

March 10, 2017

Dr. Xiu-Xia Song  
Science Editor,  
World Journal of Gastrointestinal Endoscopy

Dear Dr. Xiu-Xia Song:

Thank you for your careful editorial review and constructive criticisms of the manuscript now entitled, *“Bladder urothelial carcinoma extending to rectal mucosa and mimicking hemorrhoidal bleeding with bright red blood per rectum coating stools: Case report and comprehensive literature review”* by Drs. Aneese, Manuballa, Amin, and Cappell submitted as manuscript #32653 to the World Journal of Gastrointestinal Endoscopy. We have thoroughly revised the manuscript in accord with the reviewers’ comments and editorial style of the Journal, as follows:

## **REQUIRED DOCUMENTS**

1. The revised manuscript is presently submitted.

2. Answering reviewers’ comments/criticisms

Reviewer 02451447 Criticisms

i. *It is well accepted already that the term urothelial carcinoma is to replace the old term transitional carcinoma.*

**Authors’ response:** The old term “transitional carcinoma” or “transitional cell carcinoma” is replaced throughout the revised manuscript with the current term “urothelial carcinoma”.

ii. *The authors should realize urothelial carcinoma with rectum direct extension is not that rare, though not lots of literature can be found since many of these cases have never been reported. We saw few cases per year. But the presentation of fresh rectal bleeding may not be that common. I would not recommend to use the word “novel” in the manuscript.*

**Authors’ response:** As suggested, the word “novel” is deleted.

iii. *In the concise summary, last sentence, the authors write “This case report shows that urothelial bladder cancer can directly extend to rectal mucosa and thereby cause rectal bleeding”. I would like to suggest the authors to rephrase it, since it is well known that urothelial carcinoma can invade directly to rectum.*

**Authors’ response:** This concluding sentence changed to:

“In conclusion, a case of bladder urothelial carcinoma penetrating into the rectum via the prostate is reported, with apparently previously unreported, but likely characteristic colonoscopic findings.”

iv. *I would recommend to change urothelial cancer to urothelial carcinoma in the text, and change in situ urothelial bladder cancer to bladder urothelial carcinoma in situ. This will keep this term same as that WHO recommended.*

**Authors' response:**

A. The term “urothelial carcinoma” is used throughout the revised manuscript to replace the term “urothelial cancer”.

B. The term “bladder urothelial carcinoma in situ” is used throughout the revised manuscript to replace the term “in situ urothelial bladder cancer”.

v. *I think Figure 3C is not necessary, other figures and word description are enough to confirm the tumor nature of urothelial carcinoma.*

**Authors' response:** As suggested, Figure 3C is deleted in the paper (including Figure & Figure Legend), and replaced with a brief word description in the Case Report section. With deletion of Figure 3C, Figure 3D is renumbered as Figure 3C.

No authors' responses required to Reviewer 02505493, and no responses required to Reviewer #00742243.

3. Copyright requirements

3A. As required, the authors have submitted the copyright assignment form signed by all four authors.

3B. As required, the authors have submitted the following Open Access statement:

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/bync/4.0/> .

3C. As required, the authors have submitted the following copyright statement:

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4. As suggested, an Audio core tip is added.

5. The Institutional Review Board statement is included in the submission.

6. The following informed consent statement is added to the Methods section (on page 4, bottom):

Informed consent for publication was unobtainable from the patient because he had expired prior to writing this case report.

7. The following Conflict-of-interest statement is included in the paper:

**Conflicts of interest:** None. In particular, Dr. Cappell, as a consultant of the United States Food

and Drug Administration (FDA) Advisory Committee for Gastrointestinal Drugs, affirms that this paper does not discuss any proprietary, confidential, pharmaceutical data submitted to the FDA. Dr. Cappell is also a member of the speaker's bureau for AstraZeneca and Daiichi Sankyo, co-marketers of Movantik. This work does not discuss any drug manufactured or marketed by AstraZeneca or Daiichi Sankyo.

## **FURTHER CHANGES/REVISIONS REQUIRED BY JOURNAL**

1. As per the journal style, we have added the following COMMENTS section:

### **Case characteristics**

An 87-year-old man was treated in 1996 for prostate adenocarcinoma stage-T1c-Gleason-6 with external beam radiotherapy recurrent prostate cancer treated with leuprolide hormonal therapy in 2009, and bladder-urothelial-carcinoma *in-situ* treated with bacillus-Calmette-Guerin and adriamycin in 2010, presented in 2015 with painless, bright red blood per rectum coating stools daily for 5 months. Rectal examination revealed bright red blood per rectum; and a hard, fixed, 2.5x2.5-cm mass at the normal prostate location.

### **Clinical diagnosis/differential diagnosis**

The symptom of daily, painless, bright red blood per rectum for 5 months without other symptoms suggests hemorrhoidal bleeding. First, hemorrhoidal bleeding is very common and is typically unassociated with other symptoms. Second, hemorrhoids generally cause bright red blood because hemorrhoidal blood, despite being venous, is relatively well oxygenated. Third, hemorrhoidal bleeding is generally painless in the absence of hemorrhoidal thrombosis.

Rectal examination did not, however, support this diagnosis. No external hemorrhoids were identified by anal inspection, and no internal hemorrhoids were palpated on digital rectal examination. Moreover, rectal examination revealed a hard, fixed, multinodular, mass at the normal location of the prostate, and gross red blood on the examining finger, findings suspicious for rectal bleeding from prostate cancer. This diagnosis is further suggested by the prior history of prostate cancer in 1996, prostate cancer recurrence in 2009 six years before the current clinical presentation, and palliative hormonal therapy for cancer recurrence in 2009. The diagnosis of recurrent bladder urothelial cancer is also possible given the prior diagnosis of bladder urothelial carcinoma *in situ* in 2010; recurrent bladder urothelial carcinoma could cause rectal bleeding from metastases or direct extension to the rectum. Radiation proctitis must be included in the differential diagnosis because the patient had undergone external beam radiotherapy for prostate cancer in 1966, 19 years before the clinical presentation. Chronic radiation proctitis can cause rectal bleeding from telangiectasias caused by radiation-induced endothelial injury. Anal fissure must also be included in the differential diagnosis of bright red blood per rectum, but is unlikely in this case because anal fissure is very painful and this patient had no anorectal pain. Also the patient did not have the classic symptoms of anorectal of bleeding commencing after passing a large, hard stool, and the patient had daily rectal bleeding for 5 months which is atypical for rectal fissure, and anal fissure is relatively uncommon.

### Laboratory diagnosis

The key finding in the blood tests is a hemoglobin level of 7.6 gm/dL, with iron saturation of 9%, indicating iron deficiency anemia. Hemorrhoidal bleeding tends to produce mild anemia because of minimal daily blood, whereas prostate or bladder cancer invading rectal mucosa can cause greater blood loss and more severe anemia.

### Imaging diagnosis

Abdominopelvic CT angiography revealed focal thickening of the bladder wall at its neck; a mass containing an air cavity replacing most of the prostate; and adjacent rectal invasion. These imaging findings strongly support the diagnosis of recurrent bladder urothelial carcinoma penetrating rectal mucosa via the prostate, or less likely support the diagnosis of recurrent prostate cancer penetrating rectal mucosa. These CT findings do not support the diagnosis of hemorrhoids. Either of these malignancies would be more likely to produce iron deficiency anemia from chronic blood loss than hemorrhoidal bleeding.

Colonoscopy demonstrated an ulcerated, friable, multinodular, oval, hemorrhagic, 2.5x2.5-cm mass in the anterior rectal wall, just proximal to the dentate line, at the usual anatomic location of the prostate, no hemorrhoids, and no signs of radiation proctitis, such as mucosal telangiectasia despite the prior prostate radiotherapy. These colonoscopic findings are highly consistent with cancer invading rectal mucosa. These CT findings are most compatible with bladder urothelial carcinoma invading rectal mucosa by direct extension.

### Pathological diagnosis

Histologic examination of colonoscopic biopsies of rectal tissue biopsies revealed poorly differentiated carcinoma. Immunohistochemical analysis demonstrated the tumor cells stained positively with cytokeratin 20, indicating either a colonic or bladder (urothelial) primary. Additional diffuse positivity for cytokeratin 7, 34bE12, and GATA-3; and focal positivity for CK5/6 strongly support urothelial origin. Negative immunohistochemical staining for CDX2 (Caudal Type Homeobox 2) confirms that this tumor does not arise from colonic adenocarcinoma. The diffuse positivity for cytokeratin 20 and only focal positivity for CK5/6 (<20% of cells positive) excludes anorectal squamous carcinoma. Immunohistochemical markers for prostate carcinoma, including PSA, PAP and P501S, were all negative. The pathologic diagnosis was therefore poorly-differentiated carcinoma of urothelial origin.

This pathology explains all the findings: clinical presentation of painless, daily bright red blood per rectum from friable rectal mucosa from malignant invasion; iron deficiency anemia from chronic GI bleeding from rectal metastases; CT findings of direct cancer extension to rectal mucosa; and colonoscopic findings of an ulcerated, friable, multinodular, mass in the anterior rectal wall.

### Treatment

The patient received palliative therapy for the daily rectal bleeding. The right-superior-rectal-artery was successfully embolized during visceral angiography using embolospheres to achieve hemostasis. The patient did not undergo curative therapy in accordance with the patient's wishes, because of the minimal likelihood of cure given that the patient presented with

recurrent urothelial carcinoma spreads beyond the bladder, previously had recurrent prostate cancer, and was very elderly.

The patient experienced recurrent rectal bleeding requiring periodic packed erythrocyte transfusions three months after embolization that required palliative colostomy. The patient expired 13 months after embolization from widespread metastases from the advanced cancer with rectal penetration treated with palliative therapy.

#### Related reports

Comprehensive literature review revealed 16 previously reported cases of rectal involvement of bladder urothelial carcinoma, including 11 cases of direct cancer extension and 5 cases of metastases. The current case is novel in that the bladder urothelial carcinoma directly penetrated into rectal mucosa; in that rectal involvement caused daily bright red blood per rectum and iron-deficiency anemia; and in the colonoscopic findings that were in accord with the clinical presentation of daily bright red blood per rectum and the CT findings.

#### Experiences and lessons

This work demonstrates the novel findings that bladder urothelial carcinoma can directly extend to rectal mucosa via the prostate, can cause daily, painless, bright red blood per rectum mimicking hemorrhoidal bleeding; and produce colonoscopic findings of a multinodular rectal mucosal mass from cancer extension.

#### Peer-review

The authors thank Reviewer 02451447 for his careful review of the manuscript and constructive criticisms that has resulted in an improved manuscript. First, the term urothelial carcinoma is used throughout the manuscript to replace the old term transitional cell cancer or the less formal term urothelial cancer. Similarly, the term bladder urothelial carcinoma in situ is used to replace the term in situ urothelial bladder cancer in accordance with the World Health Organization (WHO) nomenclature. As suggested, the paper has been modified according to the reviewer's comments to reflect that rectal involvement from bladder urothelial carcinoma may not be so rare but rather infrequently reported. As suggested, the concluding statement about urothelial carcinoma invading the rectum is modified to reflect the novelty of the endoscopic findings of bladder urothelial carcinoma invading rectal mucosa rather than the rarity of bladder urothelial carcinoma invading the rectum per se. As suggested, the photomicrograph of immunohistochemistry for cytokeratin 5/6 demonstrates positive staining of cytoplasm in <20% of tumor cells (which is the expected pattern for urothelial carcinoma) is only presented as text in the Results section and the photomicrograph is omitted. The authors thank Reviewer 00742243 for his/her careful review of the manuscript and kind comments. Similarly, the authors thank Reviewer 02505493 for his/her careful review of the manuscript and kind comments.

2. As per the journal style we have added the following Core Tip section:

**Core Tip:** Comprehensive literature review revealed 16 reported cases of bladder-urothelial-carcinoma involving rectum. None of these cases presented with daily rectal bleeding. Among

11 cases with direct extension, none had pathologically-proven rectal mucosal involvement. A case is reported of recurrent bladder-urothelial-carcinoma presenting with daily bright red blood per rectum coating stools from bladder-urothelial-carcinoma involving rectal mucosa. A hemorrhagic, multinodular, rectal mass, identified by colonoscopy, from direct extension of bladder-urothelial-carcinoma via prostate to rectal mucosa underlies the presentation with daily bright red blood. This report shows that bladder-urothelial-carcinoma can cause rectal bleeding by directly extending to rectal mucosa.

3. As per the journal style, we have added the following section on author contributions:

**Author contributions:**

Dr. A. Aneese and Dr. M. Cappell are equal primary authors. Dr. Aneese wrote a large part of the case report, performed the initial literature search, and wrote a preliminary version of the Tables and Discussion.

Dr. Cappell was one of the two gastroenterologists taking care of this patient. Dr. Cappell was the mentor for Dr. A. Aneese who was a resident while participating in writing this paper. As the mentor, Dr. Cappell conceived and initiated this project, and supervised the writing of the entire paper, including editing the Introduction, Case report, Tables, and Discussion sections.

Dr. V. Manuballa was one of the 2 gastroenterologists treating this patient. She wrote a large part of the case report section.

Dr. A. Mitul performed all the pathology for this case report including the histopathology and immunohistochemistry. He retrospectively re-reviewed all the pathological slides.

4. As per editorial policy the Title is shortened.

**CHANGE TITLE TO:**

Bladder urothelial carcinoma extending to rectal mucosa and mimicking hemorrhoidal bleeding with bright red blood per rectum coating stools: Case report and literature review

**FROM:**

Urothelial bladder cancer extending to rectal mucosa via the prostate and mimicking hemorrhoidal bleeding with daily bright red blood per rectum coating stools: Novel case report and colonoscopic findings

4. As per journal editorial style, the following changes have been effected in all citations:

All citations throughout the manuscript text are listed in Arabic numerals, are in brackets, and are placed in superscript.

5. The references are all listed as per journal style with inclusion of PMID and DOI numbers.

Thank you for your interest in this manuscript. The authors will gladly perform further revisions as required for publication in this prestigious journal.

Warm regards,

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