Author's response to reviews

Title: Urothelial Carcinoma of the Upper Urinary Tract Diagnosed via FGFR3 Mutation Detection in Urine: a Case Report

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Author's response to reviews: see over
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Hayley Henderson, PhD
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Dear Dr. Hayley,

Enclosed is the revised manuscript (#7372963096532075) titled “Urothelial Carcinoma of the Upper Urinary Tract Diagnosed via FGFR3 Mutation Detection in Urine: a Case Report”. We have addressed the Reviewer’s comments and our responses are below. Changes to the manuscript are capture in track-changes.

I hope with these revisions that the manuscript is now acceptable for publication. If you have any questions, please contact me.

Sincerely,

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RESPONSE TO REVIEWER’S COMMENTS

(Reviewer’s comments are in italics)

Reviewer #1: Makito Miyake

In the clinical management of the upper urinary tract carcinomas, one of the biggest issues is that these are sometimes hard to detect and diagnose. It is problematic to perform nephroureterectomy without evidence of malignancy. As to urine-based marker, urinary cytology have been widely used for diagnosing of lower and upper urinary tract. The limitation is poor sensitivity, especially in low-grade tumors. FGFR3 mutation is the most promising marker for detecting low-grade urinary tract marker. Unfortunately, there are few reports addressing usefulness of urine-based FGFR3 mutation assay for diagnosing upper urinary tract. In this case report, a right renal pelvic tumor was diagnosed successfully as a malignancy by FGFR3 mutation assay. This article would have high educational value to urologists.

Major Compulsory Revisions

1) The author has to submit images of CT scan, retrograde pyelogram and intravenous pyelogram as Figures. The CT scan image at initial presentation would be essential. We are unable to know conditions of the patient’s right kidney, tumor location and presence or absence of hydronephrosis. The patient had a complete ureteral duplication. The retrograde pyelogram was successful? Was it possible to subject washing fluid of renal pelvic where the tumor was to cytological exam? The author should explain it in more detail and make the patient condition clearer.

Response: CT scans were done twice: on September 2010 and June 2011. Both scans showed the tumor and suggested that it may be larger in the second scan. We have now added a scan from each date to the manuscript (see Figure 1A and 1B)

Retrograde pyelogram of the lower pole was performed and was normal. It was not possible to perform a retrograde pyelogram of the upper pole unit because the ureter was only about 1 millimeter in diameter, where a normal ureter is 3-4 mm in diameter. The instruments used in our practice are sized and scaled for a normal ureter and not for this small ancillary ureter. An attempted pyelogram was unsuccessful as the contrast did not fill the ureter or renal pelvis. No images were saved from this attempted retrograde. We did not do an intravenous pyelogram as this was not appropriate due to the CT scan findings. We have added this additional information to the manuscript (see Case Presentation, paragraph 3)

2) The urine obtained after right nephroureterectomy was subjected to FGFR3 mutation detection assay? This assay seems to be so sensitive enough to detect invisible urothelial cancer. Were the patient proven to be free from tumor? The author should add some description about the follow-up for this patient.
Response: Since the nephroureterectomy, the patient has been monitored for recurrent cancer. We performed a postoperative CertNDx test in March 2012, 7 months after the nephroureterectomy, which was negative for the presence of FGFR3 mutant DNA. In addition following the uncomplicated postoperative course, the patient had surveillance cystoscopies in November 2011 and February 2012 both of which were negative. As part of the continuing follow-up, the patient will have surveillance cystoscopy several times per year for the foreseeable future. In view of the negative CertNDx test, upper tract imaging has not yet been performed. The left kidney has not been examined as it was normal at the time of the most recent CT scan (June 2011). This information has been added to the manuscript (see Case Presentation, paragraph 7)

In a multi-center US-based trial in patients being monitored for recurrent bladder cancer, the CertNDx assay demonstrated 30.2% sensitivity (19/63) and 95.5% specificity (640/670) (Fernandez and Shuber, 2012, submitted)

3) In the section of Abstract, it is described that pathology had confirmed the genetic change of FGFR3. The author should add some description about it in detail, such as mutational types and mutational codons. In the section of Case Presentation, the patient’s urine obtained before operation contained genomic DNA carrying FGFR3 mutations in exon 7, 10 and 15. According to previous reports, a single tumor carrying two different FGFR3 mutations is uncommon. A tumor with three different FGFR3 is supposed to be really rare. Some description about it could make this article’s relevance higher.

Response: We apologize for not being clear on this point. The patient’s FGFR3 DNA contained a single mutation in exon 10 (Y375C). We have added this information to the manuscript (see Abstract and Case Presentation, paragraph 5). Tumor tissue was also found using quantitative PCR to contain the same FGFR3 mutation, consistent with the tumor being the source of the mutant DNA isolated from the urine. This information has been added to the paper (see Abstract and Case Presentation, paragraph 6). We have also added “In Press” to a reference of a manuscript that describes this assay’s clinical performance in detail and has been accepted for publication.

4) The description about pathological examination is insufficient. That should be described in accordance with 2004 WHO grading criteria and 2002 TNM staging criteria.

Response: We have added more description regarding the pathology of the kidney that was removed. Due to marked autolysis, tumor grade was indeterminate. However, the pathologist favored designating it WHO 2004 low-grade. The tumor stage was Ta, N0, M0. The tumor involved the renal pelvis of the upper pole collecting system. Upon cut sections, the kidney exhibited an ill-defined partially raised, partially nodular tan-pink dense focus, located in the renal pelvis of the upper pole, which measured 1.5cm at its greatest dimension. This focal area appeared limited to the upper pole renal pelvis/calyx and abutted but did not involve kidney parenchyma or peripelvic fat. This has been added to the paper (see Case Presentation, paragraph 6)
Minor Essential Revisions

none

Discretionary Revisions

The author used words “transitional cell carcinoma” and “urothelial cancer” in the section of Background. In this article, the author described a case with a tumor of the urinary tract, so these two are synonyms. It would be better to make terminology consistent.

Response: We revised the text to make the terminology more consistent by using “urothelial carcinoma” throughout.