

Point-by-point response to reviewers

Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade C (A great deal of language polishing)

Conclusion: Major revision

Specific Comments to Authors:

Edema of limbs as the primary symptom of gastric signet-ring cell carcinoma: A rare case report and literature review. The authors reported the very interesting case of gastric signet ring cell carcinoma who presenting with lymphedema of limbs and subcutaneous metastasis. The authors should be commended on their work.

Response: Thank you very much for carefully reading and positively commenting our manuscript.

There are a few areas where additional information would enhance the manuscript.

1. Introduction of this manuscript is redundant, please rewrite it more concisely.

Response: According to your suggestion, we re-wrote the introduction section more concisely in the revised manuscript.

2. In “case presentation” part, author mentioned that patients firstly presented with cutaneous edema. To enhance the readiness, please provide the information whether it is “pitting” or “non-pitting edema”.

Response: Yes, this is a good suggestion. In the physical examination part, we have provided relevant information of pitting edema of this patient, shown as below:

“However, he had obvious pitting edema in the right lower limb but not in the left limb. When pressure was applied to the right lower limb, indentation remained in the soft tissue after the pressure was removed.”

3. In “Imaging examination” part, author described that “No pathological FDG uptake was detected in the liver, spleen, kidneys, gastrointestinal system, and both in the abdominal and pelvic lymph node groups”, but this patient was diagnosed as gastric carcinoma by pathology”. Please provide the reason why the FDG uptake was normal in patient with intra-abdominal malignant lesion like this patient.

Response: This is a very good question. Indeed, 18-fluorodeoxyglucose positron emission tomography-computed tomography (FDG PET-CT) is valuable in the management of patients with gastrointestinal tract cancer. And FDG PET-CT provides new information in a clinically useful proportion of patients, which leads to changes in treatment strategy, most frequently by detecting previously unidentified metastases. However, previous data also showed that No pathological FDG uptake existed in a small number of patients with gastric cancer (Eur J Nucl Med Mol Imaging. 2020 Apr;47(4):759-767.). In this retrospective data from 330 patients presenting with gastric adenocarcinoma between March 2014 and December 2016, 15 of 104 patients had a PET negative results. Specially, discordance between pre-treatment FDG PET-CT and histological nodal status was seen in 13 patients (Table 2; 4 FDG positive, histology negative, 9 FDG negative, histology positive).

Table 2 Concordance between lymph node status on FDG PET-CT and histological analysis

Lymph node status	Histology positive	Histology negative
FDG positive	6	4
FDG negative	9	11

(Eur J Nucl Med Mol Imaging. 2020 Apr;47(4):759-767.)

Thus, it was possible that no pathological FDG uptake was detected for a small number of patients (specially for some nodal involvement).

4. This patient had hypoalbuminemia, hyperglobulinemia, and lymphopenia (at the all-time of follow up), which consistent with triad of chyle leaks. And most common etiology of chyle leak is lymphatic obstruction. Does the author agree with this possibility. If yes, this triad resulted from cutaneous metastasis or not? And can it occur when no evidence of chyle leak from the body like this patient.

Response: Yes, this is an important concern. Thank you very much for carefully reading our manuscript. Chyle leakage is a potential complication that can occur as a result of lymphatic injury from trauma or surgery in the chest, abdomen, or neck (The incidence of postoperative chyle leak is low (1%-4%)) (Nutrition in Clinical Practice. 23(5):529-532, October 2008.). In 1998, Shibata K. et al. have reported a rare case of a woman with inflammatory carcinoma, an unusual type of cutaneous metastasis, arising from signet-ring cell carcinoma of the stomach, who developed chylothorax as the skin lesion progressed over the chest (Intern Med. 1998 Jun;37(6):538-41.), they demonstrated that inflammatory carcinoma could be a cause of non-traumatic chylothorax. Thus, we also agree with the possibility that chyle leak was associated with carcinoma (primary or metastatic) that leading to lymphatic obstruction. It was better to confirm whether chyle leak occurred or not by laboratory findings of the pleural or abdominal effusion. However, it was very regretful that the peritoneocentesis / abdominocentesis could not be taken in this patient. Actually, we have added this reference (Intern Med. 1998 Jun;37(6):538-41.) in the literature review.

5. At the 12-months visit, patient developed poly serous ascites. Is it chylous ascites? And it would be more impressive if author demonstrate the picture of imaging and fluid aspiration of the patient.

Response: This is a good question. I also agreed that it would be more impressive to show the picture of imaging and fluid aspiration of the patient. Actually, at the 12-months visit, the patient had already taken some examinations (such as blood routine, biochemistry, hypersensitive C-reactive protein, vascular and abdominal Doppler ultrasound and so on) at local hospital (not our hospital). And this patient declined to be hospitalized at that moment. Thus, it was very regretful that the peritoneocentesis / abdominocentesis could not be taken on this patient.

6. On lines 200, please provide the citation.

Response: Yes, we have inserted the relevant citation in the revised manuscript.

7. In conclusion, author stated that “Thus, a careful clinical intraoral examination must be performed on patients...”. Why author suggest physician to proceed intraoral examination while this patient had intragastric malignant lesion.

Response: Sorry about this. Here must be a mistake. We want to state that “Thus, a careful clinical physical examination must be performed on patients...”. We have made this alteration in the revised manuscript.

8. Although the language of this manuscript seem good, the content flow need to be improved.

Response: Yes, according to your suggestion, we have sent this manuscript to a professional English language editing company (editage, <https://www.editage.cn>). The content flow was greatly improved.

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors:

Page 2

Lines 32/33: the second half of this sentence is unclear.

Line 35: is there a better word than permeation

Lines 46-47: I feel this is an aggressive statement. I think the case highlights the importance of physical exam as it may localize the etiology of the edema. However, 99% of extremity edema is not gastric cancer, so excluding it is not high yield.

Response: Thank you very much for carefully reading our manuscript. According to your suggestion, we have made some revision.

Lines 32/33: We delete “for instance SRCC”. Here we want to express that “Skin metastasis may be the first sign of clinically silent visceral cancer or recurrence of an internal malignancy.”

Line 35: We replaced permeation as “generalized pitting edema”. The revised expression was shown as below: Herein we report the case of a 55-year-old man with edema of a lower extremity as the primary symptom, which progressed from local to generalized pitting edema in the year following skin involvement.

Lines 46-47: Yes, this is a very good suggestion. We have changed this sentence as below: “This rare case emphasizes the importance of physical examination as it may help elucidate the etiology of edema”.

Page 3

Lines 63-65: this highlights the change recommended above

Response: Yes, according to your suggestion, we have made a revision above and emphasized the importance of physical exam as it may localize the etiology of the edema.

Page 4

Lines 91 “underwent” may read better as “developed”

Line 92 “reason” may be better as “known cause”

Line 93 insufficiency is the correct spelling. It is correctly spelled in line 94

Response:

Lines 91: The word “underwent” was replaced by “developed”.

Line 92: The sentence here was replaced as “the patient developed edema of the right lower limb with an unknown cause.”.

Line 93: Sorry about this mistake. The correct spelling was made after revision.

Page 5

Line 112 does “depressed edema” mean “pitting edema?”

Line 113 “seemed normal” is quite informal

Line 121 appears to have an unnecessary tab/space

Response:

Yes, the expression “pitting edema” was more appropriate and we have made an alteration as below: he had obvious pitting edema in the right lower limb but not in the left limb.

Page 6

Line 141: should remove the period after SRCC and remove the capital in Gastrointestinal as these two sentences need to be combined to be a complete sentence

Line 147: add a space before Taken

Lines 158-159: “the patient also takes” would read better as “the patient underwent”

Response:

Line 141: The sentence was changed as below: “Because gastrointestinal tract is the most common source of SRCC, a gastrointestinal endoscopic examination was subsequently performed.”

Line 147: Yes, we have added a space before Taken.

Lines 158-159: “the patient also takes” was replaced by “the patient underwent” in the revised manuscript.

Page 7

Line 171-172: could be reworded to the complaint of edema worsened

Line 174-175: rather than “gave up” this could be reworded to “declined” and then “began receiving palliative diuretic therapy”

Response:

Line 171-172: Yes, we have changed this sentence to “At the 3-month visit, his limb edema worsened.”

Line 174-175: This is a good suggestion. we have revised this sentence to “After six months of treatment, the patient declined further chemotherapy and received palliative diuretic therapy.”

Page 8

Lines 203 and 204: remove the parentheses and just quote the terms searched

Line 205: “literatures” is not the proper word. Consider manuscripts instead.

Response:

Lines 203 and 204:

Yes, we have removed the parentheses and just quoted the terms searched as below: “(gastric signet-ring cell carcinoma) AND (cutaneous metastases).”

Line 205: The “literatures” was changed as “studies”.