Oncology

High-grade Carcinoma of the Proximal Ureter With Negative Nephroureteroscopy Detected by a Positive FISH Test: A Rare Case Report

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Abstract
Upper tract urothelial carcinomas in the proximal ureter are uncommon diseases. We present a case in which it was firstly detected by fluorescence in situ hybridization and not by endoscopy and radiologic imaging. Consequently, a radical nephroureterectomy with excision of the bladder cuff was performed as the gold standard treatment.

Background
Upper tract urothelial carcinomas (UTUC) are uncommon cancers located in the pyelocaliceal cavities and ureter with an annual incidence rate of about 2 per 100,000 inhabitants in Western countries.1 Because of limited access to the upper tract (UT) and difficulties in radiologic tumor imaging the recommended diagnostic approach for UTUC is multimodal and consists of radiologic imaging, urinary cytology (Cyt) and ureterorenoscopy.2 We present a case of a patient with an urothelial carcinoma of the proximal ureter with negative ureterorenoscopy in whom the detection was triggered by a positive FISH test (fluorescence in situ hybridization, UroVysion™, Abbott Molecular/Vysis, Des Plaines, IL, USA).

Case presentation
The patient was a 65-year-old non-smoking healthy man with a history of urolithiasis and hypertension. He had undergone an ureteroscopy for stone removal on the left side and two transurethral resections of the bladder without malignancy before. His physical examination was normal except for a microhematuria. Also laboratory findings were normal. Because routinely performed ultrasonography had revealed the suspicion of a complicated renal cyst and a nephrolithiasis on the right side, an abdominal and pelvic CT urography was performed (Fig. 1). It depicted a Bosniak II lower pole renal cyst (3 × 2 cm), a 6 mm pelvic stone and slightly thickened proximal ureter wall with a maximum of 3 mm on the right side.

For further investigation of the right UT, a retrograde ureteropyelography and a complete ureterorenoscopy with a rigid uretero- and a flexible nephroscope (Karl Storz, Flex X®, Tuttlingen, Germany) were performed. These examinations revealed a radiologically and endoscopically normal UT. Confirmatory biopsies of the right distal ureter were also without malignant findings. However washing urine from the UT revealed a positive FISH test (fluorescence in situ hybridization, UroVysion™, Abbott Molecular/Vysis, Des Plaines, IL, USA).

Abbreviations: UTUC, Upper tract urothelial carcinomas; FISH, fluorescence in situ hybridization; Cyt, cytology.
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carcinoma in situ of the proximal ureter. The patient recovered without any complications and had no evidence of tumor recurrence during follow-up.

Discussion

In UTUC diagnosis and staging is still hampered by limited endoscopic access to the UT and difficulties in radiologic imaging of small sized tumors and flat lesions. Currently a multimodal work-up including radiologic imaging, endoscopic tumor visualization, endoscopic biopsies and urinary cytology is recommended by the European Association of Urology guidelines for their best detection rate.\(^1\)

On imaging techniques CT urography has the highest diagnostic accuracy and is recommended as the imaging technique of choice.\(^1\) In comparison to conventional radiologic imaging like intravenous or retrograde pyelography, its major advantage is that it also detects thickening of the ureter.\(^4\) This may be a sign of UTUC as in the present case, even if there is no luminal mass effect. In the present case however the thickening of the ureter was initially not attributed to an UTUC.

If CT urography cannot be performed, MR urography remains an option. In contrast to CT and MR urographies conventional intravenous and retrograde urography can only detect flat lesions if there is an intraluminal effect like a stenosis or a change in diameter. For endoscopic tumor visualization much progress has been made in the technique of flexible ureterorenoscopy in recent years. Due to their smaller size, their better tractability and their higher degree of flexibility ureterorenoscopes they routinely allow visualization of the entire UT with high resolution images today. Additionally biopsies can be taken easily during flexible ureterorenoscopy from any region of the UT and evaluated for the

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Figure 1. Standard venous phase (A) and excretory phase (B). Axial MDCT showed circular urothelial thickening of the upper ureter with no filling defects. Potential differential diagnosis were urothelial cancer, inflammatory disease and peristalsis in the ureter.

Figure 2. Example of a fluorescence in situ hybridization test (FISH test) with nuclei of urothelial cells from the upper urinary tract. Irregularities of the chromosomes: 9 (yellow dots), 3 (red dots), 7 (green dots) and 17 (blue) can be detected either by their loss or their aneuploidy.

Figure 3. Histopathologic specimen from the transurethral biopsy of the right ureter revealing a carcinoma in situ. The basal membrane is undisturbed. The arrow is pointed at dysplastic urothelial carcinoma cells (magnification 400×).

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presence of urothelial cancer. The false negative rate of such biopsies is low, and they furthermore allow a differentiation between low and high grade tumors.

Even though therefore most tumors can be detected by means of radiologic and endoscopic imaging, the present case demonstrates that some tumors might be overseen using radiologic and endoscopic techniques only. In these cases urine-based diagnostic measures close a diagnostic gap and are of high importance.

Both cytology and FISH analysis can be performed from washing urine of the upper tract. Cytology is the current gold standard and has a high sensitivity and specificity for high-grade tumors but not for low-grade cancers. The FISH test can also be applied for the detection of upper urinary tract tumors, although the manufacturer has not officially licensed it for this indication. In our so far largest series of 82 patients with FISH and Cyt analysis from upper tract washing urine FISH revealed a sensitivity of 84% vs. Cyt of 53% and a specificity for both tests of 91%.

Conclusion

This makes the FISH test in combination with cytology according to our believes, especially if endoscopic findings are doubtful or biopsies not diagnostic, a valuable tool in a multimodal approach for UTUC detection.

Consent

The patient gave his informed written consent to the anonymous publication of his case.

Competing interests

The authors declare that they have no competing interests.

Authors’ contributions

ZGX and HM drafted the report. SD participated in FISH test. GM performed histopathological examinations. FT cared for imaging. GMO and HM were responsible for critical revision of the manuscript. All authors reviewed the report and approved the final manuscript.

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