Author response

December 12, 2017

Dear Editor

Thank you very much for your feedback on the manuscript entitled ‘Intraductal Papillary Bile Duct Adenocarcinoma and Gastrointestinal Stromal Tumor in a Case of Neurofibromatosis type 1’. We appreciate you taking the time to provide us with helpful comments.
We have revised the manuscript as you and the reviewers have recommended, and we agree with all of the points that you have made.
The revisions are as follows:

Comments to the Author

Reviewer #1

The report described a synchronous case of gastrointestinal stromal tumor (GIST) and intraductal papillary neoplasm of the bile duct (IPNB) in NF-1. This is rare and well organized report.

1. However it is necessary some corrections:

Answer: Thank you for your helpful comments.

2. The statement is that “regular screening for the development of GIST in NF-1 patients would be helpful” is overly disputed for case presentation. The related sentence must be deleted.

Answer: Thank you for your comments. We deleted sentence related to regular screening for the development of GIST in NF-1 patients.

3. The first paragraph, second sentence: (Fig. 1a, 1b) should be changed as (Figs. 1a, 1b) and the excess point in front of parenthesis should be deleted. (Fig. 3a, 3b) and (Fig. 4a,

4b, 4c) should be corrected as (Figs. 3a, 3b) and (Figs. 4a, 4b, 4c)

Answer: Thank you for your comments. We corrected that sentence as you pointed out.

After: An examination revealed multiple nodules over her face and body, café au lait spots on the body and limbs, and scoliosis (Figs. 1a, 1b).

4. The discussion is written with emphasis on general knowledge. It should be in the form of a discussion of previous reports.

Answer: Thank you for your comments. Based on your advice, we added contents of similar reports : case of a mixed periampullary adenocarcinoma and a somatostatinoma with a gastrointestinal stromal tumor in a similar patient. (Tewari N et al., JOP, 2014 Nov 28; 15 (6): 600-3). Coexistence of somatostatinoma and gastrointestinal stromal tumor in the duodenum. (Yamamoto R, et al Intern Med 2016: 55 (6): 617-22) Rare triad of periampullary carcinoid, duodenal gastrointestinal stromal tumor and plexiform neurofibroma at hepatic hilum in neurofibromatosis type 1: et al. (BMC Cancer, 2017 Aug 29; 17 (1): 579).

5. Figure's quality and legends are OK. Arrows should be added on the Figures 2, 3 and legends.

Answer: Thank you for your comments. We added white arrows in Figure 2,3 and legend.

Reviewer #2

This is a very interesting paper which should be published after certain revisions have been made. -The paper requires minor language polishing.

1. The case report is well described. However, the authors should mention the stage of this IPNB tumor.

Answer: Thank you for your comments. This case described very early stage of IPNB having component of invasive carcinoma arising from most high-grade dysplasia without regional organ involvement, and distant metastasis. We added this sentence in case presention.

After: This case described very early stage of IPNB having component of invasive carcinoma arising from most high-grade dysplasia without regional organ involvement, and distant metastasis.

2. Also they should report the follow up schedule after discharge, and for how long the patient is recurrence free so far.

Answer: Thank you for your helpful comments. We added the patient's follow up schedule and current status of recurrence-free. The patient is well on the outpatient clinic.

After: The patient was discharged without any postoperative complications and has remained stable for 8 months after surgery. During every 3 months follow-up after discharge, there was no recurrence on follow-up CT scan at 3 and 6 months.

3. It is true that it is a first case of NF-1 patient with coexisting intra-ductal papillary adenocarcinoma of biliary duct and duodenal GIST. However, similar oncological cases in NF-1 patients already have been published. The authors should mention the case of a mixed periampullary adenocarcinoma and somatostatinoma with a gastrointestinal stromal tumor in a similar patient. (Tewari N et al. JOP. 2014 Nov 28;15(6):600-3).

Answer: Thank you for your helpful comments. We inserted mentioned references and added sentence related to similar cases.

After: Although there were similar cases of periampullary tumors with GIST in NF-1 patients or GIST and somatostatinoma in patients with Von Recklinghausen's Disease, this is the first case in the global literature to demonstrate synchronous IPNB and GIST in a patient with NF-1.

4. Also another report with coexistence of somatostatinoma and gastrointestinal stromal tumor in the duodenum in a similar patient. (Yamamoto R, et al. Intern Med. 2016; 55(6):617-22). Also there is a recent paper entitled “Rare triad of periampullary carcinoid, duodenal gastrointestinal stromal tumor and plexiform neurofibroma at hepatic hilum in neurofibromatosis type 1: a case report”, by Abdessayet N et al. (BMC

Cancer. 2017 Aug 29; 17(1):579.

Answer: Thank you for your helpful comments. As you pointed out, we inserted mentioned references and added sentence related to similar cases.

After: Although there were similar cases of periampullary tumors with GIST in NF-1 patients or GIST and somatostatinoma in patients with Von Recklinghausen's Disease, this is the first case in the global literature to demonstrate synchronous IPNB and GIST in a patient with NF-1.

5. At the end of the Discussion the authors should add a comment about the expected prognosis of this patient after surgical excision of the tumors.

Answer: Thank you for your helpful comments. We added sentences as you pointed out

After: According to the references, the prognosis is determined by depth of invasion, component of invasive carcinoma, and grade. We expected a long recurrence-free survival because this case did not have poor prognostic factor.

6. Do they believe that the underline NF-1 disease may worsen the prognosis? Is there existing evidence how can this relation of NF-1 disease with malignant or benign tumors be explained? The authors should add a comment at the end of the Discussion.

Answer: Thank you for your helpful comments. In previous report, the effect of NF-1 on tumor prognosis has not been reported. However, considering the increased risk of developing tumors due to genetic abnormalities, the possibility that NF-1 may be associated with the prognosis of malignant tumors should be considered. We added these sentence at the end of the Discussion.

After : In addition, according to previous report, the effect of NF-1 on tumor prognosis has not been reported. However, considering the increased risk of developing tumors due to genetic abnormalities, the possibility that NF-1 may be associated with the prognosis of malignant tumors should be considered

Reviewer #3

The paper is well described, with significant images; only one observation: did the authors perform genetic test regarding NF1??

Answer: Thank you for your helpful comments. The patient who got NF-1 gene test and meet diagnotic criteria through clinical feature was diagnosed with NF-1 at the other hospital fourteen years ago. Therefore we did not consider re-test of NF-1 gene.