Thank you very much for reviewer's helpful comments. We tried to edit the manuscript according to reviewer's comments. Please find our response to reviewer's specific comments

Reviewer #1

Thanks for allowing me to review this manuscript. 1. The patient was diagnosed advanced cancer in colon with hematogenous metastasis in the liver, lung, bones, peritoneum, supraclavicular lymph node, and the authors did not describe the metastasis lesions in lung in detail. Regarding the lung is the second most common organ for the neuroendocrine neoplasm after the gastrointestinal tract, please present more details to distinguish the lesions in lung were primary or secondary neuroendocrine cancer. 2. Please discuss the drug therapy for this patient and patients diagnosed large cell neuroendocrine carcinoma with synchronous adenocarcinoma of the colon.

Answer)

Thank you for your kind comments.

In this case, chest CT showed tiny nodule which is suspected as metastic lesion in right lung upper lobe. We added details about metastatic lung lesion in the "imaging examination" paragraph.

We added the drug therapy for this patient and patients who diagnosed large cell neuroendocrine carcinoma with synchronous adenocarcinoma of the colon in Discussion.

Reviewer #2

The authors reported a case of Silent advanced large cell neuroendocrine carcinoma with synchronous adenocarcinoma of the colon. I think however that there are a few improvements that should be made. 1. The definition, epidemiology, diagnosis, symptoms, signs and diagnostic imaging of LCNEC can be appropriately introduced in the introduction 2. CgA and synaptophysin are necessary for diagnostic confirmation but proliferative index of Ki-67 and mitotic index are necessary for prognostic information. What was the result of CgA and proliferative index of ki-67?

3. The readers should be interested in the treatment strategy for LCNEC with synchronous adenocarcinoma. The authors should discuss treatment strategies appropriately in Discussion.

Answer)

Thank you for your kind comments.

1. We added the definition, diagnosis, symptoms and diagnostic imaging of LCNEC in the introduction. Since LCNEC is a very rare disease, it is difficult to find out the epidemiology. And the symptoms and signs of colorectal LCNEC are not different from those of conventional colonic adenocarcinoma.

2. LCNEC showed positive for synaptophysin. However, CgA was negative. As you know, neuroendocrine tumors of the gastrointestinal tract are sometimes negative for CgA. The mitotic index/10HPF was >30 and the Ki-67 index(%) was 65.7%, suggesting a poor prognosis. We added these details in pathologic report paragraph.

3. We added the treatment strategy for LCNEC with synchronous adenocarcinoma in Discussion.

Reviewer #3

The authors reported a rare case with synchronous large cell neuroendocrine carcinoma (LCNEC) and adenocarcinoma in the colon. The patient did not complain any symptom even with anemia (Hb 5.1g/dL) and refused systemic chemotherapy. The survival more than three months has been confirmed. The synchronous tumors with neuroendocrine neoplasms are reviewed and the association is discussed (Rafael Parra-Medina, PLOS One 2019). Colonic LCNEC combined with adenocarcinoma in the colon is very rare condition, and only a few case reports have been published (Mohapatra S, J Surg Case Rep 2016). One of the discussion issues is pathogenesis of the synchronous tumors. In this case presentation, further histological and genetic analysis is required. Another critical point is treatment. Systemic chemotherapy is recommended but he refused. The survival term without chemotherapy will give us very important information. Small points This patient did not complain any symptom even though he had severe anemia. “Silent advanced large cell neuroendocrine

carcinoma……" was quite strange. Red blood cell count and reticulocyte count will be informative to discriminate chronic or acute anemia. In laboratory tests, is neuron specific enolase (NSE) measured?

Answer)

Thank you for your kind comments.

We added the results of immunohistochemical staining for CK20 on colonic LCNEC and colonic adenocarcinoma to the discussion.

In laboratory tests the red blood cell count was 3.35 x 100^{3}/μl and the reticulocyte count was 2.04% , so it was considered chronic anemia. Unfortunately, NSE was not measured.

Reviewer #4

The case study: (Silent advanced large cell neuroendocrine carcinoma with synchronous adenocarcinoma of the colon: A case report) presents a interesting study of this very rare case in the colon, yet there few points to be addressed before publication:-Ethics committee approval and patient consent: mention number/date of the consent.-Case summary: How did you determine if the liver, lung, bone and lymph node metastases were LCNEC? -Discussion: "Kato et al.reported a CK20 positive (a common marker found in colorectal adenocarcinoma) large cell NET that occurred synchronously to colorectal adenocarcinoma, suggesting different types of gastrointestinal neoplasm might originate from a common stem cell clone which might share a similar genetic mutation(s) during early oncogenesis." LCNEC tumor cells are identified by immunohistochemical stain for CK20 is recommended for more confirmation of the case.

Answer)

Thank you for your kind comments.

Ethics committee approval and patient consent:

- We added Ethics committee approval of our institution in end of Introduction.
- We added patient consent(date of the consent mention number) at Title page.

Case summary: How did you determine if the liver, lung, bone and lymph node metastases were LCNEC?

- Considering of colonoscopy and abodominopelvic computed tomography, LCNEC at ascending colon was considered as an advanced carcinoma. And adenocacinoma of S-colon had pedunculated polypoid morphology which is suspected as an early stage cancer. Therefore, liver, lung, bone and lymph node metastasis was thought to be result from LCNEC.

Discussion: LCNEC tumor cells are identified by immunohistochemical stain for CK20 is recommended for more confirmation of the case.

- In our patient, an immunohistochemical stain for CK20 was performed on colonic LCNEC and colonic adenocarcinoma, and both were confirmed to be immunoreactive, supporting the theory of kato et al. And We added the mentioned content and images to discussion and figure respectively.