Original Article

Clinical and Laboratory Diagnosis of Intestinal Tuberculosis

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Abstract

Background: Tuberculosis (TB) remains a worldwide problem. Intestinal TB (ITB) constitutes a major public health problem in developing countries and has been associated with significant morbidity and mortality. The aim of this study was to characterize the clinical, radiological, endoscopic, and pathological features of ITB and to define the strategy for establishing the diagnosis.

Methods: A retrospective study (from January 2000 to June 2015) was carried out in Peking Union Medical College Hospital and all hospitalized cases were diagnosed as ITB during the study period were included. The relevant clinical information, laboratory results, microbiological, and radiological investigations were recorded.

Results: Of the 85 cases, 61 cases (71.8%) were ranged from 20 to 50 years. The ileocecal region was involved in about 83.5% (71/85) of patients. About 41.2% (35/85) of patients had co-existing extra ITB, especially active pulmonary TB. Abdominal pain (82.4%) was the most common presenting symptom followed by weight loss (72.9%) and fever (64.7%). Both T-cell spot of TB test (T-SPOT.TB) and purified protein derivatives (PPD) tests were performed in 26 patients: 20 (76.9%) positive T-SPOT.TB and 13 (50.0%) positive PPD were detected, with a statistical significant difference ($P = 0.046$). Twenty cases (23.5%) were histopathology and/or pathogen confirmed TB; 27 cases (31.8%) were diagnosed by clinical manifestation consistent with ITB and evidence of active extra ITB; 38 cases (44.7%) were diagnosed by good response to diagnostic anti-TB therapy.

Conclusions: ITB is difficult to diagnose even with modern medical techniques due to its nonspecific clinical and laboratory features. At present, combination of clinical, endoscopic, radiological, and pathological features continues to be the key to the diagnosis of ITB.

Key words: Diagnosis; Intestinal Tuberculosis; Extra-intestinal Tuberculosis

Introduction

Tuberculosis (TB) remains a worldwide problem despite the discovery of the causative organism for more than a century ago. China is one of the 22 countries identified as having a high TB burden.[1] TB primarily involves the lung but any part of the body can be affected by the disease. Intestinal TB (ITB) is a specific chronic intestinal disease caused by *Mycobacterium tuberculosis* (MTB) infection. It constitutes a major public health problem in developing countries and is associated with significant morbidity and mortality.[2-4] The clinical manifestations of ITB are nonspecific such as abdominal pain, fever, and weight loss. ITB can sometimes mimic the clinical, endoscopic, and pathological features of other gastrointestinal disorders, including Crohn's disease (CD), intestinal lymphoma, and intestinal Behcet's disease. This will inevitably lead to delays in the diagnosis and management of ITB. We analyzed the clinical, laboratory, endoscopic, and pathological features in 85 cases of ITB to investigate the relative reliability of different tools used in diagnosing ITB.

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.4103/0366-6999.182840

Methods

Ethics statement

This study was approved by the Ethics Committee of Peking Union Medical College Hospital.

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Received: 24-12-2015 **Edited by:** Li-Min Chen
How to cite this article: Shi XC, Zhang LF, Zhang YQ, Liu XQ, Fei GJ. Clinical and Laboratory Diagnosis of Intestinal Tuberculosis. Chin Med J 2016;129:1330-3.

Patients

We enrolled 85 ITB patients who were hospitalized in Peking Union Medical College Hospital from January 2000 to June 2015 retrospectively. All cases fulfilled the clinical criteria according to *Chinese Society of Gastroenterology*:[5] (1) histological biopsy showed epithelioid granuloma with caseous necrosis in intestinal tissue or mesenteric lymph nodes; (2) intestinal tissue biopsy was positive for MTB on culture or acid-fast stain; (3) patients showed a good response to anti-TB therapy with clinical manifestation consistent with active TB.

Methods

Data of these 85 ITB patients were analyzed including clinical manifestations, laboratory tests, endoscopy, gastrointestinal barium X-ray radiography, and pathology.

Statistical analysis

Statistical analysis was performed using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA). Categorical data are expressed as percentages, and variables between the two groups were assessed using the Chi-square test. A value of $P < 0.05$ was considered statistically significant.

Results

Characteristics of patients

Of the 85 patients, 42 (49.4%) were males and 43 (50.6%) were females. The mean age of the group was 36 years, and the range was 15–75 years. One or more co-existing extra ITB was diagnosed in 35 (41.2%) patients, including pulmonary TB (33 cases), tuberculous peritonitis (four cases), tuberculous meningitis (four cases), cervical lymph node TB (two cases), and hepatic TB (one case). Three patients had history of pulmonary TB, 12 cases had evidence of previous pulmonary TB in chest computed tomography (CT) scan, five cases were active pulmonary TB contacts.

Clinical manifestations

Clinical manifestations of these patients are shown in Table 1. The most common symptoms were abdominal pain, weight loss, fever, and diarrhea. Only six patients presented with alternating diarrhea and constipation which was considered a typical symptom of ITB. Fifty-five patients had different degrees of fever including high fever (23 cases), moderate fever (19 cases), and low-grade fever (13 cases). Partial intestinal obstruction and intestinal bleeding were the most common complications.

Laboratory findings

T-cell spot of TB test (T-SPOT.TB) (Oxford Immunotec, Abingdon, UK), which detects interferon-γ response to MTB-specific antigens encoded in the region of difference 1 (RD1) region, has been developed as a sensitive, specific, and rapid immunodiagnostic test for TB infection in recent years. T-SPOT.TB is an enzyme-linked immunospot assay performed on separated and counted peripheral blood mononuclear cells (PBMCs). The result is reported as the number of interferon-γ producing T-cells (spot-forming cells [SFCs]). There were 34 (34/42, 81.0%) T-SPOT.TB-positive cases in this study with a median antigen-specific interferon-γ secreting T-cells count of 370 (interquartile range 70–1252) SFCs/10^6 PBMC. The purified protein derivatives (PPD) test positive rate was only 52.5% (32/61). Both T-SPOT.TB and PPD tests were performed in 26 patients: 20 (76.9%) positive T-SPOT.TB and 13 (50.0%) positive PPD were detected, with statistical significant difference ($P = 0.046$). Elevated C-reactive protein, elevated erythrocyte sedimentation rate, hypoalbuminemia, and anemia were the most common laboratory abnormalities. These laboratory findings are summarized in Table 2.

Radiology

Thirty-one patients received gastrointestinal barium X-ray radiography, and 27 (87.1%) of these patients had abnormal radiological findings such as abnormal barium filling, bowel wall stiffness, and intestinal stricture.

Endoscopy

Colonoscopies were performed in 77 cases with abnormal findings in 76 cases (98.7%) except for one case with small ITB. According to colonoscopic diagnosis, 45 cases belonged to the ulcerative type, 11 cases belonged to the inflammatory type, five cases belonged to the hypertrophic type, and 15 cases belonged to the combination ulcero-hypertrophic

Table 1: Clinical manifestations of 85 intestinal tuberculosis patients

Manifestations	*n* (%)
Abdominal pain	70 (82.4)
Weight loss	62 (72.9)
Fever	55 (64.7)
Poor appetite	48 (56.5)
Diarrhea	43 (50.6)
Night sweat	25 (29.4)
Abdominal mass	9 (10.6)
Abdominal bulge	9 (10.6)
Alternating diarrhea and constipation	6 (7.1)
Constipation	3 (3.5)
Partial intestinal obstruction	16 (18.8)
Intestinal bleeding	9 (10.6)
Bowel fistula	3 (3.5)
Bowel perforation	1 (1.2)

Table 2: Laboratory findings of 85 intestinal tuberculosis patients

Laboratory findings	*n*/*N* (%)
Amenia	55/85 (64.7)
ESR elevated	59/82 (72.0)
T-SPOT.TB positive	34/42 (81.0)
Fecal occult blood test positive	63/81 (77.8)
Hypoalbuminemia	42/82 (51.2)
CRP elevated	58/68 (85.3)
PPD positive	32/61 (52.5)

ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; PPD: Purified protein derivatives; T-SPOT.TB: T-cell spot of tuberculosis test.

type. Double-balloon enteroscopy was performed in three patients: two cases were of the inflammatory type and one case was of the ulcerative type.

Pathology

Data of endoscopic pathology were obtained in 74 cases. Five cases presented with epithelioid granuloma with caseous necrosis with or without positive acid-fast stain; four cases presented with epithelioid granuloma with positive acid-fast stain; two cases presented with chronic inflammation with positive acid-fast stain; 19 cases presented with epithelioid granuloma without positive acid-fast stain; 44 cases presented with chronic inflammation. Data of surgical pathology were obtained in seven patients, five cases presented with epithelioid granuloma with caseous necrosis with or without positive acid-fast stain in bowel tissue; two cases presented with epithelioid granuloma with caseous necrosis with positive acid-fast stain in mesenteric lymph nodes.

Diagnosis

From onset to diagnosis, the median duration of ITB in this study was 7 months (range: 1 week to 118 months). Twenty cases (23.5%) were histology confirmed ITB; 27 cases (31.8%) were diagnosed through identifying clinical manifestations consistent with ITB, showing evidence of co-existing extra ITB and successful response to anti-TB therapy; 38 cases (44.7%) were diagnosed through clinical manifestations consistent with ITB and successful response to anti-TB therapy. Eighteen cases (21.2%) were misdiagnosed as other diseases including CD (15 cases), intestinal Behcet's disease (one case), colon cancer (one case), and acute appendicitis (one case).

The ileocecal region was not reached during colonoscopy examination in ten patients, so it is not known if the ileocecal region was affected in these patients. Among the other 75 patients, ileocecal region was involved in 71 cases except for four patients with small ITB. Rectum involvement was found in only six cases.

Discussion

ITB is considered the sixth most frequent site of extrapulmonary involvement. ITB usually affects slightly younger population,[6,7] in this study 71.8% (61/85) of the patients were between 20 and 50 years of age. Although ITB can affect almost any part of the gastrointestinal tract, the ileocecal region is the most frequent site of involvement. This study showed the ileocecal region was involved in about 83.5% of patients. This finding is in accordance with the previously published literature.[8,9] MTB reaches the gastrointestinal tract via hematogenous spread, ingestion of infected sputum, or direct spread from infected contiguous lymph nodes. In this study, active pulmonary TB was found in 33.8% of ITB patients (33 cases). However, only 11 patients had complaints of a cough, expectoration, and breathlessness. Therefore, chest X-ray or chest CT should be performed routinely in patients with suspicion of ITB. Evidence of active pulmonary TB will be an important indicator for diagnosing ITB.[8-10]

The clinical manifestations and laboratory tests of ITB are nonspecific. Previous literature has reported that T-SPOT.TB is superior to tuberculin skin test in both sensitivity and specificity for diagnosing TB.[11,12] In this study, both T-SPOT.TB and PPD tests were performed in 26 patients: 20 (76.9%) positive T-SPOT.TB and 13 (50.0%) positive PPD were detected, with a statistically significant difference. Therefore, T-SPOT.TB might be helpful to diagnose ITB.

Colonoscopy plays an important role in the management of ITB. Typical colonoscopy features described in patients with ITB are transverse or linear ulcers, nodules, a deformed ileocecal valve and cecum, presence of inflammatory polyps, and multiple fibrous bands arranged in a haphazard fashion.[8-9,13] In this study, ulcers were detected in 61 cases. Only 36.1% (22/61) were typical ulcers of ITB, whereas the others were nonspecific ulcers that did not provide confirmative diagnosis between inflammatory bowel disease (IBD) and other IBDs. Although caseating granulomas and/or acid-fast bacilli are definite evidence of TB infection, only 11 biopsy specimens obtained endoscopically were shown to be confirmative ITB in this study. Instead, a considerable number of ITB cases had biopsies with features of chronic inflammation or granulomas without caseation, a finding consistent with other reports.[8-10] In addition, multiple target biopsies, deep biopsy, and the culture of the biopsy material might increase the diagnostic yield.[14,15] Biopsy specimens obtained surgically usually provide confirmative diagnosis, and surgery might be considered in some selected difficult cases.

If the clinical and endoscopic features suggestive of ITB and multiple target biopsies do not show evidence of any other disease, then a therapeutic trial of anti-TB treatment might be considered in these cases, which should be continued if there is a good clinical response. Sometimes, clinical response is not correlated with the disease itself, colonoscopy follow-up is valuable for making an early confirmative diagnosis after 2–3 months of anti-tuberculous medication.[3] Thirty-eight cases (44.7%) were diagnosed through successful clinical and endoscopic responses to anti-TB therapy in this study.

In clinical practice, physicians have to face the task of differentiating between ITB and many other diseases, especially CD.[16-18] Fifteen cases were misdiagnosed as CD in this study. Careful interpretation and combination of clinical, radiological, endoscopic, and histological features are necessary for differential diagnosis between ITB and CD. Co-existing extra ITB is an important diagnostic clue of ITB. Therapeutic trial of anti-TB treatment might be helpful in differential diagnosis. Literature reported when differentiating ITB and CD in TB-endemic regions, T-SPOT.TB blood test might be a helpful and practical diagnostic tool for its high negative predictive value to rule out ITB.[19,20]

The retrospective nature of this study is a major limitation. It is difficult to guarantee that all relevant information was collected from all subjects. For example, only 26 patients completed both T-SPOT.TB and PPD tests. Furthermore, all enrolled subjects were hospitalized patients, whose clinical

conditions might be more severe compared to outpatients, a selection bias might limit the external validity of the study.

In conclusion, ITB is difficult to diagnose even with modern medical techniques due to its nonspecific clinical and laboratory features. Typical histologic and/or pathogenic findings provide confirmative diagnosis but have a low diagnostic yield. Evidence of co-existing extra ITB, good response to anti-TB therapy, and positive T-SPOT.TB test might be helpful in diagnosis. At present, a combination of clinical, endoscopic, radiological, and pathological features continues to be the key to diagnosing ITB.

Financial support and sponsorship

This study was supported by grants from the National Major Science and Technology Research Projects for the Control and Prevention of Major Infectious Diseases in China (No. 2014ZX10003003), and the Health Fund Industry Research and Special Projects (No. 201402001).

Conflicts of interest

There are no conflicts of interest.

References

1. WHO. Global Tuberculosis Report 2015. Geneva: World Health Organization; 2015. Available from: http://www.who.int/tb/publications/global_report/en/. [Last accessed on 2015 Dec 20].
2. Awasthi S, Saxena M, Ahmad F, Kumar A, Dutta S. Abdominal tuberculosis: A diagnostic dilemma. J Clin Diagn Res 2015;9:EC01-3. doi: 10.7860/JCDR/2015/13350.5887.
3. Weng MT, Wei SC, Lin CC, Tsang YM, Shun CT, Wang JY, *et al.* Seminar report from the 2014 Taiwan society of inflammatory bowel disease (TSIBD) spring forum (May 24th, 2014): Crohn's disease versus intestinal tuberculosis infection. Intest Res 2015;13:6-10. doi: 10.5217/ir.2015.13.1.6.
4. Cheng J, Zhang XW, Zhou Y, Luo ZQ, Peng L. Clinical analysis of the diagnosis and therapy of 94 cases with intestinal tuberculosis. J Clin Pulm Med 2012;17:463-5.
5. Zhou WH. Review of gold standard diagnosis of tuberculosis. J Prac Diagn Ther 2006;20:741-2.
6. Sharma MP, Bhatia V. Abdominal tuberculosis. Indian J Med Res 2004;120:305-15.
7. Tan KK, Chen K, Sim R. The spectrum of abdominal tuberculosis in a developed country: A single institution's experience over 7 years. J Gastrointest Surg 2009;13:142-7. doi: 10.1007/s11605-008-0669-6.
8. Shah S, Thomas V, Mathan M, Chacko A, Chandy G, Ramakrishna BS, *et al*. Colonoscopic study of 50 patients with colonic tuberculosis. Gut 1992;33:347-51.
9. Singh V, Kumar P, Kamal J, Prakash V, Vaiphei K, Singh K. Clinicocolonoscopic profile of colonic tuberculosis. Am J Gastroenterol 1996;91:565-8.
10. Park YS, Jun DW, Kim SH, Lee HH, Jo YJ, Song MH, *et al*. Colonoscopy evaluation after short-term anti-tuberculosis treatment in nonspecific ulcers on the ileocecal area. World J Gastroenterol 2008;14:5051-8.
11. Pai M, Zwerling A, Menzies D. Systematic review: T-cell-based assays for the diagnosis of latent tuberculosis infection: An update. Ann Intern Med 2008;149:177-84.
12. Lalvani A. Diagnosing tuberculosis infection in the 21st century: New tools to tackle an old enemy. Chest 2007;131:1898-906.
13. Liu SD, Jiang B, Zhou DY. Typical endoscopic features of intestinal tuberculosis. Mod Dig Interv 2003;8:240-1.
14. Marshall JB. Tuberculosis of the gastrointestinal tract and peritoneum. Am J Gastroenterol 1993;88:989-99.
15. Sekine K, Nagata N, Shindo T, Morino E, Shimbo T, Akiyama J, *et al.* Combined identifying granuloma and biopsy culture is useful for diagnosing intestinal tuberculosis. Int J Colorectal Dis 2015;30:939-45. doi: 10.1007/s00384-015-2208-8.
16. Almadi MA, Ghosh S, Aljebreen AM. Differentiating intestinal tuberculosis from Crohn's disease: A diagnostic challenge. Am J Gastroenterol 2009;104:1003-12. doi: 10.1038/ajg.2008.162.
17. Li X, Liu X, Zou Y, Ouyang C, Wu X, Zhou M, *et al.* Predictors of clinical and endoscopic findings in differentiating Crohn's disease from intestinal tuberculosis. Dig Dis Sci 2011;56:188-96. doi: 10.1007/s10620-010-1231-4.
18. Makharia GK, Srivastava S, Das P, Goswami P, Singh U, Tripathi M, *et al.* Clinical, endoscopic, and histological differentiations between Crohn's disease and intestinal tuberculosis. Am J Gastroenterol 2010;105:642-51. doi: 10.1038/ajg.2009.585.
19. Li Y, Zhang LF, Liu XQ, Wang L, Wang X, Wang J, *et al.* The role of *in vitro* interferonγ-release assay in differentiating intestinal tuberculosis from Crohn's disease in China. J Crohns Colitis 2012;6:317-23. doi: 10.1016/j.crohns.2011.09.002.
20. Lei Y, Yi FM, Zhao J, Luckheeram RV, Huang S, Chen M, *et al.* Utility of *in vitro* interferon-gamma release assay in differential diagnosis between intestinal tuberculosis and Crohn's disease. J Dig Dis 2013;14:68-75. doi: 10.1111/1751-2980.12017.