

Jun 5, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name:15738.-review.doc).

Title: Perianal tuberculosis: A case report and literature review.

Author: Sayaka Tago, Yuji Hirai, Yusuke Ainoda, Takahiro Fujita, Mikio Takamori, Ken Kikuchi

Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 15738

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

Reviewer 1.

Introduction:

(1) Best to reference the 2014 global tuberculosis report, available at: http://www.who.int/tb/publications/global_report/en/ Also some parts of Europe will have higher rates of TB than Japan (and Japan is considered a low incidence TB country), so it may be best to rephrase this statement. (p.4, line2)

Response : We agree to the reviewer's comment. We have changed the sentences (p.3, line 16) from; "Tuberculosis (TB) is still a major health problem worldwide and is more prevalent in Asia, especially Japan, than in Europe and the United States[1]."

to

" Tuberculosis (TB) remains a major health problem worldwide and is more prevalent in Asia. In Japan, where TB prevalence is decreasing, the estimated number of new TB cases per 100,000 people per year is 10-19, which is in the same range as some European countries [1]"

We have also changed the reference (p.9, line 2) from

“1. Global tuberculosis report 2013, Annex 4. Key indicators for the world, WHO regions and individual countries, p149. Available from: URL: http://apps.who.int/iris/bitstream/10665/91355/1/9789241564656_eng.pdf”

to

“1. Global tuberculosis report 2014, Figure 2.5. Estimated TB Incidence rates, 2013. p18. Available from: URL: http://www.who.int/tb/publications/global_report/en/”

(2) I think the man is a Japanese national but it would be useful to know this. Did he have a history of smoking and did you recommend an HIV test?

Response: We agree to the reviewer’s comment. We have changed the sentence (p.4, line 7) from “man”

to

“Japanese man”

And, we have added the sentences

“He smoked 20 cigarettes per day” (p.4, line 12)

and

“His HIV test was negative.” (p.5, line 10)

(3) Any family history of TB?

Response: We agree to the reviewer’s comment. We added the following sentence (p.4, line 15):

“He had no family history of TB.”

(4) I don’t think this part of the sentence is necessary (i.e. “the operation was performed at the Department of Surgery”)

Response: We agree to the reviewer’s comment. We removed the following sentence:

“the operation was performed at the Department of Surgery.”

(5) Is the literature review best placed as the results? (p.6, line 1)

Response: We agree to the reviewer’s comment. We removed literature review in from discussion to case report..

(6) There may also be another possibility, re-infection with a new strain of TB? (p.7, line 15).

Thank you for your comment

.

Response: Thank you for your comment. As I wrote “TB rarely, if ever, occurs as a primary infection in the perianal region” (p.7, line 14), we do not think that new strain of TB primarily infected in perianal region. However, we assume the re-infection with a new strain of TB in “other foci” (p. 7, line 17) which have not been sufficiently investigated

(7) Is this a mean? If so the two sample t test is appropriate? (p.7, line 20).

Response: Thank you for your comment. Yes, this is a mean. The two sample t test is appropriate, because we assumed that the population was normal distribution.

(8) According to the style of the journal you can write $P < 0.05$.

Response: We agree to the reviewer’s comment. We have changed the text (p.8, line 2) from

“ $P = 0.0380$ ”

to

“ $P < 0.05$ ”

(9) This seems a little out of place here. I think the paper needs to be restructured slightly to have the lit review as results and then a separate discussion. This information can be part of the discussion. (p.8, line 4)

Response: We agree to the reviewer’s comment. We removed literature review from discussion to case report.

(10) As well as employment situation? (p.8, line 11)

Response: We agree to the reviewer’s comment. We added the following sentence (p.8, line 15):

“and employment situation”

Reviewer 2.

(1) I don’t think this is a correct statement. I suggest that this sentence is rephrased; generally, in Asia, EPTB has been slightly more reported than in Africa and elsewhere; most authors believe that some 30% if TB is extra-pulmonary but there is no evidence that this percentage is increasing over time. Importantly, as the authors correctly state, quite some EPTB has concomitant PTB. (p.4, line3)

Response: We agree to the reviewer's comment. We deleted the description "TB has recently increased from less than 1%".

Actually reference [2] shows the data that extra-pulmonary TB occupies 3–46% of all types of TB.

We have changed the sentence from (p.3, line 19);

"The prevalence of extra-pulmonary TB has recently increased from less than 1% of all types of TB to 3–46% of cases ^[2],"

to

"Extra-pulmonary TB occupies 3–46% of all types of TB ^[2],"

Reviewer 3.

Title page:

(1) **Title:** Better: "... review of the literature"

Response: We agree to the reviewer's comment. We have changed the title (p.1, line 1) from

"Perianal tuberculosis: A case report and literature review."

to

"Perianal tuberculosis: A case report and review of the literature."

(2) **Authors:** The author "Takahiro Fujita" is not mentioned in *authors contributions*. On the other side, "Takamori M" (mentioned in *authors contribution*) is not in the list of authors. Are both persons author?

Response: Thank you for your comment. We originally mentioned "Mikio Takamori" in the list of authors as "Mikio Takamori, Department of Pulmonary Disease, Tokyo Metropolitan Tama Medical center, 2-8-29 Musashidai, Fuchu-shi, Tokyo 183-8524, Japan"

We agree to the reviewer's comment. We changed "Takamori M" to " Takahiro F" in *authors contributions*.

Abstract:

(3) The first paragraph of the *Abstract* is nearly identical to wording in the first paragraph of *Case report*. Redundancy should be avoided.

Response: We agree to the reviewer's comment. We had shorten the abstract (147 words).

(4) *Abstract* is not well-structured. In particular, research background and objective is completely missing.

Response: We agree to the reviewer's comment. We added the following sentences in abstract (p.2 ,line 9);

"Tuberculosis (TB) remains a major health problem worldwide. We present a rare case of an immunocompetent patient with perianal TB."

Introduction:

(5) The sentence "Tuberculosis is ... more prevalent in Asia, especially Japan, than in Europe .." implies that TB prevalence in Japan is as high as in Asia. That is not the case.

Response: We agree to the reviewer's comment. We had changed the sentences from (p.3, line 16);
"Tuberculosis (TB) is still a major health problem worldwide and is more prevalent in Asia, especially Japan, than in Europe and the United States ^[1]."

to

"Tuberculosis (TB) remains a major health problem worldwide and is more prevalent in Asia. In Japan, where TB prevalence is decreasing, the estimated number of new TB cases per 100,000 people per year is 10-19, which is in the same range as some European countries ^[1],"

(6) The statement ".prevalence of extrapulmonary TB has recently increased ..". contains a reference from the year 2006. A more recent reference should be used or "recently" should be replaced by "between years xxxx and xxxx". Same is true for reference (3)

Response: We agree to the reviewer's comment.

We removed the following sentence (p.3, line 19);

"TB has recently increased"

And we have changed the following reference from (p.12, line 20):

"Jayanthi V, Robinson RJ, Malathi S, Rani B, Balambal R, Chari S, Taghuram K, Madanagopalan N, Mayberry JF. Does Crohn's disease need differentiation from tuberculosis? J Gastroenterol Hepatol 1996; 11: 183-186 [PMID: 8672766]"

to

"**Yaghoobi R**, Khazanee A, Bagherani N, Tajalli M. Gastrointestinal tuberculosis with anal and perianal involvement misdiagnosed as Crohn's disease for 15 years.Acta Derm Venereol. 2011;91:

348-349. doi: 10.2340/00015555-1030.”

(7) It would be useful to know how rare is perianal TB, (xx% percentage of extrapulmonary TB)

Response: We agree to the reviewer’s comment. According to the published date, its prevalence (anal localization) is 0.7% .

We added the following text (p.4, line 1) and reference (p.9, line 11):

“(0.7%)”

And,

(3) Alvarez Conde JL, Gutierrez Alonso VM, Del Riego Tomas J, Garcia Martinez I, Arizcun Sanchez-Morate A, Vaquero Puerta C. Perianal ulcers of tubercular origin. A report of 3 new cases. Rev Esp Enferm Dig. 1992;81:46–48.

Case report

(9) Some information in this section not necessary, i.e. data on blood pressure, pulse rate, oxygen saturation (page 4/5); the unremarkable past history of the patient (p. 4); information that operation was performed at the Department of Surgery (p. 5). Removal may tighten the case report and improve readability.

Response: We agree to the reviewer’s comment. We removed oxygen saturation, and description of “operation was performed at the Department of Surgery”.

However, we think that the blood pressure, and pulse rate are important to show that he did not have septic shock because the existence septic shock is important in infectious patients.

(10) Data on diagnosis of pulmonary TB (CT, PCR and culture from sputum) and diagnosis of perianal TB (description of abscess, PCR and culture from abscess material) should be described in two different blocks:

Response: Thank you for your comment. However, we would like to describe the time course of diagnostic process of pulmonary and anal TB, not separately. Because we think that this process is very educational to clinicians and students.

(11) Page 4, line 4: better “acid-fast bacilli” instead of “bacillus”.

Response We agree to the reviewer’s comment. We have changed the following text from (p.4, line 10):

“acid-fast bacillus”

to

“acid-fast bacilli”

(12) Page 5, line 2: Redness and swelling has already noted before (page 4, first line of case report). Sentence should be removed or rephrased.

Response: We agree to the reviewer’s comment.

We removed “swelling and redness” in first line of case report (p.4, line 7), and did not remove “Redness and swelling” (p.4, line 17) as physical findings.

(13) Page 5, line 3: the cavity has already revealed before by chest X-ray. Another wording should be used.

Response: We agree to the reviewer’s comment. We have changed the following text from (p.4, line 19):

“Thoracic computed tomography revealed a cavity in the right upper lung field”

to

“Thoracic computed tomography confirmed the cavity in the right upper lung field”

(14) Page 5, line 5: what kind of PCR assay has been used for detection of MTB? Could the authors specify the target gene (if an in-house PCR protocol was used) or refer the test name (if a commercial assay has been used)?

Response: We agree to the reviewer’s comment. It is a commercial assay named Kobasu TapMan[®] MTB.

We added the following text (p. 5, line 1);

(Kobasu TaqMan[®] MTB, Switzerland)

(15) Page 5, line 7: was the abscess material investigated for the presence of AFB? If yes results should be given.

Response: We agree to the reviewer’s comment. AFB was detected in the abscess. We have changed the following text from (p.5., line 4):

“MTB was also detected in the wound pus using PCR and culture analysis.”

To

“AFB were also detected in the wound pus, and PCR and culture analysis confirmed MTB.”

(16) Page 5, line 15: “No apparent underlying disease was detected...”: do the authors speak of the pulmonary TB (cavities, cough)? What about the perianal lesions?

Response: Thank you for your comment. We want to say that we could not detect underlying diseases revealing immunodeficiency for 3-month follow-up examination.

Discussion

(17) Page 6, line 7: better “whereas” instead of “although”

Response: We agree to the reviewer’s comment. To clarify the meaning, we have changed the following text from (p.5, line 16):

“ , although 70.7% were from Asia”

to

“A total of 70.7% of the cases were from Asia [5, 6, 7-33].”

(18) Page 6, line 11: the authors should avoid the expression “our study population” since the 59 cases were not part of this study.

Response: We agree to the reviewer’s comment. We agree to the reviewer’s comment. We have changed the following text from (p.5, line 19):

“Only 18.6% of the patients in our study population had underlying diseases”

to

“A total of 18.6% of the patients had underlying diseases”

(19) Page 6, line 11: what kind of underlying diseases? Please list or exemplify.

Response: We agree to the reviewer’s comment. We added the following sentences as footnotes in Table.1.

“Underlying disease: respiratory diseases, 3; diabetes mellitus, 2; hepatitis, 1; hepatitis+HIV, 1;

chronic kidney disease, 1; malignancy, 1; autoimmune disease, 1; and cardiovascular disease, 1. “

(20) Page 6, line 16: what do the authors mean with “duration of diseases”? The time from beginning of symptoms until successfully completed treatment? This should be explained at least once.

Response: We agree to the reviewer’s comment. “duration of diseases” means the time from beginning of symptoms until diagnosed with perianal tuberculosis.

We added the following sentences (p.6, line 1):

“We researched the duration of the disease from the beginning of symptoms until diagnosis with perianal tuberculosis.”

(21) Page 6, line 18: The meaning of the sentence “ Although it is difficult to confirm...” is not clear to me. Do the authors mean that the time period from beginning of perianal symptoms until definite diagnosis of TB cannot be determined due to lack of data?

Response: Thank you for your comment. We removed the following sentences (p.7, line 3) because the sentences are confusing.

“Although it is difficult to confirm whether the timing of development of tuberculosis is related to the etiology of perianal lesions,”

(22) Page 7, line 1: the term “old tuberculosis” sounds strange. Alternative, for example, “history of TB”.

Response: We agree to the reviewer’s comment. We have changed the following text from (p.6, line 6):

“old tuberculosis“

to

“history of TB“

(23) Page 7, line 2: Better “no history of pulmonary TB” instead of “neither active nor old pulmonary TB”

Response: We agree to the reviewer’s comment. We have changed the following text from (p.6, line 7):

“neither active nor old pulmonary TB“

to

“no history of pulmonary TB“

(24) Page 7, line 2: For one case there is obviously no information on co-existing or previous pulmonary TB. On the other hand, the conclusions of the present study are mainly based on information about presence or absence of APTB. I would suggest to remove this case (this reference) completely.

Response: We agree to the reviewer’s comment. We have removed 1 case who has no information on co-existing or previous pulmonary TB. Therefore, we have changed the following texts:

“59 cases“ to “58 cases“ (p.5,line 12)

“Korea, 5 cases“ to “Korea, 4 cases“ (p. 5,line 13)

“72.8% were from Asia“ to “A total of 70.7% of the cases were from Asia“ (p.5,line 16)

“45.4 ± 15.6 years“ to “45.3 ± 10.6 years“(p.5,line 17)

“53 [89.8%] men and 6 [10.2%]women“ to “52 [89.7%] men and 6 [10.3%] women“ (p.5, line 18)

(25) Page 7, line 3: in cases of perianal TB, APTB is often present but not vice versa. The authors may reword the sentence “Since APTB is” in order to avoid misunderstanding.

Response: We agree to the reviewer’s comment. We have changed the following text from (p.7, line 5):

“Since APTB is often concomitant with perianal TB,“

to

“Because APTB is often concomitant with cases of perianal TB,“

(26) Page 7, line 8 (p.7, line 10): does the group of cases “without APTB” include patients with history of TB?

Response: Thank you for your comment. The group of cases “without APTB (n=24)” include 12 patients with history of TB and 12 patients without history of TB.

(27) Page 7, line 9: is the difference in age between both groups significant? If not, I would suggest to mention age/mean years only in the table.

Response: The difference in age between both groups is not statistically significant. We agree to the reviewer's comment. We mention about age only in the table. Therefore, We have removed the sentence (p.6, line 10):

“although the former were younger, “

(28) Page 7, line 10: what do the authors mean with “.. the occurrence of extrapulmonary TB (intestinal, military...” Be aware that perianal TB is also a form of extrapulmonary TB from which suffer all patients included. Furthermore, I don't know the term “military TB”. Please explain. To avoid misunderstandings, the authors should use the same terms as in Table 1 (i.e. intestinal TB, TB complication)

Response: We agree to the reviewer's comment. “military TB” is misspelling. “miliary TB” is correct. TB complication includes miliary TB, peritoneal TB, and iliopsoas muscle abscess by TB. We have changed the following text from (p.7, line 11):

“the occurrence of extra-pulmonary TB (intestinal, military, etc.) was“

to

“the occurrence of intestinal TB and TB complications (miliary TB, peritoneal TB, and iliopsoas muscle abscess by TB) were “

(29) Page 7, line 14: First, the formulation “reactivation of old pulmonary TB ..” is not quite correct since the authors rather mean reactivation after (hematogeneous) spread from primary lung infection.

Response: We agree to the reviewer's comment. We have changed the following text from (p.7 line 16):

“the reactivation of old pulmonary tuberculosis could be responsible”

to

“hematogeneous spread after reactivation of latent lung TB could be responsible”

(30) Page 8, line 3 to 10: information contained in this section dealing with transmission routes and sources of infection is not relevant for the present study and should be removed.

Response: Thank you for your comment. The patient of this case installed Japanese pinball

machines (pachinko) for a living. Spending time in pachinko parlors might be the risk factor for him to be infected with TB. In this section, we wanted to show the importance of an interview to collect information on the places that the patient stayed at or visited to make a diagnosis of TB.

Therefore, we added the following sentence (p.8, line 7) before the section to clarify the relevance..

“The patient in our case installed Japanese pinball machines (pachinko) for a living.”

References

(31) Actual references should be used, if possible (see *Specific comments, Introduction*)

Response: Thank you for your comment. We had changed the description of the references.

Tables and Figures

Table 1

(32) The same terms and formulation as in the text should be used, for example “Without APTB” instead of “non-active pulmonary TB”

Response: We agree to the reviewer’s comment. We have changed the following text (Table 1) from “non-active pulmonary TB”

to

“Without APTB”

(33) Please specify “TB complication” as well as “underlying disease” maybe as footnotes.

Response: We agree to the reviewer’s comment. We added the following sentences as footnotes in Table1.

“TB complication: miliary TB, peritoneal TB, and iliopsoas muscle abscess by TB.

Underlying disease: respiratory diseases, 3; diabetes mellitus, 2; hepatitis, 1; hepatitis+HIV, 1; chronic kidney disease, 1; malignancy, 1; autoimmune disease, 1; and cardiovascular disease, 1.”

3 References and typesetting were corrected.

Thank you again for publishing our manuscript in the World Journal of Gastroenterology.

Sincerely yours,

Sayaka Tago, M.D.

Department of Infectious Diseases,

Tokyo Women's Medical University,

8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan.

Telephone: +81-3-3353-8112 (39321) Fax: +81-3-3358-8995

E-mail: asahata.sayaka@twmu.ac.jp