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Dear Dr. Yuang Qi:

Thank you for your careful review and excellent criticisms of the manuscript entitled, "Limited, local, extracolonic spread of mucinous appendiceal adenocarcinoma after perforation with formation of a malignant appendix-to-sigmoid fistula" by authors: Seifeldin Hakim, Mitual Amin, Mitchell S. Cappell and Kiran Nandalur-minor-author-for-radiology submitted as a CASE Report as manuscript # 28692 to World Journal of Gastroenterology. The manuscript has been entirely revised, as per the reviewers' comments as follows:

**1. Reviewer's code: 02440510**

**COMMENTS TO AUTHORS**

This is an interesting presentation of a Case Report with literature review in which is evaluated limited, local, extracolonic spread of mucinous appendiceal adenocarcinoma after perforation with formation of a malignant appendix-to-sigmoid fistula. The main limitation of this article is the fact that this is presentation of Case Report which has generally limited scientific impact. However, the authors treated a very important topic, the manuscript is well organized and written and all limitations are mentioned in the manuscript.

Response: No changes required.

**2. Reviewer's Code: 03035498**

**COMMENTS TO AUTHORS**

There are some minors changes that should be made:

1. Abstract, page 4: "The primary tumor was surgically debulked": please state the exact surgical procedure performed.

**CHANGE TO:**

The abdominal mass was removed en-bloc including resection of sigmoid colon, cecum, appendix, and minimal amounts of anterior abdominal wall; and shaving off of small parts of the walls of the urinary bladder and small bowel.

**FROM:**

The primary tumor was surgically debulked.

2. "The patient did well during...with no clinically evident...": please add radiological also for more clarity.

CHANGE TO:

The patient did well during 1 year of follow-up with no clinical or radiologic evidence of local recurrence, metastases, or pseudomyxoma peritonei

FROM:

The patient did well during 1 year of follow-up with no clinically evident findings of local recurrence, metastases, or pseudomyxoma peritonei

3. "This case dramatically illustrates...": please remove "dramatically".

CHANGE TO:

This case illustrates

FROM:

This case dramatically illustrates

4. Core tip, page 4: "The patient presented with RLQ...": please expand RLQ.

CHANGE TO:

The patient presented with right lower quadrant

FROM:

The patient presented with RLQ

5. Case report, page 6: "The abdominal mass was resected". Please state the exact surgical procedure performed (example: enbloc right colectomy with sigmoid resection...).

CHANGE TO:

The abdominal mass was removed en-bloc, including resection of sigmoid colon, cecum (with preservation of ileocecal valve), appendix, right vas deferens, testicular vessels, and minimal amounts of anterior abdominal wall; and shaving off of small parts of the walls of the urinary bladder and small bowel.

FROM:

The abdominal mass was resected.

6. "the patient developed postoperative ileus from which he slowly recovered": please remove slowly or explain exactly when the ileus disappeared.

CHANGE TO:

The patient developed postoperative ileus from which he recovered,

FROM:

The patient developed postoperative ileus from which he slowly recovered,

7. Please remove "while tolerating normal diet": it is obvious that a patient would tolerate normal diet if he recovered.

CHANGE TO:

and was discharged 11 days postoperatively.

FROM:

and was discharged 11 days postoperatively while tolerating a normal diet.

8a. Discussion, page 7: "no cases of distant lymphatic...": for clarity, please modify the sentence: "No cases of distant lymphatic or hematogeneous metastases were reported by "author et al." ..."

CHANGE TO:

No cases of distant lymphatic or hematogenous metastases were reported by Nitecki et al.<sup>[2]</sup> among 52 patients with MAA,

FROM:

No cases of distant lymphatic or hematogenous metastases occurred among 52 patients with MAA,

8b. The same for "ovarian involvement..."

CHANGE TO:

However, ovarian involvement from MAA is common in females; among 23 female patients undergoing oophorectomy reported by Nitecki et al.<sup>[2]</sup>, 13 had ovarian involvement.

FROM:

However, ovarian involvement from MAA is common in females; 13 of 23 female patients undergoing oophorectomy had ovarian involvement<sup>[2]</sup>.

9. Page 8: please remove dramatically.

CHANGE TO:

The current case illustrates the nonaggressive biologic behavior of this low-grade malignancy.

FROM:

The current case dramatically illustrates the nonaggressive biologic behavior of this low-grade malignancy.

10. Comments, page 10: expand RLQ.

CHANGE TO:

The differential diagnosis based on patient history of right lower quadrant abdominal pain and constipation for 9 months, and physical finding of right lower quadrant tenderness without rebound tenderness

FROM:

The differential diagnosis based on patient history of RLQ abdominal pain and constipation for 9 months, and physical finding of RLQ tenderness without rebound tenderness

11. Page 11, treatment section: state the exact surgical procedure.

CHANGE TO:

The abdominal mass was removed en-bloc including resection of sigmoid colon, cecum (with preservation of ileocecal valve), appendix, right vas deferens, testicular vessels, and minimal amounts of anterior abdominal wall; and shaving off of small parts of the wall of the urinary bladder and small bowel.

FROM:

The patient underwent debulking surgery.

### **3. Reviewer's code: 03358825**

#### **COMMENTS TO AUTHORS**

1a. Abstract, introduction and core tip looks very similar in content and language. Slight modification to differentiate their purpose is recommended.

CHANGE OF ABSTRACT TO:

A 68-year-old man presented with progressive right lower quadrant abdominal pain and tenderness without rebound tenderness, and constipation during the prior 9 months. Abdomino-pelvic CT and MRI demonstrated a dilated appendix forming a fistula to the sigmoid colon. Open laparotomy revealed a bulky abdominal tumor involving appendix, cecum, and sigmoid, and extending up to adjacent viscera, without ascites or peritoneal implants. The abdominal mass was removed en-bloc including resection of sigmoid colon, cecum (with preservation of ileocecal valve), appendix, right vas deferens, testicular vessels, and minimal amounts of anterior abdominal wall; and shaving off of small parts of the walls of the urinary bladder and small bowel. Gross and microscopic pathologic examination revealed an appendix-to-sigmoid malignant fistula secondary to perforation of mucinous adenocarcinoma of the appendix with minimal local spread (stage T4). However, the surgical margins were clear, all 13 resected lymph nodes were cancer-free, and pseudomyxoma peritonei or peritoneal implants were not present. The patient did well during 1 year of follow-up with no clinically evident or radiologic findings of local recurrence, metastases, or pseudomyxoma peritonei despite presenting with extensive stage T4 cancer that was debulked without administering chemotherapy, and despite presenting with malignant appendiceal perforation. This case illustrates the non-aggressive biologic behavior of this low-grade malignancy. The fistula may have prevented free spillage of cancerous cells and consequent distant metastases by containing the appendiceal contents largely within the colon.

FROM:

A 68-year-old man presented with progressive right lower quadrant abdominal pain and tenderness without rebound tenderness, and constipation during the prior 9 months. Abdomino-pelvic CT and MRI demonstrated a dilated appendix forming a fistula to the sigmoid colon.

Open laparotomy revealed a bulky abdominal tumor involving appendix, cecum, sigmoid, and adjacent viscera, without ascites or peritoneal implants. The primary tumor was surgically debulked. Gross and microscopic pathologic examination revealed an appendix-to-sigmoid malignant fistula secondary to perforation of mucinous adenocarcinoma of the appendix with extensive local spread (stage T4). However, the surgical margins were clear, all 13 resected lymph nodes were cancer-free, and pseudomyxoma peritonei or peritoneal implants were not present. The patient did well during 1 year of follow-up with no clinically evident local recurrence, metastases, or pseudomyxoma peritonei despite presenting with extensive stage T4 cancer that was debulked without administering chemotherapy, and despite presenting with malignant appendiceal perforation. This case dramatically illustrates the non-aggressive biologic behavior of this low-grade malignancy. The fistula may have prevented free spillage of cancerous cells and consequent distant metastases by containing the appendiceal contents largely within the colon.

1b. Case details need not (be) described in the introduction.

#### CHANGE OF INTRODUCTION TO:

A case is reported of mucinous appendiceal adenocarcinoma (MAA) presenting as a bulky mass due to appendiceal perforation and fistulization, treated by debulking surgery; and presenting initially without sepsis; and subsequently at 1 year follow-up had no evident local or distant metastases despite prior malignant appendiceal perforation.

#### FROM:

A case is reported of mucinous appendiceal adenocarcinoma (MAA) presenting as a bulky mass due to appendiceal perforation and fistulization, treated by debulking surgery without chemotherapy; and presenting initially without localized sepsis/abscess/peritonitis; and subsequently at 1 year follow-up had no evident local or distant metastases despite prior malignant appendiceal perforation.

2. The authors describe in the "Methods" about review of literature. But I do not see further information on that like what are the case reports included, how many perforated, different management approaches undertaken etc.

As requested, the paper is strengthened by adding to the Discussion the following characteristics of MAA reported in the literature that are highly relevant to the currently reported patient who presented with appendiceal perforation and had no evident local or intraperitoneal spread despite this malignant perforation:

MAA frequently causes appendiceal perforation, as occurred in this case, attributed to the mucinous gel obstructing the lumen and the narrow appendiceal lumen. For example, in a comprehensive literature review encompassing 316 cases of appendiceal adenocarcinomas, 55% of patients presented with appendiceal perforation (Cerame 1988).

Local nodal involvement is also uncommon when the cancer involves only the mucosa or submucosa (Hata 2002), but the incidence increases to 20%-25% when the primary cancer more deeply invades the appendiceal wall (McCusker 2002, Ito 2004).

3. Significant discrepancy between imaging showing only fistula and the intraop showing significant local invasion with involvement of abdominal wall and bladder.

Response:

There was no involvement of abdominal wall or bladder with tumor.

CHANGE TO:

Microscopic pathology showed well-differentiated, invasive, mucinous, adenocarcinoma diffusely involving the appendix, sigmoid, and cecum through the serosa (Figure-3A,B,C). Histopathology showed no invasion of adjacent organs, such as the bladder wall or anterior abdominal wall.

FROM:

Microscopic pathology showed well-differentiated, invasive, mucinous, adenocarcinoma diffusely involving the appendix and adjacent mass (Figure-3A,B,C).

4. Also histopath did not reveal any adjacent visceral involvement?

CHANGE TO:

Microscopic pathology showed well-differentiated, invasive, mucinous, adenocarcinoma diffusely involving the appendix, sigmoid, and cecum through the serosa (Figure-3A,B,C). Histopathology showed no invasion of adjacent organs, such as the bladder wall or anterior abdominal wall. Lymphovascular invasion and satellite peritumoral nodules were not present. All surgical margins and all 13 resected lymph nodes were devoid of cancer (Stage pT4b N0).

FROM:

Microscopic pathology showed well-differentiated, invasive, mucinous, adenocarcinoma diffusely involving the appendix and adjacent mass (Figure-3A,B,C). All surgical margins and all 13 resected lymph nodes were devoid of cancer (Stage pT4b N0). .

OTHER CHANGES

1. The references are listed in the text using superscripts as per journal style.
2. The numbering of the references is adjusted because of the addition of 4 new references (due to the enhanced literature review).

Thank you for your careful review and interest in this manuscript. We would be delighted to perform further corrections as required for publication.

Warm regards,

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