

Peer Review File

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Reviewer A

1. “Would recommend highlighting with greater focus the novelty in this case report.”

Authors’ Response: We agree with the reviewer’s suggestion that there should be a more detailed presentation of the novelty of our case. We have added the following to the report:

“For our patient, the novelty in his treatment and current outcomes are related to the finding of LCNEC incidentally and early prior to the rapid metastasis to additional organs indicated by other reports.⁵ In addition, previous reports also indicated a need for further research and data discussing the standardization of treatment for patients diagnosed with LCNECs⁷. In lieu of this, our study highlights a potential standardized treatment modality via the combination of both ENETS and NANETS consensus guidelines with a minor change to replace cisplatin with carboplatin further emphasizing the novelty in our report^{10, 11}.”

2. “Furthermore, it would be valuable for the authors to explain why carboplatin/etoposide was offered over cisplatin/etoposide in curative intent setting such as this one. Perhaps rationale behind this recommendation maybe discussed further.”

Authors’ Response: We agree with the suggestion that a more formal rationale should be provided for this decision, and we have attempted to provide a concise and coherent reasoning for the treatment modality as follows:

“Post operative management of LCNECs may also include Cisplatin as an alternative to Carboplatin.¹⁰ The GI conference committee considered Cisplatin instead of Carboplatin, but proposed Carboplatin in light of it being less nephrotoxic with less neurological sequelae.”

3. “Furthermore, was adjuvant radiation considered? I understand a lot of these decisions are made at multidisciplinary conferences; however, an explanation would add value to the manuscript.”

Authors’ Response: This is a great question from the reviewer. There were no significant talks of adjuvant radiation in this case given guidelines and the successful hemicolectomy. We have added the following to the write-up: “For this patient, adjuvant radiation was not considered given current guidelines and the successful hemicolectomy,”

Reviewer B

1. In order to describe the NEC further, please describe the histology more thoroughly. Did you perform NGS?

Authors' Response: The reviewer makes a good suggestion here. We have revised our manuscript to include a more detailed histological perspective as follows:

“As a result of the positive screening test, a colonoscopy was performed, and biopsies were conducted along the proximal to distal length of the colon. Cells collected from a sample obtained within the proximal ascending colon were identified to be malignant. These cells demonstrated positively for pankeratin, synaptophysin, and dim CDX 2. Additionally, there were negative for CK 7, CK 20, chromogranin, PSAP, TTF-1, and GATA3. The Ki-67 proliferative index of this sample was approximately 75%. Further, within the distal ascending colon, biopsy indicated a separate, detached fragment of neuroendocrine carcinoma that was morphologically similar to the biopsy obtained from the proximal ascending colon. It also stained positively for synaptophysin and negatively for CK 7, CK 20, and chromogranin. The Ki-67 proliferative index in this biopsy sample was approximately 70%. Pathology further indicated the distal ascending colon biopsy was a detached fragment from the tumor within the proximal ascending colon biopsy and not a secondary site of the tumor.”

“The final report indicated that the large cell neuroendocrine carcinoma was a unifocal tumor approximately 3.6 X 3.1 X 1.1 cm in size. It invaded transmurally through the muscularis propria extending into the serosal fat, which was all resected during the operation. Histologically, the tumor had a mitotic rate of 40/10 hpf with a Ki-67 index of 70% in agreement with previously biopsied samples. Additionally, the 4/18 regional lymph nodes contained metastatic LCNEC with 2 additional larger lymph nodes showing focal extranodal extension of the tumor into the adjacent fat. All 6 identified lymph nodes were resected during the procedure. Final diagnosis by pathology indicated a poorly differentiated stage IIIA (T3, N1, M0) LCNEC of the right ascending colon with Ki 67 index at 70%.”

2. You describe that you include both ENETS and NANETS guidelines - how do the two different guidelines diverge?

Authors' Response: This is an excellent suggestion from the reviewer. In our revision, we included more specific differences between the guidelines as follows:

“ENETS and NANETS consensus guidelines follow a similar algorithm to initial evaluation and staging of the NEC^{11, 13}. According to both guidelines, colonoscopy, biopsy, and imaging should be conducted^{11, 13}. NANETS recommends Colonoscopy, CT, MRI, and Octreotide scintigraphy¹³. Whereas ENETS recommends Colonoscopy, CT, MRI, and FDG-PET be performed for

initial imaging¹¹. In our patient, we performed all of these tests except for Octreotide Scintigraphy. Both NANETS and ENETS suggested evaluation of heart, liver, and kidney function as well as pathology to look for Synaptophysin, Chromogranin A, and Ki-67^{11, 13}.”

“. Regarding follow-up, the guidelines differ slightly, ENETS recommends 3-month follow-up while NANETS recommends 3 to 6 months after resection with a shift to every 6 to 12 months for at least 7 years^{11, 13}.”

Reviewer C

Case Presentation:

1. “What was the approach for the right hemicolectomy? Open/laparoscopic/robotic?”

Authors’ Response: The reviewer made a great suggestion for revision. We have provided a more detailed account of the surgical procedure as follows:

“As per treatment guidelines, our patient was scheduled for a right hemicolectomy with ileocolic anastomosis. The procedure robotic surgery involved optical entry into the RUQ and subsequent robotic working ports into the LUQ utilizing a TAP block with Exparel and general anesthesia. During the operation, the mesentery was divided into the proximal transverse colon and dissected superiorly from inferior to the hepatic flexure. A second dissection plane was established via approach from inferior to the ileocolic vessel communicating to the first dissection plane. The mesentery of the small bowel was dissected by approximately 15 cm. Once removed, the segment of the right ascending colon was sent to pathology for final evaluation.”

2. “What was the extent of the lymphadenectomy? D2 vs D3 and what are the authors recommendation given that the pre-operative scan showed prominent ileocolic lymph nodes. Would be nice if the authors could include a surgical specimen photograph.”

Authors’ Response: The reviewer brought up an important point for discussion regarding the lymph nodes. We have provided a more detailed account of the lymph node findings during the surgical procedure as below. Unfortunately, there is no photograph of the surgical specimen, so we cannot include a picture of it.

“Additionally, the 4/18 regional lymph nodes contained metastatic LCNEC with 2 additional larger lymph nodes showing focal extranodal extension of the tumor into the adjacent fat. All 6 identified lymph nodes were resected during the procedure.”

3. “What is the short term outcome of the patient? any post operative complications?”

Authors' Response: This is a great question. We have updated our manuscript to reflect any outcomes and postoperative complications as follows:

“The patient, to date, has completed six full rounds of Carboplatin and Etoposide. Physical examination and ROS findings were unremarkable outside of changes to bowel habits associated with surgery. The patient has made a full return to all pre-disease performance without restriction as indicated by the PE Performance Scale: ECOG Performance with a grade scale score of zero.”

4. “Can the authors elaborate what immunostains were performed and given the rarity of this tumor would be good to include the histological slides”

Authors' Response: Thank you for the comment on the immunostains. Specifics regarding the stains used by pathology are not available to us. Regarding what was found histologically, this was added to the manuscript to provide more detail to this section:

“These cells demonstrated positively for pankeratin, synaptophysin, and dim CDX 2. Additionally, there were negative for CK 7, CK 20, chromogranin, PSAP, TTF-1, and GATA3. The Ki-67 proliferative index of this sample was approximately 75%. Further, within the distal ascending colon, biopsy indicated a separate, detached fragment of neuroendocrine carcinoma that was morphologically similar to the biopsy obtained from the proximal ascending colon. It also stained positively for synaptophysin and negatively for CK 7, CK 20, and chromogranin. The Ki-67 proliferative index in this biopsy sample was approximately 70%.”

Discussion and Conclusion

5. “The authors should discuss their approach to surveillance for this patient. - what is the interval for CT PET / colonoscopy / serum markers such as CGA and for how long ? 5 years vs 10 years.”

Authors' Response: We appreciated this suggestion. Specific guidelines regarding follow-up are not established. However, these are the guidelines we utilized to dictate our follow-up schedule, and have added to manuscript:

“Regarding follow-up, the guidelines differ slightly, ENETS recommends 3-month follow-up while NANETS recommends 3 to 6 months after resection with a shift to every 6 to 12 months for at least 7 years^{11, 13}.”

6. “Should expound on the ENETS and NANETS guidelines and which points are combined and the rationale for doing so.”

Authors' Response: We agree with the reviewer. As such, we included a more thorough and detailed breakdown of the guidelines.

“ENETS and NANETS consensus guidelines follow a similar algorithm to initial evaluation and staging of the NEC^{11, 13}. According to both guidelines, colonoscopy, biopsy, and imaging should be conducted^{11, 13}. NANETS recommends Colonoscopy, CT, MRI, and Octreotide scintigraphy¹³. Whereas ENETS recommends Colonoscopy, CT, MRI, and FDG-PET be performed for initial imaging¹¹. In our patient, we performed all of these tests except for Octreotide Scintigraphy. Both NANETS and ENETS suggested evaluation of heart, liver, and kidney function as well as pathology to look for Synaptophysin, Chromogranin A, and Ki-67^{11, 13}. Consensus guidelines regarding treatment suggest surgical resection of the malignancy with routine follow-up and monitoring via FDG uptake on PET scan as well as colonoscopy on a 1-to-2-year basis¹⁴. In patients with non-small cell NECs, surgery provided increased overall survival with a median of 21 months as opposed to those who did not undergo surgery with a median of 6 months ($p < 0.0001$)¹². Additionally, management post-operatively may include adjuvant chemotherapy with either Cisplatin or Carboplatin and Etoposide for 4-6 cycles¹⁰. Regarding follow-up, the guidelines differ slightly, ENETS recommends 3-month follow-up while NANETS recommends 3 to 6 months after resection with a shift to every 6 to 12 months for at least 7 years^{11, 13}.”

7. “Short follow-up length of 5 months is too early to have a meaningful discussion on oncological outcome and should be mentioned.”

Authors’ Response: This is a great point to make, and we have included a response within the manuscript to highlight that fact as follows:

“It is important to note, however, that our case report is only acknowledging a short-term perspective of 5 months, and as such, longer-term oncological outcomes are unknown.”