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Review article

Unique clinicopathologic and molecular characteristics of urinary bladder tumors in children and young adults

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Abstract

In children and young adults, urothelial carcinoma and other epithelial neoplasms of the urinary bladder are rare. When these tumors do occur, they appear to exhibit unique clinicopathologic features, with preferentially low-grade morphology and decreased likelihood of recurrence and progression, although some debate exists regarding their biologic behavior. In contrast, a subset of soft tissue tumors is more commonly seen in pediatric patients, with rhabdomyosarcoma being the most common malignancy in this location. Likewise, inflammatory myofibroblastic tumor may be a source of differential diagnostic complexity. In the setting of previous bladder augmentation, patients appear to have a distinctive disposition to develop epithelial neoplasms later in life. Data regarding the molecular characteristics and clinical behavior of pediatric bladder tumors are, with the exception of rhabdomyosarcoma, less well understood than those of adult/elderly patients. In this article, we review the distinguishing features of urinary bladder neoplasms in pediatric and young adult patients, with special emphasis on unique clinicopathologic features, molecular-genetic abnormalities, and syndromic associations of urothelial neoplasms in this patient population.

Keywords: Urinary bladder; Neoplasia; Urothelial carcinoma; Augmentation cystoplasty; Fluorescence in situ hybridization; Fibroblast growth factor receptor 3; p53 Mutation

1. Introduction

In pediatric patients, or those in the third to fourth decade of life or younger, urothelial carcinoma (UC) or transitional cell carcinoma (TCC) is distinctly less common than in elderly patients. In children, tumors of the urinary bladder are rare in general, although true UC has been reported, primarily in case studies and a few larger series [1–5]. For the most part, such tumors have been found to exhibit distinct clinical behavior with infrequent recurrence and disease progression. Molecular features of UC in young patients have been less well elucidated; however, emerging evidence appears to demonstrate decreased frequency of the genomic aberrations typical of UC [6] (Table 1). Links between familial cancer syndromes and pediatric UC are limited, although some hypotheses and associations in this area have been proposed.

In contrast, soft tissue neoplasms are characteristically described in the pediatric patient population, with rhabdomyosarcoma being the most common malignancy [7]. Likewise, inflammatory myofibroblastic tumor (IMT) is an enigmatic entity that may provide a source of differential diagnostic difficulty. Patients with history of bladder augmentation surgery at a young age are also notable for a particular predisposition to epithelial tumor development later in life. Other epithelial proliferative processes, such as polyps, papillomas, and nephrogenic adenomas (NA) may sometimes be seen, and their differentiation from UC is important to avoid overdiagnosing carcinoma, which is especially important in a population of very young patients.

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Table 1
Unique clinicopathologic and molecular characteristics of urothelial carcinoma in adult, pediatric, and augmentation cystoplasty patients

	Adult	Pediatric	Augmentation cystoplasty
Incidence	Common	Rare	Rare
Association with cigarette smoking	Strong	Conflicting data, likely absent	Absent
Association with occupational exposure	Strong	Absent	Absent
Sex predilection	Male	Male	Male and female equally affected
Tumor grade	Variable	Primarily low-grade	High-grade
Tumor stage	Variable (typically low stage)	Noninvasive (pTa)	Advanced stage
Mutifocality	Common	Uncommon	Unifocal
Location predilection	Trigone	Trigone	Adjacent to enterovesical anastomosis
Clinical presentations	Irritative symptoms and hematuria	Irritative symptoms and hematuria	Hematuria/metastatic disease
Association with dysplasia/CIS	Associated with invasive carcinoma	Uncommon	May be present
Upper urinary tract involvement	Frequent	Very rare	Very rare
Biological behavior			
Recurrence	Frequent	Infrequent	Aggressive
Progression	Infrequent	Very infrequent	Frequent
Metastasis	Infrequent	Very infrequent	Frequent
Molecular features	FGFR3 and TP53 mutations, and chromosomes 9 and 17 abnormalities are common	Molecular abnormalities frequently absent	Amplifications of 2q, 5q, 10p, 21p, 21q and deletions of 5p and 16p
UroVysion testing	Useful	May be useful	Useful

2. Urothelial carcinoma

2.1. Urothelial carcinoma in children

True urinary bladder UC in pediatric patients is highly unusual, although occasional cases do occur. In the 1969 study by Javadpour and Mostofi, only 40 primary epithelial bladder tumors were identified in the first 2 decades of life from 10,000 total cases [1]. The majority of cases (35) were papillary, non-infiltrating tumors (Fig. 1A) and interestingly, the striking male predilection common to adult UC was observed in the pediatric cases (9:1). Patients in their series ranged from 6 to 20 years of age, and most presented with gross hematuria. Less frequent presenting symptoms included microscopic hematuria, dysuria, and urinary frequency. Notably, a small minority of the studied patients exhibited invasive carcinoma [1]. In the first decade of life, primary bladder carcinoma has been suggested to be even more uncommon, [2] although some authors more recently have found up to 30% of pediatric cases to occur at 10 years of age or younger [3]. Not surprisingly, UC of the upper urinary tract is yet more unusual [8]. Owing to this rarity, several authors have warned that diagnosis of urothelial tumors in children may be somewhat delayed from the initial onset of symptoms, due to reluctance of many physicians in pursuing an aggressive hematuria work-up for these patients [4,9,10].

The rarity of urothelial tumors in the pediatric population has led to a number of questions regarding their biological behavior. Some authors have found that these tumors are primarily low-grade, with infrequent recurrence and more indolent behavior than those of adults [1,2,11]; however, other authors have suggested that pediatric UC does recur and should be followed carefully [4,5]. It has been suggested that in patients with multiple tumors, recurrence may be more likely [8]. As pediatric urothelial tumors include an abundance of low-grade lesions, the utility of urinary cytology in establishing the diagnosis has been called into question [10,11]. Recent molecular evidence contrasting abnormalities of urothelial neoplasms in pediatric and adult patients suggests that pediatric tumors indeed are distinct and may develop along different pathways [6] (Table 1). These findings are discussed in greater detail in a later section.

Fine and colleagues studied 23 urothelial neoplasms occurring in patients 20 years of age or younger, reclassifying each tumor based on the 2004 World Health Organization (WHO) and 1998 WHO/International Society of Urologic Pathology (ISUP) classification schemes [3]. Tumors included: urothelial papilloma (8.7%), papillary urothelial neoplasm of low malignant potential (PUNLMP, 43.5%), noninvasive low-grade papillary UC (34.8%), and noninvasive high-grade papillary UC (13%). Most patients were treated with transurethral resection, while 1 patient was treated with partial cystectomy and thiotepa. Another patient was additionally treated with mitomycin in conjunction with transurethral resection. Recurrences were identified in 3 of 21 patients and all were alive without evidence of disease at 6 months to 13 years (mean 4.5 years) [3], reaffirming the idea that pediatric UC is generally low-grade with low risk of recurrence.

In a later study including many of the same patients, Wild et al. found that IHC staining for cytokeratin 20 (CK20) demonstrated the normal pattern of expression (only the superficial cell layer) for the majority of the studied pediatric urothelial neoplasms. In particular, all tumors classified as PUNLMP maintained the normal CK20