

High-Grade Urothelial Bladder Cancer in Children: A Case Report and Critical Analysis of the Literature

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Abstract

Bladder cancer is relatively common in adults; however, in children, bladder malignancies are extremely rare. In the present case report, we describe the diagnostic, therapeutic, and follow-up management of bladder cancer in a 3-year-old boy. Furthermore, we focus on typical and less frequently seen histological characteristics of bladder cancer in childhood. Despite its low incidence and prevalence, it is very important to emphasize that bladder cancer is the most serious condition which should not be missed in the differential diagnosis of hematuria or urinary tract infection.

Keywords: Bladder cancer; Treatment; Children; Pathology

Clinical Practice Points

Bladder tumors are extremely rare in children. In the overwhelming majority of cases, the tumors are low grade and non-muscle invasive.

Standard treatment is transurethral resection, usually with no postoperative intravesical chemotherapy.

Bladder cancer may be mimicked by urinary tract infection and therefore lead to misdiagnosis and delayed treatment.

Introduction

Tumors of the urinary bladder are among the most important malignant diseases of the urinary tract. These tumors represent about 5%–10% of all cancers worldwide. According to Global Cancer Statistics for the year 2012, bladder cancer incidence and mortality rates are estimated to be 430,000 and 165,000 cases, respectively. Among men, the incidence is three times higher than in women [1]. Due to the incidence to mortality ratio in adults, bladder cancer is considered one of the most serious diagnoses in oncological urology. The most important risk factor is tobacco smoking where the risk is 2–6 times higher in smokers than in non-smokers [2]. From the histological point of view, transitional cell cancer (TCC) has the highest prevalence. Carcinogens causing TCC include aromatic amines (e.g., 2-naphthylamine, 4-aminobiphenyl, benzidine). The second most common type of bladder cancer is spinocellular cancer (10%) due to chronic urinary infection caused by schistosoma haematobium. At the time of diagnosis, 70%–80% of tumors are non-muscle invasive (staging Ta, T1 or carcinoma in situ).

In the pediatric population, urothelial malignancies are quite rare with a little over 100 cases described worldwide in patients under 20 years of age. Similar to adults, transitional cell cancers are histologically the most prevalent. Of these, neoplasias of low malignant

potential and low-grade tumors can occur with most tumors being non-invasive (stage pTa) [3]. Infiltrating (pT1) or high-grade cancers are exceedingly rare. Painless hematuria is usually the dominant symptom indicated for further examination. Exclusion or precise assessment of the location and extent of bladder cancer requires careful cystoscopy followed by curative transurethral tumor resection (TUR). The differential diagnosis must include urinary infection, stone formation, or possibly a foreign body in the urethra or bladder.

Case Report

We present a case of a 3-year-old boy examined by his pediatrician due to an isolated episode of painless gross hematuria in December 2013. During further urine testing, only mild microscopic hematuria was detected. Sonography revealed an exophytic tumor 13 × 6 mm on the dorsal wall of the urinary bladder with well-marked blood supply on color-flow mapping (Figures 1 and 2). Upper urinary tract sonography showed no pathology. The patient was indicated to cystoscopy under general anesthesia, which confirmed a 12-mm papillomatous tumor with a thin stalk on the back wall of the bladder. Transurethral resection with cold cup biopsy of the tumor bed was performed. The patient was discharged after permanent catheter removal on the second postoperative day. Specimens were sent for histopathological assessment and the diagnosis of high-grade stage T1 transitional cell cancer with a papillary configuration was made (Figure 3). The papillae were lined by urothelium of various widths, with evident focal nuclear atypia. Surprisingly, glandular, squamous, and osseous metaplasias were present. Immunohistochemistry revealed the positivity of p53 and aberrant expression of CK 20 in the tumor (Figure 4). The Ki-67 index as a marker of proliferation activity reached up to 20%. In the stromal papillae, metaplastic bone parts were focally present (Figure 5). The above pathologic diagnosis was confirmed independently on a second opinion obtained from an outside institution.

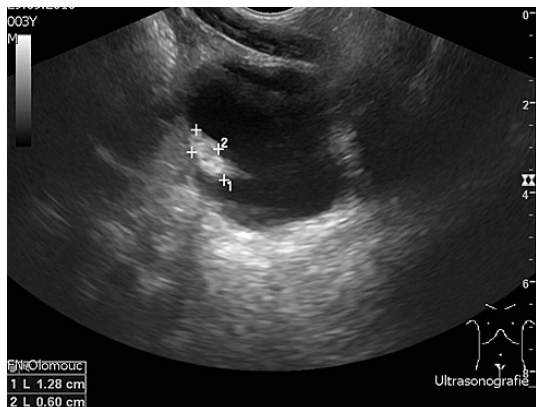


Figure 1: Transabdominal sonography - sagittal view, urinary bladder with tumour.

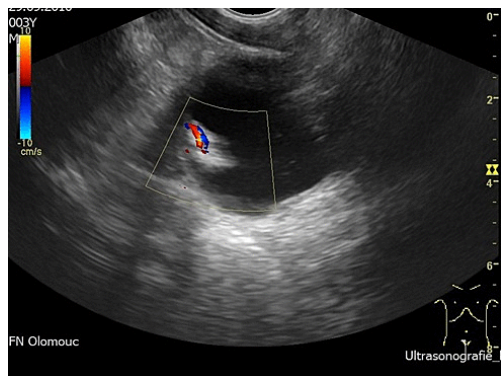


Figure 2: Transabdominal sonography - sagittal view, urinary bladder with tumour with color-flow mapping.

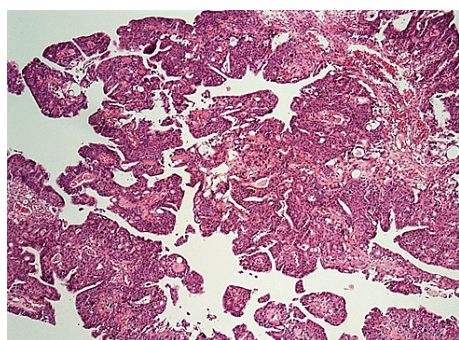


Figure 3: Microscopy - HG papilocarcinoma (H&E, 100x).

The follow-up schedule involves regular check-ups in 3–6-month intervals: urinalysis, urine cytology, and kidney and bladder sonography. One year after the initial TUR, cystoscopy under general anesthesia was indicated, with no pathological finding in the bladder.

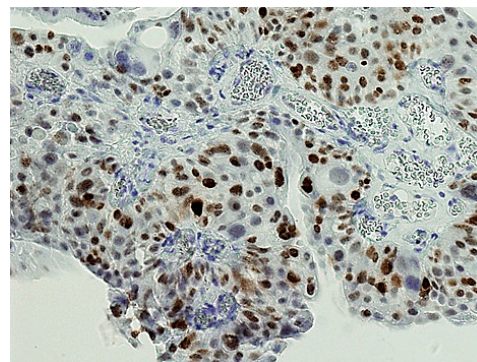


Figure 4: Microscopy - p53 positivity in tumor cells (400x).

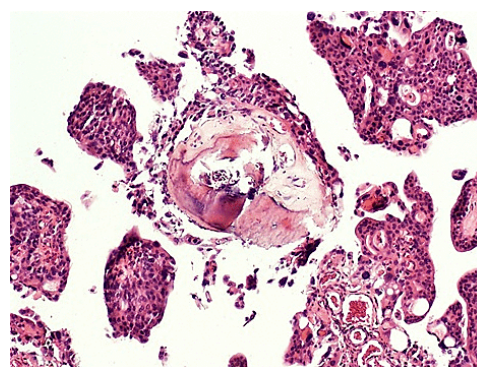


Figure 5: Microscopy - bone metaplasia in stromal papillae (H&E 200x).

Upper urinary tract tumor was ruled out by magnetic resonance urography (MR-urography). The patient remains free of any evidence of recurrent disease either locally or systemically two years after the initial diagnosis was established.

Discussion

Urinary bladder carcinomas are typical tumors with environmental background. The most important risk factor is smoking where smokers are more often affected at a younger age and they are often higher grade or stage. It is estimated that up to 50% of bladder cancers in men and 35% in women are directly caused by smoking. The male to female ratio is 3:1 and racial difference is also typical with a 39-fold higher prevalence among Caucasian men as compared to African Americans. Transitional cancer of the bladder is a very rare malignancy in patients under 40 years (1%–2.4% of all cancers) and among patients under 20 years it is extremely rare (0.1%–0.4% of all bladder cancers) [3-7]. According to a recent meta-analysis, only 103 bladder cancer patients under 20 years have been described. Moreover, while two thirds of the patients were older than 15 years, only 14 patients were under 10 years of age [3]. A typical sign is usually painless gross hematuria, often as an isolated symptom. Sonography can reveal an exophytic bladder tumor, but cystoscopy is of crucial importance with subsequent histological confirmation of the tumor by biopsy or TUR.

The configuration of the urothelial tumor is usually papillary, but it can also be solid or mixed. The lesion is often seen as a thickening of the epithelium with an increased number of cell layers evenly distributed, but densely packed. In adults, urothelial cancers are non-muscle invasive (i.e., Ta and T1) in more than 75% of cases and in children the number is even higher.

While the diagnosis and treatment of bladder cancer in children/young patients is quite straightforward and routine, there is a lack of uniformity in the postoperative follow-up in terms of the extent and frequency of examinations. In adults, the schedule of postoperative cystoscopies, cytologies, and upper urinary tract examinations is an essential part of all urological guidelines (American Urological Association, European Urological Association, National Comprehensive Cancer Network, etc.) [8]; however, there are no precise follow-up recommendations for children. Most follow-up protocols use sonography to exclude recurrence. Both cytology and cystoscopy are only seldom used on a regular basis although they have a higher recurrence detection rate compared to sonography alone. The frequency and type of examination vary according to tumor risk stratification (low – intermediate – high risk). In general, the recurrence rate after initial tumor excision/resection reaches 40%–50%, with an additional 10%–15% of progression to muscular involvement in adult patients. In children, both recurrence and progression occur rarely. According to data meta-analyses [9,10], the recurrence rate in patients younger than 20 years is only 7%, with tumor progression being almost exceptional. While single (or maintenance) intravesical instillation of chemotherapy is a standard and essential part of treatment after TUR, its use in children has only been described in few cases. Contrary to the prevalent transitional cell tumors and the less frequently diagnosed spinocellular cancers or adenocarcinomas in adults, it is urothelial tumors that are exclusively detected in pediatric patients. Transitional cell carcinoma with osseous metaplasia of the stroma is a rare variant of urothelial carcinoma. In the literature, there are only a few case reports describing this condition which must be distinguished especially from sarcomatoid carcinoma [11].

In children, it is important to particularly include two benign conditions in the differential diagnosis of bladder tumors: hamartoma and nephrogenic adenoma. Nephrogenic adenoma as a benign proliferation of the small glands of the urinary tract can almost exclusively be seen in the urinary bladder in children. The endoscopic appearance can mimic a malignant tumor due to the papillary appearance. Furthermore, the papillae may be mistaken for TCC on microscopy [12]. Bladder hamartomas are extremely rare and in children, with only few cases having been published so far. Microscopically, the glands are dilated and may be filled with eosinophilic or proteinaceous secretions. Other pathological findings include a higher vessel density and a lack of cellular atypia or mitotic activity [13]. These are crucial differences in comparison with a typical urothelial bladder malignancy.

Conclusion

After excluding urinary tract infection, stones or a foreign body in the urinary tract, urothelial bladder cancer has to be ruled out in children with gross hematuria. In pediatric cases, low-grade TCCs are typically found. It is important to differentiate urothelial cancer from hamartoma and nephrogenic adenoma and, particularly in osseous metaplasia, from sarcomatoid carcinoma. Especially in high-grade cancers, precise TUR of the tumor with a careful follow-up is essential to detect cancer recurrence and to reduce progression.

Conflict of Interests / Funding

None.

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