# Pathology of flat bladder lesions with emphasis on putative precursors

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## Abstract

Flat bladder lesions comprise a spectrum of morphologic changes ranging from reactive atypia to carcinoma in situ (CIS). Differentiating these lesions is important because of differences in patient management and clinical outcome. The precise nature of precursor lesions of bladder cancer remains incompletely understood. Urothelial CIS is the most definitely characterized precursor lesion of high grade bladder cancer. Atypia of unknown significance (AUS) is somewhat controversial. For practical purposes, AUS and reactive urothelial changes should be considered a single entity, since neither lesion has established preneoplastic potential. Simple hyperplasia and papillary hyperplasia are recently identified putative preneoplastic lesions. More recent molecular data also support the precursor nature of intestinal metaplasia and keratinizing squamous metaplasia. In this review, we also discuss the utility of molecular ancillary studies in establishing premalignant lesions, diagnosis, and differential diagnosis of flat bladder lesions.

**Keywords** atypia of unknown significance; bladder; flat lesions; molecular pathogenesis; precursors; urothelial carcinoma in situ; urothelial dysplasia

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## Introduction

Great advances have been made in recent years in the molecular characterization and biomarker identification of bladder cancer.[1–25] Malignancy-associated cellular global change is a recently introduced concept addressing urothelial abnormalities in bladders with neoplasia that are not identified by routine light microscopy, but may be found by cellular chromatin analysis or genetic studies.[26–29] The clinical relevance of malignancy-associated cellular changes remains to be established, but such changes may be important for evaluating the status of residual urothelium after surgical bladder tumour resections.[28] Recent studies have shown that 50% of the histologically normal urothelium adjacent to superficial urothelial carcinoma harbors genetic anomalies on chromosome 9 similar to the anomalies found in the coexisting carcinoma. In addition, nondiploid nuclear DNA histograms occur in 4–54% of histologically normal urothelium adjacent to bladder tumours.[27] These genetic alterations imply neoplastic potential for flat urothelial lesions, regardless of whether or not cytologic atypia is present. Knowledge about potentially precancerous conditions in the urinary bladder can assist clinicians in making rational decisions about management following bladder conserving resections. In this review, we discuss histopathologic findings of selected flat bladder lesions with focus on their putative precursor potential.

## Simple urothelial hyperplasia (flat urothelial hyperplasia)

Simple urothelial hyperplasia is defined by the presence of markedly thickened urothelium. There is an increase in the number of cell layers, usually 10 or more, with occasional pseudopapillary growth, but lacking true vascular cores.

Normal urothelium is a multilayered epithelium composed of basal, intermediate, and superficial cells. The number of cell layers (usually less than seven) may appear to vary due to tangential sectioning or distension of the bladder.[30] Urothelial hyperplasia is characterized by an obvious increase in the number of urothelial cell layers, usually 10 or more (Figure 1). It is not necessary to count the number of cell layers for the diagnosis because the thickening is widespread and accompanied by other alterations (Table 1). The cells in urothelial hyperplasia do not show any significant cytologic abnormalities, although slight nuclear enlargement may be focally present. Morphologic evidence of maturation from base to surface is generally evident with preservation of polarity that is lost in other flat benign lesions. Urothelial compression artifact or tangential sectioning of mucosa with pseudopapillary growth (lacking a true vascular core) may resemble flat urothelial hyperplasia, but is seen as a focal change in only a few areas.

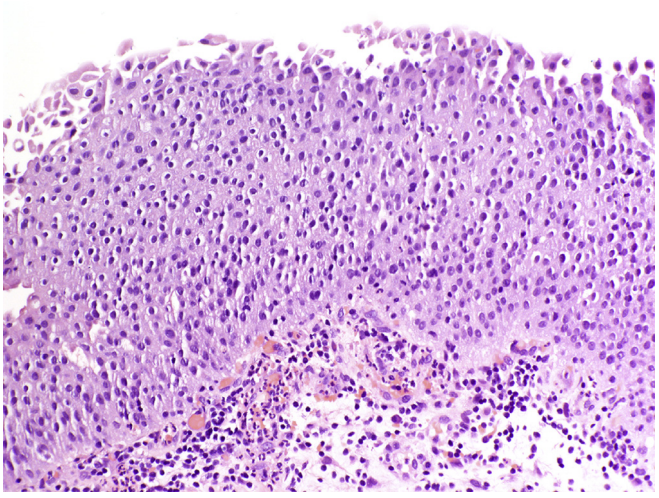

**Figure 1** Simple hyperplasia.

Flat urothelial hyperplasia has been observed in association with a variety of conditions including inflammatory disorders, urolithiasis, papillary urothelial hyperplasia, dysplasia, CIS, and low grade papillary tumours.[26] When it is seen as an isolated phenomenon, there is no evidence to suggest that it has a premalignant potential. However, molecular analyses showing chromosome 9q deletions and mutations in the fibroblast growth factor receptor 3 (FGFR3) gene in both urothelial hyperplasia and low grade papillary neoplasia[16] suggest that this lesion may be clonally related to the raised papillary tumours in bladder cancer patients.[31,32] Flat urothelial hyperplasia has been considered by some authors to be the source of papillary neoplasia, which is usually associated with low grade tumours.[33]

## Papillary urothelial hyperplasia

Papillary urothelial hyperplasia, another putative precursor of bladder cancer, is characterized by undulating, non-branching, non-arborizing, non-detached corrugated, or accordion pleat of thin mucosal papillary folds. The folds vary in height, are lined by multiple layers of cytologically normal urothelial cells with normal nuclear polarity, and are free of inflammation. Within the spectrum of urothelial hyperplasia, papillary architecture may be present, but without branching. Most of these patients have concomitant papillary urothelial neoplasia. The term "papillary urothelial hyperplasia" remains controversial and is rarely used, owing to the apparent self-contradiction. The lesion described as such is usually found with concomitant papillary urothelial carcinoma or in followup biopsies of these patients.[34–36] Undulating folds of urothelium without cytologic atypia or fibrovascular cores characterize papillary hyperplasia (Figure 2). Although considered "hyperplastic," papillary hyperplasia is typically surfaced by normal appearing urothelium only four to seven cells in thickness. Cytologically, the cells in papillary hyperplasia lack atypia and maintain nuclear polarity. There may be increased vascularity in the stroma at the base of the papillary folds, but no stromal cores. This lesion is considered by some to be the clonal precursor of papillary urothelial carcinoma based on associated genetic anomalies,[33,35] but critics contend that it actually represents early undiagnosed papillary carcinoma.

Clinical studies of papillary hyperplasia are very limited. Taylor et al. reported 16 cases of "typical" papillary hyperplasia occurring in patients with either prior or concurrent low grade papillary urothelial neoplasia.[34] The majority of the patients were men (11 men and 5 women) with a mean age of 67.5 years (range, 40—89 years). In more recent study, Swierczynski et al. reported 15 cases of papillary urothelial hyperplasia with varying degrees of atypia ranging from dysplasia to flat CIS (atypical

### Comparison of selected flat intraepithelial lesions of the urinary bladder

| | Reactive atypia | Simple hyperplasia | Dysplasia | Carcinoma in situ |
|---|---|---|---|---|
| Cell layers | Variable | >7 cells | Variable | Variable |
| Polarization | Slightly abnormal | Normal | Slightly abnormal | Abnormal |
| Cytoplasm | Vacuolated | Homogeneous | Homogeneous | Homogeneous |
| N:C ratio | Normal or slightly increased | Normal or slightly increased | Slightly increased | Increased |
| Nuclei | | | | |
| Anisonucleosis | Normal | Normal | Mild | Moderate to severe |
| Borders | Regular/smooth | Regular/smooth | Notches/creases | Pleomorphic |
| Chromatin | Fine/dusty | Fine | Slight hyperchromasia | Coarse/hyperchromatic |
| Chromatin distribution | Even | Even | Even | Uneven |
| Nucleoli | Large | Small/absent | Small/absent | Large/prominent |
| Mitotic figures | Variable | Absent | Rare | Often |
| Denudation | Variable | No | No | Variable |
| Cytokeratin 20 | Surface | Surface | Variable | Variable |
| Stromal microvascular proliferation | Variable | Variable | Less prominent | Often prominent |

N:C, nuclear-to-cytoplasmic.

**Table 1**