

List of Responses

Round 1

Dear Editors and Reviewers:

Thank you for your letter and for the reviewers' comments concerning our manuscript entitled "Isolated synchronous Virchow lymph node metastasis of sigmoid cancer: A case report with review of the literature" (68319). Those comments and suggestions are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made correction which we hope meet with approval. In addition, the revised manuscript has been polished by American Journal Experts Editing Services, and the polishing proof has been uploaded with the manuscript. In the revised manuscript, revised portion are marked in red in the paper. The main corrections in the paper and the responds to the editorial and reviewer's comments are as following:

Responds to science editor 's comments:

1. Comment to the Author: The authors need to explain the role of PET-CT in the diagnosis and treatment of the condition and explain by no significant FDG uptake was observed as shown in Figure 1B. Discuss must be expanded with additional, more current references. Other minor comments have been cited by the reviewers.

Response to comment: We would like to express our great appreciation to science editor for constructive comments on our paper. In the modified discussion section, we have affirmed the value of PET/CT in diagnosing distant metastases and explain the false negative results of PET/CT in our case (For details, please see Paragraph 4 of the Discussion). In addition, we have expanded the Discussion and cited more current references in this revised version (For details, please see Discussion and Reference) .

2. Comment to the Author: The manuscript tables need to be properly formatted and data presented clearly.

Response to comment: In this revision, we have modified the table to make its format more orderly and data presentation more clear (For details, please see Table1) .

Responds to chief editor 's comments:

1. Comment to the Author: uniform presentation should be used for figures showing the same or similar contents; for example, "Figure 1 Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...".

Responds to comment: First, we would like to thank chief editor for the positive and constructive suggestions. In this revised version, we changed the presentation of figures showing the same or similar contents to make them more normative (For details, please see Figure1-7)

Responds to Reviewer's comments:

Reviewer 1.

1. Comment to the Author: "Pedicle polyp" might be better described as "pedunculated polyp"

Response to comment: Thank you for your suggestion. As you said, our previous expression was indeed inappropriate. Therefore, we have modified the inappropriate expression as required (For details, please see Imaging examination, Figure 4 and Table2) .

2.Comment to the Author: Clarification needs to be made on the treatment regimen. It might be good to explain the initial chemotherapy regimen used since it what was mentioned was FOLFOX + capecitabine but the description in parentheses was CAPOX using a non-conventional dose (1 week of capecitabine only). FOLFOX + capecitabine is not a standard regimen. What was the basis for this regimen? And why was the treatment changed to capecitabine + cetuximab after supraclavicular node dissection? Why was cetuximab not given upfront with FOLFOX when K-ras was established to be wild-type in the beginning?

Response to comment: Considering the reviewer's suggestion, we have got in touch again with patient's family and we were told that the patient's initial chemotherapy regimen (when K-ras was established to be wild-type) was FOLFOX+ cetuximab, rather than FOLFOX + capecitabine regimen. We are very sorry for our incorrect writing and have re-written related part according to the Reviewer's suggestion. (For details, please see Treatment) . Considering the patient has reached the predetermined number of cycles of chemotherapy after sigmoid tumor resection, we gave the patient a maintenance regimen (capecitabine + cetuximab) after supraclavicular lymph node dissection. (For details, please see Treatment) .

3.Comment to the Author: Discussion on supraclavicular node dissection can be added. What is the standard procedure? What is the role of P. aeruginosa injection and is it routinely done? Why was it given for this particular patient?

Response to comment: The standard procedures for supraclavicular lymph node dissection: We removed the lymph nodes in the triangle bounded by the lower abdomen of the omohyoid, the posterior margin of the sternocleidomastoid and the superior clavicle (the level IV and VB lymph nodes of the neck) (For details, please see Treatment) .

Pseudomonas aeruginosa injection is performed using attenuated Pseudomonas aeruginosa. Previous studies have confirmed that injection of Pseudomonas aeruginosa has a significant effect on improving postoperative lymphatic leakage of thyroid cancer. The possible mechanism is as follows: Pseudomonas aeruginosa can penetrate into the subcutaneous space and produce aseptic inflammation, which promotes the closure of lymphatic vessels and reduces lymphatic leakage. In our case, the patient developed a lymphatic fistula after supraclavicular lymph node dissection. After the failure of a series of conservative treatments, we attempted to inject Pseudomonas aeruginosa from the left venous angle to reduce lymphatic leakage and achieved good results. (For details, please see Paragraph 5 of the discussion) .

4.Comment to the Author: For all figures, more detailed description would be helpful for the reader to better appreciate the images. Arrows can be added in figure 3 to point out the polyp and in figure 4 to show which is carcinoma tissue.

Response to comment: In this revised version, we changed the presentation of figures showing the same or similar contents to make them more normative. In addition, we further enriched the description and added arrows to Figures as required (For details, please see Figure1-7) .

5. Comment to the Author: For the immunohistochemistry pictures, it would be better to feature stains (whether positive or negative) that are more relevant in establishing the diagnosis of adenocarcinoma of sigmoid origin (i.e., CK7, CK20, CDX2, MLH1,

MSH2, MSH6, PMS2).

Response to comment: We have made correction according to the Reviewer's comments. In this modification, we added microscopic images of immunohistochemical staining of CK7 in Figure7, which is more related to sigmoid colon cancer.

Reviewer 2:

1. Comment to the Author: "FOLFOX + capecitabine" (P 2; Line 48, P 4; Line 4 and Table 2) is not correct.

Response to comment: Considering the reviewer's suggestion, we have got in touch again with patient's family and we were told that the patient's initial chemotherapy regimen (when K-ras was established to be wild-type) was FOLFOX+ cetuximab, rather than FOLFOX + capecitabine regimen. We are very sorry for our incorrect writing and have re-written related part. (For details, please see Treatment) .

2. Comment to the Author: P 2; Line 33, The term "interestingly" is not applicable in this section. This is a subjective expression.

Response to comment: As Reviewer suggested that the term "interestingly" is too subjective to match the objective style of case report. Therefore, we have removed this inappropriate term in this revision (For details, please see the imaging examination).

3. Comment to the Author: The author has to give the pathological findings and the TNM stage.

Response to comment: We have made some modifications according to the Reviewer's comments. In this modification, we performed ypTNM staging (yp T1N1M1) on the postoperative pathology of sigmoid tumor. (For details, please see the treatment).

4. Comment to the Author: The first sentence is duplicated in introduction and discussion section.

Response to comment: It is really true as Reviewer suggested that the first sentence is duplicated in introduction and discussion section. In this revision, we deleted this sentence from the discussion and expanded the discussion in other aspects. (For details, please see the Discussion)

5. Comment to the Author: Figure 1A (Left): Does the arrow refers to the Virchow's lymph node?

Response to comment: After a careful review of our original manuscripts, we found that the arrow in Figure 1A (axial view of contrast-enhanced CT) was not accurate enough. So we relabeled the arrow to more accurately point to the Virchow's lymph node. (For details, please see Figure 1A).

6. Comment to the Author: Table 2: "R0 surgery" is incorrect.

Response to comment: As Reviewer suggested that the patient still had supraclavicular lymph node metastases after sigmoid tumor resection, so the surgery did not meet the criteria for R0 resection. Therefore, we have deleted this incorrect expression in the original manuscripts.

Reviewer 3

1. Comment to the Author: What is the role of PET-CT in such condition and why it showed No significant FDG uptake?

Response to comment: Thank you for your suggestion. Previous literature has reported that PET/CT offers value in predicting distant tumor metastases. In our case, however, no significant FDG uptake was observed in the patients' left supraclavicular lymph nodes on PET/CT. The false negative PET/CT results of this patient may be related to the smaller diameter of the supraclavicular lymph nodes. The standard uptake value (SUV) of the lesion is generally proportional to its size, so the SUV of smaller metastatic lymph nodes is often low and more difficult to detect by PET/CT. In other words, PET/CT has lower sensitivity and higher specificity for distant metastatic lymph nodes than contrast-enhanced CT (For details, please see the fourth paragraph of discussion).

2. Comment to the Author: Why do you think that only one of pericolic lymph nodes contain metastasis while most of left supraclavicular nodes contain metastasis?

Response to comment: We are very sorry for not explaining this issue clearly earlier. Less lymph node metastasis shown in postoperative pathology may be associated with effective preoperative chemotherapy. The reason why the patient had left supraclavicular lymph node metastasis may be related to abdominal micrometastasis: this patient has developed abdominal micrometastases prior to systemic chemotherapy, and such micrometastases are difficult to be observed by imaging examination (Contrast-enhanced CT and PET/CT). Lymph nodes micrometastases enter the thoracic duct through lymphatic drainage, resulting in left supraclavicular lymph node enlargement (For details, please see the second and third paragraph of discussion).

3. You are writing that tumor erosion into blood vessel then to thoracic duct may be the mechanism, but if tumor erode into blood it will spread to other organs

Response to comment: It is really true as Reviewer suggested that the previously speculated mechanism of hematogenous spread is irrational to some extent. By reviewing the literature about the mechanism of lymph node metastasis, we believe that the cause of supraclavicular lymph node metastasis may be related to abdominal micrometastasis: this patient has developed abdominal micrometastases prior to systemic chemotherapy, and such micrometastases are difficult to be observed by imaging examination (Contrast-enhanced CT and PET/CT). Lymph nodes micrometastases enter the thoracic duct through lymphatic drainage, resulting in left supraclavicular lymph node enlargement (For details, please see the second paragraph of discussion).

4. The comment on figure 2 must be revised

Response to comment: We have made correction according to the Reviewer's comments. (For details, please see the Figure3)

5. There is discrepancy between figure 4 and 5, in figure 4 the tumor invaded the muscularis mucosa while in 5 the tumor is limited to the mucosa and in the text, the tumor is intramucosal. which is correct. Kindly revise the pathological staging?

Response to comment: We are very sorry for not explaining this issue clearly earlier. The patient's colonoscopic biopsy pathology showed that the tumor has invaded the muscularis mucosa, while the postoperative pathology showed that the tumor was confined to the mucosal. The difference between the two pathology was considered to be caused by preoperative chemotherapy. Meanwhile, we performed yp staging on resected sigmoid tumor according to the 8th edition TNM staging. (For details, please see the third paragraph of discussion).

6. If the tumor is intramucosal carcinoma, how did it spread to the lymph node. True intramucosal carcinoma also lacks the potential for metastasis?

Response to comment: Because the invasion depth was reduced by preoperative

chemotherapy, it is understandable that the tumor invaded the musculomucosal layer and has spread to lymph node before chemotherapy (For details, please see the third paragraph of discussion).

7. Figure 5, each immunostain should be written on its picture

Response to comment: Due to the limitations of the article length, parts of immunostain in the original manuscript was deleted and the more relevant immunostain to colon cancer was reserved and added. In the revised manuscript, each immunohistochemistry is written on its picture (For details, please see the Figure 1-7).

As we all know, the “*World Journal of Clinical Cases*” has been dedicated to showcase and promote distinguished research in the field of clinical medicine, to help advance development of this field.

In recent years, the academic status of the journal in the industry has growing rapidly, which is inseparable from the hard work of the editors and review experts. Conscientious and rigorous working attitude is the basic condition of academic journal editing, which directly affects the quality of editing, proofreading and publishing work. Since our manuscript was submitted, we have received comments from editors and external reviewers within one month. From the format of the paper to the content, the editorial department of “*World Journal of Clinical Cases*” and reviewer experts pointed out our shortcomings in detail, and given us instructive advices. Therefore, we are deeply moved by your professional quality and work ethics. Please allow me to thank you again on behalf of all the authors. We appreciate for warm work of editors and reviewers earnestly, and hope that the correction will meet with approval.

The COVID-19 pandemic is directly or indirectly affecting each and every one of us as members of the global community. We hope that you will continue to take the necessary precautions to stay safe and healthy while working normally. Even as the situation continues to evolve, our desire to publish quality articles in your journal is stronger than ever and will continue to guide everything we do.

Once again, thank you very much for your comments and suggestions.

Yours sincerely,

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Round 2

The manuscript has been revised well. I think this manuscript will be acceptable after a minor correction below has been done. 1. The last paragraph in the discussion section is duplicated in the conclusion. Please omit this whole paragraph.

A: We have deleted the duplicated section.