High-Grade Non-Invasive Transitional Cell Carcinoma with Osseous Metaplasia of the 3-Year-Old Boy Urinary Bladder

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Introduction

Transitional cell carcinomas of the urinary bladder are very rare in paediatrics. In children clearly outweights low grade transitional cell carcinomas, however individual cases of high grade tumors were also described.

Case report

We present the case of a 3-year-old boy who was referred to paediatric urology with attack of macroscopic hematuria with subsequent recurrent microscopic hematuria, without dysuria. Ultrasound (US) examination of kidneys showed no pathology (right kidney length 72 mm, width 9 mm, left kidney length 75 mm, width 11 mm, parenchyma with reasonable echogenity). US of the bladder revealed a 13 × 6 mm hyperechogenic, slightly irregular, oval mass on the dorsal bladder wall with apparent vascularization in color flow mode (CFM).

During cystoscopy a polypous tumor with thin stalk on the posterior bladder wall was identified and resected. Basis of the tumor was resected separately and wound bed was treated by laser and coagulation. We reviewed the pathologic specimen and the sample was then sent to the consultation examination for a second reading to an affiliated medical center. Histologically were encountered fragments of papillary configurated urothelial tumor (Figures 1 and 2).

The papillae are covered by urothel of various widths with architectonics disorder and greater focal nuclear atypia. Mitotic activity is evident, also in higher layers of urothelium. Glandular and squamous cell metaplasia is present. Positivity of p53 and aberrant expression of CK20 were evident in tumor cells in immunohistochemical examination (Figures 3 and 4).

Figure 1: Papillary configurated urothelial tumor-HG papillocarcinoma (H&E 100X).

Figure 2: Papillary configurated urothelial tumor-HG papillocarcinoma (H&E 200X).

Figure 3: Positivity of p53 in tumor cells (400X).

Figure 4: Positivity of p53 in tumor cells (400X).
Figure 4: Aberrant expression of CK20 (200X).

Figure 5: Proliferative activity measured by Ki67 index (200X).

Figure 6: Metaplastic bone parts in stromal papillae (H&E 200X).

Discussion

Bladder tumors, and in particular bladder transitional cell carcinomas, are rare in children. Nearly all reported tumors in paediatric patients are low grade and invasive disease is present in only 3% of cases [1]. Fewer than 30 cases of transitional cell carcinoma (TCC) have been reported in children less than 10 years of age [2-4]. The male-to-female ratio is 3:1. There is also an ethnic difference: white patients are 39 times more common than black patients [5]. The onset symptom is usually macroscopic haematuria, isolated or recurrent, usually with no associated dysuria. Diagnosis is occasionally delayed in paediatric patients because there is a tendency to underestimate haematuria in children [1]. Definitive diagnosis is performed by cystoscopy, which also allows evaluation of tumor extension, excision or biopsy for pathological study [6]. The histological pattern can be papillary, 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.

Proliferative activity measured by Ki67 index is up to 20% (Figure 5). Metaplastic bone parts of benign appearance are focally present in stromal papillae (Figure 6). The consensus diagnosis was high-grade transitional cell carcinoma (HG TCC) based on the 2004 WHO classification of bladder tumors. Three months from diagnosis there was no evidence of tumor recurrence on ultrasound and urine cytology had remained negative.

The nuclei often retain a semblance of normal orientation but are rounded and pleomorphic. Mitosis may be numerous. TCC is non-invasive or minimally invasive at diagnosis in 75% of cases. There is a 50-60% recurrence rate after initial excision with 10-15% progression to muscular involvement [7-8]. Transitional cell carcinoma with osseous metaplasia of the stroma is a rare variant of urothelial carcinoma. There are only a few case reports describing this condition, which must be distinguished especially from sarcomatoid carcinoma. There is no evidence for a sarcomatous component (absence of mesenchymal cell proliferation, absence of mitosis in stromal cells) in TCC with osseous metaplasia [9].

The differential diagnosis of bladder tumors, in children include especially 2 conditions: nephrogenic adenoma and hamartoma.

Nephrogenic adenoma is a benign proliferation of glands of the urinary tract which is almost exclusively seen in urinary bladder in children and can mimic a malignant tumor. Due to the papillary appearance seen on cystoscopy and predominant papillae on microscopy, it may be mistaken for TCC. Other histological differences include absence of mitosis, necrosis and significant cytological atypia, varied histological patterns, edematous lamina propria and the presence of inflammation. Immunohistochemical profile of nephrogenic adenoma includes positive staining with CK7, AMACR, PAX2 and PAX8 (TCC is negative for both AMACR and PAX8) [10].

Hamartomas of the urinary bladder are extremely rare (to date only 10 cases, 5 of them in children under 20 years old). On microscopic examination the tumor is composed of tubuloglandular, nested epithelial and fibro/myxoid mesenchymal tissues. Glands can be cystically distended and are lined by a single to a few layers of flattened urothelium. These cystic dilated glands occasionally contain amorphous eosinophilic secretory concretion or granular proteinaceous material. A part of the mesenchymal tissue can show osteoid-like metaplasia and intestinal metaplasia with goblet cells can be observed in the cystic glands. Hypervascularity, consisting of engorged thin-walled cavernous vascular tissues can also be a distinctive finding of the tumor. There are neither cellular atypia nor mitotic activity of the epithelial or mesenchymal component of the tumor suggestive of true neoplastic growth. Hematopyria associated with infection or inflammatory reaction in the bladder is a characteristic clinical sign in most reported cases [11].
**Table 1:** Differences between papilloma, LG and HG papillocarcinoma and nephrogenic adenoma [10,12,17].

<table>
<thead>
<tr>
<th>Papilloma</th>
<th>Low grade papillocarcinoma</th>
<th>High grade papillocarcinoma</th>
<th>Nephrogenic adenoma</th>
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</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>Mean age: 46 years; range 22-89 years, may occur in children</td>
<td>Mean age: 70 years; rare in children</td>
<td>Usually ages 50+; extremely rare in children</td>
</tr>
<tr>
<td><strong>Gross description</strong></td>
<td>Soft, pink, small isolated growth with delicate papillary structures, usually pedunculated, mean 3 mm.</td>
<td>More solid cores with firmer consistency than papillomas, usually solitary. Wide variation in size.</td>
<td>Sessile or cauliflower-like with necrosis and ulceration. Exophytic papillary growth.</td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td>Discrete papillary growth with a central fibrovascular core lined by urothelium of normal thickness and cytology.</td>
<td>Papillary urothelial neoplasm with some degree of cytoarchitectural disorder and distinct but low grade cytologic abnormality. No high-grade cytologic features (no pleomorphism, no mitoses toward surface, no nucleioli throughout).</td>
<td>A neoplasm with urothelium lining papillary fronds, a predominant disorderly pattern and moderate to marked architectural and cytologic atypia. Metaplastic change with papillary or cystic structures composed of small hollow tubules similar to mesonephric tubules, usually lined by a single layer of bland cuboidal or hobnail cells, surrounding eosinophilic or basophilic secretions. Absence of mitosis, necrosis and significant cytological atypia.</td>
</tr>
</tbody>
</table>
| **Positive stains** | CK20 limited to superficial umbrella cells as in normal urothelium
CK7 | CK20 is stronger and diffusely extending into the deep layers
K67 mostly about 20%
p53 index mostly less than 5%
CK7
Blood group antigens | CK20 is stronger and diffusely extending into the deep layers
K67 higher (mostly more than 40%)
p53 index mostly more than 10%
CK7
Survivin
Overexpression of p16
Beta hCG in 1/3
ER in 14% |
| **Negative stains** | p53
low K67 | Usually survivin
AMACR
PAX8 | Blood group antigens
No/weak expression of E-cadherin |

Basic differences between papilloma, low grade (LG) and high grade (HG) papillocarcinoma and nephrogenic adenoma are listed in Table 1.

**Conclusion**

In paediatric cases of haematuria, transitional cell carcinoma must be ruled out. Among carcinomas of the bladder in children, the most common is a low grade TCC, which must be distinguished especially from nephrogenic adenoma and hamartoma, in cases with osseous metaplasia also from sarcomatoid carcinoma. In the setting of HG disease, resection and adjuvant therapies should be pursued in the attempt to limit recurrences and disease progression.

**References**


17. www.pathologyoutlines.com/bladder