Author's response to reviews

Title: Non-small cell lung carcinoma in an adolescent, manifested by acute paraplegia due to spinal metastases - case report

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Author's response to reviews: see over
Re: Manuscript: „Non-small cell lung carcinoma in an adolescent, manifested by acute paraplegia due to spinal metastases - case report” (Revision)

Dear Dr. Kidd,

dear Associate Reviewers and Editorial Team,

thank you very much for reviewing the manuscript “Non-small cell lung carcinoma in an adolescent, manifested by acute paraplegia due to spinal metastases - case report” which I submitted for publication in the Journal of Medical Case Reports.

We do very much appreciate your valued hints and concerns regarding the case report. In the attached letter, they are answered point by point, and the changes in the text are highlighted.

Yours sincerely,

C.F. Classen
Dear Associate Editors and Editorial Team, dear Reviewers,
thank you for the valued hints and concerns regarding our case report which, in the following, I will answer point by point.

The Associate Editor and Editorial Team have mentioned the following aspects:

First point mentioned by the A.E.:
The manuscript should be checked over by a native English speaker and the language revised Answer: by a native speaker, several sentences of the work were changed. These are highlighted. Change in the text: for example “Their benefit is still not quite clear” (p.2), “In the grandparents and an aunt three cases of carcinomas including a bronchial carcinoma were observed” (p.3), “. Otherwise, the boy was stable condition with normal examination status” (p.3) and others.

Second point mentioned by the A.E. Please include the ethnicity of the patient in the abstract and in the case presentation section. Answer: The patient is Caucasian, Change in the text: the ethnicity was included in abstract (p.2) and case presentation (p.3)

Third point mentioned by the A.E. As the patient is a minor, please could you confirm that you have obtained written informed consent from the patient’s legal guardian for publication of the case. Your consent statement should be modified accordingly. Answer: the written informed consent from the patient’s legal guardian was obtained and is attached. Change in the text (page 5): Instead of “Written informed consent was obtained from the patient” there is now written “Written informed consent was obtained from the mother (legal guardian) of the patient”

The Reviewer 1 mentioned: Rephrase abstract introduction Answer: Reviewer 1 is right stating that in the abstract introduction, the sentences were misarranged. Change in the text: The first two paragraphs of the abstract were re-written as mentioned.

The Reviewer 2 mentioned 18 points: First Point of Reviewer 2: In the abstract all sentences should contain a verb. Answer: Reviewer 2 is right Change in the text: The abstract was re-written as mentioned previously (p.2).

Second Point of Reviewer 2: - in the 1st paragraph of introduction, the differences in prognosis are not generally accepted. Moreover the two references are not containing supporting data. I suggest the sentence should be deleted. Answer: The reviewer is right stating that there are conflicting data regarding prognosis. Change in the text: The phrase was deleted (p.2).

Third point of reviewer 2: - In the 2nd paragraph "aggressive first-line" should be replaced by "combination first-line"
Fourth point of reviewer 2:
-The sentence "As less aggressive..." should be replaced by "In second line treatment, monotherapy is proposed ..."
Change in the text:
The text was changed accordingly (p.2).

Fifth point of reviewer 2:
-I propose that irinotecan be mentioned last in the doublets choice because it is the least used in NSCLC.
Change in the text:
The text was changed accordingly (p.2).

Sixth point of reviewer 2:
- In the sentence "Gemcitabine is regarded..." "in squamous cell carcinomas" should be added for clarity.
Change in the text:
The text was changed accordingly (p.2).

Seventh point of reviewer 2:
- In the case report, presence or absence of passive smoking should be mentioned in the exposures history.
Change in the text:
The text was changed accordingly. (page 3, line 6: “He never smoked nor abused other substances, nor was he exposed to tobacco smoke, chemicals or irradiating toxins.”)

Eighth point of reviewer 2:
- After laminectomy was RT considered given the incomplete nature of resection to avoid or delay local recurrence? (an event that eventually led to repeat surgery)
This point I would like to answer together with the tenth point of reviewer 2:
-Why was the primary site irradiated in the metastatic setting? Contrary to what the authors affirm, local therapy (surgery or RT even at lower than standard doses as in the current case) for the primary tumor is not standard in the metastatic setting except if metastatic disease is well controlled by systemic treatment, which appears not to be the case with this patient, or if symptoms appear.
Answer:
Due to the location of the primary tumor and spinal metastasis, it appeared appropriate to irradiate both at the same time (or unfeasible to separate one from the other). The intention was to perform irradiation of both primary tumor and spinal metastasis at a time of maximal response to chemotherapy. Finally, this was done 3 months after disease manifestation.
Recommendations concerning palliative radiotherapy for the primary tumor in the metastatic setting are individual and may include cases of imminent symptoms.
Change in the text:
The text concerning irradiation of primary tumor and metastasis at Th5 was changed accordingly ("Since it was not feasible to separate irradiation of the main bronchial tumor and the area of Th5, combined fractionated irradiation with 30 Gy was performed subsequently." See page 3).

Ninth point of reviewer 2:
- It is not clear if EGFR was molecularly tested for mutations or for amplification. Mutations are clearly associated with response to anti-EGFR therapy.
Answer:
The reviewer is right stating that the sentence „ since k-ras mutation and EGFR were negative” is not quite clear. Molecular analysis of mutations in the EGF-R-gene were negative.
The sentence was changed accordingly here ("since k-ras mutation and EGFR mutation were negative", p.3) and in the abstract, p.2.

Tenth point see eight point.

Eleventh point of reviewer 2:
-There is no maximum of chemo cycles in the metastatic setting if there is clinical benefit (efficacy without undue toxicity). Clearly in the patient the reason for interrupting first line therapy at 6 cycles was progression.
Answer: We are not aware of recommendations for the use of more than 6 cycles of cisplatinum / gemcitabine; anyway, as the reviewer states correctly, the reason for this limitation were progression (and toxicity).
Change in the text:
The sentence was changed appropriately (p.4).

Twelveth point of reviewer 2:
- The reason for irradiation of T12-L4 should be given (analgesia? cord compression?)
Change in the text:
“Another course of palliative irradiation was given for analgesia”. (p.4)

Thirteenth point of reviewer 2:
-"nonprogredient" is not clear.
Answer: The pleural effusion remained unchanged for several weeks without therapeutical intervention.
Change in the text:
The word was omitted since it does not contain additional information (p.4)

Fourteentth point of reviewer 2:
- Was an aFP and bHCG obtained to exclude the possibility of a mediastinal non-seminomatous germ cell tumor with teratocarcinoma and metastasis of the squamous component? And in the same vain was a testicular examination and US done?
Answer: The given tumor markers and a complete clinical and ultrasound checkup were negative.
Change in the text:
“A familiar p53 mutation and a germ cell tumor were excluded” (p. 2)

Fifteenth point of reviewer 2:
-In the discussion the sentence "6 cycles..." is not correct for the metastatic (or for all cases of adjuvant ) setting and should be reconstructed.
Answer: As said above we are not aware of recommendations for the use of more than 6 cycles of cisplatinum / gemcitabine in first-line chemotherapy; in most cases this number will not be exceeded anyway for reasons of progression or toxicity.
Change in the text:
The sentence was re-arranged (“More than 6 cycles of cisplatinum and gemcitabine chemotherapy in combination with irradiation as first-line standard therapy for NSCLC patients are rarely tolerated.”), p.4.

Sixteenth point of reviewer 2:
-In the following sentence "Equally..." radiation of the primary is not state of the art (see comment above).
Answer: This point was also commented at point 8/10.
Change in the text:
“represents a common approach in adults” (p.4).

Seventeenth point of reviewer 2:
-For the anti-EGFR treatment there exist randomized studies supporting benefit for EGFR-mutant patients and it is not just opinion of "most authors".
Answer: For EGFR-mutant patients the benefit is proven. For non-mutant patients (as in our case), the absence of any benefit is very likely.
Change in the text:
“Most authors” was changed to “Randomized studies indicate” (p.4)

Eighteenth point of reviewer 2:
Quality of written English: Needs some language corrections before being published
Answer:
This point was also addressed by the associate editor (changes see above).