Author’s response to reviews

Title: Case report: term birth after fertility-sparing treatments for stage IB1 small cell neuroendocrine carcinoma of the cervix

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Author’s response to reviews:

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Title: Case report: term birth after fertility-sparing treatments for stage IB1 small cell neuroendocrine carcinoma of the cervix Pei-Ying Wu, M.D.; Ya-Min Cheng, Associate Professor; Geok Huey New, M.D.; Cheng-Yang Chou, Professor; Chun-Ting Chiang, M.D.; Hung-Wen Tsai, M.D.; Yu-Fang Huang, Associate Professor

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Dear Editors:

Thank you very much for the letter concerning our paper submitted to BMC Women’s Health. The resubmitted manuscript has been revised based on the reviewers’ comments. Those amended are highlighted with bold text with underline.
I attached the detailed responses to the reviewers’ comments and our revised manuscript.

We are grateful for the opportunity to pursue publication further and thank you very much for your attention.

Yours sincerely,

Yu-Fang Huang

Ms. No.: BMWH-D-16-00264

Editor Comments:

BMC Women's Health operates a policy of open peer review, which means that you will be able to see the names of the reviewers who provided the reports via the online peer review system. We encourage you to also view the reports there, via the action links on the left-hand side of the page, to see the names of the reviewers.

Reply: Thank you for reminding. Reply to reviewers’ comments is as it follows.

Reply to reviewer’s comments

Reviewer 1 (Ahmed A Nassr)

Comments:

An interesting case report of favorable pregnancy outcome after fertility sparing treatment for SCNEC of the cervix.
I have only two comments:

1 - Did this patient had cerclage?

2 - The discussion section is very long

Otherwise the case report is well written and adds to the literature

Question 1

Did this patient had cerclage?

Reply: Intraoperative cerclage surrounding the neocervix during radical treachlectomy was performed (page 6, line 127).

Question 2

The discussion section is very long

Reply: We agree with your point. The discussion section includes the surgical, oncologic, fertile, and obstetric aspects since there is no consensus for the treatment with neuroendocrine tumor.

Reviewer 2 (Manuel Marcos, M.D.)

Comments:

interesante comunicación de caso clinico

Reply: Thanks for your comment.
Reviewer 3 (Ahmed Hefnawy)

Comments:

This manuscript summarizes a case report of a 25-year-old nulligravida with stage IB1 small cell neuroendocrine carcinoma (SCNEC) of the cervix that was managed by neoadjuvant chemotherapy and radical abdominal trachelectomy. The patient remained disease free and had a successful delivery of a full-term baby by cesarean section 7 years later.

This manuscript is interesting to the journal readership as not only it presents a rare small cell neuroendocrine carcinoma of the cervix but it documents the success of a multimodal therapy in achieving favorable oncologic and obstetric outcomes in the absence of guidelines or consensus guiding management.

Question 1

Specific comments:

Page 5, Lines 95-100: HPV infection is a risk factor for Neuroendocrine Tumors. Can the authors clarify if the patient had any Pap smear screening before and if so, what were the results?

Reply: The patient has never had cervical screening before she presented with a cervical tumor. In Taiwan, annual cervical screening is encouraged for women aged ≥ 30 years. The sentence has been added ‘No previous cervical smear and human papillomavirus (HPV) DNA test have been obtained.’ in page 5, lines 97-98.

Question 2

Specific comments:

Page 6, Line 108: The authors reported that the patient didn't have a paraneoplastic syndrome. Can they demonstrate to the readers which tests were conducted?
Reply: Patients with cervical small cell neuroendocrine carcinoma may present with a paraneoplastic syndrome. The common syndromes are hyponatremia, hypoosmolality, and hypercalcemia. This patient in our report had normal serum levels of sodium (140 mmol/L), potassium (4.2 mmol/L), calcium (8.9 mg/dL), and normal fasting blood sugar (88 mg/dL). She had normal blood pressure and BMI (21.6 kg/M2).

The information has been added: She did not have paraneoplastic syndrome ‘(hyponatremia, hypoosmolality and hypercalcemia)’ in page 6, line 110

Reviewer 4 (Jesus Salvador Jiménez López, Ph.D, M.D.)

Comments:

Please include all comments for the authors in this box rather than uploading your report as an attachment. Please only upload as attachments annotated versions of manuscripts, graphs, supporting materials or other aspects of your report which cannot be included in a text format.

Please overwrite this text when adding your comments to the authors.

Revisión: Case report: term birth after fertility-1 sparing treatments for stage IB1 small cell neuroendocrine carcinoma of the cervix

Question 1

Abstract:

- It seems to us that the abstract is well presented, with an adequate extension and emphasizing the relevance of its case.

Reply: Thank you.

Question 1

Background

- Error line 74, respectively.5 respectively [5]
Question 2

- In general they make a good contextualization of the subject. It is somewhat incomplete because they introduce the concept of neoadjuvant chemotherapy, but the authors mention it very much above and the relevance of such therapy in these tumors is not clear.

Reply: We agree with your point. We suppose neoadjuvant chemotherapy may not only control tumor spread but also cause tumor shrinkage in SCNEC. However, no literature has reported the success of this strategy in SCNEC. We try to demonstrate the relevance of such therapy in this case report.

Question 3

- Association of SCNEC with HPV 18 has been described. We considered that the authors should mention whether the patient had performed a previous cytology study, whether it was performed after the finding and whether HPV PCR was performed.

Reply: The patient has never had cervical screening before she presented with a cervical tumor. A biopsy on exophytic cervical tumor was performed for definite pathological diagnosis, but cervical smear and HPV PCR were not available after the finding. We have added the points that you recommend in page 5, lines 97-98.

Question 4

The neuroendocrine lung tumor has a high rate of metastasis to the CNS, which is why some authors advocate a guided exploration of CNS in patients with SCNEC and even prophylactic cranial irradiation. It is important to justify the absence of a more detailed neurological study and should refer to the fact that the patient had NO clinical suggestion of CNS involvement at any time.

Reply: Neurological exam revealed normal neurological function pretreatment and during surveillance. No clinical evidence of CNS involvement was encountered. The clinical stage was
allocated to stage IB based on FIGO staging since CNS metastasis was not suspected. We have added the sentences: ‘Pretreatment neurological exam revealed normal neurological function. CNS metastasis was not suspected, because no clinical evidence of CNS involvement was encountered.’ in page 6, lines 111-113.

Question 5

We have a number of issues that we believe authors should include in the text.

Was there any more tumor marker? Only Ca125? Why Ca125 and not others?

Reply: Pretreatment levels of serum markers were within normal limits. We have amended the sentence as ‘She had elevated CA-125 level (47.1 IU/mL) and normal levels of CA-199 and carcinoembryonic antigen.’ in page 6, lines 108-109.

Question 6

Did you consider the possibility of sentinel lymph node?

Reply: The advantage of sentinel lymph node (SLNB) has not been determined 7 years ago. Wu et al (2013) addressed that limited diagnostic value of SLNB for the assessment of the nodal status in patients with cervical cancer. Sentinel lymph node was not routinely performed in our hospital at that time.


Question 7

Why not perform a technique for ovocitaria preservation? Especially knowing that a chemotherapy treatment is going to be done.
Reply: Shared decision making policy was implemented at that time. An infertility specialist was consulted pretreatment for oocyte preservation and further infertility treatment. The patient declined oocyte preservation and cryopreservation due to high medical expenses and her personal reason. She preferred to the use of GnRH agonist to protect ovarian function.

Question 8
What kind of follow-up was done to the patient?

Reply: Post-treatment physical examinations were performed every 3 months for the first 2 years, every 4 months for the third year, every 6 months for the fourth and fifth years, and annually thereafter, based on the recommendations of the Society of Gynecologic Oncologists (Salani et al. 2011). We also performed neurological exam, cervical cytology and serum marker evaluations at the same time. Surveillance examinations were performed every 3 months during pregnancy. (The follow-up protocol has been added in page 7, lines 135-139 and lines 145-146)

The reference has been added as reference 11: ‘Salani R, Backes FJ, Fung MF, Holschneider CH, Parker LP, Bristow RE, Goff BA. Posttreatment surveillance and diagnosis of recurrence in women with gynecologic malignancies: Society of Gynecologic Oncologists recommendations. Am J Obstet Gynecol 2011; 204: 466–478.’ Therefore, the following references and citation in text have been concurrently updated.

Question 9
Since when was pregnancy allowed?

Reply: Pregnancy was allowed 6 months at least after completion of adjuvant chemotherapy. This protocol has been added in page 7, line 142,
Conclusion

Regarding the comment on line 155 on QT only in stadium> IIA. QT has been proposed as an adjuvant treatment for all stages, not only advanced (Ref Neuroendocrine Tumors of the Gynecologic Tract: A Society of Gynecologic Oncology (SGO) clinical document).

Reply: We agree with your point. The sentence has been added: ‘Adjuvant chemotherapy has been proposed for SCNEC in any stage.’ in page 8, line 166.

Question 11

On the trachelectomy, the data presented are about cancer of the cervix with other histologies. This should be specified very clearly since this is NOT a recurrence in cases of neuroendocrine tumors that have a higher recurrence rate. We believe this needs to be clarified.

Reply: Thank you for your recommendation. We emphasize your point in this paragraph: The overall conversion rate from ART to radical hysterectomy was 10% of 485 patients with common pathology in a systematic review [16] (page 9, line 189). ‘...’ However, data for long-term oncologic outcome are still unavailable in common and uncommon histology’. (page 9, line 197)

Question 12

Although there are no studies designed to compare QT vs QRTT, there is some descriptive article about it (Prognostic factors in FIGO stage IB-IIA small cell neuroendocrine carcinoma of the uterine cervix surgically treated: results of a multi-center retrospective Korean study. Factors in neuroendocrine small cell cervical carcinoma: a multivariate analysis.) We believe that the authors should include it in their discussion.
Add reference


Prognostic factors in FIGO stage IB–IIA small cell neuroendocrine carcinoma of the uterine cervix treated surgically: results of a multi-center retrospective Korean study


Reply: Thank you for your recommendation. This point has been added in Discussion section. ‘Lee et al. reported that adjuvant chemoradiation was not superior to adjuvant chemotherapy alone in early-stage SCNEC patient survival [14]. Moreover, pelvic radiation is not preferred for women who want to preserve ovarian function.’ (page 8, lines 174-177)


Question 13

Perhaps they should justify more why only adjuvant QT and non QTRT, what made them opt for this alternative, the reason was because they posed a more conservative behavior?

Reply:

Thank you for your recommendation. We have added ‘Lee et al. reported that adjuvant chemoradiation was not superior to adjuvant chemotherapy alone in early-stage SCNEC patient survival [14]. Moreover, pelvic radiation is not preferred for women who want to preserve ovarian function.’ in page 8, lines 174-177.
Reviewer 5 (Mehmet Baki Şentürk)

Comments:

Why patient underwent no artificial reproductive technique? This very important issue because SCNEC has big potential in terms of relapse. How you discussed this issue with patients?

Second: How you followed the patient from first therapy to pregnancy it was 6.5 year !!! then how you followed during pregnancy?

I think you should explain the follow program in case present and discussed in comment. this is very important issue.

Question 1

Why patient underwent no artificial reproductive technique? This very important issue because SCNEC has big potential in terms of relapse. How you discussed this issue with patients?

Reply: Surely we did discuss the issue with the patient and her family and the potential in terms of disease relapse was highlighted with the literature evidence. An infertility specialist was consulted pretreatment for oocyte preservation and further infertility treatment. The patient declined oocyte preservation and cryopreservation due to high medical expenses and her personal reason. She finally decided to get conceived without artificial reproductive technique.

Question 2

How you followed the patient from first therapy to pregnancy it was 6.5 year !!! then how you followed during pregnancy?

I think you should explain the follow program in case present and discussed in comment. this is very important issue.

Reply: Post-treatment physical examinations were performed every 3 months for the first 2 years, every 4 months for the third year, every 6 months for the fourth and fifth years, and annually thereafter, based on the recommendations of the Society of Gynecologic Oncologists.
(Salani et al. 2011). We also performed neurological exam, cervical cytology and serum marker evaluations at the same time. Surveillance examinations were performed every 3 months during pregnancy. (The follow-up protocol has been added in page 7, lines 135-139 and lines 145-146)

The reference has been added as reference 11: ‘Salani R, Backes FJ, Fung MF, Holschneider CH, Parker LP, Bristow RE, Goff BA. Posttreatment surveillance and diagnosis of recurrence in women with gynecologic malignancies: Society of Gynecologic Oncologists recommendations. Am J Obstet Gynecol 2011; 204: 466–478.’ Therefore, the following references and citation in text have been concurrently updated.