Urothelial carcinoma of the urinary bladder in a 12-year-old girl: A case report with immunohistological analysis and a review of the literature

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A B S T R A C T

Urothelial carcinoma of the bladder in childhood is extremely rare. We report on a 12-year-old girl with urothelial carcinoma of the bladder who presented with gross hematuria. Immunohistochemical staining showed normal levels of cytokeratin 20 expression and decreased levels of Ki67 and p53 expression. Human papillomavirus, which can be a cause of urothelial carcinoma of the bladder, was not detected by polymerase chain reaction. We reviewed the literature focusing on diagnostic tools for urothelial carcinoma of the bladder and determined that abdominal ultrasonography, with an extremely high sensitivity of 98%, could be a useful tool for postoperative follow-up in childhood.

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1. Introduction

Urothelial carcinoma of the bladder (UCB) in childhood rarely occurs and is usually low grade and non-muscle-invasive with a low risk of recurrence and progression.1 However, why UCB has a lower rate of recurrence and progression in children than in adults is unclear. Additionally, due to the small number of cases studied, the appropriate follow-up procedures after the initial transurethral resection (TUR) remain undefined. Here, we present a case of UCB in a 12-year-old girl who presented with low-grade pTa. Furthermore, we examine the molecular profile of UCB and review the existing literature.

2. Case presentation

A 12-year-old girl was referred to our hospital with painless macrohematuria. Abdominal ultrasonography revealed a 9 × 7-mm exophytic tumor on the neck of the bladder wall (Fig. 1). Ultrasonography showed no abnormal finding in the upper urinary tract. Her physical examination was unremarkable, and she had neither a significant medical or family history, nor a history of exposure to secondhand smoking and chemical compounds. Urinalysis revealed numerous red blood cells, whereas urine cytology was repeatedly negative. Multiple T1-weighted Gd-enhanced magnetic resonance images of the bladder showed a contrasting intravesical papillary tumor on the neck of the bladder. She was indicated for cystoscopy under general anesthesia, which revealed a 10-mm papillary pedunculated tumor in the 5 o'clock direction of the bladder neck. Cold cup biopsy and transurethral resection of the tumor were performed. Histopathology revealed non-invasive papillary urothelial carcinoma of low-grade pTa according to the 2004 World Health Organization classification of bladder tumors. The muscularis propria was absent from the specimen; however, there was no invasion of atypical cells to the lamina propria. Expression of cytokeratin 20 (CK20), Ki67, and p53 was evaluated by immunohistochemistry. CK20 staining was localized to only the tumor cell...
The Ki67 tumor index was 1–2%, and a few cells were positive for nuclear p53 (Fig. 2). Cold cup biopsy and repeat cystoscopy 3 months after the initial resection revealed no residual urothelial carcinoma. One year after the initial diagnosis, abdominal ultrasonography revealed no evidence of tumor recurrence. Urine cytology and blood cells in the urine were negative.

3. Discussion

The most frequent bladder neoplasm in children is rhabdomyosarcoma, while UCB is very rare, with less than 0.4% of cases occurring within the first two decades of life. UCB is typically caused by environmental factors such as cigarette smoking, occupational exposures, e.g., aromatic amines, and intravesical chronic inflammation. However, the risk factors in children have not yet been defined. We reviewed the Pubmed and Japanese Medical Abstracts Society databases for reports in English or Japanese, using the keywords “bladder,” “urothelial carcinoma,” “transitional cell carcinoma,” and “children.” We identified 188 cases of bladder neoplasms in patients under 20 years of age from Japan and abroad. The male-to-female ratio was 3.4:1, and the number of cases increased as age increased. Typically, UCB occurs as a solitary tumor, and 89% of the cases were low-grade tumors; 87% and 9% were pTa and pT1, respectively. Most were hypothesized to have a lower rate of recurrence and progression, unlike older patients. Only 3 cases of low-grade pTa tumor recurred within 36 months after the initial surgery, and there were no cases of progression. In order to investigate the potential of recurrence, we examined the molecular profiles of CK20, Ki67, and p53 (Fig. 2). CK20 is a sensitive marker for urothelial differentiation in superficial bladder tumors, and abnormal CK20 staining is likely to be associated with a high recurrence rate. Ki67 is an established strong marker of cell proliferation, and its expression independently correlates with tumor recurrence and progression. Expression of p53 is thought to be a marker of progression and an indicator of poor prognosis. In our patient, while CK20 expression was normal, both Ki67 and p53 were expressed at low levels. Based on these results, it was determined that the patient has a relatively low risk of recurrence or progression.

The mechanisms underlying the carcinogenesis of UCB in children are not well understood. Human papillomavirus (HPV), a known risk factor for cancer development, is known to be involved in UCB. Recently, it has been reported that HPV infection occurs in more than half of young women within a few years of their sexual debut. To determine the role of HPV infection in our patient, we performed polymerase chain reaction using an HPV typing set (6603, Takara Bio Inc, Tokyo, Japan). This typing set is designed for the identification of a broad range of HPV types by using HPV-type
specific primers, and can, therefore, identify both the malignant (HPV-16, 18, 31, 33, 35, 52b, and 58) and benign (HPV-6 and 11) types of HPV. Our patient had no amplification of HPV DNA, indicating the absence of HPV infection (Fig. 3).

The management of UCB in children after the initial TUR is controversial. From the 188 cases summarized from past literature, it appears that the most frequent complaint is the occurrence of asymptomatic macrohematuria (85%). Interestingly, microhematuria was detectable in 79% of cases by urinalysis, although urine cytology was positive in only 7% at the time of the hospital visit. Abdominal ultrasonography, the main tool for diagnosis, has a 98% sensitivity because of the reduced abdominal fat and thinner muscle layers in children. Therefore, we recommend ultrasonography as the main tool for postoperative follow-up in cases of childhood UCB. Based on the results of the histopathological examination and the high sensitivity of ultrasonography, we believe that we can follow up our case without frequent cystoscopy.

4. Conclusion

UCB is extremely rare in childhood, with recurrence rates lower than those seen in adults. We believe that this difference could be due to the differences in the molecular profile of this cancer in children and adults. Furthermore, we believe that we can follow up our patient effectively with ultrasonography and urinalysis without performing repeated cystoscopy.

Declaration of interest

None.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eucr.2017.12.008.

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