



Invasive High-grade Upper Tract Urothelial Carcinoma in a 14-Year-Old Girl

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We present an unusual pediatric case of invasive upper tract urothelial carcinoma with an associated genetic predisposition. A 14-year-old female presented with intermittent right flank pain, and was found to have a poorly functioning hydronephrotic right kidney. Laparoscopic nephrectomy was performed. Pathology demonstrated upper tract urothelial carcinoma, and she subsequently underwent completion ureterectomy. Genetic studies demonstrated a double-hit constitutional deletion of a DNA mismatch repair protein, revealing a rare Lynch syndrome variant known as Constitutional Mismatch Repair Deficiency Syndrome. This disease places her at high risk for multiple malignancies, including upper tract urothelial carcinoma. *UROLOGY* 101: 145–146, 2017. © 2016 Elsevier Inc.

Urothelial carcinoma is rare in pediatric patients. When diagnosed, it most commonly involves the bladder and is usually noninvasive in nature. There are even rarer reports of high-grade invasive urothelial carcinoma of the bladder, but none of the ureter or renal pelvis. Here we describe an unusual case of invasive urothelial carcinoma of the ureter in a pediatric patient, as well as review her genetic predisposition for multiple malignancies, a heritable diagnosis known as Constitutional Mismatch Repair Deficiency Syndrome (CMMRD).

CASE REPORT

A 14-year-old female was referred for evaluation of hydronephrosis, right flank pain, and gross hematuria. Medical history was significant for stage 3 neuroblastoma, treated at age 2 with surgical resection and chemotherapy, as well as colonic polyposis with subsequent colectomy at age 13. Prior hematuria work-up with a general urologist included cystoscopy with bladder wash cytologies that were normal. A renal ultrasound demonstrated grade IV hydronephrosis. Severe right hydronephrosis with a dilated ureter extending to the vicinity of a staple line from her prior colectomy was seen on noncontrast computed tomography scan (Fig. 1). She had a normal renal ultrasound 3 years earlier. Physical examination revealed right costovertebral angle and abdominal tenderness.

A MAG-3 renal scan demonstrated <10% right renal function. She underwent cystoscopy, retrograde pyelogram, and

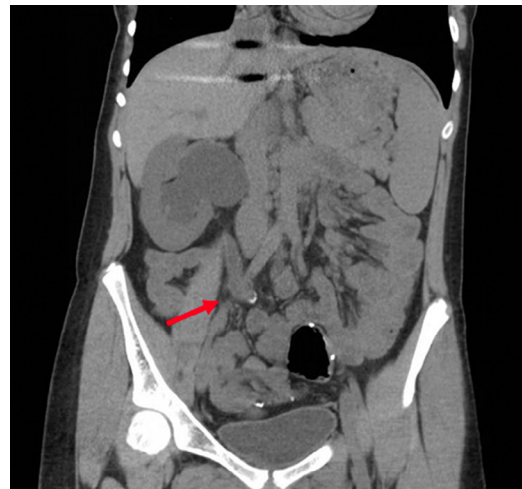


Figure 1. Hydroureteronephrosis extending to the level of the pelvic brim, ending near a staple line from prior surgery. (Color version available online.)

ureteroscopy. A long, tortuous, obstructing, narrowing of the distal ureter with medial deviation was seen (Fig. 2). On ureteroscopy, narrowing of the lumen was appreciated, but there was no obvious mass. No improvement in renal function was seen on repeat studies after stent placement.

Right laparoscopic nephrectomy was performed. The proximal ureter was removed, but dense fibrosis was encountered, and the ureter was divided and periureteral tissue was biopsied.

Pathology showed invasive urothelial carcinoma of the ureter with invasion through the wall into the surrounding tissue. She returned to the operating room 7 days after the nephrectomy for right ureterectomy and lymph node dissection. Invasive papillary transitional cell carcinoma of the ureter with metastatic disease in 1 of 10 lymph nodes

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Figure 2. Retrograde pyelogram redemonstrating dilated and tortuous right ureter, with transition point and medial deviation.



Figure 3. Urothelial carcinoma of the bladder seen on surveillance cystoscopy, near the prior surgical bladder cuff site. (Color version available online.)

was found in the resected specimen. Further imaging showed no metastatic disease. Tumor stage was pT3N1M0. She received 4 cycles of adjuvant MVAC. Genetic testing revealed mutations of both *PMS2* genes, 1 from each parent (both of them thus diagnosed with Lynch syndrome). With continued follow-up, she has since been found to have a bladder tumor (high-grade Ta, Fig. 3) and a frontal lobe astrocytoma, and has undergone resection of both. At her 12-month follow-up computed tomography scan, a new

2.4 cm lesion in the liver was identified, and biopsy was consistent with metastatic urothelial carcinoma. She is now undergoing treatment with Nivolumab.

DISCUSSION

The vast majority of case reports discuss urothelial carcinoma localized to the bladder, and from 1968 to 2005 the World Health Organization database has recorded only 80 of these patients.^{1,2} Even rarer, only a handful of non-invasive low-grade upper tract urothelial cell carcinoma case reports have been identified.³⁻⁷ High-grade upper tract urothelial cell carcinoma represents an extremely rare (if not reported) entity among the pediatric population.

This patient's unique predilection lies in her genetic susceptibility. She possessed a constitutional germline mutation of both her *PMS2* genes. By interacting with 7 other mismatch repair (MMR) proteins, the coded *PMS2* protein plays a critical role correcting errors in the DNA replicative process. Defective MMR has been associated with microsatellite instability leading to somatic mutations and the development of malignancies. Most notably, this is the cause of Lynch syndrome when it occurs in a single gene.^{8,9} Constitutional Mismatch Repair Deficiency Syndrome is associated with urothelial carcinoma of the ureter, which is generally seen in adults. The DNA MMR mechanism and multisystem consequences have been extensively reviewed by Huang et al.¹⁰ Here we report a double-hit constitutional mutation of an MMR complex protein responsible for multiple malignancies in a 14-year-old girl.

References

1. Fine SW, Humphrey PA, Dehner LP, et al. Urothelial neoplasms in patients 20 years or younger: a clinicopathological analysis using the World Health Organization 2004 bladder consensus classification. *J Urol.* 2005;174:1976-1980.
2. Chu S, Singer J. Transitional cell carcinoma in the pediatric patient: a review of the literature. *Urology.* 2016;91:175-179.
3. Koyanagi T, Sasaki K, Asikado K. Transitional cell carcinoma of renal pelvis in an infant. *J Urol.* 1975;113:114-117.
4. Nakagami Y, Horio Y, Saito T. A case of transitional cell carcinoma of the renal pelvis in a child. *Jpn J Urol.* 1968;22:523.
5. Riches EW, Griffiths IN, Thackeray AC. New growth of the kidney and ureter. *Br J Urol.* 1951;23:297.
6. Clinton-Thomas CL, Robinson TM. Adenocarcinoma of the kidney in childhood: report of a case and a review of the literature. *Br J Urol.* 1956;28:132-136.
7. Karmi S, Averill R, Young JD. Malignant urothelial tumors in childhood. *Urology.* 1983;21:178-180.
8. Skeldon S, Semotiuk K, Aronson M, et al. Patients with lynch syndrome mismatch repair gene mutations are at higher risk for not only upper tract urothelial cancer but also bladder cancer. *Eur Urol.* 2013;63:379-385.
9. Garcia-Tello A, Ramon de Fata F, Andres G, et al. DNA repair genes and prognosis in sporadic forms of urothelial carcinoma of the upper urinary tract. *Actas Urol Esp.* 2014;38:600-607.
10. Huang S, Durno C, Erdman S. Lynch syndrome: a pediatric perspective. *J Pediatr Gastroenterol Nutr.* 2014;58:144-152.