Squamous and glandular lesions of the urinary bladder

Susan Prendeville

Abstract

A wide range of squamous and glandular lesions can arise within the urinary bladder. Familiarity with benign entities is important as florid examples can mimic a neoplastic process while certain histologically bland lesions have a potential malignant association.

When dealing with overtly malignant lesions, careful morphologic assessment and clinicopathologic correlation are essential. This paper provides a broad overview of the spectrum of squamous and glandular lesions encountered in the bladder with an emphasis on important morphologic features, relevant clinical implications and common differential diagnoses in routine diagnostic practice.

Keywords bladder; glandular; squamous

Introduction

A wide variety of squamous and glandular lesions can arise within the urinary bladder. This includes a range of non-neoplastic proliferations, potential precursor lesions and overtly malignant neoplasms. Many of these entities are uncommon and can cause diagnostic difficulty in routine practice. Awareness of non-neoplastic entities is important to avoid misdiagnosis while malignant lesions raise important differential diagnostic considerations with significant implications for clinical management. This review focuses on providing a broad overview of the spectrum of squamous and glandular lesions of the bladder including key morphologic features, relevant clinical implications and differential diagnoses.

Non-invasive squamous lesions

Non-papillary lesions

The spectrum of non-papillary squamous lesions encountered in the bladder includes flat squamous metaplasia, verrucous squamous hyperplasia and squamous dysplasia/carcinoma in situ (CIS).

Squamous metaplasia: when evaluating squamous metaplasia (SM) in the bladder, it is important to differentiate between non-keratinizing and keratinizing forms. Non-keratinizing SM is a common benign finding which is considered a normal variant in the trigonal region in women, occurring under hormonal influence. In contrast, keratinizing SM is more common in men and occurs in response to chronic irritation or inflammation. Histologically a layer of keratin, often with parakeratosis, overlies variably thickened squamous epithelium (Figure 1). Importantly, keratinizing SM has been associated with concurrent or subsequent development of malignancy in a subset of cases, particularly when extensive.[1,2] In biopsy/transurethral specimens, the presence of keratinizing SM and its extent should always be reported and these lesions should be carefully evaluated for the presence of dysplasia or CIS. Cystoscopic correlation and clinical follow-up is recommended.

Verrucous squamous hyperplasia: verrucous squamous hyperplasia is a rare lesion similar to its more common counterpart in the oral cavity. Histologically it is composed of keratinizing squamous epithelium arranged in distinctive tall undulating spikes which lack true fibrovascular cores. An association with invasive squamous cell carcinoma has been documented[2,3] and these lesions are treated similar to flat keratinizing SM requiring close clinical evaluation and follow-up. The architecture of this lesion can resemble the superficial component of verrucous carcinoma, however it lacks the broad tongues of invasion at the base characteristic of the latter.

Squamous dysplasia and carcinoma in situ (CIS): all squamous lesions should be carefully examined histologically for the presence of squamous dysplasia or CIS, particularly keratinizing lesions as outlined above. Squamous CIS demonstrates severe and generally full thickness atypia of squamous epithelium (Figure 1) and is a significant risk factor for the development of invasive disease. The term squamous dysplasia may be used for cases with a milder degree of atypia. Distinction from urothelial CIS requires identification of areas of keratinization, dyskeratosis or intercellular bridges characteristic of squamous differentiation, although in some cases these features may only be focally discernible. The base of these lesions should be carefully evaluated to exclude foci of superficial invasion. It is also worth noting that the epithelium overlying some invasive squamous carcinomas can have a deceptively bland appearance (Figure 2) and caution should be exercised when interpreting superficial biopsies of squamous lesions where the subepithelial stroma is not well represented.

Papillary lesions

Papillary squamous lesions of the bladder are rare. In addition to squamous papilloma and condyloma accuminatum, invasive squamous tumours can occasionally have a papillary exophytic component, however this distinction is usually readily made on the basis of frankly malignant cytologic features and associated invasive carcinoma.

Squamous papilloma: this is a very rare benign neoplasm composed of papillary cores lined exclusively by a layer of squamous epithelium. The presence of true fibrovascular cores differentiates papilloma from verrucous squamous hyperplasia while the absence of koilocytic atypia distinguishes it from condyloma.

Condyloma acuminatum: condyloma accuminatum is an HPV-related neoplasm that only rarely involves the bladder, usually in the setting of widespread condylomata elsewhere in the

Susan Prendeville *MB BCh BAO BMedSci FRCPath Consultant Histopathologist, Cork University Hospital, Cork, Ireland. Conflicts of interest: none declared.*

Please cite this article in press as: Prendeville S, Squamous and glandular lesions of the urinary bladder, Diagnostic Histopathology (2018), https://doi.org/10.1016/j.mpdhp.2018.05.005

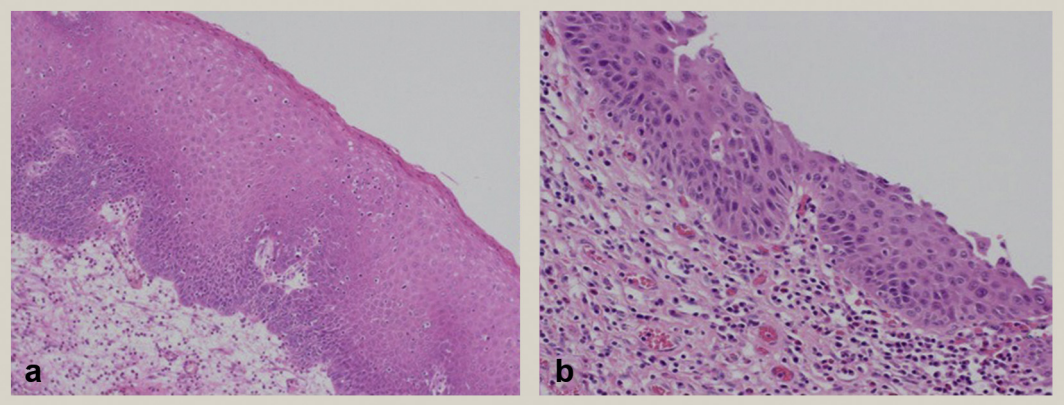

Figure 1 (**a**): Keratinising squamous metaplasia; (**b**): Squamous CIS.

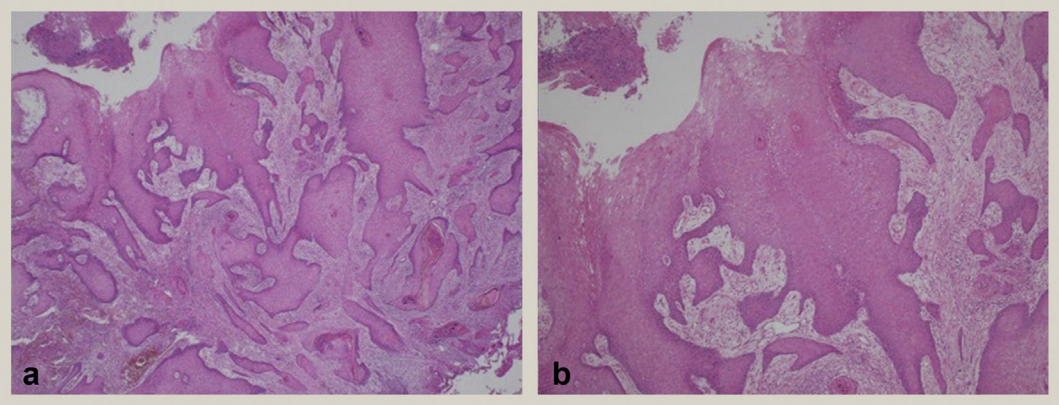

Figure 2 (**a**): Well differentiated invasive SCC, (**b**): Higher power showing bland squamous surface overlying invasion.

anogenital tract or immunosuppression. Histologically, they resemble condylomata at other sites comprising hyperplastic papillary squamous epithelium with koilocytic atypia. These lesions can be associated with invasive carcinoma and are prone to recurrence. The main differential is squamous papilloma, a benign lesion which lacks koilocytic atypia. In difficult cases, HPV analysis can be performed as this will be negative in squamous papilloma. Condyloma can also be confused with verrucous carcinoma, however it lacks the broad tongues of invasion at the base which are characteristic of the latter.

Invasive squamous cell carcinoma

Pure squamous cell carcinoma (SCC) refers to tumours that are entirely composed of malignant squamous elements and are uncommon, comprising <3% of all bladder carcinoma.[4] A major risk factor for the development of SCC is infection with *Schistosoma haematobium*, whereby deposition of Schistosome eggs provokes a severe granulomatous reaction which can lead to squamous metaplasia and carcinoma. In areas with a high prevalence of Schistosomal infection, including parts of Africa and Egypt, SCC is the most common bladder cancer subtype, although the incidence is decreasing with improved infection control. Other risk factors for the development of bladder SCC include smoking, developmental anomalies such as bladder exstrophy, neurogenic dysfunction and chronic irritation as may result from indwelling catheters and calculi. Macroscopically, bladder SCC often comprise large, necrotic masses and the presence of white friable material representing keratin is characteristic. Microscopically, bladder SCC is graded as well, moderate or poorly differentiated based on the degree of keratinization and nuclear pleomorphism, similar to SCC at other locations.

Verrucous carcinoma is a rare but distinctive subtype of SCC in the bladder, with the majority of cases arising in association with Schistosomal infection. The histologic features are similar to those of verrucous carcinoma at other locations. These are well differentiated by definition and comprise hyperkeratotic papillary or undulating projections with a 'pushing' type of invasion at the base comprising rounded, broad-based tongues of epithelium (Figure 3). They lack irregular, infiltrative nests of invasion and significant cytological atypia. The diagnosis of verrucous SCC should only be made in the absence of any component of conventional SCC and thus requires examination of the entire tumour. Prognosis is more favourable than conventional SCC.

Differential diagnosis of bladder SCC

The principal differential of bladder SCC is urothelial carcinoma (UC) with extensive squamous differentiation, a relatively common form of divergent differentiation in UC. This distinction is made on morphologic grounds following careful evaluation of the invasive

Please cite this article in press as: Prendeville S, Squamous and glandular lesions of the urinary bladder, Diagnostic Histopathology (2018), https://doi.org/10.1016/j.mpdhp.2018.05.005