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Rare cause of macroscopic hematuria in a pediatric patient: Nephrogenic adenoma of the bladder

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Abstract Pediatric nephrogenic adenoma (NA) is an uncommon benign metaplastic lesion occurring in the urothelium. Herein we report a case of NA of the urinary bladder in a 14-year-old boy. The patient presented with macroscopic hematuria and had a history of ureteral surgery and long-term smoking. NA should be considered in the differential diagnosis of any urinary tract tumor in the pediatric population.

Key words hematuria, nephrogenic adenoma.

Pediatric nephrogenic adenoma (NA) is a rare benign proliferative urinary tract tumor. Predisposing factors are urothelial irritation by calculi, foreign bodies, chemical agents, chronic cystitis, trauma and surgery including ureteric re-implantation.[1] The prevalence is 3:1 with a female predominance in the pediatric age group but the ratio is reversed in favor of the male gender in adults. NA arise mostly in the bladder (80%), and at other urinary tract sites including urethra (15%), ureter (5%) and rarely in the renal pelvis (1%). Also some reports have shown that it could be detected at bladder extrophy, urethral diverticula, in an ileal conduit, bowel portion of an augmented bladder and bladder diverticula.[2,3] Hematuria, dysuria and urinary frequency are usually the first and the most common presenting symptoms. This report describes an adolescent patient who was admitted with macroscopic hematuria and subsequently had diagnosis of NA after cystoscopy.

Case report

A 14-year-old boy presented with macroscopic hematuria in the absence of dysuria and urinary frequency. Physical examination indicated no abnormality except typical pfannenstiel operation scar. He had a previous history of bilateral ureterovesical junction obstruction 7 years previously and had undergone ureteric re-implantation surgery. He had been smoking 1 pack/day for 7 years. Urine analysis indicated trace protein, 249 red blood cells and 68 white blood cells per high-power field. Ultrasound showed atrophic right kidney and right-sided grade 2 hydroureteronephrosis. Also a 4 cm lesion protruding into the lumen at the anterior bladder wall was detected. Cystoscopy showed 4 cm of papillary lesion; and a complete transurethral resection was performed (Fig. 1). On pathology, NA of the urinary bladder was noted (Fig. 2). Immunohistochemistry was as follows: cytokeratin (CK) 7(+), CK20 (–), uroplakin (–), gross cystic disease fluid protein (–), thyroid transcription factor 1 (–). After 3 months, control cystoscopy was performed and a biopsy of the resected area indicated cystitis cystica and cystitis glandularis in the absence of any malignancy. At the time of writing the patient has been symptom free for 1 year and continues on routine urinalysis, ultrasound and cystoscopy.

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Discussion

The NA constitutes an infrequent benign metaplasia of the urothelial mucosa in children and should be considered in the differential diagnosis of macroscopic hematuria, especially in the pediatric age group with the appropriate antecedent history. Only 10% of all cases are reported in the pediatric age group.[4]

The etiology of NA is not certain but history of chronic irritation or inflammation is present in almost all cases. Predisposing factors include trauma, chronic infection, previous urinary surgery, urinary calculi, irradiation and urinary catheterization. Also, bacillus Calmette–Guerin treatment may induce NA. Moreover, post-transplantation cases are reported, so immunosuppression may be a contributory factor.[5] The present patient had a history of repeated urinary tract infection and bilateral ureteric re-implantation as the predisposing factor. Interestingly, this patient had a history of extensive and long-term cigarette smoking. Cigarette smoking is a well-known risk factor for bladder cancer but the relation with NA has not been reported.[1,4–6] Nevertheless the present case involves a remarkable combination of intensive smoking and NA.

Nephrogenic adenoma may appear on ultrasonography, i.v. pyelogram, and voiding cystourethrogram as a filling defect.[7] Cystoscopically NA has been reported to look like a papillary (55%), sessile (35%) or polypoid (10%) mucosal mass. Lesions are generally <1 cm, but up to 7 cm has been reported. Typical histology includes tubular, tubulocystic, polypoid and/or papillary features, and most common forms are tubular and in 96% of cases.[4,8] The macroscopic appearance of the lesion varies but is generally highly vascularized.[3]

Recognition of the characteristic patterns and awareness of the unusual architectural and cytologic features are critical to make a diagnosis of NA, and to distinguish this lesion from

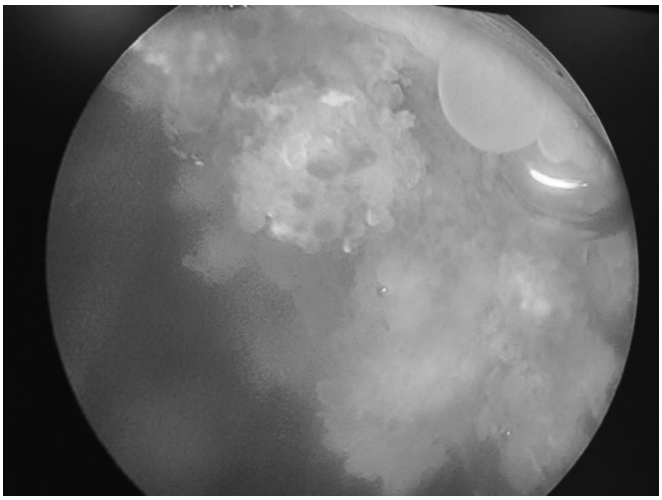

Fig. 1 Cystoscopic findings of nephrogenic adenoma.

malignant neoplasms occurring at the same site. The following features favor NA: absence of necrosis, lack of significant atypia or mitotic activity, presence of a mixture of tubular and papillary components and edematous/inflammatory stroma.[1,2,8]

Immunohistochemistry also can differentiate NA from malignant processes. Paired-box 2, α-methylacyl CoA racemase, CD10, epithelial membrane antigen, CK7, CAM 5.2 and aquoporin staining favor NA. The negative immunomodulins are uroplakin, thrombomodulin, p63, ca-125, carcinoembryonic antigen, CK20 and prostate-specific antigen immunostain.[2]

Management includes resection and fulguration of the lesion. Increased risk of infection and recurrence necessitates prophylactic antibiotic therapy and routine cystoscopy. Generally cystoscopy is advised to be done every 3 months for 2 years, every 6 months for 3 years and then once per year in the absence of infection or voiding complaints,[2] but some authors have suggested that cystoscopy may itself stimulate new lesions.[9] Also, patient compliance with recurrent cystoscopy is low; if symptoms recur, cystoscopy should be strongly suggested. Spontaneous remission of the lesion, however, has been reported.[10]

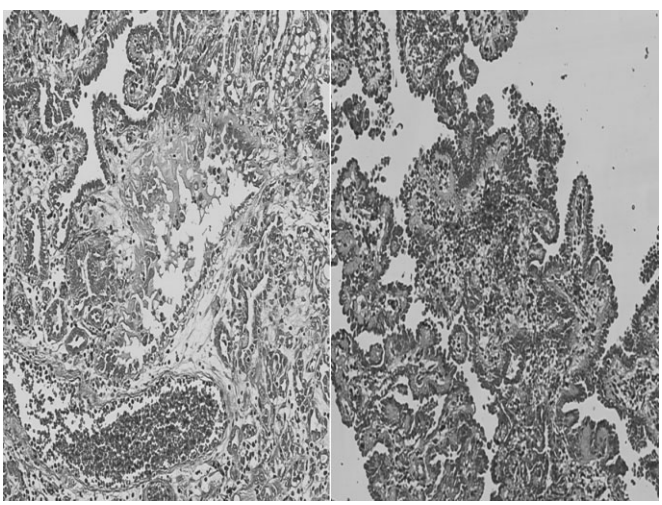

Fig. 2 Prominent papillary pattern with cellular atypia and hobnail type epithelium (HE).

Pediatric case reports are remarkable for the medical history of bladder surgery 3 months–7 years previously. Most children present with non-specific symptoms of gross hematuria, dysuria and bladder instability. Micro- or macro-hematuria are present in 40% of cases and suprapubic or flank pain in 15% and 5%, respectively. Tumor recurrence develops in 80% of children with a latency period of 4 years.[7,9] With respect to high recurrence rates, there have been no reported cases of malignant transformation or metastatic disease in pediatric patients.[5]

Macroscopic hematuria is a common cause of referral to urology or pediatric nephrology clinics. Urinary infection and calculi are usually associated with pain, but glomerular disease and arteriovenous malformation are painless. In the pediatric age group tumors are a very rare reason for painless macroscopic hematuria. In the present case an adolescent boy had been admitted with macroscopic hematuria, and ultrasonography showed a mass lesion in bladder. He had urinary tract operation 7 years previously, and pathology indicated NA. Past history of surgery is the most important predisposing factor in NA. Also, the present patient was an early smoker and had a considerably high cigarette exposure. In the literature, cigarette smoking has not been reported with NA. Long-term and heavy smoking in this age group is also a rare entity. In the etiology of NA, therefore, the contribution of smoking is not exactly known. Although, we cannot speculate that this contributed to the development of NA, smoking should also be kept in mind in these particular cases.

Conclusion

Nephrogenic adenoma is a rare entity, and pediatric patients constitute the minority of cases. Patients with NA may be questioned for risk factors such as chronic inflammation or urinary surgery. NA should be included in the differential diagnosis of macroscopic hematuria. Despite the fact that NA is a benign lesion, long-term follow up is needed due to the high recurrence rate and the potential, although rare, for malignant transformation.

References

1 Pavlidakey PG, MacLennan GT, Goldman HB. Nephrogenic adenoma of the bladder. *J. Urol.* 2010; **184**: 2535–6.
2 Amin W, Parwani AV. Nephrogenic adenoma. *Pathol. Res. Pract.* 2010; **206**: 659–62.
3 Boscolo-Berto R, Lamon C, Gardi M, Vezzaro R, Gardiman M. Recurrent nephrogenic adenoma in bladder diverticulum: Case report and literature review. *Can. Urol. Assoc. J.* 2012; **6**: 34–7.
4 Iva E, Young RH. Nephrogenic adenoma of the urinary tract: A review of the microscopic appearance of 80 cases with emphasis on unusual features. *Mod. Pathol.* 1995; **8**: 722–30.
5 Chen CS, Cheng CL. Nephrogenic adenoma of the urinary bladder: Clinical experience and review of literature. *J. Chin. Med. Assoc.* 2009; **69**: 166–8.
6 Letasiova S, Medve'ova A, Sovcikova A *et al*. Bladder cancer, a review of the environmental risk factors. *Environ. Health* 2012; **11** (Suppl. 1): S11.

7 Zougkas K, Kalafatis M, Kalafatis P. Nephrogenic adenoma of the bladder. *Int. Urol. Nephrol.* 2005; **37**: 477–81.
8 Rahemtullah A, Oliva E. Nephrogenic adenoma: An update on an innocuous but troublesome entity. *Adv. Anat. Pathol.* 2006; **13**: 247–55.
9 Heidenreich A, Zirbes TK, Wolter S, Engelmann UH. Nephrogenic adenoma: A rare bladder tumor in children. *Eur. Urol.* 1999; **36**: 348–53.
10 Grasa Lanau V, Gaurch Troyas R, Montesino Semper M *et al*. Nephrogenic adenoma: Study of 9 cases, including one of the urethra in a 14 years old male. *Arch. Esp. Urol.* 1998; **51**: 138–44.

Ex utero intrapartum treatment for an infant with cerebro-costo-mandibular syndrome

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Abstract Cerebro-costo-mandibular syndrome (CCMS) is a rare disorder characterized by multiple rib abnormalities, micrognathia described as Pierre–Robin sequence, and cerebral involvement. Appropriate management of respiratory distress immediately after birth is crucial to rescue these patients. A boy, having a mother with Pierre–Robin sequence and a sister with CCMS, was diagnosed prenatally with CCMS and successfully treated with *ex utero* intrapartum treatment (EXIT) at 36 weeks 6 days of gestation. EXIT would be an effective option for rescuing patients with prenatally diagnosed CCMS and preventing neonatal hypoxia.

Key words cerebro-costo-mandibular syndrome, *ex utero* intrapartum treatment, Pierre–Robin sequence, prenatal diagnosis.

The present patient was a boy aged 4 years 1 month at the time of this report. His mother had, at birth, micrognathia and cleft palate and was diagnosed with Pierre–Robin sequence. Her cleft palate was surgically repaired. His elder sister was born at 38 weeks 6 days of gestation by normal vaginal delivery. She weighed 2525 g and had severe micrognathia, cleft palate, small ears, and a small thorax radiologically characterized by rib-gap defects. She had normal psychomotor development. She was diagnosed with cerebro-costo-mandibular syndrome (CCMS).

Case report

The present patient's status was complicated by polyhydramnios found on routine ultrasound (US) at 18 weeks. At 32 weeks of gestation, severe micrognathia and a narrow thorax with short defective ribs were noted on US (Fig. 1) and magnetic resonance imaging (MRI; Fig. 2). These findings strongly supported the diagnosis of CCMS. Elective cesarean section was scheduled at 36 weeks of gestation, but severe postnatal respiratory distress was anticipated, therefore, we chose to use *ex utero* intrapartum treatment (EXIT) at birth. Consequently, the patient was born at 36 weeks 6 days of gestation by cesarean section under deep general anesthesia to facilitate uterine relaxation, minimize uterine bleeding, and maintain fetal circulation. A transverse incision was made in the lower uterine segment, and EXIT was carried out. The baby was delivered to the level of the upper abdomen, at which point pulse oximetry monitors were placed on the right upper extremity. The pulse rate was 140–160/min and SpO_2 was around 70%. After aspiration of fluid in the oral cavity, an airway was established using a 3.5-mm endotracheal tube, then the umbilical cord was clamped. The Apgar scores were 2 and 4 at 1 and 5 min, respectively. Measurements at birth were as follows: birthweight, 2458 g (−1.1 SD); length, 45.0 cm (−1.5 SD); head circumference, 33.2 cm (mean); and chest circumference, 26.0 cm (−2.9 SD). Physical examination showed micrognathia, cleft palate, and small ears. He was sent to the neonatal intensive care unit for further management and investigation. Chest X-ray showed a bell-shaped thorax and only 11 pairs of ribs with characteristic bilateral rib-gap defects in ribs 2–9 (Fig. 3). Cranial US detected no anomalies or dilated ventricles.

On day 31 he was extubated and placed on nasal intermittent positive airway pressure (CPAP). His respiratory status gradually improved and CPAP was ceased on day 150. He was discharged home at age 6 months. No subsequent hypoxic events or nutritional impairments occurred after discharge.

When last seen by us at age 4 years, his height was 90.4 cm (−2.3 SD) and weight was 12.0 kg (−1.8 SD). Although he initially had speech difficulties, recently he has shown remarkable progress in language expression.

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