Adenocarcinoma of the Urinary Bladder

Somak Roy, MD; Anil V. Parwani, MD, PhD

- Primary adenocarcinoma of urinary bladder is an uncommon neoplasm and is a source of diagnostic confusion with adenocarcinomas arising in adjacent organs, especially colon. These tumors show varied histologic picture and degree of differentiation. Clinical association with bladder extrophy and schistosomiasis has been well documented. Primary bladder adenocarcinomas have overlapping histologic and immunohistochemical features with adenocarcinomas arising from other primary sites and the suggested immunohistochemical panel includes cytokeratins 7 and 20, 34BE12, thrombomodulin, CDX2, and β-catenin. Clinical, imaging, histologic, and immunohistochemical correlation should be done while rendering this diagnosis, as prognosis and therapeutic options for primary versus metastatic adenocarcinoma vary widely. (Arch Pathol Lab Med. 2011;135:1601–1605; doi: 10.5858/arpa.2009-0713-RS)

Adenocarcinoma of the urinary bladder arising from the urothelial lining is an uncommon malignant neoplasm, accounting for 0.5% to 2.0% of all malignant vesical tumors. The histologic variants show a predominant colonic (enteric) type glandular morphology with varied histologic patterns. Based on the morphology they are classified as follows: colonic (enteric) type, adenocarcinoma not otherwise specified, mucinous, signet ring cell (SRC), clear cell type, hepatoid, and mixed forms. These tumors are also grouped as urachal and nonurachal type, the latter being the focus of this review.

Irrespective of the various histologic patterns, there is usually evidence of cystitis cystica et glandularis or surface glandular metaplasia in the adjacent benign urothelium. Recent molecular studies using quantitative fluorescence in situ hybridization hypothesize that intestinal metaplasia in the bladder could be a precursor lesion for vesical adenocarcinoma.

**CLINICAL FEATURES**

Patients are usually in their sixth decade of life with a male predilection. The most common clinical presentation is hematuria. Bladder irritation symptoms are also frequently reported. About 90% of the tumors arising in exstrophied bladder are adenocarcinomas. They are also more prevalent in settings of vesical schistosomiasis.

Adenocarcinomas can arise anywhere in the urinary bladder. However, they involve the trigone and posterior bladder wall in most cases. About two-thirds of the adenocarcinomas present as solitary, discrete lesions, unlike the "usual" urothelial carcinomas, which tend to be multifocal.

**GROSS AND MICROSCOPIC PATHOLOGY**

Adenocarcinomas can have a papillary, nodular, flat, or ulcerated architecture. Some of the adenocarcinoma variants (SRC) tend to present with prominent bladder wall thickening ("linitis plastica" like) without apparent growth due to diffuse infiltration of the bladder wall by tumor cells. Microscopically, these tumors show pure glandular morphology. Usually they show well to moderately differentiated colonic-type infiltrating glands with or without abundant extracellular mucin (Figure 1). However, in some cases, highly cellular and poorly differentiated morphology may be seen in the absence of the more common colonic glandular histology. The not otherwise specified type shows nonspecific glandular growth pattern. Foci of cystitis cystica may also be seen in some of these tumors (Figure 2).

The SRC variant of bladder adenocarcinoma is an aggressive, poorly differentiated rare subtype. This entity is defined as a tumor composed entirely of SRCs or as a poorly differentiated round cell tumor with intracytoplasmic mucin without extracellular mucin. This variant resembles mammary lobular carcinoma with the exception of large cell size. A dense layer of cells in the lamina propria with diffuse infiltration into the muscularis is commonly seen. The tumors tend to be aggressive with propensity for extravesical soft tissue extension at the time of presentation (higher stage). This variant can bear morphologic resemblance to plasmacytoid urothelial carcinoma, an unusual bladder tumor that is characterized by large cells with abundant eosinophilic cytoplasm and eccentrically placed vesicular nucleus with prominent nucleolus, closely resembling a plasma cell. Signet ring cell variant, in contrast, has cells with a clear cytoplasmic vacuole and an indented eccentrically placed nucleus. The plasmacytoid urothelial carcinomas are poorly differentiated high-grade tumors and often have a coexisting high-grade conventional urothelial carcinoma or a sarcomatoid carcinoma component. This is, however, an uncommon finding in SRC variant. The mucinous (colloid) variant displays abundant pools of extracellular mucin with groups of tumor cells floating.
This variant is usually well differentiated and mimics many extravesical mucinous tumors histologically (Figure 3). They may show SRCs with intracellular mucin (Figure 4); however, they do not qualify to be classified as SRC variant by the definition stated previously.

The grading system of bladder adenocarcinomas is based on the degree of glandular differentiation and nuclear pleomorphism (well, moderate, and poorly differentiated).\(^3\)

**DIFFERENTIAL DIAGNOSIS AND IMMUNOHISTOCHEMISTRY**

Bladder adenocarcinoma needs to be distinguished from the more common metastatic adenocarcinoma (direct spread, lymphatic, and hematogenous). The principal primary organs to be considered include prostate, colon, female genital tract, appendix, stomach, and breast.\(^2,15,16\)

The evidence supporting the fact that the entity represents a primary vesical adenocarcinoma is the presence of flat carcinoma in situ. The latter is difficult to document, particularly in transurethral resection specimens due to extensive thermal artefact, incomplete sampling, and presence of mucosal ulcerations.\(^2\) Also, secondary adenocarcinomas tend to colonize the native epithelium mimicking a carcinoma in situ component. The most frequent and challenging differential diagnosis remains metastatic or directly spreading colonic adenocarcinoma. The latter is virtually indistinguishable on histomorphology as well as on immunohistochemistry.\(^2,3,15,17,18\)

Differential diagnosis is even more difficult on small biopsies with poorly differentiated tumors. The extreme similarity of vesical and colonic adenocarcinomas has raised the interesting, though controversial, proposition of the pathogenic relationship of these tumors. It is hypothesized that due to the common
embryologic origin of the bladder and the rectum from the cloaca, vesical adenocarcinomas may arise from pluripotent cloacal cells that undergo similar genetic changes as seen in colonic adenocarcinomas. The immunohistochemical panel used to distinguish primary vesical adenocarcinoma from metastatic colonic adenocarcinoma includes cytokeratin (CK) 7, CK20, 34βE12, thrombomodulin, villin, CDX-2, and β-catenin. CK7 and CK20 are reported to be positive in more than half of primary bladder adenocarcinomas (Figure 5, A). The typical colonic adenocarcinoma staining profile, CK7 negative and CK20 positive, has been reported in 29% of primary vesical adenocarcinomas. A combination of CK7 and CK20 by itself does not appear to differentiate primary bladder from colonic adenocarcinomas.

Thrombomodulin, an endothelial thrombin receptor, is a sensitive urothelial marker. Wang et al reported 90% expression of thrombomodulin in urothelial carcinoma. However, only 59% of the bladder adenocarcinomas and none of the colonic adenocarcinomas were positive for this marker (Figure 5, B).

CDX-2 is a homeobox gene implicated in regulation of growth and differentiation of intestinal epithelial cells. It acts as a nuclear transcription factor and therefore demonstrates nuclear staining in normal colonic epithelial cells and colonic adenocarcinomas. Its expression was initially thought to be restricted to colonic adenocarcinomas. However, recent studies have shown the immunexpression of CDX-2 in vesical adenocarcinomas as well (Figure 5, C). This overlapping immunophenotype diminishes the utility of CDX-2 in the differential diagnosis between the 2 entities.

β-catenin is a key component of the cadherin-mediated cell-cell adhesion system and is abnormally accumulated in the nucleus of tumor cells (colorectal adenocarcinomas) due to impaired adenomatous polyposis coli–β-catenin interaction. Wang et al found consistent nuclear expression of β-catenin in 81% of colonic adenocarcinomas metastatic to the bladder. Nuclear pattern of staining was restricted to this group of tumors. Membranous staining pattern was observed in 88% of primary vesical adenocarcinomas and in all cases of colorectal adenocarcinomas (Figure 5, D). It was concluded that the β-catenin

Figure 5. A, Adenocarcinoma of bladder. Tumor cells show focal strong positivity for cytokeratin 20. B, Adenocarcinoma of bladder. Tumor cells demonstrating weak immunexpression of thrombomodulin. C, Adenocarcinoma of bladder; strong diffuse nuclear expression of CDX2. D, Adenocarcinoma of bladder; membranous staining pattern of β-catenin (original magnification ×200 [A]; original magnification ×400 [B]; original magnification ×100 [C]; original magnification ×400 [D]).
dysregulation mechanism is not functional in bladder adenocarcinomas and also that nuclear versus membranous staining pattern is a good marker for distinction between these 2 tumor entities. Thomas et al. studied β-catenin expression in conjunction with E-cadherin expression in SRC primary bladder adenocarcinoma. They demonstrated membranous staining of β-catenin in all foci of colonic-type adenocarcinoma and 78% of the SRC foci. The study concluded that the decreased expression of both markers in SRC foci might be attributed to alteration in the signaling pathway. Sordo et al. demonstrated only membranous expression in all cases of SRC adenocarcinoma. No nuclear staining was observed. Gopalan et al. in their study of urachal adenocarcinomas demonstrated 93% of cases with membranous expression of β-catenin with focal nuclear staining in 1 of the cases. They concluded that the presence of predominant nuclear expression of β-catenin would not be compatible with primary urachal adenocarcinoma.

34βE12, a high-molecular-weight cytokeratin, is a sensitive and relatively specific marker for basal cells of prostatic acini. It demonstrates strong cytoplasmic staining in these cells. Gopalan et al. reported 66% and 11% positivity of 34βE12 in urachal and colonic adenocarcinomas, respectively. They concluded that a strong diffuse positivity would favor urachal over colonic adenocarcinoma.

Urachal carcinoma is a less common tumor that can present as a bladder mass and should be considered in the list of differential diagnoses. This tumor tends to occur in the dome and anterior bladder wall and usually has a male predominance. Adenocarcinoma with enteric features is the most common histologic subtype and can also show mucinous and SRC variants. Diagnostic criteria for urachal carcinoma include (1) tumor in the dome; (2) absence of cystitis cystica and cystitis glandularis; (3) predominant invasion of the muscularis or deeper tissues with a sharp demarcation between the tumor and surface bladder urothelium that is free of glandular or polypoid proliferation; (4) urachal remnants within the tumor; (5) extension into the bladder wall with involvement of the space of Retzius, anterior abdominal wall, or umbilicus; and (6) no evidence of a primary neoplasm elsewhere. The previous criteria help in differentiating it from primary vesical adenocarcinomas. Immunohistochemical profile is similar to primary vesical adenocarcinomas and hence is of no practical utility. The management of urachal carcinoma is typically a partial cystectomy as opposed to a radical cystectomy for primary bladder adenocarcinomas.

Prostatic adenocarcinomas often directly extend into the bladder and may coexist with a bladder adenocarcinoma. The most reliable immunohistochemical marker is prostate-specific antigen, which stains approximately 90% of poorly differentiated prostatic adenocarcinomas and is negative in bladder adenocarcinomas. CA 125, which stains the tumor cells of endometrial and ovarian malignancies, has been reported to be of use to differentiate endometrial and ovarian carcinoma from primary bladder adenocarcinomas. Vimentin highlights endometrial carcinoma cells as opposed to bladder adenocarcinoma cells.

Metastatic breast carcinoma may be differentiated from SRC vesical carcinoma using estrogen receptor and gross cystic disease fluid protein 15, which stain breast carcinoma cells.

OTHER VARIANTS OF VESICAL ADENOCARCINOMA

Clear Cell Adenocarcinoma

Clear cell adenocarcinoma is an unusual and rare variant of bladder adenocarcinoma with a particularly strong predilection for females, with a reported mean age of 57 years. Gross hematuria, dysuria, suprapubic pain, and discharge are the usual presenting symptoms. Clear cell adenocarcinoma is histologically and ultrastructurally similar to clear cell tumors of the female genital tract of possible müllerian origin. The tumor has an exophytic, polyoidal, or papillary appearance and usually involves the posterior and lateral walls or the trigone. Histology is characterized by varied architectural patterns of tubulocystic to papillary or diffuse sheets of cells. The tumor cells range from flat, cuboidal to columnar cells with eosinophilic to clear cytoplasm, often containing glycogen. They occasionally demonstrate prominent hobnailing. There is moderate to severe nuclear atypia with frequent mitosis. Associated histologic features include concurrent presence of urothelial carcinoma, adenocarcinoma not otherwise specified type, cystitis glandularis, and prominent inflammatory infiltrate.

Immunohistochemically, the tumor cells are positive for CA 125, CK7, and CK20 (variable). The tumor cells variably express S100 protein, carcinoembryonic antigen, Leu-M1, and CA 19.9 and are consistently negative for prostate-specific antigen and prostatic acid phosphatase. Nephrogenic adenoma is the most important differential diagnosis. Both entities have overlapping morphologic and immunohistochemical profiles. However, clear cell adenocarcinomas demonstrate pronounced nuclear atypia and numerous mitoses. A higher MIB-1 index and a stronger p53 staining have been reported in clear cell adenocarcinomas unlike in nephrogenic adenomas.

Urothelial carcinomas can occasionally display abundant glycogen-rich clear cells and lack the other histologic features of clear cell adenocarcinoma. Other lesions that need to be distinguished from clear cell adenocarcinoma include vaginal or cervical clear cell carcinomas, clear cell prostatic adenocarcinoma, and metastatic clear cell renal cell carcinoma. Overall, these entities are rare and clinicoradiologic correlations with immunohistochemistry are helpful in arriving at the correct diagnosis.

Hepatoid Adenocarcinoma

Hepatoid adenocarcinoma is an extremely rare tumor of the bladder, described in very few case reports. Clinically, this is an aggressive tumor primarily affecting elderly men. Diagnosis is based on morphologic resemblance to hepatocellular carcinoma and positive immunostaining for α-fetoprotein. The tumor cells are large and polygonal with abundant granular eosinophilic cytoplasm and vesicular nuclei with prominent nucleoli. The cells are arranged in a trabecular pattern. Hyaline globules and bile production can also be seen. Hepatocellular differentiation can be documented by expression of α-fetoprotein, α1-antitrypsin, albumin, HepPar-1, epithelial membrane antigen, and carcinoembryonic antigen.

THERAPY AND PROGNOSIS

The mainstay of treatment is surgery with or without adjuvant radiation or chemotherapy. Radical or partial
cystectomy with or without node dissection is the commonly used surgical procedure. The most important prognostic factor is tumor stage. Histologic subtypes especially SRC and clear cell variants behave more aggressively.

CONCLUSION
Primary adenocarcinoma of the bladder is an uncommon neoplasm with a spectrum of histomorphologic appearances. The more common metastatic adenocarcinomas, especially colonic, need to be ruled out before making a diagnosis of primary vesical adenocarcinoma. Because histologically and immunohistochemically there is considerable overlap between colonic and vesical adenocarcinoma, extensive clinical and radiologic workup is required for diagnostic accuracy. The panel of markers required for primary versus secondary adenocarcinomas should be carefully selected based on the morphology of the tumor and its related entities in the differential diagnosis. Although the immunomarkers discussed previously do not individually prove to be diagnostically significant, a panel of stains is helpful such as a combination of CK7, CK20, thrombomodulin, b-catenin, 34BE12, and prostate-specific antigen.

References