Professor Damian Garcia-Olmo

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Editor-in-Chief

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Dear Editor-in-chief

Re: Manuscript No: 34784

We appreciate the editors and reviewers for careful review and insightful comments to improve the quality of our manuscript. We are grateful for the opportunity to respond to these comments and believe that our manuscript has now a significantly better quality than the original version. We hope that our revision and the updates are satisfactory and that the manuscript is now suitable for acceptance.

We have carefully considered the points raised by the reviewers and have addressed to each concern in a point-by-point fashion in the attached letter and in the revised manuscript.

Revision or insertions are shown as highlighted in yellow.

Thank you again for your kind consideration in advance and I am looking forward to hearing good news.

Sincerely yours,

Byong Duk Ye, on behalf of the co-authors

Point-by-point responses to the comments of the reviewers

We appreciate the reviewers' detailed and constructive review of our manuscript and their suggestions.

Response to Reviewer 1:

The authors present data about high rates of misdiagnosing CD as ITB and vice versa. Do I understand Figure 1 correct that at the beginning of the observation period about 40% of cases with CD have been misinterpreted as ITB? Fortunately, this rate went down to less than 10%. I suggest to include these figures in the text, because the reader would find them more alarming than if one only reads about the rates of decreasing misdiagnosis rates. The chocking data are a loud "wake-up" to the clinicians!

Response:

Thank you for the reviewer's valuable insight. Following the reviewer's comments, the figures of rates of misdiagnosing CD as ITB at the beginning and at the end of the observation period were added as follows in the Results section (revised manuscript page 9 line 21); "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), 33.2% of final CD group have been misdiagnosed as ITB, but the rate of misdiagnosing CD as ITB went down to 9.9% during the last 5 years (2010-2014) of study period."

2. How can we understand the increasing rate of misdiagnosing ITB as CD? Have the authors analyzed the reasons for that? Or did they only focus on the data?

Response:

Our study has started with the hypothesis that the changing epidemiology of tuberculosis (TB)

and Crohn's disease (CD) may affect the misdiagnosis rate between CD and intestinal tuberculosis (ITB) in areas with a still high prevalence of TB but increasing incidence of CD. We understand that the increasing rate of misdiagnosing ITB with CD as a phenomenon secondary to declining incidence of TB and increasing incidence of CD in Korea. In addition, a growing interest and concern about CD than about ITB among general practitioners and gastrointestinal specialists in Korea may lead them to misdiagnosing ITB as CD. However, it is very difficult to prove a direct correlation between the changing epidemiology of two diseases and the changes in misdiagnosis rates. Unfortunately, we could not analyze the changes in direct reasons of misdiagnosis, for examples, a low index of suspicion in cases with sufficiently evident clinical manifestations, misinterpretation of colonoscopic or radiologic findings, or missing critical tests such as *M. Tb* culture. This is because most of misdiagnosis were made at other institutions before visiting our center, as described in detail in the reply to *the comment 4*. Therefore, we had no choice but to provide a possible explanation for the phenomena we observed. We already described our hypothesis in the Discussion section as follows (revised manuscript page 12 line 1); "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."

3. It would be interesting to learn something about the lag time between initial and final diagnosis. Did the lag time vary? I hope it became shorter!

Response:

Thank you for the reviewer's insightful comment. Following the reviewer's comment, we analyzed further about trends in the interval from misdiagnosis to correct diagnosis over

observation period. Unfortunately, there were no significant changes in the lag time between initial misdiagnosis to final diagnosis during the study period, as shown in Figure 2, which is added in the revised manuscript. 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. This finding emphasizes the importance of the initial correct diagnosis and necessitates the application of diagnostic algorithms or prediction models for differential diagnosis between two diseases.

We added the sentence regarding the statistical analysis for the interval from misdiagnosis to correct diagnosis in the Methods section as follows (revised manuscript page 8 line 27); "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."

We also added the Figure 2 which shows temporal trends in the intervals from misdiagnosis to correct diagnosis in two groups (revised manuscript page 26).

We also described the data presented in Figure 2 in detail in the Results section as follows (revised manuscript page 10 line 6); "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 months (IQR, 2.3-12.2) in final CD group and 4.0 months (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) (Figure 2)."

We also added the paragraph regarding this observation in the Discussion section as follows (revised manuscript page 12 line 23); "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 diagnostic guidelines or consensus[26,41] and the application of the appropriate scoring systems, diagnostic algorithms, or prediction models according to the regional epidemiology of two diseases[3,16,18-25].”

4. Which were the reasons for misdiagnosis? The authors themselves present criteria for correct diagnosis of ITB and CD: Did the clinicians not follow these instructions. I understand that the shocking data are not the faults of the authors. But here they have the opportunity to give some suggestions to the clinicians to avoids these mistakes.

Response:

Thank you for the reviewer’s important comments. Unfortunately, we could not investigate the reasons for misdiagnosis in each case because only 68 (13.8%) of 494 cases in final CD group and only 7 (8.4%) among 83 patients in final ITB group were misdiagnosed at our institution. There was a limitation in looking into the reasons for each misdiagnosis made at other institutions before visiting our center. In our study, most cases of misdiagnosis were made at tertiary referral hospitals. However, in Korea, nearly all cases for which differential diagnosis is difficult, are referred to tertiary care centers. This is why misdiagnosis of 63.6% of final CD cases and 49.4% of final ITB cases was made at tertiary referral hospitals. However, considering low proportion of misdiagnosis made at our center, which is a specialized center for inflammatory bowel disease (IBD), we think that many doctors with less experience in IBD have been made misdiagnosis between two diseases. Following the reviewer’s recommendation, we can suggest the followings (revised manuscript 12 page 14); “In the absence of a confirmatory test to differentiate ITB from CD, the current Asia-Pacific

consensus recommend 8–12 weeks 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."

5. In how many patients with ITB misdiagnosed as CD the outcome was fatal?

Response:

Thank you for the reviewer's important comments. Out of 83 ITB patients initially misdiagnosed as CD, there was no case of mortality. We added the sentence regarding this at the last paragraph of the Results section as follows (revised manuscript 10 page 30); "There were no mortalities in two groups."

Response to Reviewer 2:

1. Were all the diagnoses achieved in the Asan Medical Center, or did the Authors manage patients diagnosed in other non-tertiary center? This is crucial, since it has been demonstrated that the risk of misdiagnosis is higher in peripheral centers without selective specialization. This point is shown in table 1, but it should be remarked in the Results paragraph.

Response:

Thank you for the reviewer's comment. Following the reviewer's comment, the sentences regarding this issue was added at the Results section as follows (revised manuscript page 9 line 9); "Among 494 patients in final 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 institutions where misdiagnoses were made was unclear. Among 83 patients in final ITB group, misdiagnoses were made at primary clinics in 12 patients (14.5%), at secondary referral hospitals in 30 patients (36.1%), at the tertiary referral hospitals other than our institution in 34 patients (41.0%), and at our institution in 7 patients (8.4%, Table 1)."

The information about the proportion of misdiagnoses which were made at our institution was also added as footnotes of Table 1 as follows (revised manuscript page 28); "[h]Misdiagnoses were made at our institution in 68 patients (13.8%); [i]Misdiagnoses were made at our institution in 7 patients (8.4%)."

2. Some socio-demographic characteristics, such as low income, low schooling level and familiarity with subjects with tuberculosis are lacking, therefore they should be analyzed as well.

Response:

Thank you for the reviewer's perceptive comment. We totally agree with that some socio-demographic characteristics are related to the risk of tuberculosis and should be analyzed as well. However, our study was based on the retrospective review of the medical records of other centers as well as our own and the IBD registry of our center, and it is impossible to fill up the incomplete data which were not investigated at the time of actual clinical management of patients. We described this limitation of our study in the Discussion section as follows (revised manuscript page 14 line 6); "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."

3. Table 2, please define "immunomodulators" (thiopurine, biologics…)

Response:

Thank you for the reviewer's detailed comment. Following the reviewer's comment, all terms *immunomodulators* were replaced by terms *thiopurines* as follows;

"Seventeen patients (20.5%) in final ITB group had inappropriately received corticosteroids and/or thiopurines due to misdiagnosis as CD." (revised manuscript page 4 line 24)

"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[14]." (revised manuscript page 6 line 21)

"In 40 patients (48.2%), favorable response to empirical tuberculosis treatment was applied as diagnostic criteria of ITB. In 17 patients (20.5%), corticosteroids and/or thiopurines were inappropriately given due to misdiagnosis as CD (Table 2)." (revised manuscript page 10 line 27)

"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." (revised manuscript page 12 line 10)

"5-ASA + Thiopurines (%)" (revised manuscript page 29 Table 2)

"5-ASA + Corticosteroids + Thiopurines (%)" (revised manuscript page 29 Table 2)

4. In this last regard, TB screening is usually advised to patients before starting biologic drug. Did this strategy impact on the rate of CD misdiagnosed instead of ITB?

Response:

Thank you for the reviewer's valuable comment. As already shown in Table 2, seventeen patients (20.5%) in final ITB group were treated with corticosteroids and/or thiopurines, but none of the patients received biologic agents. In our detailed review, none of the patients in

final ITB group were diagnosed correctly with the help of latent TB screening test just prior to starting biologic agents. In most cases, uncertainty about diagnosis or unresponsiveness to medications for CD led to referral of patients to a more specialized center and a re-evaluation of those with a high index of suspicion for ITB. Therefore, the strategy of screening latent TB before starting biologics probably had little impact on the rate of misdiagnosis as CD instead of ITB.

5. As displayed in figure 1, in 2010 the cases of CD misdiagnosis overcame the ITB misdiagnosis. This finding deserves further discussion in an appropriate paragraph.

Response:

Thank you for reviewer's insightful comments. Following the review's comment, we added a sentence regarding this observation in the discussion section as follows (revised manuscript page 12 line 7): "The rate of misdiagnosing ITB as CD overcame the rate of misdiagnosing CD as ITB in 2010."

Unfortunately, we think that we cannot provide an explanation on why the cross of graphs in figure 1 developed in 2010. We suggested that the changes in misdiagnosis rates would probably be the results of changes in the epidemiology of CD and ITB and increasing attention of clinicians to CD in Korea. However, it is very difficult to find the reason why the misdiagnosis rates of two diseases interchanged at a certain time point. We think that the giving the message raising the alarm to clinicians is more important than finding the reason. We emphasizes the importance of not misdiagnosing ITB as CD and suggests followings (revised manuscript page 12 line 14); "In the absence of a confirmatory test to differentiate ITB from CD, the current Asia-Pacific consensus recommend 8–12 weeks 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 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."

Response to Reviewer 3:

MAJOR:

1. I am not convinced that the misdiagnosis of incidence of cases of ITB as CD has increased – the line looks pretty flat.

Response:

Thank you for reviewer's insightful comments. We agree with that the line representing the expected misdiagnosis rate of ITB as CD may look flat in Figure 1. However, at the beginning of the observation period, less than 10% of cases with ITB have been misdiagnosed as CD, while the rate of misdiagnosing ITB as CD went up above 10% at the end of the observation period. This change appears not as clear as the decrease in the rate of misdiagnosing CD as ITB. However, the rate of misdiagnosing ITB as CD increased, which was statistically significantly. The logistic regression analysis showed the 6% increase per year in the rate of misdiagnosing ITB as CD, which was statistically significant (P = 0.013). We added the figures of rates of misdiagnosing ITB as CD at the beginning and at the end of the observation period in the Results section as follows (revised manuscript page 9 line 29); "In the cases with ITB, no patient was misdiagnosed initially as CD in 1996, but 15.6% were misdiagnosed initially as CD 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)."

2. Overall- it would be very informative to the reader to know more about how to prevent misdiagnosis. Authors should provide more facts on how to differentiate the two and maybe offer some pearls of wisdom (If patient has X, CD may be more likely.)

Response:

Thank you for reviewer's valuable comments. As we described in the introduction section, although previous studies have suggested the combination of 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 a recently published large meta-analysis including 38 studies comprising 2,117 CD and 1,589 ITB patients, diarrhea, hematochezia, presence of perianal disease, and extraintestinal manifestations significantly favored CD, whereas fever, night sweats, lung involvement, and ascites significantly favored ITB (Limsrivilai J., et al., Meta-Analytic Bayesian Model For Differentiating Intestinal Tuberculosis from Crohn's Disease. Am J Gastroenterol 2017;112:415-427). Those results were in line with the findings of our study in that diarrhea, hematochezia/melena, active and/or past perianal fistula were more common in final CD group, whereas active or inactive pulmonary TB was observed more often in final ITB group. The sentences regarding this observation was added in the Discussion section (revised manuscript page 13 line 5).

However, clinical manifestations which favor either CD or ITB are not infrequently observed in the opposite condition as our study results have shown, and the diagnosis should be made comprehensively by combining clinical, endoscopic, radiologic, and pathological findings because there is no single gold standard criteria for diagnosing CD. Following the reviewer's recommendation, we can suggest the followings (revised manuscript page 12 line 14); "In the absence of a confirmatory test to differentiate ITB from CD, the current Asia-Pacific consensus recommend 8–12 weeks 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 between 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[26,41] 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].”

3. Abstract, last sentence: Needs to finish with description of what outcome in the final ITB group inappropriately treated.

Response:

Thank you for the reviewer’s insightful comment. We added the sentence about final outcomes in the last part of the Results of the Abstract as follows (revised manuscript page 4 line 25); “However, there were no mortalities in both groups.”.

MINOR:

3. Pg 4- Results, 2nd to last sentence, change “was” to “were”.

Response: The sentence was corrected as the reviewer suggested. (revised manuscript page 4 line 23)

4. Pg 6- Introduction, prefer more facts as opposed to "expected to decrease" and "could be increasing"

Response:

Thank you for the reviewer's comment. The sentence the reviewer commented demonstrates our hypothesis, that the changing epidemiology of TB and CD may affect the misdiagnosis rates between two diseases in areas with a high prevalence of TB but increasing incidence of CD. We could not find more facts in previous epidemiologic studies and, therefore, we made this hypothesis and performed our study.

5. Pg 7- Methods, Study Population- State guidelines used to diagnose ITB, if possible

Response: The sentence regarding this comment was inserted in the Methods section as follows (revised manuscript page 7 line 10); "The diagnosis of ITB was based on Korean diagnostic guideline of ITB[26]."

6. Core tip, 2nd page: move "the" from before "inverse" to after "trends in".

Response: The sentence was corrected as the reviewer suggested. (revised manuscript page 5 line 6)

7. Core tip: Spell out what is opposite in the 2nd to last sentence.

Response: The sentence was corrected as the reviewer suggested. (revised manuscript page 5 line 8)

8. "Clues" p. 6, bottom. This might be a good place to put answer to major point #2.

Response:

Thank you for the reviewer's valuable comment. We fully agree with that the detailed

description of features which had been previously suggested as being helpful in distinguishing CD and ITB, would be very informative to the readers. However, we had no choice but to provide a further explanation about this issue in the Discussion section to avoid redundancy in the Introduction section.

9. Introduction, needs reference after "anti TNF agents can aggravate ITB."

Response: The reference was added as the reviewer suggested. (revised manuscript page 6 line 24)

10. Study population, p7. Mention which colonoscopic findings are noted.

Response: The sentence regarding this was added as follow (revised manuscript page 7 line 18): "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[16]."

11. Page 9: give percent of pulmonary TB seen in 2 groups. Should also discuss why so low in cases of ITB (only 10%)

Response: The proportions of concurrent pulmonary TB in two groups were noted in Table 1. The sentence regarding this finding was revised in the Results section as follows (revised manuscript page 10 line 23); "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%, $P < 0.001$)."

We already suggested a possible explanation for the reason why the rate of concurrent active pulmonary TB was so low in cases of ITB in the Discussion section as follows (revised

manuscript page 13 line 23); “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 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].”