

Review Article

Adenocarcinoma of the urinary bladder

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Abstract: Adenocarcinoma is an uncommon malignancy in the urinary bladder which may arise primarily in the bladder as well as secondarily from a number of other organs. Our aim is to provide updated information on primary and secondary bladder adenocarcinomas, with focus on pathologic features, differential diagnosis, and clinical relevance. Primary bladder adenocarcinoma exhibits several different growth patterns, including enteric, mucinous, signet-ring cell, not otherwise specified, and mixed patterns. Urachal adenocarcinoma demonstrates similar histologic features but it can be distinguished from bladder adenocarcinoma on careful pathologic examination. Secondary bladder adenocarcinomas may arise from the colorectum, prostate, endometrium, cervix and other sites. Immunohistochemical study is valuable in identifying the origin of secondary adenocarcinomas. Noninvasive neoplastic glandular lesions, adenocarcinoma in situ and villous adenoma, are frequently associated with bladder adenocarcinoma. It is also important to differentiate bladder adenocarcinoma from a number of nonneoplastic lesions in the bladder. Primary bladder adenocarcinoma has a poor prognosis largely because it is usually diagnosed at an advanced stage. Urachal adenocarcinoma shares similar histologic features with bladder adenocarcinoma, but it has a more favorable prognosis than bladder adenocarcinoma, partly due to the relative young age of patients with urachal adenocarcinoma.

Keywords: Urinary bladder, adenocarcinoma, urachal adenocarcinoma, metastasis

Bladder cancer is a common malignancy in the United States with an estimated 74,000 new cases every year. The vast majority of bladder cancers are urothelial carcinomas, which demonstrate a high tendency for divergent differentiation, leading to a variety of histologic variants. Adenocarcinoma is an uncommon histologic variant and accounts for 0.5-2% of bladder cancers in the United States [1-3]. Bladder adenocarcinoma may be primary or secondary, and secondary adenocarcinomas are more common than primary adenocarcinomas in the bladder [4]. Primary bladder adenocarcinoma is derived from the bladder urothelium but shows a histologically pure glandular phenotype. Secondary adenocarcinomas involve the bladder either by direct extension or by metastasis from a distant site. The common origins of secondary bladder adenocarcinomas include the colon, prostate, endometrium, cervix, breast and lung [4, 5]. Strictly speaking, the urachus is not an anatomic component of the urinary bladder, but urachal adenocarcinoma is usually described together with bladder adeno-

carcinoma because they share similar pathologic and clinical features.

Primary adenocarcinoma

Primary adenocarcinoma of the bladder is derived from the urothelium of the bladder but exhibits a pure glandular phenotype. Patients are usually in the sixth and seventh decade of life with male predominance [6-8]. Hematuria is the most common symptom, but some patients may present with bladder irritation symptoms and rarely, mucusuria [8]. Approximately one-third of the patients have lymph node metastasis at the time of presentation [9, 10]. Although the pathogenesis of bladder adenocarcinoma is not yet entirely understood, several risk factors have been described. Most notably, almost 90% of bladder tumors in patients with exstrophy of bladder are adenocarcinoma [11]. Up to 10% of all bladder cancers are adenocarcinomas in areas where schistosomiasis is endemic [12-14]. Other possible risk factors include chronic irritation, obstruction, cystocele and

Bladder adenocarcinoma

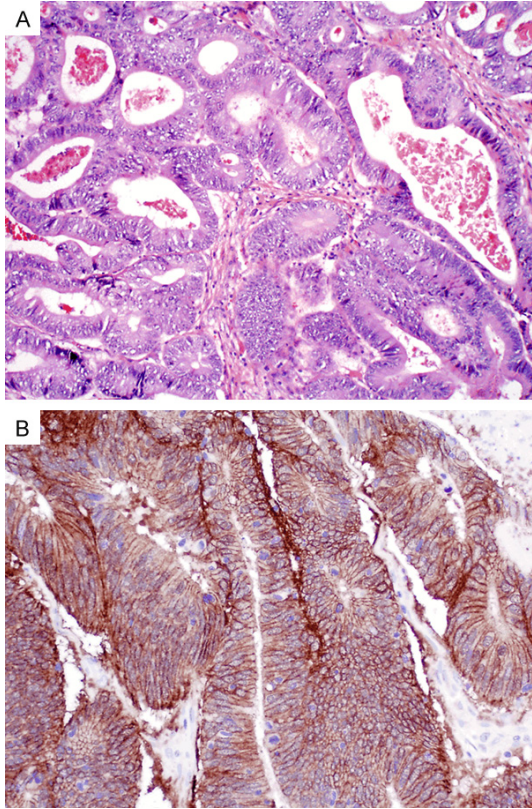


Figure 1. Enteric-type bladder adenocarcinoma shows intestinal-type glands with columnar cells and marked cytologic atypia (A). The carcinoma cells exhibit cytoplasmic and membranous immunostaining for β -catenin (B).

endometriosis [15]. Cystitis glandularis and intestinal metaplasia are often found adjacent to bladder adenocarcinoma, but recent studies have showed that cystitis glandularis and intestinal metaplasia are not associated with an increased risk for adenocarcinoma [16].

Grossly, bladder adenocarcinoma usually arises from the trigone and posterior wall but can be found anywhere in the bladder [11]. It usually presents as a solitary lesion, unlike urothelial carcinoma, which tends to be multifocal [5, 17]. Grossly, the tumor may appear as a papillary, sessile, solid, or ulcerating lesion. The cut surface is often gelatinous due to abundant mucin production.

Histologically, bladder adenocarcinoma exhibits various growth patterns: (a) enteric (colonic or intestinal); (b) mucinous (colloid); (c) signet ring cell; (d) not otherwise specified (NOS); and (e) mixed patterns [8]. The enteric pattern is composed of intestinal-type glands with pseu-

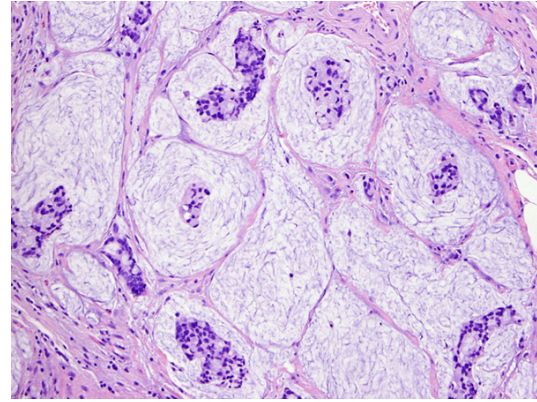


Figure 2. Mucinous-type bladder adenocarcinoma produces abundant extracellular mucin, forming a pool of mucin with floating tumor cells.

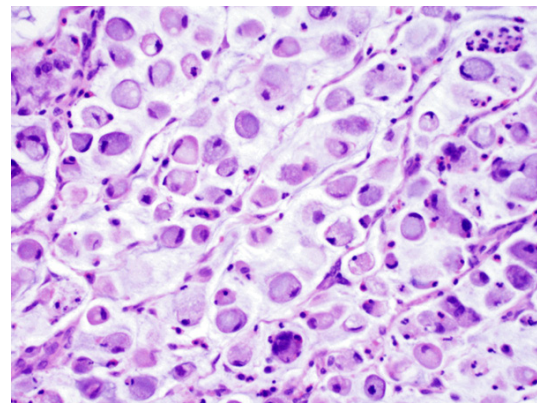


Figure 3. Signet ring cell-type bladder adenocarcinoma is characterized by large intracellular mucin vacuoles that displace nuclei to the periphery.

dostratified columnar cells and nuclear atypia, closely resembling colorectal adenocarcinoma (Figure 1). It may produce intracellular or extracellular mucin, and necrosis is not infrequent. The mucinous pattern produces abundant extracellular mucin with tumor cells floating in a pool of mucin (Figure 2). The signet ring cell pattern is composed of diffusely infiltrative poorly differentiated cells with prominent intracellular mucin and indented eccentric nuclei (Figure 3). These tumors tend to present at an advanced stage and carry a worse prognosis than other variants [18, 19]. The NOS type has non-specific glandular growth. Tumors with more than one pattern are classified as the mixed type. In addition to the above mentioned variants, very few cases of hepatoid variant of adenocarcinoma have been reported in the literature [20-22]. These tumors mimic hepato-

Bladder adenocarcinoma

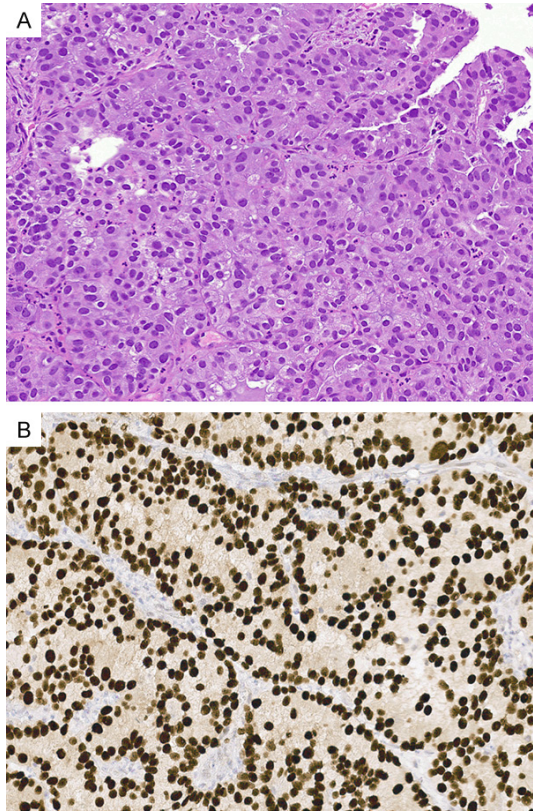


Figure 4. Clear cell adenocarcinoma exhibits solid and papillary growth patterns (A). The carcinoma cells show nuclear immunostaining for PAX-8 (B).

cellular carcinoma and express alpha-fetoprotein, HepPar-1 and alpha-1 antitrypsin. The tumor cells have abundant eosinophilic cytoplasm with hyaline globules, arranged in solid sheets and trabeculae. Bile production can be seen. Although several grading systems have been proposed for primary bladder adenocarcinoma, they have not been uniformly adopted [1, 8, 9].

The diagnosis of primary bladder carcinoma should be made only after exclusion of secondary involvement by adenocarcinoma from other organs. Secondary bladder adenocarcinomas are more common than primary adenocarcinoma and commonly arise from the colorectum, prostate, endometrium, cervix and other sites (discussed later).

Microcystic variant of urothelial carcinoma exhibits variable sized tubules and cysts, mimicking adenocarcinoma in the bladder. But the tubules and cysts are not lined by enteric-type columnar cells, and this microcystic variant

often coexists with conventional urothelial carcinoma.

A number of benign glandular lesions should be also considered in the differential diagnosis of bladder adenocarcinoma. Cystitis cystica et glandularis may become florid, mimicking adenocarcinoma. However, unlike adenocarcinoma, it usually shows a lobular architecture at a superficial location and lacks complex cribriform structures as well as atypical columnar cells. Sometimes, urothelial carcinoma in situ may involve cystitis cystica et glandularis, but it lacks enteric type columnar cells and true glandular differentiation. Intestinal metaplasia is characterized by enteric-type columnar cells and goblet cells. Occasionally, it may produce abundant mucin with extravasation, resembling mucinous adenocarcinoma [23]. However, intestinal metaplasia generally lacks complex architecture and atypical epithelial aggregates in a pool of mucin. The urinary bladder is the most common site for endometriosis in the genitourinary tract. Occasionally, endometriosis is associated with endometrial carcinoma [24, 25]. Endocervicosis and endosalpingiosis, which are characterized by cervical type mucinous glands or glands with tubal-type epithelium, respectively, may also affect the bladder wall. The diagnosis of müllerianosis is rendered when a glandular lesion in the bladder wall exhibits mixture of endometrial, endocervical and tubal epithelium.

Clear cell adenocarcinoma

Clear cell (mesonephric) adenocarcinoma is a unique variant of bladder adenocarcinoma. Unlike other bladder adenocarcinomas, clear cell adenocarcinoma more frequently affects women than men [26]. The mean age of patients is 57 years (range 22-83 years) [26]. Hematuria and dysuria are common presenting symptoms, and some patients may present with obstructive symptoms or abdominal pain [27]. Clear cell adenocarcinoma is considered of a müllerian origin, as it is morphologically similar to female genital tract clear cell carcinoma and often associated with endometriosis or müllerianosis [28-30].

Grossly, the tumor is more frequent in the urethra than in the bladder [28]. In the bladder, it is usually located in the trigone or posterior wall. The tumor may appear as a polypoid, nodular,

Bladder adenocarcinoma

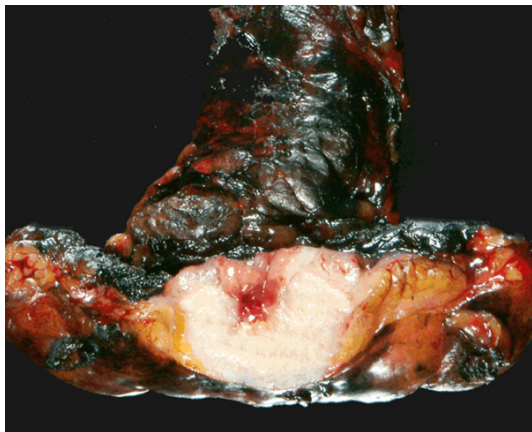


Figure 5. Urachal adenocarcinoma. Resection of the bladder dome and urachal remnant shows a glistening, tan-white tumor at the bladder dome, with an epicenter in the muscular wall.

papillary, or sessile mass [26]. Microscopically, clear cell adenocarcinoma exhibits papillary, solid or tubulocystic pattern (**Figure 4**). The papillae or tubules are lined by a single layer of flat, cuboidal or columnar cells with clear or lightly eosinophilic cytoplasm. Hobnail cells are frequently found. The nuclei are large with finely granular chromatin and prominent nucleoli. Tubules may have small amount of mucin. Papillae are usually small with fibrohyaline core. In the solid variant, tumor cells are arranged in sheets. Mitosis can be easily seen-ranging from 2-17 mitotic figures per 10 high power fields [26, 30].

It is important to differentiate nephrogenic adenoma from clear cell adenocarcinoma in the bladder. Nephrogenic adenoma may show cuboidal or hobnail cells similar to clear cell adenocarcinoma [31], but it lacks prominent cytoarchitectural atypia and solid growth areas [32, 33]. While clear cell adenocarcinoma is more common in females, nephrogenic adenoma more frequently affects males. As nephrogenic adenoma may involve the muscularis propria, the presence of muscle involvement does not exclude nephrogenic adenoma [32, 34]. Immunohistochemistry may have some value in differentiating clear cell adenocarcinoma from nephrogenic adenoma. Clear cell adenocarcinoma usually demonstrates more robust staining for p53 than nephrogenic adenoma [30]. Mean Ki67 positive cells in nephrogenic adenoma is 5.5 per 200 cells whereas in clear cell adenocarcinoma the count is > 32/200 cells

[30]. PAX2, PAX8 and racemase are expressed in both lesions and have limited utility in the differential diagnosis [35-38].

Other important differential diagnoses include metastatic clear cell adenocarcinoma from the female genital tract and metastatic clear cell renal cell carcinoma. It is difficult to differentiate primary and metastatic clear cell adenocarcinoma in the bladder, as they share similar histologic and immunohistochemical features. Clinical history and radiographic study are critical in the differential diagnosis.

Urachal adenocarcinoma

Urachal adenocarcinoma is an uncommon tumor that develops from the urachal remnant [39, 40]. The urachus is a fibrous allantoic remnant that connects the bladder to the umbilical cord during embryogenesis. After birth, the lumen of the urachus is usually obliterated. However, an autopsy series has found that urachal remnant persists as a tubular or cystic structure in the dome and elsewhere along the midline of the bladder in one third of adults [41]. Although the majority of urachal remnants are lined by urothelium, most urachal tumors are composed of adenocarcinoma. Urachal adenocarcinoma is less common than primary adenocarcinoma of the bladder, accounting for approximately one-third of primary adenocarcinomas involving bladder [8]. Patients with urachal adenocarcinoma present in the fifth to sixth decade of life, a decade earlier than bladder adenocarcinoma [39, 40]. Like bladder adenocarcinoma, males are more frequently affected than females [8, 39]. Patients usually present with hematuria, abdominal pain, irritative symptoms, mucusuria, and umbilical discharge [39, 42].

Urachal adenocarcinoma usually presents as a solitary discrete polypoid mass in the dome of the bladder, although they may be seen anywhere along the anterior midline of the bladder wall. The bladder mucosal surface may be intact or ulcerated. The cut surface often has a glistening appearance due to production of abundant mucin (**Figure 5**). The epicenter of the mass is usually in the muscular wall rather than the mucosa. When it grows larger, the tumor may involve the Retzius space (retropubic space) and the anterior abdominal wall.

Bladder adenocarcinoma

Table 1. Sheldon staging system for urachal carcinoma

Stage I: No invasion beyond the urachal mucosa

Stage II: Invasion confined to the urachus

Stage III: Local extension into bladder (IIIA), abdominal wall (IIIB), peritoneum (IIIC), or other viscera (IIID)

Stage IV: Metastasis to regional lymph nodes (IVA) or distant sites (IVB)

Microscopically, similar to bladder adenocarcinoma, urachal adenocarcinoma may exhibit enteric, mucinous, signet ring cell, NOS, and mixed types. The mucinous type is the most frequently observed in urachal adenocarcinomas and characterized by abundant extracellular mucin with floating carcinoma cells. The enteric type is also common and displays similar histology as colorectal adenocarcinoma. Focal areas of signet ring cells may be present in urachal adenocarcinoma [18, 19]. The immunohistochemical staining pattern of urachal adenocarcinoma shows significant overlap with primary bladder adenocarcinoma as well as metastatic colorectal adenocarcinoma. Almost all urachal adenocarcinoma expresses CK20 and CDX2 and shows variable expression of CK7, β -catenin, high molecular cytokeratin [39].

It is difficult to differentiate urachal from non-urachal bladder adenocarcinoma because of the overlapping histologic and immunohistochemical features. Several diagnostic criteria have been proposed for the diagnosis of urachal adenocarcinoma. Wheeler et al. initially proposed a comprehensive set of criteria: tumors located in the bladder dome, absence of cystitis cystica et glandularis, invasion of muscle or deeper structures, presence of the urachal remnant, sharp demarcation between the tumor and surface epithelium, presence of the suprapubic mass, and tumor growth in the bladder wall that extends into the space of Retzius [43]. However, the criteria were too strict and very few cases would meet all the requirements. Subsequently Johnson et al. modified the criteria, including tumors located in the bladder dome, a sharp demarcation between the tumor and the surface epithelium, and the exclusion of adenocarcinoma of other organs that has spread secondarily to the bladder [40]. This approach is practical and has been widely adopted.

It is problematic to stage urachal adenocarcinoma using the TNM staging system for bladder cancer, as most urachal carcinomas are

muscle-invasive due to their anatomical location. Some urachal adenocarcinomas do not invade the bladder at all, causing further difficulty in using this staging system. Sheldon et al. proposed a specific staging system for urachal tumors (**Table 1**) [44]. Even according to this system, most urachal adenocarcinomas are classified as stage III or IV, since urachal tumor needs to grow sufficiently large enough to become symptomatic. Nonetheless, this system with some modifications has shown a good association with the patient's prognosis [42].

Secondary adenocarcinoma

Although the bladder is not a common site for metastasis, secondary adenocarcinoma is more common than primary adenocarcinoma. The secondary adenocarcinomas may arise from the colorectum, prostate, female genital tract, breast, stomach, lung and other sites [4, 5, 45]. They may spread by direct extension or via a hematogenous/lymphatic route. It may be challenging to distinguish primary from secondary adenocarcinoma in the bladder. The histologic findings often need to be correlated with immunohistochemical study and clinical history to reach the correct diagnosis.

Colorectal adenocarcinoma

Colorectal adenocarcinoma is the most frequent metastasis in the bladder. It is important to differentiate primary bladder adenocarcinoma from secondary colorectal adenocarcinoma. However, it is generally difficult based on morphologic features, especially on small biopsy specimens, as they share similar histologic features (**Figure 6**). Although the presence of intestinal metaplasia may favor primary bladder adenocarcinoma, their role in pathogenesis of adenocarcinoma is still uncertain [16, 46]. In addition, secondary colorectal adenocarcinoma occasionally demonstrates finger-like projections which are indistinguishable from bladder villous adenoma, and it may also spread along the bladder surface epithelium, resembling adenocarcinoma in situ [47]. Mucin histo-

Bladder adenocarcinoma

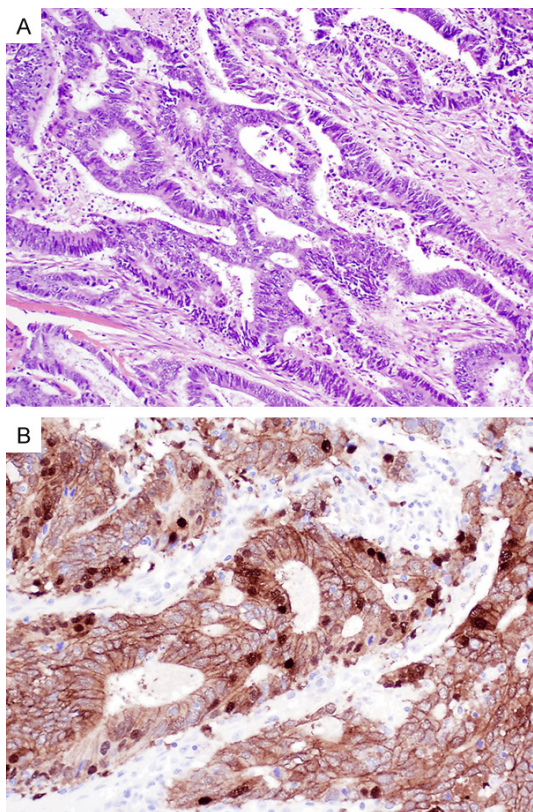


Figure 6. Colonic adenocarcinoma invades the bladder wall (A). The carcinoma cells show nuclear and cytoplasmic immunostaining for β -catenin (B).

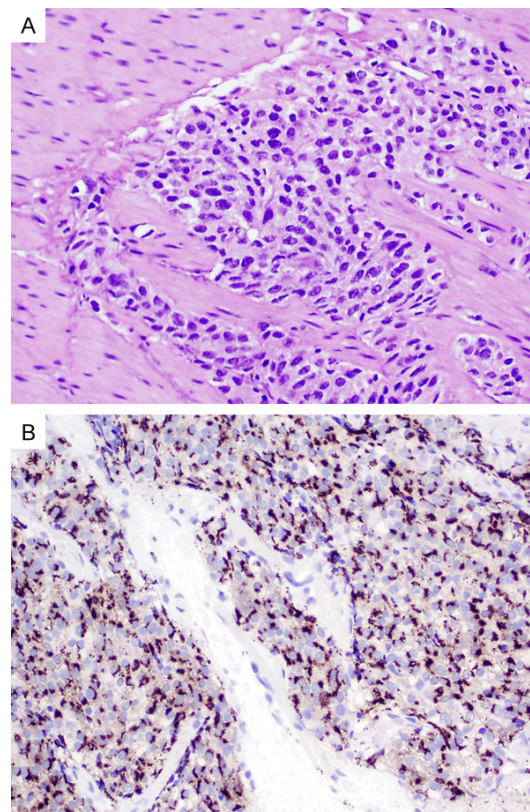


Figure 7. Poorly-differentiated prostatic adenocarcinoma invades the bladder wall (A). The carcinoma cells show prominent dot-like Golgi complex immunostaining for prostein (B).

chemistry is not useful in the differential diagnosis [48].

Immunohistochemistry has limited utility in differentiating primary bladder adenocarcinoma from metastatic colonic adenocarcinoma [6, 49, 50]. CDX2 and villin are expressed in both bladder and colorectal adenocarcinoma [51, 52]. Thrombomodulin is rarely positive in colorectal adenocarcinoma but may be positive in 59% of the bladder adenocarcinoma [6]. Primary bladder adenocarcinoma usually lacks GATA3 staining, rendering this stain useless in differential diagnosis from secondary colorectal adenocarcinoma [53]. A panel consisting of CK7, CK20, β -catenin and thrombomodulin has some value in differentiating primary bladder adenocarcinoma from metastatic colorectal adenocarcinoma [6]. A nuclear β -catenin and CK20 positive stain favors colorectal origin, while primary bladder adenocarcinoma is usually positive for CK7 and thrombomodulin and shows membranous staining for β -catenin [6, 54]. However, clinical history and colono-

scopic findings are essential to reach the correct diagnosis in most cases.

Prostatic adenocarcinoma

Due to its close proximity, prostatic adenocarcinoma frequently involves the bladder by direct invasion, particularly the bladder neck and trigone regions. It is critical to distinguish prostatic adenocarcinoma from bladder adenocarcinoma, as they are managed differently. In most cases, prostatic adenocarcinoma demonstrates distinct morphology and can be easily identified by histology alone. However, prostatic ductal adenocarcinoma shows large cribriform glands with focal central necrosis, mimicking the enteric-type bladder adenocarcinoma. It is also difficult to recognize secondary involvement of the bladder by previously treated (radiation or hormonal) prostatic adenocarcinoma. Although most prostatic adenocarcinomas express PSA and PSAP, some poorly differentiated or previously treated prostatic adenocarci-

Bladder adenocarcinoma

noma may not be positive for PSA and PSAP on immunohistochemical staining [55, 56]. Additional prostate specific markers, including PSMA, prostein (P501S) and NKX3.1, may also be considered in the differential diagnosis (**Figure 7**) [57]. The common markers for urothelial carcinoma, including GATA-3, uroplakin, thrombomodulin, high molecular cytokeratin and p63, are rarely positive in prostatic adenocarcinoma. It is recommended to use a panel of antibodies instead of relying on single antibody to differentiate prostatic adenocarcinoma from bladder adenocarcinoma, especially in poorly differentiated tumors [57].

Endometrial and cervical adenocarcinoma

Endometrial and cervical adenocarcinomas may involve the bladder at advanced stages [4, 58, 59]. Most of these adenocarcinomas result from direct extension from the adjacent uterus, although adenocarcinoma may occasionally arise from endometriosis, endocervicosis or müllerianosis of the bladder wall. While endocervical adenocarcinoma, characterized by complex glandular structures with mucin-containing columnar cells, is less likely confused with primary bladder adenocarcinoma, endometrial adenocarcinoma and serous adenocarcinoma exhibit histologic features that closely resemble primary bladder adenocarcinoma. Immunohistochemical studies are useful in distinguishing these tumors. Endometrial carcinoma is usually positive for PAX-8 and vimentin, whereas bladder adenocarcinoma does not express either [59, 60]. However, estrogen receptor has limited utility as some urothelial tumors may expression estrogen receptor [61]. In situ hybridization for HPV DNA is usually positive in endocervical adenocarcinoma. Although most endocervical adenocarcinomas are positive for p16 on immunohistochemical staining [62], some bladder adenocarcinomas also express p16 [63, 64]. Correlation with clinical history is critical to resolve the tumor origin.

Metastasis from other organs

The bladder is rarely involved by metastasis from the breast, lung, renal, and other adenocarcinomas. As these metastatic adenocarcinomas show overlapping morphologic patterns with primary bladder adenocarcinoma [4, 65], immunohistochemistry and clinical history will be required for an accurate diagnosis. Both

lobular and ductal type of breast adenocarcinoma can involve the bladder, but the lobular type is more frequent [65]. The lobular carcinoma can be confused with the signet ring cell type of bladder adenocarcinoma. Breast adenocarcinoma may be favored when estrogen receptor (ER) and progesterone receptor (PR) are coexpressed. Bladder adenocarcinoma usually does not express GATA3, while breast adenocarcinoma is positive for GATA3 [66-68]. Mammoglobin and GCDFP may be useful in this setting; however, they have not been well studied in bladder adenocarcinoma. Adenocarcinoma of the lung is positive for TTF-1, while bladder adenocarcinoma is negative. Infrequently, renal cell carcinoma may metastasize to the urinary bladder, which needs to be differentiated from clear cell adenocarcinoma of the bladder. PAX2 and PAX8 are expressed in both lesions and not helpful in the differential diagnosis [35, 36]. While clear cell renal cell carcinoma expresses CD10, vimentin, carbonic anhydrase IX and RCC, bladder clear cell adenocarcinoma usually expresses CK7 and CK20 [69].

Villous adenoma

Villous adenoma is an infrequent glandular lesion of the urinary bladder [70, 71]. It affects men and women equally with a mean age of 65 years (range 23-94 years) [70, 71]. The presenting symptoms include hematuria, irritative bladder symptoms and rarely, mucusuria. The preferred sites of the tumor are trigone, dome and urachal remnant [70, 71]. On cystoscopy, the lesion appears as an exophytic papillary mass closely resembling papillary urothelial carcinoma.

Microscopically, villous adenoma is identical to its counterpart in the gastrointestinal tract. It exhibits finger-like projections covered by mucin producing pseudostratified columnar cells. The nuclei are hyperchromatic, oval, enlarged with crowding and show variable atypia. Some cases show abundant mucin production, mimicking mucinous adenocarcinoma. Up to half of the villous adenomas have been associated with adenocarcinoma in situ or invasive adenocarcinoma; therefore, a careful search for the invasive component is essential [70, 71]. It is advisable to submit the entire specimen for evaluation to exclude the possibility of adenocarcinoma. The other lesions that should be consid-

Bladder adenocarcinoma

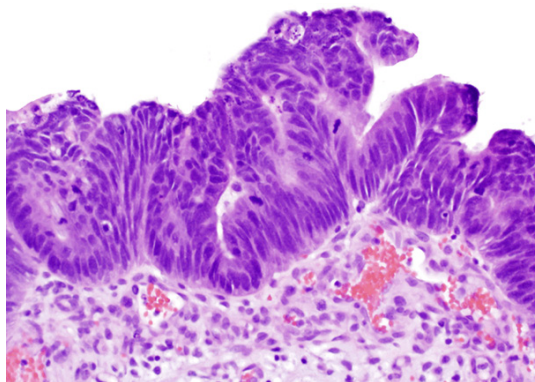


Figure 8. Adenocarcinoma in situ shows glandular and papillary structures lined by atypical columnar cells.

ered in differential diagnosis are adenocarcinoma in situ and urothelial carcinoma with villoglandular differentiation [72, 73]. Adenocarcinoma in situ with papillary architecture may mimic villous adenoma, however it should not show finger like projections of villous adenoma. Papillae of urothelial carcinoma with villoglandular differentiation are covered with mucin secreting intestinal type of cells, often with gland formation. However, this morphology is usually intermixed with more typical papillary urothelial carcinoma. The immunohistochemical staining pattern of villous adenoma is similar to colonic adenocarcinoma with CK20 positivity and variable staining for CK7 [70].

Adenocarcinoma in situ

Adenocarcinoma in situ and noninvasive urothelial carcinoma with glandular differentiation have been used interchangeably in the literature [72, 74]. However, adenocarcinoma in situ is usually characterized by a noninvasive glandular lesion with colonic-type neoplastic epithelium (**Figure 8**), while noninvasive urothelial carcinoma with glandular differentiation usually demonstrates conventional urothelial carcinoma mixed with glands lined by atypical columnar epithelium. Adenocarcinoma in situ is usually associated with invasive adenocarcinoma. Chan and Epstein reported 19 cases of bladder adenocarcinoma in situ that was not associated with infiltrating adenocarcinoma [72]. The mean age of patients was 70 years (range, 48-88 years) with male predominance. Adenocarcinoma in situ exhibited papillary, cribriform, and flat growth patterns, and the

tumor cells were columnar, with apical cytoplasm. In most cases, urothelial carcinoma in situ or papillary urothelial carcinoma was also present. Most patients subsequently developed invasive carcinoma with an unusually high incidence of aggressive variants, including small cell carcinoma and micropapillary urothelial carcinoma. Therefore, patients with in situ adenocarcinoma should be followed up closely.

Urothelial carcinoma with glandular differentiation

Urothelial carcinoma has a great propensity for divergent differentiation, which may lead to squamous, glandular or neuroendocrine differentiation [75, 76]. Glandular differentiation is the second most common form of differentiation after squamous differentiation [77, 78]. True glandular component should be composed of enteric-type glands with columnar epithelium and mucin production. In contrast, pseudoglandular or microcystic changes urothelial carcinoma are composed of small gland-like cysts, which are not lined with columnar cells and lack mucin production [79]. As adenocarcinoma is only reserved for the bladder tumor that is entirely composed of glandular differentiation, it is necessary to examine the entire tumor specimen to rule out any urothelial component before making the diagnosis of adenocarcinoma. This means a diagnosis of adenocarcinoma should be made only on resection specimens. The prognostic value of presence of glandular differentiation in urothelial carcinoma is controversial. While some studies suggest no prognostic differences when adjusted for pathologic stage, other studies have reported urothelial carcinoma with glandular differentiation carry a worse prognosis than pure urothelial carcinoma [80, 81]. However, despite these controversies it is recommended to mention the presence of glandular differentiation in the pathology report.

Management and clinical outcome

The majority of patients with primary bladder adenocarcinoma have a muscle-invasive disease, and these patients are usually treated with radical cystectomy and pelvic lymph node dissection [82-84]. Primary radiation therapy may be considered for some patients who are

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not appropriate cystectomy candidates. The efficacy of primary radiation therapy in comparison to surgery is unclear due to the limited experience with this rare disease. The traditional cisplatin-based chemotherapy regimens (i.e., MVAC) that are used effectively for urothelial carcinoma appear to have little impact on adenocarcinoma.

A minority of bladder adenocarcinomas may present as a non-muscle-invasive tumor, and these patients are often treated with cystoscopy and transurethral resection of tumor [83, 84]. Some patients may also respond to intravesical therapies with BCG or mitomycin-C [85]. Most patients will experience tumor recurrence and progression after local treatment.

Urachal adenocarcinoma is treated differently from bladder adenocarcinoma. The standard of care is en-bloc resection of the bladder dome, urachal ligament, and umbilicus [86, 87]. As up to 7% of urachal adenocarcinomas involve the umbilicus, the relapse rate is generally higher in patients that do not undergo en-bloc resection [88].

Several retrospective studies have reported that bladder adenocarcinoma has a poorer clinical outcome than urothelial carcinoma [10, 89, 90]. However, the aggressive behavior of bladder adenocarcinoma is likely due to the frequent presence of advanced disease at the time of diagnosis [10]. When adjusting for tumor stage and grade, recent studies display similar survival outcomes between urothelial carcinoma and bladder adenocarcinoma [10].

Urachal adenocarcinoma patients appear to have a better prognosis than those with primary bladder adenocarcinoma [87, 88]. The favorable prognosis is due partly to the fact that urachal adenocarcinoma is often diagnosed in younger patients than those with bladder adenocarcinoma, thus it is associated with fewer comorbidities. However, a recent retrospective study found that the 5-year overall survival is still more favorable for patients with urachal adenocarcinoma (48%) than those with non urachal adenocarcinoma (35%), even after adjusting for grade, histologic subtype, stage, age, gender, and surgical management [91]. Intrinsic anatomic and molecular differences between urachal adenocarcinoma and bladder adenocarcinoma may also contribute to the different clinical outcome.

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Disclosure of conflict of interest

None.

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