Precursor Lesions of Urologic Malignancies

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Context.—Precursor lesions of urologic malignancies are established histopathologic entities, which are important not only to recognize for clinical purposes, but also to further investigate at the molecular level in order to gain a better understanding of the pathogenesis of these malignancies.

Objective.—To provide a brief overview of precursor lesions to the most common malignancies that develop within the genitourinary tract with a focus on their clinical implications, histologic features, and molecular characteristics.

Data Sources.—Literature review from PubMed, urologic pathology textbooks, and the 4th edition of the World Health Organization Classification of Tumours of the Urinary System and Male Genital Organs.

Precursor lesions to most urologic malignancies are important to recognize in pathologic samples for clinical purposes and are also increasingly important to study in order to better understand the pathogenesis of these malignancies. The main (and proposed) precursor lesions to invasive prostatic adenocarcinoma, invasive urothelial carcinoma, renal cell carcinoma, and testicular germ cell tumors will be discussed, with an emphasis on histologic features and mimics, clinical implications, and molecular characteristics of each particular lesion. Updates to the World Health Organization (WHO) Classification of Tumours of the Urinary System and Male Genital Organs, as they pertain to these precursor lesions, will also be highlighted.

PROSTATE

The main precursor lesion to invasive adenocarcinoma of the prostate is high-grade prostatic intraepithelial neoplasia (HGPIN), with abundant clinical, pathologic, and molecular evidence supporting this notion. HGPIN previously had been distinguished from low-grade prostatic intraepithelial neoplasia (LGPIN) a few decades ago, but LGPIN is no longer routinely reported owing to its poor diagnostic reproducibility, lack of clinical relevance, and debatable association with prostate cancer. Other precursor lesions to prostate cancer have been proposed, such as adenosis and proliferative inflammatory atrophy, although evidence for these lesions being true precursors of malignancy is also relatively weak.

Intraductal carcinoma of the prostate (IDC-P) is an entity that recently has been formally recognized and defined by the WHO in its latest classification of genitourinary tumors. Although most of the current and original literature supports that IDC-P represents progression of invasive disease, there is also some emerging evidence to suggest that at least in a subset of cases, IDC-P may represent a precursor lesion to invasive (and presumably high-grade) disease. This section will focus on the clinical importance, histologic features and mimics, and molecular characteristics of HGPIN, with a brief discussion of other proposed precursor entities.

Epidemiology and Clinical Implications of HGPIN

HGPIN is identified on prostate biopsies in the absence of invasive carcinoma with a frequency of about 5%, although there is much variability in the incidence rate with reports ranging up to 25%. Interobserver variability in diagnosing HGPIN likely accounts for the variability in incidence rate, as well as technical factors in the processing of core biopsy specimens, which affect histologic quality. The incidence of HGPIN increases with patient age and is highest among African American men and lower among Asian men, paralleling the disparate incidences of cancer in these ethnic groups. On prostatectomy specimens with cancer, coexisting HGPIN is identified in more than 85% of cases and is usually located in the peripheral zone of the prostate, supportive evidence of its premalignant nature.

The clinical significance of HGPIN is most important to consider when it is identified in prostate biopsy specimens. Multiple studies have shown that HGPIN alone does not...
elevate serum prostate-specific antigen levels, and thus does not account for a patient’s elevated prostate-specific antigen level (which is the most common indication for prostate biopsy). Given this and the relatively infrequent occurrence of isolated HGPIN on biopsies, it is not uncommon for urologists to question how best to manage these patients, especially since definitive criteria regarding the necessity of and interval time to rebiopsy have not yet been established. In most studies performed during the past 2 decades, the risk of detecting cancer in a subsequent biopsy after a biopsy with HGPIN (~21%) does not significantly differ from the risk of detecting cancer after a benign biopsy result (~19%), which presumably occurs as a result of initial undersampling. In the largest study by Merrimen et al, as well as several smaller studies, the risk of cancer on subsequent biopsy is increased when 2 or more biopsy cores are initially involved by HGPIN. These findings have led experts in urologic pathology to recommend repeated biopsy within 1 year when more than 1 biopsy core is involved by HGPIN. Given that most patients with HGPIN who are found to have cancer on subsequent biopsy have more favorable pathologic findings (ie, low Gleason grade, low-stage disease at radical prostatectomy), it is reasonable for urologists to follow up these patients similarly to those on active surveillance with low-risk invasive cancers.

From a biological and clinical standpoint, another interesting question is whether it may be possible to prevent the development of cancer from HGPIN. Multiple clinical trials have investigated the use of a variety of pharmacologic agents and nonpharmacologic supplements, such as 5-α-reductase inhibitors, 3,3'-diindolylmethane, selenium, soy compounds, toremifene citrate, green tea catechins, and lycopene, among others, but none of these agents has emerged as particularly promising for effective chemoprevention of prostate cancer (as reviewed in DeMarzo et al), although some trials are still ongoing to date. Furthermore, all of these trials are confounded by the potential sampling error of biopsy diagnoses; patients enrolled in these chemopreventive trials with supposedly isolated HGPIN may have undetected cancers from the start. The possibility of preventing prostate cancer development in patients with HGPIN remains a remote one at the present time.

**Histologic Features of HGPIN**

Prostatic intraepithelial neoplasia (PIN) is broadly characterized by the growth of cytologically atypical cells within architecturally benign prostatic ducts or acini and is classified as either low or high grade (LGPIN or HGPIN). LGPIN should not be diagnosed on core biopsies anymore, owing to poor interobserver variability and lack of clinical significance. HGPIN is distinguished from LGPIN by the presence of prominent nucleoli; however, standard accepted criteria do not exist regarding the degree of nucleolar prominence. For relative consistency in diagnosing of HGPIN, urologic pathology experts recommend that nucleoli be visible with a ×20 objective lens. Overdiagnosis of HGPIN should be avoided, since this may lead to unnecessary follow-up biopsies, subjecting patients to the risks inherent to biopsy procedure.

Although the prostatic ducts and acini involved by HGPIN are architecturally benign in that they are typically large glands with branching and papillary/undulating luminal surfaces, they also have different morphologic features from those in benign prostatic tissue. From low magnification, HGPIN is characterized by a distinctly basophilic appearance, a feature that is attributable to nuclear enlargement, overlapping, and hyperchromasia, as well as amphophilic cytoplasm within the glands. The main architectural patterns of HGPIN include micropapillary, tufting, flat, and cribriform (Figure 2, A through D), but there are no known clinically relevant differences among these architectural patterns; their recognition is useful merely for diagnostic purposes. The glands in HGPIN may lack a clearly visible basal cell layer on hematoxylin-eosin (H&E), and immunohistochemical stains used to highlight basal cells (high-molecular-weight cytokeratin and p63) typically show disruption of this layer with patchy discontinuous staining. In addition, the cytoplasm in HGPIN is typically positive for α-methylacylcoenzyme A racemase immunostain. However, with rare exceptions, we caution against performing any immunostaining to diagnose HGPIN alone, since the morphologic features should be evident on H&E, and glands of LGPIN (and occasionally benign prostatic tissue) show similar staining patterns.

**Histologic Mimickers of HGPIN**

Several benign and malignant entities in the prostate can histologically mimic HGPIN, and pathologists should be aware of them to avoid misdiagnosis. These entities in the differential diagnosis of HGPIN are briefly described below.

**Benign Mimics.—Central Zone Histology.**—The central zone of the prostate is characterized by a complex architectural appearance with numerous papillary infoldings and tall pseudostratified epithelium (Figure 2, A). Roman bridge formation and/or cribriform glandular patterns also may be present, features that can sometimes mimic HGPIN. Furthermore, a relatively prominent basal cell layer with visible nucleoli may be present in central zone glands, which may be mistaken for the nucleoli seen in HGPIN. Aside from the basal cell layer, however, nucleoli in the central zone are otherwise not typically prominent, while in HGPIN, the basal cell layer altogether is usually indistinct. The cells within the glands of the central zone also lack the full-thickness nuclear atypia and hyperchromasia seen in HGPIN and bear more eosinophilic cytoplasm. Although HGPIN may be identified within the central zone, it is more often found in the peripheral zone of the prostate.

**Clear Cell Cribriform Hyperplasia.**—Clear cell cribriform hyperplasia is a benign proliferative process that occurs typically in the transition zone. It is characterized by crowded glands filled with cells with clear cytoplasm demonstrating cribriform growth, which can mimic HGPIN (Figure 2, B). In contrast to HGPIN, clear cell cribriform hyperplasia does not show any nuclear atypia, and a distinct basal cell layer is often visible in some of the glands.

**Basal Cell Hyperplasia.**—Basal cell hyperplasia is also a benign proliferative process that is typically seen in the transition zone; it may be mistaken for HGPIN owing to its basophilic appearance, prominent nucleoli, and mitotic activity that may be seen. Basal cell hyperplasia is characterized by crowded small glands filled with cells showing rounded nuclei, often scant/atrophic cytoplasm, and sometimes formation of small solid basaloid nests (Figure 2, C). In contrast, HGPIN shows atypical cells with apical cytoplasm involving larger benign glands in a pseudostratified/columnar arrangement and where more intervening stroma is present between the glands. Another distinction is that basal cells in basal cell hyperplasia tend to
stream parallel to the basement membrane, whereas in HGPIN there is full-thickness cytologic atypia with nuclei oriented perpendicularly. Like clear cell cribriform hyperplasia, basal cell hyperplasia is typically located in the transition zone (an unlikely location for HGPIN) and thus is usually seen in transurethral resection specimens.

**Prominent Basal Cell Nucleoli.**—Even in the absence of a true proliferative process, basal cells in normal glands can show prominent nucleoli, depending on the histologic preparation/processing (Figure 2, D). When basal cell nucleoli are prominent, they may be mistaken for the nucleoli of HGPIN. In addition to the aforementioned features of HGPIN that are lacking in these normal glands, a helpful distinction is that basal cell nuclei typically exhibit a blue-gray hue and the normal secretory cell nuclei overlying them are usually red-violet.

**Malignant Mimics.**—**Invasive Adenocarcinoma.**—Given that HGPIN is a precursor to invasive adenocarcinoma, it is not uncommon to see small atypical glands adjacent to HGPIN (Figure 3, A). In prostate biopsy specimens, it may be difficult to determine if these small atypical glands represent tangential sectioning of the glands of HGPIN or a focus of invasive acinar adenocarcinoma. The quantity of atypical glands and their relative distance from the HGPIN glands are the most helpful features in establishing a diagnosis of invasive carcinoma in such cases. Ancillary immunostains for basal cells (p63, high-molecular-weight cytokeratin) may be used in these instances; a definitive invasive cancer diagnosis should only be rendered if a sufficient quantity of these atypical glands are present that show a lack of staining for basal cell markers. The presence of a patchy basal cell layer, which may be highlighted by immunostains in the glands, favors tangential sectioning of HGPIN. An insufficient quantity of glands adjacent to HGPIN that are negative for basal cell markers should be diagnosed descriptively as atypical glands adjacent to HGPIN with an explanation of the differential diagnosis.

**Ductal Adenocarcinoma.**—Ductal adenocarcinomas of the prostate are aggressive tumors associated with poor prognosis, making their distinction from HGPIN important. They are typically located in the transition zone (unlike HGPIN) and are characterized by true papillary fronds with fibrovascular cores lined by pseudostratified epithelial cells with abundant, amphophilic cytoplasm (Figure 3, B). The complexity of their architecture and prominent nucleoli seen may mimic HGPIN, although HGPIN typically shows micropapillary fronds lined by columnar epithelium, lacking true fibrovascular cores. Additionally, ductal carcinomas

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**Figure 1.** Morphologies of high-grade intraepithelial neoplasia: micropapillary (A), tufting (B), both tufting (left) and flat (right) (C), and cribriform (D) (hematoxylin-eosin, original magnifications ×200 [A, B, D] and ×400 [C]).
may have associated necrosis and may involve larger-than-normal crowded glands, unlike HGPIN, which lacks necrosis and typically involves glands of same size and distribution of benign glands. The use of basal cell markers in this distinction is not helpful, as both entities may show a patchy basal cell layer. Ductal adenocarcinomas also can have various and mixed architectural patterns aside from papillary (eg, cribriform, solid papillary, solid nests, and individual glands), and a flat arrangement of stratified columnar epithelium in “PIN-like” pattern may also be seen (Figure 3, C). These PIN-like ductal carcinomas resemble flat and tufting HGPIN but may be distinguished by the quantity and crowding of atypical glands, which are negative for basal cell markers (Figure 3, D).31,32 Cystic dilation of the glands in PIN-like ductal carcinomas is also usually observed.

Intraductal Carcinoma of the Prostate.—Intraductal carcinoma of the prostate is an entity that is now recognized and defined in the most recent classification of genitourinary tumors by the WHO. Believed to represent retrograde spread of invasive prostatic adenocarcinoma in most cases, IDC-P is characterized histologically by prostatic adenocarcinoma cells filling large acini or ducts with preservation of basal cells (Figure 3, E and F). Intraductal carcinoma of the prostate exhibits a cribriform or micropapillary growth pattern composed of cells within the ducts/acini with the cytologic features of prostatic adenocarcinoma (nuclear enlargement, hyperchromasia, prominent nucleoli), which are similar features to those seen in HGPIN. Intraductal carcinoma of the prostate is distinguished from HGPIN and defined by a dense or solid cribriform growth pattern completely filling the lumen or by loose cribriform or micropapillary growth pattern showing either marked nuclear atypia (nuclei 6× normal) or with necrosis.8,17 The distinction between IDC-P and HGPIN is critical, since IDC-P is associated with advanced, aggressive disease and poor prognosis and HGPIN may be relatively indolent. Consequently, on the rare occasion when IDC-P is seen on biopsy in the absence of invasive cancer or with concomitant low-grade (grade group 1) invasive cancer, definitive therapy for prostatic adenocarcinoma is warranted.9,30 In borderline cases, where features are identified that are worse than HGPIN but not meeting the aforementioned diagnostic criteria of IDC-P, they can be diagnosed descriptively as such, with a strong recommendation for repeated biopsy.17,33,34
Molecular Characteristics of HGPIN

Many molecular aberrations have been identified in HGPIN, which are also observed in adenocarcinoma, supporting its role as a precursor to malignancy. Early studies reported loss of heterozygosity in regions of chromosome arm 8p in HGPIN, but with less frequency than that seen in invasive carcinoma, suggesting that HGPIN is a molecular intermediate between benign...
prostatic tissue and invasive carcinoma. Similar loss of heterozygosity in these and other chromosomes by allelotyping also has been observed between multifocal HGPIN and concurrent invasive carcinomas. Copy number gains in 8q24 (containing the MYC gene) have also been observed in both HGPIN and invasive carcinoma. However, not all studies have found such similarities; some early studies found that HGPIN lesions have additional molecular alterations that are not present in adjacent carcinoma, and a relatively more recent study by Bethel et al found no 8p22 losses or 8q24 gains in isolated lesions of HGPIN. Interestingly, a study by Gurel et al also showed a lack of 8q24 gains in HGPIN, but these authors also observed an incremental increase in MYC protein levels from normal to LGPIN to HGPIN, with MYC protein levels in HGPIN similar to those of invasive carcinoma. Most recently, Jung et al performed a more comprehensive analysis of copy number alteration profiles in HGPIN and prostate cancer by using whole-exome sequencing and array-comparative genomic hybridization, and based on several different gene mutations, as well as copy number alterations in 1q, 8q, and 8p, the authors supported this notion that prostate cancer progresses directly from HGPIN, with additional genomic alterations required for this progression to occur.

ETS gene rearrangements, most of which involve the ERG gene, represent a group of recurrent molecular alterations seen in prostatic carcinoma, identified in approximately 50% of prostate cancers in white men. In HGPIN within this population, however, they have been detected at a lower rate (5%–20%). ERG rearrangements are more frequently present in HGPIN located near invasive carcinoma compared to HGPIN located distantly, further evidence to support HGPIN as a precursor to invasive disease. There is potential clinical significance to these findings, since isolated HGPIN with ERG overexpression on biopsy has been shown to have a higher rate of cancer on repeated biopsy than isolated HGPIN without ERG overexpression. While most HGPIN cases likely represent a precursor lesion, a recent and robust study by Haffner et al has shifted this paradigm; by examining ERG rearrangements in addition to PTEN deletion to track the temporal evolution of HGPIN and invasive carcinoma, the authors demonstrated that in some cases, HGPIN arises from nearby invasive cancers, likely through retrograde colonization. Distinguishing such cases where HGPIN may represent progression of disease is clinically important and further work likely is needed in this area.

Other similarities in molecular aberrancies have been observed between HGPIN and prostate cancer that are not typically seen in benign prostatic tissue, such as somatic DNA methylation and telomere shortening. Studies have shown that hypermethylation of the CpG island upstream of GSTP1 is commonly present in both carcinoma and HGPIN, and a relatively more recent study found a high frequency and extent of hypermethylation of GSTP1, RARB, and APC in both entities. Telomere shortening is also believed to play a role in prostate carcinogenesis, and telomeres have been found to be short in both HGPIN and invasive cancer, with one study showing shorter telomeres in HGPIN located near carcinoma compared to distantly located HGPIN.

Evidence for Other Prostate Cancer Precursor Lesions: IDC-P A Likely Candidate?

In addition to HGPIN, there have been other proposed entities as possible precursor lesions to invasive prostatic adenocarcinoma, such as proliferative inflammatory atrophy and adenosis. Proliferative inflammatory atrophy is characterized by simple atrophy and postatrophic hyperplasia that are associated with inflammation, and it has been found, although quite rarely, to be associated with small invasive carcinomas in the peripheral zone. The evidence for proliferative inflammatory atrophy being a true precursor lesion is not strong; possibly, it leads to carcinoma indirectly via HGPIN.

Adenosis, typically observed in the transition zone, is associated with low-grade cancers in this region and has been proposed as a precursor lesion to these cancers. Although some early molecular evidence exists to support this notion, a more comprehensive molecular analysis in a study by Bettendorf et al did not show common genomic alterations between adenosis and adjacent cancers. Overall, the data to support proliferative inflammatory atrophy or adenosis as precursor lesions are relatively weak, especially when compared to HGPIN.

Another consideration for a possible precursor lesion of invasive prostatic adenocarcinoma is IDC-P, recently recognized by the WHO, and described histologically in the previous section (see Histologic Mimickers of HGPIN). Given ample evidence spanning more than 30 years that in most cases, IDC-P is associated with a high volume of high-grade invasive disease and advanced stage in radical prostatectomy specimens, combined with several more recent and innovative molecular studies supporting that it represents progression of invasive disease, it is reasonable to conclude that IDC-P usually does not represent a precursor lesion. However, contained within some of these previously cited studies in addition to others, there is evidence that IDC-P may be a precursor lesion to invasive disease in at least a small subset of cases in which it is present. In 2 separate studies, the authors identified radical prostatectomy specimens with IDC-P that had either no invasive cancer or concomitant low-grade (grade group 1) invasive cancer. Similarly, Miyai and colleagues identified areas of IDC-P in radical prostatectomy specimens, which were regionally distant from invasive cancers, terming IDC-P as “precursor-like” in these cases. In this latter study, cases with “precursor-like” IDC-P had favorable prognoses. In the rare cases reported of entirely submitted radical prostatectomy specimens with IDC-P and no invasive cancer, there likely is no metastatic potential of the tumor, and thus these patients may be considered effectively cured. Intraductal carcinoma of the prostate that precedes the development of invasive cancer may be similar in concept to high-grade ductal carcinoma in situ of the breast, where it is a precursor lesion of high-grade invasive cancer. Further molecular work is needed to support this theory, and distinguishing the rare instances of IDC-P existing as a precursor lesion then will be important for prognostic risk stratification.

URINARY BLADDER

While the molecular pathology of urothelial carcinoma is becoming increasingly complex, the morphologic classification of malignant and premalignant lesions of the bladder has remained relatively unchanged. Urothelial carcinomas...
have historically been classified into 2 categories on the basis of their architectural growth pattern—either flat or papillary. Similarly, precursor lesions of bladder cancer can generally be simplified into those that are either flat (ie, urothelial carcinoma in situ and urothelial dysplasia) or hyperplastic (ie, urothelial proliferation of uncertain malignant potential). While this is certainly an oversimplification of these lesions, since flat lesions can have thickened urothelium for instance, it serves as a basic framework for understanding the general clinical and molecular significance of each precursor lesion. As will be discussed in the sections below, flat lesions are frequently characterized by high-grade disease and loss-of-function mutations in tumor suppressor genes, while hyperplastic lesions are generally associated with low-grade neoplasms and gain-of-function mutations in genes that drive cell growth and proliferation.8,69

Urothelial Carcinoma In Situ

Not surprisingly, the most well-studied precursor lesion, urothelial carcinoma in situ (UCIS), is also the most aggressive of all the precursor lesions. While UCIS is most commonly seen either concurrently or in follow-up of patients with high-grade papillary urothelial carcinoma or invasive urothelial carcinoma, it may be seen as a de novo lesion in approximately 3% of patients diagnosed with bladder cancer.6,70–75 If treated by resection/fulguration alone, progression to muscle-invasive disease will occur in 50% to 100% of patients, often within 2 years.73,72,76–83 For this reason, UCIS is treated by resection plus intravesical chemotherapy or immunotherapy, most commonly bacillus Calmette-Guérin (BCG). However, even with intravesical BCG or chemotherapy, disease recurrence and/or progression to muscle-invasive disease can be seen in up to 50% of patients.74,79,84–87 Thus, close clinical follow-up is required, typically for the remainder of the patient’s life. Patients with persistent UCIS following intravesical therapy or those at high risk for progression should be offered radical cystectomy.70

Histologically, UCIS is defined by the presence of cytologically malignant cells confined to the urothelial mucosa. The cells need not involve the full height of the urothelium, and the thickness of the urothelium may be normal (~7 cell layers), thin, or thick. Generally, UCIS cells are pleomorphic with nucleomegaly (~5× the size of a lymphocyte), hyperchromasia, and irregular nuclear membranes (Figure 4, A and B). Prominent nucleoli are not usually present, but when nucleoli are seen they tend to be multiple and irregular. The cytoplasm can be either scant or abundant, but typically will be denser and more eosinophilic than benign urothelium. Architectural disorganization is almost always present and characterized by nuclear crowding, loss of polarity, and cellular disintegration. In cases where the cells are extremely discohesive, the urothelial surface may be entirely or almost entirely denuded (ie, “clinging” CIS), requiring additional deeper H&E levels for a definitive diagnosis of UCIS. While several groups have described morphologic subtypes of UCIS, these have generally not been shown to have clinical or prognostic significance, and we do not specify the UCIS subtype(s) in our pathology reports.86–90

The most common lesions included in the differential diagnosis of UCIS are reactive atypia (which we report as “reactive epithelial changes” to avoid any confusion for our clinical colleagues by using the word “atypia” or “atypical”) and urothelial dysplasia (discussed in the next section). In cases of reactive change, the architecture is typically undisturbed or only minimally altered with the cells maintaining their polarity and showing no nuclear crowding or overlap. Cytologically, the nuclei are relatively uniform with smooth, regular nuclear membranes and only slight enlargement (2–3× the size of a lymphocyte). They also lack the hyperchromasia of UCIS and more frequently have nucleoli. A background of acute and/or chronic inflammation is also frequently present.

Several studies have reported on the utility of various immunohistochemical markers to aid in the distinction of reactive epithelial changes from UCIS. In our practice, we have found cytokeratin (CK) 20 to be most useful, followed by p53. In UCIS, CK20 will generally show full-thickness staining of the urothelium, whereas benign/reactive urothelium shows CK20 positivity in the umbrella cell layer only.94–96 Diffuse, strong (3+) positivity for p53 is also supportive of UCIS, while benign urothelium typically shows only weak and patchy p53 positivity in the basal layer of the urothelium.91,93,94,96,97 Caution should be taken, though, when interpreting p53 in reactive or irradiated urothelium, as these lesions can show moderate (1–2+) intensity staining of urothelial cells above the basal layer; however, full-thickness staining is still usually absent.98 Other groups90,99–102 have also reported varying degrees of success with CD44 and Her2/neu in the diagnosis of UCIS, but we have generally found CK20 and p53 to be sufficient in making a definitive diagnosis. Lastly, since reactive urothelial lesions and UCIS can both be highly proliferative, we recommend against using Ki-67 as a marker to distinguish between reactive epithelial changes and UCIS.94

Urothelial Dysplasia

Urothelial dysplasia, formerly referred to as low-grade intraurothelial neoplasia, is the term used to refer to premalignant lesions that cytologically and architecturally fall short of the diagnosis of UCIS. Similar to UCIS, urothelial dysplasia is most commonly seen in patients with concurrent or prior urothelial carcinoma where it is associated with an increased risk of recurrence and progression to muscle-invasive bladder cancer, though still lower than patients with UCIS (roughly one-third of patients with dysplasia experience progression, while around half of patients with UCIS experience progression).74,79,84–87,103 While the incidence of de novo dysplasia has not been well established, one autopsy series104 demonstrated urothelial dysplasia in roughly 6% of cases. Based on a few case series,74,103,105–107 the rate of progression of de novo urothelial dysplasia to frank carcinoma has ranged from 15% to 19%. Given this risk of progression, patients with de novo urothelial dysplasia are usually followed up clinically for the development of urothelial carcinoma.

As mentioned above, urothelial dysplasia has cytologic and architectural features that are worrisome for UCIS but fall short of that diagnosis. While nuclei are generally larger than benign or reactive urothelium, they do not show the degree of nucleomegaly seen in UCIS (~5× the size of a lymphocyte). Similarly, the variability in nuclear size is less extreme than in UCIS, and the nuclei show only mild hyperchromasia and slight nuclear membrane irregularity (Figure 4, C and D). Nucleoli are generally pinpoint or absent. Architecturally, some disorganization and nuclear crowding is evident, but this will generally only involve the
Figure 4. Precursor lesions of urothelial carcinoma. Urothelial carcinoma in situ exhibiting marked nuclear pleomorphism, hyperchromasia, and disorganization (A, B). Urothelial dysplasia characterized by mild nuclear enlargement, hyperchromasia, pleomorphism, and disorganization that is beyond that seen in reactive urothelium but falls short of a diagnosis of urothelial carcinoma in situ (C, D). Urothelial proliferations of uncertain malignant potential with cytologically bland but thickened urothelium overlying an undulating or “tented” mucosa (E, F) (hematoxylin-eosin, original magnifications ×400 [A through D], ×100 [E], and ×200 [F]).
basal and intermediate layers of the urothelium. Similar to UCIS, though, the urothelium may be of variable thickness in urothelial dysplasia.

The differential diagnosis for urothelial dysplasia primarily includes reactive epithelial changes and UCIS, which have both been described previously in the section on UCIS. If intense acute and/or chronic inflammation is present, one should be cautious in making a diagnosis of urothelial dysplasia, particularly if it is a diagnosis of de novo urothelial dysplasia that may result in lifelong clinical follow-up. Likewise, if the distinction between dysplasia and UCIS is at all uncertain, we would recommend conveying this information to the clinician, since recurrent/refractory UCIS can lead to immediate radical cystectomy.

Some authors have reported that immunohistochemical stains can be helpful in distinguishing reactive epithelial changes from urothelial dysplasia, similar to the use of immunohistochemistry in the distinction of reactive epithelial changes from UCIS. Immunohistochemistry is of little to no use, however, in distinguishing between urothelial dysplasia and UCIS.

Urothelial Proliferation of Uncertain Malignant Potential

The most recent WHO Classification of Tumours of the Urinary System and Male Genital Organs introduces the term urothelial proliferation of uncertain malignant potential (UPUMP) to serve as a unifying diagnosis for hyperplastic lesions previously diagnosed separately as “flat urothelial hyperplasia” and “papillary urothelial hyperplasia.” This simpler terminology generally makes sense since both flat and papillary hyperplasias are most frequently seen in follow-up of patients with a history of urothelial neoplasia (typically papillary neoplasms), and both lesions often share some of the early, common genetic alterations seen in urothelial carcinomas. In patients with a history of urothelial carcinoma, nearly half of those diagnosed with a UPUMP will develop overt urothelial carcinoma within 5 years. However, the “uncertain malignant potential” aspect should be emphasized in patients with a de novo diagnosis of UPUMP, since the precursor nature of the lesion is less certain in these patients, with only around 25% developing a urothelial neoplasm during long-term follow-up.

Morphologically, UPUMPs are cytologically bland, and the cells resemble normal urothelial cells. The polarity of the cells is also maintained, and nuclear crowding is absent. The most prominent feature is the undulation or “tenting” of the mucosa due to the presence of thin mucosal folds of varying heights (Figure 4, E). The urothelium is often thickened, and increased vascularity may be seen at the base of the folds (Figure 4, F). Nonfocal branching or arborization of the folds should not be seen, though, and in such cases a diagnosis of a low-grade papillary urothelial neoplasm (eg, urothelial papilloma or papillary urothelial neoplasm of low malignant potential [PUNLMP]) should strongly be considered. In cases of purely flat mucosa, UPUMPs are defined by a markedly thickened (>10 cells) urothelium.

When urothelial dysplasia is present in conjunction with the narrow mucosal folds and rare arborizing papillae of a UPUMP, some urologic pathologists will diagnose an “early” noninvasive low-grade papillary urothelial carcinoma, particularly in patients with a history of urothelial carcinoma, as these lesions likely represent a recurrence of the patient’s known bladder cancer. Similarly, when UCIS cells line a tenting mucosa with blunt and/or branching papillae, the terminology “early, noninvasive high-grade papillary urothelial carcinoma” or “urothelial carcinoma in situ with early papillary formation” may be used. This classification of high-grade lesions is supported by the study of Swierczynski and Epstein of “atypical papillary urothelial hyperplasia” showing that most of these lesions have concurrent or subsequent high-grade papillary urothelial carcinomas.

The 2 major considerations in the differential diagnosis of UPUMP are reactive epithelial changes (particularly polypoid/papillary cystitis) and a low-grade papillary urothelial neoplasm (ie, papilloma or PUNLMP). In neither situation will immunohistochemistry be helpful in the diagnosis, and the final diagnosis will rely on histologic features alone. In polypoid/papillary cystitis, the presence of acute and/or chronic inflammation is often noted, and the cytologic changes of reactive urothelium described previously are also commonly seen. Architecturally, the mucosal folds are typically more broad based and have a more variable height and width as compared to the more uniform and slender UPUMP. In more polypoid lesions, the mucosa is frequently edematous and the folds more bulbous. On the other hand, lesions of polypoid/papillary cystitis that are more papillary appearing commonly have more elongate and fibrotic mucosal folds that are still wider at the base than UPUMP. In neither the polypoid nor the papillary pattern should true arborization or branching papillae be seen.

When the differential diagnosis is between UPUMP and papilloma or PUNLMP, the primary diagnostic feature that distinguishes these lesions is the presence or absence of truly branching papillary fronds. In UPUMP, the narrow mucosal folds should not arborize or branch, and “free-floating” cross-sections of fibrovascular cores should be rare or altogether absent. However, in papillomas and PUNLMPs, branching fibrovascular cores should be present, and “free-floating” papillary cores should be evident and often extend across a large swath of the mucosa and relatively far out from the mucosal surface.

Molecular Characteristics of Precursor Urothelial Lesions

Just as the morphologic classification of urothelial carcinoma can be broadly categorized into flat and papillary lesions, the molecular classification of bladder cancer can be framed as either “high grade” or “low grade.” Of course, both of these classifications are oversimplifications, as we routinely see tumors with both papillary and flat components, and it is not uncommon for patients to have both low-grade and high-grade morphologies—sometimes even present within the same tumor. This section will highlight some of the common genetic changes seen in urothelial carcinoma; however, for a more detailed understanding of the molecular pathology of bladder cancer, we refer readers to several major studies and recent reviews on the subject.
grade as well as papillary and flat tumors is mutation in the promoter region of the TERT gene. These mutations are activating and lead to overexpression of telomerase, which allows cancer cells to evade senescence from telomere shortening. Kinde et al. showed that TERT promoter mutations are present in roughly 75% of all noninvasive urothelial carcinomas, making this alteration one of the most frequent in bladder cancer.

High-grade urothelial carcinomas, both papillary and flat types, are predominantly characterized by loss-of-function mutations in tumor suppressor genes, especially those that involve cell cycle regulation. Mutations in TP53 have been reported in up to three-fourths of cases of UCIS, and alterations in TP53 are seen in approximately half of muscle-invasive bladder cancers. Another common mutation in high-grade tumors involved the RB1 gene on chromosome arm 13q, with alterations in RB1 detected in roughly one-third of muscle-invasive tumors. Taken together, mutations in TP53, RB1, or another gene in the p53/RB pathway were seen in 93% of all muscle-invasive bladder cancers in the Cancer Genome Atlas Research Network study, confirming the significance of this pathway in high-grade, aggressive disease.

In contrast to high-grade carcinomas, low-grade tumors are generally papillary in nature and show frequent gain-of-function mutations in oncogenes involved in cell growth and proliferation. Most commonly seen are activating mutations in FGFR3 or HRAS, both of which encode proteins involved in the mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (P3K) pathways. In fact, FGFR3 and HRAS mutations have been shown to be mutually exclusive, and mutation in 1 of the 2 genes is present in around 80% of all noninvasive urothelial carcinomas. By contrast, mutations in FGFR3 and HRAS were seen in only 20% or so of muscle-invasive cancers in the Cancer Genome Atlas Research Network cohort. Mutations in PI3K are also common in noninvasive low-grade papillary urothelial carcinomas, identified in one-quarter to one-half of cases, and can be seen in conjunction with FGFR3 mutations.

**TESTIS**

The most common malignant neoplasms of the testis are seminomatous germ cell tumors (GCTs) and nonseminomatous germ cell tumors (NSGCTs) occurring in postpubertal men, and germ cell neoplasia in situ (GCNIS) is the precursor lesion to both entities. (It should be noted that GCNIS is the precursor lesion only to those postpubertal GCTs; it is not a precursor to prepubertal GCTs or spermatocytic tumors, both of which are rarer by comparison.) Previously most commonly referred to as "intraductular germ cell neoplasia--unclassified," the recent 2016 edition of the WHO has officially renamed this entity germ cell neoplasia in situ, although its morphologic definition essentially remains the same. The evolution of the new terminology from historical terms recently was reviewed by Berney and colleagues. In short, there are numerous advantages to the change: It acknowledges that GCNIS is a precursor to both seminomas and NSGCTs without the confusing "unclassified" term in the name, it allows distinction from other more differentiated forms of intratubular germ cell neoplasia (intratubular seminoma and intratubular embryonal carcinoma, discussed further below in the Histologic Features of GCNIS section), the "in situ" component more accurately refers to the specific area where this type of GCT arises (the spermatogonial niche), and lastly, it is more consistent with the nomenclature of other precursor lesions in human malignancies. The epidemiology and clinical ramifications of GCNIS, as well as the histologic features and molecular pathogenesis of this entity, will be briefly reviewed in this section.

**Epidemiology and Clinical Significance of GCNIS**

The epidemiologic associations of GCNIS parallel those of invasive testicular GCTs, since GCNIS is almost always identified in association with both seminomatous GCTs and NSGCTs. These neoplasms are relatively rare, accounting for 1% of all male cancers worldwide, but are the most common cancers among white men between puberty and their early 40s in industrialized countries. There are notable differences in incidence of this malignancy among different ethnic populations and in different global regions. In the United States, the incidence of testicular GCTs in white persons is roughly 5 times higher than it is in African Americans. Globally, the incidence is highest in Scandinavian countries such as Norway and Switzerland, and lowest in Africa and Asia. Interestingly, the incidence of these tumors is increasing, particularly among people in previously low-incidence regions and ethnic groups. Both genetic susceptibility and environmental factors are believed to play a role in the different incidence rates observed among populations.

The risk of GCNIS is increased in developmental reproductive disorders; the prevalence is highest (up to 70%) in those with disorders of sex development, and it is also high in men with various testicular dysgenesis syndrome anomalies, such as cryptorchidism, hypospadias, and some types of infertility. In postpubertal men who are subfertile or infertile, the prevalence of GCNIS has been found to range from approximately 1% to 4%, although this depends on selection criteria for biopsy and the population demographics. Germ cell neoplasia in situ is also associated with microlithiasis (although this finding is nonspecific), which may partially account for the scrotal ultrasound irregularities that are often seen in testes with GCNIS. Biopsy has long been and remains the gold standard for detection of isolated GCNIS when clinically suspected or in high-risk patients, in contrast, radical orchiectomy is performed and is both diagnostic and therapeutic in men with invasive GCTs, who typically present with a painless, palpable testicular mass.

Although GCNIS is rarely seen in isolation of invasive GCTs, it is critical for pathologists to recognize and report this lesion, particularly in testis biopsy specimens. Studies have shown a high rate of progression of GCNIS to invasive testicular GCTs (both seminomatous GCT and NSGCT), with a 50% progression rate in 5 years in one study by von der Maase et al., which was based on patients who had an invasive GCT on one side and contralateral isolated GCNIS. The administration of chemotherapy in such patients does not appear to cause regression of contralateral GCNIS, but since it is so rarely seen in isolation of invasive GCTs, the current assumption is that all GCNISs eventually progress to an invasive GCT; however, this remains to be proven.

There are other instances where recognition of GCNIS is clinically important and diagnostically helpful. In radical orchiectomy specimens with spontaneously and completely regressed tumors (a phenomenon that can occur in invasive GCTs), it may be difficult to prove that a GCT had ever
Histologic Features of GCNIS

Germ cell neoplasia in situ is characterized morphologically by the presence of enlarged, atypical germ cells with abundant clear cytoplasm and large angulated nuclei with coarsely clumped chromatin and enlarged nucleoli, which are the same cytologic features as those seen in seminomatous GCTs. The cells of GCNIS are located inside the seminiferous tubule, initially just above a typically irregularly thickened basement membrane in the spermatogonial niche. These atypical cells are typically present in a single layer and active spermatogenesis is typically absent. The nuclei are often in a linear “string of beads” arrangement separated from the tubule lumen by an adluminal arrangement of uniform Sertoli cell nuclei. As the lesion progresses, GCNIS cells can be stacked in several layers and are present in the tubular lumen. Germ cell neoplasia in situ can spread in a pagetoid fashion along the basement membrane into uninvolved tubules with active spermatogenesis and into the rete testis. Although commonly, the atypical cells of GCNIS are readily recognized on H&E, they are immuno-histochemically positive for OCT3/4, c-kit (CD117), and PLAP, stains that show positivity in embryonic germ cells and seminomas but negativity in normal spermatogenesis. Examples of normal seminiferous tubules in comparison to GCNIS are illustrated in Figure 5, A through D.

Histologic Features of Other Types of Intratubular Germ Cell Neoplasia: Intratubular Seminoma and Intratubular Nonseminoma

Germ cell neoplasia in situ ideally should be distinguished from other types of intratubular proliferations that are commonly seen in association with both GCNIS and invasive GCTs. These other types comprise intratubular seminoma and intratubular nonseminoma. These entities are also believed to be precursor lesions at an intermediate stage between GCNIS and invasive GCTs, although it is quite possible that they represent retrograde spread of invasive GCTs into seminiferous tubules, analogous to IDC-P.

In contrast to GCNIS, intratubular seminoma shows complete filling and expansion of the seminiferous tubules by neoplastic germ cells and an absence of Sertoli cells or any normal seminiferous tubule components (Figure 5, E). Often, lymphocytes are present within and surrounding the tubules. Intratubular nonseminoma is almost exclusively composed of embryonal carcinoma and is believed to arise from reprogramming of GCNIS within the microenvironment of the seminiferous tubule. The seminiferous tubules are often distorted and enlarged, with central necrosis and calcification, resembling ductal carcinoma in situ of the breast (Figure 5, F). The tumor cells have cytology resembling embryonal carcinoma with pleomorphism, crowding, and overlapping, which is dissimilar from GCNIS and seminoma. Intratubular nonseminoma is only seen in association with NSGCTs, and it is believed that as intratubular nonseminoma becomes invasive, it may differentiate into the different lineages of NSGCT (ie, yolk sac tumor, teratoma, choriocarcinoma). Although positive for OCT3/4 by immunohistochemistry, intratubular nonseminoma cells are positive for CD30 and negative for c-kit, unlike in GCNIS.

Molecular Pathogenesis of GCNIS and Progression to Invasive GCT

The most widely accepted hypothesis regarding the pathogenesis of GCTs involves a complex multistep process that begins in utero, where primordial germ cells or gonocytes fail to differentiate into prespermatogonia. This arrest in differentiation is believed to be a result of a combination of genetic predisposition, environmental exposures, and an altered microenvironment with disturbed functions of somatic Sertoli/Leydig cells. Abnormal divisions of these arrested primordial germ cells/gonocytes likely leads to polyploidization and genomic instability of these cells, resulting in the development of GCNIS. These transformed germ cells are thought to remain dormant until puberty, when the influence of sex hormones and normal spermatogenesis are believed to trigger malignant transformation to either seminomas or NSGCTs.

A possible driver of neoplastic transformation of matura­tion-arrested gonocytes is the failure of these cells to downregulate expression of OCT3/4, an antiapoptotic oncofetal protein, a process that normally occurs when gonocytes relocate from the center of the seminiferous tubule to the spermatogonial niche. In the normal spermatogonial niche, testis-specific Y-encoded protein, which stimulates proliferation, is expressed and OCT3/4 is not; failure of these dysregulated gonocytes to downregulate OCT3/4 results in coexpression of both of these proteins, likely contributing to their neoplastic transformation into overt GCNIS. Expression of KIT ligand by neighboring Sertoli cells is also believed to play a role in this process. There is an association between single nucleotide polymorphism variants of KITLG and risk of testicular GCTs, and thus it is plausible that interference with KIT signaling between Sertoli cells and gonocytes plays a mechanistic role.

Malignant transformation from GCNIS to both seminomatomatous GCTs and NSGCTs results from the accumulation of additional genomic alterations. Believed to be critical to this transformation is the acquisition of the testicular GCT-specific isochromosome 12p, which is of uniparental origin in most cases, and is present in the vast majority of both seminomatous GCTs and NSGCTs. A variety of genes are located on chromosome arm 12p, which are often amplified and contribute to malignant transformation. DADR, BCAT1, and EKI reduce apoptotic susceptibility, STELLAR, GDF3, and EDRI maintain pluripotency of cells, and CCND2 and KRA5 provide cells with a proliferative advantage, among other genes on chromosome arm 12p that confer a survival benefit to cells.

Genetic reprogramming is believed to contribute to the development of NSGCTs from GCNIS or a seminoma cell via transformation to an embryonal carcinoma cell, although the mechanisms underlying this transformation are unclear. Loss of N-myc and c-kit activity and activation of pRB, HER2, and p53 are believed to be involved. Epigenetic phenomena likely play a role in this transformation, as GCNIS and seminoma cells are characterized by low levels of DNA methylation (with decreased hypermethylated CpG islands and increased hypomethylation of global DNA),
whereas NSGCTs show high levels of DNA methylation (with increased hypermethylated CpG islands and decreased hypomethylation of global DNA).^{182–184}

Much is known about the molecular pathogenesis of GCNIS and its malignant transformation, which is rather complex. Recent advances also have been made in discovering the expression of specific microRNAs in GCNIS and invasive GCTs, since microRNAs can be detected in serum and seminal fluid, which could be useful for diagnosis and clinical follow-up.^{185,186}

Figure 5. Testis. Normal seminiferous tubule showing complete maturation of spermatozoa (A), germ cell neoplasia in situ (GCNIS) (B, C), GCNIS showing pagetoid spread into rete testis (D), intratubular seminoma (E), and intratubular embryonal carcinoma with abundant necrosis (F) (hematoxylin-eosin, original magnifications ×400 [A and C] and ×200 [B, D, E, F]).
Of the 4 organs covered in this review, precursor lesions of the kidney are the most enigmatic. Imperceptible to most imaging studies and nearly impossible to survey by biopsy, our knowledge of these lesions is derived almost entirely from association studies of lesions identified adjacent to tumors in nephrectomy specimens and, to a lesser extent, of lesions seen in animal models. Whereas high-grade prostatic intraepithelial neoplasia, urothelial carcinoma in situ, and germ cell neoplasia in situ are all discussed in the recent WHO publication on tumors of the genitourinary system, not a single mention is made of any lesion being premalignant in the kidney.8 (Note: Papillary adenoma is discussed, but its potential as a precursor lesion is not mentioned.) Perhaps our lack of understanding of these lesions partly explains why kidney cancer has the lowest 10-year survival rate (60%) when compared to other genitourinary cancers (prostate, 97%; testis, 95%; and bladder, 74%).187 This section will discuss the 3 most commonly purported precursor lesions of the kidney: atypical renal cysts, papillary adenomas, and renal intraepithelial neoplasia.

Atypical Renal Cysts

Renal cysts are not an uncommon finding, and their prevalence increases with age, such that roughly one-third of septuagenarians have at least 1 renal cyst.188 However, most cysts are benign, simple cortical cysts with little to no risk of progression to malignancy. In certain scenarios, though, the development of cysts is associated with the development of renal cell carcinoma (RCC), such as in patients with acquired cystic disease of the kidney (prostate, 97%; testis, 95%; and bladder, 74%).187 This section will discuss the 3 most commonly purported precursor lesions of the kidney: atypical renal cysts, papillary adenomas, and renal intraepithelial neoplasia.

Atypical renal cysts may be uniloculated or multiloculated and are lined by multilayered epithelium and/or papillary projections (Figure 6, A). The nuclear features should be low grade, and there should be no solid or expansile nodules of cells. Presence of either of these 2 latter features should raise the possibility of RCC. Atypical renal cysts have been categorized into 3 groups by their cyst lining: clear cell, eosinophilic papillary, and eosinophilic stratified/foamy.181,192 Clear cell cysts are lined by cuboidal cells with clear cytoplasm, and they are frequently seen in association with clear cell papillary RCC. They also often show a similar immunohistochemical staining pattern as these tumors (ie, CK7 and CA-IX positive). The eosinophilic papillary cysts contain short papillary projections or tufts lined by cuboidal cells with scant eosinophilic cytoplasm. Eosinophilic stratified cysts are generally uniloculated and are lined by pseudostratified cells with a moderate amount of eosinophilic cytoplasm. In patients with acquired cystic disease of the kidney, atypical renal cysts are a probable precursor lesion of acquired cystic disease–associated RCC (ACD-RCC), with these cysts lined by cells resembling those of ACD-RCC and frequently containing calcium oxalate crystals.

The main differential diagnosis of an atypical renal cyst includes a benign simple cyst and a cystic renal neoplasm. In benign simple cysts, the cyst wall is lined by a single layer of flattened or cuboidal cells without atypia. The cells may be clear or eosinophilic, and some of the cysts may show no lining at all. Nodules of cells within the cyst lumen or cyst wall should be absent. This latter finding suggests a cystic renal neoplasm, such as a multilocular cystic renal neoplasm of low malignant potential or ACD-RCC.8 Expansile nodules of clear cells or complex papillary structures should indicate a clear cell RCC or papillary RCC, respectively. Clear cell papillary RCC and translocation–associated RCC may also show extensive cystic change, as well as some benign lesions, such as cystic nephroma and angiomylipoma with epithelial cysts.193

Several studies190,192,194 have demonstrated that the epithelial cells lining some renal cysts harbor cytogenetic alterations similar to those seen in RCC, such as 3p deletion.

Figure 6. Precursor lesions of the kidney. Atypical renal cyst with intracystic papillary proliferations (A). Papillary adenomas are defined as cytologically bland, unencapsulated papillary tumors measuring less than 15 mm in greatest dimension (B) (hematoxylin-eosin, original magnifications ×200 [A] and ×40 [B]).
in clear cell RCC and trisomy of 7 and/or 17 in papillary RCC. Such findings support the notion that at least some cysts are precancerous. In patients with von Hippel–Lindau syndrome, who frequently develop clear cell RCC among other tumors, clear cell cysts can be innumerable, and VHL inactivation has been shown to predispose cells to ciliary dysfunction and cyst development.\(^{184,194,195}\) In mouse models, the combination of ciliary dysfunction, VHL mutation, and TP53 mutation leads to the development of cysts and clear cell RCC.\(^{195}\)

**Papillary Adenoma**

Papillary adenomas are common tumors whose prevalence, like that of renal cysts, increases with age, and they are a common finding in end-stage kidneys.\(^{196}\) They have been associated with hereditary papillary renal cell carcinoma,\(^{197}\) and in cases of sporadic RCC, papillary adenomas are more frequently seen in association with papillary RCC than other types of RCC.\(^{198,199}\) These findings suggest an association of papillary adenoma with papillary RCC, and an adenoma–carcinoma sequence, similar to that in the colon, has been proposed by some authors.\(^{198,200,201}\)

Papillary adenomas are morphologically indistinguishable from papillary RCC, and the distinction between adenoma and carcinoma is currently based solely on size. Previously defined as smaller than 5 mm, the most recent WHO classification defines papillary adenomas as smaller than 15 mm.\(^{8}\) Histologically, they are expansile papillary or tubulopapillary proliferations that are frequently unencapsulated (Figure 6, B). Papillary adenoma cells generally have scant, clear cytoplasm and uniform, small nuclei without prominent nucleoli. Psammoma bodies and/or foamy macrophages may be present.

As mentioned above, lesions larger than 15 mm, even if cytologically bland, are defined as papillary RCC. However, lesions smaller than 15 mm that show marked cytologic atypia, nuclear pleomorphism, or prominent nucleoli, also warrant a diagnosis of papillary RCC rather than adenoma. Also in the differential diagnosis of papillary adenoma is tubulopapillary hyperplasia and metanephric adenoma. Tubulopapillary hyperplasia is also cytologically bland, but in contrast to papillary adenoma, these lesions do not form expansile nodules and simply grow between the renal tubules, leaving the underlying renal architecture undisturbed. Metanephric adenomas tend to have a more tubular rather than true papillary growth pattern and are composed primarily of tightly packed tubules and occasional glomeruloid structures. In addition, the low-power appearance of metanephric adenomas is often “bluer” than that of papillary adenoma, as the cells of metanephric adenomas have extremely scant cytoplasm. If ever in doubt, immunohistochemistry for WT1 can be performed, as papillary adenomas are WT1 negative while metanephric adenomas are WT1 positive.

Given their close relationship, papillary adenoma and papillary RCC frequently share the same fundamental cytogenetic aberrations, namely trisomy 7, trisomy 17, and loss of Y.\(^{8,200,202}\) In keeping with an adenoma–carcinoma sequence, papillary RCC also typically shows additional mutations on top of these alterations, including trisomies of chromosomes 12, 16, and 20.\(^{201-203}\)

**Renal Intraepithelial Neoplasia**

Renal intraepithelial neoplasia (RIN) is a controversial entity that, despite its hypothetical similarity to precursor lesions of other organ systems, has garnered little attention or acceptance as such. In the few studies that have examined it, RIN has been reported in 23% to 30% of kidneys removed for RCC, and in most cases it has only been noted within renal tubules near or immediately adjacent to the tumor.\(^{204-206}\) Most of the support for RIN as a precursor lesion comes from older animal studies in which rodents show renal tubular dysplasia following exposure to known carcinogens.\(^{207-209}\) Since it has been rarely discussed in modern scientific literature, the diagnosis, natural history, and clinical significance of RIN in humans remains unknown.

Histologically, RIN has been described as “crowding of the involved renal tubules by cells with nuclei two to three times the size of normal or reactive tubular epithelial cells. The enlarged nuclei are vesicular with prominent eosinophilic macronucleoli with a few mitoses.”\(^{201}\) Yörükoglu et al\(^{215}\) add that the cells have an increased nucleus to cytoplasm ratio, clumped chromatin, hyperchromasia, and nuclear membrane irregularity. The authors emphasize that the hyperchromasia and increased nucleus to cytoplasm ratio help distinguish RIN from reactive tubular epithelium, and, in addition to reactive tubular epithelium, the differential diagnosis of RIN should include pagetoid spread of carcinoma cells among existing tubules. However, this phenomenon is much more frequently seen with collecting duct carcinomas and renal pelvis urothelial carcinomas than with renal cortical carcinomas.\(^{204,210,211}\)

Few studies in humans have examined the molecular features of RIN. Lai et al\(^{212}\) reported intense immunohistochemical staining for p53 in roughly half of their RIN cases compared to none of their controls. However, they also reported that one-third of nonlesional tubules adjacent to RIN had focal intense p53 staining, raising the possibility that some of their reported p53 staining might be due to physiologic upregulation rather than accumulation of mutant p53. Furthermore, large-scale genomic studies\(^{213,214}\) have not revealed a high frequency of TP53 mutations in RCC. Other more recent studies, though, have provided stronger molecular evidence for an intratubular precursor lesion of the kidney. Pehlivan et al\(^{215}\) found that RIN and its adjacent invasive tumor cells share common genetic alterations, and Arai et al\(^{216}\) showed that nonneoplastic renal cortex and its adjacent RCC show similar methylation changes. It should be noted, though, that Arai et al\(^{216}\) did not specifically assess for the presence of RIN in the nonneoplastic renal cortex.

**CONCLUSIONS**

Some precursor lesions of the genitourinary tract, such as those of the prostate and bladder, have been well characterized, and recognition and accurate diagnosis of these proliferations are important for optimal patient care. Precursor lesions of the testis and kidney, on the other hand, are rarely identified preoperatively, and our knowledge of the natural history and clinical relevance of these entities is limited. Future research, particularly on the molecular underpinnings of these lesions, will hopefully allow for improved diagnosis, management, and potentially prevention of urologic malignancies.

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