Kathie Schmidt
Rostock University Medical Center
Department of Medicine, Clinic III - Hematology, Oncology, Palliative Medicine
Ernst-Heydemann-Str. 6
18057 Rostock, Germany
kathie.schmidt@med.uni-rostock.de

Lian-Sheng Ma
Science Editor, Company Editor-in-Chief
Baishideng Publishing Group Inc
7041 Koll Center Parkway
Pleasanton, CA 94566, USA
l.s.ma@wjgnet.com

April 6, 2021

Subject: Revision and resubmission of manuscript 61547, Case Report

Dear Mr. Ma,

Thank you for your letters and the opportunity to revise our Case Report 'Long-term survivor of metastatic squamous-cell head and neck carcinoma with occult primary after cetuximab-based chemotherapy – a case report'. We appreciate your helpful observations and comments on revising the paper.

The revision has been developed in consultation with all coauthors, and each author has given approval to the final form of this revision.

We hope the revised manuscript will better suit the World Journal of Clinical Cases and we thank you for your continued interest in our research.

Sincerely,

Kathie Schmidt

Reviewer Comments, Author Responses and Manuscript Changes

Reviewer #1

Comment 1: Although it was reported that the patient achieved complete response after four cycles of chemotherapy, no figures showing the response to chemotherapy were not represented.

Response: Both you and other reviewers requested a figure showing response to therapy. Therefore, we added one further figure outlining regression of cervical lymph nodes.

Comment 2: The details of treatment course were not described especially with regard to chemotherapy. Which platinum agent was used, cisplatin or carboplatin? How many courses of chemotherapy were conducted?

Response: Thank you for your assessment. The patient received 6 courses of 5-fluorouracil (1000 mg/m²), cisplatin (40 mg/m²) and cetuximab (first course 400 mg/m², following courses 250 mg/m²). Docetaxel was added to the first course (70 mg/m²). Due to severe nausea and emesis cisplatin was replaced by carboplatin (AUC 5) after the fifth course.

Changes: We added details of treatment course within the treatment section.

Comment 3: The standard regimen for cancer of primary unknown is carboplatin plus paclitaxel. Meanwhile, cetuximab-based therapy which is targeted to head and neck cancer was successful in this case, suggesting the usefulness of site-specific therapy. The advantage of site-specific therapies over empirical chemotherapy is still controversial (Hayashi H, et al. J Clin Oncol. 2019 Mar 1;37(7):570-579.). This should be discussed more.

Response: Thank you for your suggestions. We have made good use of the article you mentioned and added a remark in the discussion section.

Comment 4: The authors mentioned the value of biomarker analyses. However, whole genome sequence or gene expression analysis was not conduced. This limitation should be described.

Response: The goal of this case report was to draw attention to the tiny subgroup of long-term survivors after treatment with platinum and cetuximab based therapy. To our knowledge there were no studies published in the recent years. In a second step we aim to establish a register and have genetic testing.

Comment 5: Further English proofing may be needed. For example, “ECOG 0” should be “ECOG PS 0” (Page 7, Line 19).

Response: Thank you so much for your language comments. We have gone through the entire manuscript carefully and resolved the language issues (for example ECOG performance status 0).

Reviewer #2

Comment 1: The author could control the unknown primary carcinoma in head and neck by Extreme regimen. However, in accordance with TNM Classification of Malignant tumors -8th edition, unknown primary carcinoma with p16 positive was regarded as p16 positive oropharyngeal cancers. Not surprisingly, p16 positive oropharyngeal cancer has good prognosis for chemotherapy. First of all, the author should correct this.

Response: We agree that HPV surrogate marker p16 has positive predictive value. Alterations of the tumor staging from UICC7 to UICC8 included mainly UICC stage III or IVa according to the 7th edition. Our patient remained at the same stage UICC IVc and had in both TNM classifications the lowest overall survival (UICC IVc TNM7 12 month; UICC IVc TNM8 5 month according to Boeker R et al, Carcinoma of Unknown Primary and the 8th Edition TNM Classification for Head and Neck Cancer, Laryngoscope. 2021 Mar 18. doi: 10.1002/lary.29499).

Reviewer #3

Comment 1: Treatment is effective, but more specific treatment details should be described for reference. For example, what is the dose of chemotherapy and what is the target area of radiotherapy.

Response: Thank you for your comment. The patient received 6 courses of 5-fluorouracil (1000 mg/m²), cisplatin (40 mg/m²) and cetuximab (first course 400 mg/m², following courses 250 mg/m²). Docetaxel was added to the first course (70 mg/m²). Due to severe nausea and emesis cisplatin was replaced by carboplatin (AUC 5) after the fifth course. Metastatic lymph nodes in the para-aortic region were irradiated up to 36 Gray. Four month later, bone metastasis in the fifth lumbar bone was irradiated up to 35 Gray.

Changes: We added details of treatment course within the treatment section. Details of irradiation can be found in the outcome and follow up section.

Comment 2: The data before and after treatment should be compared. The images of lymph nodes after treatment should be provided, and the situation of lymph node regression should be reflected by data.

Response: Both you and other reviewers requested a figure showing response to therapy. We added one further figure which showed complete regression of the cervical lymph nodes after four courses.

Comment 3: Did the patient have a genetic test?

Response: Unfortunately, the patient did not have a whole genome sequence or gene expression analysis yet. The goal of this case report was to draw attention to the tiny subgroup of long-term survivors after treatment with platinum and cetuximab based therapy. To our knowledge there were no studies published in the recent years. In a second step we aim to establish a register and have genetic testing.

Reviewer #4

Comment 1: In the Figure 1, arrows should be added to point out the representative swollen lymph nodes you mentioned.

Response: Thank you for your observation. We added an arrow in the figure pointing out the swollen lymph nodes.

Comment 2: In the Section of Imaging examination, the compression of the right renal artery and osteolyses of the third and fifth lumbar vertebral bodies should be presented in the figure for the reader of Journal.

Response: Thank you for the comment. We added CT/FDG-PET images of the osteolysis and the para-aortic swollen lymph nodes in the imaging section.

Comment 3: The authors did not find out the primary lesion by Gastroscopy, coloscopy, and bronchoscopy. The blood system should also be considered as one of the sources of primary lesions. PET-CT examination would be very helpful for discovery of primary lesions.

Response: Thank you for your assessment. We agree with you, that a PET-CT would be very helpful to discover the primary lesion. Unfortunately, there was no PET-CT in 2010 available. First PET-CT examination was performed in 2013 as part of the follow-up diagnostic (see figure 3 and 4). With regard to the blood system, we found typical deviations that could be explained by pregnancy rather than by lymphoma: anemia (hemoglobin 7,1 mmol/l [7,5-10,0 mmol/l]), elevated Lactate Dehydrogenase (298 U/l [< 247 U/l]; faster sed rate (54 mm/hr [< 20 mm/hr]. There were no signs of hemolysis, thrombopenia or leucopenia.

Changes: We added the findings of the blood system in the laboratory section.

Company editor-in-chief

Comment 1: The title of the manuscript is too long and must be shortened to meet the requirement of the journal (Title: The title should be no more than 18 words).

Response: I apologize for neglecting that requirement when we originally submitted the manuscript. We shortened the title to 'Long-term survivor of metastatic squamous-cell head and neck carcinoma with occult primary after cetuximab-based chemotherapy – a case report.' (18 words).