

June 1, 2022

Editor-in-Chief

World Journal of Clinical Cases

Dear Dr. Wang,

Thank you for your letter and for the reviewers' comments concerning our manuscript entitled "Gastrointestinal metastasis secondary to invasive lobular carcinoma of the breast: A case report".

Your comments and those of the reviewers were highly insightful and enabled us to greatly improve the quality of our manuscript. In the following pages are our point-by-point responses to each of the comments of the reviewers as well as your own comments. Revisions in the text are shown using "TRACK CHANGES" mode. We hope that the revisions in the manuscript and our accompanying responses will be sufficient to make our manuscript suitable for publication in *World Journal of Clinical Cases*.

We look forward to hearing from you at your earliest convenience. If you have any further questions, please do not hesitate to contact me.

Yours sincerely,

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Our point-by-point responses to the peer review are, as follows:

Responses to Reviewer #1

1. While reading the manuscript the question occurred to me, why there was no colon endoscopy performed when the patient presented with the above-mentioned symptoms. Is there no regular CRC screening for population >50 years and older at elevated risk due to cancer?

Response: The patient initially showed mild elevation of CA15-3, but no abnormal symptoms of the digestive tract. Until July 2018, the patient experienced mild symptoms, including lack of appetite, fullness of the abdomen, and fatigue. These symptoms are mild and lack specificity, and they may also occur during a period of endocrine therapy and may be easily overlooked. On a subsequent visit, these symptoms had worsened, so she underwent a colonoscopy. This is also the value of this case report. Gastrointestinal metastases in breast cancer patients are exceedingly rare. Colon endoscopy is not a routine review item, so gastrointestinal metastases are often easily overlooked.

The Chinese Society of Clinical Oncology guidelines recommend direct colonoscopy for people aged ≥ 50 years (level II recommendation) and colonoscopy for patients with positive fecal occult blood (level I recommendation). However, in fact, most people are reluctant to undergo colonoscopy, especially healthy people without obvious discomfort.

2. The performed imaging methods did not reveal significant signs of cancer. However, therapy was switched from letrozole to exemestane. What was the reason for that?

Response: The main reason for switching the treatment plan from letrozole to exemestane was that CA15-3 level was found to have increased again, based on previous levels. While breast cancer-related lesions indicating recurrence and metastasis were not identified on imaging, we could not completely rule this out. Switching from a steroidal directional enzyme inhibitor to a non-steroidal aromatase inhibitor was more of an attempt. First, if a patient does not have recurrence and metastasis, exemestane is recommended as endocrine maintenance therapy for postmenopausal women with breast cancer. The efficacy and safety of exemestane is similar to that of letrozole. Second, if a patient has recurrence and metastasis, this means that the tumor is letrozole-resistant, and exemestane may have a certain curative effect.

3. For better understanding the authors should already clarify in the introduction the histological and molecular subtype of the presented breast cancer patient.

Response: Thank you for this important suggestion. We agree with this comment and we have now clarified the histological and molecular subtype of the reported patient with breast cancer in our revised manuscript.

4. Line 3: metastatic site Line 5:...diagnosis and treatment (no comma) Line 9. Abbreviation CA15—3 should be placed here instead of Line 15.

Response: Thank you for these detailed comments. We apologize for typographical and grammatical errors in the manuscript. Our manuscript has been edited and proofread by a native English-speaking medical editor.

5. Why is this explained but not GATA-3 and others?

Response: Thank you for raising this important question. Our patient's diagnosis of breast cancer with gastrointestinal metastases was based on pathological and immunohistochemical findings. As we have described in the Discussion section, commonly used differential molecules include CK7, CK20, gross cystic disease fluid protein 15 (GCDFP-15), and GATA-3. These molecules are an important basis for identifying the origin of tumors from the breast. Of course, they also include molecules commonly used in breast cancer, such as ER, PR, and HER2. These above-mentioned molecules are based on the detection of tumor tissue, but for tumor markers in blood, CA15-3 and CA125 are the most commonly used auxiliary markers in breast cancer to monitor recurrence and evaluate efficacy.

6. Page 4 line 6: GATA3 should be GATA-3 as throughout the manuscript

Response: Thank you for highlighting this. We apologize for this error. We have changed 'GATA3' to 'GATA-3' in the revised manuscript.

7. In the passage "history of present illness" it does not become clear were the information was received and where the patient was treated. Further the letrozole treatment is mentioned but not the molecular subtype. ,

Response: To provide readers with a better understanding of this case, we have placed "past medical history" before "present illness" in the revised manuscript. As shown in the "present illness" section of the revised manuscript, the patient underwent a modified radical mastectomy for right breast cancer in our hospital. Immunohistochemistry showed Luminal B type, indicating sensitivity to endocrine therapy, so the patient was treated with letrozole.

8. I do not understand sentence in line 7 page 4 (page numbers are missing!): The therapeutic evaluation indicated progression diseased (PD).

Response: Thank you for highlighting these points. What we had hoped to express that the patient was diagnosed with breast cancer with gastrointestinal metastasis, which may not have been expressed clearly enough in the original manuscript. In the revised manuscript, we have changed the following sentence:

"Based on these results, the patient was diagnosed with breast cancer-related gastrointestinal metastasis." (Page 4, lines 21-22)

9. Next, the passage "history of past illness" should be placed before present illness for better understanding the case.

Response: Thank you for your suggestion. We have shifted this section accordingly in the revised manuscript.

10. Line 25 page 4: This would be luminal A. Page 5 Line 24: Stage IV Luminal B (HER-2 negative): Does this refer to the primary breast tumor? It was luminal A due to low Ki-67. Or does it refer to the gastrointestinal metastasis? It was described above to be HER2+.

Response: Thank you for your careful consideration of our manuscript and for your pertinent questions. PR is an important prognostic indicator for breast cancer. The Chinese Society of Clinical Oncology 2021 guidelines recommend a PR-positive value of 20% as the cut-off for Luminal A and Luminal B. According to this criterion, the molecular type of both the primary and metastatic lesions of this patient was

Luminal B (HER-2 negative). In the revised manuscript, we supplement the criteria for molecular typing of breast cancer in detail.

HER-2 positive was defined as IHC 3+ or IHC 2+ and HER-2 in situ hybridization (ISH) results were positive with dual probes. HER-2 negative was defined as IHC 0/1+ or IHC 2+ and ISH negative.

11. Treatment: typing error. Palbociclib.

Response: Thank you for highlighting this typographical error, which we have now corrected in the revised manuscript.

12. Line 7: Space after indicators.

Response: Thank you for highlighting this. We have modified the text accordingly.

13. What is meant by routine review? Routinely scheduled follow up consultation?

Response: Thank you for your valuable question. In the revised manuscript, "routine review" has been changed to "...regular follow-up consultations for active surveillance".

14. Outcome and follow-up: It would be interesting to receive the data from the local hospital. Is there no way to contact the patient and ask her permission? It would be very interesting.

Response: Thank you for raising this point. Regrettably, details concerning the patient's treatment and examination at the local hospital were not available, which was a pity.

15. Discussion: Line 23. The most common site of GASTROINTESTINAL metastasis....otherwise it would be wrong.

Response: Thank you for alerting us to this. In the revised manuscript, the relevant text has been amended and now reads as follows: "The most common sites in relation to gastrointestinal metastases..." (Page 6, lines 26-27)

16. Line 7 page 7: ILC abbreviation should be introduced.

Response: ILC, which is the abbreviated term for invasive lobular carcinoma, has been included in the revised manuscript.

17. Page 8 Line 20-22 contains relevant conclusions but the wording should be more scientific.

Response: Thank you for your guidance here. We agree with your comment, and we have re-written the conclusion in the revised manuscript.

18. Line 23: Treatment and diagnosis -> diagnosis and treatment sound better

Response: Thank you for this suggestion. In the revised manuscript, "Treatment and diagnosis" have been changed to "diagnosis and treatment".

19. Concerning the figures, the IHC staining of the described cells in primary vs. metastatic tissue would be more interesting compared to the macroscopic images.

Response: We agree with your comment. It was a pity that we were unable to provide IHC staining because the operation time of the primary tumor was too early, and the slice of the primary tumor cannot be obtained. We have expanded the descriptions in as much detail as possible to present the most complete case report for the reader.

Responses to Reviewer #2

Response: We appreciate your positive evaluation of our work. Given your experience and expertise in this field, we consider that your valuable suggestions have further improved the quality of our paper. We hope to have more opportunities to get your professional guidance in the future.

As the revision process results in changes to the content of the manuscript, language problems may exist in the revised manuscript. Thus, it is necessary to perform further language polishing that will ensure all grammatical, syntactical, formatting and other related errors be resolved, so that the revised manuscript will meet the publication requirement (Grade A).

Response: We are very sorry for the grammatical problems in the original manuscript. We understand that language polishing helps to enhance the fluency and readability of the text for scientific papers considered for publication in English. Our paper has been edited and proofread by a native English-speaking medical editor from **Editage**, and we have provided a **Certificate of Editing** to accompany our re-submission to your journal.

Our responses to the Scientific Editor's comments

The authors presented a case report describing a rare case report of gastrointestinal metastasis of invasive lobular carcinoma of breast. The topic of the manuscript is within the scope of the journal. The findings of the report will be useful for the clinicians to consider the possibility of gastrointestinal metastasis in breast carcinoma and plan treatment protocol accordingly.

Scientific Quality: Grade C (Good)

Response: Thank you for your consideration of our case report and for your positive comments. We apologize for the language issues and grammatical errors in the original manuscript. We have revised the manuscript accordingly for typographic, grammatical, and formatting errors.

The authors are requested to modify the manuscript as per the report of the peer reviewers to improve the quality of the manuscript.

Response: Your comments and those of the reviewers were highly insightful and enabled us to greatly improve the quality of our manuscript. We provide point-by-point responses to each of the reviewers' comments. In the revised manuscript, revisions in the text are shown using the "TRACK CHANGES" mode.

The English language grammatical presentation needs improvement to a certain extent. There are few errors in the grammar and format which requires modification.

Language Quality: Grade B (Minor language polishing)

Response: We apologize for grammatical issues in the original manuscript. We have corrected the errors in the manuscript, which has now been professionally edited and proofread.

In discussion, the authors can highlight the literature review of previous studies with regard to the treatment protocol employed and the prognosis of the patients described

in those manuscripts. While there is no standard treatment protocol, it is possible to arrive at some understanding based on the literature.

Response: In the revised manuscript, we have included further detailed content in the Discussion and Conclusion sections. According to previous literature reports, the treatment plan of patients with breast cancer gastrointestinal metastases has been summarized, and we have included our opinions based on the previous literature.

Kindly consider if the title can be modified to Gastrointestinal metastasis of invasive lobular carcinoma of breast: A case report?

Response: Thank you for your suggestion. We agree with your suggestion to change the title to "Gastrointestinal metastasis of invasive lobular carcinoma of breast: A case report". Given that this pathological type of breast cancer with gastrointestinal metastases is mainly invasive lobular carcinoma, and that invasive ductal carcinoma is rare, this further demonstrates the value and clinical significance of our case report.

Our responses to the Editor-in-Chief

I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Clinical Cases, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors.

Response: Thank you for your positive comments.

However, the quality of the English language of the manuscript does not meet the requirements of the journal. Before final acceptance, the author(s) must provide the English Language Certificate issued by a professional English language editing company. Please visit the following website for the professional English language editing companies we recommend: <https://www.wjnet.com/bpg/gerinfo/240>.

Response: We apologize for the language issues and errors in the original manuscript. We have polished the language in the revised manuscript. Our paper has been edited and proofread by a native English-speaking medical editor from **Editage**, and we have provided a **Certificate of Editing** to accompany our re-submission to your journal.

Before its final acceptance, the author(s) must provide the Signed Consent for Treatment Form(s) or Document(s). For example, authors from China should upload the Chinese version of the document, authors from Italy should upload the Italian version of the document, authors from Germany should upload the Deutsch version of the document, and authors from the United States and the United Kingdom should upload the English version of the document, etc.

Response: The Consent for Treatment Form has been signed.

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Response: We have checked to confirm that all the uploaded images meet publication requirements, and the figures are original.

Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript.

Response: Thanks for your kind reminder. We have added and updated the latest cutting-edge research results in the Discussion section.

To this end, authors are advised to apply a new tool, the RCA. RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision. Please visit our RCA database for more information at: <https://www.referencecitationanalysis.com/>.

Response: Thank you for recommending the RCA database. We will certainly consider it further in the follow-up research.