### Title

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# Urothelial Proliferation of Unknown Malignant Potential Involving the Bladder:

## Histopathologic Features and Risk of Progression in De Novo Cases and Cases With Prior Neoplasia

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## Abstract

**Context.——**Urothelial proliferation of unknown malignant potential (UPUMP) is a 2016 World Health Organization classifier that encompasses prior categories of flat and papillary urothelial hyperplasia. In addition, UPUMP occurs in settings of both de novo and prior bladder neoplasia.

**Objective.——**To identify UPUMP features associated with subsequent neoplastic development.

**Design.——**Sixty-eight patients were identified from the archives, including 26 patients with de novo and 42 patients with prior bladder neoplasia. Patient slides and clinical course were reviewed.

**Results.——**Patients with de novo UPUMP were detected through clinical findings (26/26; 100%), whereas surveillance cystoscopy primarily detected UPUMP in patients with prior neoplasia (29/42; 69%). Histopathologic criteria evaluated included urothelial hyperplasia, urothelial cytology, vascular ingrowth, denudation, inflammation, edema, and fibrosis. Mean clinical follow-up was 68.9 months in patients with de novo neoplasia and 69.5 months in patients with prior neoplasia. Subsequent neoplasia developed in 4 of 26 (15.4%) of patients with de novo UPUMP and was associated with cystoscopic papillary appearance ($P = .02$) or microscopic thin papillary ingrowths or papillations ($P = .02$; median time to progression, 4.1 months). Of 42 patients with prior neoplasia, 17 (40.5%) had subsequent neoplasia, significantly associated with an absence of prominent lamina propria edema ($P < .001$; median time to progression, 11.0 months). A higher rate of progression to high-grade disease was present in patients with a prior neoplasia versus those with de novo disease (58.9% versus 25%).

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**Conclusions.——**Urothelial proliferation of unknown malignant potential shows subsequent risk of neoplastic development of 17% in patients with de novo disease and 40% in patients with prior neoplasia. The greatest risk of progression is associated with early papillary formation.

Urothelial proliferation of uncertain malignant potential (UPUMP) is a new term used in the 2016 *World Health Organization (WHO) Classification of Tumours of the Urinary System and Male Genital Organs*.[1,2] The term *UPUMP* encompasses the previously separate categories of *flat* and *papillary urothelial hyperplasia*, which are no longer recommended as diagnostic terms.[1,2]

The definition of *UPUMP* encompasses urothelial hyperplasia associated with flat-surface architecture and also early papillations of the urothelium that fall short of true papillary neoplasia. Those papillations lack the detached papillary structures seen in papillary neoplasia, are nonbranching, and are associated with thickened urothelium or a focal increase in cell number.[3,4] In both the earlier categories of flat and papillary hyperplasia, as well as the new UPUMP category, nuclear atypia is limited to, at most, that seen in reactive atypia.[1] By contrast, lesions with cytologic features consistent with dysplasia or carcinoma in situ have been excluded from both the current UPUMP classification and prior categories of hyperplasia and papillary hyperplasia.[5]

UPUMP may be identified in a de novo setting or in the context of surveillance cystoscopy or clinical findings in patients with prior bladder neoplasia. Previous studies on progression in flat or papillary hyperplasia have addressed these 2 patient subsets to varying degree, although data are more robust in the setting of papillary hyperplasia.[3–9] One study[4] on papillary hyperplasia reported a higher rate of conversion to true neoplasia in patients with precedent bladder neoplasia, suggesting that the incorporation of patient context is relevant in assessment of outcomes in the UPUMP category.

Given that *UPUMP* is a new term that combines features related to 2 previously distinct categories, literature is not available on symptoms, cystoscopic appearance, or histopathologic features that are associated with progression to neoplasia. We sought to address those aspects of UPUMP in patients with or without prior bladder neoplasia and to use histopathologic criteria from prior and current classification schema. To our knowledge, this is the first study on UPUMP as promulgated by the WHO, and it represents the largest study to date incorporating prior concepts of papillary and flat urothelial hyperplasia in the context of progression.

## MATERIALS AND METHODS

### Patient Specimen Selection and Clinical Evaluation

This study was approved by the University of California, San Diego (UCSD) institutional review board. To identify potential cases for analysis, we performed a search of pathology reports in UCSD's pathology laboratory information system generated from 2001 to 2017 for the terms *bladder* and *hyperplasia*. We excluded cases in which either flat or papillary hyperplasia were identified in conjunction with definitive neoplastic lesions. We identified an initial cohort of 81 patients. All slides stained with hematoxylin-eosin were rereviewed

by 3 urologic pathologists to confirm the diagnosis and to exclude true neoplastic lesions. Lesions with branching fibrovascular cores were also excluded from the UPUMP category.[3,4] Rereview of those cases excluded 2 patients with diagnoses of urothelial carcinoma in situ, 5 patients with low-grade papillary urothelial carcinoma, 2 patients with high-grade papillary urothelial carcinoma, and 2 cases that showed tangential sectioning, leaving 70 patients for analysis.

We next reviewed patient clinical records for cystoscopy findings, clinical follow-up, and subsequent clinical specimens, including cytology and surgical pathology specimens. Urine-based fluorescence in situ hybridization testing was not performed on these patients. We excluded an additional 2 patients who lacked clinical follow-up. This resulted in a final cohort of 68 patients, 26 (38%) of whom were diagnosed in the de novo setting and 42 (62%) of whom had a precedent history of bladder neoplasia. Additional information collected included age at UPUMP diagnosis, sex, medical history, presenting signs or symptoms, length of clinical follow-up, subsequent cystoscopy report findings, and subsequent pathology findings. *Progressors* were defined as patients who developed subsequent neoplasia, whereas *nonprogressors* were defined as patients without subsequent neoplasia.

## Histopathologic Analysis

Histopathologic features analyzed included architecture, urothelial thickness, cytologic features, and stromal alterations. Architecture was subdivided into flat urothelium or urothelium with papillations. In the latter instance, which was previously classified *papillary hyperplasia*, the urothelium was further characterized as hyperplastic (>10 cell layers resulting in a thickened appearance) or as an increase in cells, per original descriptions.[3,4] Reactive nuclear atypia was categorized as *none* (normal urothelium), *mild* (small pinpoint nucleoli), or *moderate/marked* (small pinpoint nucleoli with mild disorganization). Additional features that were categorized included denudation (present or absent), inflammation (severity as *none, mild*, or *moderate/marked* and the location), lamina propria fibrosis (present or absent), prominent edema resulting in bulbous projections (present or absent), and degree of vascular ingrowth into the upper lamina propria (none, mild, or moderate/marked). Each case was reviewed by 3 urologic pathologists. In instances of disagreement, rereview of the features and discussion was undertaken to achieve agreement.

## Statistical Analysis

All statistical analyses were performed in R (version 3.0.2, September 25, 2013, open-source software; R Foundation for Statistical Computing, Vienna, Austria). We performed 2 sample *t* tests for unequal variance and the Welsh degree-of-freedom modification in R for continuous variables such as age and clinical follow-up. For categorical variables such as sex and the presence or absence of histopathologic features, we performed the 2-proportions *z* test. All tests were 2 sided and considered significant at $P \leq .05$.

# RESULTS

## Patient Demographics and Clinical Features Associated with UPUMP

Patient sex, age, clinical symptoms, and length of clinical follow-up are presented in Table 1. Patients with UPUMP were subdivided into those with disease that occurred in the de novo setting (no history of prior neoplasia or abnormal urine findings) and those that occurred in the setting of a prior tissue diagnosis of bladder neoplasia. Most patients in each cohort were men, with an approximate male to female ratio of 3:1 to 4:1, similar to that reported for patients with bladder neoplasia.[1,2] Patients were most commonly in their seventh decade of life, although a broad age range was present in each cohort. Clinical symptoms were significantly different between the 2 groups ($P < .001$). That difference was due to all patients in the de novo setting being detected by their onset of clinical symptoms (26 of 26; 100%), whereas patients who developed UPUMP after neoplasia were detected primarily during surveillance cystoscopy (29 of 42; 69%) rather than by symptomology.

## UPUMP Cystoscopic and Histopathologic Features: Relationship to Progression

Clinical data, including cystoscopy findings, were reviewed (Table 2). Two features that were consistently reported in all cystoscopy notes were the presence or absence of an exophytic-appearing lesion and the presence of single or multiple lesions. In cases with multifocal lesions, each lesion was sampled as part of the patient's clinical evaluation. The presence of an exophytic or papillary lesion evident on cystoscopy was significantly correlated with a risk of subsequent neoplasia (*progressor* subcategory; $P = .02$) in the de novo category only.

Major histopathologic criteria assessed are described in Table 2. Microscopic appearance of the urothelium was subclassified into *flat, thickened urothelium* or *urothelium with papillations*. In the latter instance, the urothelium was either thickened or had increased cellularity (Figure 1, C and D). In de novo lesions, papillations were associated with progression ($P = .02$), although the papillations were often small and not always correlated with a cystoscopic papillary appearance. The presence of microscopic papillations approached, but did not reach, significance in the setting of prior neoplasia ($P = .09$). Assessment of the degree of reactive atypia, subdivided into *absent, mild*, and *marked* (Figure 2), was not associated with progression. Features of the underlying lamina propria, including degree of vascular ingrowth (Figure 3), degree and location of inflammation (Figure 4, A and B), degree of lamina propria fibrosis (Figure 4, C and D), and denudation, were not associated with progression. Only the lack of prominent edema in patients with a prior history of bladder neoplasia was associated with an increased risk of progression ($P < .001$; Figure 4, E and F).

## Subsequent Neoplastic Lesions That Occur After UPUMP Diagnosis

Median follow-up was shorter for patients with de novo UPUMP than it was for patients with prior bladder neoplasia, although the difference was not significant ($P = .14$; Table 3). The longer follow-up in patients with prior history likely reflects ongoing surveillance protocols in that context. Four patients in the de novo category developed subsequent bladder neoplasia (4 of 26; 15.4%) and included 3 patients with low-grade papillary

urothelial carcinoma and 1 patient with invasive high-grade urothelial carcinoma. By contrast, patients with precedent bladder neoplasia developed neoplastic lesions at a higher frequency after a UPUMP diagnosis (17 of 42; 40.5%). Furthermore, those lesions were more likely to demonstrate high-grade morphology (10 of 17; 58.9%).

Examples of UPUMP lesions that were associated with subsequent progression are shown for both UPUMP in the de novo context (Figure 5, A through C) and in the context of prior bladder neoplasia (Figure 5, D through F).

## DISCUSSION

Urothelial proliferation of unknown malignant potential is a diagnostic category recently added to the World Health Organization classification of urothelial lesions.[1] It combines the prior categories of *flat urothelial hyperplasia* and *papillary hyperplasia* and excludes lesions that reach the threshold of urothelial dysplasia and true papillary neoplasms with branching fibrovascular cores.[2] Diagnosis of UPUMP occurs in both the de novo setting and in the context of prior bladder neoplasia. However, there is limited information on the rates of progression in those 2 categories and limited information on histopathologic features more likely to portend progression to a neoplastic lesion. This study was undertaken to address those limitations and, to our knowledge, represents the largest study to date on this entity.

Histologically, UPUMP is defined either as a marked thickening of the urothelium irrespective of architectural background or as a repetitive upward tenting of the urothelium with the absence of well-developed, branching fibrovascular cores with increased thickening of the urothelium or increased cellularity.[1–4] The latter definition is derived from the descriptions of *papillary urothelial hyperplasia* in Taylor et al[3] and Readal and Epstein,[4] who analyzed 16 and 53 patients, respectively. Papillary urothelial hyperplasia has been suggested to represent a clonal proliferation that may indicate subsequent development to urothelial neoplasia[3,6] and has been associated with a progression rate of 17% in the de novo setting and 37% when occurring in the setting of prior neoplasia, which closely reflects results from this study.[4] Although most flat and papillary urothelial hyperplasia categories have been associated with low-grade papillary urothelial neoplasia, a subset of previously described atypical hyperplasia has been associated with development of high-grade disease.[4] Given the broad histopathologic features and the varied context of UPUMP development, the current study sought to better define the critical histopathologic features associated with lesion progression in the largest cohort of UPUMP patients to date.

In our study, the de novo UPUMP category most commonly presented with microscopic hematuria or urinary tract symptoms in men in their sixth decade, raising the clinical suspicion of a urothelial lesion. Most de novo lesions were cystoscopically unremarkable, although a small percentage demonstrated visible exophytic growth. The presence of papillary features at cystoscopy or papillations at microscopic analysis was the only feature significantly associated with subsequent neoplasia; 3 patients had papillary features at cystoscopy and 3 patients had microscopic papillations, although these were not concurrent findings in all cases. In a subset of cases with papillations, increased urothelial thickness was not present, but instead increased cellular numbers were seen similar to earlier reports of

papillary hyperplasia.[3,4] The current WHO definition includes hyperplastic urothelium as a component of the histopathologic criteria.[1,2] In, to our knowledge, the largest study to date on this entity, we have identified the importance of papillations as the primary factor in the development of subsequent neoplasia in the de novo setting, irrespective of the presence of thickened urothelium. Thus, there may be an opportunity to expand the definitional criteria of UPUMP to include papillations or early papillary architecture of varying urothelial thickness.

Urothelial proliferation of unknown malignant potential in the setting of prior bladder neoplasia was more common. This patient population demonstrated a diverse range of precedent bladder neoplasia treated with various approaches. Many of the histopathologic findings in this group may have resulted from prior therapy, including the findings of broad-based, polypoid cystitis-like protrusions, fibrosis of the lamina propria and the presence of inflammation. In this context, papillations approached significance, suggesting this histopathologic feature may be an important feature of progression. In addition, the absence of marked edema was also associated with progression in this patient population, although the significance of that is unclear. It may be possible that the lack of edema is associated with a less-robust therapeutic response in this setting.

The rates of progression were 15.4% (4 of 26) in the de novo setting and 40% (17 of 42) in the setting of prior bladder neoplasia. These data are almost identical to the progression rate described for prior “papillary hyperplasia” in the de novo setting.[4] We have identified papillations and the degree of edema as associated with increased progression risk, although additional factors may affect outcomes, such as molecular alterations of the urothelium.[10–12] In both the de novo setting and the setting of prior neoplasia, progression to a true neoplastic lesion had a median time of 4.1 and 11.0 months, respectively. This relatively short period may reflect concurrent unsampled neoplastic foci present within the bladder. Most patients progressed to low-grade papillary neoplasms, irrespective of the UPUMP clinical context. The one patient who progressed to invasive high-grade carcinoma in the de novo setting was a woman with multifocal flat lesions. She was also the only patient with a history of prior radiation to the pelvis, which has been shown to increase the risk of high-grade urothelial neoplasia development.[13]

Many UPUMP features did not reach statistical significance in the prediction of subsequent neoplasia development. Multifocality did not affect that risk of progression in either category. Vascular ingrowth, which has often been associated with tumor-associated neovasculature,[14,15] was not significantly associated with development of subsequent neoplasia. Other features selected for review included denudation, which may be seen with emerging loss of cell cohesion and E-cadherin expression[16]; inflammation, which may indicate ongoing epithelial turnover and increased risk of neoplastic development in some systems[17]; and fibrosis of the lamina propria, which may indicate fibroconnective tissue reaction to epithelial alterations. None of those features was associated with progression in either UPUMP category.

The differential diagnosis of UPUMP in the setting of flat architecture includes dysplasia and nonpleomorphic forms of carcinoma in situ. In contrast to UPUMP, lesions diagnosed as

dysplasia of the bladder show cytologic atypia that is clearly not ascribable to reactive processes and that fall short of the threshold for designating carcinoma in situ. We used strict criteria to exclude cases that could potentially be categorized as *dysplasia*, including cases that had nuclear membrane irregularities, nuclear hyperchromasia, nuclear molding, and loss of polarity. However, we recognize that significant interobserver variability exists in this setting.[18–21] Furthermore, we did not use immunohistochemical stains such as p53, CK20, or CD44, because they are not indicated for routine diagnostic use in exclusion of urothelial dysplasia and urothelial carcinoma in situ. When UPUMP contains papillations, the differential diagnosis includes papillary cystitis and early papillary neoplasia, including papillary urothelial neoplasia of low malignant potential. The architecture in papillary cystitis is primarily due to fibrosis of the lamina propria caused by long-standing edema and inflammation, which results in a secondary papillary architecture of the overlying urothelium. In contrast to the papillations in UPUMP, papillary cystitis is less likely to contain thickened urothelium or the increased cellularity associated with UPUMP. Another differential diagnosis in the setting of UPUMP with papillations is *dysplasia with early papillary features*, which has been promulgated by experts to describe lesions in which the papillary architecture is not fully established, but the lining mucosa is clearly felt to have cytologic atypia in the neoplastic (nonreactive) range.[22] Finally, the distinction between UPUMP and papillary urothelial neoplasia of low malignant potential can also be quite difficult, especially in the subset of UPUMP cases that contain thickened urothelium. Based on WHO criteria, a diagnosis of papillary urothelial neoplasia of low malignant potential encompasses papillary stalks lined by thickened urothelium with minimal atypia.[1,2] By contrast, the prior papillary hyperplasia category describes similar characteristics but includes nonbranching fibrovascular cores within the description.[3,4] Thus, in our study, we included in the UPUMP category lesions that showed low papillary structures of any thickness but that lacked the development of branching fibrovascular cores.

Several caveats exist related to this study. First, papillations range from small, nonbranching papillary structures to extensive, repetitive upward tenting of the urothelium. A subset of these cases may be designated as an early papillary neoplasm by some researchers, rather than as UPUMP. Thus, development of clear definitions to subdivide UPUMP from early papillary neoplasia, including the use of biomarkers, should be an emphasis in future studies. Second, UPUMP lesions are typically fully excised on clinical evaluation and their natural biologic progression has not been assessed in human or animal studies. Although certain features in UPUMP lesions may indicate future neoplasia, this has not been demonstrated in an experimental system. Third, the finding of UPUMP in the setting of prior bladder neoplasia remains somewhat unclear, given that existing alterations, independent of UPUMP development, may drive overall progression rates in some patients. Fourth, the outcomes associated with UPUMP lesions in other regions of the urinary tract was not explored as part of this study, and findings from our bladder analysis may not be representative of progression in other parts of the urinary tract.

Future studies that incorporate additional analysis of molecular or immunohistochemical markers to further stratify these lesions hold potential. A few prior studies have undertaken molecular analysis to better define flat and/or papillary hyperplasia. In one study[12] using fluorescence in situ hybridization, the authors identified alterations in chromosome bands

9q22 (*FACC* gene), 9p21 (*p16/CDKI2* gene), or 17p13 (*TP53* gene) in most cases of flat urothelial hyperplasia associated with a known papillary neoplasm. In a subsequent study,[13] the authors examined *FGFR3* gene mutations and loss of heterozygosity of chromosomes 9p/q and 8p/q in flat urothelial hyperplasia with or without associated papillary lesions. Chromosome 9 deletions were detected in 37% of cases, chromosome 8 deletions in 10% of cases, and *FGFR3* mutations in 23% of cases, although several of these hyperplasias were not associated with concurrent or subsequent neoplasms at the time of publication. Additional alterations in chromosome bands 2q, 4, 8p, 11p, and 17 and amplification of 11q12q13 were identified through a combination of fluorescence in situ hybridization, loss of heterozygosity and comparative genomic hybridization (CGH) analysis.[11] In one study[23] that used 4 cases of papillary urothelial hyperplasia, that lesion was not associated with p53 nuclear overexpression and showed only a mild increase in Ki-67 labeling, which was less than that seen in true papillary neoplasia. In animal models, activation of H-*ras* in transgenic mice has been associated with the development of flat urothelial hyperplasia and the development of noninvasive papillary neoplasms in mouse bladders.[24] Rat studies with carcinogen induction of bladder neoplasia have also shown a graded increase in urothelial expression of cytokeratin 20, uroplakin III, and nuclear cyclin D1 within the full thickness of the urothelial lining in the context of flat urothelial hyperplasia, although these have not been recommended for routine clinical use in this setting.[25] Given the limited nature of these lesions, studies that maintain tissue architecture in the analysis process and that undertake longitudinal analysis to identify subsequent neoplasia are needed.

In summary, the finding of de novo UPUMP with early papillary-like features or papillations on cystoscopy and/or microscopic evaluation, similar to the prior diagnostic category of *papillary hyperplasia*, is most closely associated with an increased risk of progression to bladder neoplasia that is most commonly low grade. The effect of UPUMP in the treatment of patients with known bladder neoplasia requires further investigation, and the histopathologic features identified in the current study require validation in an independent cohort of patients with a diagnosis of UPUMP. Future studies that emphasize reliable biomarkers and/or molecular tests to predict progression may further benefit the diagnosis and management of this lesion.

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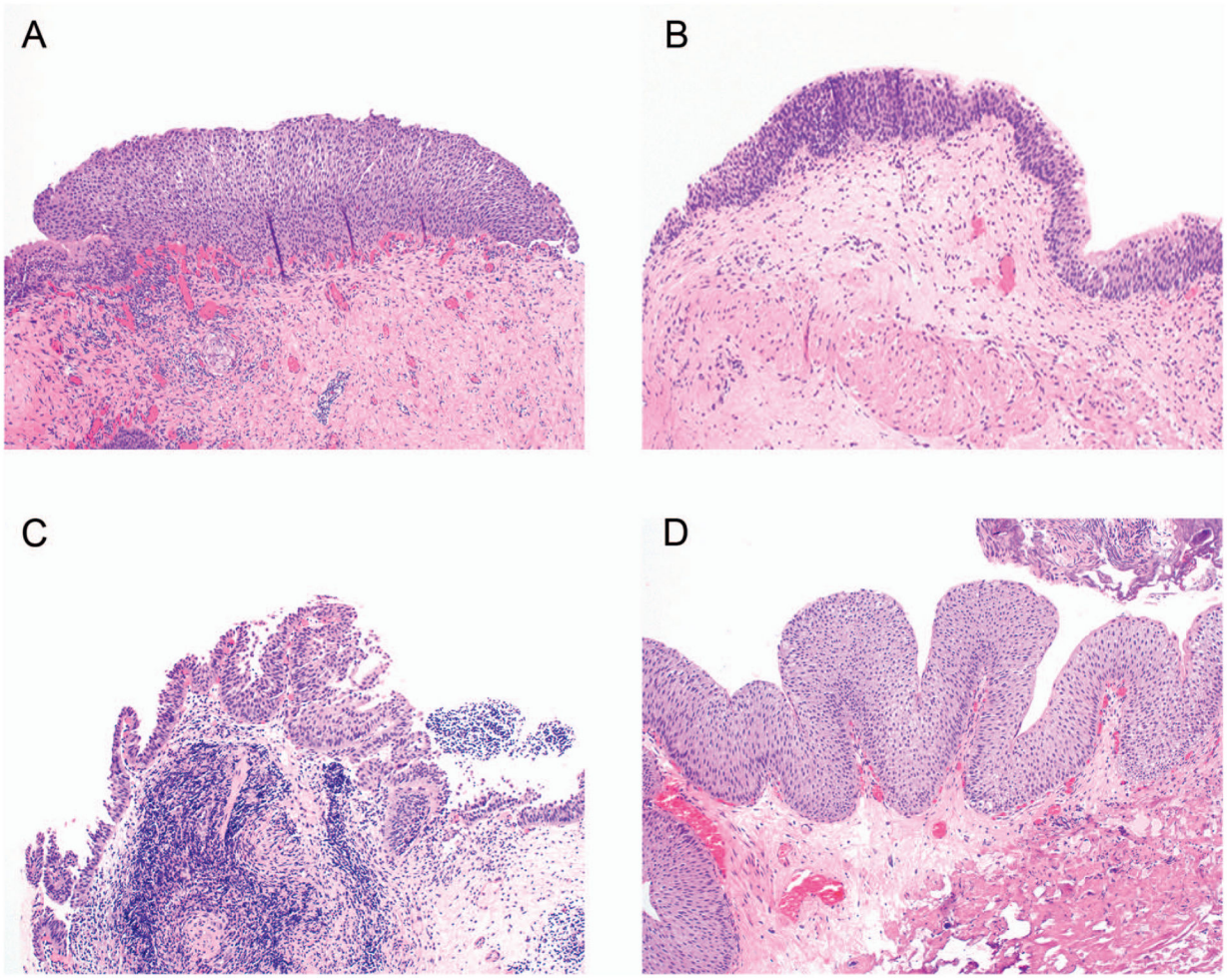


**Figure 1.**

Architectural features associated with urothelial proliferation of unknown malignant potential included flat urothelial hyperplasia (A and B) or tented thin, nonbranching papillations lined by thickened urothelium or urothelium with increased cellularity (C and D). These lesions were all diagnosed in patients who did not progress to urothelial neoplasia (hematoxylin-eosin, original magnification ×100).

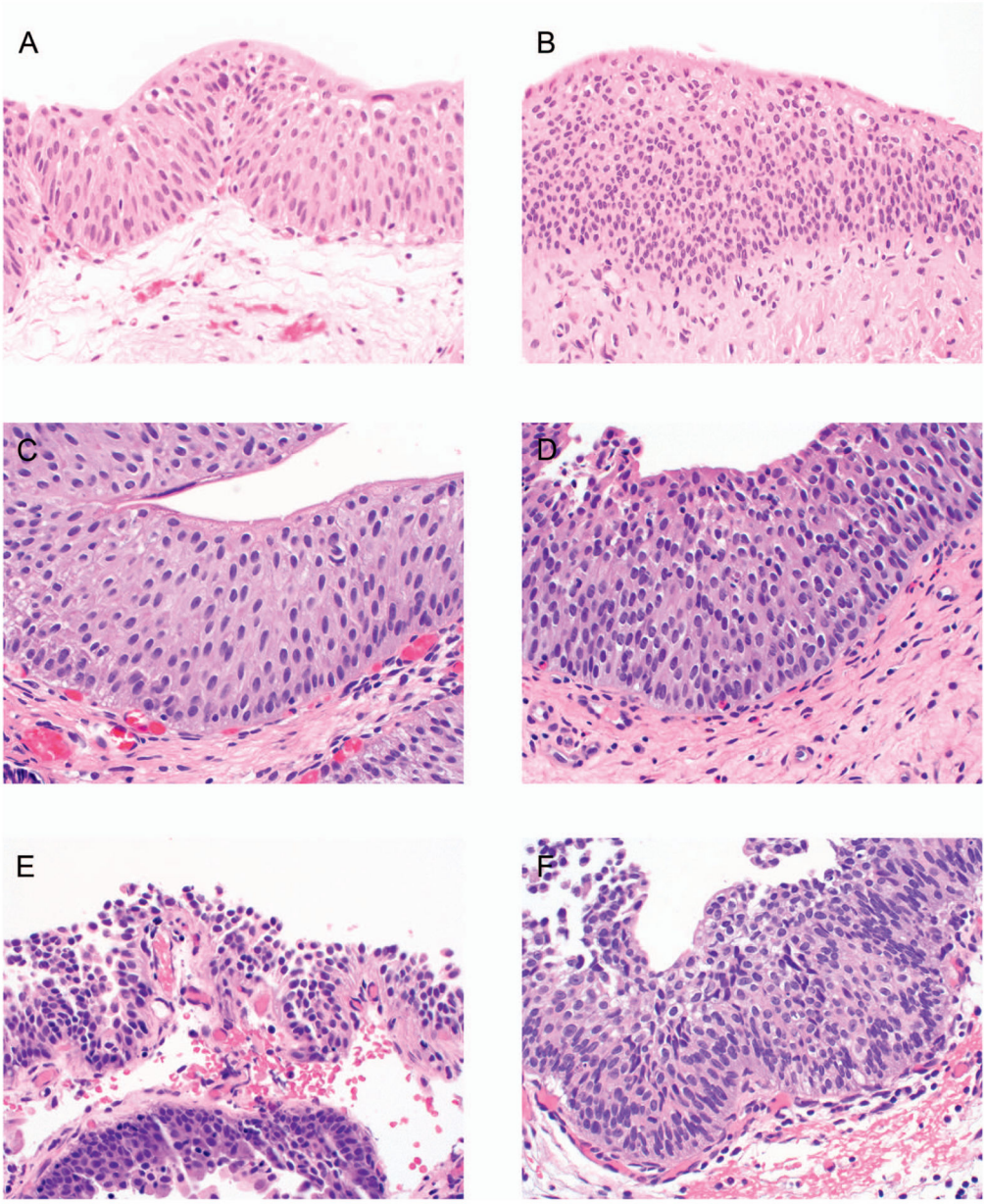


**Figure 2.**

Categories of cytologic atypia included absent (A and B), mild reactive atypia (C and D), and marked reactive atypia (E and F). Reactive features included open nuclear chromatin with or without pinpoint nucleoli and mild variations in nuclear size and shape. F, Only this lesion was associated with progression to neoplasia (hematoxylin-eosin, original magnification ×400).

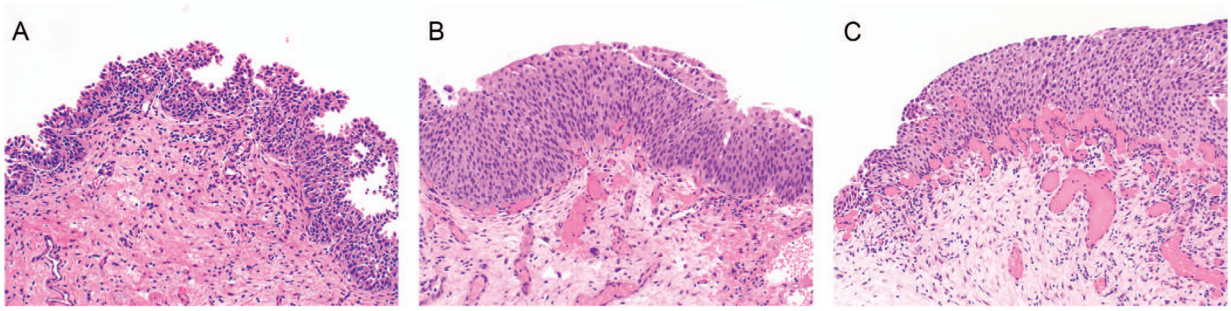


**Figure 3.**

Vascular ingrowth classification included absent to minimal (A), mild (B), and marked (C). All lesions shown were from patients who did not progress (hematoxylin-eosin, original magnification ×200).

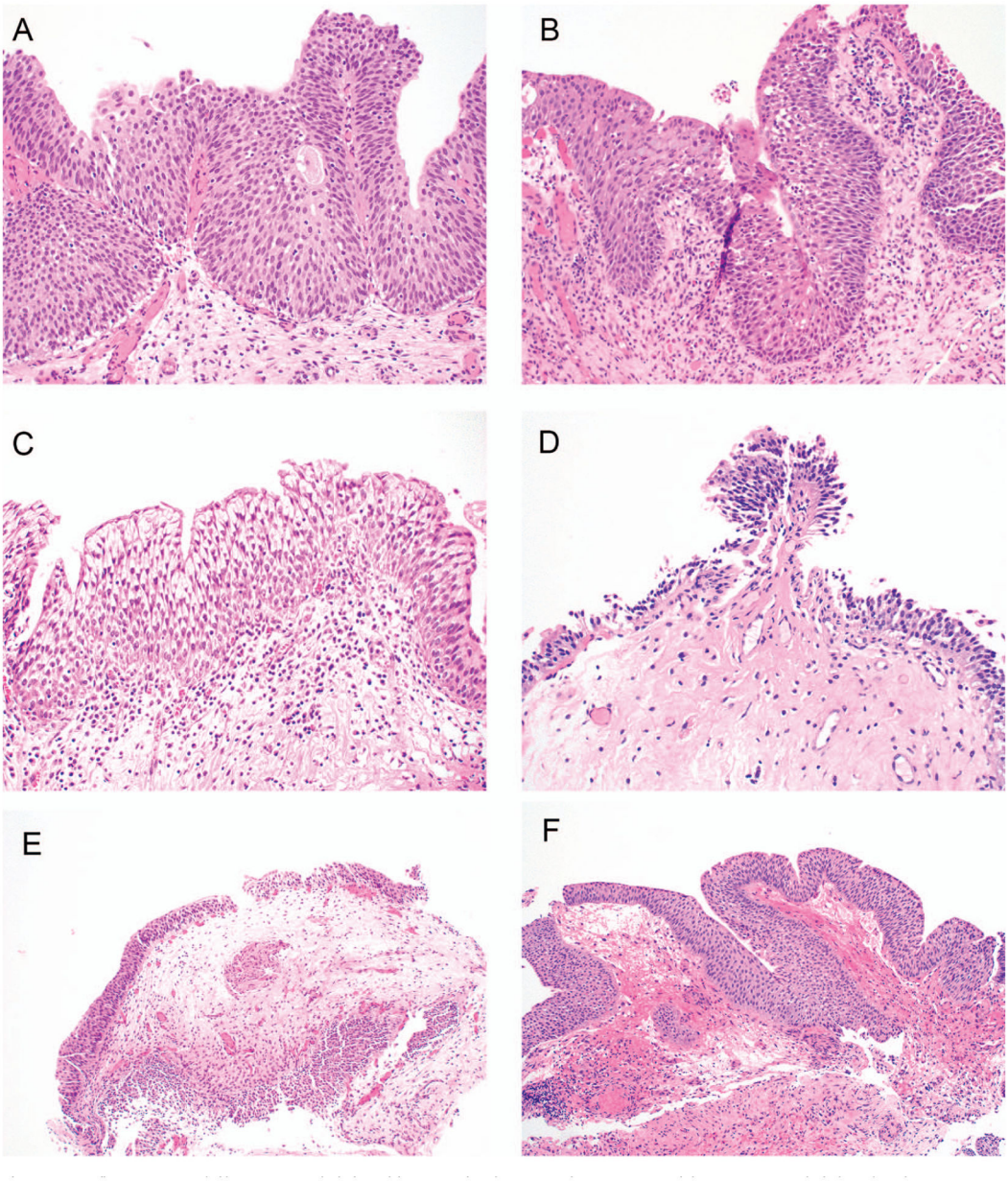


**Figure 4.**

Inflammation and fibrosis in urothelial proliferation of unknown malignant potential lesions. Intraepithelial and/or lamina propria inflammation absent (A) or present (B). Lamina propria fibrosis was classified as absent (C) or present (D) and further subdivided into mild or marked. E and F, Presence of marked edema seen resulting in bulbous protrusions of the urothelium. C and D, These lesions were associated with progression (hematoxylin-eosin, original magnifications ×200 [A through D] and ×100 [E and F]).

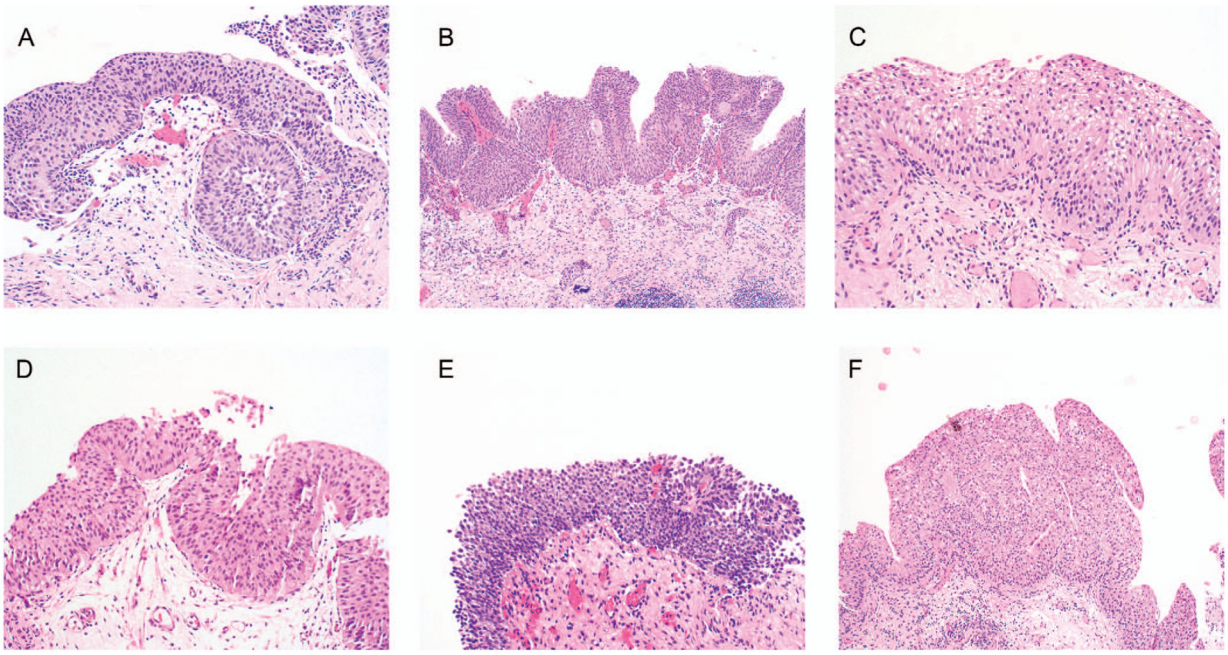


**Figure 5.**

Lesions from patients with urothelial proliferation of unknown malignant potential (UPUMP) who progressed to bladder neoplasia. A through C, UPUMP lesions seen in the de novo setting that were associated with progression. D through F, UPUMP lesions in the setting of prior bladder neoplasia that were associated with subsequent progression (hematoxylin-eosin, original magnification ×400).

**Table 1.**

Urothelial Proliferation of Unknown Malignant Potential (UPUMP) Patient Cohorts: De Novo UPUMP and UPUMP in the Setting of Prior Bladder Neoplasia

| Characteristics | De Novo UPUMP | UPUMP With Prior Urothelial Neoplasia | *P* Value[a] |
|---|---|---|---|
| No. of patients | 26 | 42 | |
| Sex | | | .45 |
| M, No. (%) | 19 (73.1) | 34 (81.0) | |
| F, No. (%) | 7 (26.9) | 8 (19.0) | |
| Age, y | | | .53 |
| Mean; median | 65.5; 67.1 | 67.5; 70.1 | |
| Range | 21.9–84.5 | 36.3–89.1 | |
| Clinical symptoms and signs | | | **<.001** |
| Microscopic hematuria, No. (%) | 16 (61.5) | 13 (31.0) | |
| Urinary retention, No. (%) | 4 (15.4) | 0 (0) | |
| Urinary incontinence, No. (%) | 2 (7.7) | 0 (0) | |
| Urinary tract infection, No. (%) | 2 (7.7) | 0 (0) | |
| None (surveillance) | 0 (0) | 29 (69.0) | |
| Other | 2 (7.7) | 0 (0) | |
| Follow-up, mo | | | .97 |
| Mean; median | 68.9; 59.5 | 69.5; 50.0 | |

[a]Bolded *P* values are significant at $P \leq .05$.

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**Table 2.**

Cystoscopic and Urothelial Findings Associated With Urothelial Proliferation of Unknown Malignant Potential (UPUMP)

| Characteristics | De Novo UPUMP | | | UPUMP With Prior Urothelial Neoplasia | | |
|---|---|---|---|---|---|---|
| | Nonprogressor, n = 22 | Progressor, n = 4 | *P* Value[a] | Nonprogressor, n = 25 | Progressor, n = 17 | *P* Value |
| Patients with subsequent neoplasia, % | 17.3 | | | 40.5 | | |
| Cystoscopic findings, No. | | | | | | |
| Cystoscopic appearance | | | | | | |
| Flat | 18 | 1 | | 10 | 7 | |
| Papillary | 4 | 3 | **.02** | 15 | 10 | .94 |
| Multifocality on cystoscopy | | | | | | |
| No | 18 | 2 | | 16 | 13 | |
| Yes | 4 | 2 | .16 | 9 | 4 | .39 |
| Histologic findings, No. | | | | | | |
| Urothelium | | | | | | |
| Increased cellularity | 3 | 1 | | 7 | 2 | |
| Hyperplastic, thickened | 19 | 3 | .56 | 18 | 15 | .21 |
| Urothelial architecture | | | | | | |
| Flat | 18 | 1 | | 17 | 7 | |
| Papillations | 4 | 3 | **.02** | 8 | 10 | .09 |
| Reactive atypia | | | | | | |
| Absent | 6 | 0 | .23 | 7 | 3 | .44 |
| Mild | 13 | 3 | .60 | 8 | 10 | .09 |
| Moderate/marked | 3 | I | .56 | 10 | 4 | .27 |
| Vascular ingrowth | | | | | | |
| Absent | 8 | I | .66 | 8 | 9 | .17 |
| Mild | 9 | 3 | .21 | 11 | 4 | .17 |
| Moderate/marked | 5 | 0 | .29 | 6 | 4 | .97 |
| Marked edema, bulbous projections | | | | | | |
| Absent | 14 | 4 | | 11 | 15 | |
| Present | 8 | 0 | .15 | 14 | 2 | **<.001** |
| Intraepithelial inflammation | | | | | | |

| Characteristics | De Novo UPUMP | | | UPUMP With Prior Urothelial Neoplasia | | |
|---|---|---|---|---|---|---|
| | Nonprogressor, n = 22 | Progressor, n = 4 | *P* Value[a] | Nonprogressor, n = 25 | Progressor, n = 17 | *P* Value |
| Absent | 17 | 2 | .26 | 15 | 14 | .12 |
| Mild | 3 | 2 | .09 | 7 | 3 | .44 |
| Moderate/marked | 2 | 0 | .53 | 3 | 0 | .14 |
| Lamina propria inflammation | | | | | | |
| Absent | 4 | 2 | .16 | 9 | 7 | .73 |
| Mild | 6 | 1 | .93 | 10 | 6 | .76 |
| Moderate/marked | 12 | 1 | .28 | 6 | 4 | .97 |
| Denudation | | | | | | |
| No | 18 | 4 | | 22 | 12 | |
| Yes | 4 | 0 | .35 | 3 | 5 | .16 |
| Lamina propria fibrosis | | | | | | |
| No | 13 | 4 | | 17 | 15 | |
| Yes | 9 | 0 | .11 | 8 | 2 | .13 |

[a]Bolded *P* values are significant at $P \leq .05$.

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**Table 3.**

Patient Outcome Following a Diagnosis of Urothelial Proliferation of Unknown Malignant Potential (UPUMP)

| Characteristics | De Novo UPUMP | UPUMP With Prior Urothelial Neoplasia | *P* Value |
|---|---|---|---|
| Time to progression, mo | | | .14 |
| Mean; median | 4.6; 4.1 | 22.1; 11.0 | |
| Range | 1–10 | 1–85 | |
| Subsequent diagnoses in progressor subset, No. | | | |
| PUNLMP | 0 | 1 | |
| Low-grade papillary urothelial carcinoma (noninvasive) | 3 | 6 | |
| High-grade papillary urothelial carcinoma (noninvasive) | 0 | 5 | |
| Urothelial carcinoma in situ | 0 | 1 | |
| Invasive carcinoma | 1 | 2 | |
| Positive high-grade cytology (urine) | 0 | 2 | |

Abbreviation: PUNLMP, papillary urothelial neoplasm of low malignant potential.

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