Primary Adenocarcinoma of the Urinary Bladder
Differential Diagnosis and Clinical Relevance

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Context.—Glandular lesions of the urinary bladder include a broad spectrum of entities ranging from completely benign glandular lesions to primary and secondary malignancies. Common benign bladder lesions that exhibit glandular differentiation include cystitis cystica, cystitis glandularis, von Brunn nests, nephrogenic adenoma, intestinal metaplasia, urachal remnant, endometriosis, and prostatic-type polyp. The World Health Organization defines primary adenocarcinoma of the bladder as an epithelial malignancy with pure glandular differentiation without evidence of typical urothelial carcinoma. Malignant lesions that should be included in the differential diagnosis of a primary adenocarcinoma of the bladder include noninvasive and invasive urothelial carcinoma with glandular differentiation and secondary malignancies involving the bladder by direct extension or metastasis. The recognition and distinction of these different entities may be a challenge for pathologists, but they are of great clinical importance.

Objective.—To review features of primary bladder adenocarcinoma as well as those entities that need to be differentiated from primary bladder adenocarcinoma, with emphasis on clinical findings, pathologic characteristics, and immunoprofiles.

Data Sources.—Selected original articles published in the PubMed service of the US National Library of Medicine.

Conclusions.—The accurate diagnosis of adenocarcinoma of the urinary bladder is important and challenging. It has to prompt an extensive clinical workup to rule out other glandular lesions in the urinary bladder, especially the possibility of secondary involvement of the bladder by an adenocarcinoma from a different site.

Primary adenocarcinoma of the urinary bladder is an uncommon tumor accounting for approximately 2% of all primary bladder malignancies. Secondary involvement of the bladder by carcinoma either by direct extension or metastasis is also uncommon but, interestingly, is actually more common than primary adenocarcinoma when all sites of tumor origin are considered together. Secondary tumors involving the bladder most commonly originate from adenocarcinoma of the colon, prostate, breast, endometrium, lung, or other organs.

The accurate diagnosis of adenocarcinoma of the urinary bladder can be very challenging, as a wide variety of benign and malignant glandular lesions occur in the urinary bladder. The differential diagnosis of a lesion exhibiting glandular differentiation in the bladder includes benign entities, putative precursor lesions, primary malignancies, and secondary malignancies. The benign lesions include cystitis cystica, cystitis glandularis, von Brunn nests, nephrogenic adenoma, mesonephric remnant, intestinal metaplasia, and urachal remnant. The precursor lesions of primary bladder adenocarcinoma are not as well established as those of other organs, such as colon and breast. However, some glandular lesions, such as intestinal metaplasia, urachal remnant, and tubular adenoma, are believed to be precursors of primary adenocarcinoma of the bladder.

Strictly speaking, adenocarcinoma of the bladder is defined as a tumor composed entirely of malignant glandular epithelium. In contrast, a tumor with both typical urothelial carcinoma and adenocarcinomatous components is classified as urothelial carcinoma with glandular differentiation. Therefore, primary glandular malignancies in the bladder are heterogeneous and may include noninvasive urothelial carcinoma with glandular differentiation (including adenocarcinoma in situ), invasive urothelial carcinoma with glandular differentiation, urachal adenocarcinoma, and pure adenocarcinoma of the bladder. All of these primary lesions can, in certain cases, exhibit significant overlap with carcinomas secondarily involving the bladder. The recognition and distinction of these different entities—especially distinguishing primary from secondary tumors—is of great clinical importance in terms of accurate staging, prognosis, and most importantly, appropriate treatment. It has been well documented that primary and secondary glandular lesions of the bladder often have overlapping features, not only morphologically but also at the immunohistochemical and molecular levels. Therefore, clinicopathologic
correlation and careful interpretation of ancillary tests are crucial to resolve diagnostic dilemmas in challenging cases.

Radical cystectomy or cystoprostatectomy with pelvic lymph node dissection is the preferred therapy for primary adenocarcinoma of the bladder. Secondary adenocarcinoma of the bladder requires systematic treatment of the primary cancer. The optimal application of radiation therapy and chemotherapy in the context of primary adenocarcinoma of the bladder remains unclear, owing to the relative infrequency of adenocarcinoma of the bladder and exclusion of these tumors from randomized controlled trials. Thus, further basic and clinical studies are needed to establish evidence-based treatment recommendations for this specific tumor type.

**PRIMARY GLANDULAR MALIGANCIES OF THE BLADDER**

**Noninvasive Urothelial Carcinoma With Glandular Differentiation (Adenocarcinoma In Situ)**

Noninvasive urothelial carcinoma with glandular differentiation is a rare entity that has not been well studied. By definition, it is a noninvasive glandular lesion characterized by atypical columnar epithelium, often with prominent apical cytoplasm. True glandular differentiation is a necessary criterion for diagnosis. Urothelial carcinomas with small cystic spaces containing mucin or cell debris (Figure 1) and involvement of a von Brunn nest by urothelial carcinoma, which is not lined by columnar epithelium (“glandlike lumina”), should not be confused with adenocarcinoma. The distinction between in situ and invasive adenocarcinoma is based on criteria analogous to those used in the diagnosis of malignant glandular lesions in the gastrointestinal tract.

In a large reported series of noninvasive urothelial carcinoma with glandular differentiation, Chan and Epstein reported 19 cases that accounted for 0.14% of their institution’s bladder biopsy specimens and 0.61% of all bladder biopsies from both consult and in-house cases. Noninvasive urothelial carcinoma with glandular differentiation is often a small lesion with papillary (fibrovascular cores lined by columnar epithelium; Figure 2, A), cribriform (columnar cells making large or small individual glandular spaces; Figure 2, B), and flat architectural patterns (columnar cells lining a flat surface; Figure 2, C). The morphology of these lesions may overlap with that of tubulovillous adenoma, invasive papillary urothelial carcinoma with glandular differentiation, and urothelial carcinoma in situ. However, noninvasive urothelial carcinoma with glandular differentiation contains atypical columnar cells, exhibits true glandular and urothelial differentiation, and lacks stromal invasion—all features that help differentiate this entity from its morphologic mimics. For unknown reasons, noninvasive urothelial carcinoma with glandular differentiation is rarely seen by itself and is often associated with invasive urothelial carcinoma and/or aggressive variants of urothelial carcinoma, such as micropapillary carcinoma and small cell carcinoma. Thus, patients with noninvasive urothelial carcinoma with glandular differentiation appear to have a poor prognosis because of the aggressive nature of the associated invasive tumor components.

**Invasive Urothelial Carcinoma With Glandular Differentiation**

Urothelial carcinoma has a great capacity for morphologic plasticity. In particular, high-grade urothelial carcinoma often shows divergent differentiation in the form of squamous, glandular, and/or neuroendocrine morphology. Glandular differentiation, which is less common than squamous differentiation, is the second most common form of divergent differentiation.

On the other hand, urothelial carcinoma, both low grade and high grade, may show small glandlike lumina, mimicking glandular formation. However, these small spaces do not have cuboidal or columnar epithelial lining. The pseudoglandular spaces are likely caused by degenerative changes, necrosis, or artifacts and should not be considered evidence of glandular differentiation. Instead, such areas are referred to as “pseudoglandular” differentiation or microcystic changes.

The diagnosis of primary adenocarcinoma should only be made when a tumor exhibits pure (100%) glandular differentiation. Urothelial carcinoma with glandular differentiation is the preferred term for a lesion that exhibits true glandular differentiation or microcystic changes, necrosis, or artifacts and should not be considered evidence of glandular differentiation. Instead, such areas are referred to as “pseudoglandular” differentiation or microcystic changes.

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The prognostic relevance of glandular differentiation in urothelial carcinoma is not clear and remains controversial. Some authors have reported that such tumors are associated with a worse prognosis when compared to pure urothelial carcinomas. It has been hypothesized that the difference in prognosis may be due to resistance of tumors with glandular differentiation to chemotherapies directed at usual urothelial carcinoma—however, data supporting this hypothesis are lacking. In contrast, other studies have suggested that glandular differentiation does not affect prognosis after adjusting for pathologic stage. Despite these controversies, it is recommended that divergent differentiation within a urothelial carcinoma should be documented in surgical pathology reports. In our practice, we always make a comment on the presence of divergent differentiation and, in particular, make a point to emphasize the presence of glandular differentiation, especially when it is extensive.

Primary Adenocarcinoma of the Urinary Bladder

By definition, primary adenocarcinoma of the bladder is a malignant neoplasm derived from urothelium of the bladder showing histologically pure glandular differentiation. Primary adenocarcinoma of the bladder is a rare malignancy, representing only 0.5% to 2.5% of all malignant bladder neoplasms. This tumor is more common in males than females with a mean age of 63 years. The tumor generally is very aggressive, with metastatic disease reported in up to 40% of patients at the time of diagnosis. The pathogenesis of primary adenocarcinoma of the urinary bladder has not been fully elucidated. Intestinal metaplasia has been speculated to be a precursor lesion, largely because it is often seen in mucosa adjacent to primary adenocarcinoma of the urinary bladder.

 Morphologically, adenocarcinoma of the bladder can be divided into intestinal (enteric) type and nonintestinal (nonenteric) type. Intestinal-type adenocarcinoma is composed of tall columnar tumor cells with abundant eosinophilic cytoplasm, with or without necrosis, morphologically identical to colonic adenocarcinoma (Figure 4, A). Nonintestinal adenocarcinoma can be clear cell adenocarcinoma or adenocarcinoma of nonspecific type.

As discussed above, the diagnosis of a primary adenocarcinoma of the bladder should only be made when the carcinoma exhibits pure glandular differentiation. In many cases of adenocarcinoma of the bladder, the most important and the most difficult task is to differentiate these tumors from metastatic adenocarcinoma from other organs such as colon, lung, prostate, breast, and uterus. The most frequent secondary tumor to involve the urinary bladder is adenocarcinoma of the colon, which morphologically resembles adenocarcinoma of the urinary bladder, enteric type.

Figure 2. Noninvasive urothelial carcinoma with different glandular differentiation growth patterns. A, Papillary type (fibrovascular cores lined by columnar epithelium). B, Cribriform type (columnar cells surrounding small “sieve-like” spaces). C, Flat type (columnar cells lining a flat surface) (hematoxylin-eosin, original magnifications ×200 [A through C]).

Figure 3. Invasive urothelial carcinoma with glandular differentiation. A, Malignant columnar cells (left) along with the typical urothelial carcinoma cells (right) indicate glandular differentiation. B, It is not uncommon to see invasive urothelial carcinoma with both glandular (right upper corner) and squamous (left lower corner) differentiation (hematoxylin-eosin, original magnifications ×200 [A and B]).
Therefore, it is of the utmost importance that pathologists confronted with a malignant glandular lesion of the bladder obtain adequate clinical information, as this is often the key to the correct diagnosis. Immunohistochemical stains may help to distinguish these 2 entities in some cases and this will be discussed later.

In addition to enteric morphology, primary adenocarcinoma of the urinary bladder can exhibit other histologic growth patterns, including nonspecific (Figure 4, B), mucinous, signet ring cell (Figure 4, D), and clear cell types.1 Mucinous adenocarcinoma of the urinary bladder is a specific subtype that is characterized by large lakes of extracellular mucin admixed with collections of tumor cells. By definition, these mucinous foci should constitute at least half of the tumor mass.1 Prognosis varies with stage, with better survival rates seen among patients whose tumors are confined to the urinary bladder. Unfortunately, low-stage cancers account for fewer than 30% of reported cases.1

Signet ring cell adenocarcinoma (Figure 4, D) is another rare morphologic manifestation of primary adenocarcinoma of the bladder.26,27 The diagnostic criteria require at least focal signet ring cell differentiation within an adenocarcinoma without evidence of urothelial carcinoma. The signet ring cells within these tumors can demonstrate a plasmacytoid or monocyteid appearance or can have the classic signet ring cell morphology, characterized by a large cytoplasmic vacuole compressing the nucleus to one side of the cell. Pure primary signet ring cell adenocarcinoma of the bladder is rare and carries a worse prognosis.26,27 Primary adenocarcinoma usually presents at an advanced stage with a poor prognosis.1 However, in a large, contemporary North American cohort study,28 stage- and grade-adjusted cancer-specific mortality was found to be the same between patients with primary adenocarcinoma and patient with urothelial carcinoma.

**Micropapillary Carcinoma**

Histologically, micropapillary carcinoma of the bladder (Figure 4, C) resembles micropapillary adenocarcinoma of the ovary, breast, and lung.29 Twenty-five percent of micropapillary cases in the bladder show glandular differentiation. Rare cases demonstrate pure micropapillary morphology without recognizable urothelial carcinoma. All of these suggest that micropapillary carcinoma of bladder
In some scenarios, if Pathologic stage is an important prognostic factor in urachal carcinoma. The tumor cells floating in pools of extracellular mucin may have signet ring cell or columnar cell morphology. The next most common type is enteric adenocarcinoma, which is morphologically identical to colorectal adenocarcinoma. Immunostains do not unequivocally discriminate urachal from colorectal adenocarcinoma. Diffuse positivity for 3βE12 may support a diagnosis of urachal carcinoma, while diffuse nuclear staining for β-catenin would favor a colorectal origin. It also has been reported that the most remarkable difference in staining pattern between urachal adenocarcinoma and bladder adenocarcinoma is the homogeneous positivity for carcinoembryonic antigen in 100% of urachal adenocarcinomas and in only 29% of bladder adenocarcinomas. However, clinically ruling out metastasis from a colorectal origin is a critical step to establish the diagnosis. Other rare patterns, such as limitis plastica-like signet ring cell carcinoma, has also been reported. Patients with urachal adenocarcinoma are usually in their fifth to sixth decade of life, which is approximately 10 years younger than patients with primary adenocarcinoma of the bladder. Pathologic stage is an important prognostic factor in urachal carcinoma. Overall mortality and disease-specific mortality are more favorable for patients with urachal adenocarcinoma than for patients with nonurachal adenocarcinoma, even after controlling for numerous patient and tumor characteristics. The treatment of urachal adenocarcinoma remains to a certain extent unsettled. In general, surgical approaches to these tumors usually call for en bloc resection of the bladder dome and of the entire urachal tract including the umbilicus. Urachal adenocarcinoma appears resistant to radiation therapy.

Urachal Adenocarcinoma

Urachal adenocarcinoma (Figure 5) is a unique tumor that develops within urachal remnants located in the dome of the bladder and often secondarily invades the bladder. The urachal remnants are residual tissues from the embryonic allantoic stalk connecting the umbilicus and bladder. The diagnosis of urachal adenocarcinoma is a diagnosis of exclusion. One needs to exclude the possibility of nonurachal adenocarcinoma, either primary or secondary.

Different diagnostic criteria for urachal adenocarcinoma have been proposed. The criteria of Johnson et al. are perhaps the most practical: (1) location in bladder dome, (2) sharp demarcation between tumor and surface benign urothelium, and (3) exclusion of other primary sites. From this study and the criteria discussed therein, the presence of adjacent or distant cystitis glandularis and intestinal metaplasia does not exclude the diagnosis of urachal adenocarcinoma, as long as no transition from dysplasia to malignancy can be identified. Urachal adenocarcinoma, especially after it has advanced to a late stage, can involve the urothelium overlying the tumor. However, a clear histologic demarcation should be identified between tumor and benign urothelium. Earlier-stage tumors may only involve the muscular wall of the bladder and in such situations, suspicion for metastatic adenocarcinoma from other organs should be high.

Urachal adenocarcinoma can have a variety of morphologic appearances. However, none of these features are specific enough to distinguish urachal and nonurachal tumors. Mucinous tumors are the most frequent type of urachal adenocarcinoma. The tumor cells floating in pools of extracellular mucin may have signet ring cell or columnar cell morphology. The next most common type is enteric adenocarcinoma, which is morphologically identical to colorectal adenocarcinoma. Immunostains do not unequivocally discriminate urachal from colorectal adenocarcinoma. Diffuse positivity for 3βE12 may support a diagnosis of urachal carcinoma, while diffuse nuclear staining for β-catenin would favor a colorectal origin. It also has been reported that the most remarkable difference in staining pattern between urachal adenocarcinoma and bladder adenocarcinoma is the homogeneous positivity for carcinoembryonic antigen in 100% of urachal adenocarcinomas and in only 29% of bladder adenocarcinomas. However, clinically ruling out metastasis from a colorectal origin is a critical step to establish the diagnosis. Other rare patterns, such as limitis plastica-like signet ring cell carcinoma, has also been reported.

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Immunoprofile of Adenocarcinoma

As discussed above, the differential diagnosis of bladder adenocarcinoma is very extensive and consists of a broad spectrum of lesions including entirely benign lesions, putative precursor lesions, primary malignancies, and secondary malignancies. Careful morphologic examination and thorough evaluation of the clinical history are initial and key steps to yield an accurate diagnosis.

Metastatic adenocarcinoma or adenocarcinoma from direct extension of adjacent organs is more common than primary adenocarcinoma. In some scenarios, if not most, these tumors cannot be clearly distinguished from primary bladder adenocarcinoma by histologic evaluation. Appropriate immunohistochemical stains may be helpful in some cases. Among all secondary malignancies involving the urinary bladder, colorectal adenocarcinoma is the most common and probably the most difficult entity to differentiate from primary adenocarcinoma. These 2 malignancies have significant overlap at the morphologic and immunohistochemical level. In addition, during embryologic development, the posterior walls of the bladder and rectum have the same origin and are separated by a urorectal septum during the seventh week of gestation. All of these suggest that these 2 malignancies may be pathogenetically related. In fact, some authors believe that primary bladder adenocarcinoma may derive from pluripotent stem cells of colonic origin.
origin that retain the ability to differentiate along a colonic pathway as a result of accumulation of specific genetic alterations similar to those occurring in the development of conventional colorectal adenocarcinoma. While this is an intriguing theory, the definitive pathogenesis of primary adenocarcinoma of the bladder is still not clear.

Immunostaining for cytokeratin (CK) 7 and CK20 has been routinely used in surgical pathology to help determine the origin of epithelial malignancies. Positive labeling for CK20 and negative labeling for CK7 is usually indicative of colorectal adenocarcinoma. However, the same immunoprofile is present in 29% of primary bladder adenocarcinomas. In addition, rare colorectal adenocarcinomas have been found to be positive for CK7, which also shows positivity in 82% of primary adenocarcinomas of bladder.

Thus, immunostaining for CK7 and CK20 does not provide sufficient specificity to allow definitive distinction between primary bladder adenocarcinoma and secondary colorectal adenocarcinoma.

Other immunohistochemical stains have demonstrated a utility for solving this differential diagnostic dilemma. Thrombomodulin (TM) is a specific marker for primary bladder tumors and very rarely shows positivity in colorectal tumors. Unfortunately, the sensitivity of TM is low, with only 59% positivity in primary bladder adenocarcinoma. On the other hand, nuclear staining of β-catenin is relatively specific for colorectal tumors. Negative or cytoplasmic staining for β-catenin is usually seen in primary bladder adenocarcinoma. However, this pattern (lack of nuclear staining) is also seen in 19% of secondary colorectal adenocarcinomas.

In general, the immunohistochemical panel of CK7, CK20, TM, and β-catenin has been recommended to distinguish primary bladder adenocarcinoma from secondary colorectal adenocarcinoma. The profile of CK7+/CK20+/TM+/β-catenin+ is usually seen in secondary colorectal adenocarcinoma, while CK7+/CK20+/TM+/β-catenin− may be suggestive of primary bladder adenocarcinoma. As a general rule, the final interpretation should be a combination of histomorphology, immunohistochemical profile, and clinical correlation.

In the setting of other secondary adenocarcinomas, the following immunohistochemical panels have been used: prostate-specific antigen (PSA), prostatic acid phosphatase (PSAP), and Leu 7 (positive in prostate), estrogen receptor (ER), progesterone receptor (PR), and paired box gene 8 (Pax8) (positive for gynecologic origin), thyroid transcription factor-1 (positive in lung), and mammaglobin (positive in breast). Finally, it should be noted that many high-grade adenocarcinomas lose expression of differential markers, and often immunohistochemistry has limited utility in determining the origin of a tumor in this situation.

Secondary Adenocarcinoma

The bladder is not a common site for metastatic adenocarcinoma. However, primary bladder adenocarcinoma is even rarer than secondary malignancies in the bladder. A more common clinical scenario is adenocarcinoma originating in an organ adjacent to the bladder, typically the colon, prostate, or female genital organs, with direct invasion or metastatic spread into the bladder. Therefore, the diagnosis of primary bladder adenocarcinoma is a diagnosis of exclusion. Ruling out the possibility of secondary malignancy is a necessary step for diagnosing primary bladder adenocarcinoma and can be very challenging for the pathologist. The histopathologic features of these 2 entities can be indistinguishable. The only helpful clue for primary bladder adenocarcinoma is to see a transition from adenocarcinoma into typical urothelial carcinoma or the finding of a noninvasive urothelial component. However, these “transitions” can be very difficult to identify or are absent in many cases, particularly when dealing with small biopsy samples.

The precise molecular mechanism responsible for distant metastases has not been elucidated thus far. To produce metastases, malignant cells must exhibit successful invasion, embolization, survival in circulation, arrest in a distant capillary bed, and extravasation into and multiplication in organ parenchyma. The further understanding and translation of this information into a better classification of tumors on the basis of molecular markers of metastatic potential will provide a reliable tool for us to differentiate primary bladder adenocarcinoma from secondary malignancies.

Colonic Adenocarcinoma

The most frequent secondary malignancy to involve the urinary bladder is colorectal adenocarcinoma. Often the morphologic appearance is similar to that of primary bladder adenocarcinoma and histology alone is not sufficient for distinguishing these entities (Figure 6, A). It has even been suggested that these 2 tumors may arise through similar mechanisms. Immunohistochemical stains are often a necessity in establishing a proper diagnosis when both urinary bladder adenocarcinoma and colorectal adenocarcinoma are in the differential. Although colonic adenocarcinoma is typically CK7 negative, some cases have been shown to be CK7 positive; therefore, colonic and bladder adenocarcinoma cannot be distinguished by staining for only CK7 and CK20. A panel including CK7, CK20, TM, and β-catenin is useful in this setting (Table 1). Colorectal adenocarcinoma is usually positive for CK20 and β-catenin, while bladder adenocarcinoma is CK20 and TM positive.

Please refer to the “Immunoprofile of Adenocarcinoma” section for a complete discussion on the utility of immunohistochemical stains in this setting.

Prostatic Adenocarcinoma

Direct extension of prostatic adenocarcinoma into the bladder is a common occurrence because of the close anatomic relationship of the urinary bladder and prostate. Often, histology can be used to differentiate urinary bladder adenocarcinoma from prostatic adenocarcinoma. Metastatic prostate cancers predominantly have a cribriform and solid architecture similar to Gleason pattern 4 or 5 (Figure 6, B). Well-formed glands similar to Gleason pattern 3 are only seen in a minority of cases and almost always coexist with higher-grade patterns when tumors involve the bladder. In general, the nuclear pleomorphism seen in prostate cancers that involve the bladder is not as prominent as that seen in primary bladder tumors with glandular differentiation. However, histology alone may not suffice in the following settings: high-grade or poorly differentiated prostatic adenocarcinoma, prostatic ductal carcinoma, and prostatic adenocarcinoma with hormone or radiation treatment. In these circumstances, immunohistochemical stains are often necessary to accurately establish the origin of the adenocarcinoma. A panel including AMACR (α-methylacyl coenzyme A racemase [pS904S]), prostate membrane–specific antigen, PSA, PSAP, Leu 7, 34βE12, and ERG (encoded
by the ETS-related gene) is useful in distinguishing these 2 entities (Table 1). Labeling for AMACR, prostate membrane–specific antigen, PSA, PSAP, ERG encoded by the ETS-related gene, and Leu 7 is typically positive in tumors of prostatic origin, while labeling for 34βE12, CK7, and p53 is negative in prostatic adenocarcinoma. However, pitfalls in the interpretation of immunohistochemical stains are worth mentioning. For example, 34βE12 labeling can be focally positive in a small number of prostatic adenocarcinoma cases. Additionally, there is often decreased expression of PSA and PSAP in metastatic prostatic adenocarcinoma, especially when the tumor is poorly differentiated.

**Breast Adenocarcinoma**

Rarely, metastatic breast cancer involves the urinary bladder. Invasive lobular carcinoma is more likely to metastasize to the bladder than ductal carcinoma (Figure 6, C). Bladder metastases from breast carcinoma usually occur

<table>
<thead>
<tr>
<th>Prostatic adenocarcinoma</th>
<th>AMACR (cytoplasmic coarse granular pattern), PSA/PSAP, PMSA, ERG (very specific and 50% sensitivity)</th>
<th>TM, 34βE12, P63</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal adenocarcinoma</td>
<td>CK20, β-catenin (nuclear)</td>
<td>CK7, TM</td>
</tr>
<tr>
<td>Endometrial adenocarcinoma</td>
<td>ER/PR, Pax8</td>
<td>TM, 34βE12, P63</td>
</tr>
<tr>
<td>Breast adenocarcinoma</td>
<td>CK7, ER/PR</td>
<td>CK20, TM, 34βE12, P63</td>
</tr>
<tr>
<td>Lung adenocarcinoma</td>
<td>CK7, TTF-1</td>
<td>CK20, TM, 34βE12, P63</td>
</tr>
</tbody>
</table>

Abbreviations: AMACR, α-methylacyl coenzyme A racemase (p504S); CK, cytokeratin; ER, estrogen receptor; ERG, encoded by ETS-related gene; Pax8, paired box gene 8; PMSA, prostate membrane–specific antigen; PR, progesterone receptor; PSA, prostate-specific antigen; PSAP, prostate acid phosphatase; TM, thrombomodulin; TTF-1, thyroid transcription factor-1; 34βE12, high-molecular-weight cytokeratin 34βE12.
in the setting of disseminated disease. Immunohistochemistry is beneficial when there is no known evidence of disseminated disease. Seventy percent to 80% of breast carcinomas are positive for ER and PR. Mammaglobin is a sensitive but not specific marker for breast carcinoma (Table 1). Most cases of primary urinary bladder adenocarcinoma are negative for ER, PR, and mammaglobin.35

**Endometrial Adenocarcinoma**

The close proximity of the urinary bladder and uterus in the pelvis makes direct extension by endometrial adenocarcinoma into the bladder a possibility (Figure 6, D). Clinical history is one of the most useful ways to determine the origin of a patient’s adenocarcinoma. When morphology alone is not adequate for diagnosis, immunohistochemical stains can be useful. A panel of stains including ER, PR, and Pax8 should be used (Table 1). Pax8 is expressed in most of both endometrioid- and nonendometrioid-type endometrial adenocarcinomas.39 Endometrial adenocarcinoma is positive for the previously mentioned stains, while bladder adenocarcinoma is negative.

**DIFFERENTIAL DIAGNOSIS**

A number of benign and malignant lesions with glandular differentiation may be confused with adenocarcinoma of the bladder. To avoid a misdiagnosis, one should become familiar with these lesions.

**Cystitis Glandularis and Cystitis Cystica**

These 2 terms are often used interchangeably. We refer to a lesion as **cystitis glandularis** when there is benign glandular differentiation in the von Brunn nests,40 while **cystitis cystica** is used when glandular structures show cystic dilatation. These lesions are usually easy to distinguish from adenocarcinoma since there is no cytologic atypia or infiltrating patterns (Figure 7, A). However, florid von Brunn nests, the nested variant of urothelial carcinoma, and urothelial carcinoma involving von Brunn nests can mimic adenocarcinoma.40 It is unclear whether cystitis cystica/cystitis...
glandularis are precursor lesions of adenocarcinoma, but the bulk of the evidence does not support a pathogenesis relationship between the former and the latter.

Intestinal Metaplasia

Intestinal metaplasia is characterized by the presence of intestinal-type epithelium, particularly the presence of goblet cells in the urothelium (Figure 7, B). It can be associated with cystitis cystica/glandularis or present alone. Similar to Barrett esophagus, intestinal metaplasia is considered to be the precursor lesion of adenocarcinoma. Therefore, the diagnosis of intestinal metaplasia should be made when these changes are identified, regardless of the presence of cystitis glandularis/cystica.

Nephrogenic Adenoma

Nephrogenic adenoma is a benign lesion characterized by small clusters of glandular or tubular structures resembling renal tubules. There is usually a history of urothelial injury such as instrumentation, calculi, prior biopsy, or prior transurethral resection.

Nephrogenic adenomas are typically small polypoid or papillary lesions, ranging from 1 to 8 mm. There are many different patterns such as tubular (Figure 7, C), papillary, capillary, or signet ring–like. Most often the pattern is mixed. The shape of the epithelial cells of this lesion vary from flat (capillary type), cuboidal, to columnar. Hobnail cells, cells with cytoplasmic vacuoles (signet ring–like), or isolated cells with cytologic atypia can be seen. Diffuse cytologic atypia is generally not present. Two common features found in nephrogenic adenomas but not in adenocarcinoma are (1) thick basement membranes and (2) granulation tissue–like background with prominent stromal edema and inflammatory cell infiltrate. Large amount of mucin, mitoses, and necrosis are uncommon in nephrogenic adenomas. The diagnosis of nephrogenic adenoma should be primarily based on hematoxylin-eosin staining, because of its variable immunoprofile, which can be similar to that of adenocarcinoma. Nephrogenic adenomas are positive for AMACR (50%), high-molecular-weight CK (30%–50%), and CK7, and are negative for PSA and p53. PAX2- or PAX8-positive staining, in conjunction with morphologic features, can be diagnostic for nephrogenic adenoma.

Endometriosis

Endometriosis, when present in the bladder, can exist as either a cystic lesion with a flat epithelial lining or glandular clusters with tall columnar cells in the bladder wall. The presence of glandular structures alone may be difficult to recognize. First, the patient has to be female, typically of a reproductive age. Recognition of the endometrial stroma is the key for diagnosis (Figure 7, D). In addition, the presence of hemorrhage or hemosiderin-laden macrophages can be a clue. Although the epithelial cells in endometriosis can be highly proliferative, they are usually benign appearing, lacking significant cytologic atypia. PAX8 labeling is almost always positive in the epithelial cells of endometriosis. Additional immunohistochemical stains, such as ER, PR, and CD10, can be used for establishing a definitive diagnosis of endometriosis in difficult cases.
Urothelial Carcinoma Involving von Brunn Nests

Urothelial carcinoma can extend into von Brunn nests, mimicking adenocarcinoma. Typically, a portion of the nest is filled with malignant urothelial cells, while the uninvolved portion is occupied by benign urothelium (Figure 8).

Pseudoglandular Differentiation of Reactive Urothelium and Urothelial Carcinoma

Benign urothelium may sometimes show small intraepithelial spaces, particularly in reaction to inflammation or other injury. These spaces are often filled with pink cytoplasmic fragments or mucinous material, but they do not have a glandular epithelial lining. These findings represent degenerative changes rather than true glandular differentiation. The same phenomenon can be seen in urothelial carcinoma, where there are intraepithelial spaces without lining glandular epithelium. Thus, these features, whether they occur in benign reactive urothelium or urothelial carcinoma, are often referred to as “pseudoglandular features” or “pseudoglands.”

Prostatic Type Polyp

Benign prostatic hyperplasia can protrude into the bladder neck or prostatic urethra, giving an appearance of a polypoid lesion. This finding often occurs in patients with benign prostatic hyperplasia or prostatic urethra, giving an appearance of a polypoid lesion.45 This finding often occurs in patients with benign prostatic hyperplasia, while the uninvolved portion is occupied by benign urothelium (Figure 9).46

Table 2. Differential Diagnoses of Bladder Benign and Malignant Lesions With Glandular Differentiation, Other Than Secondary Adenocarcinoma

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystitis glandularis and cystitis cystica</td>
<td>Benign glandular differentiation and cystic dilation in the von Brunn nests without cytologic atypia or infiltrating patterns.</td>
</tr>
<tr>
<td>Intestinal metaplasia</td>
<td>Presence of intestinal-type epithelium and/or goblet cells in the urothelium.</td>
</tr>
<tr>
<td>Nephrogenic adenoma</td>
<td>Small clusters of glandular or tubular structures resembling renal tubules without diffuse cytologic atypia, in the background of inflammation.</td>
</tr>
<tr>
<td>Endometriosis</td>
<td>Endometrial glandular structures without significant cytologic atypia in the presence of endometrial stroma, hemorrhage, or hemorrhage-laden macrophages.</td>
</tr>
<tr>
<td>Prostatic type polyp</td>
<td>Polypoid lesion with benign prostatic glands protruding into the bladder neck or prostatic urethra.</td>
</tr>
<tr>
<td>Pseudoglandular differentiation of reactive urothelium and urothelial carcinoma</td>
<td>Small intraepithelial spaces filled with pink cytoplasmic fragments or mucinous material, due to degenerative changes rather than true glandular differentiation.</td>
</tr>
<tr>
<td>Urothelial carcinoma involving von Brunn nests</td>
<td>Urothelial carcinoma extends into von Brunn nests. Sometimes, the uninvolved portion is occupied by benign urothelium.</td>
</tr>
<tr>
<td>Noninvasive urothelial carcinoma with glandular differentiation</td>
<td>Noninvasive urothelial carcinoma with glandular differentiation contains atypical columnar cells with papillary, cribriform, and flat architectural patterns.</td>
</tr>
<tr>
<td>Invasive urothelial carcinoma with glandular differentiation</td>
<td>The presence of true glandular spaces within malignant urothelium (a mixture of typical urothelial carcinoma and adenocarcinoma). Other differentiation component, especially squamous differentiation, may also be seen in the same sample.</td>
</tr>
<tr>
<td>Bladder primary adenocarcinoma</td>
<td>A malignant neoplasm derived from the urothelium, showing histologically pure glandular phenotype.</td>
</tr>
</tbody>
</table>

SUMMARY

Adenocarcinoma of the bladder is an uncommon tumor that is not frequently encountered in clinical practice. However, pathologists need to be familiar with this entity and other lesions with similar histologic features as well as their clinical implications. There is a wide range of benign and malignant lesions (summarized in Table 2), which can develop in the bladder and display true glandular differentiation or glandlike structures, that need to be distinguished from primary adenocarcinoma of the bladder. The clinical implications of a diagnosis of adenocarcinoma of the bladder are important, since the diagnosis of bladder adenocarcinoma will prompt a clinical workup to rule out the possibility of secondary involvement of the bladder by adenocarcinoma from a different site.

References