Reviewer 02729829

The manuscript describes well the characterictics, clinical and pathological picture, and also the therapy of a rare duodenal tumor. I would be interested in some technical details, if they are available in the articles, namely the local excision of the tumor, especially in the second part of the duodenum. How the duodenotomy opening was closed in the reviewed articles? Whether a jejunal loop was used?

Author's response: Thank you for your comments. I would be interested to know exactly how all the local excision were performed. Unfortunately, none of these details were provided in the articles.

Reviewer 00058446

Comments to Authors:

Gangliocytic paraganglioma (GP) is a rare tumor of uncertain origin most often located in the second portion of the duodenum, which is composed of three cellular components: epithelioid endocrine cells, spindle-like/sustentacular cells, and ganglion-like cells. GPs are the malignant potential and usually restricted to the duodenal submucosa, a small but significant proportion demonstrates metastasis. Even with distant metastatic disease, patients seem to generally have a good prognosis according the reports. But the rarity of this tumor has made it difficult to determine a standard of care, especially for patients with metastatic lesion. The author's aim was to characterize the behavior of cases of GP with regional lymph node metastasis to help guide diagnosis and management.

(1) Is there any reliable risk factor or molecular biomarkers for GP progression and follow-up?

Author's response: As discussed in Paragraphs 2 and 3 of the Discussion, many factors (Bcl-2, p53, proliferative index, mitotic index, and necrosis) have been considered and not shown to be indicators of progression. As discussed, mast cell infiltration has also been considered. As such, we stained for mast cells (CD117 surrogate marker) in the current case and were not able to corroborate mast cell infiltration as a useful marker (This statement was added to the end of Paragraph 3 of the Discussion). The only feature that seems to be an indicator for progression/metastasis is primary tumor extending beyond the submucosal layer. We discuss these findings in the mentioned paragraphs as well.

(2) Which kind of surgical treatment is suitable for GP with regional lymph node metastasis?

Author's response: In the final paragraph of the Discussion, we have more clearly stated our recommendations, as well as added Table 3 to quickly summarize them. In brief, we advocate every effort to achieve a complete surgical resection. Pancreaticoduodenectomy should be performed if the tumor is in such a location that local resection is not possible (i.e. would compromise blood flow to the pancreas). If tumor location permits, local resection is adequate. We do not promote aggressive lymph node dissection, beyond the removal of suspicious lymph nodes. For surgically unfit patients or cases in which a complete resection will not be achieved, we promote medical management with somatostatin analogues. When possible, tumor debulking should be attempted.

(3) Is the FNA of this tumor necessary before planning surgical treatment?

Author's reponse: In the final paragraph of the Discussion, as well as the added Table 3, we have clarified our recommendations for FNA biopsy. In brief, we believe cytology evaluation should be attained in the event of a peripancreatic tumor to rule out pancreatic adenocarcinoma, and thus the need for neoadjuvant therapy. In the case of tumors away from the pancreas, the determination for cytology evaluation should be made on a case-by-case basis.

Reviewer 00077376

This is an interesting case report and collective review of previous case reports on paraganglioma with lymph node metastasis. The followings are my comments.

(1) In your case, was resection of hepatic artery performed. If it is ture, please explain its reason and which hepatic artery, common, right or left, is resected. Additionally, is the resected hepatic artery reconstructed?

Author's response: The hepatic artery lymph node was resected, not the hepatic artery itself. In the Case Presentation section, the words "lymph node" were inserted after "hepatic artery" to make this clearer.

(2) In figure 1 [now Figure 3], the letters of A and B are unclear.

Author's response: The letters "A" and "B" were adjusted.

(3) Figure 2 appearing after the sentence of lymph node metastasis should be figure 3.

Author's response: "(Figure 2 [now 4])" was deleted from this sentence, and "(Figure 2D [now 4D])" was added to the end of the preceding sentence, as it is referring to CD117 staining within the primary tumor.

(4) Figure 2 appearing after the sentence of lymph node metastasis should be figure 3.

Author's respons: Repeat; please see (3) above.

(5) The following descprition, "Metastases stained similarly to the primary with regard to S-100, chromogranin, and synaptophysin, but stained negatively for calretinin (Figure 3)", is not acceptable, because figure 3 does not contain special staining photos.

Author's response: "(Figure 3)" was removed from the end of this sentence and moved to the end of the preceding sentence. The caption of Figure 3 [now Figure 5] was changed to indicate that the pictomicrograph depicts a "representative" lymph node metastasis.

(6) In Table 1, the case of Henry et al. (2003 50 M) seems to me that lymph node metastasis was not found but that manubrium is only the metastatic site.

Author's response: This is correct. Thank you for pointing out the necessity for clarification. While our focus was on lymph node metastases, we felt in necessary to include this remarkable case as well. Changes were made throughout the paper to reflect that while 31 cases are reported on, one of the cases had only bony metastases identified. The title of Table 1 was also altered to indicate the includion of all cases with metastatic disease.

(7) If the authors summaraize the histopathological findings in Table 2, it will be much easier to understand the features of this tumor.

Author's response: Table 2 (referenced at the beginning of the "Histopathological findings" section in the Discussion) is created, summarizing the general, clinical, gross, and histologic features for this described group of patients with metastatic tumor.

Additional changes made:

1. An author was added to the manuscript, and authors order was rearranged.
2. Author contributions, IRB, informed consent, and conflict of interest statements were added per manuscript formatting requirements.
3. The abstract was formatted into a single paragraph, and the general sentence about immunohistochemical stains was deleted to shorten the text.
4. Additional follow-up time was added to the current case.
5. FNA findings from the current case were added to the case presentation and Table 1. Discussion, Paragraph 9: case numbers were changed to reflect the added FNA case.
6. CT finding from the current case were added to the case presentation.

7. Table 1 was reformatted per publications standards (removed shading and adjusted lines) and “location” column was edited to abbreviate the word “duodenum” as per the footnotes. Additionally, the title was altered as discussed above.
8. Figures were added depicting CT (Figure 1) and FNA (Figure 2) findings.
9. Referrences are edited, as well as added to Table 1.
10. A “Comments” section is added per publications requirements.
11. Results, Paragraph 1: language regarding regional lymph node involvement versus systemic metatstatic disease was slightly altered to reflect the subtle difference between these two disease states.
12. Additional very minor changes are made throughout.