Reviewer #03261379:

Thank the reviewer for these precious comments concerning my manuscript entitled "Functional neuroendocrine tumor of the gallbladder with carcinoid syndrome: A case report". These comments are all valuable and very helpful for revising and improving my paper. We have studied comments carefully and have made corrections which we hope meet with approval. The response to the reviewer's comments are as follows:

Question1. Did you determine any other markers for NETs, such as serum chromogranin A, serum serotonin or urinary 5-HIAA?

Response: Indeed, it will be more convincing if we determine more markers, such as serum chromogranin A, serum serotonin and urinary 5-HIAA before surgery. However, our hospital does not provide with the laboratory examination of serum serotonin. Serum chromogranin A and 5-HIAA not be determined either.

We searched the diagnosis criteria of carcinoid syndrome and found the excessive production of serotonin is one of the diagnosis conditions. So we can't diagnosis the patient's disease as carcinoid syndrome.

However, the patient's symptom was of 2 months duration and obviously relieved at day 5 postoperatively. In addition, we ruled out immunological disease and dermatosis by the examination of antinuclear antibody titer, antibodies to double-stranded DNA, ribonucleoprotein, Sm nuclear antigen, scleroderma-70 protein, Jo-1 protein and pathological finding of the flushed skin. Therefore, his disease was suspected of carcinoid syndrome.

We changed the title "Functional neuroendocrine tumor of the gallbladder with carcinoid syndrome: A case report" to "Flushing as atypical initial presentation of functional gallbladder neuroendocrine carcinoma: case report ". We changed the phrase "carcinoid syndrome" to "distinctive manifestation" in our case.

We added discussion about the limitation "Our case report has several

limitations. First, we didn't determine levels of serum CgA, serum serotonin and urinary 5-hydroxyindole acetic acid preoperatively. So we can't diagnosis the patient's disease as carcinoid syndrome[37]. However, the patient's symptom was of 2 months duration and was obviously relieved at day 5 postoperatively. In addition, we ruled out immunological disease and dermatosis by the examination of antinuclear antibody titer, antibodies to double-stranded DNA, ribonucleoprotein, Sm nuclear antigen, scleroderma-70 protein, Jo-1 protein and pathological finding of the flushing skin. Therefore, his disease was suspected as carcinoid syndrome."

Question2. Are there any intra-operatory images available?

Response: A photograph of the resected tumor or an intra-operatory image will enhance the manuscript. However, it was a pity that the thought of taking a photo didn't struck me at that time. We provided with findings such as size of the tumor and location in the manuscript to make up the weakness. In consideration of this valuable comment, we discussed the weakness of lack of intra-operatory images in the part of discussion: "Second, our case report is lack of intra-operatory images and photographs of the resected neoplasm. We provide with size of the neoplasm and location to make up the weakness".

Question3. A discussion on the type of PET-CT to be used in NETs should be useful.

Response: Thank you for your suggestion, we added discussion about PET-CT: "^{18}F-FDG PET/CT plays an important role in defining aggressiveness of high-grade gastro-entero-pancreatic NENs and providing with prognostic information, especially when combined with ^{68}Ga-labelled somatostatin analogues PET/CT[20]. High sensitivity has been proved for PET/CT with ^{68}Ga-labeled peptides in patients with suspected NENs[21,22]. The utility of

Gallium-68-1,4,7,10-tetraazacyclododecane-N,N',N″,N‴-tetra acetic acid-D-Phe1-Tyr3-octreotate (^{68}Ga-DOTATATE) PET/CT has been discussed recently, which gives relevant information for accurate staging of gastro-entero-pancreatic NENs and selection of appropriate treatment intervention[23]. Gallium-68-1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetra acetic acid-D-Phe1-Try3-octreotide (^{68}Ga-DOTATOC) PET/CT is reported as an effective tool in the localization of unknown primary NENs[24,25].” Besides, we deleted the sentence “However, it is generally almost impossible to differentiate GB-NET from other subtypes of GB carcinoma preoperatively.”

Question4. There is an interesting comparison between gallbladder NETs and adenocarcinomas in Chen, Chen et al. “Gallbladder neuroendocrine carcinoma: report of 10 cases and comparision of clinicopathologic features with gallbladder adenocarcinoma.” International journal of clinical and experimental pathology

Response: According to your suggestion, we added discussion about the comparision of GB-NEC and GB adenocarcinoma, which refers to Chen, Chen et al’s paper:” Compared to GB adenocarcinomas, GB-NEC has a tendency of advanced disease progression at diagnosis, poor differentiation of cells and high rate of lymphatic metastases[8].”

Reviewer # 03548113:

Thank the reviewer for the approval of my manuscript entitled “Functional neuroendocrine tumor of the gallbladder with carcinoid syndrome: A case report”.

Reviewer #03388124:

Thank the reviewer for these precious comments concerning my manuscript entitled "Functional neuroendocrine tumor of the gallbladder with carcinoid syndrome: A case report". These comments are all valuable and very helpful for revising and improving my paper. We have studied comments carefully and have made corrections which we hope meet with approval. The response to the reviewer's comments are as follows:

Question1.1 The classification of neuroendocrine neoplasm was published in WHO tumor classification in 2010 and further revised in 2019. It is very important to classify the tumor into one of the two major categories: well-differentiated neuroendocrine tumor or poorly differentiated neuroendocrine carcinoma.

Response: Thank you for your reminding, we changed the discussion "According to the World Health Organization Classification of Tumors of the Digestive System in 2010, NETs are divided into three categories: G1 tumors with Ki-67 < 3%, G2 tumors with 3–20% Ki-67, and G3 tumors with > 20% Ki-67. Our patient had a G3 tumor according to the criteria, because Ki-67 was > 80% and the tumor was poorly differentiated" to "According to the 2019 World Health Organization classification of tumors of the digestive system[11], our patient had high-grade and poorly differentiated NEC, because Ki-67 index was > 80% and the carcinoma was small-cell type."

Question1.2 The manuscript mentioned NET at one place and NEC at another, and also used the phrase "poorly differentiated NET". The authors need to arrive at a correct and consistent diagnosis according to current WHO criteria.

Response: Thank you for your comment. We arrived at a consistent diagnosis "gallbladder neuroendocrine carcinoma (GB-NEC)" in the case report according

to the new criteria. And we changed the phrase "gallbladder neuroendocrine tumors (GB-NETs)" to "gallbladder neuroendocrine neoplasms (GB-NENs)" throughout, according to "the 2019 WHO classification of tumors of the digestive system." *Histopathology* 2019. Besides, we changed the word "tumor" to "neoplasm" throughout for fear of readers' misunderstanding.

Question2 Carcinoid syndrome is typically associated with well-differentiated NET. The authors need to re-review the patient's presentation and the criteria for carcinoid syndrome, to see whether he fitted the diagnosis. In particular, this patient only had flushing, and did not have diarrhea. Carcinoid syndrome is caused by excessive production of serotonin. Is there any evidence that there was elevated serum serotonin, or secretion of serotonin by the tumor cells?

Response: Thank you for your reminding and query. I am sorry that our hospital does not provide with the laboratory examination of serum serotonin. So we didn't get evidence of elevated serum serotonin or secretion of serotonin by the tumor cells.

We searched the diagnosis criteria of carcinoid syndrome and found the excessive production of serotonin is one of the diagnosis conditions. So we can't diagnosis the patient's disease as carcinoid syndrome.

However, the patient's symptom was of 2 months duration and obviously relieved at day 5 postoperatively. In addition, we ruled out immunological disease and dermatosis by the examination of antinuclear antibody titer, antibodies to double-stranded DNA, ribonucleoprotein, Sm nuclear antigen, scleroderma-70 protein, Jo-1 protein and pathological finding of the flushed skin. Therefore, his disease was suspected of carcinoid syndrome.

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carcinoid syndrome: A case report" to "Flushing as atypical initial presentation of functional gallbladder neuroendocrine carcinoma: case report ". We changed the phrase "carcinoid syndrome" to "distinctive manifestation" in our case.

We added discussion about the limitation "Our case report has several limitations. First, we didn't determine levels of serum CgA, serum serotonin and urinary 5-hydroxyindole acetic acid preoperatively. So we can't diagnosis the patient's disease as carcinoid syndrome[37]. However, the patient's symptom was of 2 months duration and was obviously relieved at day 5 postoperatively. In addition, we ruled out immunological disease and dermatosis by the examination of antinuclear antibody titer, antibodies to double-stranded DNA, ribonucleoprotein, Sm nuclear antigen, scleroderma-70 protein, Jo-1 protein and pathological finding of the flushing skin. Therefore, his disease was suspected as carcinoid syndrome."

We hope the revision meet with your approval.

Question3.1 A gross photo of the resected tumor will enhance the manuscript.

Response: A photograph of the resected tumor or an intra-operatory image will enhance the manuscript. However, it is a pity that the thought of taking a photo didn't struck me at that time. We provided with findings such as size of the tumor and location in the manuscript to make up the weakness. In consideration of this valuable comment, we discussed the weakness:" Second, our case report is lack of intra-operatory images and photographs of the resected neoplasm. We provide with size of the neoplasm and location to make up the weakness."

Question3.2 In addition, it is advisable to include AJCC TNM stage.

Response: We referred to the Eighth Edition of the AJCC Cancer Staging Manual and added the explanation"According to the Eighth Edition of the AJCC Cancer Staging Manual, the NEC in our case report is classified as T4N0M0".

Question4 The CT images are in high quality, however, patient identifier such as name should be cropped out.

Response: Thank you for your detailed review. We cropped out the patient identifier.

Question5 The authors are advised to refrain from using layman language such as "swollen" lymph node. "Enlarged lymph node" would be more professional.

Response: We reviewed and revised the language throughout the manuscript several times. And we requested a native speaker to check once again.

Question6 Please check the spelling and grammar carefully. For example, it is NSE, not NES.

Response: Thank you for your detailed review. We checked and revised the spelling and grammar throughout the manuscript.