Patterns of Urachal Remnant Involvement by Urothelial Carcinoma

Intraluminal Noninvasive Spread Can Mimic a Deep-seated Bladder Invasion

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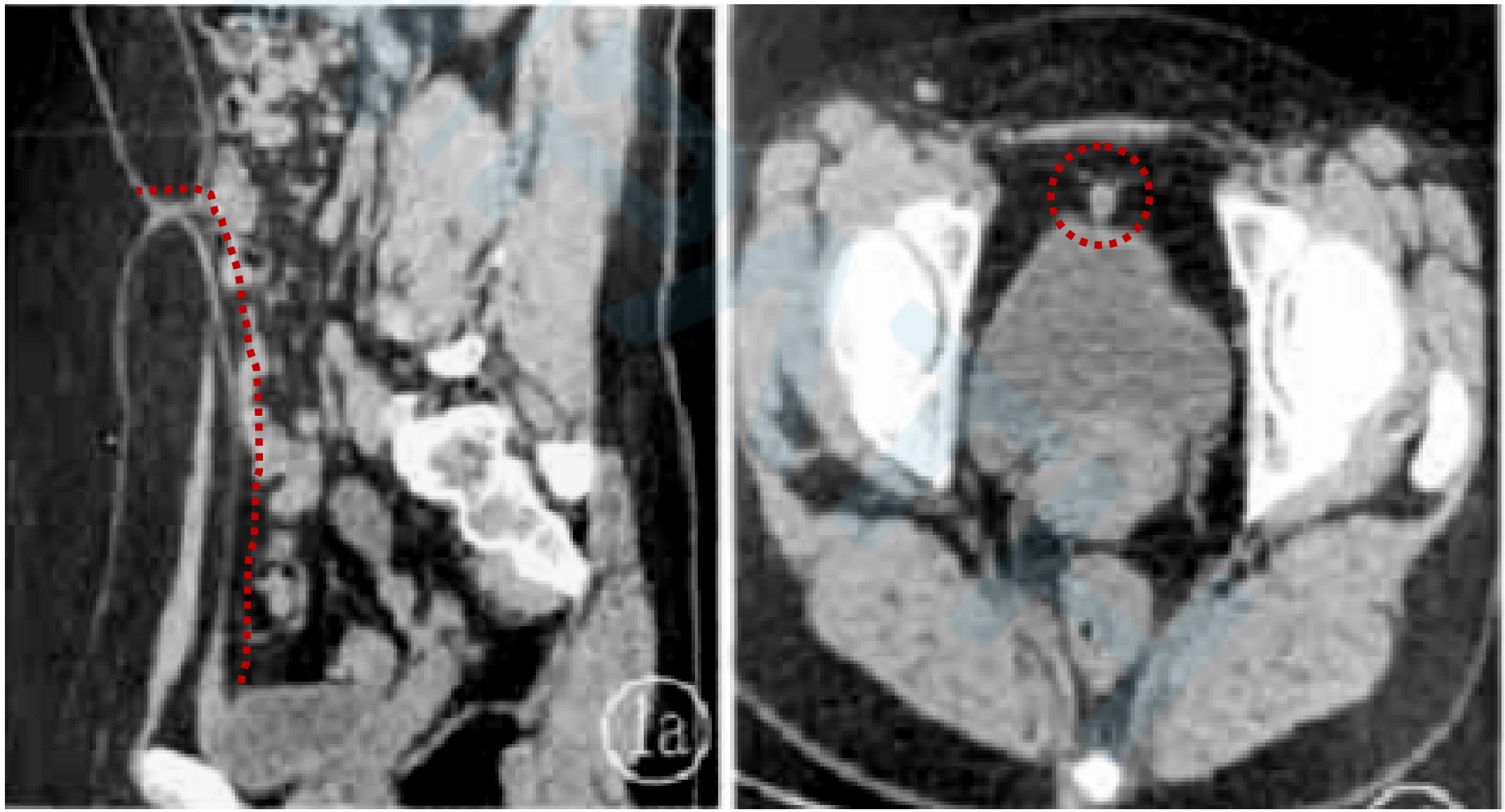
Urachal Remnant

- The urachus is a fibrous remnant of the allantois.
- The allantois is a canal that drains the urinary bladder of the fetus and runs within the umbilical cord.
- The urachus is a band of fibrous tissue extending from the dome of the bladder to the umbilical cord.
- By 32 weeks, the urachus is obliterated and becomes a vestigial structure known as the median umbilical ligament.
- The urachus remnant lies in the space of Retzius（雷丘斯间隙）, between the transversalis fascia anteriorly and the peritoneum posteriorly.

An Illustrated Guide To Pediatric Urology (2017)

Urachal Remnant

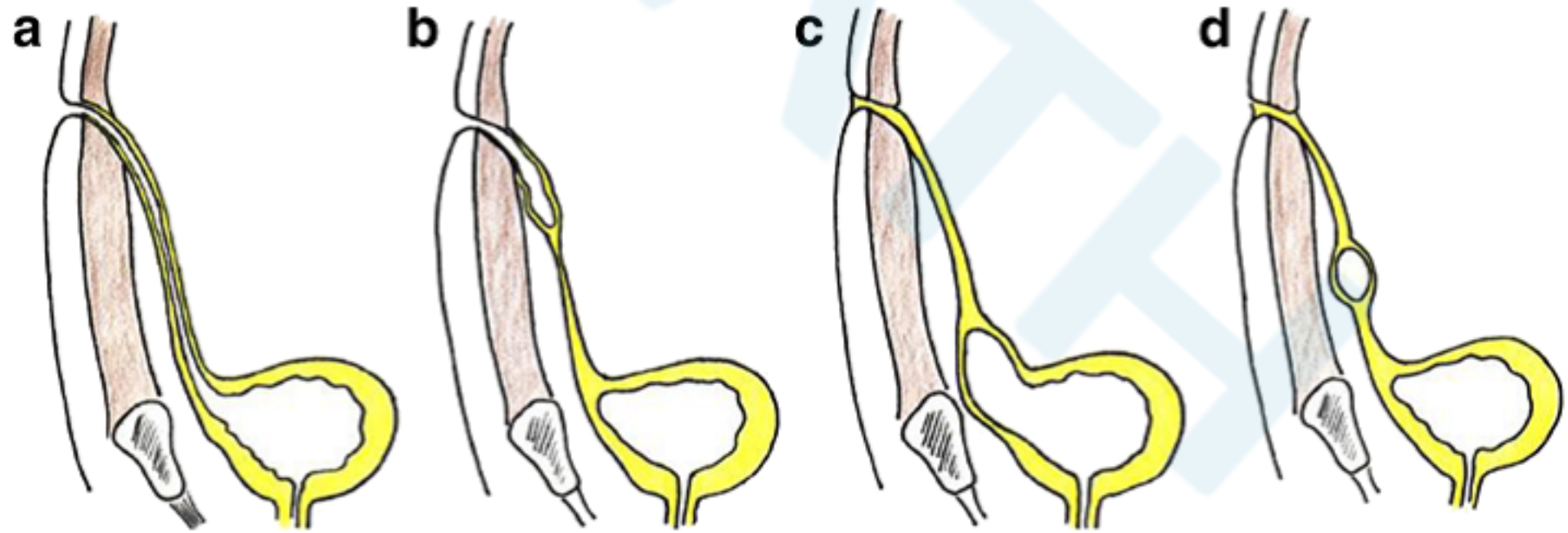


Classification

There are four types of congenital urachal remnant anomalies.

•They are:

– Patent urachuss(50 %)
– Urachal cyst (30 %)
– Urachal-umbilical sinus (15 %)
– Vesicourachal diverticulum (5 %)



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•Inflammation and malignancy are the commonest complications of urachal remnants.

•Inflammation occurs more frequently in children and young adults.

•Malignant degeneration of urachal remnants occurs more frequently in middle-aged and older people.

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Tumors and Urachal Remnants

- Urachal tumors are extremely rare and can be benign or malignant.
- Benign urachal tumors include:
  - Adenomas
  - Fibromas
  - Fibroadenomas
  - Hamartomas

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- Malignant urachal neoplasms represent less than 0.5 % of all urinary bladder cancers.
- The normal urachus is commonly lined by urothelium, but it was found that urachal carcinoma predominantly are adenocarcinoma (90% of cases) and 75% of these cases are mucin producing. This is probably due to the metaplasia of the urachal mucosa into columnar epithelium followed by malignant transformation.
- The remaining urachal carcinomas are uroepithelial, squamous, or anaplastic carcinomas.

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WHO classification of tumours of the urothelial tract

Urothelial tumours	
Infiltrating urothelial carcinomas	
with divergent differentiation	8120/3
Nested, including large nested	
Microcystic	
Micropapillary	8131/3
Lymphoepithelioma-like	8082/3
Diffuse/ Plasmacytoid/ Signet ring cell	
Sarcomatoid	8122/3
Giant cell	8031/3
Undifferentiated	8020/3
Lipid rich	
Clear cell	
Non-invasive urothelial carcinoma	
Urothelial carcinoma in situ	8120/2
Papillary urothelial carcinoma, low grade	8130/2
Papillary urothelial carcinoma, high grade	8130/3
Papillary urothelial neoplasm of low malignant potential	8130/1
Urothelial papilloma	8120/0
Inverted urothelial papilloma	8121/0
Urothelial hyperplasia	
Urothelial dysplasia/atypia	
Squamous cell carcinoma	
Squamous cell carcinoma	8070/3
Verrucous carcinoma	8051/3
Squamous cell papilloma	8052/0
Glandular neoplasms	
Adenocarcinoma NOS	8140/3
Enteric	8144/3
Mucinous	8480/3
Mixed	8140/3
Villous adenoma	8261/0
Urachal carcinoma	8010/3
Tumours of Müllerian type	
Clear cell carcinoma	8310/3
Endometrioid carcinoma	8380/3

Neuroendocrine tumours	
Small cell neuroendocrine carcinoma	8041/3
Large cell neuroendocrine carcinoma	8013/3
Well-differentiated neuroendocrine tumour	8240/3
Paraganglioma	8693/1
Melanocytic tumours	
Malignant melanoma	8720/3
Naevus	8720/0
Melanosis	
Mesenchymal tumours	
Rhabdomyosarcoma	8900/3
Leiomyosarcoma	8890/3
Angiosarcoma	9120/3
Inflammatory myofibroblastic tumour	8825/1
Perivascular epithelioid cell tumour	
Benign	8714/0
Malignant	8714/3
Solitary fibrous tumour	8815/1
Leiomyoma	8890/0
Haemangioma	9120/0
Granular cell tumour	9580/0
Neurofibroma	9540/0
Urothelial tract haematopoietic and lymphoid tumours	
Miscellaneous tumours	
Carcinoma of Skene, Cowper and Littre glands	8140/3
Metastatic tumours and tumours extending from other organs	
Tumours of the upper urinary tract	
Tumours arising in a bladder diverticulum	
Urothelial tumours of the urethra	8120/3

The morphology codes are from the International Classification of Diseases for Oncology (ICD-O) {917A}. Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; and /3 for malignant tumours. The classification is modified from the previous WHO classification {756A}, taking into account changes in our understanding of these lesions.

* These new codes were approved by the IARC/WHO Committee for ICD-O.

Urachal carcinoma

Definition

Urachal carcinomas are malignant epithelial neoplasms arising from urachal remnants. Most urachal carcinomas are adenocarcinomas.

Epidemiology

Urachal carcinoma is rare. Most cases occur in the fifth or sixth decade of life. predominates in men, with a male-to-female ratio of 2:1 to 3:1.

Etiology

Although the etiology is unknown, intestinal metaplasia of the urachal epithelium is believed to be the predisposing factor for adenocarcinoma.

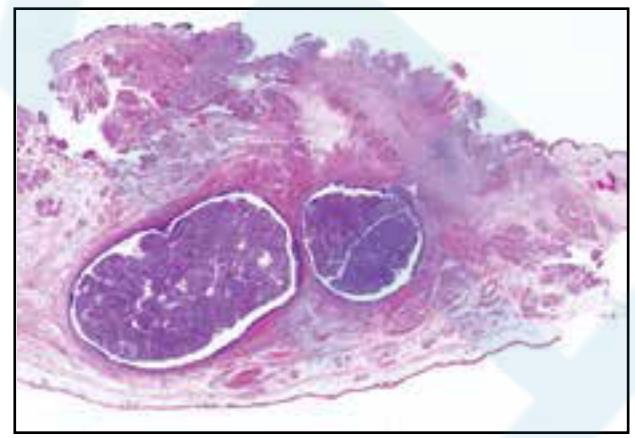
Localization

Urachal carcinoma may present in the bladder dome or the anterior or posterior wall, and may extend to the umbilicus. These neoplasms are often associated with urachal remnants.

WHO Classifcation of Tumours of the Urinary System and Male Genital Organs (2016)

Macroscopy

Urachal carcinomas are located in the dome and/or anterior wall and predominantly invade the muscularis propria or deeper tissues. They are typically firm, whitish grey infiltrative masses, but can also be discrete, cystic, or cavitary tumours. Associated urachal remnants or cysts may be present.



WHO Classifcation of Tumours of the Urinary System and Male Genital Organs (2016)

Table 2.04 Epithelial neoplasms of the urachus. Modified from Amin MB et al. {90}.

Adenomas
Villous adenoma
Mucinous cystadenoma[a,b]
Adenocarcinomas
Non-cystic adenocarcinomas
Enteric (intestinal) adenocarcinoma
Mucinous (colloid) adenocarcinoma
Signet ring–cell adenocarcinoma
Adenocarcinoma, NOS
Mixed adenocarcinoma
Cystic[a] adenocarcinomas
Mucinous cystic tumour of low malignant potential[c]
Mucinous cystadenocarcinoma[d]
Non-glandular neoplasms
Urothelial neoplasms
Squamous cell neoplasms
Neuroendocrine neoplasms
Mixed-type neoplasms
Mixed carcinomas[e]

[a]Cystic tumours classification, modified from Amin et al. {90}; [b]Cystic wall lined by single layer of mucinous columnar cells with no atypia; [c]Epithelial abnormalities range from low-grade cytological atypia to intraepithelial carcinoma; [d]May present with microinvasion (< 2 mm and constituting < 5% of the tumour) or as a frankly invasive neoplasm; [e]Specify types and relative percentage of each component.

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Histopathology

●The most common are non-cystic adenocarcinomas (accounting for 83% of cases) , followed by cystic tumours (17% of cases).

●**Non-cystic urachal adenocarcinomas** resemble the primary urinary bladder adenocarcinomas and exhibit a similar histological spectrum.
---enteric type, mucinous (colloid) type, signet ring–cell type

●**Mucinous cystadenocarcinoma** has a prominent cystic component. The morphological spectrum similar to ovarian mucinous tumours.

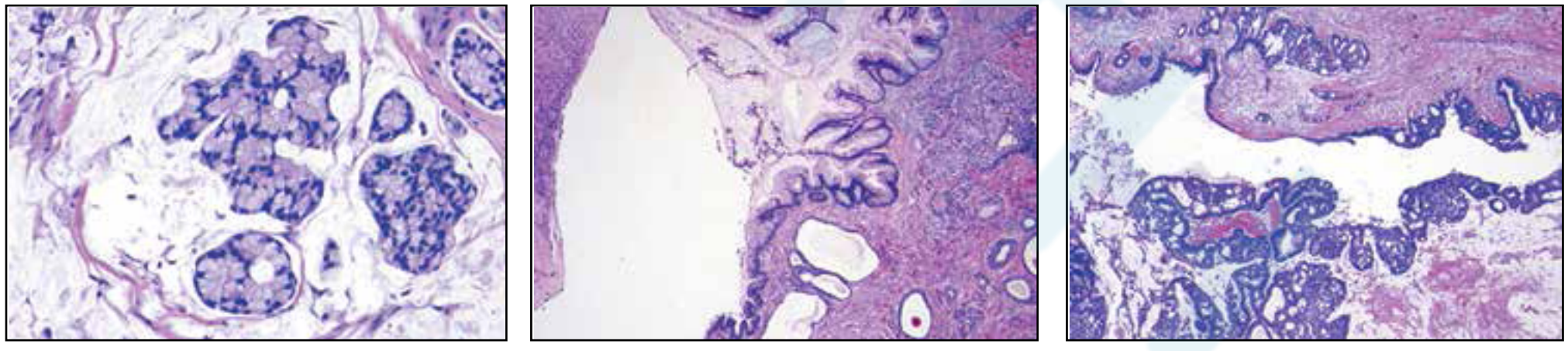

Fig. 2.42 A Mucinous (colloid) adenocarcinoma. **B** Urachal mucinous cystic tumour of low malignant potential. Associated urachal remnants can also be seen (right). **C** Frankly invasive urachal mucinous cystadenocarcinoma.

- **For confirmation of the urachus as the primary tumour location, these adenocarcinomas must meet strict criteria.**

Table 2.03 Criteria for diagnosis of urachal adenocarcinoma. Adapted from Gopalan A et al. {1025}.

1. Location of the tumour in the bladder dome and/or anterior wall[a]
2. Epicentre of carcinoma in the bladder wall
3. Absence of widespread cystitis cystica and/or cystitis glandularis beyond the dome or anterior wall
4. Absence of a known primary elsewhere
[a]The presence of urachal remnant in association with the tumour is supportive of the diagnosis, but its absence does not preclude a urachal origin.

WHO Classifcation of Tumours of the Urinary System and Male Genital Organs (2016)

- **The non-glandular carcinomas** are rare and can be pure or mixed. Conventional urothelial, squamous, and neuroendocrine carcinomas are morphologically and immunophenotypically similar to their non-urachal counterparts. **Urothelial carcinoma** can have papillary or in situ carcinoma components within the urachal lumina/remnant and can occur concomitantly with urothelial neoplasms elsewhere in the genitourinary tract.

WHO Classifcation of Tumours of the Urinary System and Male Genital Organs (2016)

Immunohistochemistry

- urachal adenocarcinomas express CDX-2, CK20, Reg IV, and 34 β E12.
- About half are positive for CK7 and claudin 18.
- Nuclear β -catenin is almost always negative and does not exhibit diffuse staining.
- The various adenocarcinoma morphologies appear to have similar immunophenotypic and mRNA expression profiles.

WHO Classifcation of Tumours of the Urinary System and Male Genital Organs (2016)

Genetic profile

•Microsatellite instability and mutations of *KRAS* at codon 12 have each been reported in about 40% of cases of urachal adenocarcinoma.

•Microsatellite instability and *KRAS* mutations have been shown to be mutually exclusive.

•Patients with *KRAS* mutations typically have markedly better overall survival despite advanced stage.

•*KRAS* mutation appears to be more frequent in the mucinous type and in younger patients.

WHO Classifcation of Tumours of the Urinary System and Male Genital Organs (2016)

Prognosis and Predictive Factors

•The issue of whether urachal adenocarcinoma is associated with better survival than non-urachal adenocarcinoma is still controversial.

•The 5- and 10-year cancer-specific survival rates for urachal carcinoma patients are 40–64% and 31–49%, respectively.

•Tumour staging (regardless of the staging system used) is an important independent predictive factor of survival. The most widely used staging system is the Sheldon system.

•Complete resection is also a significant independent predictive factor.

•The predictive value of histological type (glandular or nonglandular) is unknown, because data are limited.

WHO Classifcation of Tumours of the Urinary System and Male Genital Organs (2016)

Table 2.05 The Sheldon staging system for urachal carcinoma. From Sheldon et al. {2506}.

Stage	Definition
I	Carcinoma confined to the urachal mucosa
II	Carcinoma invasion confined to the urachus.
III	Local carcinoma extension
IIIA	Extension into the bladder
IIIB	Extension into the abdominal wall
IIIC	Extension into the peritoneum
IIID	Extension into other viscera
IV	Metastasis
IVA	Metastasis to lymph nodes
IVB	Metastasis to distant sites

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WHY?

Benign urachal remnants can be encountered in the adult urinary bladder and it is recognized that these can uncommonly give rise to urachal urothelial carcinoma. However, urachal remnants containing urothelial carcinoma incidentally encountered in cystectomies for bladder cancer has not been previously described.

WHY?

- It is well-recognized that urothelial carcinoma in situ (CIS) may spread into von Brunn's nests, cystitis cystica or cystitis glandularis within the lamina propria and mimic invasion.
- The urachal remnant extends far deeper in the bladder wall than these subepithelial structures and we have encountered in our practice, examples of urothelial CIS spreading within an urachal remnant.
- To the best of our knowledge, this phenomenon has not been previously described in the literature.

WHY?

- Primary urachal urothelial carcinoma is rare with about 25 examples reported in the literature, and it is unclear, how this tumor correlates with the incipient involvement of urachal remnant by urothelial carcinoma.
- Herein, we present examples of urachal remnants containing urothelial carcinoma incidentally encountered in cystectomies for bladder cancer to elucidate on its histology, potential impact to bladder tumor staging, and correlation to primary urachal urothelial carcinoma.

MATERIALS AND METHODS

•Seven urinary bladder cystectomies containing urothelial carcinoma with an incidentally discovered urachal remnants containing tumor were identified from the surgical pathology files of the University of Chicago Medical Center (UCMC) from 2011 to 2017. One additional case was identified in our consultation service.

•The bladder cancers were staged according to the 8th AJCC staging system and the primary urachal cancer by the Sheldon staging system.

RESULTS

TABLE 1. Clinicopathologic Characteristics of Bladder Cancer Cystectomies With Incidental Urachal Remnants Involved by Urothelial Carcinoma

			Main Bladder Urothelial Carcinoma			Urachal Remnants			Urachal Remnant Tumor	
Case	Age (y)/ Sex	Specimen	Stage	Dome Involved	Overlying Urachal Remnant	Location	Transected Segment(s), Largest Size	Benign Epithelium	Type	Deepest Extent (+Deeper than Bladder Tumor)
1	68/M	CP	pTis	Yes	CIS	Dome	Multiple, <1 mm	Urothelial	CIS	MP, upper half+
2*	86/M	CP	pT2b	No	CIS (separate focus)	Dome	Single, 3 mm	Cuboidal	Noninvasive HG PUC (inverted)	MP, lower half
3	65/M	CP	pT1	Yes	CIS and noninvasive HG PUC	Dome	Multiple, 7 mm (tubulocystic)	Urothelial	Noninvasive HG PUC and CIS	MP, lower half+
4	53/M	CP	pT1	Yes	Noninvasive HG PUC	Dome	Multiple, 2 mm	Urothelial and glandular	CIS	MP, upper half+
5	87/M	CP	pT3b	Yes	CIS	Dome	Single, 3 mm	Absent	CIS	MP, upper half
6	64/M	CP	pT4a	Yes	Invasive†	Dome	Multiple tight aggregate, 8.5 mm	Absent	CIS†	MP, upper half
7	87/M	PC	pTis	Yes	CIS	Dome	Single, 2 mm	Cuboidal	CIS	MP, lower half+
8‡	59/M	CP	pTis	No	Benign urothelium	Dome	Multiple, 2 mm	Urothelial and glandular	CIS	MP, upper half+

*Concomitant pT2 prostatic urethral cancer.
†Remnant with tumor intermingles with invasive nests of urothelial carcinoma.
‡Concomitant pT3 renal pelvis cancer.
HG PUC indicates high-grade papillary urothelial carcinoma; M, male; NA, not applicable; PC, partial cystectomy.

- The 8 patients were all male ranging from 53 to 87 years old (mean: 71 y, median: 66 y).
- All 8 cystectomies contained urothelial carcinoma in the bladder surface; 5 with invasive urothelial carcinomas of conventional morphology and in 3 only urothelial CIS.
- Tumor stages of the bladder cancers were pTis (3), pT1 (2), pT2b (1), pT3b (1), and pT4a (1).
- Four of the 5 invasive carcinomas also had concomitant CIS in other regions of the bladder. The 3 bladders with CIS only had extensive and/or multifocal disease.

- All 8 cystectomies had incidental urachal remnants, all in the dome, that were comprised of tubular to elongated tubulocystic structures.
- The remnants varied from a single to multiple loose or tight aggregates of tubular segments; the individual transected segments ranged from <1 to 8.5mm in dimension.
- Most segments showed lumina and were surrounded by a thin layer of connective tissue and an inconsistent layer of thin smooth muscle bundle.

- In 2 of 8, continuity of the remnant tubular tract to the bladder surface could be visualized on the plane of section, and in 4 of 8 an invagination at the bladder surface likely representing the outlet of the noncontiguous underlying remnant could be appreciated.

Of the 8 urachal remnants, 6 contained urothelial CIS, 1 contained noninvasive high-grade papillary urothelial carcinoma (PUC), and 1 contained concomitant urothelial CIS and noninvasive high-grade PUC.

In each case, the remnant with tumor had regular epithelial to stromal boundary with no surrounding desmoplastic response.

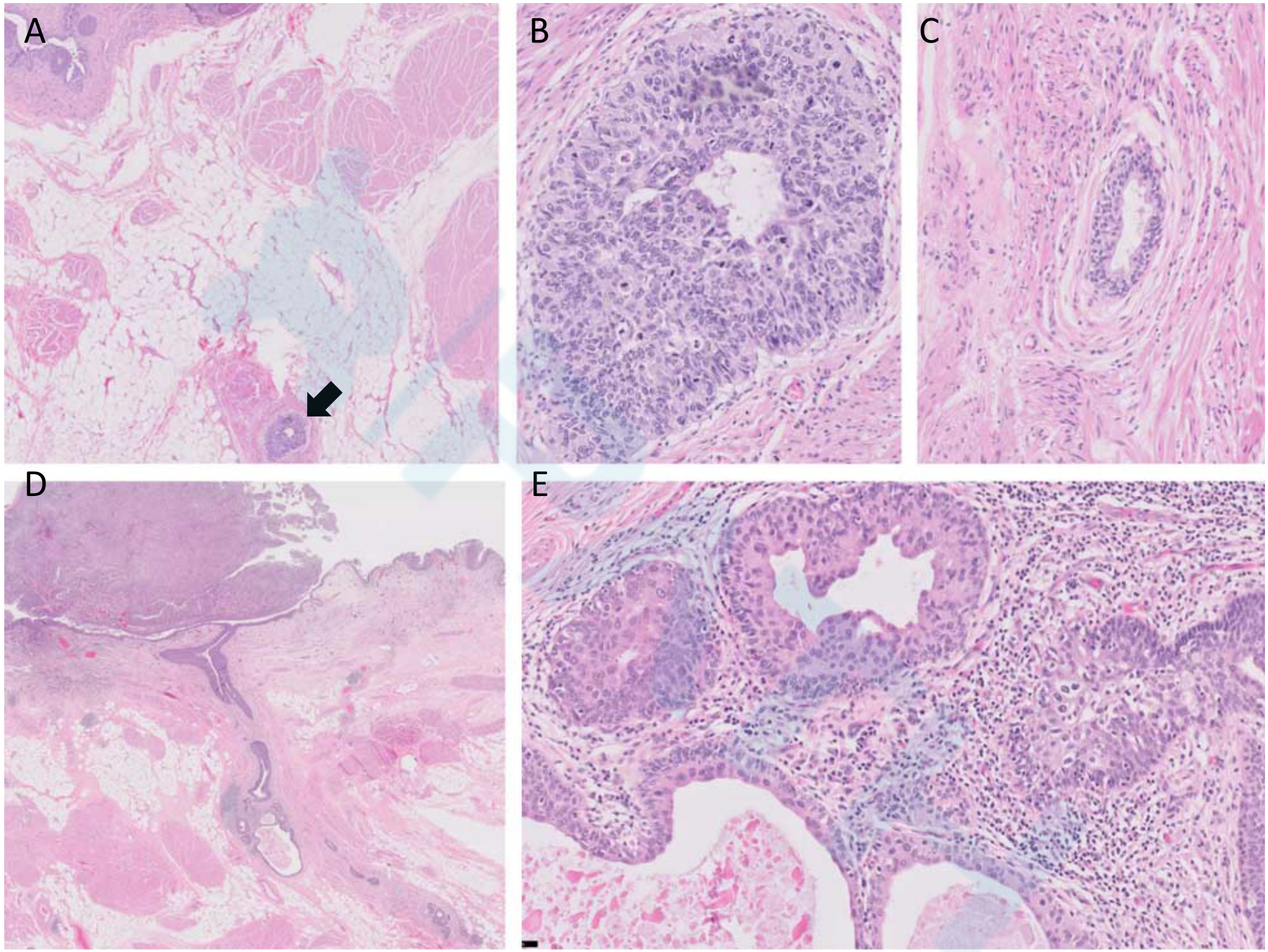


FIGURE 1. Urachal remnant within the muscularis propria layer (arrow) (A) with urothelial CIS (B) and associated benign urothelial cells (C) (case 1). Urachal remnant tracks underneath a PUC at the surface (D) and shows urothelial CIS admixed with benign urothelial cells (E) (case 4).

- One remnant with PUC (case 2) showed expansile bulbous outward growth akin to an inverted (endophytic) papillary urothelial neoplasm if it were situated on the bladder surface.

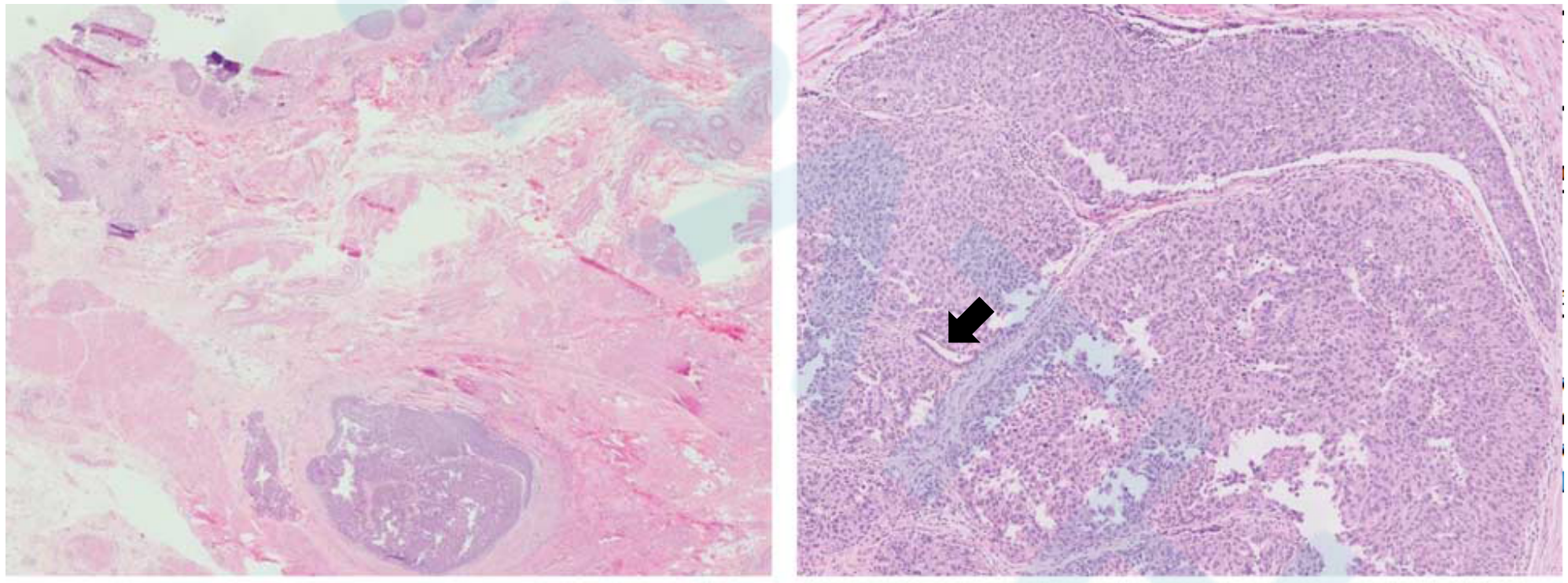
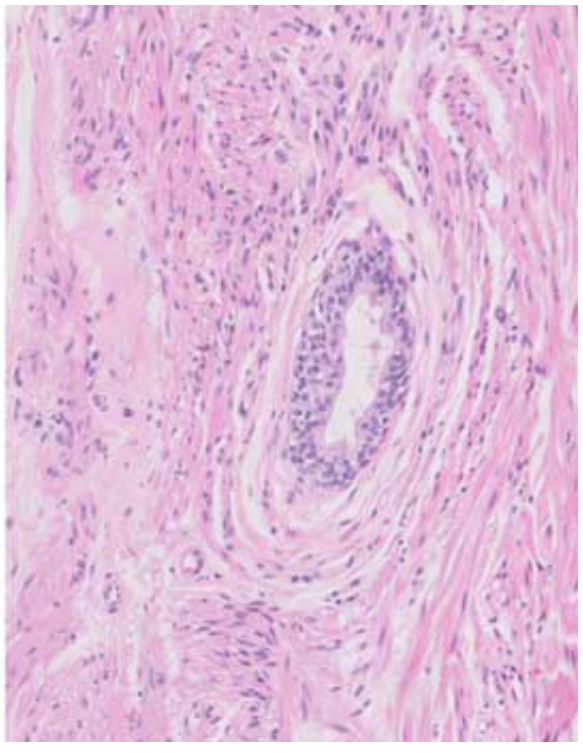
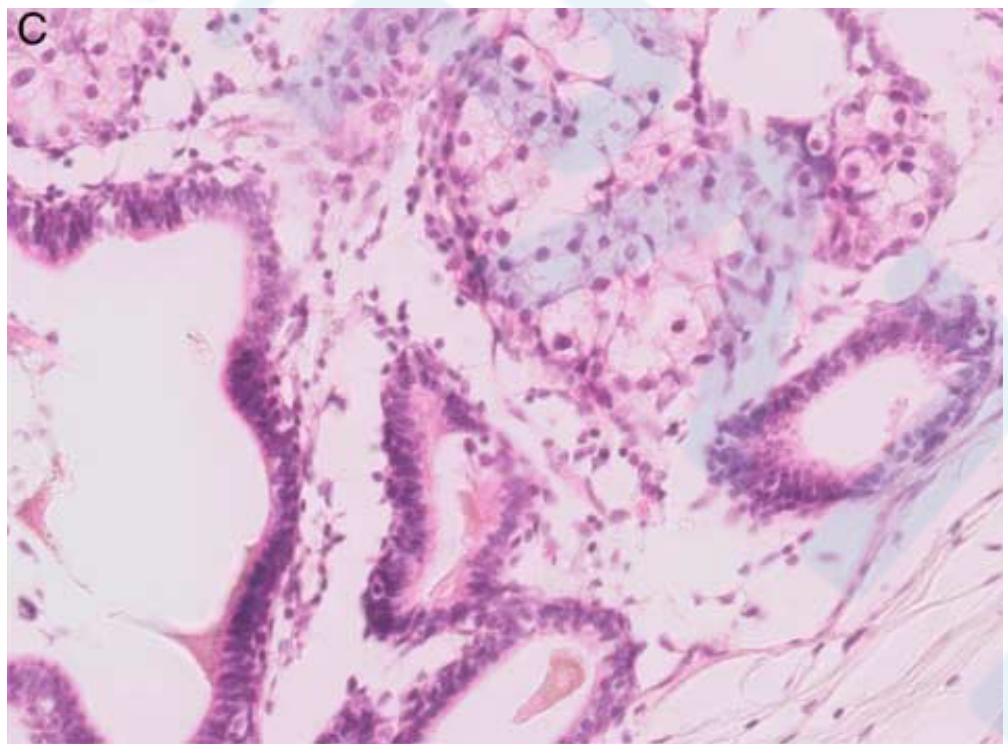
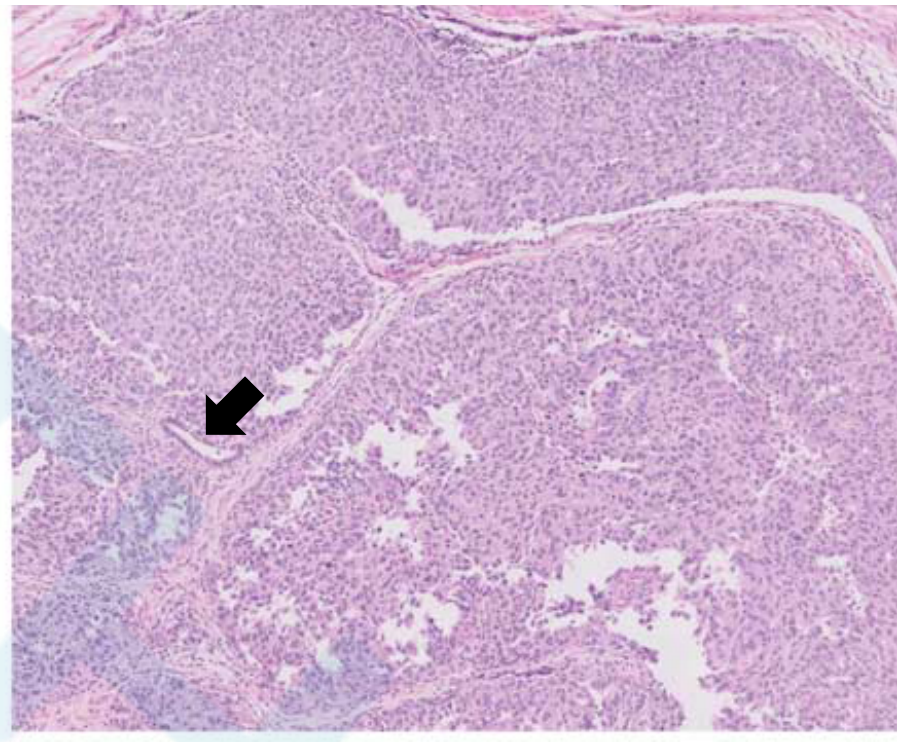


FIGURE 2. Urachal remnant within muscularis propria layer (A) composed of thickened layer of noninvasive high-grade urothelial carcinoma with inverted growth (B). Note the benign tubule (arrow) (case 2) (B).

- Benign remnant epithelium was identified in 6 of the 8 remnants with tumor including urothelial cells (2), mixed urothelial and glandular cells (2) , and cuboidal cells (2) .







- The other remnant with PUC (case 3) showed intraluminal exophytic papillary structures within a dilated portion of the remnant.

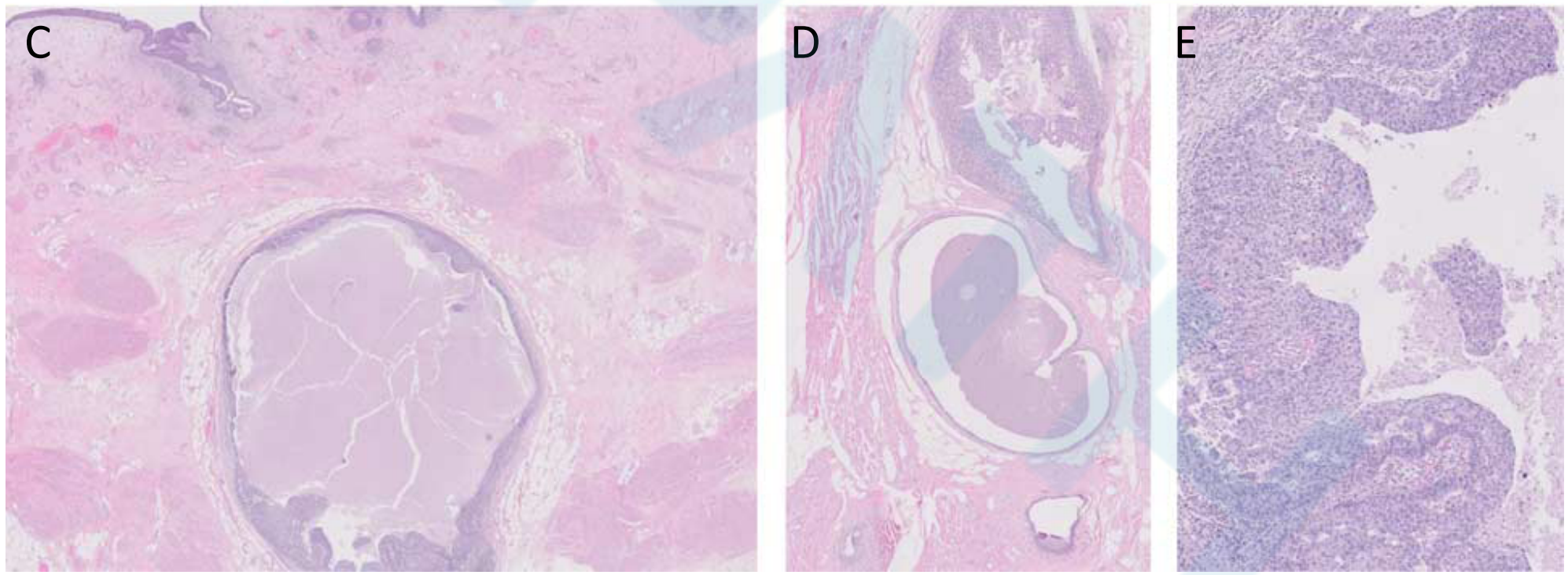


FIGURE 2. C–E, Tubulocystic urachal remnant containing noninvasive papillary urothelial carcinoma within the lumen (case 3).

- Urothelial CIS populated the tubular lining or form solid nests similar to CIS involvement of cystitis cystica/ glandularis or von Brunn's nests on the bladder surface, respectively.

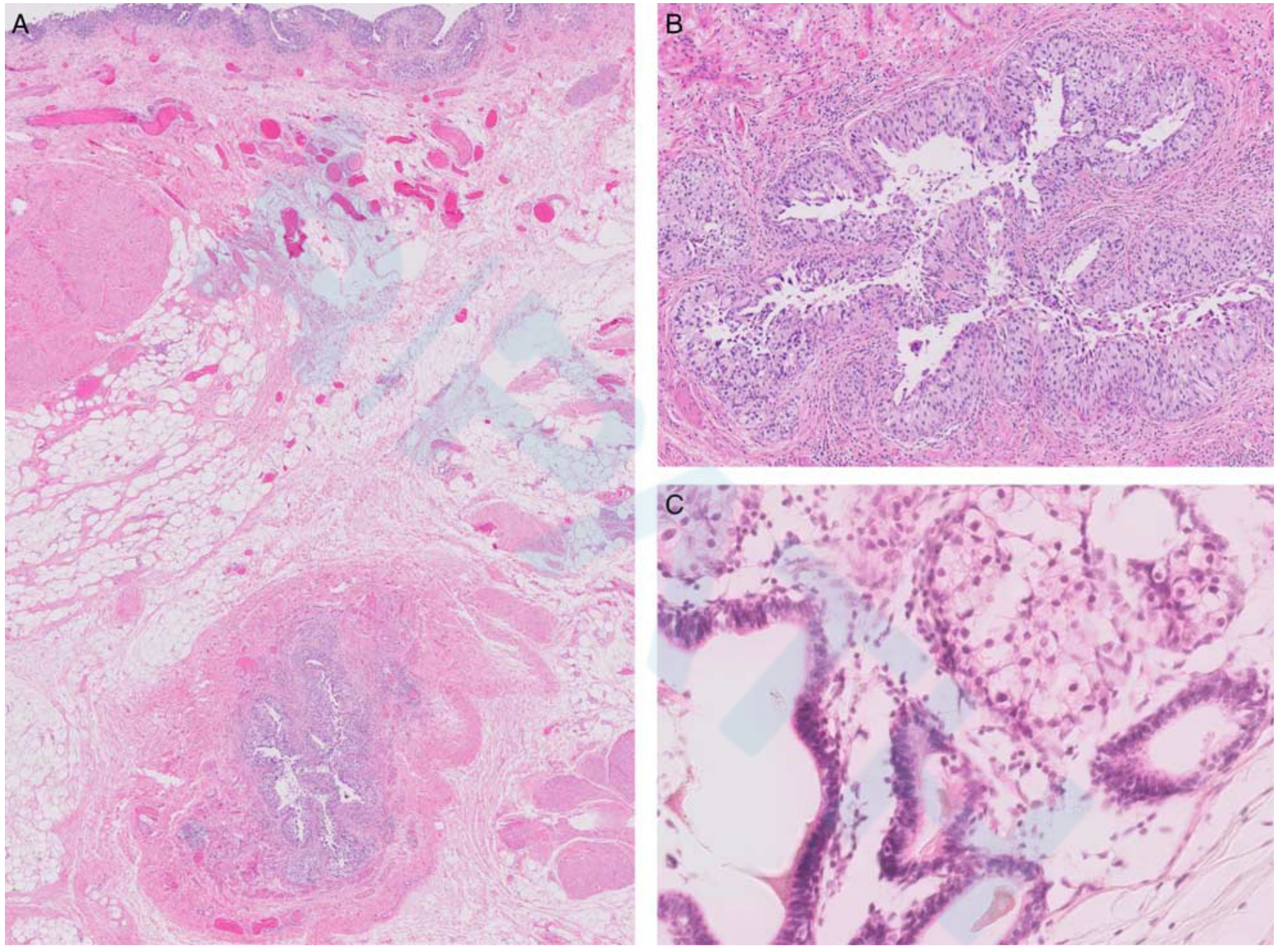


FIGURE 3. Urachal remnant within muscularis propria layer (A) lined by urothelial CIS (case 7) (B). C, Urothelial CIS cells populating urachal remnant with benign glandular cells (case 8).

- In 7 of 8 cystectomies, the remnants with tumor were not surrounded by invasive carcinoma, although in 6 of these cases, the remnant with tumor was situated in the same region as the main bladder tumor (ie, involved dome). There was, however, 1 case (case 6) in which nests of invasive carcinoma directly intermingled with the urachal remnant which was also involved by tumor.

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*Concomitant pT2 prostatic urethral cancer.
†Remnant with tumor intermingles with invasive nests of urothelial carcinoma.
‡Concomitant pT3 renal pelvis cancer.
HG PUC indicates high-grade papillary urothelial carcinoma; M, male; NA, not applicable; PC, partial cystectomy.

- Of the 8 cystectomies, the remnants with tumor were overlaid at the bladder surface by CIS (4), PUC (1), combined CIS and PUC (1), invasive urothelial carcinoma (1), and benign urothelium (1).
- The 2 remnants with tumor away from the main bladder tumor were overlaid by CIS and benign urothelium at the surface.

- The deepest extent of the tumor in remnant was into the upper half of muscularis propria (MP) (5) and lower half of MP (3).

DISCUSSION

- Similar in the bladder lumen, the incipient or early tumor within the remnants can assume urothelial CIS or PUC morphologies.
- The presence of bladder luminal urothelial carcinoma in the same region indicate that most of the tumors in the urachal remnants are direct continuation or spread from the bladder surface carcinoma (7/8 in our series) and this can be explained by the potential communication of the tubular remnants to the bladder surface.

- Benign urachal remnants can mimic an invasive tumor, and this mimicry can be compounded if the urachal remnants contain noninvasive urothelial carcinoma spreading intraluminally from the surface.
- As urachal remnants can extend deep into the MP, care should be exercised not to over interpret the focus as MP invasion.
- In our series, if remnants with tumor were misinterpreted as MP invasion, 5 of the bladder tumors would have been overstaged, from pTis to pT2 in 2 cases and from pT1 to pT2 in 3 cases.

- **Helpful clues** to the identification as urachal remnant with intraluminal tumor (vs. an invasive urothelial carcinoma focus) include:

1 its dome location

2 tubular or tubulocystic pattern

3 regular boundary

4 absent desmoplastic response

5 intermingled benign remnant epithelial cells

Intramural ureter segments / Urachal remnants?

- The supposition that the tubular structures represent intramural ureter segments and not urachal remnants was ruled out.
- As both ureters in 7 cystectomies were identified at their appropriate sites distinct from the remnants (1 case was partial cystectomy only).
- Further, the tubular structures were in the dome, their tubular segment(s) had smaller lumina, and lacked organized surrounding MP bundles.
- Intramural ureter has a distinct MP composed of a layer muscle bundles thinner than the bladder MP muscle bundles, which is not present in urachal remnants.

Summary

- Uurachal remnant involvement by urothelial carcinoma can be divided into:

(a) spread from a bladder urothelial carcinoma,

(b) separate tumor focus from a concomitant bladder urothelial carcinoma,

(c) isolated (primary) urachal urothelial carcinoma.

- Urachal remnant involvement by urothelial carcinoma can be an urothelial CIS, PUC, or invasive disease, similar in the bladder proper.
- Caution should be exercised not to over interpret deep extension into the MP of an urachal remnant involved by a noninvasive urothelial carcinoma as a MP-invasive focus.

Thanks!