

# Misdiagnosis and Mistherapy of Crohn's Disease as Intestinal Tuberculosis

## Case Report and Literature Review

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**Abstract:** The differential diagnosis of Crohn's disease (CD) and intestinal tuberculosis (ITB) remains difficult as the clinical symptoms of the 2 digestive diseases are so similar. Here we report a case where a patient was initially misdiagnosed with ITB prior to the correct CD diagnosis. The 46-year-old male patient was hospitalized elsewhere for pain in the right lower abdomen and underwent an appendectomy. The pathological diagnosis was ITB and the patient was administered antituberculosis therapy for 1 year. Afterward, the patient was readmitted to the hospital for a right lower abdominal mass. A computed tomography scan revealed intestinal gas, fistula, and abdominal mass. We performed a right hemicolectomy on the patient. Postoperatively, we diagnosed the patient with CD, based on patient history and pathological examination. According to the CD active index (CAI), the patient was at high risk and began treatment with infliximab. The patient has remained in complete remission and made a good recovery after 8-months follow-up. We compared this case with the results of a literature review on the misdiagnosis between CD and ITB (26 previously reported cases) to determine the characteristics of misdiagnosed cases. We found that distinguishing between ITB and CD is difficult because of their varied clinical presentation, nonspecific investigative tools, and profound similarities even in pathological specimens. Although a CT scan to determine the morphology of the bowel wall is a key for correct diagnosis, each case still poses challenges for diagnosis and administering the appropriate treatment.

(*Medicine* 95(1):e2436)

**Abbreviations:** CD = Crohn's disease, CAI = Crohn's disease active index, CT = computed tomography, ITB = intestinal tuberculosis.

Editor: Samantha Martin.

Received: September 4, 2015; revised: December 7, 2015; accepted: December 10, 2015.

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The authors have no funding or conflicts of interest to disclose.

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ISSN: 0025-7974

DOI: 10.1097/MD.0000000000002436

## INTRODUCTION

Crohn's disease (CD) and intestinal tuberculosis (ITB) are intestine diseases, which are chronic granulomatous. They exhibit similar manifestations in clinic, but their most important courses, as well as treatments, are far from being the same. On one hand, ITB can be cured, but CD cannot, so individual diagnosis is needed. However, differential diagnosis of CD and ITB remains difficult when the presentation is ambiguous. Here, we report a case whereby a male patient was diagnosed with CD presenting with a recurrent abdominal mass and intestinal fistula, whose initial diagnostic work-up suggested ITB. We compare our new case with the results of a literature review on the misdiagnosis between CD and ITB (26 previously reported cases) to summarize the characteristics of misdiagnosed cases.

## PATIENTS AND METHODS

The patient signed the permission for the publication when he was admitted in our hospital. Written informed consent was obtained, and the study was approved by the Research Ethics Committee of the Tianjin Medical University General Hospital.

We performed a PubMed (National Library of Medicine, Bethesda, MD) search using the terms "Crohn AND Intestinal tuberculosis," retrieving all available articles published in English up to May 2015. We combined these data with our new case report to describe the differential characteristics between ITB and CD.

## CASE REPORT

On April 30, 2014, a 46-year-old male patient was admitted to the gastroenterology department with dyspepsia, abdominal pain, vomiting, and a 4 kg weight loss. The patient had previously undergone an appendectomy and abdominal abscess debridement for right abdominal pain and fever in January 2008. Seven months after the operation, he underwent a resection of the ileocecum for a spontaneous perforation that occurred in August 2008. The pathological diagnosis was ITB and the patient underwent antituberculosis therapy for 1 year.

The patient was hospitalized for right lower quarter pain on April 30, 2014. He had a fever, and physical examination revealed a bulge on the right lower abdomen, obvious tenderness, no fluctuation, no rebound pain, and muscle tonus. The laboratory results for the patient revealed the following: a white blood cell count of  $11.77 \times 10^9/L$  (normal range  $4-11 \times 10^9/L$ ), thrombocytosis (platelet concentration of  $469 \times 10^9/L$ , normal range  $100-300 \times 10^9/L$ ), and a fecal occult blood test of 1+. All other tests were normal. The computer tomography (CT) scans showed a segmental and irregular thickening of the anastomosis, ascending colon, and hepatic flexure with thickened mesenteric fat; dense shadows of anastomosis; and multiple stripes, nodes, exudation, and bubbles. Colonoscopy revealed a severe

hyperemia and edema of mucosa in the anastomosis that was associated with inflammation, a fistulous opening, mucopurulent exudate, and multiple deep ulcers. The pathology showed mucosal chronic inflammation associated with ulcers and acute inflammation, moderate atypical hyperplasia of the glands, and a crypt abscess. The patient became asymptomatic after anti-inflammatory and nutritional support therapy.

The patient was hospitalized for right lower quarter pain again on June 15, 2014. His vital signs were normal and physical examination revealed a mass on the right lower abdomen ( $5 \times 4$  cm in size). All laboratory tests were normal. The CT scan showed the wall thickness of the right colon and the anastomosis, and the gas shadow in swelling soft tissue of the right lower abdominal wall (Figure 1). A right hemicolectomy was performed after the preparation because of the persistent right lower abdominal mass. Macroscopic histopathology showed that the intestinal wall was thickened with luminal narrowing (Figure 2).

The pathology after the operation showed colic mucosal ulceration along with transmural inflammation, mixed inflammatory infiltrate, and granuloma (ie, lymph cells and plasmacytes infiltrated the abdominal wall, and a granulomatous change occurred in the muscular layer) (Figure 3). The Ziehl–Neelson stain for acid-fast bacilli was negative. As the time between the first diagnosis and the second diagnosis was 6 years, 2 of our pathology experts rechecked the pathological data with the permission of the patient and the hospital. Both experts considered that the pathological diagnosis should be CD rather than ITB. Ultimately, we made a diagnosis of CD, which is indicative of the pathological changes and the history of recurrent intestinal fistula. According to the patient’s CDAI, he was treated with infliximab. At the time of the 8-month follow-up, the patient had remained in complete remission and made a good recovery.

## RESULTS

### Comparison With Literature

To date, we identified 26 cases in the literature regarding misdiagnoses between ITB and CD. Among them, there were 22 cases in which ITB was misdiagnosed as CD. In these 22 cases, there were 14 females, and 13 males, yielding a



**FIGURE 1.** Computed tomography of the right lower abdomen showing the wall thickness of the ascending colon with the gas shadow in swelling soft tissue of the right lower abdominal wall.



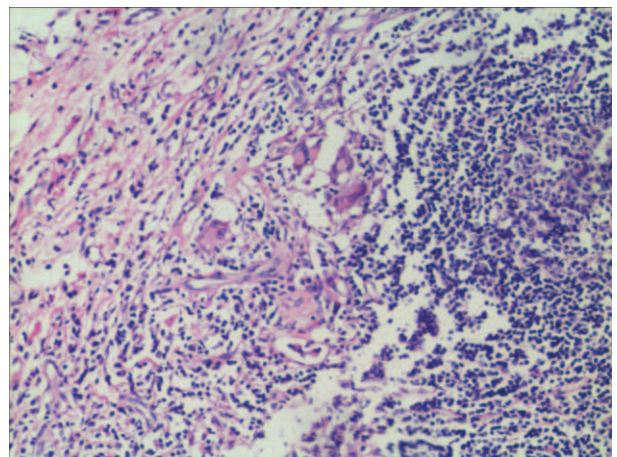
**FIGURE 2.** Macroscopic histopathology showing that both the ascending colon and anastomosis wall are thickened and the lumen is narrowed.

female to male sex ratio of 1.07. The mean age of the patients at diagnosis was 37.7 (15–80) years. Combined with our case, there were 5 cases where CD was misdiagnosed as ITB.

### ITB Misdiagnosed as CD

#### Clinical and Laboratory Features

In these cases, the initial symptoms include abdominal pain,<sup>1–17</sup> diarrhea,<sup>1,2,4,7–9,11,12,14,17–20</sup> weight loss,<sup>1,4,7,9–11,13–19</sup> fever,<sup>2,3,6–9,11,13,16,17,19</sup> hematochezia,<sup>5,18,21,22</sup> anorexia,<sup>1,6,10,14,15,17</sup> vomiting,<sup>1,7,10,15,17</sup> intestinal obstruction,<sup>3,6</sup>



**FIGURE 3.** The pathology of the ascending colon biopsies showing granuloma.

and dyspnea.<sup>2</sup> The abdominal physical examinations were normal or not described in most cases. These data indicated that discriminating between ITB and CD is especially difficult because the clinical presentation is equivocal and nonspecific, and the diagnostic value of the clinical features is not high. The laboratory features mainly included anemia,<sup>1,2,9–12,16,18,19</sup> raised erythrocyte sedimentation rate (ESR),<sup>4,9,12,17–19</sup> and raised C-reactive protein (CRP).<sup>4,14,18,19</sup> Other laboratory features were normal or not described. The clinical and laboratory features observed in the patients are summarized in Table 1.

**Location of Involvement and Morphology of Bowel Segment**

The CT images indicated that the locations of the lesion involvement were as follows: ileum,<sup>1,2,6,8–10,17,23</sup> ileocecal valve,<sup>2,3,8,12,19</sup> right colon,<sup>2,4,5,8,11,13–16</sup> sigmoid colon,<sup>8,22</sup> rectum,<sup>18,19</sup> and stomach.<sup>7</sup> Both CD and ITB can involve any segment of the gastrointestinal tract. The lesion sites that are commonly involved in patients with misdiagnoses were the ileum (33.3%), right colon (33.3%), and ileocecal valve (18.5%).

The CT imaging morphology findings can be summarized as follows: segmental and irregular thickening of the involved bowel,<sup>1,4,6,8,9,11,12,14,16,22,23</sup> enlarged lymph nodes,<sup>4,8,12,14,23</sup> fistula,<sup>18</sup> and ascites.<sup>14</sup> However, none of these findings could be used to distinguish CD from ITB. Interestingly, almost all ITB patients were associated with normal chest radiographs. Among the colonoscopy features, pseudopolyps<sup>1,2,5,9,11,19</sup> and ulcerative lesions<sup>1,2,4–6,9,10,12,14,15,17–20,23</sup> were the most common reasons for misdiagnosis. Other reasons included

exudates,<sup>2,4</sup> nodularity,<sup>2,16,17</sup> cobblestone mucosa,<sup>4</sup> and skip areas of inflammation and ulceration.<sup>18</sup> For most of the misdiagnosed patients, the main pathological characteristics contributing to the wrong diagnoses were noncaseating granuloma<sup>1,3,6,10–12,15,18,19,22</sup> and nonspecific inflammation.<sup>3,4,6,10–12,15,17,19,22</sup> The features observed in the patients are summarized in Table 2.

**Drug Treatment and Outcomes**

Twelve patients (44.4%) received CD-related drugs as the initial treatment, 9 patients were given corticosteroids<sup>1,2,7,10,14,15,17–19,23,24</sup> (methylprednisolone and prednisone), 1 patient was given azathioprine,<sup>1,14</sup> 7 patients were discharged with 5-aminosalicylic acid (5-ASA),<sup>2,9–12,14,15,18,24</sup> 1 patient was given budesonide.<sup>11</sup> After failure of corticosteroid treatment, 6 patients received surgical treatment.<sup>1,9,11,14,17,23,24</sup> The remaining 6 patients were given antituberculosis therapy due to the presence of TB in the pulmonary site,<sup>2,7,15</sup> positive cultures of *M. tuberculosis*,<sup>15,18,19</sup> and the diagnostic treatment.<sup>10,11</sup>

For all patients, the initial detection of mycobacteria was negative. The final diagnoses of ITB were mostly based on surgical treatment,<sup>1,3,6,8,9,12–14,16,17,22–24</sup> cultures of *M. tuberculosis*,<sup>4,5,14,15,18,19</sup> symptoms of pulmonary TB,<sup>2,7,8,15,19</sup> and diagnostic treatment.<sup>8,10,11</sup> All patients finally received anti-tuberculosis therapy and showed a good response.

**CD Misdiagnosed as ITB**

Among the 4 cases, the initial symptoms included abdominal pain,<sup>25,26</sup> anorexia,<sup>25</sup> weight loss,<sup>7,25</sup> diarrhea,<sup>7</sup> and constipation.<sup>25</sup> The laboratory features mainly included anemia,<sup>7,25,26</sup> raised ESR,<sup>7,25</sup> and raised CRP.<sup>7</sup> The CT images show that the locations of involvement were as follows: ileum,<sup>26,27</sup> left colon,<sup>25</sup> and the duodenum.<sup>7</sup> The morphologies of the bowel

**TABLE 1.** Clinical and Laboratory Features Observed in the 27 Patients

Parameter	TB Misdiagnosed as CD	CD Misdiagnosed as TB
<b>Demographic features</b>		
Gender (male/female), ratio	13/14	3/2
Age (range), yr	37.7 (15–80)	31.4 (23–46)
<b>Clinical features</b>		
Abdominal pain, n(%)	17 (63.0)	3 (60.0)
Diarrhea, n(%)	13 (48.1)	1 (20.0)
Constipation, n(%)	N	1 (20.0)
Weight loss, n(%)	13 (48.1)	3 (60.0)
Fever, n(%)	11 (40.7)	N
Hematochezia, n(%)	4 (14.8)	N
Anorexia, n(%)	6 (22.2)	1 (20.0)
Vomit, n(%)	5 (18.5)	N
Intestinal obstruction, n(%)	2 (7.4)	3 (60.0)
Dyspnea, n(%)	1 (3.7)	N
Perforations, n(%)	1 (3.7)	3 (60.0)
<b>Laboratory features</b>		
Anemia, n(%)	9 (33.3)	3 (60.0)
Raised ESR, n(%)	6 (22.2)	2 (40.0)
Raised CRP, n(%)	4 (14.8)	1 (20.0)

CD, confidence interval; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; TB, tuberculosis.

**TABLE 2.** Location, CT, Colonoscopy, and Pathological Characteristics Observed in the 27 Patients

Characteristic		
<b>Locations of involvement</b>		
Ileum involved, n(%)	9 (33.3)	2
Ileocecal valve involved, n(%)	5 (18.5)	N
Right colon involved, n(%)	9 (33.3)	1
left colon involved, n(%)	N	1
Sigmoid colon involved, n(%)	2 (7.4)	N
Rectum involved, n(%)	2 (7.4)	N
Stomach involved, n(%)	1 (3.7)	N
<b>Duodenum, n(%)</b>		
CT features	N	1
Thickened wall bowel, n(%)	11 (40.7)	
Larged lymph nodes, n(%)	5 (18.5)	1
Fistula, n(%)	1 (3.7)	1
Ascites, n(%)	1 (3.7)	
<b>Colonoscopy features</b>		
Pseudopolyp, n(%)	6 (22.2)	
Ulcerative lesions, n(%)	15 (55.6)	
<b>Pathological features, n(%)</b>		
Noncaseating granuloma, n(%)	10 (38.5)	N
Nonspecific inflammation, n(%)	10 (37.0)	

CT, computed tomography.

segments included: close stenosis,<sup>25</sup> nodular,<sup>7</sup> perforation,<sup>26,27</sup> peritoneal cavity, and skip lesions of fibrotic stenosis.<sup>26</sup> Pathological examination of the specimen showed longitudinal ulcers,<sup>26</sup> noncaseating granulomas,<sup>7</sup> and inflammation.<sup>25,26</sup> Three patients underwent surgical treatment,<sup>25–27</sup> 1 for exploratory laparotomy and 2 for obstruction.

## DISCUSSION

Both intestinal TB and CD are difficult to diagnose and require a high level of evidence. Even though the misdiagnosis between ITB and CD are rare events, they can lead to serious outcomes, because the natural courses of these 2 diseases are quite different.<sup>28</sup> ITB can be cured, but CD, as a progressive relapsing illness, is much complex.<sup>29</sup> We can have diagnostic approaches through radiological, endoscopic, pathological, and clinical findings.

A thorough history and detailed physical examination should be the first step in revealing features that are more suggestive of CD than TB. Some studies had summarized the overlapping clinical presentations to make a definitive diagnosis ITB and CD,<sup>30–32</sup> but as shown in our review, any 1 or a combination of these findings do not help the clinician in making a diagnosis for an individual patient, as none of these findings have a high enough likelihood ratio to make a definitive diagnosis.<sup>33</sup>

Epstein et al<sup>34</sup> described 4 endoscopic features that could be used to distinguish CD (longitudinal ulcers, aphthous ulcers, cobblestone appearance, and anorectal lesions) from ITB (transverse ulcers, pseudopolyps, involvement of fewer than 4 segments, and a patulous ileocecal valve). Using these features, a predictive value for CD of 94.9% and a value of 88.9% for ITB were achieved.<sup>35</sup> Although CD is relatively easily diagnosed when classical morphological findings are present, it is difficult to differentiate from other diseases when only early findings or nonclassical findings are present.<sup>36</sup> No diagnosis can be made based on some nonspecific findings because a substantial number of CD cases do not satisfy the diagnostic criteria, whose definitive diagnosis requires repeated observations.<sup>37</sup> If the diagnosis between these entities is not clear, many experts suggest an 8-week trial of antituberculosis therapy.<sup>34</sup> But this strategy may not always be decisive, as many patients with CD are known to respond to antituberculosis drugs at least initially.<sup>38</sup>

CT diagnosis is needed to tell CD apart from ITB, for its inflammatory process determination and reference effect on involved bowel wall, extraluminal, and mesentery complications.<sup>29,32</sup> Morphology of the bowel wall is key for the diagnosis. In CD, the bowel wall circumferential thickening is usually symmetric and concentric. Other features of CD include intestinal stenosis, fistula formation, multiple levels, or segmental involvement.<sup>39,40</sup> On the other hand, asymmetric thickening of the bowel wall and large necrotic lymph nodes in the mesentery should raise the suspicion of ITB.<sup>41</sup>

The most characteristic microscopic features of CD are its multifocal involvement and a triad of histological features: focal ulceration, and transmural inflammation in the form of lymphoid aggregates and granulomas.<sup>42</sup> Caseating granulomas and noncaseating granulomas play a decisive role in the diagnosis of TB and CD. As expressed above, pathologists tend to make a CD diagnosis when they find noncaseating granulomas in biopsies. But, some studies found that the typical histological features of TB, such as caseating granulomas and a positive acid fast stain, are observed in <33% of cases.<sup>43,44</sup> Indeed, caseating or confluent granulomas on histology lack sensitivity and provide only limited significance.<sup>32</sup> Therefore, increasingly

pathologists are questioning the absolute sensitivity and specificity of granulomas for the diagnosis of intestinal CD, especially in biopsy pathology.<sup>42,45</sup> In the above retrospective cases, most correct diagnoses were gained based on resection specimens, in which the large sample size and availability of all layers of the bowel wall facilitated identification of pathognomonic lesions. It is important to take multiple biopsies from all segments of the bowel, including both endoscopically normal and abnormal areas, when the diagnosis is not clear.<sup>46</sup>

In conclusion, distinguishing between ITB and CD is difficult because of their variegated clinical exhibition, general investigative and diagnosis tools, and high pathological similarities. Features of both diseases have been reported many times, but it is still difficult in diagnosis of each case and investigating suitable treatment therapy.

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