Author’s response to reviews

Title: Pancreatic hamartoma: A case report and literature review.

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Version: 1 Date: 13 Nov 2015

Author’s response to reviews:

Dear Editors and Reviewers,

We really appreciate every reviewers for their insightful and helpful comments.

We have made revised points in the red as following, and we hope these revisions make our manuscript to be significantly improved.

Reviewer #1: Summary:

The authors present the case of a 68 year old patient with a pancreatic hamartoma who underwent surgery after the tumor size increased within after 31 month.

Review:
The case summarizes an interesting finding in a patient with a pancreatic tumor. However, there is no real new aspect presented in the case here. The proceedings with pancreatic tumors are often difficult and as such there is no unambiguous way what to do, but the proposed strategy in this case is difficult to follow. The authors propose that the patient underwent surgery since the tumor progressed in size (42 x 39 mm at first diagnosis; after resection 40 x 40 mm), so this seems to be not the best argument. The option of a puncture of the tumor to support the final decision is not discussed. The summary of the formerly published cases in Table 2 is not very helpful.

We appreciate your helpful comments. We tried to examine the EUS biopsy, the patient refused the examination because of the risk of the puncture. So, we couldn’t do it. And we changed Table 2 more simply.

Minor points:

The manuscript can be shortened. There is information in the manuscript that is not needed.

We shortened it.

The conclusion in the abstract is difficult to understand.

We changed it. We want to emphasize that we could observe time-shift change of the pancreatic hamartoma.

The authors claim that surgical resection is still required for diagnosis. This is somehow true, but the sentence is misleading (I guess the meaning shall be that surgery is often needed to diagnose hamartomas).

We correct the sentence as you mean.

The sentence about the allergic reaction after the CT is not useful.

This is a reason why we didn’t approve the enhanced-CT examination since then.

Why did the patient get a CT, an MRI, and EUS at 21 months. I would assume that the CT is not really needed.

We performed CT and MRI as a routine examination for uncommonly tumor. And the clinical diagnosis was so difficult, EUS was performed as an additional examination.

The descriptive part of the MRI findings (page 7) is hard to read and should be revised.

Yes, we revised.

The histology that finally led to the diagnosis hamartoma should be described.
Some more information on hamartomas (cystic, solid, or both) might be integrated in the text.

We have changed.

The suggestion on page 12 line 24-31 is speculative and might be revised.

Are really more reports necessary to clarify the clinicopathological features of hamartomas (page 14, line 2-6) What about other hamartomas (etc. periampullary)?

Reported pancreatic hamartoma are only 30 cases, so that we think there are no decisive evidences and more information will be need. Hamartoma is a malformation and the behavior depends on the original organs where it located, so we consider that we should exclude the “periampullary hamartoma” in this report.

What does the review of the literature give us for a conclusion in the end?

We hope the revised table will be more informative for clinical diagnosis.

Reviewer #2:

The paper by Dr Matsushita et al. is a case report about pancreatic hamartoma which is rare pancreatic tumor. They described that case presentation and a review of pancreatic hamartoma.

The following suggestions would improved the manuscript:

#1. In preoperative MRI imaging study, they should describe a connection of tumor and pancreatic duct.

Yes, we think it is one of the important point in this case, the evidence of communications between the tumor and MPD was unfortunately not found.

#2. Before surgical resection, did they perform a ERCP examination and ERCP cytology? If they do this exanimation, they should report.

We performed ERCP, but there were no information for diagnosis. Tumor was not detected and there were no evidence of MPD dilation. (Data not shown)

#3. In discussion, they should consider in terms of pre-operative imaging diagnosis .

Thank you for pointing this out. We have changed the sentence as you mentioned (page 11, line 1-4).
Reviewer #3:

Thank you for the opportunity to review this manuscript. The authors describe an unusual case of a pancreatic hamartoma. I have some suggestions to further improve this manuscript prior to acceptance.

1. The conclusion on the abstract needs to be reworded instead of simply listing descriptive phrases for pancreatic hamartoma.

We have changed it.

2. Is this really true that cystic neoplasms of the pancreas are that rare. My impression is that cystic neoplasms are more common that once thought and may be underdiagnosed.

As you mentioned, IPMN is now one of the commonly benign disease of the pancreas. We have added a sentence about this point (page 6, line 6-7).

3. The included figures help augment the paper well.

4. Overall, while this is an interesting case, I think the authors need to better portray the conclusion - I don't think identifying descriptive phrases for pancreatic hamartoma is sufficient for the conclusions. The authors need to emphasize what is novel about this case, what are the key clinical take away points, why this is important to recognize, etc. The paper is well written, but the conclusion I think is severely lacking.

We thank you for pointing out of it. What we most emphasize in this paper is we could observe the morphological changes of pancreatic hamartoma. The histopathological features of pancreatic hamartoma have already been reported by several authors, so we want to demonstrate clinical findings more impressive and simply as the term of “morphological change”.

Reviewer #4:

A pancreatic hamartoma is a rare benign tumor and difficult to diagnose correctly because of the absence of characteristic differential features. In this paper, the authors described the clinicopathological features of pancreatic hamartomas. This case of a pancreatic hamartoma, which has been observed long-term, is interesting. However, a major revision of manuscript is needed before it will be acceptable for BMC Gastroenterology.

Major
The authors concluded that clinicopathological features of pancreatic hamartomas could be "well-demarcated solid and cystic tumor", "scattered normal acini and varied dilated duct size without atypia," "mature adipose tissue and fibrosis," and "chronological morphological changes." However, 3 of the features, "well-demarcated solid and cystic tumor," "scattered normal acini and varied dilated duct size without atypia" and "mature adipose tissue and fibrosis" have already been described in previous reports (Kawakami F, World J Gastrointest Oncol. 2012; Inoue H, Endoscopy. 2014). I consider it controversial to call "chronological morphological changes" a feature of pancreatic hamartomas on the base of only two cases (present case and reference 15). The authors should review other case reports in regard to possible "chronological morphological changes"

We thank the reviewer for this comment. We tried to find other reports as you mentioned, we unfortunately couldn’t any more. The term “chronological morphological changes” have not been focused so far, and we want to suggest the possibility of its clinical meaning.

(2) The authors should, if possible, describe the differential point between pancreatic hamartoma and intraductal papillary mucinous neoplasm (IPMN).

The histological findings show that this tumor is constituted mainly of normal fatty tissue, and include several dilated ducts and acinar cells. It means the origin of this tumor (hamartoma) is not the intra-duct but the parenchyma of the pancreas.

Minor

Fig. 2-g: It is better to have the arrow point to the tumor.

Thank you for pointing out of it, we have added arrows in the figures.

Reviewer #7:

The authors reported an extremely rare case of pancreatic hamartoma arising in a 68-year-old man and reviewed the literature of this rare pancreatic entity. This article is potentially important and interesting for readers of BMC Gastroenterology. However, there is plenty of room for improvement in this manuscript.

1. A total of 12 cases of pancreatic hamartoma cited in Table 2 are collected from 5 English literatures reported from Japan, including 8 cases reported by Yamaguchi et al. (Ref. 20). These 8 cases were collected from 8 hospitals in Japan, namely, it was not a single-institute experience. Therefore, the authors are required to deny any overlap between cases cited in Table 2.
We appreciate the reviewer’s comment of this point. To see the data, reference 17 and one case of reference 19 has quit similar features and these two were reported from same institution, so we think these two cases are overlapped as you mentioned and we retract reference 17.

2. There is too much repetition in the manuscript. The first paragraph in the Discussion session should be deleted.

We have deleted it.

3. The explanation of Figures 1 and 2 is obscure and confused. Arrows or arrowheads should be indicated in the Figures. In addition, there are some discrepancies in description between the manuscript and Figure Legends, e.g., "The size of the pancreatic tumor had become smaller, measuring 2.5 cm in maximum diameter" in the Text (Page 7, lines 10 to 11) and "The tumor shown is 3.9 x 3.6 cm in size" in the Figure Legends (Figure 1-b).

We added arrows in the figures and corrected the size you mentioned.

4. The multi-cystic lesion was located within a soft-tissue mass to form a pancreatic tumor and the soft-tissue mass consisted of fatty tissue based on density of CT and signal intensity of MRI. Why did the authors suppose the pancreatic tumor as to be a malignant transformation of IPMN of the pancreas?

We couldn’t deny the possibility of the mural nodule of IPMN because of the emerging nodule lesion.

5. The title of Table 1 is inadequate.

We have changed it for “Differential diagnosis of the rare cystic lesion of the pancreas”

6. Finally, the manuscript, including Tables, needs to be revised by a native English speaker with more extensive experience in medical and scientific editing before submitting the paper to the Journal

We thank for your suggestion and this manuscript was check by English speaker, again.

Reviewer #8:

The authors report the case of a 68 year-old man with a pancreatic tumor with initial benign presentation, who required surgery due to an increase in tumor size and suspicion of IPMN with malignant transformation. The tumor was classified as a pancreatic hamartoma based on its histological description (mature adipose tissue and colonization of dilated pancreatic ducts with mild fibrosis).

The case is clearly exposed and well illustrated.
However, I have some concerns regarding the clinical management and the final diagnosis:

MAJOR CONCERNS

- Regarding the initial case presentation (first paragraph): the authors describe the lesion at imaging but do not provide their initial diagnostic hypothesis to justify how they managed the patient.

Can the authors indicate what was their initial diagnosis? They indicate in the next paragraph that they had a suspicion of IPMN with malignant transformation. Was the lesion compatible with benign IPMN at baseline imaging? Was there a communication between the cysts and the pancreatic ducts at MRI that could have supported this diagnosis? If not, based on what criteria did they decide to follow-up the patient? If the nature of the lesion was uncertain and given its size > 3 cm, a biopsy under EUS could have been discussed: did the authors consider this option and can they explain why they decided not to perform a biopsy at this stage to support them in a non-invasive therapeutic strategy?

- In the second paragraph of case presentation: can the authors discuss why they decided to go directly to surgery and not to perform a biopsy at this stage (benefit/risk balance of the biopsy given the morbidity/mortality of the surgical procedure vs. risk of sample bias, fear of biopsy complication such as pancreatitis or tumor cell dissemination, typical aspect of the lesion on imaging…)?

We appreciate your significant comments.

In accordance with the initial diagnosis, the tumor was initially diagnosed benign tumor such as lipoma, dermoid cyst or the other rare benign tumor. (page 7 line 10-11)

MRCP demonstrated that there were no MPD dilation and no evidence of communication between cyst and MPD. Once we suggested EUS-biopsy for this patient, he however refused it and we couldn’t perform it.

- Regarding the final diagnosis of hamartoma: the histological description of the lesion is not typical of a hamartoma; it seems very uncommon in other reported cases to observe such an abundant adipose component within the lesion. Can the authors comment on this? Were there other cases in the literature of hamartoma with similar aspect of predominant adipose tissue? If not, the conclusion should not be so affirmative (when describing pancreatic hamartoma as "mature adipose tissue and fibrosis"). We agree that a lipoma does not typically present with trapped ducts inside the lesion and is not the most probable diagnosis. However, this presentation may be compatible with a lipomatous pseudohypertrophy (example of reported cases: Altinel D et al, Pancreas 2010; Shimada M et al, Case Reports in Gastroenterology 2010), a differential diagnosis that the authors do not discuss. Could the authors comment on
this? Can they add a paragraph in the discussion about this differential diagnosis? Can they provide the results of the CD34 and CD117 immunostaining that are typically positive in hamartoma to reinforce their diagnosis?

We read these papers. It seems that there are a lot of similarity between pancreatic hamartoma and lipomatous pseudohypertrophy. It is very important suggestion, we are sorry that we can’t explain the differential points of these two diseases at this time.

MINOR CONCERNS

- The first paragraph of the discussion is redundant with the introduction and may be deleted.
  
  Yes, we have changed it.

- The table 2 is quite buzzy. It would be valuable if the authors add a bottom line to summarize the data (median age, sex ratio, % of cases in the pancreatic head/body/tail, median size, % of positive cases for each feature…) of each column.
  
  We have changed Table 2 more simply as you mentioned. We appreciate your big help.

Reviewer #9:

Nice paper with a detailed review of the clinical features, as well as the radiographical/surgical/immunohistological features of the tumor. It was also a nice presentation of all the hamartomas reported up to date summarized in a table format. There are no major concerns. I do have the following suggestions for consideration:

I suggest mentioning that the patient did not have any symptoms (abdominal pain, post-prandial satiety or pain, malabsorption symptoms)

Yes, this case had no symptoms. We wrote it clearly at end of “CASE PRESENTATION”

Last sentence of the abstract background should read: "The tumor was then diagnosed as a pancreatic hamartoma", or "Given these findings, the tumor was diagnosed as a pancreatic hamartoma", or "A diagnosis of pancreatic hamartoma was made"

We changed the sentence for “"The tumor was then diagnosed as a pancreatic hamartoma”

Just being curious, why do you use the abbreviation of "enhanced CT" in your case presentation (ref page 6, line 56 but in your abstract/background wrote it out as "enhanced computed tomography")?
We think the abbreviations should be avoided in the ABSTRACT and the first use in the manuscript.

Fig. 1-c was not mentioned in the text.

Fig 1-c is demonstrated in the page 7 line 17 to page 8 line 2.

I would suggest adding the month (diagnosis, follow-up timeline e.g. 21 months to the Figures 1 and 2. e.g. Fig. 1-b (21mo) but the editor may have different opinion.

We thank your mention of it. We are afraid that the regulation maybe does not allow your suggested option.

Ref page 9, line 50, I would not use the word "Finally". Suggestions: "Based on the above findings, the tumor was..." or "Giving these findings, the tumor was..." of "The final diagnosis of the tumor was..."

We changed the sentence as you mentioned.

Ref page 9, line 53, may consider stating how it was determined that there was no recurrence. CT? MRI? EUS?

We follow up this case using plain CT.

Ref page 10, line 31 - instead of "non-aggressive", use "not aggressive"

We changed it as you mentioned.

Ref page 11, line 8 - suggest "There are only 30 cases of pancreatic hamartoma reported in the English literature to date (ref 4-21), including the first case reported by Anthony et al. in 1977 (ref4)"

We changed the sentence as you mentioned

Ref page 11, line 30-31 - it was not clear whether Noltenius had a case series on pancreatic hamartomas. It doesn't seem so, the way I read it sounds like it was a case series on patients with alcoholic pancreatitis but the authors suggested relationship between chronic pancreatitis and hamartomas by appearance. It just needs to be a little more clear.

As the reviewer mentioned, Noltenius’s case were seemed to be a mass forming pancreatitis and we wrote it clearly at the manuscript.

Reviewer #10:
I think this case report is worth reporting since there have not been many papers about pancreatic hamartoma. The literature review is well done in this manuscript, although their discussion doesn't add much to what is already known. Some recommendations I should like to make are as below.

1. Who rendered the pathological diagnosis of pancreatic hamartoma? Usually, at least one pathologist is involved in every final diagnosis of tumor or tumor-like lesion. Moreover, pathological diagnosis is the main point at issue. However, no pathologist is included in this paper as a co-author. The authors should put the names of pathologists in the list of authors, unless the pathological diagnosis was made only by the surgeons in this case.

   We have added the pathologist as one of the author as you mentioned.

2. Citation order of the references is wrong, e.g. the reference #3 first appears after #4 (line 40-50, page 10).

   We appreciate your kindly help and we checked all references again.

3. Figure 4-b has two histological images. It is much easier for the readers to understand the authors' intention if they are separated into Figure 4-b and 4-c.

   We changed it as you mentioned.

4. What made the lesion decrease in size 21 months after the initial visit and increase in size 7 months later? The authors' comment is "this type of chronological morphological change is likely one of the clinical features of pancreatic hamartoma". Are there any other specific considerations regarding this point?

   Our hypothesis is that the ducts exist in the tumor are obstructed accidentally and it is relieved from the obstructions accidentally. The diluted MPD, however, were never observed because the hamartoma doesn’t product any mucus and the ducts were not so large so that we couldn’t describe the communication between MPD and hamartoma.

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Editorial Requests
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Ethics:
If your study involves humans, human data or animals, then your article should contain an ethics statement which includes the name of the committee that approved your study.

If ethics was not required for your study, then this should be clearly stated and a rationale provided.

Consent:
If your article is a prospective study involving human participants then your article should include a statement detailing consent for participation.

If individual clinical data is presented in your article, then you must clarify whether consent for publication of these data was obtained.

Availability of supporting data:
BioMed Central strongly encourages all data sets on which the conclusions of the paper rely be either deposited in publicly available repositories (where available and appropriate) or presented in the main papers or additional supporting files, in machine-readable format whenever possible. Authors must include an Availability of Data and Materials section in their article detailing where the data supporting their findings can be found. The Accession Numbers of any nucleic acid sequences, protein sequences or atomic coordinates cited in the manuscript must be provided and include the corresponding database name.

Authors Contributions:
Your 'Authors Contributions' section must detail the individual contribution for each individual author listed on your manuscript.

We really appreciate for Editors to give the chance to revise this paper.

We have made changes as all reviewer mentioned and editor’s mentions above.

We apologize for late submission and we hope this revised manuscript will be improved for the publication in your journal.