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Multifocal diffuse large cell neuroendocrine carcinoma of the colon

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1st Editorial decision
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Ref.: Ms. No. JCTRes-D-22-00035
Multifocal Diffuse Large Cell Neuroendocrine Carcinoma of the Colon
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Dear Dr Goksoy,

Reviewers have now commented on your paper. You will see that they are advising that you revise your manuscript. If you are prepared to undertake the work required, I would be pleased to reconsider my decision.

For your guidance, reviewers' comments are appended below.

If you decide to revise the work, please submit a list of changes or a rebuttal against each point which is being raised when you submit the revised manuscript. Also, please ensure that the track changes function is switched on when implementing the revisions. This enables the reviewers to rapidly verify all changes made.

Your revision is due by May 29, 2022.

To submit a revision, go to https://www.editorialmanager.com/jctres/ and log in as an Author. You will see a menu item call Submission Needing Revision. You will find your submission record there.

Yours sincerely

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Reviewers' comments:

Reviewer #1: The manuscript describes an interesting case of Large cell NEC of the colon, which is reported to be multifocal. It is reported therefore as the first case of multifocal large cell NEC. The manuscript is well-written and the discussion provides a proper review of the literature. Several elements need however to be clarified.

*The authors report that 3 tumors were objectified, and they were reported as mutlifocal, which implies that their occurrence was potentially independent. However, all 3 tumors were found in the sigmoid colon, and this raises the question of whether it is simply the same tumor that induced tumor cells seeding in the same region. As this cancer is very aggressive and has the ability to disseminate rapidly, the contiguous tumors may be extentions of the primary tumor. Did the tumors share the same histopathological characteristics, or were there any differences to support the mutlifocal aspect.

*The case presentation requires some clarifications:

oThe colonoscopy confirmed the presence of a necrotic tumor in the sigmoid. Were the other 2 tumors visible during colonoscopy? And was the whole colon inspected for the presence of other tumors in the right and transverse colon?

oSince fatty liver degeneration was noted on CT scan, was another hepatic imaging technique performed (e.g. MRI) to rule out metastasis as CT may not be able to detect them.

oWere any immunohistochemical markers assessed on the endoscopic biopsy samples to help orient the diagnosis before surgery.

*A TEP-scan was performed one month after surgery, but the reason is not mentioned, as this imaging is not routinely performed that early during follow-up. If it was because of a suspicion of a metastatic disease, it would be interesting to report when metastatic lesions were first suspected after surgery.

*It would relevant to discuss in the discussion the potential role of neoadjuvant therapy with this disease, was it previously described or considered?

Authors’ response

First of all, I would like to thank you for your interest in our article and the Reviewers for their valuable comments and contributions.

Reviewers' comments:

Reviewer #1: The manuscript describes an interesting case of Large cell NEC of the colon, which is reported to be multifocal. It is reported therefore as the first case of multifocal large cell NEC. The manuscript is well-written and the discussion provides a proper review of the literature. Several elements need however to be clarified.

*The authors report that 3 tumors were objectified, and they were reported as mutlifocal, which implies that their occurrence was potentially independent. However, all 3 tumors were found in the sigmoid colon, and this raises the question of whether it is simply the same tumor that induced tumor cells seeding in the same region. As this cancer is very aggressive and has the ability to disseminate rapidly, the contiguous tumors may be extentions of the primary tumor. Did the tumors share the same histopathological characteristics, or were there any differences to support the mutlifocal aspect.

Response to this comment

There is not a clear definition of the necessary minimal distance between colonic NECs to distinguish a double tumor from a satellite lesion. In a study of appendiceal NETs, a 5mm distance was used for multifocality (doi: 10.1177/1066896919845048). In our case, according to the histopathology results, three different polypoid masses were detected 2cm apart, which were not continuous with each other. On the other hand, the histomorphological characteristics of all three tumors are exactly the same. Therefore, they may have developed due to cultivation. However, we interpreted it as multifocal because three masses were seen far from each other.

oThe colonoscopy confirmed the presence of a necrotic tumor in the sigmoid. Were the other 2 tumors visible during colonoscopy? And was the whole colon inspected for the presence of other tumors in the right and transverse colon?

Response to this comment

The patient's colonoscopy was complete (examined up to the cecum). The other two tumors were not seen, frankly, this region may not have been carefully examined since surgery was already planned due to the mass in the sigmoid colon. However, other colon segments were carefully examined.

oSince fatty liver degeneration was noted on CT scan, was another hepatic imaging technique performed (e.g. MRI) to rule out metastasis as CT may not be able to detect them.

Response to this comment

If there is a suspicion of metastasis in the liver on CT performed for preoperative staging, then we apply MRI. Since this patient was an overweight patient (BMI was 39 kg/m2) , we did not evaluate fatty liver as a suspected metastasis, so no further imaging was performed.

oWere any immunohistochemical markers assessed on the endoscopic biopsy samples to help orient the diagnosis before surgery.

Response to this comment

No. Colonoscopic biopsy examination was performed at another hospital, and the biopsy result was reported as a "malignant epithelial tumor". Honestly, we didn't think about doing a biopsy again.

*A TEP-scan was performed one month after surgery, but the reason is not mentioned, as this imaging is not routinely performed that early during follow-up. If it was because of a suspicion of a metastatic disease, it would be interesting to report when metastatic lesions were first suspected after surgery.

Response to this comment

Since the postoperative histopathology result was reported as NEC, PET scan was requested by oncologist to evaluate systemic metastasis. Due to the extremely rare and aggressive nature of NEC. Since we did not expect such a result before, we thought that CT was sufficient.

*It would relevant to discuss in the discussion the potential role of neoadjuvant therapy with this disease, was it previously described or considered?

Response to this comment

Added information to the discussion section.

There are studies of neoadjuvant therapy in NECs of other organs and promising results continue to be published.

Such as;

Locally advanced NECs of stomach (doi: 10.1007/s00432-020-03214-w), cervix (doi: 10.21873/anticanres.15250), breast (doi: 10.1097/MD.0000000000022652), rectum and anal canal (doi: 10.1097/COC.0000000000000211)

However, we could not find any information in the literature regarding neoadjuvant therapy in NECs of the colon.

The study by Fields et al using the National Cancer Database (NCDB) (1208 colorectal high grade NEC in total) is the largest ever. However, unfortunately, there is no information about neoadjuvant therapy in the study.

According to the results of this study:

→In patients with localized disease, 5-year survival was 0% for patients not receiving chemotherapy or surgery, 15.9% for patients receiving only chemotherapy, 31.7% for patients receiving only surgery, and 37.0% for patients receiving both surgery and chemotherapy ($p < 0.001$)

→In patients with metastatic disease, 5-year survival was 0% for patients not receiving chemotherapy or surgery, 1.6% for patients receiving only chemotherapy, 3.7% for patients receiving only surgery, and 6.1% for patients receiving both surgery and chemotherapy ($p < 0.001$)

2nd Editorial decision
01-May-2022

Ref.: Ms. No. JCTRes-D-22-00035R1
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Dear authors,

I am pleased to inform you that your manuscript has been accepted for publication in the Journal of Clinical and Translational Research.

You will receive the proofs of your article shortly, which we kindly ask you to thoroughly review for any errors. Please make a note to correct the color designation of the arrow in Figure 1A (blue instead of white). Also, it would benefit the article if the figures could be augmented. For example, the panels in Figure 1 were laterally compressed, which reduces the esthetics. Also, the H&E histological panels are color-saturated. These could be easily improved in Photoshop or other image editing software.

Thank you for submitting your work to JCTR.

Kindest regards,

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Comments from the editors and reviewers: