Temporal trends in the misdiagnosis rates between Crohn’s disease and intestinal tuberculosis

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Abstract

AIM
To investigate the temporal trends in the misdiagnosis rate between Crohn’s disease (CD) and intestinal tuberculosis (ITB) in South Korea.

METHODS
We retrospectively reviewed the medical records of patients managed for CD or ITB at Asan Medical Center, a tertiary referral hospital, Seoul, Korea between 1996 and 2014. The temporal trends in the misdiagnosis rates between the two diseases were analyzed. The demographic and clinical characteristics were compared between CD patients who were initially misdiagnosed as ITB (final CD group) and vice versa (final ITB group). Final diagnostic criteria for ITB and medication for CD before definite diagnosis of TB were also analyzed in final ITB group.

RESULTS
In total, 2760 patients were managed for CD and 772 patients for ITB between 1996 and 2014. As well, 494 of the 2760 CD patients (17.9%) were initially misdiagnosed as ITB and 83 of the 772 ITB patients (10.8%) as CD. The temporal trend in misdiagnosing CD as ITB showed a decrease (OR = 0.89, 95%CI: 0.87-0.91, P < 0.001), whereas the temporal trend in misdiagnosing ITB as CD showed an increase (OR = 1.06, 95%CI: 1.01-1.11, P = 0.013). Age at diagnosis, presenting symptoms, and proportion of patients with active/past perianal fistula and active/inactive pulmonary tuberculosis (TB) were significantly different between final CD group and final ITB group. Forty patients (48.2%) in final ITB group were diagnosed by favorable response to empirical anti-TB treatment. Seventeen patients (20.5%) in final ITB group had inappropriately received corticosteroids and/or thiopurines due to misdiagnosis as CD. However, there were no mortalities in both groups.

CONCLUSION
Cases of CD misdiagnosed as ITB have been decreasing, whereas cases of ITB misdiagnosed as CD have been increasing over the past two decades.

Key words: Crohn’s disease; Intestinal tuberculosis;
with a favorable outcome, while CD is a chronic disease needing lifelong management. Moreover, the misdiagnosis of ITB as CD can lead to worse outcomes, because immunosuppressive drugs, such as corticosteroids, thiopurines, and anti-tumor necrosis factor agents can aggravate ITB. Conversely, the misdiagnosis of CD as ITB can render the CD patients exposed to the potential toxicity of anti-TB drugs and delay the proper treatment of CD. Therefore, making an accurate differential diagnosis between CD and ITB at the earliest possible stage is very critical. Although previous researchers have suggested clinical, endoscopic, and pathologic clues that could be helpful in a differential diagnosis between these two diseases, it is still not easy to tell them apart.

In this study, we aimed to analyze the temporal trends in the misdiagnosis rates between CD and ITB in Korea. In addition, we analyzed the clinical characteristics of ITB cases initially misdiagnosed as CD and CD cases initially misdiagnosed as ITB.

MATERIALS AND METHODS

Study population
Between January 1996 and December 2014, 2723 and 772 patients were managed for CD and ITB, respectively, at the Asan Medical Center, a tertiary university hospital in Seoul, South Korea, and they were included in this study. The diagnosis of ITB was based on Korean diagnostic guideline of ITB and was considered established when at least one of the following criteria was met: (1) histological demonstration of caseating granulomas; (2) identification of acid-fast bacilli in a histological specimen; (3) positive culture of Mycobacterium tuberculosis from a biopsy specimen; (4) clinical, colonoscopic, radiologic, and/or operative evidence of ITB associated with proven TB elsewhere; and (5) response to anti-TB therapy without subsequent recurrence in patients with clinical, colonoscopic, radiologic, and/or operative evidence of ITB. Colonoscopic findings which favor a diagnosis of ITB were as follows: involvement of fewer than four segments, anorectal lesions, patulous ileocecal valve, and scars or pseudopolyps, as described previously.

Some of the ITB patients in this study were described previously. CD was diagnosed based on conventional clinical, radiologic, endoscopic, and histopathologic criteria.

Study design
For the characterization of study subjects, we retrospectively reviewed the medical records and the IBD registry of the Asan Medical Center. The IBD registry of the Asan Medical Center and the characteristics of this hospital-based cohort of CD patients has been described previously. To evaluate the initial clinical presentation, we also reviewed the medical records and endoscopic images provided by referring physicians.

Through the reviewing process, the following characteristics were abstracted and compared between CD patients misdiagnosed as ITB (final CD group) and ITB patients misdiagnosed as CD (final ITB group): gender, age at diagnosis, interval from misdiagnosis to definite diagnosis, presenting symptoms, active and/or past perianal fistula, active pulmonary TB (PTB), radiologic evidence of old PTB, and institutions where misdiagnosis was made. For the final ITB group, medication for CD before definite diagnosis of ITB was also abstracted. We also analyzed the final diagnostic criteria for ITB in the final ITB group. The study protocol was approved by the Institutional Review Board of the Asan Medical Center.

Temporal trends in the misdiagnosis rates
To evaluate the temporal trends in the misdiagnosis rates between CD and ITB, the number of patients diagnosed with CD at the initial evaluation but finally diagnosed with ITB and vice versa were verified every year between 1996 and 2014. The annual rate of misdiagnosing CD as ITB was defined by the proportion of patients with a preceding misdiagnosis as ITB (final CD group) among the patients diagnosed definitely with CD at that year. The rate of misdiagnosing ITB as CD was calculated by the opposite method.

Statistical analysis
Continuous variables were expressed as the mean with SD or the median with ranges. Discrete data were expressed as numbers and percentages. The clinical characteristics of the final CD group and the final ITB group were compared using the Student’s t-test or the Mann-Whitney U test for continuous variables and the χ² test or the Fisher’s exact test for categorical variables, where appropriate. The temporal trends in the misdiagnosis rates of CD and ITB were analyzed by the logistic regression analysis. We also calculated the intervals from misdiagnosis to correct diagnosis in each patient and values were expressed as median with interquartile range (IQR). The intervals from initial misdiagnosis to correct diagnosis in periods divided into 6 (1996-1999, 2000-2002, 2003-2005, 2006-2008, 2009-2011, and 2012-2014) were compared using the Kruskal-Wallis test.

A statistical analysis was carried out using IBM SPSS statistics, ver. 21.0 (IBM Co., Armonk, NY, United States) and SAS version 9.3 (SAS Institute Inc., Cary, NC). A P value < 0.05 was considered statistically significant.

RESULTS
During the 19-year study period, 494 of the 2760 patients with CD (17.9%) were initially misdiagnosed as ITB (final CD group) and ITB patients misdiagnosed as CD (final ITB group): gender, age at diagnosis, interval from misdiagnosis to definite diagnosis, presenting symptoms, active and/or past perianal fistula, active pulmonary TB, radiologic evidence of old PTB, and institutions where misdiagnosis was made. For the final ITB group, medication for CD before definite diagnosis of ITB was also abstracted. We also analyzed the final diagnostic criteria for ITB in the final ITB group. The study protocol was approved by the Institutional Review Board of the Asan Medical Center.
CD group, misdiagnoses were made at primary clinics in 44 patients (8.9%), at secondary referral hospitals in 118 patients (23.9%), at the tertiary referral hospitals other than our institution in 246 patients (49.8%), and at our institution in 68 patients (13.8%). In 18 cases (3.6%), information on the institution where misdiagnoses were made was unclear. Among 83 patients in final ITB group, misdiagnoses were made at primary clinic in 12 patients (14.5%), at secondary referral hospital in 30 patients (36.1%), at the tertiary referral hospital other than our institution in 34 patients (41.0%), and at our institution in 7 patients (8.4%, Table 1).

The yearly trends in the misdiagnosis rates between CD and ITB are plotted in Figure 1. Although the misdiagnosis rates showed variability every year, the rate of misdiagnosing CD as ITB showed a decreasing tendency and the rate of misdiagnosing ITB as CD showed an increasing tendency over time. In 1996, a total of 34.3% of patients in final CD group were misdiagnosed initially as ITB, but the proportion of misdiagnosed cases was decreased to 8.1% in 2014. During the initial 5 years of observation period (1996-2000), only 3.0% of final ITB group have been misdiagnosed as CD, whereas the rate of misdiagnosing ITB as CD increased to 13.1% during the last 5 years (2010-2014). Therefore, the trend in the rate of misdiagnosing ITB as CD showed a significant increase (OR = 1.06; 95%CI: 1.01-1.11 per year increase in the study period; \( P = 0.013 \)).

We analyzed the temporal trends in the intervals from initial misdiagnosis to correct diagnosis (Figure 2). The median intervals from misdiagnosis to correct diagnosis were 5.2 mo (IQR: 2.3-12.2) in final CD group and 4.0 mo (IQR: 1.6-13.4) in final ITB group. During the study period, the intervals from initial misdiagnosis to final diagnosis were not changed significantly in both final CD group (\( P = 0.394 \) by Kruskal-Wallis test) and final ITB group (\( P = 0.748 \) by Kruskal-Wallis test) during study period (Figure 2).

Table 1 shows the demographic and clinical characteristics of the final CD group and of the final ITB group, respectively. The age at definite diagnosis was younger in the final CD group than in the final ITB group (median 23.4 years vs 35.8 years, \( P < 0.001 \)). The most frequent symptom of both groups was abdominal pain. However, diarrhea and hematochezia/melena were more common in the final CD group than in the final ITB group (\( P < 0.001 \) and \( P = 0.023 \), respectively). Alternatively, an incidental diagnosis without any related symptom was more common in

### Table 1  Demographic and clinical characteristics of Crohn’s disease patients misdiagnosed as intestinal tuberculosis (final Crohn’s disease group) and intestinal tuberculosis patients misdiagnosed as Crohn’s disease (final intestinal tuberculosis group) \( \eta \) (%)

| Deaths (\( \eta \), \%) | \( \eta \) | \( \eta \) | \( \eta \) |
|------------------------|--------|--------|--------|
| Final CD group (\( \eta = 494 \)) | Final ITB group (\( \eta = 83 \)) | \( P \) value |
| Male | 342 (69.2) | 49 (99.0) | \( 0.066^2 \) |
| Age at definite diagnosis (yr) | 23.4 (19.5-30.3) | 35.8 (27.3-46.0) | \( < 0.001^3 \) |
| Interval from misdiagnosis to definite diagnosis (mo) | 5.2 (2.3-12.0) | 4.0 (1.7-13.2) | \( 0.082^4 \) |
| Presenting symptoms | | | |
| Abdominal pain | 318 (64.4) | 46 (55.4) | \( 0.118^5 \) |
| Diarrhea | 293 (59.3) | 22 (26.5) | \( < 0.001^6 \) |
| Weight loss | 104 (21.1) | 12 (14.5) | \( 0.165^7 \) |
| Hematochezia/melena | 84 (17.0) | 6 (7.2) | \( 0.023^8 \) |
| Constipation | 1 (0.2) | 2 (2.4) | \( 0.056^9 \) |
| Asymptomatic (incidentally diagnosed at routine health check-up) | 8 (1.6) | 10 (12.0) | \( < 0.001^10 \) |
| Medical institutions where misdiagnosis was made | | | |
| Primary clinic | 44 (8.9) | 12 (14.5) | |
| Secondary referral hospital | 118 (23.9) | 30 (36.1) | |
| Tertiary referral hospital | 314 (63.6) | 41 (49.4) | |
| Unknown | 18 (3.6) | | |

\(^1\)The \( P \) value by the \( \chi^2 \) test; \(^2\)The \( P \) value by the Mann-Whitney U test; \(^3\)The \( P \) value by the Fisher’s exact test; \(^4\)The Median (Interquartile range); \(^5\)Not evaluated in one patient; \(^6\)Not evaluated in four patients; \(^7\)Patients who had active pulmonary TB and patients whose chest X-ray film was unavailable were excluded; \(^8\)Misdiagnoses were made at our institution in 68 patients (13.8%); \(^9\)Misdiagnoses were made at our institution in 7 patients (8.4%). CD: Crohn’s disease; ITB: Intestinal tuberculosis; TB: Tuberculosis.
the final ITB group than in the final CD group ($P < 0.001$). Only seven patients (8.4%) had an active and/or past perianal fistula in the final ITB group, whereas 192 (38.9%) patients in the final CD group had an active and/or past perianal fistula ($P < 0.001$). None of patients in final CD group had active PTB, but 10 patients (12.7%) in final ITB group had active PTB ($P < 0.001$). Inactive PTB in the radiologic evaluation were also more commonly observed in final ITB group (38.9% vs 8.4%, $P < 0.001$). Table 2 shows the final diagnostic criteria for ITB and history of inappropriate medication for CD in the final ITB group. In 40 patients (48.2%), favorable response to empirical tuberculosis medication was applied as diagnostic criteria of ITB. In 10 patients (12.7%) in final ITB group had active PTB, but finally diagnosed with ITB. None of patients in final CD group had active PTB, but finally diagnosed with ITB.

### DISCUSSION

In the present study, we demonstrated the inverse trends in the misdiagnosis rates between CD and ITB over the last two decades in South Korea. Comparing the final CD group and the final ITB group, different characteristics, such as age at diagnosis, presenting symptoms, presence of perianal fistula, and concurrent PTB could be identified.

In this study, we included all patients managed for CD or ITB in our institution and enrolled patients who were finally diagnosed as CD or ITB before referral to our institution to minimize referral bias. In addition, by thoroughly reviewing the IBD registry of our hospital, which has been maintained since 1997[30], as well as medical records and colonoscopic images from referring physicians, we could gather valid information on our study subjects to ensure diagnostic accuracy for study participants.

The incidence of active PTB in Koreans was as high as 393/10^5 person-year between 1988 and 1990, and 202/10^5 person-year between 1992 and 1994[31,32]. However, it appears to be decreasing with time, showing 119.3/10^5 person-year between 2006 and 2008[6]. Although the exact incidence of ITB is not well known, a previous Korean study reported that 32 of 59 patients (54.2%) with active PTB, but without any gastrointestinal symptoms were diagnosed with ITB by total colonoscopy, thereby suggesting a high concurrence of ITB among PTB patients[33]. Although
the actual incidence of ITB is uncertain, the incidence of ITB is also expected to have been decreasing together with PTB. On the other hand, the incidence of CD, which was once thought to be very rare compared to Western countries, has been increasing recently in South Korea[9,34]. There have been several studies showing similar trends in TB epidemiology in other endemic areas, such as South Asia, India, Saudi Arabia, and South Africa[35-37]. For CD, as with Korea, the increasing incidence could be also observed in other Asian and Middle Eastern countries, such as Japan[38], Hong Kong[39], Taiwan[40], and Saudi Arabia[36].

With the changing epidemiology of TB and CD, general practitioners and gastrointestinal specialists in Asian areas could be becoming more concerned with CD than with ITB. In addition, with the decreasing incidence of TB, ITB cases that could have been correctly diagnosed may be misdiagnosed as CD. Actually, for the 19-year period in this study, the misdiagnosis rate of ITB as CD showed a statistically significant increase, and vice versa, although they were relatively stable since 2009. The rate of misdiagnosing ITB as CD overcame the rate of misdiagnosing CD as ITB in 2010. The misdiagnosis between CD and ITB and inappropriate treatments based on the misdiagnosis could cause serious harm to patients, especially for ITB cases. In our study, corticosteroids and/or thiopurines were inappropriately given to 20.5% of ITB patients because of misdiagnosis as CD, which could have led to disseminated TB disease. Therefore, our study results are calling for more attention to the physicians managing patients with inflammatory disorders of the bowel. In the absence of a confirmatory test to differentiate ITB from CD, the current Asia-Pacific consensus recommend 8-12 wk of empirical anti-TB treatment for patients with diagnostic uncertainty[41], and one thing we should remember is that about a half of ITB cases (48.2%) with previous misdiagnosis as CD in our study could have been correctly diagnosed with ITB after anti-TB treatment. The finding that the other half of ITB patients (49.4%) were correctly diagnosed based on positive culture of M. Tb emphasizes the importance of M. Tb culture study when performing colonoscopy for cases having ileocolonic inflammation which is difficult to make a differential diagnosis.

Unfortunately, there were no significant changes in the lag time from initial misdiagnosis to correct diagnosis during the study period. This is probably because most of the misdiagnosed cases have been referred to the more specialized centers or have been re-evaluated after a few months of unresponsiveness to treatment, which emphasizes the importance of the initial correct differentiation between two diseases. Therefore, we suggest the strict following of guidelines or consensus[36,42] and the application of the appropriate scoring system, diagnostic algorithms, or prediction models according to the regional epidemiology of two diseases[3,16,18-25].

In daily clinical practice, relatively simple clinical information could be helpful in the differential diagnosis between CD and ITB. In the current study, the younger age at diagnosis was observed in CD patients than in ITB patients, which is consistent with the results of previous studies[42,43]. The frequency of initial presenting symptoms was different between the two groups in our study. Diarrhea, hematochezia/melena, active and/or past perianal fistula were common in final CD group, whereas active or inactive pulmonary TB was observed more often in final ITB group. It was in line with a recently published large meta-analysis including 38 studies comprising 2117 CD and 1589 ITB patients, which has shown that diarrhea, hematochezia, presence of perianal disease, and extraintestinal manifestations significantly favored CD, whereas fever, night sweats, lung involvement and ascites significantly favored ITB[45]. However, symptoms are not always helpful for a differential diagnosis, because they are subjective and conflicting results on the frequency of symptoms in CD and ITB patients have been reported, depending on the study population[3,44-47].

According to the previous report from our institution, 43.2% of CD patients showed an active and/or past perianal fistula at the time of CD diagnosis[48]. In line with that study, among the final CD group, 38.9% of subjects showed an active and/or past perianal fistula at initial presentation, which was significantly higher than the figure for the final ITB group. Although a perianal fistula and anorectal lesion could also be manifestations of ITB[49,50], a concurrent perianal fistula could strongly suggest the probability of CD rather than ITB[3].

There has been a report that the features of old or active PTB were found in 35% of Indian patients with ITB[51]. Similarly, in South Korea, active PTB was accompanied in 28%-49% of ITB patients, and evidence of old PTB was shown in 14%-24.8% of ITB patients[27,52,53]. However, in our final ITB group, active PTB was accompanied only in 12.7%, although it was significantly more frequent than in final CD group. Because only cases initially misdiagnosed as CD were enrolled in the final ITB group, a lower proportion of patients might have concurrent active PTB compared with previous studies[27,52,53]. Nonetheless, a simple chest X-ray is always needed for a correct differential diagnosis, because findings of active PTB could be a clue to the diagnosis of ITB.

There are a few limitations to this study. First, the study design was retrospective. However, we made every effort to gather reliable data from electronic medical records, the IBD registry, endoscopic images, and information from referring doctors to avoid information bias. Regardless of our effort, some important variables which would affect the risk of ITB and CD, such as socioeconomic characteristics, could not be analyzed in this study. Second, this study was based on a single referral center and the real-life situations of primary and secondary facilities could be somewhat
different, maybe showing higher rates of misdiagnosis than in this study. However, because about one third of the final CD group and about a half of the final ITB group were initially misdiagnosed at the primary clinics or secondary hospitals, and because misdiagnosed cases in tertiary hospitals were also referred from primary or secondary facilities because of diagnostic uncertainty, our results could represent a general phenomenon in our country.

In conclusion, cases of ITB misdiagnosed as CD have been increasing in Korea over the past two decades. Conversely, CD cases misdiagnosed as ITB have been decreasing. More attention is needed for the correct diagnosis of CD or ITB, which could improve patients’ outcome with proper management.

COMMENTS

Background

Differential diagnosis between intestinal tuberculosis (ITB) and Crohn’s disease (CD) is a challenging issue in areas with a high prevalence of tuberculosis (TB) and an increasing incidence of CD. However, rates of misdiagnosis of CD and ITB as each other disease and their temporal trends are not well known.

Research frontiers

The incidence rate of TB is still high in Asia, but it is declining gradually with socioeconomic development. Meanwhile, the increasing incidence rate of CD is a widely observed phenomenon in most Asian countries. Most recent studies have focused on identifying clinical, endoscopic, radiologic, and histopathologic features which can be helpful to distinguish between two diseases and on suggesting predictive models or scoring systems. However, only a few studies have addressed how many patients are misdiagnosed as each other disease and none of studies have demonstrated how the misdiagnosis rates between CD and ITB have altered with changing epidemiology of two diseases.

Innovations and breakthroughs

This was the first study which has demonstrated inverse trends in misdiagnosis of CD as ITB and that raises the alarm for physicians so as not to expose patients to potentially harmful immunosuppressive therapy.

Terminology

ITB is tuberculosis involving intestinal tract, which is one of the forms of extrapulmonary tuberculosis.

Peer-review

In the present original paper, the authors showed temporal trends of the misdiagnosis rates between CD and ITB from a patient cohort managed at a specialized center for inflammatory bowel diseases. As a result, the rates of misdiagnosis as ITB in cases of actual CD has been decreasing and the opposite has been increasing. Overall, findings of this study are novel and this is a well-written and interesting paper.

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