

Dear Editor in Chief,

Thank you very much for handling the review of our manuscript. We are sending you our revised manuscript entitled “Ankylosing spondylitis coexisting with *Clonorchis sinensis* infection: A rare case report” (Manuscript NO.: 90448, Case Report). We are grateful for the insightful comments that have contributed to enhancing the quality of our manuscript. We have diligently reviewed the comments and made necessary revisions to address the concerns and incorporate the suggested changes. Our point-by-point response are provided below. We genuinely hope that the revisions meet your approval, and we greatly appreciate your favorable consideration of our manuscript.

Best regards,

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Round 1

Reviewer: 1

1. The English need improvement since there are some grammatical and syntax errors in the manuscript. For example, • in page 1, in line number 23, the words “the the manuscript” may be as “the manuscript”; • in page 3, in line number 6-7, “conducted indeed” as “conducted”; • in page 3, in line number 8, “and fungal and” as “fungal and”; • in page 3, in line number 16, “stable” as “a stable”; • in page 3, in line number 29, “etiology, offering” as “etiology, and offering”; • in page 5, in line number 19-20, “the improvement” as “an improvement”; • in page 5, in line number 25, “a positivity” as “positivity”; • in page 5, in line number 27, “an edema” as “edema”; • in page 6, in line number 13, “a percussive” as “percussive”; • in page 6, in line number 14, “finger-to-ground” as “the finger-to-ground”; • in page 6, in line number 23, “blood” as “and blood”; • in page 8, in line number 22, “often” as “are often”. The grammar mistakes which are not mentioned here are also to be checked and corrected properly.

Response: We appreciate the reviewer's comments. We have conducted a second reviewed of the manuscript and revised the errors you listed.

2. There are some typing mistakes as well, and authors are advised to carefully proof-read the text. For example, • in page 3, in line number 19, the words “joint ,” may be as “joint,”; • in page 4, in line number 26, “occurred by” as “occurs by”; • in page 8, in line number 10, “study” as “studies”; • in page 8, in line number 27, “however we” as “however, we”. The typos not mentioned here are also to be checked and corrected properly.

Response: Thank you for your insightful feedback. We have ensured a thorough review of the entire text to catch and rectify any additional typos.

3. Check the abbreviations throughout the manuscript and introduce the abbreviation when the full word appears the first time in the abstract and the remaining for the text and then use only the abbreviation (For example, Ankylosing spondylitis (AS), IgG, etc.,). Make a word abbreviated in the article that is repeated at least three times in the text, not all words to be abbreviated

Response: Thank you for your suggestions. We checked and corrected the use of abbreviations as your suggestion.

4. The authors should italic the term either "*Clonorchis sinensis*" or "*C. sinensis*" all over the manuscript uniformly

Response: Thank you for your comment. We have ensured uniformity in italicizing these terms throughout the entire manuscript.

5. The introduction part appears less informative about Ankylosing spondylitis and *Clonorchis sinensis*, thus this section should be indicated as detailed to understand the manuscript in clear since the main objectives is focused on Ankylosing spondylitis coexisting with *Clonorchis sinensis* infection.

Response: Thank you for your comment. We have enhanced the introduction to provide more detailed information on AS and *C. sinensis*. "The prevalence of AS per 10,000 individuals is 23.8 in Europe, 31.9 in North America, 16.7 in Asia, 10.2 in Latin America, and 7.4 in Africa^[2]. " "*C. sinensis* infection triggers the activation of sphingosine 1-phosphate receptor 2, leading to the injury and fibrosis of the hepatobiliary^[7]. Recent research in a rat model found that *C. sinensis* infection increases the risk of hepatocellular carcinoma by stimulating

hepatic progenitor cell proliferation^[8]. Complications of *C. sinensis* infection include cholestasis, cholangitis, biliary system fibrosis, and in severe cases, the development of cholangiocarcinoma^[9].” “While there is existing literature on the coexistence of AS and parasitic infections, there is limited research specifically addressing the simultaneous presence of AS and *C. sinensis* infection. This case report details a rare scenario of AS coexisting with *C. sinensis* infection, underscoring the potential impact of *C. sinensis* infection on AS disease activity.” (Page 4, Line 15-16, Line 25-29; Page 2, Line 1-2, Line 6-10)

Reference:

2 **Dean LE**, Jones GT, MacDonald AG, Downham C, Sturrock RD, Macfarlane GJ. Global prevalence of ankylosing spondylitis. *Rheumatology (Oxford)* 2014; 53: 650-657 [PMID: 24324212 DOI:10.1093/rheumatology/ket387]

7 **Liu JX**, Liu M, Yu GZ, Zhao QQ, Wang JL, Sun YH, Koda S, Zhang B, Yu Q, Yan C, Tang RX, Jiang ZH, Zheng KY. Clonorchis sinensis infection induces hepatobiliary injury via disturbing sphingolipid metabolism and activating sphingosine 1-phosphate receptor 2. *Front Cell Infect Microbiol* 2022; **12**: 1011378. [PMID: 36339341 DOI: 10.3389/fcimb.2022.1011378]

8 **Qi Y**, Hu J, Liang J, Hu X, Ma N, Xiang B. Clonorchis sinensis infection contributes to hepatocellular carcinoma progression in rat. *Parasitol Res* 2022; **121**: 3403-3415 [PMID: 36266591 DOI: 10.1007/s00436-022-07699-x]

9 **Harrington D**, Lamberton PHL, McGregor A. Human liver flukes. *Lancet Gastroenterol Hepatol*. 2017; **2**: 680-689 [PMID: 28786389 DOI: 10.1016/S2468-1253(17)30111-5]

6. In introduction, the authors may cite recent prevalence or incidence data about Ankylosing spondylitis and *Clonorchis sinensis* and it should be in 2022 or 2023.

Response: Thank you for your valuable suggestion. We have carefully revised

the introduction section of the manuscript to incorporate the most recent prevalence and incidence data for both Ankylosing spondylitis and *Clonorchis sinensis*. "The prevalence of AS per 10,000 individuals is 23.8 in Europe, 31.9 in North America, 16.7 in Asia, 10.2 in Latin America, and 7.4 in Africa^[2]. " "*Clonorchis sinensis* (*C. sinensis*) infection is a severe parasitic disease affecting millions globally, especially prevalent in China, South Korea, the far east of Russia, and Vietnam, with an estimated 15 million cases^[5]. " (Page 4, Line 15-16, Line 20-22)

Reference:

- 2 Dean LE, Jones GT, MacDonald AG, Downham C, Sturrock RD, Macfarlane GJ. Global prevalence of ankylosing spondylitis. *Rheumatology (Oxford)* 2014; 53: 650-657 [PMID: 24324212 DOI:10.1093/rheumatology/ket387]
- 5 Qian MB, Zhou XN. *Clonorchis sinensis*. *Trends Parasitol* 2021; 37: 1014-1015 [PMID: 34229953 DOI: 10.1016/j.pt.2021.05.011]

7. The figure legends should be improved and a proper footnote should be given. All legends should have enough description for a reader to understand the figures without having to refer back to the main text of the manuscript. For example, the necessary abbreviations should be given which are used in the present investigation.

Response: Thank you for your insightful feedback. We have revised the figure legends, ensuring that each legend now provides sufficient description for readers to understand the figures.



Figure 1 Routine stool examination. On September 29, 2022, the presence of *Clonorchis sinensis* (*C. sinensis*) eggs (arrow) was confirmed through microscopic examination of stool samples uring hospitalization.

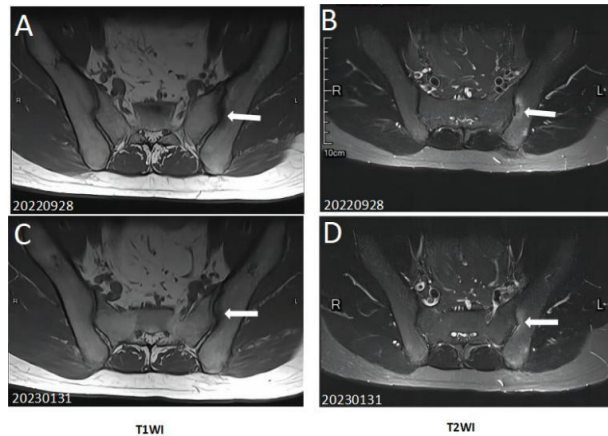


Figure 2 MRI of the sacroiliac joint. On September 28, 2022, A: Axial T1-weighted MRI of the sacroiliac joint showing bone marrow edema in the left sacroiliac joint. B: T2-weighted MRI of the sacroiliac joint showing bone marrow edema in the left sacroiliac joint. The patient's condition at the time of admission indicates the presence of inflammation and edema in the left sacroiliac joint.

On January 31, 2023, C: Axial T1-weighted MRI of the sacroiliac joint showing a reduction in the area around the bone marrow edema in the left sacroiliac joint. D: T2-weighted MRI of the sacroiliac joint showing a reduction in the area around the bone marrow edema in the left sacroiliac joint. After treatment, follow-up at 4 months indicated a reduction in inflammation and edema of the sacroiliac joint.

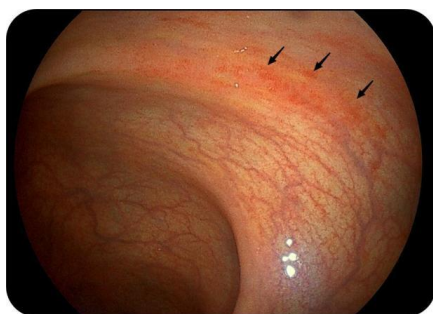


Figure 3 Colonoscopy image. On September 29, 2022, colonoscopy performed during hospitalization revealed scattered congestion in the descending colon, sigmoid colon, and rectum.

(Page 14, Line 3-5; Page 15, Line 2-11; Page 16 Line 3-5)

8. The authors may improve the discussion of their results by focusing on the present findings and introducing data from other authors who also worked with the same or other studies with recent references since it is lack of sufficient references and its seems in general.

Response: Thank you for your comments, we have improved the discussion by focusing on the present findings. "The prevalence of AS in China is currently 0.29%, showing an upward trend. Sex-based differences in prevalence have been observed, with males exhibiting a prevalence rate 2.8 times higher than that of females^[11]." "A study emphasized the potential risk of latent infection reactivation in individuals undergoing immunosuppressive anti-TNF treatment^[12]." "Additionally, another study supported a notable link between *C. sinensis* infection and immune suppression, influenced by gender dynamics^[15]." "This case report provided significant insights, an imbalance in the Th1/Th2 immune response might compromise the body's defense mechanisms against specific viral, bacterial, and parasitic pathogens, potentially heightening the risk of opportunistic infections^[19]. Patients with rheumatic diseases are frequently treated with biologicals, such as anti-TNF, which increases susceptibility to opportunistic infections^[20]. Therefore, rheumatologists must evaluate the patient's condition and manage the duration of biologic treatment appropriately. Various microbial infections should be ruled out before initiating biologicals, particularly parasitic infections that might be overlooked due to improving environmental conditions." (Page 7, Line 26-28; Page 8, Line10-17, Line20-22, Line29-30; Page 9, Line1-9)

Reference:

11 **Zhao J**, Huang C, Huang H, Pan JK, Zeng LF, Luo MH, Liang GH, Yang WY, Liu J. Prevalence of ankylosing spondylitis in a Chinese population: a

systematic review and meta-analysis. *Rheumatol Int* 2020; **40**: 859-872 [PMID: 32125505 DOI: 10.1007/s00296-020-04537-0]

15 **Kan S**, Li Q, Li HM, Yao YH, Du XY, Wu CY, Chen GJ, Guo XK, Qian MB, Wang ZJ. Clonorchis sinensis infection modulates key cytokines for essential immune response impacted by sex. *PLoS Negl Trop Dis* 2022; **16**: e0010726 [PMID: 36083861 DOI: 10.1371/journal.pntd.0010726]

19 **Rostevanov S**, Betesh-Abay B, Nassar A, Rubin E, Uzzan S, Kaplanski J, Biton L, Azab AN. Montelukast induces beneficial behavioral outcomes and reduces inflammation in male and female rats. *Front Immunol* 2022; **13**: 981440 [PMID:36148246 DOI:10.3389/fimmu.2022.981440]

20 **Byun JM**, Lee CK, Rhee SY, Kim HJ, Kim JW, Shim JJ, Jang JY. The risk of tuberculosis in Korean patients with inflammatory bowel disease receiving tumor necrosis factor- α blockers. *J Korean Med Sci* 2015; **30**: 173-179 [PMID: 25653489 DOI: 10.3346/jkms.2015.30.2.173]

Round 2

Reviewer:

1. There are some grammatical, alignments and typographical errors are noted in the manuscript and it should be thoroughly checked and corrected throughout the manuscript. For example, the words "the innate" may be as "innate"; "far east" as "Far East"; "for 10 days before hospital" as "10 days before a hospital"; "to Rheumatology" as "to the Rheumatology"; "did not alleviate" as "was not alleviated"; "routine" as "a routine"; "Figure 2 A and B" as "Figures 2 A and B"; "Figure 2 C and D" as "Figures 2 C and D"; "of biologic" as "of biological"; "areas, when" as "areas when".

Response: We appreciate the reviewer's comments. We have conducted a second reviewed of the manuscript and revised the errors you listed. (Page 1, Line 10, 12; Page 4, Line 12, 20; Page 5, Line 12, 18, 20, 29; Page 6, Line 19, 27; Page 7, Line 16, 26; Page 8, Line 26; Page 9, Line 12)

2. This suggestion is not carried out properly (Check the abbreviations throughout the manuscript and introduce the abbreviation when the full word appears the first time in the abstract and the remaining for the text and then use only the abbreviation) For example, the expansion is not given for IgG. This types of correction need to be checked all other abbreviations used in the manuscript.

Response: Thank you for your suggestions. We checked and corrected the use of abbreviations as your suggestion. (Page 3, Line 11; Page 5, Line 26; Page 6, Line 18, 29)