Response letter

Thank you for your constructive comments. By reading your suggestions, I have once again double-checked and refined this paper.

REVIEWER'S COMMENTS

Reviewer #1:

1. Care must be taken not to identify any personal information from the date in the text or the information in the image.

Response: Thank you for your constructive comments. Upon examination, neither the date nor the image in the article confirmed any personal information.

2. The interpretation of the pathology results is important, but there are no detailed comments. In addition, there is a lack of description of the evidence that the cancer was not primary skin cancer but metastatic. In particular, please provide detailed descriptions of the pathological findings and immunostaining.

Response: Thank you for your constructive comments. We have revised it accordingly as following:

Infiltration of cancer cells was observed in the fibrous connective tissue by the puncture. The cancer cells were distributed in nests, with enlarged nuclei, hyperchromatic nuclei, heteromorphism, increased nucleo-plasma ratio, and crowded arrangement (Fig.3A, B). Further immunohistochemical results showed that skin was positive for CK(Fig.3C), P40(Fig.3D), P63(Fig.3E), CK5/6(Fig.3F), partially positive for P53(Fig.3G), and about 20% positive for Ki67(Fig.3H). The pathological results revealed that the skin metastasis was derived from the poorly differentiated squamous cell carcinoma of the esophagus (Fig. 3).

3. One feature of this case seems to be the characteristic skin metastasis findings. It would be interesting to discuss the characteristics of skin metastasis of esophageal cancer and other cancers in the literature.

Response: Thank you for your constructive comments. We have revised it accordingly as following:

Melanoma and breast cancer is the most prone to metastasize to the skin and subcutaneous tissue (9,13). However, other malignancies such as lung, colon, head, and

neck, and hematologic diseases also have been described with a degree of frequency (cited from Strickley JD, Jenson AB, Jung JY. Cutaneous Metastasis. Hematol Oncol Clin North Am 2019 Feb;33(1):173-197. DOI: 10.1016/j.hoc.2018.08.008. PMID: 30497674.). Furthermore, esophageal carcinoma cutaneous metastasis is rare, especially in esophageal squamous cell carcinoma, and the risk of skin metastasis is lower. However, esophageal adenocarcinoma more commonly metastasizes to the skin (11). The manifestation of skin metastasis from esophageal cancer reported by most of the literature is scattered nodules that are rarely painful (12). The retrospective analysis reported by Joaquim Marcival *et al.* revealed that similar to esophageal cancer, adenocarcinoma is the histological type of lung cancer most prone to skin metastasis（cited from Ferreira L, Luís F, Cabral F. Cancro do pulmão e metastases cutâneas [Lung cancer and cutaneous metastasis]. Rev Port Pneumol 2004 Nov-Dec;10(6):475-84. Portuguese. DOI: 10.1016/s0873-2159(15)30615-2. Erratum in: Rev Port Pneumol. 2005 Mar-Apr;11(2):195. PMID: 15735887.）. However, the most common clinical manifestation of skin metastasis of lung cancer is single nodules, and the most common site is the head（cited from Marcoval J, Penín RM, Llatjós R, Martínez-Ballarín I. Cutaneous metastasis from lung cancer: retrospective analysis of 30 patients. Australas J Dermatol 2012 Nov;53(4):288-90. DOI: 10.1111/j.1440-0960.2011.00828.x. Epub 2011 Nov 15. PMID: 23157780.）. Different from esophageal and lung cancer, typical ductal or lobular carcinoma tends to involve skin metastases to the thorax and abdomen, occasionally with hardened, erythematous plaques（cited from Choate EA, Nobori A, Worswick S. Cutaneous Metastasis of Internal Tumors. Dermatol Clin 2019 Oct;37(4):545-554. DOI: 10.1016/j.det.2019.05.012. Epub 2019 Jul 10. PMID: 31466594.）. But the most common clinical presentation is single or multiple skin-stoned or pink nodules（8）

4. There are many stained images, but are all the slides necessary for diagnosis?

Response: Thank you for your constructive comments. 我们对图片进行了删减, leaving only those related to the diagnosis.

5. Figure 4 has too many images. It is not really related to the main purpose of this case,

so it would be better to narrow down the images.

Response: Thank you for your constructive comments. We have narrowed down Figure

Reviewer #2:

1. The title should contain “cutaneous” or “skin” to clarify the main point of this manuscript.

Response: Thank you for your constructive comments. We have revised it accordingly as following:

Cutaneous Metastasis from Esophageal Squamous Cell Carcinoma: A Case Report

2. The abstract should be rewritten thoroughly since the time series of the proposed publication does not appear clearly. Besides, several grammatical errors were observed in this section (e.g. “symptoms were relived . After that,” or “did not undergo a regular chest lesion review, and returned home”).

Response: Thank you for your constructive comments. We have revised it accordingly as following:

Case summary: In this case report, we describe an 82-year-old male who was diagnosed with esophageal squamous cell carcinoma. The tumor was staged as T4N3M1 (Stage IVB). The pathological findings revealed poorly differentiated squamous cell carcinoma of the esophagus. Four months after diagnosis, the patient began chemotherapy, and symptoms were relieved after four cycles of chemotherapy. After that, the patient returned home without a systematic physical examination. One year after diagnosis, the patient realized that the skin of the abdominal wall was hard and rough without pain, and the color became darker than normal skin. Thirteen months after diagnosis, a biopsy of the patient's abdominal lesion revealed that the skin metastasis was derived from the esophagus. And then, the patient received two cycles of apatinib combined with docetaxel, but the abdominal lesion worsened. So two cycles of nivolumab were administered, but the patient eventually died of multiple organ failure.

3. From the perspective of privacy protection policy, the date of death should be

deleted.

Response: Thank you for your constructive comments. The date of death has been deleted.

4. Due to pleural effusion and its uptake of FDG in PET-scan, the patient was diagnosed with Stage IVB. However, these findings occur in benign diseases. Was cytology from pleural effusion examined?

Response: Thank you for your constructive comments. We have revised it accordingly as following:

Because the cytology of the patient's pleural fluid revealed pleural metastases, the tumor was staged as T4N3M1 (Stage IVB).

5. In the Figure 1, images of stomach seem unnecessary. This reviewer would suggest to omit these images.

Response: Thank you for your constructive comments. 我们删减了 Figure 1.

6. The dose of S-1 plus cisplatin seems relatively low. Was dose reduction performed or

was this dosage based on previous reports?

Response: Thank you for your constructive comments. The patient is old and the ECOG score is only 2, 因为担心病人不能耐受, so the drug dosage is low.

7. Figure 4 contains too many images. In addition, C and C4 were partially cut off.

Response: Thank you for your constructive comments. We have abridged the Figure.

8. Although the authors cited the results of a phase II study of nivolumab (ref 3), this is not appropriate and the better reference here is Kudo, et al. (Lancet Oncol. 2017).

Response: Thank you for your constructive comments. We have revised it accordingly as following:

A phase 2 clinical study confirmed the nivolumab monotherapy for advanced esophageal squamous cell carcinoma, which was performed for 64 patients. The primary endpoint was the objective response rate, and the objective response rate was 17%. The conclusion suggests that Nivolumab showed promising activity with a

manageable safety profile in patients with esophageal advanced squamous-cell carcinoma refractory or intolerant to standard therapies (Cited from Toshihiro Kudo, Yasuo Hamamoto, Ken Kato, Takashi Ura, Takashi Kojima, Takahiro Tsushima, Shuichi Hironaka, Hiroki Hara,Taroh Satoh, Satoru Iwasa, Kei Muro, Hirofumi Yasui, Keiko Minashi, Kensei Yamaguchi, Atsushi Ohtsu, Yuichiro Doki, Yuko Kitagawa. Nivolumab treatment for oesophageal squamous-cell carcinoma: an open-label, multicentre, phase 2 trial[J]. The Lancet Oncology 2017,18(5) [PMID: 28314688 DOI: 10.1016/S1470-2045(17)30181-X])

9. In the manuscript, it was stated that immunotherapy would be less effective due to poor immune function for patients with skin metastasis. However, it appears overstated because this outcome is not validated enough.

Response: Thank you for your constructive comments. We have revised it accordingly as following:

这句话"However, for patients with skin metastasis, the immune checkpoint inhibitor would be less effective due to poor immune function"被删除了 同时进行了其他更改 This may be correlated to the low immunity of the patient, the lack of immune cell reserves, and the inability to mobilize effective immune cells to clear the tumor. But that's just speculation, and more experiments are needed.

10. There were several errors especially when using a space (e.g. "the patient s symptoms were relived . After that," (Page 1) or "the estimated number of esophageal carcinoma cases in 2015 was 0.37 million(2)" (Page 2)). The manuscript should be rechecked.

Response: Thank you for your constructive comments. We have corrected the incorrect use of Spaces.

Once again, thank you for your valuable comments.

EDITORIAL OFFICE'S COMMENTS

(1) Science editor:

The authors report a case of metastatic esophageal carcinoma. Since cutaneous metastasis of esophageal cancer is rare, this topic is interesting. There are many grammatical errors in the article, so it is necessary to revise the language. Some conclusions are not supported by sufficient data, and the authors' conclusions are exaggerated. Language Quality: Grade C (A great deal of language polishing).Scientific Quality: Grade C (Good)

Response: Thank you for your constructive comments. Language changes have been made. 这句话"However, for patients with skin metastasis, the immune checkpoint inhibitor would be less effective due to poor immune function"被删除 同时进行了其他更改: This may be correlated to the low immunity of the patient, the lack of immune cell reserves, and the inability to mobilize effective immune cells to clear the tumor. But that's just speculation, and more experiments are needed.

Once again, thank you for your valuable comments.

(2) Company 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. 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.wjgnet.com/bpg/gerinfo/240. 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. Before final acceptance, 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: ...” . Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor.

Response: Thank you for your constructive comments. We have revised it accordingly as following:

An English language certificate from a professional English language editing company, a signed treatment consent form, and charts prepared and arranged using PowerPoint have been uploaded along with the revised article. We have adopted a uniform expression for graphics with the same or similar content. For example Figure 3 Histological pattern of skin lesions. The hematoxylin and eosin staining of sites for the fine needle biopsy specimen revealed esophageal squamous cell carcinoma in A(magnification×10), B(magnification×20). C(magnification×20): Representative immunohistochemical staining for CK in the skin; D(magnification×20): Representative immunohistochemical staining for P40 in the skin; E(magnification×20): Representative immunohistochemical staining for P63 in the skin; F(magnification×20): Representative immunohistochemical staining for CK5/6 in the skin; G(magnification ×20): Representative immunohistochemical staining for P53 in the skin; H(magnification×10): Representative immunohistochemical staining for Ki67 in the skin.

Once again, thank you for your valuable comments.