

Research Article

Intestinal Epithelium in Pediatric and Adult Urachal Remnants: Metaplasia or Embryonal Migration Defect?

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Abstract

Background: Urachal remnants are fairly common. Patients may display urachal disease, or urachal remnants may represent an incidental finding. These lesions are more common in the pediatric population, and may give rise to malignant tumors, essentially adenocarcinomas, in adults mainly.

Aim: To study the prevalence of intestinal-type epithelium in pediatric and adult urachal remnants.

Materials and methods: Histological findings in 39 pediatric and 22 adult specimens sent as urachal remnant, or for a suspicion of urachal tumor were available for review.

Results: An epithelial lining was seen in 80.7% of the non-neoplastic cases, and was mainly of the transitional type. Foci of intestinal-type epithelium or scattered goblet cells within a transitional epithelium were identified in 10.9% of all non-neoplastic epithelial remnants, more frequently so in the pediatric cohort. Squamous epithelium was also seen, either as sole finding, or in association with transitional epithelium in 17.4% of the cases. Adenocarcinoma was observed in 3 adult patients and a high-grade intestinal-type adenoma in a further adult patient. Cytokeratin 20 and CDX-2 reactivity was seen in all three adenocarcinomas and in the adenoma, whereas cytokeratin 7 was negative in an enteric-type adenocarcinoma. No β -catenin nuclear delocalization was observed.

Conclusion: The intestinal-type epithelium is thought to originate either from cloacal inclusions or from enteric rests, or to result from metaplasia. Dysplasia and invasive adenocarcinoma may further develop. Intestinal foci being diagnosed by histology only, surgical resection is recommended to avoid the rare development of adenocarcinoma. Consensus for surgical resection of urachal remnants is however lacking, since urachal remnants may also involute.

ABBREVIATIONS

AB: Alcian Blue; PAS: Periodic Acid-Schiff; CK: Cytokeratin; SMA: Smooth Muscle Actin

INTRODUCTION

The urachus is a vestigial structure of the cloaca and the allantois, connecting the bladder dome to the umbilicus [1]. The allantois derives from an outpouching of the yolk sac, and forms the urachus, as well as the umbilical arteries and vein. During fetal development and descent of the bladder at months 4th or 5th of gestation, the urachus fails to grow and involutes as a fibromuscular cord, thereby becoming the median umbilical ligament [1]. Defective obliteration leads to urachal remnants, namely to totally patent urachus/sinus tract, or to urachal cyst, umbilical-urachal sinus or vesico-urachal diverticulum [2].

The exact incidence of urachal remnant disease is not known. An autopsy series has reported urachal remnant as an incidental microscopic finding in 32% (39/122) of adult bladder autopsy specimens [3]. In the general pediatric population, a prevalence

of 1.03% has been reported [4]. Upon histological evaluation, the urachus is composed of an epithelial lining, usually urothelial or transitional, resting on submucosal connective tissue, and surrounded by a smooth muscle layer [1].

Epithelial lining however may also be of the columnar, intestinal type. Confronted to this finding in pediatric urachal remnant specimens, we retrospectively reviewed all urachal remnants, adult and pediatric, sent to our tertiary center over a twenty-year period. The aim was to determine the prevalence of intestinal-type lining.

MATERIALS AND METHODS**Patient selection**

We reviewed the histological findings in all specimens sent for pathological evaluation with a clinical and/or radiological diagnosis of urachal remnant or suspicion for urachal cancer, during a 20-year period (1997 to March 2017). Omphalomesenteric ducts were not considered.

Stains and immunohistochemistry

Histological analysis was performed after gross processing and paraffin-embedding. Hematoxylin and Eosin (H&E) stains were performed on 3 µm thick sections of the paraffin-embedded tissue. Alcian blue (AB) and Periodic acid-Schiff (PAS) were performed on cases showing mucinous epithelium.

Immunohistochemistry was conducted on the neoplastic cases. High temperature antigen retrieval was applied. Incubation time was one hour for the primary antibody, and 30 minutes for the secondary antibody. A ready-to-use anti-mouse Envision (Dako) kit was used as secondary antibody. The Envision visualization system (Dako) and DAB as the chromogen substrate were used for the following antibodies: Beta-Catenin (β-catenin-1, NOVOCASTRA mouse monoclonal, clone 17C2, 1:20 dilution); CDX-2 (BIOGENEX mouse monoclonal, clone 88, 1:100 dilution); Cytokeratin 7 (CK7, DAKO mouse monoclonal, clone OV-TL12/30, 1:50 dilution); Cytokeratin 20 (CK20, DAKO mouse monoclonal, clone KS20.8, 1:100 dilution); Smooth Muscle Actin (SMA, DAKO mouse monoclonal, clone 1A4, 1:300 dilution). Pictures were acquired using a Digital Sight DS-Fi1 camera (Nikon), and the NIS Elements Documentation software (Nikon).

All pathology results were independently reviewed by two authors (AB & ALR); the diagnostically challenging cases were further discussed with a third senior pathologist (JCT).

RESULTS

Urachal remnants

A total of 61 cases were retrieved from the archives of the Division of clinical pathology. Most patients were aged 18 years or younger, and composed the pediatric cohort (39 patients, aged 1 day to 18 years; mean age 7.6 years, median 6 years). The adult patient cohort comprised 22 patients aged 23 to 81 years (mean age 53.9 years, median 57.5 years). A male predominance was observed (37 males, versus 24 females).

Mean age at surgical resection was 6 years in the pediatric cohort. One adolescent patient however, had suffered umbilical discharge 15 years prior to surgery, performed at age 16 years. In the pediatric cohort, the most frequent mode of presentation was umbilical discharge (14/39, 35.9%), followed by incidental discovery (11/39, 28.2%). Most of the urachal lesions in adults were also incidentally observed (10/22, 45.5%); 5 cases (22.7%) were referred for suspicion of malignancy. Clinical findings and mode of presentation are reported in Table (1).

The remnants appeared as sinuses or cysts, and a bladder ostium was documented in a few cases. The pediatric cases tended to be composed of a well-formed tubular structure, with frond-like intraluminal projections, resembling a ureter (Figure 1A). In the better-defined structures, the epithelium rested on a submucosal fibrovascular tissue, surrounded by a smooth muscle coat (Figure 1B). No bladder diverticulum was seen in our series. Additionally, obliterated or involuting umbilical vessels were seen in 12 children, and one adult patient.

An epithelial remnant was seen in 46 of the 57 non-neoplastic cases (80.7%); the 4 tumor cases were not considered due to probable overgrowth of the preexistent urachal epithelium.

		PEDIATRIC (N=39; 63.9%)	ADULT (N=22; 36.1%)
AGE		1D-18Y (MEAN 7.6, MEDIAN 6)	23Y-81Y (MEAN 53.9, MEDIAN 57.5)
SEX		24M (61.5%) 15F (38.5%)	13M (59.1%) 9F (40.9%)
CLINICAL PRESENTATION	UMBILICAL DISCHARGE	14 (35.9%)	2 (9.1%)
	OMPHALITIS	4 (10.3%)	3 (13.6%)
	SUSPICIOUS FOR MALIGNANT TUMOR	0	5 (22.7%)
	CYST OR NODULE	5 (12.8%)	2 (9.1%)
	INCIDENTAL FINDING	11 (28.2%)	10 (45.5)
	UNSPECIFIED	5 (12.8%)	0
ABBREVIATIONS: D: DAYS; Y: YEARS; M: MALE; F: FEMALE			

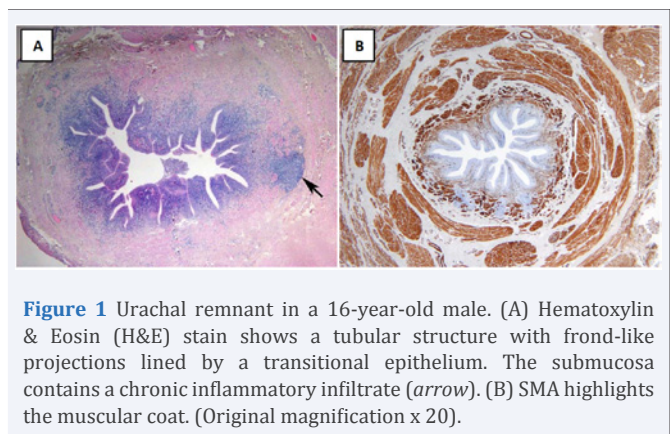


Figure 1 Urachal remnant in a 16-year-old male. (A) Hematoxylin & Eosin (H&E) stain shows a tubular structure with frond-like projections lined by a transitional epithelium. The submucosa contains a chronic inflammatory infiltrate (arrow). (B) SMA highlights the muscular coat. (Original magnification x 20).

The remaining 11 cases were composed of a fibrovascular cord or of granulation tissue, except for 3 cases that showed only fibroadipose tissue. Inflammation was seen in 27/57 cases (47.4%), and was mostly chronic. Histiocytic or giant cell reaction was seen in a few cases, and was suggestive of previous rupture.

The epithelium lining the urachal remnant was in most cases of pure transitional type (33/46, 71.7%), with or without areas lined only by an attenuated cubical layer. Additionally, coexistence with another type of epithelium, intestinal or squamous, was seen in respectively 5 (10.9%), and 3 cases (6.5%). Squamous epithelium only was seen in 5 further cases (10.9%).

Histological evaluation is summarized in Table (2).

Intestinal-type epithelium

Mucinous goblet cells were identified in 4 pediatric specimens (4/39, 10.3%; 4/35 specimens with an epithelial lining, 11.4%), whereas only one adult case showed rare goblet cells scattered within a transitional type epithelium (1/22, 4.5%; 1/11 specimens with an epithelial lining, 9.1%). The pediatric cases all showed an abrupt transition between two types of epithelium, transitional and intestinal (Figures 2A,2B). A few goblet cells were however also seen within the transitional lining. Additionally,

	Pediatric (n=39)	Adult (n=22)
Epithelial urachal remnant	35 (89.7%)	11 (50%)
Transitional epithelium only	26/35 (74.3%)	7/11 (63.6%)
Intestinal and transitional epithelium	4/35 (11.4%)	1/11 (9.1%)
Squamous and transitional epithelium	2/35 (5.7%)	1/11 (9.1%)
Squamous epithelium only	3/35 (8.6%)	2/11 (18.2%)
No evidence of epithelial urachal remnant	4 (10.3%)	7 (31.8%)
Adenocarcinoma	0	3 (13.6%)
Adenoma	0	1 (4.5%)
Obliterated umbilical vessels	12	1

the specimen from one pediatric patient displayed a few Paneth cells alternating with the goblet cells. The acid mucins in the cytoplasm of the goblet cells stained intensely with Alcian Blue (Figure 2C). PAS (Figure 2D), that stains neutral polysaccharides and acid mucins that contain significant quantities of sialic acid, usually decorated more intensely the cytoplasm of the scattered mucinous cells within the transitional epithelium.

Adenocarcinoma

Three urachal adenocarcinomas were seen, in adult patients only (3/22, 13.6%). Two were of the mucinous subtypes, and one of the enteric subtypes (Figure 3 A-J). No urachal remnants were found. CK20 reactivity was strong in all three adenocarcinomas, whereas CK7 reactivity was seen only in the two mucinous adenocarcinomas. CDX-2 staining was observed in all three tumors. Membranous and cytoplasmic staining with β-catenin was seen in all cases, in the absence of nuclear accumulation. One further male patient, aged 58 years, showed a large intestinal-type adenoma with high-grade dysplasia, and no invasive component (Figure 4 A-F). The dysplastic cells showed intense reactivity to Cytokeratins 7 and 20, and to CDX-2. In the depth of the lesion, an urachal remnant was lined by a transitional epithelium with scattered mucinous goblet cells. Localization and immunohistochemistry in all 4 cases were consistent with an urachal origin.

Associated malformations

Vesicoureteral reflux was the mode of presentation in only one of the 39 pediatric patients in our series. Two patients had anorectal malformation, and in three further patients, the urachal remnant was discovered during a Mitrofanoff procedure for neurogenic bladder, in the setting of spina bifida. Therefore, in total, 6 patients had associated anomalies or malformations (6/39, 15.4%).

DISCUSSION

In order to study the epithelial lining and in particular of intestinal-type lining in urachal remnants, we performed a 20-year retrospective review. Mean age at surgical resection was 6 years in the pediatric cohort. Similarly, previous studies

have reported a mean age at surgical resection of 5.6 years [4]. Epithelial remnants were identified in 80.7% of the non-neoplastic cases. Previous studies have reported an epithelial component in 69% [5] to 72% [4] of excised urachal lesions.

The epithelium lining the urachal remnant was in most cases of pure transitional type (71.7%), whereas coexistence with another type of epithelium, intestinal or squamous, was seen in a subset of the cases (10.9% and 6.5% respectively). No remnant was composed of pure intestinal-type epithelium, lending no support to a differential diagnosis with a vitelline duct (omphalomesenteric duct).

Intestinal-type epithelium consisted of mucinous goblet cells. The transition between the transitional and intestinal-type epithelia was mainly abrupt. Goblet cells were also scattered within the transitional-type epithelium. The presence of mucinous cells, described either as metaplasia of superficial cells overlying a transitional epithelium, or occurring as a single layer of cells was described by Schubert et al., in their adult autopsy series [3], in 13 of the 39 bladders with urachal remnant (33.3%). In a series of 60 patients aged 18 years or younger, intestinal epithelium was observed in 18% of the cases (11/60) [4].

Various theories have been proposed as explanations to the presence of glandular or intestinal epithelium in the urachus. An embryological theory suggests that the intestinal epithelium originates from cloacal inclusions or enteric rests [6]. In accordance with this theory, normal-appearing intestinal epithelium was essentially observed in the pediatric population in our series. Alternatively, the mucinous cells may result from Metaplasia [6]. Accordingly, inflammation was frequently observed in our series of urachal remnants. However, inflammation was lacking in one of the five cases with intestinal type epithelium.

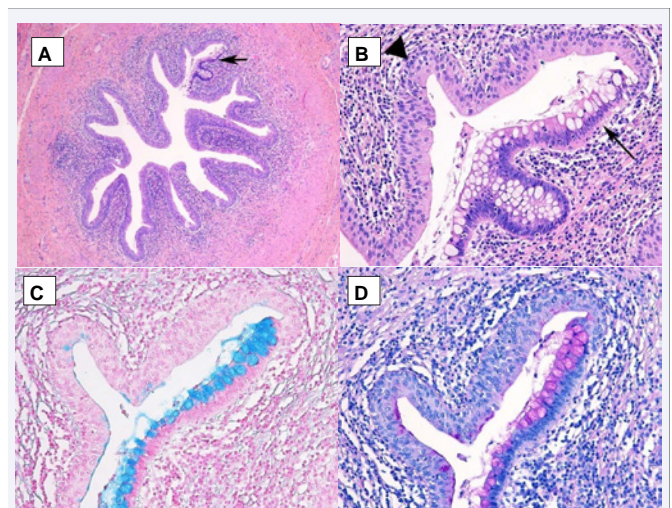


Figure 2 Intestinal-type epithelium in the urachal remnant from a 13-year-old male patient. (A, B) H&E stain shows the abrupt transition between a mainly transitional epithelium (arrow head), and a more focal intestinal type lining (arrows) (original magnification x40, and x200). (C, D). The focus of intestinal epithelium composed of goblet cells shows intense Alcian Blue (C), and more moderate PAS staining (D) (original magnification x 200).

In adults, urachal carcinoma is rare, representing 0.17% to 0.34% of all bladder tumors, and 20% to 39% of bladder adenocarcinomas [6]. Prognosis is poor, with a 5-year cancer specific survival rate of 49% [7], and a median cancer-specific survival of 45 months [8]. The histologic type of urachal tumor is not a significant predictor of outcome [9]. Less than 5% of

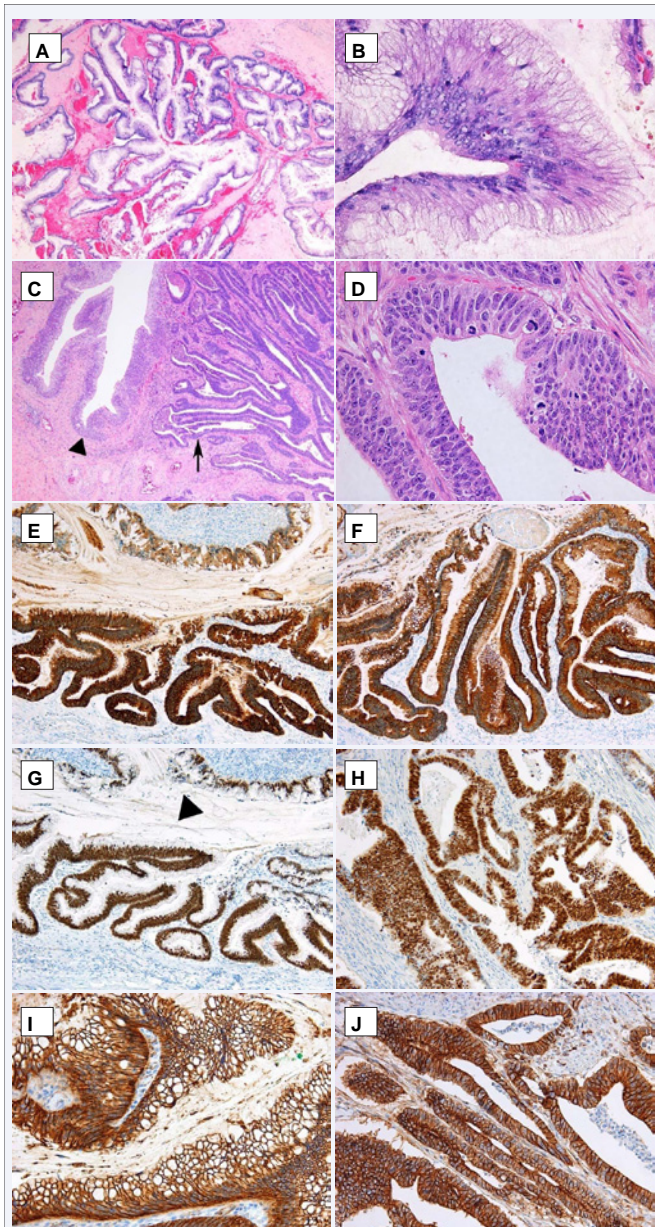


Figure 3 Histological subtypes observed in urachal adenocarcinoma. H & E, low magnification x40; high magnification x400 (A-D). (A, B) Mucinous adenocarcinoma. (C, D). Enteric-type adenocarcinoma, closely resembling adenocarcinoma of the colon. At lower magnification, adenocarcinoma (arrow) undermines the bladder urothelium (arrowhead). Immunohistochemistry findings; arrowheads point to extracellular mucin accumulation (E-H, x100; I-J, x200). Cytokeratin 7 (E) and Cytokeratin 20 (F) reactivity in mucinous adenocarcinoma. CDX-2 immunoreactivity in mucinous (G) and enteric (H) adenocarcinoma subtypes. Absence of β -catenin nuclear accumulation in both mucinous (I) and enteric (J) urachal adenocarcinoma.

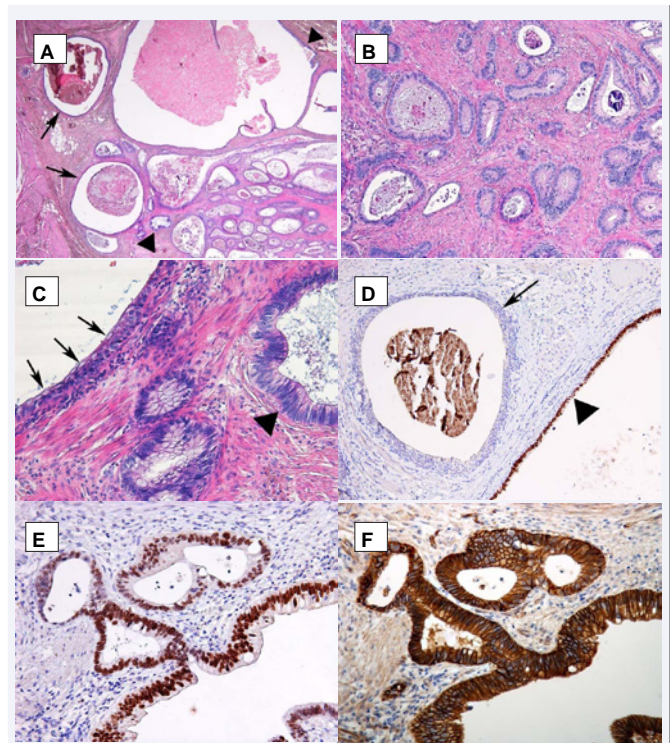


Figure 4 (A-C) Intestinal-type adenoma (arrowheads) in close association with an urachal remnant (arrows) (H&E, low magnification x20; intermediate x100; high magnification x200). Dilated urachal glandular remnants are seen in the deeper portions of the adenoma (A). The intestinal-type adenoma composed of dysplastic glands (B). On higher magnification, the urachal remnant is lined by an attenuated transitional epithelium with coexisting mucinous cells. Immunohistochemistry findings (D-F, x200). CDX-2 immunoreactivity is observed in the intestinal-type adenoma (D,E), whereas the urachal remnant remains negative (D). There is no β -catenin nuclear delocalization in the intestinal-type adenoma (F).

urachal tumors are not of epithelial origin, consisting of sarcoma mainly [10]. Similar theories underlie the development of benign glandular epithelium in the urachal, and the development of urachal malignancy. Namely, the development of urachal adenocarcinoma may involve a metaplastic process [11], or proceed from progenitor cells arising from an enteric rest in the urachus⁹. CK20 reactivity is described in close to 100% of urachal adenocarcinomas. CK7 positivity varies between 36% in the enteric subtype and 61% in the other urachal adenocarcinoma subtypes [11]. CDX-2 is an intestine-specific transcription factor showing nuclear expression under normal conditions in the intestinal epithelial cells. CDX-2 reactivity has been described in 85% to 100% of urachal adenocarcinomas [11,12] usually with a diffuse pattern of expression. Moderate nuclear β -catenin staining may rarely be observed, in 6% to 7% of urachal adenocarcinomas [11,12]. Therefore, diffuse nuclear β -catenin staining is against a diagnosis of primary urachal adenocarcinoma, and instead favors metastatic colonic adenocarcinoma [11]. Accordingly, we observed strong CK20 and CDX-2 staining in all three adenocarcinomas and in the adenoma in our series; no nuclear β -catenin accumulation was seen. CK7 was negative in the enteric-type adenocarcinoma.

Children may seldom develop tumors of the urachus, other than adenocarcinoma. For instance, rhabdomyosarcoma [13] and germ cell tumors such as teratoma [14] or yolk sac tumor [15] have been reported.

To prevent future medical problems and potential malignant transformation, excision of even incidentally discovered urachal remnants has been recommended in adults [16]. However, some urachal lesion will involute with time [17], especially so in children, and risk of malignancy is low. Therefore, some authors believe that excision of simple and asymptomatic lesions may be of no benefit to pediatric patients [4].

Other genitourinary anomalies may occur together with urachal remnants. Vesicoureteral reflux was reported by Copp et al. [5], to occur in 5 of the 29 pediatric patients of their series (17%). However, vesicoureteral reflux was the mode of presentation in only one of the 39 pediatric patients in our series.

CONCLUSION

In a series of 61 adult and pediatric surgical specimens sent as urachal remnant or tumor, a mucinous epithelium was identified in 8% of all submitted cases, and in nearly 11% of all non-neoplastic epithelial remnants, being more frequent in the pediatric population. The origin of intestinal-type epithelium in urachal remnants, whether embryonal or metaplastic, remains unsettled. Additionally, 18% of all adult specimens showed adenoma or adenocarcinoma.

Most tumors of the urachus being adenocarcinomas, foci of mucinous epithelium may be considered as precursors. The identification in our cohort of an intestinal-type adenoma lends further support to this hypothesis. Since histological evaluation only can identify a glandular component, we feel that surgical resection remains recommended.

REFERENCES

1. Begg RC. The Urachus: its Anatomy, Histology and Development. *J Anat.* 1930; 64: 170-183.
2. Yu JS, Kim KW, Lee HJ, Lee YJ, Yoon CS, Kim MJ. Urachal remnant diseases: spectrum of CT and US findings. *Radiographics.* 2001; 21: 451-461.
3. Schubert GE, Pavkovic MB, Bethke-Bedürftig BA. Tubular urachal remnants in adult bladders. *J Urol.* 1982; 127: 40-42.
4. Gleason JM, Bowlin PR, Bagli DJ, Lorenzo AJ, Hassouna T, Koyle MA, et al. A comprehensive review of pediatric urachal anomalies and predictive analysis for adult urachal adenocarcinoma. *J Urol* 2015; 193: 632-636.
5. Copp HL, Wong IY, Krishnan C, Malhotra S, Kennedy WA. Clinical presentation and urachal remnant pathology: implications for treatment. *J Urol.* 2009; 182: 1921-1924.
6. Sheldon CA, Clayman RV, Gonzalez R, Williams RD, Fraley EE. Malignant urachal lesions. *J Urol.* 1984; 131: 1-8.
7. Ashley RA, Inman BA, Sebo TJ, Leibovich BC, Blute ML, Kwon ED, et al. Urachal carcinoma: clinicopathologic features and long-term outcomes of an aggressive malignancy. *Cancer.* 2006; 107: 712-720.
8. Dhillon J, Liang Y, Kamat AM, Siefker-Radtke A, Dinney CP, Czerniak B, et al. Urachal carcinoma: a pathologic and clinical study of 46 cases. *Hum Pathol.* 2015; 46: 1808-1814.
9. Grignon DJ, Ro JY, Ayala AG, Johnson DE, Ordóñez NG. Primary adenocarcinoma of the urinary bladder. A clinicopathologic analysis of 72 cases. *Cancer.* 1991; 67: 2165-2172.
10. Molina JR, Quevedo JF, Furth AF, Richardson RL, Zincke H, Burch PA. Predictors of survival from urachal cancer: a Mayo Clinic study of 49 cases. *Cancer.* 2007; 110: 2434-2440.
11. Gopalan A, Sharp DS, Fine SW, Tickoo SK, Herr HW, Reuter VE, et al. Urachal carcinoma: a clinicopathologic analysis of 24 cases with outcome correlation. *Am J Surg Pathol.* 2009; 33: 659-668.
12. Paner GP, McKenney JK, Barkan GA, Yao JL, Frankel WL, Sebo TJ, et al. Immunohistochemical analysis in a morphologic spectrum of urachal epithelial neoplasms: diagnostic implications and pitfalls. *Am J Surg Pathol.* 2011; 35: 787-798.
13. Cheikhelard A, Irtan S, Orbach D, Minard-Colin V, Rod J, Martelli H, et al. Urachal rhabdomyosarcoma in childhood: a rare entity with a poor outcome. *J Pediatr Surg.* 2015; 50: 1329-1333.
14. Kingo PS, Høyer S, Marinovskij E, Rawashdeh YF. Paediatric urachal benign teratoma: a case report and review of the literature. *APMIS.* 2014; 122: 761-765.
15. D'Alessio A, Verdelli G, Bernardi M, DePascale S, Chiarenza SF, Giardina C, et al. Endodermal sinus (yolk sac) tumor of the urachus. *Eur J Pediatr Surg.* 1994; 4: 180-181.
16. Ashley RA, Inman BA, Routh JC, Rohlinger AL, Husmann DA, Kramer SA. Urachal anomalies: a longitudinal study of urachal remnants in children and adults. *J Urol.* 2007; 178: 1615-1618.
17. Galati V, Donovan B, Ramji F, Campbell J, Kropp BP, Frimberger D. Management of urachal remnants in early childhood. *J Urol.* 2008; 180: 1824-1826.

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