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# Intestinal tuberculosis can masquerade as Crohn's disease: A teachable moment

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## Abstract

Intestinal tuberculosis and Crohn's disease are chronic granulomatous diseases with similar clinical presentations and can mimic one another. Their treatment modalities are completely different; however, sometimes it is challenging to differentiate them. We report a case of a 51-year-old female presenting with abdominal pain and on-and-off diarrhea for 4 years with weight loss. Clinical symptoms along with multiple aphthous ulcers in the terminal ileum and negative tuberculin test favored the diagnosis of Crohn's disease. The patient did not respond to steroids. A repeat colonoscopy with acid-fast bacilli stain showed *Mycobacterium tuberculosis*. This case highlights that acid-fast bacilli culture and tuberculosis polymerase chain reaction to confirm or rule out the diagnosis of intestinal tuberculosis in all patients suspected of Crohn's disease.

## Keywords

Crohn's disease, intestinal tuberculosis, colonoscopy, acid-fast bacilli

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## Introduction

Crohn's disease (CD) and intestinal tuberculosis (ITB) are chronic granulomatous disorders with similar clinical pictures, making it challenging to differentiate them and poses misdiagnosis. The incidence of CD in Nepal was 1.6 per 1000 colonoscopic examinations.[1] The annual incidence of tuberculosis (TB) in Nepal is 245 per 100,000 population.[2] Abdominal TB accounts for nearly 1%–3% of TB worldwide;[3,4] however, exact data of Nepal are unavailable. The symptoms of abdominal pain, diarrhea, fever, and weight loss are common to both CD and ITB. Therefore, it is crucial to consider pathological features, colonoscopy findings, and biopsy specimens for bacterial examination to arrive at a correct differential diagnosis.[5,6] The treatment modalities of these two diseases are completely different. Administering immunosuppressive medications to a patient misdiagnosed with ITB as CD can be fatal. Similarly, treating with antitubercular therapy to a patient with CD can delay treatment.[7] We report a case of 51-year-old female presenting with chronic diarrhea for 4 years and weight loss and misdiagnosed as CD.

## Case presentation

A 51-year-old female presented with abdominal pain, diarrhea, and weight loss for 4 years. The abdominal pain was localized to epigastric region, non-radiating, and not associated with meals. She had loose bowel movements on-and-off with bowel movements occurring approximately five to six times per day. Initially, the stool was watery and mucoid with no foul odor, and not tinged with blood. The patient had significant weight loss despite good appetite and adequate oral intake. There was no associated

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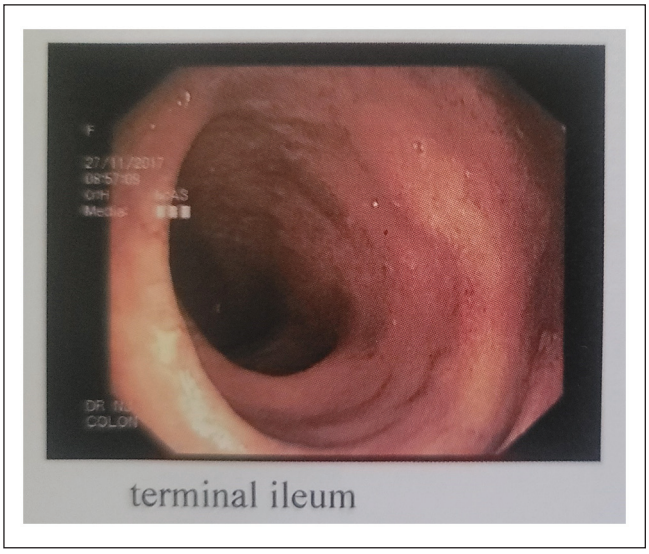


**Figure 1.** Colonoscopy showing multiple aphthous ulcers with normal intervening mucosa in terminal ileum.

fever, sweating, evening rise of temperature, vomiting, jaundice, mouth ulcers, or joint pain.

Patient was diagnosed with generalized anxiety disorder and has been on treatment with selective serotonin receptor inhibitors. She had previously presented to a local hospital, where she was treated with triple therapy for *Helicobacter pylori* and vitamin D supplementation for a low vitamin D level. She had no significant surgical history.

During physical examination, the patient did not have a fever peripheral lymphadenopathy or skin discoloration. Upon palpation, the abdomen was soft and non-tender, and no palpable mass or organomegaly was present. The rectal examination was non-painful and revealed no palpable rectal mass. The hematological reports showed a hemoglobin level of 13.6 g/dL and a white blood cell count of 7400/mm$^3$ with 57% neutrophils, 39% lymphocytes, and 3% monocytes. The patient had an elevated level of anti-cyclic citrullinated peptide (CCP) at 22.83 U/mL and an anti-nuclear antibody (ANA) level of 81.31 AU/mL. The liver and renal function tests were within normal limits.

The stool test for occult blood was negative, and both the serum and stool tests for *H. pylori* were negative. The stool and urine cultures showed no growth after 48 h of incubation, and no eggs or intestinal parasites were seen on stool microscopy.

Ultrasonography of abdomen and pelvis showed no abnormality. Chest X-ray did not reveal any fibrosis or cavitations. Tuberculin skin test (TST) was negative. Colonoscopy with biopsy showed multiple aphthous ulcers with normal intervening mucosa in terminal ileum suggesting CD (Figure 1). Biopsy specimens showed focal active neutrophilic inflammation with villitis on terminal ileum. CD was suspected and patient was treated with tapering dose of steroids for 3 weeks. However, patient's symptoms were not improving. Subsequently, a repeat TST was done that was positive with an induration of 27 mm diameter. On GeneXpert test, *Mycobacterium tuberculosis* was not detected. A repeat colonoscopy with biopsy was performed and specimen was sent for acid-fast bacilli (AFB) stain where *M. tuberculosis* was detected. The patient started on antitubercular therapy with rifampicin, isoniazid, pyrazinamide, and ethambutol according to the national guideline of Nepal.[8] Patient responded well to the antitubercular regimen leading to resolution of symptoms and weight gain.

## Discussion

Inflammatory bowel disease (IBD) and CD are two bowel disorders that have distinct etiologies, pathophysiology, and treatments. It is difficult to differentiate ITB and CD as clinical presentations, radiological findings, and histologic features are similar and non-specific.[5,6] The pathological features, colonoscopy findings, and biopsy specimens for bacterial examination are very important to reach the differential diagnosis.[9] It has been reported that the misdiagnosis rate for the two diseases can reach 50%–70%.[10]

Abdominal pain, weight loss, fever, bowel obstruction, bloody diarrhea, endoscopic findings of ulcerations, skip lesions, ulcerations, and terminal ileum involvement are the common clinical symptoms of both the diseases.[7] Longitudinal ulcers, aphthous ulcers, anorectal lesions, cobblestone appearance, and involvement of more than four segments are the colonoscopy features suggestive of CD, while involvement of fewer than four segments, transverse ulcers, a patulous ileocecal valve, and pseudo polyps or scars are features suggestive of ITB.[11,12] The most definitive method of differentiation of CD from ITB is histology. Caseating granulomata and confluent granulomata are features found only in ITB.[13] Other suggestive features to suggest ITB are disproportionate submucosal inflammation, large granulomata ($\geqslant$0.05 mm), large numbers of granulomata ($\geqslant$10 per biopsy site), and ulcers lined by epithelioid histiocytes.[14] AFB in biopsy specimens are not frequently encountered even though they are very specific.[7,15] Target sign, comb sign, and adipose creeping sign are important imaging findings that are typical of CD, while involvement of fewer than four segments is more likely to be ITB.[12,16]

The use of steroids in patients with undiagnosed or suspected TB carries risks. Steroids suppress the immune system that can increase the risk of disease progression or dissemination if it is actually TB.[16] So, use of steroids increases the risk of flaring up of the TB and the cost to the existing treatment during hospitalization.[16] The use of steroids in context of diagnostic uncertainty requires careful consideration of the potential risks and benefits especially in cases with possibility of TB.[16] In our patient, colonoscopy with biopsy showed multiple aphthous ulcers with normal intervening mucosa in terminal ileum with suggesting CD due to which the patient was treated with tapering dose of

steroids for 3 weeks, which did not relieve the symptoms. In our patient, ITB was not completely ruled out before initiating steroids. Though a strong clinical picture, an absence of caseating granuloma in pathologic findings and a negative tuberculin skin test point toward diagnosis of CD; intestinal biopsy sample should have been sent for AFB stain or culture from the first colonoscopy.[17]

Finding *Mycobacterium* bacilli in the intestinal tissues would have been the best way to confirm the diagnosis of TB, just like it would be for any other infectious disease. The simplest method to demonstrate the bacillus is using AFB staining, but this has a very low sensitivity range of 2.7%–37.5%. Since ITB is a paucibacillary disease, it is difficult to demonstrate the organism, which explains the low sensitivity of these tests.[18] Mantoux and interferon-gamma release assays (IGRAs) are markers for latent TB. However, a positive or negative IGRA will not prove or disprove the diagnosis of ITB because the IGRA and Mantoux both predict latent TB rather than active TB. The performance of a TST as a diagnostic tool is not very satisfactory, and as a result, it has been phased out in recent years.[12]

Less than half of ITB patients have positive TB cultures.[19] In a meta-analysis by Sharma et al.,[20] the usage of fully automated real-time polymerase chain reaction (PCR)-based GeneXpert test for diagnosis ITB using ascitic fluid was 64% when compared to peritoneal culture and 30% when compared to the composite reference standard. The sensitivity of Xpert MTB was 23% when compared to the composite reference standard using the intestinal tissue.[20] The specificity of Xpert MTB was 100% for diagnosis of ITB compared against peritoneal culture and composite reference standard.[20] Ileocecal mucosal specimens and fecal specimens used for reverse transcription PCR (RT-PCR) show higher specificity to establish a diagnosis of ITB, but their sensitivity is low. Fecal PCR is suggestive to be more sensitive than tissue PCR, but this needs to be investigated further.[19] The background incidence of TB in a geographic area significantly affects the positive predictive value (PPV) and negative predictive value (NPV) of diagnostic tests. In regions with a higher background incidence, the likelihood of true positive results increases, leading to a higher PPV. However, the NPV may be lower due to the higher chance of false negatives, potentially resulting in TB cases being missed.[21] Understanding the local epidemiology of TB is essential for correctly interpreting test results and making informed clinical decisions.

Differentiating ITB from CD is a continual problem, and a negative AFB stain, culture, or PCR should be considered in initial workup especially given the rising prevalence of inflammatory bowel illness in TB-endemic regions. Our patient was placed on a trial of steroids, but she did not get any better. A lack of response should prompt consideration of an alternative diagnosis like ITB and CMV (Cytomegalovirus) colitis for patients who are under steroids therapy.[7] Appropriate reevaluation strategies can include testing for TB, repeating a colonoscopy with terminal ileum intubation, a trial for anti-TB therapy, or repeating a computed tomography (CT) scan.[7] ITB mimicking CD is very confusing to clinicians, and it becomes more challenging in resource-limited setting and patient with low economic background. Since the treatments are radically different, administering immunosuppressive medications to an ITB patient misdiagnosed as a CD can be fatal. Therefore, it is critical to differentiate between these two diagnoses, posing more difficulty and dilemma to clinicians.[7] Fortunately, for our patient despite use of steroids, no life-threatening systemic flare-up of TB ensued.

According to a study by Wu et al.,[22] a clinician-friendly five-marker predictive model (which includes perineal involvement, longitudinal ulcer, pulmonary involvement, left colon, and ratio of TB-specific antigen to phytohemagglutinin) could be effectively employed to aid clinicians in establishing a dependable differential diagnosis between IBD and CD in real-world medical settings. It has a good diagnostic accuracy with sensitivity and specificity of 96.7% and 90.7%, respectively.[17]

In most TB-prevalent countries, a large number of ITB cases are diagnosed based on the assessment of response to anti-TB therapy (ATT). In cases with uncertain initial diagnosis, it is important to observe objective evidence of response to antitubercular therapy. The standard strategy to discriminate ITB and CD in TB endemic areas is to perform triad of antitubercular therapy (variably diagnostic trial or therapeutic trial). Diagnostic delay to CD due to initial regimen of antitubercular therapy can lead to stenosing complications and the need for surgery. A 2-month colonoscopy done to observe early mucosal response can help address the causes for lack of response, drug resistance, or alternative diagnosis. Fecal calprotectin can be a better marker for mucosal response in patients not willing to undergo colonoscopy.[17] Clinicians treat for ITB and evaluate the response when all the conventional methods fail to distinguish them. This approach is safe for cases treated as for CD in the setting of missed ITB in the TB-endemic region where life-threatening flare-up of ITB can occur especially with immunosuppressive agents and biologics. Contrarily, the ATT can delay CD treatment, and ATT has its own pharmacological side effects.[14] In addition, it is critical to comprehend the risks associated with anti-tumor necrosis factor (anti-TNF) therapy when treating CD in patients with undiagnosed TB. An evaluation of the risk of TB is advised by international guidelines prior to beginning anti-TNF therapy. Consideration of epidemiological risk factors, a physical exam, chest radiography, and either a TST or an IGRA are all part of this assessment. It is crucial to keep in mind that specific recommendations for using these diagnostic modalities may change based on regional policies and customs.[23]

Hence, clinical judgment plays a crucial role in this type of cases for which clinicians should update themselves with current progression of diagnostic tools, technique, and strategies and utilize it in treating the patient.

## Conclusion

For all patients suspected with CD, we advise routinely sending additional samples in saline for AFB culture and TB PCR. Taking extra samples, we believe, is a low-risk, low-cost intervention that can improve diagnostic accuracy and reduce the need for repeat procedures. We propose that patients with "uncontrolled" CD who have not previously had intestinal biopsies for AFB culture be considered for a repeat colonoscopy to investigate the possibility of ITB. We believe this approach will uncover cases of intestinal TB misdiagnosis, leading to more accurate diagnoses and better outcomes.

### Author contributions

P.K.C., M.B., S.A., and P.P. wrote the original manuscript, reviewed, and edited the original manuscript. S.B., H.B.B., N.K.S., S.K., S.A., and B.B. reviewed and edited the original manuscript.

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