July 11, 2017

The Editorial Office of World Journal of Clinical Case
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA

Dear Professor Giuseppe Di Lorenzo

We thank the referee for fruitful suggestion, especially for suggesting the better terms and sentences. We have revised the manuscript # 34766 on the basis of the referee's comments.

We look forward to a publication of our manuscript in World Journal of Clinical Cases.

Sincerely, yours

The original comments of the Referees are as follows.

Comment of the first referee

This report presents a case of gastric NEC possibly generated from NET component by analyzing allelic imbalance (AI) and shows unconventional carcinogenic pathway in neuroendocrine tumorigenesis. Although this case report was informative, there are points as described below to be clarified. Major or minor revision 1. In this study, AIs analyses for gastric NET and NEC were performed according to previously report for colorectal cancer. These analyses directly reflect the character or progression between NET and NEC? 2. In page 5, “adjuvant” should be deleted because of chemotherapy for recurrent NEC with liver metastasis.

Comment of the second referee

This is an interesting case of gastric neuroendocrine carcinoma showing a tumorigenic pathway. The main concern is that it is only a hypothesis and lacks further experimental or clinical validation. Emerging evidence suggest that the cellular composition of neuroendocrine carcinoma is highly heterogeneous. Thus, the authors need to be careful to get conclusions.

Comment of the tertial referee:

This is a manuscript by Uesugi N et al. reporting on a tumorigenic pathway from NET G2 to NEC. This is an interesting case report using information obtained by allelic imbalance on various chromosomes. Major points: According to the WHO 2010 classification of tumors of the digestive system Chapter: “Neuroendocrine neoplasms of the stomach” by Solcia E. et al pages 64-68, gastric Neuroendocrine neoplasms of the stomach are divided in NET

G1 and G2 and NEC (large and small cell) that are G3 lesions (see even in the same book the Chapter 1: "Nomenclature and classification of neuroendocrine neoplasms of the digestive system" by Rindi G et al. p 13-14). G3 are NECs. The authors make their own classification distinguishing G3 from NECs when according to WHO 2010 classification are the same tumors. The G2 NET is not well characterized. Is it an ECL-NET or a non-ECL-NET? Which are the features of the adjacent to the tumor mucosa? Which are the CgA and gastrin blood levels before the surgery? If the tumor is an ECL-NET which is the type of the tumor (e.g. type 1 or 3?). I suggest to immunostain the lesion with VMAT2 (indirect ECL marker) which would be of importance for the characterization of the tumor. Which are the endoscopical features of the tumor and the adjacent to the tumor oxyntic mucosa? Are their signs of chronic atrophic gastritis type A or intestinal metaplasia? Is Helicobacter pylori staining available?

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

Response for the first referee

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1. We think these microsatellite markers using analysis for allelic imbalance are useful for detecting allelic imbalance in gastric cancers, not only for colorectal cancers. Indeed, we previously reported several research articles for allelic imbalance using same microsatellite markers in gastric carcinomas (Sugai T, Habano W, Jiao YF, Toyota M, Suzuki H, Tsukahara M, Koizuka H, Akasaka R, Koeda K, Wakabayashi G, Suzuki K. Molecular analysis of single isolated glands in gastric cancers and their surrounding gastric intestinal metaplastic mucosa. Oncol Rep. 23; 25-33: 2010). Although allelic imbalance in gastric NET and NEC are not necessarily established, we think that these markers are sufficient to exact for the molecular pathway of gastric NET and NEC.

Thus, we replace the reference into report for gastric carcinomas (reference [3], with underlined).

2. We deleted "adjuvant" in line 20 of page 5, according to referee's suggestion.

Response for the second referee

Although it is impossible for further experimental and clinical validation, we carefully discussed the tumorigenic pathway of this case in consideration with heterogeneity of tumor components.

Response for the tertial referee

We supposed this case as non-ECL-NET, because surrounding mucosa show chronic atrophic gastritis with intestinal metaplasia, but not type-A gastritis and no endocrine-cell micronest. CgA and gastrin blood levels before the

surgery were not measured. Although Giemsa staining was performed to detect Helicobactor pylori for biopsy specimen, it is negative for Helicobactor pylori.

Thus, we put additional some sentences into (1) line 17-20, page 5 in “Case Report”, (2) line 1-3, page 7 in “Pathological findings”, (3) line 17-21, page 9 in “Discussion”.