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Case Report

Papillary Urothelial Neoplasia with Low Malignant Potential (PUNLMP) in a 9-year-old Child: A Case Report and Review of Literature

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Abstract:
Papillary bladder tumors in children are rare. They comprise urothelial papilloma, inverted urothelial papilloma, papillary urothelial neoplasm of low malignant potential (PUNLMP), non-invasive low grade papillary urothelial carcinoma, and non-invasive high grade papillary urothelial carcinoma. PUNLMP are the commonest bladder tumors in children. They are typically solitary, small, non-invasive lesions that do not spread. The majority of children present with urinary bladder masses and lower urinary tract symptoms such as hematuria, dysuria, frequent urination, or urgency. Ultrasound is the first line imaging tool for assessing bladder lesions, followed by cross-sectional imaging examinations such as computed tomography or magnetic resonance imaging if the diagnosis is uncertain. The bladder tumor is typically removed through the urethra. We describe a 9-year-old boy who presented with painless gross hematuria for three months. An ultrasound revealed a left bladder tumor, which was treated with a transurethral resection of bladder tumor (TURBT) laser. Histopathology of the removed bladder tissue showed a well-circumscribed PUNLMP, with an immune-profile positive for GATA-3, p63, and CK7, and a low proliferative index. The PUNLMP recurred in the trigone of the bladder a month later. Pediatric PUNLMP is an exceptionally rare neoplasm in children with a low recurrence rate that is amenable to treatment. Pediatric PUNLMP diagnosis is to be suspected in any child with painless hematuria. Recurrence is part of the spectrum of PUNLMP. Hence, follow up of any diagnosed case with PUNLMP is imperative. Given the very small number of cases, it is difficult to determine a clear treatment and follow-up strategy; more cases and research are required to develop specific guidelines.

Level of Evidence of Study: IV (*1*)**.**
Keywords: Papillary urothelial neoplasia with low malignant potential; bladder cancer; PUNLMPs; TURBT; pediatrics; Papillary urothelial neoplasia; painless hematuria
Abbreviations: PUNLMP: Papillary urothelial neoplasia with low malignant potential; TURBT: transurethral resection of bladder tumor; UC: urothelial carcinoma

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Introduction

Papillary bladder tumors in children are rare. They include non-invasive papillary urothelial neoplasms of the bladder: urothelial papilloma, inverted urothelial papilloma, papillary urothelial neoplasm of low malignant potential (PUNLMP), non-invasive low grade papillary urothelial carcinoma, non-invasive high grade papillary urothelial carcinoma and urothelial carcinoma in situ (*2*). Bladder urothelial carcinoma (UC) is the fifth most common carcinoma in humans, with a very low incidence of 0.1–0.4% in the first two decades of life (*3*). The most common form of young age is papillary urothelial neoplasm of low malignant potential (PUNLMP), which grows slowly and has a low tumor grade and stage (*4*). Most children present with lower urinary tract symptoms such as hematuria macro or micro, dysuria, frequent urination, and urgency, whereas systemic symptoms are uncommon and typically limited to advanced disease (*5*). Ultrasound is the first-line imaging tool for detecting urothelial carcinoma, but multidetector computed tomography (MDCT) urography provides the best imaging accuracy. However, flexible ureteroscopy (URS) allows for the exploration of the entire upper urinary tract as well as the biopsy of the tumor (*5*, *6*). Differential diagnoses include exophytic growths,

urothelial papilloma, urothelial dysplasia, and urothelial proliferation with uncertain malignant potential (UPUMP) (*7*). Regarding treatment, transurethral resection of bladder tumor (TURB) frequently allows for complete resection. As a result, a follow-up based primarily on serial US may be considered in the younger age group [6]. We present the case of a 9-year-old boy with painless gross hematuria as the primary complaint. Ultrasound of the urinary tract followed by cystoscopy revealed an intravesical mass that was resected, diagnosed as PUNLMP by histopathology.

Case Presentation

We present the case of a 9-year-old boy who was admitted to the hospital after suffering from painless gross hematuria for three months, as well as generalized fatigue and decreased appetite. The patient's medical, family, and surgical histories were unremarkable. During the patient's physical examination, no pain was felt on palpation of the kidneys or any other part of the genitourinary system. The remainder of the examination was also normal. His height was 130 cm (50th percentile), and his weight was 28 kg (50th percentile for his age). Following that, a complete blood count (CBC) revealed microcytic anemia with normal creatinine. In addition, a urine analysis revealed numerous red blood cells, and no casts were observed but the urine culture came back negative. For further investigation, the patient underwent urinary tract ultrasonography, which revealed a right 23 mm heterogeneous intravesical mass with papillary projections on the surface but no extravesical extension (Figure 1). Based on these findings, the patient underwent a cystoscopy under general anesthesia in a lithotomy position. The cystoscopy revealed a 2 cm papillary lesion in the left lateral wall of the bladder. A TURBT (trans urethral resection of bladder tumor) was used to remove the mass, and histopathology revealed PUNLMP (Figure 1). Microscopic examination showed a urothelial lining several layers thick without significant cytologic atypia. Nuclei were uniformly small to intermediate in size, round to oval, with finely granular chromatin. No hyperchromasia was noted, and nuclear polarity was well maintained. Mitotic figures were rare, and the immune-profile was positive for GATA-3, p63, CK7, and HMWCK. The Ki-67 proliferative index was low (<5%), consistent with a diagnosis of PUNLMP. Three months later, the patient returned for a follow-up cystoscopy without any urinary symptoms. The cystoscopy revealed no tumor in the old resection site, but a new 1 cm papillary lesion in the bladder's trigone area (Figure 3).

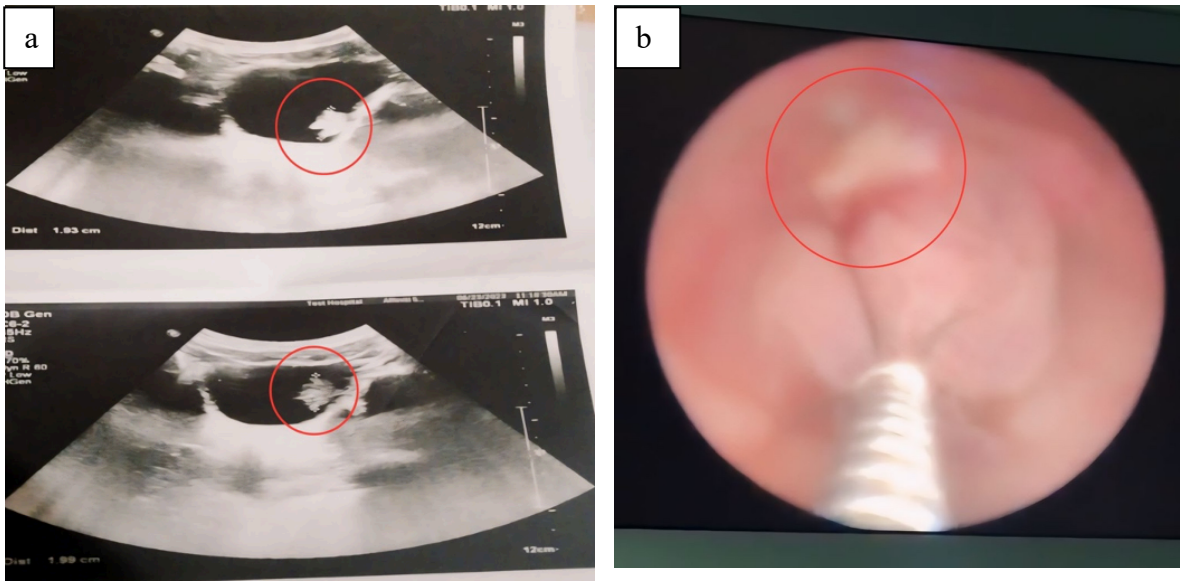

Figure 1. Initial Ultrasound and Cystoscopy intervention images of reported child with papillary urothelial neoplasm of low malignant potential. (a) ultrasound of the bladder demonstrating the papillary lesion at the left lateral wall. (b) The transurethral resection of the tumor with grasper forceps after En Bloc Resection.

Following this finding, a TURBT was performed, and histopathology revealed the recurrence of PUNLMP. (Figure 2). Microscopic examination of the recurrent tumor showed similar features to the initial lesion. The tumor was lined by urothelium, several layers thick, without significant cytologic atypia. The nuclei were uniformly small to intermediate in size, round to oval, with finely granular chromatin. Nuclear polarity was well preserved, and there was no evidence of hyperchromatic nuclei. Mitotic figures were rare. The overall features were consistent with PUNLMP.

Following that, the patient was scheduled for a follow-up cystoscopy three months later. The final cystoscopy showed no evidence of tumor recurrence at either the initial or subsequent resection sites, and the bladder mucosa appeared normal. No new lesions were identified.

We searched PubMed for similar case reports. The search strategy included the terms papillary, neoplasm, malignancies, potentiality, pediatrics, and case reports. Only three cases were found to be similar (Table 1).

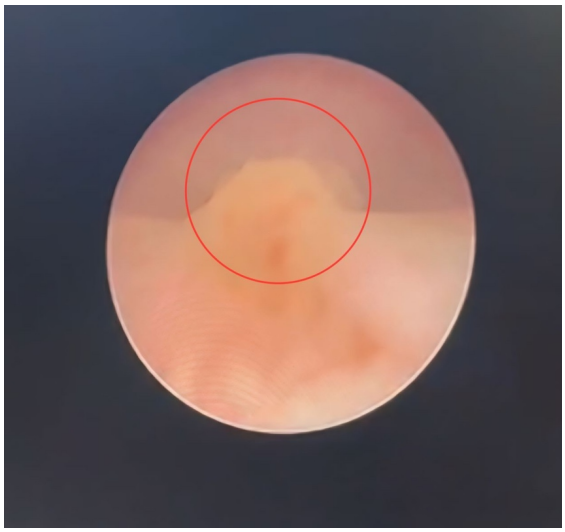

Figure 2. Recurrence of the bladder urothelial papillary neoplasia with a low degree of malignancy at the trigone 3 months later to the resection of initial neoplasm.

Discussion

Urinary bladder urothelial carcinoma is the most common malignant tumor in the urinary system, while non-invasive urothelial neoplasms accounting for the vast majority of bladder cancers at first diagnosis [7]. Non-invasive urothelial neoplasms are classified into two types: flat and papillary [8]. Papillary neoplasms are further classified as urothelial papilloma, inverted urothelial papilloma, papillary urothelial neoplasm with low malignant potential (PUNLMP), non-invasive low grade papillary urothelial carcinoma, and non-invasive high grade papillary urothelial carcinoma [7]. The World Health Organization/International Society of Urological Pathology 2004 classification defines PUNLMP as a papillary urothelial tumor that resembles an exophytic lesion but has increased cellular proliferation that exceeds normal urothelium thickness [9]. Urothelial bladder neoplasms are extremely rare in children under the age of ten, with fewer than 35 cases reported [2]. Yet, in a child with painless hematuria PUNLMP should be suspected. While PUNLMP might be recurrent, it runs a more benign course than carcinoma. Hence, diagnosis of PUNLMP is important to relive the patient and his family anxiety.

Table 1. Previously reported cases of papillary urothelial neoplasm of low malignant potential in children.

	Sex and Age	Past medical history	Symptoms	Imaging	Diagnosis	Management
Maurizi *et al.*, 2019 (*4*)	Male 9 years old	nothing	Gross hematuria	cystoscopy : presence at the right ureteral meatus of papillomatous structure (of about 2 cm of diameters)	urothelial papillary neoplasia with a low degree of malignancy, without infiltration of the sub-epithelial connective tissue	transurethral resection (TUR) : removed entirely

Alam *et al*., 2010 (*8*)	Female 10 years old	- End stage renal disease secondary to Branchio Oto-Renal Syndrome - received a living related renal transplant at the age of six year -urinary tract infections -biopsy proven transplant allograft nephropathy	UTI and an associated serum creatinine elevation 4 years after transplant	Cystoscopy: large papillary tumor emanating from the anterior surface of the bladder approximately 2 cm from the bladder neck	urothelial papillary neoplasia with a low degree of malignancy	- Failing graft was removed to limit the amount of urothelium available for neoplasia -Tumor resection - Chronic dialysis nine months after tumor resection and transplant nephrouretere ctomy
Abbasion *et al*., 2020 (*9*).	Female 7 years old	was treated for urinary tract infection several times	dysuria and painless gross hematuria of a three-month duration	Cystoscopy: a vegetative lesion on the right lateral aspect of the bladder	papillary urothelial neoplasm of low malignant potential	Transurethral resection of the bladder (TURB)

It is difficult to accurately describe the etiology of PUNLMP in adults, but it is thought to have the same etiologic factors as urothelial carcinoma, which include smoking, exposure to other chemicals, heredity, infection, prior radiation, and prior chemotherapy with cyclophosphamide (*10*). Clinical presentation includes macroscopic hematuria, lower urinary tract symptoms, or both, as well as a palpable suprapubic mass, which may be discovered incidentally during imaging (*5*). Our patient was admitted with a three-month history of painless gross hematuria. PUNLMP usually presents as a solitary and small mass, measuring 1-2 cm, appearing on the bladder's posterior lateral walls and ureteric orifices, non-invasive, and increasing in size by approximately 10% if not treated (*10*). Ultrasonography, urinalysis, urinary culture, cystoscopy, biopsy, and transurethral resection of bladder tumor (TURBT) are the diagnostic modalities used, while other tests, such as immunohistochemistry, are optional (*5*, *11*). The work-up includes measuring hemoglobin, assessing inflammatory marker levels, and determining renal function if hydronephrosis is suspected (*5*). A prior history of urothelial carcinoma rules out the diagnosis of PUNLMP (*10*). Immunophenotyping in diagnosis of PUNLMP is helpful, it reveals GATA-3+, p63+, high molecular weight cytokeratin+, CK5/6+ (basal layer) and CK7+ (may have STAG2 loss) with a possibility of lost mismatch repair proteins (Lynch syndrome-associated tumors) (*11*), but not a routine diagnostic tool (*12*).

Cystoscopy can detect single or multiple intraluminal bladder papillary masses of varying sizes, with the most common locations being the lateral and posterior walls, but PUNLMP can be found anywhere in the urinary tract with urothelium [8]. In our case, ultrasound was followed by cystoscopy, which revealed a papillary lesion that TURBT and histopathology confirmed as PUNLMP. Cystoscopy was also used to diagnose the other two reported cases, with Alam *et al.*, describing a large papillary tumor emanating from the anterior surface of the bladder, 2 cm from the bladder neck, seen on cystoscopy in their patient (*8*), and Maurizi *et al.,* describing a papillomatous structure of 2 cm at the right ureteral meatus in a 9-year-old patient (*4*). When it comes to diagnostic modalities, post-operative follow-up remains contentious, with some advocating cystoscopy for its high accuracy and others supporting ultrasound and urine cytology for their less invasiveness and ease of use. However, cystoscopy remains the gold standard for follow-up because mostly recurrences are asymptomatic (*13*).

Recurrence is part of the spectrum of PUNLMP. Hence, follow up of any diagnosed case with PUNLMP is imperative. Our reported patient demonstrated during a follow-up cystoscopy three months later, followed by TURBT and histopathology, that the old resection area was tumor-free, but that PUNLMP had recurred in the trigone area. Another follow-up cystoscopy is scheduled in three months. A similar follow-up plan was recommended in the case described by Alam *et al.* (*8*). Maurizi *et al.,* recommended a 6 months follow-up with renal function, renal and urinary ultrasound, and urodynamic evaluation, followed by chemical and cytological urinary tests, cystoscopy, and random biopsies of the most affected areas three months later, and TUR during cystoscopy one year later (*4*). PUNLMP treatment varies by risk group. Because of the high rate of recurrence and progression, most urologists treat patients with PUNLMP in the

same way they would treat low-grade non-invasive carcinomas, which includes transurethral resection of the tumor and subsequent follow-up with regular cystoscopy (*12*). Our patient was treated with TURBT, but a three-month follow-up revealed a recurrence of PUNLMP in another location. More detailed guidelines should be developed through multi-centered additional research to determine the best course of treatment and follow-up procedure for PUNLMP in the pediatric population.

Conclusion

Pediatric PUNLMP is an exceptionally rare neoplasm in children with a low recurrence rate that is amenable to treatment. Pediatric PUNLMP diagnosis is to be suspected in any child with painless hematuria. Recurrence is part of the spectrum of PUNLMP. Hence, follow up of any diagnosed case with PUNLMP is imperative. Given the very small number of cases, it is difficult to determine a clear treatment and follow-up strategy; more cases and research are required to develop specific guidelines.

Author Contributions:

A.B writing and searching in the literature for similar cases. A.C writing the manuscript. Z.K: writing the manuscript. I.B: collecting of data from hospital and writing the manuscript. B.A: collecting of data from hospital and writing the manuscript. L.C: writing the manuscript. H.I: writing the manuscript and editing the figures. M.M: writing the manuscript and editing. H.H: writing the manuscript, assembling the manuscript, reviewing and editing.

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CONFLICT OF INTEREST

The authors declare no conflict of interest in connection with the reported study. Authors declare veracity of information. Authors declare receiving parental consent to publish this case.

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