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Original Article

The value of empiric anti-tuberculosis therapy in the differential diagnosis between intestinal tuberculosis and Crohn's disease in China

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Abstract: Objective: To find out the criteria, the suitable duration and the efficacy of using empiric anti-tuberculosis to differentiate intestinal tuberculosis (ITB) from Crohn's disease (CD). Methods: Forty-eight patients receiving empiric anti-tuberculosis therapy were retrospectively analyzed and underwent 4-10 years follow-up. Among them, 28 were confirmed as ITB and 20 as CD at final evaluation. Clinical manifestations, endoscopic changes and the response to anti-tuberculosis therapy were compared between ITB and CD groups. Results: 1) The baseline clinical characteristics anal fistula/perianal abscess and aphthous ulcers were significantly different between 2 groups. Strong positive skin test (PPD test) result was also not comparable between 2 groups; 2) Clinical symptoms improved in both groups after 3 mo empiric anti-tuberculosis therapy. The non-improvement rate in ITB group was 0%, whereas that of CD group was 15.0% (P=0.007); 3) Endoscopic appearance improved significantly in ITB group but not CD group after 3 mo or 6 mo empiric anti-tuberculosis therapy, Ulcer disappearance rate in ITB group was 90.9% (20/22) in 3 mo and 100% (28/28) in 6 mo. Nodular transformation disappearance rate of in ITB group was 58.8% (10/17) in 3 mo and 76.5% (13/17) in 6 mo. There was no obvious improvement of active ulcer or nodular transformation in CD group at any time point (P<0.001 compared with ITB). Conclusions: Three months of empiric anti-tuberculosis therapy was a proper duration for the purpose of differentiating ITB from CD. Disappearance of active ulcer and nodular transformation endoscopically, together with clinical cure or obviously improvement are engraved as effective.

Keywords: Intestinal tuberculosis, Crohn's disease, empiric anti-tuberculosis therapy, differential diagnosis

Introduction

Intestinal tuberculosis (ITB) and Crohn's disease (CD) are not rare in China, but the differential diagnosis of the two diseases is still very challenging [1]. In Chinese consensus on diagnosis and treatment of inflammatory bowel disease, key points for differentiating these two diseases were raised. The consensus also emphasized that empiric anti-tuberculosis should be employed when there was difficulty in the differential diagnosis [2]. However there was still no consensus on how to evaluate the efficacy of empiric anti-tuberculosis therapy. As we know, patients' clinical symptoms improved in both ITB and CD patients after short-term anti-tuberculosis therapy, therefore, CD cannot be simply ruled out in this situation. On the other hand, 6 mo to 12 mo of anti-tuberculosis is the routine course of treatment for curing ITB [3], but for CD, such a long duration of anti-tuberculosis therapy will put patients at the risk of medicine side effects and the possibility of disease aggravation. A recent study in South Korea reported that disappearance of active ulcers after 3 mo of anti-tuberculosis therapy was valuable for making early confirmative diagnosis of ITB [4]. But this study only included small sample, therefore, further investigation is needed to confirm its conclusion. Thus, we retrospectively evaluated the clinical manifestations and colonoscopic findings after anti-tuberculo-

Table 1. Baseline clinical and colonoscopic characteristics in CD and ITB patients

	ITB (n=28)	CD (n=20)	*P* value
Gender (male), n (%)	12 (42.9)	13 (65.0)	0.154
Age (year)	31.4±11.7	29.8±10.8	0.626
Tuberculosis exposure, n (%)	3 (10.7)	0 (0.0)	0.255
Chest X-ray			
Active pulmonary tuberculosis, n (%)	5 (17.9)	0 (0.0)	0.066
Obsolete pulmonary tuberculosis, n (%)	5 (17.9)	1 (5.0)	0.379
PPD test strong positive, n (%)	12 (42.9)	3 (15.0)	0.059
ESR (mm/h)	31.9±25.2	52.8±36.7	0.008
CRP (u/L)	8.0±7.5	10.2±8.4	0.355
Abdominal pain, n (%)	25 (89.3)	17 (85.0)	0.683
Diarrhea, n (%)	12 (42.9)	11 (55.0)	0.559
Hematochezia, n (%)	1 (3.6)	3 (15.0)	0.294
Abdominal mass, n (%)	4 (14.3)	3 (15.0)	1.000
Fever, n (%)	3 (10.7)	8 (40.0)	0.034
Weight loss, n (%)	12 (42.9)	15 (75.0)	0.040
oral ulcer, n (%)	3 (10.7)	6 (30.0)	0.137
Anal fistula/perianal abscess, n (%)	2* (7.1)	8 (40.0)	0.010
Colonoscopic characteristics			
Irregular ulcers, n (%)	22 (78.6)	12 (60.0)	0.206
Aphthous ulcers, n (%)	0 (0.0)	6 (30.0)	0.003
Transverse ulcers, n (%)	11 (39.3)	3 (15.0)	0.108
Longitudinal ulcers, n (%)	0 (0.0)	2 (10.0)	0.168
Stricture, n (%)	7 (25.0)	3 (15.0)	0.488
Mucosal nodules, n (%)	17 (60.7)	9 (45.0)	0.381
Patulous ileocecal valve, n (%)	5 (17.9)	0 (0.0)	0.066
Cobblestone appearance, n (%)	0 (0.0)	3 (15.0)	0.066
Involvement of more than four segments, n (%)	6 (21.4)	10 (50.0)	0.062

*Two cases in ITB group had past history of perianal abscess, but cured at baseline follow-up.

sis treatment in patients who was suspected as ITB originally, and confirmed as ITB or CD at the end of study, to find out the criteria, the suitable duration and the efficacy of using empiric anti-tuberculosis to differentiate ITB from CD.

Materials and methods

Patients

A retrospective analysis of cases from May 2005 to March 2011 was conducted on 48 consecutive patients who received empiric anti-tuberculosis therapy and underwent 4-10 years follow-up at the Inflammatory Bowel Disease Center of Sun Yat-Sen University, China. All the following criteria must be fulfilled in patients enrolled in our study: ① Clinical features including abdominal pain, diarrhea, fever, weight loss, or abdominal mass; ② Ulcers accompanying other inflammatory lesions were found in segmental or regional distribution in ileo-colon area under colonoscopy; ③ Pathologically confirmed ITB (caseating granuloma) or clinically suspected ITB, or hard to differentiate ITB from CD clinically; ④ Patients who needed anti-tuberculosis therapy or empiric therapeutic trial; ⑤ All patients received anti-tuberculosis treatment for at least 3 months. Colonoscopy was enrolled in 3 mo, 6 mo, and 12 mo; ⑥ Confirmed diagnosis of ITB or CD was based on pathology or cases follow-up (criteria appear below). The recommended regimens for anti-tuberculosis in our study was 2 HRZE/7~10 HR, or adjusted according to pulmonary tuberculosis chemotherapy regimens (WHO, 1988).

Methods

Patients evaluation and follow-up: Patients' general date, epidemiological data, symptoms and physical signs, including perianal lesions of

Table 2. Clinical assessments after anti-tuberculosis therapy, n (%)

Follow-up duration	Clinical assessment	ITB (n=28)	CD (n=20)	*P* value
1~2 week	Cured	2 (7.2)	3 (15.0)	0.885
	Obviously improved	25 (89.2)	15 (75.0)	
	Non-improved	1 (3.6)	2 (10.0)	
1 mo	Cured	6 (21.4)	4 (20.0)	0.471
	Obviously improved	22 (78.6)	14 (70.0)	
	Non-improved	0 (0.0)	2 (10.0)	
3 mo	Cured	20 (71.4)	7 (35.0)	0.007
	Obviously improved	8 (28.6)	10 (50.0)	
	Non-improved	0 (0.0)	3 (15.0)	

CD, extra-intestinal manifestations and complications were retrospectively analyzed. Results of colonoscopy, chest X-ray, PPD-test, PPD-IgG, ESR, and CRP were collected as baseline data. Clinical evaluation was carried out in 1 wk, 2 wk, 1 mo, 3 mo, 6 mo and 12 mo after the start of anti-tuberculosis treatment.

Clinical assessments of the efficacy of anti-tuberculosis therapy. Cured: Disappearance of symptoms; obviously improved: severity of symptoms reduced up to half or above; non-improved: Severity of symptoms reduced less than half, symptoms aggravated or recurred.

Endoscopic assessments of the efficacy of anti-tuberculosis therapy. Colonoscopy was performed at baseline, and 3 mo, 6 mo, 12 mo after the start of anti-tuberculosis therapy. Endoscopic features including ulcers, mucosal nodules, pseudopolyps, and luminal strictures, as well as their distribution and range were evaluated. Healed: Disappearance of all ulcers, with/without polypoid changes; Improved: Mucosa ulcer area reduced equaled or more than half of the previous; Non-improved: Mucosa ulcer area reduced less than half of the previous, unchanged or aggravated.

Diagnostic criteria for ITB and CD: A final confirmed diagnosis of ITB or CD was based on pathology of surgical specimens, or endoscopic results and disease course after a 12 mo follow-up.

Criteria for confirmed ITB: ① Formal anti-tuberculosis therapy for 6 mo, clinically cured, endoscopically healed, and no recurred in 12 mo follow-up. ② Caseating granuloma on mucosal biopsy or/and an acid fast stain positive before empiric therapy were considered as confirmed ITB as well.

Criteria for confirmed CD: ① Non-improved endoscopically after 3 mo empiric anti-tuberculosis therapy; ② Medications for treating CD for 12 mo, symptoms alleviated or disappeared (CDAI decreased ≥ 100 compared to baseline or CDAI<150); ③ CD complications appeared during anti-tuberculosis therapy, such as enterocutaneous fistula, anal fistula, perianal abscess and intestinal perforation; ④ Surgery on any cause, pathology of excised intestine or lymph node showed no evidence of caseating granuloma and evidence that supporting CD.

Clinical confirmation: two or more out of criteria ①, ②, ③ were met; Pathological confirmation: ④ was met.

Statistical analysis

Statistical analysis was performed with SPSS-18.0 software. Results of quantitative variables were reported as median ± SD, whereas qualitative and ranked variables were reported as frequency or percentages. Fisher exact test was used to compare the categorical variables between ITB and CD group, Kruskal-Wallis test was used for intergroup comparison of non-parametric variance, Wilcoxon test was used for comparisons of endoscopic assessments during follow-up. A significant result is indicated by a $P<0.05$.

Results

Forty-eight cases were enrolled, among which 28 were ITB (3 cases were confirmed by pathology before empiric anti-tuberculosis therapy), 20 were CD.

Clinical findings

Patients' general date, laboratory findings and clinical features were summarized in **Table 1**. The percentage of active pulmonary tuberculosis in ITB and CD group was 17.9% and 0% respectively, and strong positive skin test was 42.9% and 9.0% respectively, but no significant difference was found between 2 groups for these two relatively specific indexes.

Table 3. Endoscopic assessments after anti-tuberculosis therapy

	ITB			CD		
	3 mo n=22	6 mo n=28	12 mo n=24	3 mo n=16	6 mo n=8	12 mo n=5
Active ulcers	22	28	24	16	8	5
Disappeared, n (%)	20 (90.9)	28 (100.0)	24 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lesions area reduced ≥1/2, n (%)	2 (9.1)	0 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lesions area reduced ≤1/4, unchanged or aggravated, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	16 (100.0)	8 (100.0)	5 (100.0)
Mucosal nodules	17	17	17	13	8	5
Disappeared, n (%)	10 (58.8)	13 (76.5)	15 (88.2)	0 (0.0)	0 (0.0)	0 (0.0)
Lesions range reduced ≥1/2, n (%)	7 (41.2)	4 (23.5)	2 (11.8)	0 (0.0)	0 (0.0)	0 (0.0)
Lesions range reduced ≤1/4, unchanged or aggravated, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	13 (100)	8 (100.0)	5 (100.0)
Pseudopolyps	12	12	12	7	5	2
Disappeared, n (%)	0 (0.0)	5 (41.7)	8 (66.7)	0 (0.0)	0 (0.0)	0 (0.0)
Lesions range reduced ≥1/2, n (%)	4 (33.3)	4 (33.3)	3 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lesions range reduced ≤1/4, unchanged or aggravated, n (%)	8 (66.7)	3 (33.3)	1 (8.3)	7 (100)	5 (100.0)	2 (100.0)

Comparison between CD and ITB: Active ulcers: 3 mo $P<0.001$ ($\chi^2=34.716$); 6 mo $P<0.001$ ($\chi^2=35.000$); 12 mo $P<0.001$ ($\chi^2=28.000$). Mucosal nodules: 3 mo $P<0.001$ ($\chi^2=24.587$); 6 mo $P<0.001$ ($\chi^2=19.048$); 12 mo $P<0.001$ ($\chi^2=16.500$). Pseudopolyps: 3 mo $P=0.094$ ($\chi^2=2.800$); 6 mo $P=0.011$ ($\chi^2=6.537$); 12 mo $P=0.025$ ($\chi^2=5.056$).

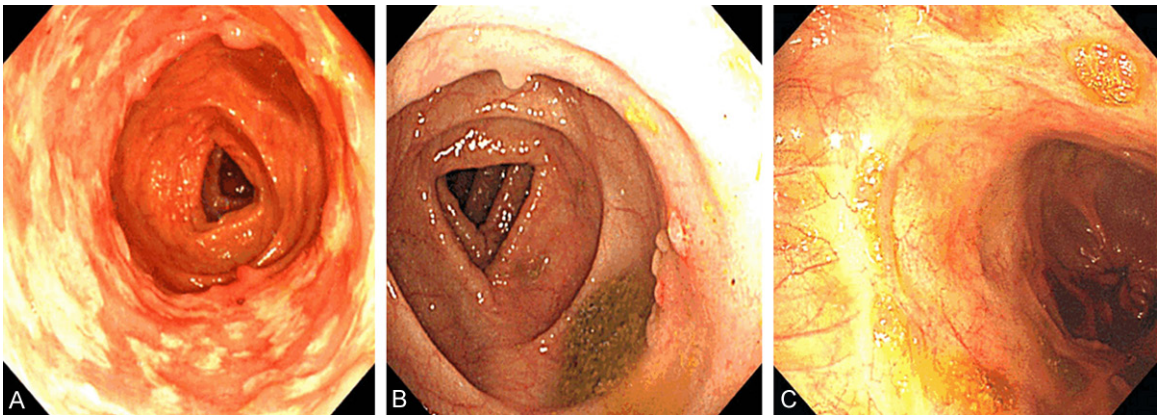

Figure 1. A female intestinal tuberculosis patient aged 25. A. Before anti-tuberculosis therapy; B. 3 mo after anti-tuberculosis therapy; C. 12 mo after anti-tuberculosis therapy.

Patients with a tentative diagnosis of intestinal tuberculosis demonstrated at least one of the following criteria: ① evidence of caseating granulomas; ② positive acid-fast staining; ③ active extra-intestinal tuberculosis; ④ strong positive skin test. Among all 28 ITB patients, 13 cases fulfilled one criteria (46.4%), 4 cases fulfilled two, 1 case fulfilled three at their initial work-up. Only three cases in CD group had strong positive skin test.

Colonoscopy findings

As shown in **Table 1**, patulous ileocecal valve and transverse ulcers were more common in ITB, but no statistical significance was found when compared with those in CD. Longitudinal ulcers, cobblestone appearance, involvement of more than four segments and aphthous ulcers were more frequent in CD, but no statistical significance was found when compared with those characteristics in ITB except aphthous ulcers.

Clinical outcomes after empiric anti-tuberculosis therapy

As shown in **Table 2**, clinical symptoms of most patients in both groups improved after 1 to 2 week on anti-tuberculosis treatment, the Cured-Obviously improved rate was 96.4% and 90.0% in ITB and CD group respectively, no statistical significance was found. In 1 mo, the Cured-Obviously improved rate reached 100% in ITB group, but still 90.0% in CD group, no statistical significance was found between two

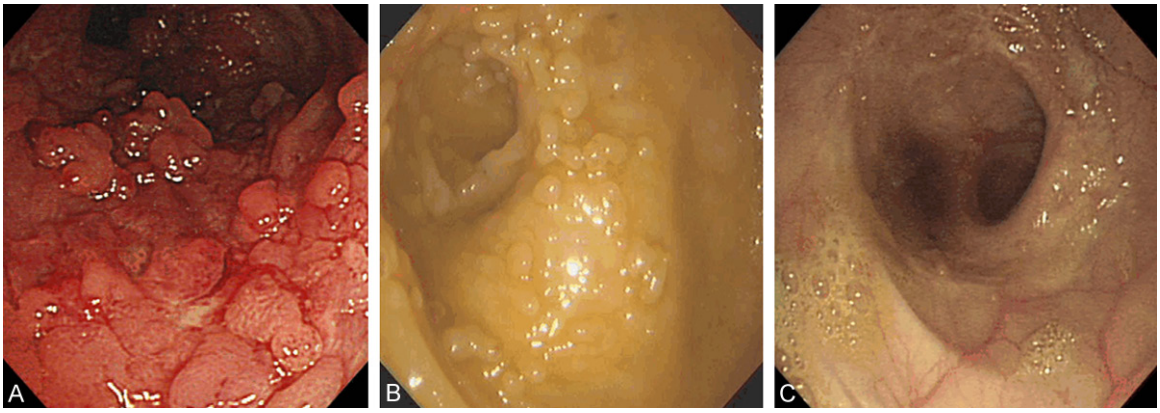

Figure 2. A female intestinal tuberculosis patient aged 26. A. Before anti-tuberculosis therapy; B. 3 mo after anti-tuberculosis therapy; C. 12 mo after anti-tuberculosis therapy.

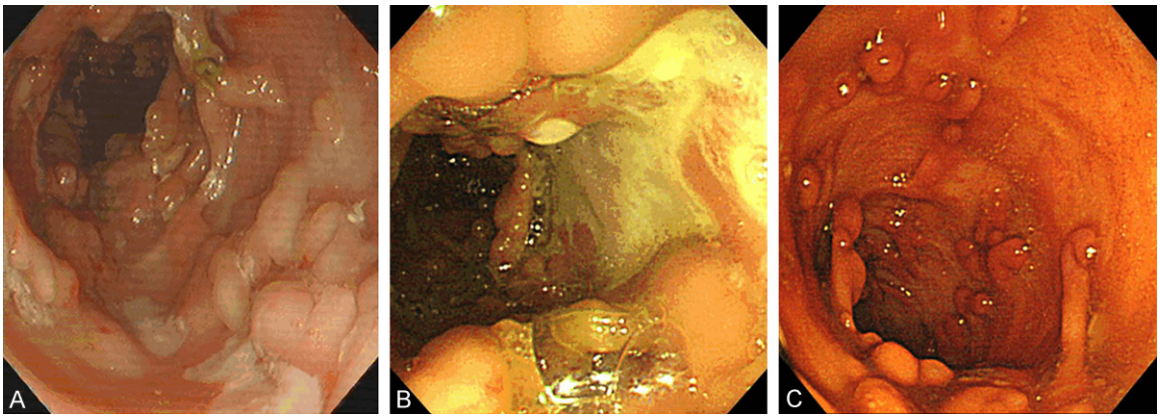

Figure 3. A male Crohn's disease patient aged 25. A. Before anti-tuberculosis therapy; B. 3 mo after anti-tuberculosis therapy; C. 12 mo after switching to steroid and azathioprine due to no response to 3 mo anti-tuberculosis therapy.

groups. In 3 mo, the Cured rate was 71.4% in ITB group and 35.0% in CD group, the Non-improved rate was 0 in ITB group and 15.0% in CD group (P=0.007).

Endoscopic assessments in the course of anti-tuberculosis therapy

(**Table 3**; **Figures 1**-**3**). As shown in **Table 3**, for the assessments of active ulcers, the Healed rate and Improve rated in ITB group was 90.9% (20/22) and 9.1% (2/22) respectively in 3 mo after empiric therapy, and 100% (28/28) and 0 respectively in 6 mo. Statistical significance was found in both 3 mo and 6 mo when compared with the changes in CD group in which all cases remained Non-improved during the empiric therapy (P<0.001). For the assessments of mucosal nodules, the disappeared rate in ITB group was 58.8% in 3 mo and 76.5% in 6 mo after empiric therapy. As evaluated the rest 23.5% cases with still existed lesions in 6 mo, the amounts of mucosal nodules reduced obviously when compared with the baseline changes. For the assessments of pseudopolyps, in 3 mo after empiric therapy, some cases in ITB group had fewer lesions, some had more, and some remained unchanged when compared with the baseline lesions. But in 6 mo and 12 mo, the amount of pseudopolyps reduced obviously in 75.0% and 91.7% cases respectively in ITB group. Three cases in ITB group had luminal stricture before therapy, which leading to the failure of completing colonoscopy examination. All strictures improved 3 mo after anti-tuberculosis therapy with successful pass of colonoscope. But one new situation emerged which was narrowing of ileocecal valve with the failure of pass of colonscope. All the above lesions in CD group, including

mucosal nodules, pseudopolyps and strictures, did not improve in both 3 mo and 6 mo after anti-tuberculosis therapy.

The follow-up

Duration of following-up was 4 to 10 years since the end of empiric anti-tuberculosis in ITB group. No patients diagnosed as ITB recurred so far. As for the outcome of the 20 patients diagnosed and treated as CD, 1 received surgery because of intestinal obstruction, 1 developed abdominal abscess in 4 mo but refused surgery, the other 18 cases improved obviously on medicines for treating CD, 10 of them received colonoscopy with mucosal healing or improvement.

Discussion

A number of reports have documented the differential diagnosis between ITB and CD [1-5]. Some characteristics are specific for ITB, such as caseating granulomas or acid-fast bacilli identified in the histological specimens; Co-existing active extra-intestinal tuberculosis or strong positive skin test suggests the necessity of empiric anti-tuberculosis. Other characteristics are likely to be found in CD, such as anal fistula/perianal abscess, extra-intestinal manifestations, intestinal fistula and abdominal abscess [2]. However above characters are absent in most patients and not golden standards for diagnosing CD or ITB [5, 6]. In our study, only 3 out of 28 ITB patients (10.7%) were confirmed at the initial work-up by histological evidence. Less than half ITB patients (13/28) met any one of the following criteria: caseating granulomas, positive acid-fast staining, active extra-intestinal tuberculosis, strong positive PPD-test. Perianal abscess which was inclined to CD diagnosis existed in two ITB patients. Eight CD patients (40.0%) had perianal abscess, but still received empiric anti-tuberculosis therapy because of the consideration of the possibility of ITB based on other manifestations in this patient. From above we can see, due to the lack of specific characteristics for differentiating ITB from CD, adequate course of empiric anti-tuberculosis therapy should be considered in patients with difficulty in differential diagnosis between ITB and CD.

The endoscopic findings for distinction between ITB and CD have been well described recent years [5-12]. Segmental longitudinal ulcers and cobble stone appearance are regarded as typical colonoscopy features described in patients with tuberculous colitis. By contrast, transverse or linear ulcers are considered as typical changes in CD. We reviewed the endoscopic findings in our study, longitudinal ulcers and/or a cobblestone appearance existed in about 1/3 cases in CD group, transverse or linear ulcers was found in about 1/3 cases in ITB group. Hence judge based on combining endoscopic and clinical features would make empiric anti-tuberculosis treatment more targeted. For better differentiating CD from ITB, the direction of our further study should be focus on standardizing and quantizing the criteria of disease features [1].

There was still no consensus on how to evaluate the efficacy of empiric anti-tuberculosis therapy. There are two requirements for evaluating the empiric therapy as efficacy [4, 13]. The first is about the extent of clinical and/or endoscopic improvement. Second is about the suitable duration of this empiric therapy. The latter is more important since as we know that at least 6 mo is needed for a formal anti-tuberculosis therapy, and it usually takes 9-12 mo as literature reported [3]. Obviously, this long duration doesn't meet the requirement for 'empiric' therapy. It is clearly irrational to adopt full-course anti-tuberculosis therapy to access the treatment response before turning to the right therapy in CD patients. It is also irrational to withdraw anti-tuberculosis therapy in those non-response ITB patients due to inadequate course of anti-tuberculosis therapy. As our study suggested, with anti-tuberculosis therapy, active ulcers and erosions healed in most ITB patients in 3 mo and in all ITB patients in 6 mo. However active ulcers remained unchanged or aggravated in all CD patients 3 or 6 mo after anti-tuberculosis therapy. Mucosal nodules were also important endoscopic feature. A dramatic improvement of this feature was achieved in ITB patients 3 mo after anti-tuberculosis therapy, and nearly all lesions disappeared after 6 mo of treatment. At early stage when using anti-tuberculosis therapy, the amount of pseudopolyps usually reduced with the disappearance of active ulcer in ITB patients, but sometimes it could increase at the beginning, lessen subsequently. In some situation the pseudopolyps could exist for one year or longer. From our study, we can see a 3 mo trial of anti-tuberculosis treatment and colonoscopy follow-up is very useful for differential diagnosis

between CD and ITB. Disappearance or obvious improvement of active ulcer accompanied by the improvement of nodular transformation is engraved as responding to anti-tuberculosis therapy, and the therapy should be continued. For those with obvious improvement of ulcers instead of disappearance in 3 mo, the lesions are supposed to disappear in 6 mo after therapy or the diagnosis should be reconsidered. For the management of pseudopolyps, the duration of therapy should be long enough till pseudopolyps disappear. On the contrary, those with non-improvement of ulcers in 3 mo after anti-tuberculosis should be considered as ineffective empiric therapy and the strategy should be shift to CD therapy.

Our study showed that the clinical symptoms started to improve within 2 weeks and improved obviously in 1 mo after anti-tuberculosis therapy in ITB group. The obviously improved rate reached 100% in 1 mo. Cured was achieved in 3 mo in most patients. Noteworthily, clinical symptoms also improved obviously in a proportion of CD patients in the early stage of anti-tuberculosis and this could last 3 mo or longer after the stop of empiric therapy. But eventually recurrence took place thereafter. These CD patients may be misdiagnosed as ITB if judged only by symptoms improvement. Therefore, to evaluate the effectiveness of the empiric therapy, we should combine colonoscopy with symptoms evaluation instead of evaluating symptoms only. Endoscopic healed together with the evidence of clinical cured or nearly cured is engraved as effective. From our study we can also see that an understanding of how the intestine responds to the treatment of TB or CD is fundamental to decide whether empiric therapy should be chosen or not.

Although we have well-organized follow-up system and file management for CD and ITB patients, and our results were similar to those from Korea [4], the limitations of this study due to retrospective reason were needed to be solved. Further large sample prospective investigations should be carried out to achieve more reliable conclusions.

Disclosure of conflict of interest

None.

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