Large Bladder Mass and Renal Failure in a 14-Year-Old Boy

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A 14-year-old, otherwise healthy adolescent male originally presented to his primary care physician with abdominal pain and distention. Ultrasound revealed a complex mass with cystic components along the superior pole of the bladder and bilateral hydroureteronephrosis down to the level of the bladder.

The Case

A 14-year-old, otherwise healthy adolescent male originally presented to his primary care physician with abdominal pain and distention. The initial examination was unremarkable and his symptoms were attributed to constipation. After 2 months of persistent pain, he returned with obstructive uropathy and ongoing renal failure, evidenced by a serum creatinine level of 13 mg/dL. He was transferred to our institution for further care.

Renal and bladder ultrasound revealed a complex mass with cystic components along the superior pole of the bladder and bilateral hydroureteronephrosis down to the level of the bladder. Obtaining a voiding cystourethrogram was technically challenging due to severe bladder spasms, but this study did show a small functional-capacity bladder and an irregular bladder surface, consistent with an intrinsic bladder mass. Magnetic resonance imaging (MRI) of the abdomen and pelvis revealed a 4-cm intraluminal mass along the posterior/superior bladder wall and massive bilateral hydroureteronephrosis (Figure 1). A chest computed tomography scan did not show evidence of metastatic disease.

The patient was taken to the operating room for cystoscopic evaluation, biopsy of the bladder mass, and bilateral ureteral stent placement. A large sessile mass with extensive fronds of urothelium was encountered along the posterior wall and dome of the bladder; the trigone and ureteral orifices were spared from involvement. Grossly, the mass appeared consistent with urothelial carcinoma (Figure 2). Bilateral retrograde ureteropyelograms revealed tortuous, dilated ureters bilaterally, with distal ureteral narrowing just proximal to the bladder. Bilateral “double J” ureteral stents were placed. Pathologic evaluation of the bladder biopsies revealed papillary cystitis with focal metaplasia, but no evidence of malignancy.

Postoperatively, neither his serum creatinine level nor his hydronephrosis was improving, prompting placement of bilateral percutaneous nephrostomy tubes (Figure 3). Afterward, his creatinine level declined progressively over 2 weeks until it stabilized near 1 mg/dL. Unexpectedly, over the next few days, he developed intermittent fever and leukocytosis, which were persistent despite a negative infectious evaluation. In addition, his inflammatory markers were consistently and significantly elevated, with an erythrocyte sedimentation rate (ESR) of 127 mm/hr and a C-reactive protein (CRP) level of 16.8 mg/dL, both of which were many times the upper limit of normal values. He continued to suffer severe bladder spasms even though he was receiving regularly scheduled doses of antispasmodics.

Because of his continued symptoms and a nondiagnostic initial biopsy, cystoscopy was repeated 2 weeks later to complete a more extensive transurethral resection of the bladder tumor (TURBT). Postoperatively, his fever and leukocytosis quickly resolved, and his abdominal pain progressively improved. Final pathology of the TURBT specimen revealed an inflammatory myofibroblastic tumor (IMT) with marked atypia and anaplastic lymphoma kinase-1 (ALK-1) gene rearrangement.

Which of the following represents the best next step in management for this patient?

A. Therapy with an ALK inhibitor
B. Medical management with corticosteroids and anti-inflammatory agents
C. Cytotoxic chemotherapy
D. Repeat TURBT
E. Partial or total cystectomy
Discussion

We present a case of an IMT of the bladder causing compression of the ureters and obstructive uropathy. Historically considered part of a group of inflammatory pseudotumors, IMTs are highly vascularized neoplasms of unclear pathogenesis. Although overwhelmingly benign, local infiltration and very rare cases of metastasis have led the World Health Organization to classify IMTs as having intermediate biological potential.[1] Pediatric bladder IMTs, however, have not been associated with metastasis in several series, including a systematic literature review.[2]

IMTs of the bladder in children must first be distinguished from soft-tissue malignancies, most commonly rhabdomyosarcoma (RMS), because the management differs drastically. For a bladder RMS, upfront resection is often associated with significant morbidity. Therefore, neoadjuvant cytotoxic chemotherapy is frequently given prior to local treatment with radiation or surgery. In contrast, IMTs may be amenable to upfront resection or, if necessary, neoadjuvant anti-inflammatory therapy can be given; however, cytotoxic chemotherapy (Answer C) is not routinely employed.

Correct Answer: B

The clinical presentation of an IMT often resembles the typical presentation of other bladder tumors: it can include hematuria, dysuria, obstructive uropathy, abdominal pain, and/or imaging revealing a bladder mass.[3] Constitutional symptoms of malaise, fever, and weight loss may also be present in up to 15% to 30% of patients with IMTs.[4] Histologic analysis reveals spindle-shaped myofibroblasts with inflammatory cells and cytologic atypia—findings that overlap significantly with those of malignant spindle-cell tumors.[3] Recent studies have shown that IMTs have variable ALK-1 expression in 33% to 89% of cases, effectively differentiating IMTs from the adult spindle-cell tumors, sarcomatoid carcinoma and leiomyosarcoma. RMS exhibits ALK expression 20% of the time, although more commonly in alveolar RMS; nonetheless, IMT must be distinguished from RMS by an absence of myogenin and MyoD on immunohistochemical staining.[5,6]

For IMTs, surgical resection remains the mainstay of treatment, with durable results for complete resection; however, removal of large tumors can lead to considerable morbidity because of organ compromise. For example, in this case, because of the location of the mass and its large volume, initial surgical resection would likely require complete cystectomy or an extensive partial cystectomy (Answer E), which would leave the patient with a restrictively small-capacity bladder. The location and large volume also mean that repeat resection with TURBT (Answer D) would not result in complete resection.

Several reports of reduction in tumor size and even complete response with a combination of corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs) prior to surgical intervention (Answer B) have been published.[7,8] In a Children’s Oncology Group study of 18 IMT specimens, vascular endothelial growth factor and cyclooxygenase 2 (COX-2) expression were seen in all samples. This supports the hypothesis that anti-angiogenesis underlies the significant improvements noted in tumor size with NSAID and corticosteroid combination therapy.[8,9] Because of the locally infiltrative nature of IMT, surgery can be highly morbid when extensive resection of the bladder or adjacent organs is required.[10] However, significant reduction in tumor volume can result from neoadjuvant anti-inflammatory therapy. Tumor size reduction may make it possible to avoid complete cystectomy and may allow for partial cystectomy with preservation of larger functional-bladder capacity.

KEY POINTS

- Inflammatory myofibroblastic tumors (IMTs) are highly vascular neoplasms of unclear pathogenesis that must be differentiated from rhabdomyosarcomas.
- No pediatric cases of IMT have been associated with metastasis, but because IMTs are locally infiltrative, resection can lead to...
significant morbidity.

- Combination
  therapy with corticosteroids
  and NSAIDs
  can reduce tumor
  size, allowing less
  morbid resection, or
  may even lead to a
  complete response.
- Approximately 50%
  of IMTs have ALK
gene rearrangements;
targeted therapy
may hold promise for
future treatment.

The fact that some IMTs are unresectable or locally recurrent has encouraged investigation into the use of targeted therapies. Although there has been no direct association established between ALK expression and aggressive forms of IMT, certain IMTs with ALK-rearranged fusion proteins share common morphologic features and behavior.[11] A targeted ALK inhibitor, crizotinib, was shown in a recent clinical trial to induce a sustained partial response in an adult patient with an aggressive, ALK-translocated IMT as opposed to no response in a patient without ALK-translocation.[12] A phase I trial of crizotinib in pediatric patients enrolled seven patients with IMTs; all of these patients had a partial response or stable disease.[13] Since approximately 50% of IMTs have an ALK rearrangement, such targeted therapy may hold promise for future cytoreduction and treatment options in a segment of the IMT population. While clinical trials (Answer A) are currently ongoing, these studies hold an inherent risk of randomization to nontreatment, and this uncertainty may not be acceptable to patients when successful treatments are available.

**Outcome of This Case**

Initial surgical resection would have required complete cystectomy or an extensive partial cystectomy, which would have left the patient with a restrictively small-capacity bladder; therefore, preoperative medical management was instituted in an attempt at cytoreduction. With the assistance of pediatric oncology, the options of combination therapy with a corticosteroid and a COX-2 inhibitor vs a clinical trial with a targeted ALK inhibitor were presented to the patient and his family. Because of the undertainty of treatment in a clinical trial of an ALK inhibitor, the family decided on an 8-week course of prednisone and celecoxib, hoping that this would decrease the size of the tumor sufficiently to enable partial cystectomy.

After 2 months of neoadjuvant therapy, the patient’s ESR and CRP level normalized. A follow-up MRI scan revealed a decrease in mass size and resolved hydronephrosis; therefore, partial cystectomy was planned. Intraoperatively, the ureters were found to be obstructed bilaterally just proximal to the bladder, secondary to a mass effect. The ureters were therefore divided and reimplanted in a refluxing fashion, because of limited ureteral length and small bladder capacity. Bilateral double J ureteral stents were placed, and bilateral pelvic lymph node dissection was completed. Pathology revealed an IMT with focal atypia and a focal positive posterior margin; lymph nodes were all negative. Additional medical management after surgical resection was not instituted.

At his 9-month follow-up visit, the patient remained radiographically recurrence-free, and his inflammatory markers (ESR, CRP level) remained normal.

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E. David Crawford, MD, serves as Series Editor for Clinical Quandaries. Dr. Crawford is Professor of Surgery, Urology, and Radiation Oncology, and Head of the Section of Urologic Oncology at the University of Colorado School of Medicine; Chairman of the Prostate Conditions Education Council; and a member of ONCOLOGY’s Editorial Board.

If you have a case that you feel has particular educational value, illustrating important points in diagnosis or treatment, you may send the concept to Dr. Crawford at david.crawford@ucdenver.edu for consideration for a future installment of Clinical Quandaries.
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