Author's response to reviews

Title: Aldosterone-producing adrenocortical carcinoma with prominent hepatic metastasis diagnosed by liver biopsy: a case report

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Dear the Editor and reviewers,

We appreciate the referee for fruitful suggestions, especially for suggesting the better terms, sentences and especially comment 2. We have revised the manuscript "Aldosterone-producing adrenocortical carcinoma with prominent hepatic metastasis diagnosed by liver biopsy: a case report" (BEND-D-15-00034) on the basis of the Referee's comments. We are sending the new manuscript which we corrected and responsive letter.
Comment 1.

The original comments of the Referee are as follows.

English grammar should be checked. There are many misspelled words (i.e. dexamethazone, sytoplas, inceased, hepatoceller, etc.) and grammatical errors (i.e. "We here report the first case…", "As for tumor markers, …").

Our responses to the referee's comments are as follows:

According to your recommendation, we had native English speaker check our manuscript, and we corrected spelling errors and grammar more than 100.

Comment 2.

The original comments of the Referee are as follows.

Lines 39-42, it is stated "Aldosterone producing adrenocortical carcinoma diagnosed by immunohistochemical staining…” The IHC staining was performed in the liver biopsy and even in that case staining for CYP11B2 was not performed.

Our responses to the referee's comments are as follows:

That is just as you indicated. That case staining for CYP11β2 was not performed. We corrected Lines 39-42 in first manuscript (new manuscript: P3, Lines 39-45, "Aldosterone-producing adrenocortical carcinoma is a rare malignancy, which is usually diagnosed by histopathological examination of the excised tumor. In inoperable cases, aldosterone-producing ACC diagnosed by immunohistochemical staining of the metastatic tumor for Cytochrome P450 (CYP) 11β has not previously been reported and even in that case staining for adrenocortical-specific adrenal 4 binding protein/steroidogenic factor1 (Ad4BP/SF1) and steroidogenic enzymes has not been reported.").
Comment 3.

The original comments of the Referee are as follows.

The authors should make an effort to clarify through the text if the IHC was performed in the liver and/or the adrenal. When finished reading the manuscript, it is clear that the IHC was performed in the liver biopsy and that the adrenal was not available for IHC. However, the reader has to finish reading the manuscript to have this concept clear. It would be much easier for the reader if this was more clearly stated through the manuscript.

Our responses to the referee's comments are as follows:

We corrected a manuscript to clarify our concept. We described the reason that the immunohistochemical staining was performed in the liver tumor and that the adrenal was not available for immunohistochemical staining in new manuscript (new manuscript: P4, Lines 56-60, "Adrenocortical carcinoma with metastatic liver cancer was strongly suggested, however surgery could not be considered due to stage IV disease: the liver tumor was too large and cardiac ultrasonography indicated that her cardiac function was poor. Therefore, a liver biopsy was taken to properly determine the diagnosis." and P7, Lines 120-124, "We wanted to excise the adrenal tumor including the liver tumor for diagnosis and treatment. But this case could not be considered for surgery because of stage IV disease: the liver tumor was too large and cardiac ultrasonography indicated that her cardiac function was poor (ejection fraction: 32%). Therefore a liver biopsy was taken to determine the diagnosis.").

Comment 4.

The original comments of the Referee are as follows.

4. Lines 162-164, it is stated "There is no evidence that this tumor produced aldosterone, because we could not apply immunohistochemical staining for CYP11β1 and CYP11β2 in those days." It is not clear if "tumor" refers to liver or adrenal. Furthermore, CYP11B1 and CYP11B2 should be written with "B" and not the Greek betta symbol.
Our responses to the referee's comments are as follows:

4. This tumor is metastatic liver tumor. We added "in a metastatic tumor" in new manuscript (P11, Line 182). And we corrected CYP11β1 and CYP11β2 to the Greek betta symbol (P11, Line 181).

Comment 5.

The original comments of the Referee are as follows.

5. Lines 164-166, it is stated "Despite these limitations, however, we report the first case of aldosterone producing ACC diagnosed by immunohistochemical staining for both Ad4BP/SF1 and steroidogenic enzymes in a metastatic tumor." Was the aldosterone secretory activity of the ACC diagnosed by Ad4BP/SF1 and steroidogenic enzymes IHC in the metastatic tumor? Again, manuscript should be improved for clarity.

Our responses to the referee's comments are as follows:

5. We improved Lines 164-166 in first manuscript. We could not apply immunohistochemical staining for CYP11β1 and CYP11β2. We corrected a manuscript (new manuscript: P11, Lines 182-184, "We strongly suspected that these tumors produced aldosterone because PAC increased significantly as a result of endocrinological examination.").

We look forward to hearing from you regarding our submission. We would be glad to respond to any further questions and comments that you may have.
Sincerely,

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