocolonoscopy	Deep irregular ulcers, nodular mucosa, skip lesions (cecum, ascending colon)	Compatible with CD or ITB
Histology	Severe active chronic colitis, cryptitis, non-caseating granulomas; AFB stain negative	Favors CD; does not exclude ITB
Fecal Xpert MTB/RIF	M. tuberculosis detected; rifampicin resistance not detected	Microbiological evidence of tuberculosis
Chest radiograph	Normal	No evidence of pulmonary tuberculosis

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; AFB, acid-fast bacilli.

Treatment and follow-up

Treatment for tuberculosis began before treatment with immunosuppressive agents for CD. Standard tuberculosis treatment drugs include isoniazid, rifampin, pyrazinamide, and ethambutol for two months and two months of isoniazid and rifampin dosed by weight. Supportive nutrition was given. Gastrointestinal symptoms and weight gain began to improve one month after tuberculosis treatment started.

Discussion

This case represents an association between CD and ITB. Clinical features of CD, such as skip lesions and noncaseating granulomas, as well as proof of M. tuberculosis infection by stool molecular diagnostics, were seen in this patient. Few cases of CD and ITB association have been reported. A splenic concentration of tuberculosis

was found in a 5.5-year-old girl who later developed CD during treatment with ATT [12]. Another recent report described CD and ITB association [13]. Tuberculosis has developed after CD was treated with anti-TNF agents in other patients, including cases of miliary and later spinal tuberculosis in adolescents treated with infliximab [14]. Signs of tuberculosis and lack of response to ATT for more than a year before diagnosis of CD have been reported in other patients [15].

The main other differential diagnoses are ITB alone, with granulomatous colitis and skip lesions mimicking CD. Noncaseating granulomas are common in ITB. Only 21% of ITB biopsies have caseating granulomas [3]. Several case reports exist of ITB that was initially misdiagnosed as CD and successfully treated with ATT [16,17]. Strategies for distinguishing CD from ITB include clinical response to ATT. More than 90% of ITB patients have clinical improvement after 3-6 months, and nearly all ITB patients have endoscopic healing after 6 months, compared with less than 5% of CD patients [3,18]. Repeat ileocolonoscopy at the end of ATT is recommended to help differentiate between CD and ITB. Lingering endoscopic disease in patients cured by microbiologic testing and treated with ATT is more consistent with CD, and healing is more consistent with ITB.

Stool Xpert testing detects bacilli from all parts of the gastrointestinal tract, including swallowed bacilli from the respiratory tract. Stool Xpert testing for tuberculosis has 99% specificity and detected tuberculosis in 67% of children with culture-confirmed pulmonary tuberculosis [19]. Positive stool Xpert testing results can confirm tuberculosis but cannot confirm other forms of extrapulmonary disease. Diagnostic imaging may be necessary. Standard Xpert MTB/RIF testing of gastrointestinal samples has a pooled sensitivity of 48% and specificity of 99% [20]. The newer Xpert Ultra testing method has led to false-positive results in intestinal samples and controls with Crohn disease [21]. The World Health Organization now recommends stool Xpert Ultra testing in children [22]. Be cautious when interpreting low-level Xpert Ultra results in patients with histologic evidence of Crohn disease.

Tuberculosis in children receiving anti-TNF therapy is severe. In a European multicenter study of 19 children, 78% had disseminated tuberculosis, and one child died or had complications. The most common associated condition in children was CD [9]. In a study of Korean children with IBD receiving anti-TNF therapy, 1.2% developed active tuberculosis, with onset after a median of 3 months of anti-TNF therapy [23]. Pretherapy screening is not useful. Of 15 children screened in Europe who subsequently developed tuberculosis, only 1 tested positive [9]. Published reports of prior positive tuberculin skin tests or IGRA results in children with confirmed tuberculosis are lacking [12,24]. Malnutrition and hypoalbuminemia, as seen in our patient, may interfere with test results. In endemic areas, a lack of prior positive test results should not exclude the diagnosis in a child strongly suspected of having tuberculosis.

Management

Tuberculosis should be treated before initiating immunosuppressive therapy, as recommended by international guidelines [10,25]. The recommended duration of treatment for abdominal tuberculosis in children is six months with a combination of isoniazid, rifampin, pyrazinamide, and ethambutol [26]. Corticosteroid treatment should be avoided while tuberculosis is uncontrolled. Patients with tuberculosis should be given nutritional support. Exclusive enteral nutrition, a first-line induction therapy for pediatric Crohn's disease involving the bowel [27], can provide nutritional support and mucosal healing without other immunosuppressive therapies.

After ATT, treatment strategies for CD must consider the risk of tuberculosis. Thalidomide led to remission in 60% of children with CD and a previous tuberculosis infection [15]. The intestinal CD medication vedolizumab was successful in a patient with CD and a posttuberculosis spinal infection [14]. Anti-TNF medications should be used cautiously in patients with a history of tuberculosis and may be given during or after tuberculosis treatment, with appropriate monitoring tests and imaging as needed [10,25]. Findings of ascites in this patient raise the possibility of peritoneal tuberculosis, which can be supported by measuring adenosine deaminase levels in ascitic fluid if other tests for peritoneal tuberculosis are negative [16]. See Figure 3 for a proposed treatment strategy based on findings from this case report and other studies.



Figure 3. Suggested approach to a child with suspected Crohn's disease in a tuberculosis-endemic setting. AFB, acid-fast bacilli; ATT, anti-tuberculous therapy; CD, Crohn's disease; IGRA, interferon-gamma release assay; ITB, intestinal tuberculosis; TNF, tumor necrosis factor; TST, tuberculin skin test.

Strengths and limitations

This report presents a case of concomitant CD and ITB in a child diagnosed with endoscopic, histopathologic, and molecular tests. Limitations of this report include the absence of mycobacterial culture and tissue PCR and limited follow-up with endoscopic evaluation after treatment with ATT. Conclusions about the incidence of concomitant CD and ITB cannot be made based on this case report.

Conclusion

CD and ITB can coexist in the same patient. CD and ITB should be considered in all patients in countries with high TB burden in whom IBD is suspected. Histologic testing does not exclude TB. Stool and tissue Xpert tests provide rapid and reliable supplemental testing for TB. Imaging of the chest may help identify TB infection in the lungs. Treatment for TB should be initiated before immunosuppression and continued along with nutrition therapy for patients with suspected CD. Endoscopy following ATT may be used to diagnose CD. Nonbiologic therapies targeting the gut and careful use of anti-TNF therapies at certain times may help treat both CD and TB.

Declarations

Conflicts of interest: The authors declare no conflicts of interest.

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Data availability: All data relevant to the case are included in the article.

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