**Author's response to reviews**

**Title:** Concurrence of villous adenoma and non-muscle invasive bladder cancer arising in the bladder: a case report

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Dr. Hayley Henderson

Executive Editor
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Dear Dr. Henderson,

Thank you for your letter dated March 12, 2013. We were pleased to learn that our manuscript was evaluated as being potentially acceptable for publication in BMC Urology, depending on adequate revision and response to the comments raised by Dr. Rosser the referee of our manuscript.

Please find the original and the revised manuscript.

As you notice, we have revised the manuscript by modifying the Title, Abstract, Introduction, Case presentation, Discussion and Conclusion sections, based on the comments made by Dr. Rosser. Accordingly, we attached the original manuscript marked with all the changes made during the revision process indicated by shading. The new text is underlined and in a red color.

Please also find our point-by-point response including below to the comments raised by Dr. Rosser. As you notice, we agreed and complied with all the comments. We would like to take this opportunity to express our sincere thanks to Dr. Rosser who identified areas of our manuscript that needed corrections or modification. We would like also to thank you for allowing us to resubmit a revised copy of the manuscript.

I hope that the revised manuscript is now acceptable for publication in BMC Urology.

Sincerely Yours,

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Comments from Referee #1:

**Comment 1.** Perhaps change to Concurrent villous adenoma and non-muscle invasive bladder cancer: a case report and review of the literature.

**Response 1.** Thank you for your comment. We revised from “Concurrence of villous adenoma and non-muscle invasive bladder cancer arising in the bladder: a case report” to “Concurrence of villous adenoma and non-muscle invasive bladder cancer arising in the bladder: a case report and review of the literature” in title on page 1.

**Comment 2.** Could be re-organized and reworded to help the reader. Conclusions should state...To the best of our knowledge.... Premalignant villous adenoma of the bladder is extremely rare and difficult to diagnose without histologic examination. Any suspicious lesion of the bladder should be biopsied and/or resected to confirm histology.) Remove citations from abstract. Start citation #1 in main text not abstract.

**Response 2.** Thank you very much for pointing out and modifying. We revised from “However, to the best of our knowledge, this is only the second report of villous adenoma in the bladder of coexisting urothelial carcinoma that has been published in the literature.” to “However ... literature. Premalignant villous adenoma of the bladder is extremely rare and difficult to diagnose without histologic examination. Any suspicious lesion of the bladder should be biopsied and/or resected to confirm histology.” on page 3. And we removed citations from abstract.

**Comment 3.** Can reorganize. Perhaps give a paragraph about villous adenoma in the colon. Who gets it (Sex, race, age), risk factors. Presentation. How treated. Outcomes. Then transition that this has been seen in bladders. Next paragraph brief describe some of the case reports describing villous adenoma in bladders.

**Response 3.** Thank you for your pointing out. We reviewed references and revised that from “Up to two-thirds of these lesions occur in the rectum [4]. However, the villous adenoma in the urinary tract is rare. The most common coexisting tumor is adenocarcinoma which is associated with urachus tumors [5]. Typical clinical presentations are hematuria and irritative symptoms [1]. In the rectum, recurrence is seen in up to 40% of cases even despite complete excision. On the other hand, the prognosis of pure villous adenoma is excellent.” to “Up to two-thirds of these lesions occur in the rectum [4]. There are no differences in distribution between men and women and a peak incidence in the 60’s and 70’s [2]. Whenever possible, local excision and
sphincter preservation is the procedure of choice for accessible lesions with favorable characteristics. However, the recurrence is seen in up to 40% of cases even despite complete excision in the rectal [3]. On the other hand, the villous adenoma in the urinary tract is rare. The most common coexisting tumor is adenocarcinoma which is associated with urachus tumors [4]. Typical clinical presentations are hematuria and irritative symptoms [5]. In the rectum, recurrence is seen in up to 40% of cases even despite complete excision. On the other hand, the prognosis of pure villous adenoma is excellent. The prognosis of pure villous adenoma in the urinary tract is excellent.” on page3-4.

Please note that we reviewed the published references which vilous adenoma in the colon, but we could not find the information about “race”, and that the reference number have changed because we cited new references.

Comment 4. Reorganize…Informed consent and institutional review board above obtained. An85 year old with no significant past medical history, including colon cancer, etc,etc. presented with painless gross hematuria? Did patient have history of UTI,stones, or hematuria? Urinalysis showed microscopic or gross hematuria? AnyWBC? Bacteria? If not state only blood. Was urinary cytology performed or any other urine-based biomarker?

Response 4. Thank you very much for your comment. We have obtained prior consent from the patient and she signed her name in “Bio Med Central official Consent form”. According to medical history, she had never suffered from UTI, stones or pyuria except for this hematuria. We apologize for not having checked urinary cytology and urine-based biomarker (e.g. NMP-22 or BTA). So we revised from “An 85-year-old woman presented at our office because of gross hematuria. She had a past history of urethral caruncle two years ago.” to “An 85-year-old woman with no significant past medical history, including colon cancer but urethral caruncle two years ago presented at our office because of painless gross hematuria.” on page4.

Comment 5. Then imaging was performed with US and MRI? Why MRI? Is this standard in Japan? Was contrast used? Any abnormalities of the upper tracts or of the colon?

Response 5. We agree with everything you said. Of course we have done an enhanced computed tomography scan to check the precise staging, but no particularly findings more than MRI. So we omitted the report of CT scan to simplify the manuscript. We ought to have included the report of CT. So we added the report of enhanced CT on page5; “Both … (Figure 1-A, B). An enhanced computed tomographic (CT) scan of the bladder showed two masses. Larger one measuring 16mm was in the right wall and the other was 9mm mass.
in the left bladder wall, with enhancement. Moreover, no other masses or no enlarged lymph nodes were seen except for the bladder. On magnetic…."

Please note that the text “CT” was added on page 2, 7, and 11.

Comment 6. Since this is a rare entity can another pathologist from another institute confirm? Here in the US we can send to AFIP to confirm.

Response 6. Thank you for your comment. In this case, two pathologists diagnosed to receive a definitive diagnosis. First, the pathologist who was a staff of pathological company which was commissioned by the Ninohe Hospital undergone TUR. Then, we consulted “Tamotsu Sugai” the professor of Department of Diagnostic Pathology, Iwate Medical University to have each bladder tissue diagnosed. The diagnoses for two tissues between two pathologists were on common.

Comment 7. Was immediate post-op chemotherapy instilled into the bladder? Is this not standard of care in Japan? Bladder tumor recurred very soon after the TUR. Can you report (even in text only) the results. H&E was more like the TCC and not villous, correct? And the IHC?

Response 7. Thank you very much for your comment. It was very difficult for us to decide to perform intravesical chemotherapy immediately, because the patient was 85 years old and the size of urothelial carcinoma in the left side wall was single (though with satellite tumors), 9mm size, primary, category T1, no concomitant CIS, grade 2. According to the guideline of EAU, the recurrence and progression score was 2points (T1, G2) and 4points (T1), respectively and both in intermediate risk group. Each result would be 24%/46% in 1y/5y recurrence and 1%/6% in 1y/5y progression, respectively. Moreover, we did not find the reports that the BCG therapy would have good effect in villous adenoma. Finally, she recurred after 3 months of TUR-BT. As you mention, we should have immediate post-op chemotherapy.

The pathological diagnosis of recurrence tissue was diagnosed urotelial carcinoma by two pathologists. We are sorry for not checking IHC for recurrence tissue but the recurrent tissue was apparently different from villous adenoma in morphologically.

Comment 8. So if I am correct, follow-up is quite short to date. Maybe 3 months? To wait for slightly longer follow-up, i.e., 12 or even 24 months would be better to at least ensure the villous does not recur rapidly.

Response 8. We agree with your comment. So we updated our follow up period. Then we revised from “After BCG therapy, she has been followed by cystoscopic examination for three months.” to “After BCG therapy, she has been followed by
cystoscopic examination for **every** three months. At the last follow-up, **24 months after surgery**, no local recurrences were detected.” on page7.

**Comment 9.** Mild anemia is not relevant and could be deleted from case presentation and discussion.

**Response 9.** Thank you for your pointing out. We omitted the text “mild anemia”. We revised from “The clinical manifestations included gross hematuria and mild anemia, but none led to an increased suspicion of villous adenoma.” to “The clinical manifestations included gross hematuria and mild anemia, but none led to an increased suspicion of villous adenoma.” on page7.

**Comment 10.** So for each case report what was the sex, age, race, etc. of the patients. Most common presenting symptom(s) and sign(s). Anything unique on histologic examination? Outcomes? So information should be in Table and in text of discussion.

**Response 10.** We deeply agree with your comment. So we summarized the age, gender, top of three common symptoms, locations and treatments and recurrence and progress rate. Then we analyzed and discussed the results. So we attached new Table and added the text “Moreover, clinical features of published reports according to the types of concurrence carcinomas are presented in Table2 [5-24]. Though there are some variabilities of fineness, this table shows us some differences and similarities between solitary villous adenoma and concurrence villous adenoma and adenocarcinoma. The other types including our case are too small number of cases to compare. Age, gender, predominant symptoms and locations are similar between solitary villous adenoma and concurrence villous adenoma and adenocarcinoma. On the other hand, treatments and recurrence and progression rate are differences between groups. Though, the cases of concurrence villous adenoma and adenocarcinoma were received more radical therapies than solitary villous adenomas, the rate of the recurrence or progress were higher than solitary villous adenomas. These outcomes would be attributed to the malignant grade of adenocarcinoma.” on page8.

Please note that we cited new references, so the reference number were changed and added widely.

**Comment 11.** Authors report how colonic tissue may be incorporated into the bladder by describing embryology. This is good but would one no expect to see this tumor earlier instead of when the patient is 85 years of age?
Response 11. This comment was very difficult for us to reply. Because of the small number of the villous adenoma cases, there are a few references which commented how glandular tissue especially villous adenoma generated in the bladder? The youngest case was 23 years old, the fact that the risk factor would not only be of age but also other factors (e.g. gene or environment of life styles). And to uncover the cause of that, it would be necessary for us to get more cases.

Comment 12. Could this villous adenoma not be PUNLMP? Perhaps compare and contrast.

Response 12. Thank you for your pointing out. The papillary urothelial neoplasm of low malignant potential (PUNLMP) is defined as papillary urothelial tumors which resemble exophytic UP, except for an increased cellular proliferation that exceeds a normal thickness. (Ref. Jung-Weon Shim, et al. Virchows Arch (2008)) While the villous adenoma in this case was reported that histologically, the former consisted of tall columnar epithelium which formed a villous pattern with vessels and stroma consisting of hypo connective tissues, few nuclear atypia, and few mitotic figures. The differences between PUNLMP and villous adenoma were the type of tissue. The former was urothelial tissue on the other hand the latter was all columnar epithelium. That was why we thought that the villous adenoma of our case would not be PUNLMP.

Comment 13. Remove references [1,2] from next the last sentence on page 8.

Response 13. Then we removed reference as you mentioned, thank you. We revised from “No progressive cases of isolated villous adenomas have been found except for Powell’s report [1, 2].” to “No progressive cases of isolated villous adenomas have been found except for Powell’s report [1, 2].” on page10.

Comment 14. FIGURE 1 and FIGURE 2: Could be combined

Response 13. We agree with your comment. We made the two figures combined to one figure. So the figure legend and texts changed respectively from “Figure 1: A Villous adenoma: Cystscopy findings of villous adenoma. The papillary tumor with steel was in the right wall. B Urothelial carcinoma: Cystscopy findings of urothelial carcinoma. The papillary tumor in the left wall in this case the columnar epithemium of tumor was longer than that of the villous adenoma. Figure 2: HE histopathologic findings and representative immunohistochemical findings for cytokeratin (CK) 7, CK20 and Ki-67. A, Villous adenoma. B, Urothelial carcinoma. 1, HE. 2, CK7. 3, CK20. 4, Ki-67.” to “Figure 1: Cystscopy findings and HE histopathologic findings and
representative immunohistochemical findings for cytokeratin (CK) 7, CK20 and Ki-67.

A and a, Villous adenoma: The papillary tumor with steel was in the right wall. 
B and b, Urothelial carcinoma: The papillary tumor in the left wall in this case the columnar epithelium of tumor was longer than that of the villous adenoma.

1. HE. 2. CK7. 3. CK20. 4. Ki-67” and the texts from “Figure1, Figure2” to “Figure 1-A, B, Figure 1-a, b”. on page18.