



Management of High-grade, Nonmuscle Invasive Urothelial Carcinoma in a Prepubertal Patient With TURBT and Intravesical BCG

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High-grade urothelial carcinoma of the bladder is rare in the pediatric population with no established guidelines for management. We treated a single female patient, 10 years of age, who was found to have high-grade, nonmuscle invasive urothelial carcinoma endoscopically and with intravesical bacille calmette guerin (BCG). Given the child's age, no local adult institution could provide BCG therapy. Utilizing the experience of the local adult institutions, we developed a comprehensive protocol for first-time delivery of BCG at a free-standing children's hospital. The patient has undergone successful induction and maintenance BCG for 7 cycles without disease recurrence and minimal side effects. *UROLOGY* 124: 257–259, 2019. © 2018 Elsevier Inc.

Urothelial carcinoma (UC) of the bladder is exceedingly rare in the pediatric population with an incidence reported as low as <0.5% in patients under 20 years of age, with few reported cases of high-grade disease.¹⁻³ Given the rarity of disease, there are no guidelines for management and surveillance and limited reports of the use of intravesical therapies, which are commonplace in the treatment of intermediate and high-risk UC in adults. Therefore, the safety and efficacy of intravesical BCG in pediatric patients with high-grade disease remains unknown.

CASE REPORT

A 10-year-old female presented for presumed early menses. She had a 6-month history of nausea, vomiting, abdominal pain, and a report of blood in the toilet. Hematuria evaluation identified a bladder mass on ultrasound (Fig. 1). Staging computed tomography demonstrated a 2.5 × 2.4 × 2.3 cm lobulated, polypoid lesion at the posterior aspect of the right bladder base (Fig. 2) with no other disease.

Transurethral resection of a bladder tumor identified a broad-based mass lateral to the right ureteral orifice. Pathology demonstrated high-grade papillary UC with invasion of the lamina propria and no muscle involvement. Random bladder biopsies and re-resection of the tumor bed identified

no residual disease, no carcinoma in situ (CIS), and no muscle invasion. She was staged as high-grade T1, nonmuscle invasive UC. A 29-gene panel for genitourinary (GU) malignancy was negative for germline mutations. Molecular testing did identify alterations consistent with UC in adults. The patient had no identifiable exposures predisposing her to malignancy or family history of malignancy.

A multidisciplinary tumor board, including medical oncology and pediatric and adult urology recommended induction and maintenance intravesical BCG. Given her age, she was not eligible for treatment at any local adult institutions and therefore a new pediatric protocol was developed.

The patient underwent a 6-week induction course. One month after induction, surveillance cystoscopy was performed with concern for recurrence at the initial resection site as well as new disease at the bladder dome. Biopsies were obtained and pathology returned with chronic inflammation without evidence of malignancy. Maintenance BCG was recommended given tolerance of induction and no disease recurrence.

Maintenance started 3 months after completion of induction BCG with 3 weekly instillations followed by surveillance cystoscopy at 1 month. She has undergone a total of 7 cycles without evidence of disease recurrence. Cystoscopy, urine cytology, and upper tract surveillance imaging has been negative. She has noted transient urinary urgency, frequency (1-3 days), and occasional fatigue which have not limited continued treatment.

INTRAVESICAL BCG PROTOCOL

A pretreatment urine culture and a day of treatment urinalysis are checked. Positive results, any systemic/flu-like symptoms or fever, delay treatment. She is premedicated with Oxycodone

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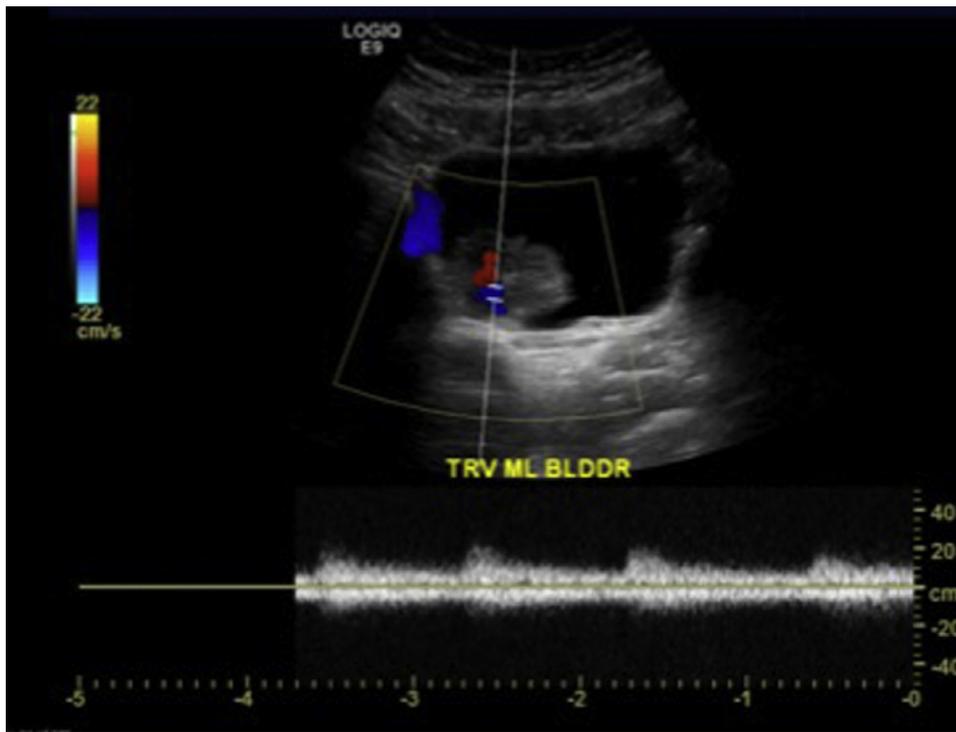


Figure 1. Ultrasound image of polypoid lesion on the right posterior bladder wall in transverse plane. (Color version available online.)

to limit bladder spasms. 50 mg of BCG reconstituted in 50 mL of normal saline is then instilled through a 10 Fr catheter. The catheter is removed and the solution is left in place for 2 hours with changes in patient positioning every 15-30 minutes. At the end of treatment, the patient empties her bladder. Post-treatment, she is given Oxybutynin, Pyridium, Acetaminophen, and Ibuprofen as needed based on irritative symptoms.

Maintenance therapy is continued every 3 months with 3 weekly instillations and interval surveillance cystoscopy

under general anesthesia 1 month after each treatment course, with plans for a total of 3 years of therapy. Upper tract imaging is performed every 6 months with magnetic resonance (MR) urography without anesthesia. Urine cytology is also collected every 3 months prior to subsequent treatments.

COMMENTS

Pediatric bladder lesions tend to be low-grade, solitary lesions with minimal risk of disease progression or local

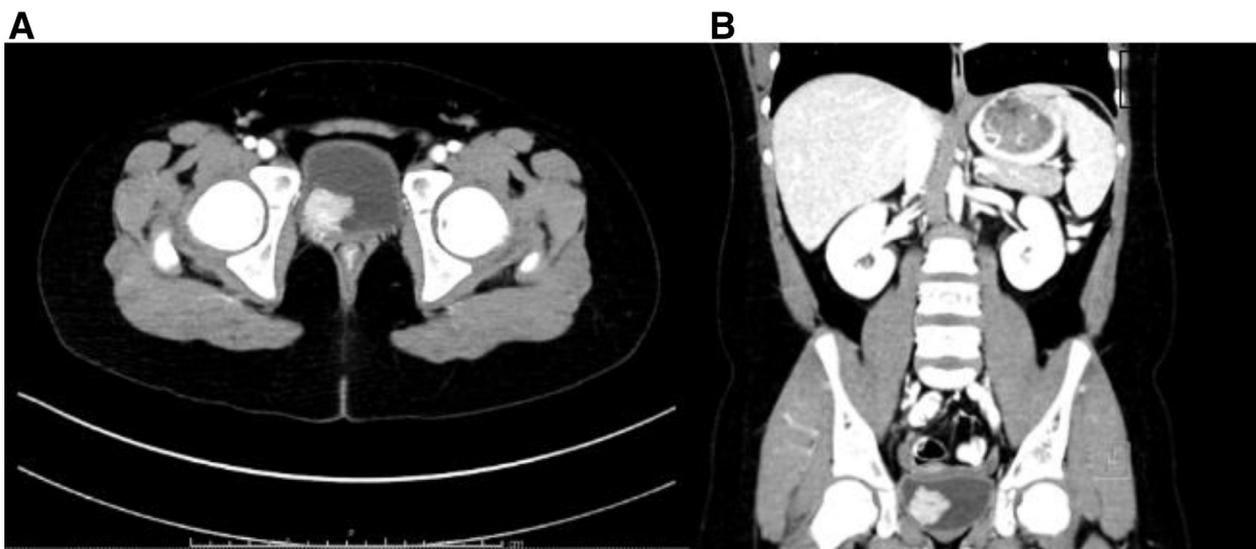


Figure 2. Contrast-enhanced CT images (A. axial and B. coronal) demonstrating large, irregular appearing bladder lesion on right posterior bladder wall. CT, computed tomography.

recurrence.²⁻⁴ Urothelial papilloma and papillary neoplasm of low malignant potential are more common than UC in this population.² Most pediatric tumors appear to have unique pathologic and molecular features, leading to a benign course after initial resection.³ There are fewer than 10 reported cases of high-grade bladder tumors in patients under 18 years of age and disease progression with poor outcomes has been reported.^{2,3}

Intravesical chemotherapy and immunotherapy is commonplace in adult nonmuscle invasive UC. A single postoperative instillation of intravesical chemotherapy after complete tumor resection is recommended for low- or intermediate-risk bladder cancer. High-risk adults, including newly diagnosed CIS, high-grade T1, or high-risk Ta UC, should undergo a 6-week induction course of BCG after complete resection. In complete responders, maintenance BCG is recommended for 3 years, as tolerated.^{5,6} There is a 30% absolute advantage for disease recurrence in those treated with intravesical BCG compared to transurethral resection alone and a 27% reduction in disease progression in patients who receive maintenance therapy.^{7,8} Superiority of BCG over intravesical mitomycin C has also been shown in intermediate to high-risk patients.^{8,9}

The role of intravesical therapies in pediatric patients as well as the potential side effects remains unclear. There is only 1 identifiable case report of induction BCG in the setting of high-risk disease in a prepubertal patient. However, surgical management was with partial cystectomy as opposed to transurethral resection alone, and maintenance therapy was not performed given poor patient tolerance.¹⁰ There is 1 report of successful maintenance BCG therapy for low-grade disease in a postpubertal pediatric patient.¹¹ There are limited pediatric reports of the use of postoperative intravesical mitomycin C in either low-risk or high-risk disease.¹²

Given the lack of existing BCG protocols in pediatric patients, we developed our own multidisciplinary protocol for administration and surveillance based on the existing adult literature.¹³ We opted to be more aggressive with maintenance therapy intervals (~q3 months for 3 years) and surveillance than recommended in adult guidelines given her high-grade disease.

Various case series have suggested that given the generally benign nature of disease in the pediatric population, ultrasound alone is a sufficient means of surveillance.¹⁰ Our patient however has high-grade disease, and we believe that frequent cystoscopy is required. We also obtain urine cytology in 3-month intervals.

Major complications from BCG are very rare and the most common side effects are local bladder symptoms, such as dysuria, urgency, and frequency.¹³ Although, the safety of BCG in the pediatric population has not been established, we anticipated a similar side effect profile in our patient, leading to pretreatment and post-treatment with anticholinergics and non-narcotic analgesics.¹⁴

While 1 patient is insufficient to determine efficacy and safety of the drug in pediatric patients, our experience suggests that future patients with similar disease presentation

can be successfully managed endoscopically followed by induction and maintenance BCG with the goal of decreasing disease recurrence, progression, and patient morbidity.

CONCLUSION

Here, we discuss a single prepubertal patient who presented with gross hematuria and was diagnosed with high-grade T1 UC. Surgical management was performed endoscopically. Given concern for aggressive nature of disease, and no local adult institutions able to provide intravesical therapy, a comprehensive protocol for delivery of BCG was created. The patient tolerated instillation well with only mild, local, self-resolving side effects. She has now completed induction BCG followed by 7 cycles of maintenance therapy without evidence of disease recurrence. Our experience suggests that similar patients in the future may be managed successfully with intravesical BCG after endoscopic resection with good efficacy and low risk of treatment-associated side effects.

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