Pseudoneoplastic Mimics of Prostate and Bladder Carcinomas

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Context.—The differential diagnoses of prostatic carcinoma and bladder epithelial neoplasms include several histologic mimics that should be known to avoid misdiagnosis.

Objective.—To discuss pseudoneoplastic lesions of the prostate and bladder that could potentially be confused with prostatic carcinoma and bladder epithelial neoplasms, respectively, with specific focus on their distinguishing histopathologic features.

Data Sources.—Relevant published literature and authors’ experience.

Conclusions.—Pseudoneoplastic lesions in the prostate include those of prostatic epithelial origin, the most common being atrophy, adenosis (atypical adenomatous hyperplasia), basal cell hyperplasia, and crowded benign glands, as well as those of nonprostatic origin, such as seminal vesicle epithelium. Such lesions often mimic lower-grade prostatic adenocarcinoma, whereas others, such as clear cell cribriform hyperplasia and granulomatous prostatitis, for example, are in the differential diagnosis of Gleason adenocarcinoma, Gleason grade 4 or 5. Pseudoneoplastic lesions of the urinary bladder include lesions that could potentially be confused with urothelial carcinoma in situ, such as reactive urothelial atypia, and others, such as polypoid/papillary cystitis, where papillary urothelial neoplasms are the main differential diagnostic concern. Several lesions can mimic invasive urothelial carcinoma, including pseudocarcinomatous hyperplasia, von Brunn nests, and nephrogenic adenoma. Diagnostic awareness of the salient histomorphologic and relevant immunohistochemical features of these prostatic and urinary bladder pseudoneoplasms is critical to avoid rendering false-positive diagnoses of malignancy.

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MIMICKERS OF PROSTATIC ADENOCARCINOMA

There are many lesions that can mimic prostatic adenocarcinoma histologically. Such lesions can be broadly divided into those that mimic lower-grade adenocarcinomas (Gleason grade ≤3) and those that mimic higher-grade tumors. A more detailed and practically useful classification that we1 and others2 have used in classifying these lesions is based on the architectural patterns seen in routine hematoxylin and eosin (H&E)–stained sections (Table 1).

The benign entities most often misdiagnosed as prostatic adenocarcinoma are atrophy, crowded benign glands, adenosis (atypical adenomatous hyperplasia), and basal cell hyperplasia, depending on the study and type of tissue sample (needle biopsy versus TURP). In one review of 535 consecutive needle biopsies, 7 (1.3%) were classified as false-positives.3 These 7 cases comprised 5 cases of adenosis (atypical adenomatous hyperplasia) and 2 cases of atrophy. A second investigation on needle core biopsy tissue found partial atrophy and crowded benign glands to be the most frequent benign mimickers of prostatic carcinoma.4 In a study that focused on TURP chips, cases misinterpreted as adenocarcinoma included atypical adenomatous hyperplasia (26% of the false-positive cases), basal cell hyperplasia (26%), atrophy (16%), sclerosing adenosis (10%), high-grade prostatic intraepithelial neoplasia (10%), xanthogranulomatous prostatitis (6%), florid cribriform hyperplasia (3%), and postatrophic hyperplasia (3%).5

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Table 1. Histologic Mimickers of Prostatic Adenocarcinoma

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Small Gland Pattern: Lesions of Prostatic Epithelial Origin

Atrophy.—Atrophy is a common age-related process that represents one of the benign lesions most frequently misdiagnosed as carcinoma. Atrophy may be classified as simple atrophy, simple atrophy with cyst formation, and postatrophic hyperplasia. Sclerotic atrophy has also been recognized as a possible diagnosis. Atrophy may be classified as simple atrophy, with inconspicuous nuclei and small nuclei, with high nuclear/cytoplasmic ratios, in the face of gland space formation by the atrophic glands. Furthermore, the glands may assume a lobular or circumscribed arrangement (Figure 1, A), without infiltration around and between larger, clearly benign glands. Basal cells may be difficult to recognize in atrophic glands because of nuclear compression and crowding. Additionally, it is sometimes difficult to identify basal cells even with the use of immunohistochemistry (IHC) because up to 23% of atrophic glands can be completely negative for basal cell markers. A disrupted basal cell layer can also be seen, with fewer basal cells in individual glands. Compared with simple atrophy, partial atrophy and postatrophic hyperplasia are usually more difficult to distinguish from prostatic adenocarcinoma. Partial atrophy usually appears as a collection of crowded, small, pale glands, sometimes with a stellate shape, composed of clear cells, and usually with bland nuclei and inconspicuous nucleoli (Figures 1, B through D, and 2, A and B). The nuclei in partial atrophy glands can assume an elongated, cylindrical shape, and visible nucleoli can be seen in up to one-quarter of cases. Partial atrophy can resemble prostatic adenocarcinomas composed of clear cells, such as some low-grade and transition-zone carcinomas, as well as foamy gland carcinoma. In postatrophic hyperplasia (Figure 1, E and F), the small regular acini are closely packed, and a central duct may be seen. The constituent cells may harbor prominent nucleoli, particularly when acute inflammation is present, further contributing to the difficulty in separating it from adenocarcinoma. The stroma in atrophy is altered by a pale fibrosis (Figure 1, E), with pericinar collagen deposition, which can impart a sclerotic appearance. This alteration is present in all forms of atrophy except partial atrophy. This sclerosis should not be confused with a desmoplastic response to invasive prostatic carcinoma, which is unusual. Inflammation is common in atrophy and infrequent in adenocarcinoma. Other minor diagnostic criteria include luminal contents: Corpora amylacea are more likely to be detected in atrophic glands than in adenocarcinoma, whereas crystalloids and wispy blue mucin are conversely more prevalent in adenocarcinoma than in benign atrophy. In addition, atrophy, and especially partial atrophy, may also be mistaken for prostatic adenocarcinoma because of its frequent (at least focal) expression of α-methylacyl coenzyme A racemase (AMACR)4,10,15 (Figure 2, C). This, along with basal cells often being difficult to discern in this form of atrophy as well (Figure 2, D), may also account, at least in part, for why it represented the most frequent lesion sent in for consultation in a recent study. The presence of elongated nuclei that are perpendicular to the gland circumference, irregular nuclear placement, identification of basal cells (by H&E or IHC), and merging into adjacent simple atrophy, when present, can all help point to the correct diagnosis of partial atrophy. Lastly, one should be cognizant that atrophic-pattern adenocarcinoma does exist. Features favoring benign atrophy rather than atrophic-pattern adenocarcinoma include lack of infiltrative pattern of atrophic glands between larger benign glands, lack of coexisting usual acinar adenocarcinoma with a moderate amount of cytoplasm, and lack of diffuse, significant cytologic atypia in the glands of concern.

Adenosis (Atypical Adenomatous Hyperplasia).—Adenosis, or atypical adenomatous hyperplasia, is another common mimicker of prostatic adenocarcinoma on both needle biopsy and transurethral resection specimens. It is invariably an incidental histologic finding, usually localized in the transition zone, and is thereby seen more often in TURP chips. The incidence in needle biopsy is less than 1%. Histologically, it is characterized by a nodular proliferation of closely packed, small glands that often merge with larger, more complex glands (Figure 3, A and B). Although the periphery is typically rounded, in a few cases the small acini can extend into surrounding stroma in a pseudoinfiltrative pattern. Uncommonly, the small acini exhibit a more extensive, crowded, and nonlobular distribution, in a pattern termed diffuse adenosis of the peripheral zone. By definition, the basal cell layer in adenosis is fragmented, with some small acini completely lacking basal cells. Immunohistochemical staining with antibody 34BE12 demonstrates the absence of basal cells in about one-half of all glands (with a range of 10%-90%). Cytologically, the luminal cells have cytoplasm that is pale and clear to granular and round to oval nuclei, usually with inconspicuous nucleoli. Intraluminal wispy blue
mucin or crystalloids are sometimes present and up to 18% of cases express AMACR, all features that may lead to diagnostic confusion with adenocarcinoma. Very useful to remember here is that basal cells are at least focally evident (by H&E or IHC) in all cases of adenosis and that the nuclear atypia in adenosis is not as marked as in adenocarcinoma.

Crowded, Benign Glands.—Foci of crowded, small, benign prostatic glands (Figure 3, C), less than what would be considered diagnostic of adenosis, may also

**Figure 1.** Prostatic atrophy. A, Simple atrophy is composed of darkly basophilic glands with a distinct lobular pattern of growth. B through D, Prostatic glands with partial atrophy are less basophilic because of the presence of residual, pale or clear cytoplasm and less-crowded nuclei. E, Postatrophic hyperplasia glands are crowded but lobular. F, The presence of enlarged hyperchromatic nuclei with nucleoli in postatrophic hyperplasia can be confused with adenocarcinoma (hematoxylin-eosin, original magnifications ×20 [A, C, and E], ×10 [B], ×60 [D and F]).
simulate adenocarcinoma (Figure 3, D) and have also been found to be common benign lesions for which a second opinion is requested. Although a lobular pattern of growth may not be easily identified in needle biopsy samples, an infiltrative pattern of growth and cytologic atypia are lacking, and basal cells can almost always be identified (at least focally) by routine H&E sections or IHC.

**Sclerosing Adenosis.**—This lesion, rarely seen in needle biopsy specimens, is characterized by a circumscribed proliferation of small glandular structures, separated by a cellular and myxoid spindle cell stroma (Figure 4, A and B). The glands of sclerosing adenosis are surrounded by a thick, eosinophilic, basement membrane–like structure in most cases. There is true myoepithelial differentiation, with the spindled cells being immunoreactive for muscle-specific actin and S100 protein. Basal cells are also present. The spindled stroma, identification of basal and myoepithelial cells, and lack of appreciable nuclear atypia are useful in distinguishing sclerosing adenosis from adenocarcinoma.

**Basal Cell Hyperplasia (BCH).**—Basal cell hyperplasia is classically seen in the transition zone but can also occur in the peripheral zone and may cause diagnostic confusion with high-grade prostatic intraepithelial neoplasia or adenocarcinoma in TURP chips and needle core tissue. Basal cell hyperplasia is characterized by 2 or more layers of basal cells with a range of growth patterns, including acinar, cribriform/pseudocribriform, and solid patterns or mixtures of these patterns (Figure 5). These growths are often focal, but in the transition zone they can form nodules and also may involve nodules of benign prostatic hyperplasia. An infiltrative appearance due to presence of the hyperplastic foci between benign glands may be seen. There can be focal, eccentric, partial gland involvement to a symmetrical, circumferential proliferation, with central retention of secretory cell layer. Complete luminal space loss with the creation of solid, small nests may also be noted in basal cell hyperplasia. The cribriform (adenoid basal cell) pattern is rare. Additional unusual morphologic patterns include basal cell hyperplasia with intracytoplasmic eosinophilic globules and squamous features. The stroma surrounding basal cell hyperplasia may be similar to adjacent uninvolved prostate, may reveal a few concentric layers of cellular or myxoid compressed stroma, or may show a hypercellular, hyperplastic stroma, which has been called sclerosing basal cell hyperplasia. Microcalcifications are seen in nests in about one-half of cases. The basal cells

![Figure 2. Immunohistochemical stains in atrophy. Given a histologic appearance (A and B) classic for atrophy, one should steer away from a diagnosis of adenocarcinoma, despite the presence of focal α-methylacyl coenzyme A racemase (AMACR) expression (C) and no basal cells detected by p63 labeling (D) (hematoxylin-eosin, original magnifications ×20 [A], ×40 [B]; immunoperoxidase, original magnification ×20 [C and D]).](image)
themselves are basophilic or slate grey with scant cytoplasm and round to oval nuclei.

The differential diagnosis for basal cell hyperplasia centers mainly on high-grade prostatic intraepithelial neoplasia, particularly when nucleoli are present, but basal cell hyperplasia is a uniform cell population and does not exhibit the tufted and micropapillary patterns commonly present in prostatic intraepithelial neoplasia. Tubular and cribriform basal cell hyperplasia can be mistaken for adenocarcinoma, but again, the multilayered uniform basaloid cell population is the key finding that aids in diagnostic recognition. The finding of small, solid, basaloid nests is a diagnostic clue pointing toward basal cell hyperplasia because such nesting is not typical of adenocarcinoma unless the carcinoma is high grade and extensive. The aforementioned stromal alterations favor basal cell hyperplasia rather than adenocarcinoma. Microcalcifications also suggest the possibility of basal cell hyperplasia because they are hardly ever seen in adenocarcinoma. Cytologically, the occasional presence of prominent nucleoli can be concerning for neoplasia but is allowable in basal cell hyperplasia. Demonstration of strong immunoreactivity for basal cell markers and lack of AMACR positivity can be useful to confirm the diagnosis of basal cell hyperplasia if doubt is persistent, although the differential diagnosis can usually be resolved by examination of H&E-stained sections.

Finally, basal cell hyperplasia should be separated from basal cell carcinoma: Infiltrative permeation, extraprostatic extension, perineural invasion, necrosis, and stromal desmoplasia are characteristics of basal cell carcinoma that can help in the differential diagnostic distinction from basal cell hyperplasia. Immunohistochemical marker studies for BCL2 and Ki67 may also be of value in this separation because the proliferative index in basal cell hyperplasia is low (<5%) and BCL2 is not overexpressed.

Radiation Atypia in Benign Glands.—Radiation atypia in benign glands is seen in follow-up needle biopsy tissue or salvage prostatectomy specimens following brachytherapy or external beam radiotherapy for prostate carcinoma. The degree of histologic alteration in benign glands depends on dose and duration of irradiation and interval from therapy. Radiation therapy effects may persist for years. Changes include stromal...
Figure 4.  A and B, Sclerosing adenosis is characterized by a circumscribed collection of small glands or tubular structures separated by a cellular spindle-cell stroma (hematoxylin-eosin, original magnifications ×20 [A], ×40 [B]).

Figure 5. Basal cell hyperplasia appears as variably sized, dark, basophilic glands. The surrounding stroma is also often quite cellular (hematoxylin-eosin, original magnification ×20).

Figure 6. A, Radiation atypia can be seen in prostatic glands of different size and is manifested by nuclear enlargement and hyperchromasia. B, Basal cell markers, such as 34βE12, are usually strongly positive in these glands (hematoxylin-eosin, original magnification ×20 [A]; immunoperoxidase, original magnification ×20 [B]).

Figure 7. Verumontanum mucosal gland hyperplasia appears here as closely packed small- to medium-sized glands some of which contain eosinophilic secretions (hematoxylin-eosin, original magnification ×10).
dominance with smaller and fewer glands, glandular atrophy, and nuclear atypia, including nuclear enlargement and prominent nucleoli (Figure 6, A). Basal cells, with nuclear atypia, often predominate. In the nonglandular components of the needle biopsy, there can also be evidence of radiation effect with stromal fibrosis, slight nuclear atypia of stromal cells, and vascular damage.

The assessment of radiation atypia versus persistent adenocarcinoma is best made at low power and based on glandular architecture. A noninfiltrative glandular pattern should prompt consideration of a diagnosis of benign glands with radiation atypia. The cytologic and nuclear atypia induced by radiation in benign glands can mimic malignancy. In difficult cases, positive basal cell immunostains (Figure 6, B) and negative AMACR staining can be extremely valuable in establishing a diagnosis of benign atypia.

Reactive Epithelial Atypia.—Reactive epithelial atypia may be noted in association with acute and chronic inflammation or infarction or both. A noninfiltrative pattern and the presence of basal cells point to a nonmalignant diagnosis. Reactive squamous metaplasia of glands with radiation atypia (Figure 6, A). Basal cells, with nuclear atypia, are usually identified with ease.

Small Gland Pattern: Lesions of Nonprostatic Epithelial Origin

Seminal Vesicle and Ejaculatory Duct.—Both the ejaculatory duct and seminal vesicle may be incidentally sampled by routine needle biopsy; the latter is sometimes also specifically targeted for biopsy by the urologist. Both are characterized by branching glandular structures, often with numerous small glands that can resemble adenocarcinoma (Figure 8, A and B). The presence of nuclear hyperchromasia, with smudged chromatin and scattered pleomorphic cells (sometimes striking) beyond what is seen in acinar adenocarcinoma, as well as the presence of lipofuscin granules, occasional intranuclear inclusions, and in the case of the seminal vesicle, a muscular wall, are all helpful clues leading toward the correct diagnosis. However, the mere presence of lipofuscin granules is not specific for seminal vesicle and ejaculatory duct epithelium because they can also be seen in normal, hyperplastic, and carcinomatous glands. Difficult cases can be resolved by IHC because seminal vesicle and ejaculatory duct epithelium is usually prostate specific antigen (PSA) and prostatic acid phosphatase (PAP) negative (they have been reported to be occasionally positive with polyclonal antibodies), and the epithelial structures are surrounded by basal cells.

Cowper (Bulbourethral) Glands.—These glands may be sampled by needle biopsy and TUR procedures. They are characterized by closely packed, rounded, mucinous glands with a central duct in a lobular configuration (Figure 8, C and D). Because of their pale cytoplasm and their bland, basally situated nuclei, Cowper glands can resemble foamy-gland adenocarcinoma; however, their classic appearances are sufficiently distinctive and should allow for an accurate diagnosis.

Mesonephric Remnants.—These rare remnants in needle biopsy and TUR material can undergo hyperplasia where there might be a greater chance of being misdiagnosed as prostatic adenocarcinoma. They are histologically identical to what is seen in the female genital tract, being composed of small glandular structures lined by a single layer of cuboidal cells, usually with dense eosinophilic intraluminal secretory material (Figure 8, E). The characteristic lack of PSA and PAP expression can be useful in confirming the diagnosis in difficult cases.

Colonic Glands.—Although quite frequently present in prostate needle biopsy and rarely a differential diagnostic issue, colonic glands can be significantly distorted during the biopsy procedure and may cause diagnostic difficulty, especially when blue-tinged mucin or prominent nuclei are evident. This problem can be compounded by colonic glands usually being negative for basal cell markers and positive for AMACR. Identification of other colonic structures, such as the lamina propria or muscularis propria and, if necessary, a negative PSA immunostain should be able to resolve the problem.

Nephrogenic Adenoma.—As noted earlier, the nephrogenic adenoma (NA) lesion, of presumed renal tubular origin, can be seen in different locations within the urinary system, including the renal pelvis, ureters, urinary bladder (most common location), and prostatic urethra. The latter location is where it might cause confusion with prostatic adenocarcinoma. Histologically, papillary structures, small tubules, or cystically dilated tubules lined by cuboidal, low columnar, or hobnail-shaped eosinophilic cells are seen. Lesions predominantly composed of small tubules (Figure 9, A and B) are those most likely to be confused with prostatic adenocarcinoma. This is compounded by NA frequently being negative for basal cell markers and not infrequently positive for AMACR (Figure 9, C), PSA and/or PAP by IHC. The characteristic histomorphologic and immunohistochemical features, possibly supplemented by positive PAX2 and/or PAX8 immunostains, both recently described specific markers for NA, can be used to arrive at the correct diagnosis.

Large and Cribriform Gland Patterns

(Clear Cell) Cribriform Hyperplasia.—This lesion is usually seen in the transition zone as part of benign nodular epithelial hyperplasia. As its name indicates, it is characterized by a complex cribriform proliferation composed of pale/clear cells. These cells are cuboidal to low columnar in shape, lack cytologic atypia, and are surrounded by basal cells (Figure 10). The latter 2 features serve to distinguish this pattern of hyperplasia from Gleason grade 4 cribriform adenocarcinoma. Healthy central zone glands, occasionally sampled by needle biopsy, can also have a pattern of growth similar to clear cell cribriform hyperplasia.

Cribriform Basal Cell Hyperplasia.—See above section on basal cell hyperplasia.

Medium- to Large-Sized Hyperplastic Glands.—Hyperplastic glands are characterized by complex, large, often cystically dilated glands, with luminal undulation, papillary formations, or branching (Figure 11, A). For the most part, such glands can readily be recognized as...
benign and easily distinguished from prostatic adenocarcinoma. However, a variant of acinar adenocarcinoma, termed pseudohyperplastic carcinoma (Figure 11, B through D), can, especially on lower-power magnification, look very much like such benign hyperplastic glands even in needle biopsy material. Features of benign hyperplastic glands in comparison to pseudohyperplastic glands include lack of crowding, lack of association with

Figure 8. Lesions of nonprostatic epithelial nature. The degree of cytologic disorder and atypia seen in seminal vesicle and ejaculatory duct epithelium (A and B) is beyond what is seen in the small-gland adenocarcinomas they may resemble. The presence of lipofuscin pigment (B) and intranuclear inclusions (B; arrow) can also be useful in the distinction. Cowper glands are characterized by mucinous glands arranged in a tightly packed, lobular pattern (C), usually surrounding a central duct (D). Mesonephric remnants are seen here as small glandular structures, some with dense, eosinophilic, intraluminal material (E) (hematoxylin-eosin, original magnifications ×10 [A and C], ×20 [E], ×40 [B and D]).
usual acinar adenocarcinoma, benign-appearing nuclei, presence of a basal cell layer by H&E and IHC, and absence of AMACR staining. It should be noted, however, that about one-quarter of pseudohyperplastic adenocarcinomas are negative for AMACR.50

Solid and Nonglandular Patterns

Granulomatous Prostatitis.—In addition to being a histologic mimicker of carcinoma, this lesion is also a clinical mimicker because it is frequently associated with abnormal digital rectal examination findings53 or elevated serum PSA levels52 or both. It is characterized histologically by a granulomatous inflammatory infiltrate that is usually noncaseating and often includes giant cells (Figure 12, A and B). The problem with granulomatous prostatitis is that the sheets of epithelioid (or foamy) macrophages, as well as scattered epithelial cells from remnants of ruptured prostatic ducts and acini, may all be confused with high-grade (Gleason grade 5) adenocarcinoma. Finding the presence of giant cells, identifying a lobulocentric pattern of growth, and remembering that prostatic adenocarcinoma is rarely associated with an inflammatory infiltrate are usually sufficient to arrive at the correct diagnosis. In difficult cases, the lack of cytokeratin, PSA, or PAP expression in the epithelioid histiocytes (which usually express CD68) by IHC is diagnostic. It should also be noted that nongranulomatous “usual prostatitis” may also be occasionally confused with prostatic adenocarcinoma, especially in the presence of significant crush artifact.2

Prostatic Xanthoma.—Although rare, a collection of lipid-laden, foamy macrophages in the prostate (Figure 13) can be confused with the foamy gland variant of prostatic adenocarcinoma or, if appearing as individual cells, with Gleason grade 5 adenocarcinoma.53,54 The presence of additional inflammatory cells can be helpful in diagnosis, but IHC for cytokeratin (using antibody CAM 5.2), CD68, and AMACR is often needed to resolve problematic cases. Xanthomas will be CD68 positive and negative for cytokeratin and AMACR. Foamy gland
Figure 11. Glands of prostatic epithelial hyperplasia (A) and those of pseudohyperplastic prostatic adenocarcinoma (B) are both medium to large in size and display cystic dilatation and tufting. Prominent nucleoli (C) or absent basal cells by p63 immunohistochemistry (D), as seen in this case of pseudohyperplastic carcinoma, are features that are useful in the distinction (hematoxylin-eosin, original magnifications ×10 [A and B], ×60 [C]; immunoperoxidase, original magnification ×10 [D]).

Figure 12. Sheets of dispersed inflammatory cells (A) in granulomatous prostatitis may lead to confusion with high-grade prostatic adenocarcinoma. The presence of giant-cell macrophages and granulomas with necrosis (B) are useful diagnostic clues in this case (hematoxylin-eosin, original magnifications ×20 [A], ×60 [B]).
Figure 13. Prostatic xanthoma is characterized by collections of foamy macrophages that can potentially be confused with prostatic adenocarcinomas composed of clear or foamy cells (hematoxylin-eosin, original magnification ×20).

Figure 14. Signet ringlike change in stromal cells can resemble signet ring prostatic adenocarcinoma (hematoxylin-eosin, original magnification ×40).

Figure 15. Reactive urothelial atypia. In this bladder biopsy one sees a thickened hyperplastic urothelial lining with an underlining inflammatory infiltrate. The urothelial cell nuclei are enlarged and show small nucleoli (hematoxylin-eosin, original magnification ×40).

Figure 16. In radiation atypia, the atypical urothelial cells usually have a nuclear to cytoplasmic ratio within reference range, and nuclear or cytoplasmic vacuolization is sometimes evident (hematoxylin-eosin, original magnification ×60).

Figure 17. Polypoid and papillary cystitis are characterized by short and blunt papillary projections (A) that are lined by reactive inflamed urothelium (B) (hematoxylin-eosin, original magnifications ×10 [A], ×60 [B]).
carcinoma can be negative for AMACR, however, in up to one-third of cases.56,57

**Paraganglia.**—Usually located in periprostatic soft tissues, paraganglia are occasionally sampled by needle biopsy and may cause diagnostic concern for adenocarcinoma.56,57 The presence of a nestedzellballen growth pattern, including identification of sustentacular cells and a sinusoidal vascular pattern, are key to a correct diagnosis. Negative immunostain findings for PSA and PAP and positive findings for neuroendocrine markers, such as chromogranin, can resolve difficult cases.

**Signet Ringlike Change in Nonepithelial Cells.**—Lymphocytes58 and prostatic stromal cells59 (Figure 14) can, rarely, display a signet ringlike morphology secondary to thermal injury (in TUR specimens). It is important to be aware of this possibility to avoid misinterpretation as a high-grade signet ring adenocarcinoma of the prostate.

**Mimickers of Urinary Bladder Epithelial Neoplasms**

The International Society of Urological Pathology and World Health Organization classification systems of neoplastic urothelial lesions of the urinary tract include flat, noninvasive; papillary; and invasive lesions.60,61 We use that framework to discuss their mimickers (Table 2).

**Mimickers of Flat, Noninvasive Urothelial Neoplasia**

**Reactive Urothelial Atypia.**—Reactive urothelial atypia is usually seen in the setting of acute or chronic inflammation secondary to infection, stones, or instrumentation. Histologically, the urothelium is often thickened and surface umbrella cells are still preserved. The most characteristic histologic feature is the presence of nuclear enlargement with open chromatin and conspicuous nucleoli (Figure 15). Inflammatory cells are usually present, and mitoses can also be seen. The presence of associated inflammation, the preservation of cell polarity, and the existence of the characteristic nuclear features are helpful in distinguishing this lesion from urothelial carcinoma in situ (CIS), in which cell polarity is not well preserved, and the nuclei are enlarged, and frequently pleomorphic and hyperchromatic, with coarse chromatin. Nucleoli may be observed in reactive atypia and urothelial CIS, but atypical mitoses are seen only in CIS. Although the expression patterns of p53, cytokeratin 20, CD44, and Ki-67 by IHC have been found to be discriminatory in distinguishing between reactive atypia and CIS (Table 3),52-55 the distinction should be mostly based on histologic findings, with only judicious use of IHC in select cases.60,67

**Radiation Atypia.**—The degree of atypia sometimes seen in association with radiation, as well as with chemotherapy, is usually much more marked than that seen in reactive atypia and may be very difficult to distinguish from CIS.64 The cells are usually enlarged and display prominent hyperchromasia, often with markedly bizarre nuclei and multinucleation. Cytoplasmic and nuclear vacuolization may also be seen (Figure 16). Helpful diagnostic clues include an overall low nuclear-to-cytoplasmic ratio and underlying radiation-associated stromal changes, including stromal edema, vascular ectasia with fibrin deposition, extravasated red blood cells, inflammation, and hemosiderin deposition. On occasion, a proliferative epithelial reaction resembling invasive carcinoma may also be seen secondary to radiation (see below).

**Polymavirus Infection.**—Polyoma virus can infect the bladder in immunocompromised individuals (seen most frequently in renal and bone marrow allograft recipients) and may be asymptomatic or cause hemorrhagic cystitis. In such patients, cells with the characteristic intranuclear inclusions are frequently identified in urine cytology material but not so often in tissue sections, especially because biopsies are rarely obtained in this situation. Recognition of these large homogeneous inclusions is the key to differentiating this lesion from pagetoid urothelial CIS, in which only rare carcinomatous cells might populate the urothelium.

**Mimickers of Exophytic Papillary Urothelial Neoplasms**

**Polypoid/Papillary Cystitis.**—This lesion, originally described in association with indwelling catheter use,66 represents a nonspecific mucosal reaction. The lesion grossly appears as friable, broad-based, often edematous, polypoid, or papillary projections, which can mimic a papillary urothelial neoplasm cystoscopically.70,71 Histologically, the classic examples show polypoid edematous and variably inflamed lamina propria, covered by reactive urothelium. More problematic are cases in which the fronds of the lesion undergo fibrosis and have more of a papillary configuration (Figure 17, A), especially if associated with reactive urothelial atypia (Figure 17, B), when they can be mistaken for papillary urothelial neoplasms.72 Key to the distinction is the reactive and inflammatory nature of the process, and, unlike those of papillary neoplasms, the fibrovascular cores in polypoid cystitis tend to be simple and broad based.

**Nephrogenic Adenoma.**—In the bladder (its most common location), NA can present as a papillary or polypoid mass that resembles neoplasm cystoscopically. Although tubular differentiation is its most frequent histologic pattern (where it needs to be differentiated from neoplastic processes with glandular differentiation—see below), NA can predominantly display a papillary appearance (Figure 18), which might also lead to confusion with papillary urothelial neoplasms. The absence of epithelial stratification and the characteristic eosinophilic, cuboidal, low columnar, or hobnail cells should alert the pathologist to the correct diagnosis. As discussed earlier, IHC can be useful, with the potential for

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also using p63 and high molecular weight kininogen immunostains that, in contrast to urothelial lesions, are negative in NA.

**Mimickers of Invasive Carcinoma**

**Inflammatory Lesions.**—Invasive urothelial carcinoma is, not infrequently, associated with some degree of inflammatory response, which, at times, can be quite prominent. Inflammation in conjunction with tissue damage and repair associated with TUR procedures can obscure neoplastic cells. These appearances, as well as some unusual variants of invasive urothelial carcinoma, including lymphoma-like, lymphoepithelioma-like, and plasmacytoid variants, may be mimicked by lesions associated with a prominent inflammatory infiltrate, such as follicular and eosinophilic cystitis. Careful histologic

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### Table 3. Classic Expression Patterns of Several Immunohistochemical Markers in Normal and Abnormal Bladder Epithelium Observations

<table>
<thead>
<tr>
<th>Marker</th>
<th>Healthy</th>
<th>Reactive Atypia</th>
<th>Carcinoma In Situ</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK20</td>
<td>Expression limited to umbrella cells</td>
<td>Expression limited to superficial cells</td>
<td>Full-thickness expression throughout urothelium</td>
</tr>
<tr>
<td>p53</td>
<td>Absent or focally expressed in basal cells</td>
<td>±Scattered expression throughout urothelium</td>
<td>Increased expression throughout urothelium</td>
</tr>
<tr>
<td>CD44</td>
<td>Expressed only in basal layer</td>
<td>Increased expression in all layers</td>
<td>Markedly decreased or absent expression</td>
</tr>
<tr>
<td>Ki-67</td>
<td>Limited expression throughout urothelium</td>
<td>Increased expression throughout urothelium</td>
<td></td>
</tr>
</tbody>
</table>

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Figure 18. Papillary nephrogenic adenoma has an exophytic pattern of growth resembling exophytic papillary urothelial neoplasms (hematoxylin-eosin, original magnification ×20).

Figure 19. Atypical stromal cells, such as these, can be seen in association with prior surgery or radiation (hematoxylin-eosin, original magnification ×60).

Figure 20. Pseudocarcinomatous hyperplasia is characterized by epithelial nests that are embedded in an edematous and inflamed stroma with ectatic vessels (A) that sometimes contain fibrin thrombi. Squamous metaplasia may also be seen (B) (hematoxylin-eosin, original magnifications ×20 [A], ×40 [B]).

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Prostate and Bladder Carcinoma Mimics—Hameed & Humphrey
evaluation, occasionally supplemented by cytokeratin immunostains, should be able to resolve most of these diagnostic dilemmas.

Malakoplakia may be a pitfall because of the epithelioid histiocytes in the lamina propria infiltrate, the cells of which can also be confused with carcinoma. The presence of the intracytoplasmic Michaelis-Gutmann bodies, best visualized with calcium (von Kossa) and iron (Perl Prussian blue) histochemical stains, are diagnostic and not seen in carcinoma.

Giant cell cystitis is typified by mononucleated or multinucleated mesenchymal cells in the lamina propria. It is a misnomer because such cells can be seen in the absence of cystitis. These isolated, atypical stromal cells (Figure 19) may be detected after chemotherapy or radiation therapy and are rarely confused with isolated carcinoma cells or a mesenchymal malignancy. The nuclei may show irregular contours and hyperchromasia, but mitotic figures should not be seen.

Pseudocarcinomatous Epithelial Proliferation or Hyperplasia.—This lesion was first described in association with radiation therapy, but may also follow chemotherapy and, most recently, has been reported as unassociated with either. It is characterized histologically by pseudoinfiltrative nests of epithelium (Figure 20, A), sometimes with squamous metaplasia (Figure 20, B), which are adjacent to ectatic blood vessels that often contain fibrin thrombi. As the name suggests, these nests, especially because of their irregular shape, can resemble invasive carcinoma. Awareness of the existence of this entity and identification of other classic radiation-associated findings are important to avoid a diagnosis of malignancy.

Von Brunn Nests.—Von Brunn nests are aggregates of urothelial cells that represent invaginations from the surface urothelium. These nests may occasionally lose their connection to the surface and become isolated in the lamina propria. Prominent or florid von Brunn nests (Figure 21, A and B) may resemble the nested variant of invasive urothelial carcinoma (Figure 21, C and D). The latter is an aggressive tumor also characterized by nests of relatively bland neoplastic cells. Regular distribution of nests that parallel the surface epithelium and absence of cytologic atypia would favor von Brunn nests, whereas closely packed, irregular, or anastomosing nests; subtle,

Figure 21. Florid von Brunn nests are enlarged but usually stay close to and parallel to the urothelial surface (A) and also lack cytologic atypia (B). Their main differential diagnosis is the nested variant of invasive urothelial carcinoma, which tends to have more irregular and deeper nests that are often associated with an inflammatory or desmoplastic response (C), as well as a certain degree of cytologic atypia (D) (hematoxylin-eosin, original magnifications X20 [A and C], X60 [B and D]).
cytologic atypia (especially in deeper portions of lesion); and an infiltrative pattern would favor carcinoma. Immunohistochemistry does not have a role.78

Cystitis Cystica and Cystitis Glandularis.—These represent a continuum of proliferative and presumed reactive changes that can involve von Brunn nests anywhere along the urinary tract and are usually named accordingly (cystitis cystica, ureteritis cystica, urethritis cystica). Cystitis cystica is characterized by variably sized nests of urothelial cells with central cystic luminal spaces that often contain eosinophilic secretions (Figure 22, A). Cystitis glandularis is used when the epithelium lining the cysts undergoes glandular metaplasia (Figure 22, B); if that epithelium acquires intestinal-type goblet cells (Figure 22, C), then the term cystitis glandularis with intestinal metaplasia is used. In addition to inverted urothelial papilloma, which can sometimes have cystic areas, the differential diagnosis of these related lesions centers on variants of invasive urothelial carcinoma that have glandular features, including invasive urothelial carcinoma with glandular differentiation, the microcystic variant, and the tubular variant, as well as invasive adenocarcinoma. Many of the features that are used to distinguish noncystic von Brunn nests from the nested variant of urothelial carcinoma (see above) can also be used in this differential diagnostic setting. In addition, the absence of significant cytologic atypia and desmoplasia should also steer one away from a diagnosis of invasive adenocarcinoma.

Nephrogenic Adenoma.—As noted earlier, tubular differentiation is the most frequent histologic pattern of NA. As such, it can also mimic the glandular neoplastic lesions discussed in the differential diagnosis of cystitis cystica and cystitis glandularis. Identification of its characteristic morphologic features and immunohistochemical profile (see above) should be able to distinguish NA from these neoplastic lesions.

Endometriosis and Related Lesions.—Endometriosis of the bladder most frequently occurs as part of pelvic endometriosis,79 in which the serosal aspect is usually involved; however, foci of endometriosis may also be identified in the muscularis propria (Figure 23, A), the lamina propria, or the mucosa, and a tumorlike lesion at presentation is quite common.80 The identification of the characteristic endometrial stroma surrounding orderly endometrial glands (Figure 23, B), with or without evidence of hemorrhage, should clinch the diagnosis. Unusual cases with scant or absent stroma are more likely to resemble adenocarcinoma. Also more difficult to diagnose might be cases of bladder endocervicosis81 and mullerianosis.82 The former is characterized by the presence of mucin-secreting endocervical glands within the bladder wall, whereas the latter also includes other benign mullerian components, including endometrial or tubal epithelium. Both of these can involve the bladder extensively, and only the absence of significant atypia, mitotic activity, and a desmoplastic reaction can distinguish them, as well as endometriosis with scant stroma, from adenocarcinoma of the bladder.

Paraganglia.—Paraganglia are commonly found in the wall of the urinary bladder and may be seen in biopsy. The sinusoidal vascular pattern, bland nuclear cytology, and lack of a desmoplastic stromal response will allow for correct recognition.

Ectopic Prostatic Tissue.—Small foci of ectopic prostatic tissue are occasionally identified in the bladder wall, most commonly in the trigone area.83 Although such benign prostatic glands could potentially be confused with other benign glandular lesions in the bladder, their

Figure 22. Cystitis cystica appears similar to, and is often associated with, florid von Brunn nests; however, there are cystic spaces within the nests that usually contain eosinophilic secretions [A]. Cystitis glandularis [B] is characterized by well-formed glandular lumina with a columnar lining and may be associated with intestinal metaplasia [C] (hematoxylin-eosin, original magnifications ×20 [A and C], ×10 [B]).
blunt morphology should make the distinction from adenocarcinoma easy. Immunostains for PSA and PAP are confirmatory.

References