Responses to the reviewers' comments

The comments provided by the two reviewers have been helpful in the revision of our manuscript. We have attempted to address the concerns raised by the reviewers as follows.

Reviewer's code: 03388124

1. The nature of the cyst in this case appears to be hemorrhagic cyst or pseudocyst. It would be helpful to list the nature of the cyst in each case. Was there any case with dilated duct appearing as a cyst on imaging?

A1. We thank the reviewer for this important comment and valuable suggestion. Kosmahl et al [1] classified 38 cases of pancreatic ductal adenocarcinoma (PDAC) and its variants with cystic features into the following four categories according to the nature of the formed cysts: large-gland features that were lined by atypical cuboidal to flat epithelial cells, intratumoral degenerative cystic changes, retention cysts, and attached pseudocysts. All 24 cases with large-gland features were PDAC, whereas five of eight cases with intratumoral degenerative cystic changes were ACP or undifferentiated carcinoma with osteoclast-like giant cells. In the present review, the wall of the formed cyst was composed of tumor cells that showed hemorrhagic necrosis at the inner surface of the cyst in most previously reported cases as well as in the present case, indicating degenerative cystic changes. Only three case reports described that the cysts in the tumors were lined by normal or atypical epithelial cells and formed a single cell layer, and imaging studies did not provide cystic parts as the dilatation of the pancreatic

ducts in any cases. We have cited this reference and have discussed the differences in the nature of formed cysts between ACP and PDAC in the Discussion section.

[1] Kosmahl et al. Pancreatic ductal adenocarcinomas with cystic features: neither rare nor uniform. Mod Pathol. 2005 Sep;18(9):1157-64.

2. The assertion "Clinically the combination of severe anemia and laboratory data showing elevated leucocyte counts and serum CA19-9 levels might help differentiate ACP from other pancreatic neoplasms without requiring an invasive procedure" appears too strong. This conclusion should be substantiated by statistically significant difference between ACP and conventional ductal carcinoma, which was not provided. In addition, a comment on cystic formation in conventional ductal carcinoma may also be helpful.

A2. We have revised this assertion to the following: "ACP should be considered when diagnosing pancreatic tumors with a cyst-like appearance, especially in the presence of severe anemia, elevated leucocyte counts, or elevated serum CA19-9 levels."

PDAC with cystic features has been reported to account for 7-11% of all PDAC cases[2][3]. We have mentioned and cited these references in the Discussion section.

[2] Kosmahl et al. Cystic neoplasms of the pancreas and tumor-like lesions with cystic features: a review of 418 cases and a classification proposal. Virchows Arch. 2004 Aug;445(2):168-78.

[3] Nitta et al. Pancreatic ductal adenocarcinomas with multiple large cystic structures: a clinicopathologic and immunohistochemical study of seven cases. Pancreatology. 2013 Jul-Aug;13(4):401-8

3. Appropriate statistical analysis (such as Chi square) should be performed throughout the manuscript.

A3. As the reviewer indicated, the comparison the clinical, radiological, and morphological findings between ACP and PDAC is very important. However, the collection of data from PDAC patients who underwent surgery in our institution is outside the scope of the approval provided by the Institutional Review Board at this time. We will seriously consider collecting these data in a future study.

4. The authors are aware that the JPS classification is different from WHO classification, thus it would be helpful to use the WHO classification to attract audience outside of Japan.

A4. The subtypes of ACP in the JPS classification do not parallel those in the WHO classification. Moreover, we could not assign the ACP subtypes of the included cases according to the WHO classification because of the limited pathological descriptions in each case report. For this reason, we used the JPS classification throughout the manuscript.

Reviewer's code: 00722122

1. The abstract need to be corrected and should be more or rather correctly informative. In the 9th line authors observed 77% and 33% respectively but it is not clear what two groups they are mentioning. Furthermore they write that including ACP in differential diagnosis..... To my understanding it is already included and therefore it is a wrong statement. It may be that because of its rare occurrence the diagnosis may be delayed due to unawareness.

A1. We thank the reviewer for this important comment about our assertion regarding the diagnosis of ACP.

We have corrected this sentence for clarity as follows: "Macroscopically, hemorrhagic necrosis was observed in 77% of cases, and cyst formation was observed in 33% of cases." Additionally, we have revised "We suggest including ACP in differential diagnosis…" to "ACP should be considered when diagnosing pancreatic tumors with a cyst-like appearance, especially in the presence of severe anemia, elevated leucocyte counts, or elevated serum CA19-9 levels."

2. In the case report there is a duplication of the information about serum level of CA19-9, please correct it.

A2. We have deleted a duplicated sentence concerning the serum CA19-9 levels.

3. In the discussion part 5th para it will be more appropriate to write ' the finding..... of a large series...., rather than largest. Similarly in the 6th para 5th

line 'Clark reported a study of the largest series' seems inappropriate . In the 14th line, it is not clear which relevant data authors are indicating. They should write survival analysis if that is the case.

A3. We have revised "the largest" to "a large" and revised "for whom relevant data were available" to "for whom survival data were available". As the reviewer noted, survival analysis of patients with ACP is highly important. However, this review is based on the cases reported in the Japanese language literature. Therefore, we expected that considerable publication bias might affect the survival rate. For this reason, we did not perform survival analysis. We have described the lack of survival analysis as a weakness of this review in the Discussion section.

4. Table1: the information about age and median tumour size should be removed and can be mentioned only in text as these information is not following the table format. Also please check the numbers of the patients with recurrence rate. Authors write n = 34 whereas the summation of the individual recurrences is equal to 48 or they should clarify otherwise the numbers.

A4. We have removed the age and tumor size information from Table 1. Of 34 cases with recurrence, some exhibited recurrence at more than two sites. For clarity, we have revised "Recurrence was reported in 34 cases at the following sites…" to "Recurrence was reported in 34 cases at one or more sites. The representative sites of recurrence were…".

Thank you for your consideration of the revised version of this manuscript.

Sincerely,

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