Author's response to reviews

Title: Cutaneous paragonimiasis presented as non-migratory subcutaneous nodule due to triploid Paragonimus westermani: a case report

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Author's response to reviews: see over
Dear Referees,

We appreciate the opportunity to resubmit our article retitled: Cutaneous paragonimiasis presented as non-migratory subcutaneous nodule due to triploid Paragonimus westermani: a case report. We greatly thank the constructive comments by the referees. We have addressed all the comments and this has strengthened the revised manuscript. In the following lines, we outline point by point responses to the comments by Referee 1 and Referee 3, which are shown in italics below. We hope our revised version will be received favorably and look forward to hearing from you soon.

Referee 1’s comments:
Would you please add the past history of patient if she ingest the raw crab or crawfish?
(Our response)
In the first paragraph of page 5 (the first paragraph of the Case presentation) of the original manuscript, we had actually described that “she had frequent opportunities to have drunken crab; raw crab soaked in rice wine”. To more clearly state her past history related to raw crab ingestion, we have erased the sentence prior to the above description, “she had no specific family or past history”, and added the following sentences “As past history, she had frequent opportunities to have drunken crab; raw crab soaked in rice wine, especially before she settled in Japan 7 years ago. Additionally, she had smoking history in her twenties (5 cigarettes per day). No specific family history was addressed.”

Journal title of ref. no. 11 should be abbreviated.
(Our response)
We appreciate this comment and have abbreviated the journal title of ref. no. 11 together with ref. no. 3.

Referee 3’s comments:
- General comments:
  1. The difficulty in diagnosis of ectopic paragonimiasis is not because of its rarity and variable symptoms as described by the authors but it is due to the ignorance and unfamiliar of this medical condition.
(Our response)
We appreciate this comment and have replaced the expression “because of its rarity and variable symptoms with “due to ignorance and unfamiliarity of the disease” in the first
paragraph on page 3 (Introduction section of the Abstract) of the original manuscript. Furthermore, we have added “, which caused ignorance and unfamiliarity of the disease” after “because of its rarity and variable symptoms” in the third paragraph on page 4 (Introduction) of the original manuscript.

1. (Continued) There are several case reports on cutaneous paragonimiasis from several parts of the world including India, China, Thailand, Korea, Japan and North Americas.

(Our response) We thank this comment and have modified the sentence in the third paragraph on page 7 (the second paragraph of the Discussion) of the original manuscript: “Subcutaneous paragonimiasis is particularly rare and has not been well documented in the literature,” to “Subcutaneous paragonimiasis is particularly rare.”

2. Cutaneous paragonimiasis can be diagnosed by proper history taking including history of consumption of fresh water crabs, endemic areas of paragonimiasis and clinical presentation of migratory or non-migratory (rarely) subcutaneous nodules.

3. The diagnosis can be easily confirmed by excision biopsy for histopathological and parasitological examination for the presence of worm and or Paragonimus ova or Paragonimus specific serological test. Magnetic resonance imaging is not helpful in the diagnosis of cutaneous paragonimiasis. The test is unnecessary so it should be omitted.

(Our responses) We take seriously this comment that cutaneous paragonimiasis can be diagnosed by proper history taking, excision biopsy and Paragonimus specific serological test. Therefore, we have deleted the sentence “Any diagnostic clues should be helpful, but have not been fully provided in the literature.” in the first paragraph on page 3 (Introduction section of the Abstract) and the third paragraph on page 4 (Introduction) of the original manuscript.

Also, the first paragraph on page 4 of the original manuscript (Conclusion section of the Abstract) has been replaced with “We report a case presenting only a non-migratory subcutaneous nodule without any pleuropulmonary lesion, which was initially suspected of lipoma but denied by MRI findings. The case was subsequently diagnosed as subcutaneous paragonimiasis by histopathological analysis and serological examination.”

Similarly, in the first paragraph on page 3 (Introduction section of the Abstract) and the third paragraph on page 4 (Introduction), we have deleted the expression
“examined by magnetic resonance imaging”. The following sentence has been used in both places, “We experienced a case with subcutaneous paragonimiasis diagnosed by histopathological analysis and serological test”.

Regarding MRI findings including Figure 1, we would like to retain them in the revised version due to following reason. The present case in our report with the non-migratory subcutaneous nodule was initially suspected of lipoma and thus subjected to MRI examination. Clinicians, particularly in non-endemic area of paragonimiasis, are highly likely to encounter the similar situation. Documentation of MRI findings of subcutaneous paragonimiasis may help them to include subcutaneous paragonimiasis as a differential diagnosis. Therefore, MRI findings have not been deleted in the second paragraph on page 3 (the Case presentation section of the Abstract), the second paragraph on page 5 (the second paragraph of the Case presentation) and in the second paragraph on page 8 (the third paragraph of the Discussion) of the original manuscript. However, the sentence in the last place has been deleted: “the MRI findings observed in this case should be helpful for the diagnosis of subcutaneous paragonimiasis.”

4. The authors should have examined the whole worm after borax carmine staining to identify the species.
(Our response)
We agree with this comment, but we have not preserved the whole worm unfortunately. As described in the manuscript, the species of the worm in the present case was identified by histopathological findings such as the size of the ova and the presence of one single worm producing ova, and the serological test result.

- Revisions necessary for publication
1. The title of the article is not appropriate. It may be modified as “Cutaneous paragonimiasis presented as non-migratory subcutaneous nodule due to triploid Paragonimus westermani: a case report”
(Our response)
We thank this suggestion and have revised the title as “Cutaneous paragonimiasis presented as non-migratory subcutaneous nodule due to triploid Paragonimus westermani: a case report”

2. Recommended for revision of the manuscript taking into account the points given in the general comments.
Please refer to the above-mentioned responses to the general comments.

3. More references on cutaneous paragonimiasis are needed.

Following the Journal style to limit the number of references (no more than 15 references), we have cited two more references (ref. no. 13 and 14) reporting the cutaneous paragonimiasis cases infected by *P. westermani* to discuss diagnostic methods.

4. Emphasis should be given to the findings of non-migratory subcutaneous nodule that is a rare presentation and triploid form of *P. westermani*

We appreciate this comment and have added more explanation about triploid *P. westermani*, for the readers who are not familiar with this unique species producing ova parthenogenetically, in the third paragraph on page 4 (Introduction) of the original manuscript.

Although we basically understand that parasites are migratory, we are not absolutely sure that non-migratory subcutaneous nodules are rare, particularly with regard to the present case at a chronic infection phase. We have revisited the references related to cutaneous paragonimiasis. Cutaneous/subcutaneous nodules are migratory in some reports e.g., Intern Med 2000, 39:433-436 (ref. no. 14), but not migratory in the other reports e.g. Int J Dermatol 2003, 42:699-702 (ref. no. 13). In our opinion, more cutaneous paragonimiasis cases are needed with detailed analyses to come to the conclusion. Anyway, we have emphasized MRI less and discussed diagnostic methods of cutaneous paragonimiasis more appropriately in the revised manuscript.

5. revise the figures accordingly

Refer to the above-mentioned response to the general comments, No. 3.

Referee 3 suggested minor revisions in the original manuscript submitted as an additional material. Those revisions have been made in the revised manuscript along his recommendation. The revisions are underlined below:

(In the second paragraph on page 4 of the original manuscript: Keywords)

Subcutaneous nodule, *Paragonimus westermani*, histopathology
*We have erased “ectopic infection, magnetic resonance imaging”.
(In the second paragraph on page 5 of the original manuscript: the second paragraph of the Case presentation)
“Subsequently, a surgical resection was performed.”
(In the first paragraph on page 6 of the original manuscript: the third paragraph of the Case presentation)
“a triploid form of *P. westermani* producing ova *parthenogenetically*, not a diploid form of *Paragonimus* species.”
(In the second paragraph on page 6 of the original manuscript: the fourth paragraph of the Case presentation)
“On serological examination using multiple-dot enzyme-linked immunosorbent assay with antigens of *P. westermani* and *P. skrjabini miyazakii*,”

Referee 3 also suggested to *discuss more on the usefulness of excision biopsy, histopathological and serological tests as recommended for diagnosis of cutaneous paragonimiasis* on page 8 (Discussion) in the original manuscript. We have newly added one more paragraph at the end of the Discussion. We have cited two more references (ref. no. 13 and 14) describing that cutaneous paragonimiasis can be diagnosed by excision biopsy for histopathological examination and serological test.

Best regards,

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