Tumour-like lesions of the urinary bladder

Hemamali Samaratunga1,2, Brett Delahunt1,3, John Yaxley4, Lars Egevad5

1Aquesta Uropathology, Brisbane, Qld, Australia; 2University of Queensland, Brisbane, Qld, Australia; 3Department of Pathology and Molecular Medicine, Wellington School of Medicine and Health Sciences, University of Otago–Wellington, Wellington, New Zealand; 4Wesley Hospital, Brisbane, Qld, Australia; 5Department of Oncology-Pathology, Karolinska Institute, Stockholm, Sweden

Summary
There are a number of benign epithelial proliferations in the bladder that may be difficult to distinguish from carcinomas, including urothelial carcinoma and its variants, squamous cell carcinoma and adenocarcinoma. If misdiagnosed, there is the potential for over treatment, with its attendant risk of complications, as well as errors relating to prognostic assessment. In the case of the misdiagnosis of high grade proliferative lesions that mimic invasive carcinoma, unnecessary radical surgery, chemotherapy and radiotherapy may result. Similarly, the misdiagnosis of lesions that have the appearance of low grade carcinoma can prompt a lifetime of radiological investigation and cystoscopies. In this review, we discuss a variety of entities that may be diagnostically challenging and emphasise the importance of identifying key morphological features that have diagnostic utility. We also highlight the importance of relevant clinical information and the clinical settings in which these lesions may occur. In this review we have divided the lesions on the basis of morphology in order to facilitate discussion relating to the differential diagnosis. The architectural patterns we discuss include papillary lesions (polypoid/papillary cystitis and papillary urothelial hyperplasia), pseudocarcinomatous proliferations (pseudocarcinomatous urothelial hyperplasia, florid proliferation of von Brunn nests and fibroepithelial polyps), glandular lesions (intestinal metaplasia and müllerianosis) and lesions with several different patterns (prostatic type urethral polyps and nephrogenic adenoma or metaplasia).

Key words: Carcinoma-like lesions; urinary bladder; benign proliferations.

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INTRODUCTION
The urinary bladder is the site of a number of benign proliferative lesions that can mimic carcinoma.1,2 These are of varied aetiology and sometimes occur in recognised clinical settings. In some cases, there is evidence of iatrogenic causes such as instrumentation, chemotherapy or radiotherapy.3,4 In other cases, carcinoma-like lesions are encountered, without an apparent cause and in these instances the assignment of a correct diagnosis may be particularly problematic. A misdiagnosis of a benign lesion as cancer can result in unnecessary radical surgery and neoadjuvant or adjuvant chemotherapy or radiotherapy. For patients who are misdiagnosed as having low grade neoplasia, there is the possibility of unnecessary follow-up cystoscopies and/or radiological investigations over a protracted period.

Numerous benign lesions of the bladder may be mistaken for urothelial carcinoma (UC) or its variants, squamous cell carcinoma or adenocarcinoma and these may show a variety of architectural patterns. In general, it is useful to consider these lesions in terms of their dominant pattern which may, in combination with the clinical features of the case, assist in the diagnostic process. In this review we have divided lesions on the basis of their morphology into those with a papillary, pseudocarcinomatous or glandular architecture. We also discuss those lesions that exhibit more than one morphological pattern. Specifically, we describe the key diagnostic features for each of the lesions that may be mistaken for cancer, emphasise the morphological features that are of practical diagnostic value and consider the differential diagnosis for each entity.

PAPILLARY LESIONS
Polypoid/papillary cystitis
Polypoid/papillary cystitis is a reactive proliferative lesion of the urinary bladder, being relatively commonly encountered in routine practice. These lesions are most frequently associated with catheterisation, the presence of stents or previous instrumentation. Additionally, bladder irritation or injury from calculi, urinary outflow obstruction, colovesical fistulae, radiation, ischaemia and pelvic inflammatory conditions can also result in the development of polypoid cystitis.5,6,7 While the clinical features often provide an important clue as to the diagnosis, on occasion no precipitating cause may be apparent.8

Polypoid cystitis can occur at any age and has been reported in neonates.9 It is more common in males and patients can present with haematuria or voiding dysfunction. Lesions may also be discovered incidentally at cystoscopy, particularly on follow-up after treatment for prostate or bladder cancer.5,6,7,10 The papillary and polypoid architecture, typical of these lesions, results from inflammation and oedema in the
and in most cases, the cystoscopic impression is that of a reactive proliferative lesion. Despite this, on rare occasions, the features may be suspicious for a neoplastic process on cystoscopy.\textsuperscript{6,10}

Grossly, the lesions are usually polypoid or papillary. They can appear as grossly oedematous bullous polyps in the bladder and may extend into the prostate and vesico-ureteric junction.\textsuperscript{8} Lesions may be large and individual polyps >6 cm in maximum extent have been reported.\textsuperscript{8} There is typically a simple, non-branching papillary architecture, although early branching may occur rarely. Prominent oedema of the lamina propria is present, particularly in early cases and this is labelled polypoid cystitis, whereas in long standing cases, fibrosis is prominent and the term papillary cystitis is preferred. The base of the papillae is typically broad, but these can be interspersed with narrow papillae. The overlying urothelium is usually of normal thickness but can be focally or diffusely thickened. Inflammatory changes, ranging from active chronic inflammation to chronic inflammation, are present in many cases and can be mild to moderately severe (Fig. 1A–D). The urothelium can display reactive atypia. Mitotic figures are seen in some cases and may be numerous.\textsuperscript{6,10}

Papillary structures with a urothelial lining can suggest the possibility of a urothelial neoplasm, including urothelial carcinoma. In contrast to urothelial neoplasms, these are stromal based proliferations with prominent stromal oedema or fibrosis, inflammation and predominantly simple non-branching, broad based papillae. In urothelial neoplasms the papillae are often complex and branching, with narrow necked, thin, delicate fibrovascular cores and often thickened urothelium. Oedema and inflammation are only rarely found in these papillary structures. Focal or diffuse urothelial thickening with atypia can, in some cases, add to the difficulty in differentiating polypoid cystitis from papillary urothelial neoplasms. In one series, 26% of consultation cases of polypoid cystitis had been originally diagnosed as papillary urothelial neoplasms and these diagnoses included low grade and high grade carcinomas, as well as papillary urothelial neoplasms of low malignant potential.\textsuperscript{11} Polypoid/papillary pyelitis, ureteritis and urethritis can be particularly challenging to distinguish from urothelial neoplasia, due to the small size of the biopsies that are often obtained from these locations.

The diagnosis should be based on examination at low magnification, at which the prominent stromal nature and the presence of oedema can be appreciated. Narrow papillae are in the minority and often there is inflammation. Also, if atypia is present it is reactive in type with uniform nuclear enlargement and prominent nucleoli. Sometimes the clinical findings, the knowledge of causative factors such as catheterisation, cystoscopic findings and the urologist’s gross findings provide clues as to the correct diagnosis. These are benign lesions with no malignant potential.\textsuperscript{2,3,6} Local mucosal resection/curettage of the lesion and removal of the cause are curative.

**Papillary urothelial hyperplasia/urothelial proliferation of uncertain malignant potential**

Papillary urothelial hyperplasia is a morphologically distinct papillary urothelial proliferation, first reported in 1975\textsuperscript{12} and

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Fig. 1 Polypoid cystitis. (A–D) Simple, non-branching papillary architecture, with broad oedematous stromal cores displaying inflammatory changes. The overlying urothelium is focally thickened and displays reactive changes.
mucosa has also been reported.\textsuperscript{13,14} Histologically, there is undulating urothelium forming narrow or broad mucosal papillary structures, covered by thickened urothelium with intact polarity and displaying no significant atypia or inflammation. Papillae show a parallel arrangement and can be of varying heights (Fig. 2A,B). There are no well-formed arborising papillary fronds and dilated blood vessels are often seen at the base of the papillae.\textsuperscript{13–15} These lesions can be multifocal. In the 2004 World Health Organization (WHO) Classification these lesions are labelled as papillary urothelial hyperplasia,\textsuperscript{15} while in the 2016 WHO blue book, this lesion, in addition to flat urothelial hyperplasia, has been classified as urothelial proliferation of uncertain malignant potential (UPUMP).\textsuperscript{16} In reported series, UPUMP detected at follow-up cystoscopy for pre-existing urothelial neoplasia, has been found to have a high risk of developing subsequent urothelial neoplasia, while this risk is much lower in cases without a prior history of urothelial neoplasia. This is not surprising as patients with prior urothelial neoplasia already have a higher risk of subsequent urothelial neoplasia, even without papillary urothelial hyperplasia,\textsuperscript{17} hence the necessity to follow up these patients.

In a study by Readal and Epstein,\textsuperscript{14} 30 of 53 cases of papillary urothelial hyperplasia had a prior history of urothelial neoplasia. The 5-year actuarial risk for development of urothelial neoplasia was almost 50% in patients with a prior history of urothelial neoplasia and 27% in those without. In a study of UPUMP (papillary and flat urothelial hyperplasia) from 68 patients, including 26 patients with de novo lesions, the risk of subsequent neoplasia was 15.4% compared with 40% in patients with prior neoplasia.\textsuperscript{18} This study showed that the greatest risk of progression was in those with papillary architecture. Some studies have suggested that a number of cases of papillary urothelial hyperplasia, predominantly those with a prior history of urothelial neoplasia, are clonal proliferations with frequent genetic alterations.\textsuperscript{19,20} Chow et al.\textsuperscript{19} examined 15 foci of papillary urothelial hyperplasia from seven patients and found loss of heterozygosity (LOH) of at least one microsatellite marker in 53% of lesions. The most frequent loss was on chromosome 9q (4/15), which is thought to be one of the earliest events of urothelial tumourigenesis.\textsuperscript{19} Hartmann et al.\textsuperscript{20} examined 31 biopsies from 12 patients with urothelial hyperplasia and superficial papillary tumours. Deletions of chromosome 9 were seen in 70% of hyperplasias, with similar genetic changes being present in adjacent papillary tumours in most cases. Interestingly, six of 12 samples of microdissected normal urothelium also showed genetic alterations on chromosome 9. Despite the varying risk of the subsequent development of neoplasia, this lesion cannot be considered a carcinoma because, by itself, it has no propensity to invade and metastasise and for this reason it is included here as a carcinoma-like lesion.

Papillary urothelial neoplasms, in contrast to papillary urothelial hyperplasia, display well developed, branching, complex papillae with arborisation with cellular features indicating a tumour of low malignant potential or low grade or high grade urothelial carcinoma.\textsuperscript{10} There are papillary lesions with the architectural pattern of papillary hyperplasia, but with the overlying urothelium demonstrating varying degrees of atypia. These should be considered carcinoma in situ or dysplasia with early papillary formation and must be distinguished from papillary urothelial hyperplasia without atypia.\textsuperscript{21,22}

**PSEUDOCARCINOMATOUS PROLIFERATIONS**

**Pseudocarcinomatous urothelial hyperplasia**

Pseudocarcinomatous urothelial hyperplasia of the bladder is a proliferative lesion in which ischaemia appears to be a major contributing factor.\textsuperscript{4,23–26} Many patients have a history of previous pelvic irradiation, while there can also be a past history of systemic or intravesical chemotherapy.\textsuperscript{23,24,27} Some patients have associated peripheral vascular disease, vascular malformations in the bladder, or a history of prior radical prostatectomy or indwelling catheters.\textsuperscript{25} Males are more commonly affected, with an age range of 42–81 years. For lesions that develop following radiation these most commonly occur within 2 years, but have been reported many years after radiation. Patients present with gross haematuria and on cystoscopy most have polyoid lesions with prominent oedema and haemorrhage of the bladder mucosa.

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Fig. 2 Papillary urothelial hyperplasia. (A–B) Undulating urothelium forming narrow mucosal papillary structures, covered by urothelium with intact polarity and displaying no atypia or inflammation. Papillae show a parallel arrangement and contain delicate blood vessels.
The extent of epithelial proliferation varies, with some cases displaying many small nests having rounded or irregular borders with an infiltrative growth pattern within the lamina propria. These cells have prominent eosinophilic cytoplasm, variable nuclear atypia, with some cases displaying prominent nuclear pleomorphism, rare mitoses and prominent nucleoli. Epithelial proliferation occurs in a background of dilated vascular channels with extensive haemorrhage, oedema, fibrin deposition and fibrin thrombi. Acute and chronic inflammation, ulceration, as well as haemosiderin deposits are often seen. Radiation associated epithelial and stromal changes, including vascular ectasia and the presence of atypical fibroblasts, have also been described (Fig. 3A–D).

Proliferative nests of urothelial cells within the lamina propria, particularly with nuclear pleomorphism and prominent nucleoli can suggest invasive UC. Abundant stromal haemorrhage, fibrin, haemosiderin, inflammation and oedema, associated with ectatic blood vessels, are striking in these cases and this contrasts with a neoplastic process. A very useful finding is the intimate association between urothelial nests and prominent dilated blood vessels, often containing fibrin thrombi. Nests of urothelial cells wrapping around blood vessels are a characteristic feature of pseudocarcinomatous hyperplasia (Fig. 3D). The nuclear atypia appears to be degenerative in type. This lacks hyperchromasia, which contrasts with the prominent pleomorphism and hyperchromasia found in invasive high grade UC. Cases with limited atypia need to be differentiated from the nested variant of UC which shows closely packed small nests of bland urothelial cells. Pseudocarcinomatous hyperplasia has not been known to involve muscularis propria, whereas the nested variant of UC is frequently invasive. Nested UC usually exhibits significant atypia focally and does not show urothelial nests encircling blood vessels with extravasated fibrin.

In some long standing cases, stromal fibrosis may be seen, with radiation associated epithelial and stromal changes. In these cases, there can be severe nuclear pleomorphism, hyperchromasia and abundant cytoplasm, sometimes with prominent nucleoli, raising the possibility of squamous cell carcinoma. However, the presence of a low nuclear to cytoplasmic ratio, smudged nuclear chromatin, prominent cytoplasmic and nuclear vacuolisation, radiation induced stromal and vascular hyalinisation, and atypical stromal fibroblasts can be helpful in differentiating these lesions from squamous cell carcinoma.

There is no evidence that these lesions predispose to subsequent invasive carcinoma in the short term, with reported follow-up limited to 3 years. Clearly, longer follow up is

![Fig. 3](https://example.com/fig3.png)
necessary to ascertain if there is a long term risk of malignancy. On follow-up cystoscopy normal bladder mucosa has been found, although in some cases there was inflammation and scarring.

**Florid proliferation of von Brunn nests**

Although common in the urinary tract, on occasion von Brunn nests may display florid proliferations extending deeply into the lamina propria mimicking UC. These lesions have been associated with a wide range of ages (2–83 years), with both sexes affected equally. These proliferative lesions can occur anywhere in the urinary tract, with haematuria being the most common presenting feature. Rarely, urinary tract obstruction may be encountered and cystoscopy may give the impression of a tumour. Florid von Brunn nests in the bladder are composed of large crowded nests of urothelial cells. In contrast, those in the upper urinary tract are smaller and more unevenly spaced. Importantly both these lesions extend to the same horizontal level at the base of the proliferation (Fig. 4A–C). Although most cases have rounded nests, which are situated superficially in the lamina propria, some may have irregular contours and extend more deeply into the lamina propria. These proliferative lesions often show cystitis glandularis and cystitis cystica, but significant atypia is not seen. In cases with focal atypia this is reactive in type and occasionally prominent nucleoli and mitoses may also be present. The stroma is loose connective tissue.

The presence of crowded nests of urothelial cells extending deeply into the lamina propria can suggest the possibility of a low grade urothelial neoplasm displaying a largely endophytic growth pattern. Fragmentation or unraveling of the lesion can result in papillae-like structures further adding to the problem (Fig. 4D). The absence of urothelial cellular enlargement and significant atypia within a lesion which has a flat non-infiltrative base can help with this differentiation. This lesion can also mimic nested variant of UC which is cytologically bland. Nested UC lacks mitotic activity and a stromal reaction in the superficial part of the tumour. For these reasons it is difficult to diagnose nested UC in superficial mucosal biopsies, when the deep part of the lesion cannot be observed. In contrast to florid von Brunn nests which have crowded, evenly spaced nests with a flat non-infiltrative base and no involvement of muscularis propria, the nested variant of UC has smaller nests, with an infiltrative base often extending into the muscularis propria. These nests display a haphazard proliferation; this feature, together with smaller nests displaying confluence, help to alert to the possibility of the nested variant and repeat biopsy is recommended. Cyst formation, apical glandular differentiation and eosinophilic secretions are also more common in florid von Brunn nests. While focal significant atypia is seen in the nested variant of UC, florid von Brunn nests display no atypia or only reactive atypia. Given that von Brunn nests in the upper urinary tract are smaller and unevenly spaced when compared with those in the bladder, the diagnosis of nested

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**Fig. 4** Florid von Brunn nests. (A–D) There are large crowded rounded nests of urothelial cells located superficially in the lamina propria. No significant atypia is seen. (D) Fragmentation or unravelling of the lesion resulting in papillae-like structures.
variant of UC should not be made on a small biopsy of the upper tract.28

von Brunn nests can also mimic the large nested variant of UC.31 In comparison to crowded smooth contoured von Brunn nests, the large nested variant has variably sized and haphazardly shaped infiltrating nests with abundant intervenering stroma. These also display some cytological atypia and in contrast to von Brunn nests often involve the muscularis propria. Expression of p53, p27, cytokeratin 20 and MIB-1 is highly variable and not useful in routine practice in differentiating between these two lesions.28 Polymerase chain reaction (PCR) and sequencing have shown that up to 85% of cases of nested variant of UC display TERT promoter mutations, while no such mutation was found in any benign mimics, including five cases of von Brunn nests.32 These lesions do not display any malignant potential.

Fibroepithelial polyps

Fibroepithelial polyps of the urinary tract are non-neoplastic lesions most frequently located in the ureter or renal pelvis (87%) with the remainder occurring in the bladder and urethra. Another half of reported cases occur in neonates and children, some of which are associated with urogenital malformations. In adults, these lesions occur more commonly in males.34–36 Clinical symptoms include haematuria, urinary urgency, urinary hesitancy, dysuria, enuresis and flank pain. Some cases are asymptomatic with lesions discovered incidentally. Fibroepithelial polyps occasionally display a striking epithelial proliferation mimicking cancer.2 On cystoscopy, solitary exophytic polypoid lesions are seen, while the remainder of the bladder appears relatively normal.36 Although most lesions are small (<3 cm), rare giant polyps up to 15 cm in maximum extent have been reported.37 Polyps are lined by normal urothelium or columnar epithelium and in some cases there can be prominent epithelial proliferation. Club-like protrusions into the stroma may be present and these can show cystitis glandularis and cystica. In other cases these lesions can be papillary with numerous rounded fibrovascular structures containing dense fibrovascular cores. Some cases have tall papillary structures protruding from polypoid lesions. The stroma is typically fibrotic and can contain degenerative type atypical stromal cells. These lesions lack prominent oedema and inflammation.3,34

In a small biopsy, fibroepithelial polyps can be mistaken for other benign entities such as polypoid cystitis, papilloma and inverted papilloma.2,34–36 The cystoscopic appearance of a single exophytic mass, with absence of prominent oedema and inflammation and relatively normal background bladder mucosa help differentiate this lesion from polypoid cystitis. Fibroepithelial polyps with long papillary structures can be mistaken for a urothelial papilloma. The urothelium appears normal in both. Papillomas have branching papillary structures with thin delicate stromal cores in contrast to fibroepithelial polyps, which have broad based stromal cores protruding from a single exophytic mass. In contrast to inverted papilloma with uniform invaginated cords, fibroepithelial polyps have club-like invaginations resembling a cloverleaf, often displaying cystitis glandularis/cystica.

The presence of atypical stromal fibroblasts in a polypoid lesion, particularly in children and rarely even in adults, can suggest a malignant mesenchymal neoplasm such as a botryoid rhabdomyosarcoma.37,38 However, the atypia in the cells of fibroepithelial polyps is degenerative in type with smudged chromatin and should not lead to confusion. Rarely, in a small biopsy, the nested variant of UC can enter into the differential diagnosis. A monotonous urothelial proliferation with the cloverleaf pattern of a fibroepithelial polyp contrasts with small haphazardly arrayed nests displaying confluence and focal prominent atypia in the nested variant of UC. The fibrotic stroma with atypical stromal fibroblasts seen in fibroepithelial polyps is not a finding in the nested variant of UC. A high prevalence of fibroepithelial polyps has been reported in families with pleuropulmonary blastoma.38 Recently, a DICER1-positive giant fibroepithelial polyp of the urinary bladder in an adult has been reported.38 These lesions usually do not recur and local resection is curative.

GLANDULAR LESIONS

Intestinal metaplasia (cystitis glandularis of intestinal type)

A spectrum of glandular metaplastic lesions including cystitis glandularis, cystitis cystica and intestinal metaplasia, also known as cystitis glandularis of the intestinal type, have been described in the bladder. These usually result from long standing inflammation or irritation as seen in patients with neurogenic bladder, long term catheterisation or calculi. Metaplasia occurs in adults with a mean age of 57, with ages ranging from 23 to 81 years in one series.39 These lesions are more commonly found in males and patients may present with haematuria, mucusuria, dysuria, urgency or obstructive symptoms. Cystitis glandularis may be focal or diffuse. Diffuse large lesions can produce abundant mucin which can dissect the stroma, even extending into muscularis propria.40–42 and cystoscopic and radiological appearances may suggest a malignant tumour.2,41 These lesions have a predilection for the bladder neck and trigone. Grossly intestinal metaplasia may be flat and inconspicuous or produce nodules, papillary lesions or gelatinous tumour-like masses. Histologically, there are numerous glands and cysts lined by tall columnar cells with abundant intracytoplasmic mucin, resembling intestinal type epithelium. Atypia is usually absent (Fig. 5A,B), although in some cases focal mild cytological atypia, rare mitoses, extensive lamina propria involvement, focal muscularis propria involvement and abundant stromal mucin may be seen. Intestinal metaplasia commonly expresses nuclear staining for CDX2, in contrast to typical cystitis glandularis, which is negative. CK20 immunostaining is also commonly seen, but CK7 expression is rarely observed in intestinal metaplasia. This contrasts with typical cystitis glandularis, where CK7 positivity is found in almost all cases, while CK20 expression is rare. Hep is negative in both of these lesions.36 The mucin core proteins in intestinal metaplasia have been shown to be MUC5AC and MUC2, with absence of MUC1 and CD10 expression seen in typical cystitis glandularis and normal urothelium, suggesting an incomplete form of urinary bladder metaplasia.43

In some cases, it may be difficult to differentiate widespread intestinal metaplasia from mucinous adenocarcinoma, particularly if there is abundant extravasated stromal mucin (Fig. 5C,D). In contrast to adenocarcinoma, intestinal metaplasia does not display significant atypia, frequent mitoses, free floating epithelial elements, signet ring cells or necrosis. The amount of dissecting mucin and depth of extension into
the bladder wall is generally less than that seen in adenocarcinoma.\textsuperscript{40–42} It is unclear if intestinal metaplasia has the potential to progress to malignancy. One study found significant telomere length shortening, suggesting that it is a precursor of invasive adenocarcinoma.\textsuperscript{45} A recent study also found mutation of genes commonly associated with colonic cancer in a minority of cases of intestinal metaplasia examined, suggesting malignant potential.\textsuperscript{46} However, it has also been shown that cystitis glandularis and intestinal metaplasia occur as frequently in benign bladders as in bladders with adenocarcinoma. There was no evidence that the presence of these lesions increases the subsequent risk of malignancy.\textsuperscript{47} This was supported by a study of 53 cases with long term follow-up, in which none of the patients developed adenocarcinoma of the bladder.\textsuperscript{48} In apparent contradiction of this, a recent study found concurrent adenocarcinoma in a significant proportion of cases of intestinal metaplasia with dysplasia.\textsuperscript{49} While this does not prove that intestinal metaplasia with dysplasia is a risk factor for development of subsequent carcinoma, given a reported association with carcinoma, patients with this lesion should be closely followed up.

Müllerianosis

Müllerianosis of the bladder is defined as the presence of two or more of müllerian-type tissues of endometriosis, endosalpingiosis or endocervicosis within the bladder wall.\textsuperscript{50,51} An ectopic or metaplastic origin for this entity has been postulated. Endometriosis of the bladder is relatively common, with bladder involvement in approximately 1% of women with endometriosis. Interestingly a history of pelvic surgery has been reported in 50% of cases of bladder endometriosis.\textsuperscript{2,50–53} In approximately 12% of cases, extravesical endometriosis is not present. Endocervicosis of the bladder is a very rare tumour-like lesion and less than 30 cases have been reported to date.\textsuperscript{54–57} Müllerianosis occurs in females of child bearing age with an reported age range of 28–55 years. It is not seen in males. The presenting features are usually haematuria, dysuria and pelvic pain, which may or may not coincide with menstruation.\textsuperscript{50–52} Radiologically, a polypoid mass may be found.

Grossly, polypoid or nodular masses are present and these are typically seen in the dome or posterior wall of the bladder. Histologically the lesion consists of glands, cysts and tubules lined by endocervical, tubal epithelium or endometrial epithelium that extend into the lamina propria and muscularis propria. Sometimes there is typical endometrial stroma. Urothelium may be seen associated with müllerian tissue.\textsuperscript{50–52} Endocervicosis is characterised by tumour-like collections of glands which may produce a mass up to 5 cm in size.\textsuperscript{54} Glands are lined by columnar mucinous cells resembling endocervical glands. Some are cystically dilated and the lining can display mild atypia. There can also be

\begin{figure}[h]
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\caption{Intestinal metaplasia. (A–D) Numerous glands lined by tall columnar cells with abundant intracytoplasmic mucin, resembling intestinal type epithelium. There is no atypia. Gland rupture and extravasated stromal mucin displays no free floating epithelial elements, signet ring cells or necrosis.}
\end{figure}
haphazard proliferation of these glands with rupture causing extravasation of mucin. Immunoexpression of AE1/AE3, CAM 5.2, cytokeratin (CK) 7, CK19, HBME-1, CA125, and carcinoembryonic antigen, have been shown while the stromal cells are positive for oestrogen and progesterone receptors as well as CD10.54–57

The histological identification of endometrial glands and stroma, and ciliated tubal epithelium is not usually problematic. On occasion a lesion composed largely of endocervical glands can be extensive within the posterior wall and dome, and if composed of haphazardly arrayed irregular glands lined by mucinous epithelium, may suggest adenocarcinoma, particularly of urachal type. A location in the dome is common to both lesions and some cases of müllerianosis may even display reactive atypia and mucin extravasation. In contrast to adenocarcinoma, in endocervicosis there is no overt infiltration, significant atypia, mitoses or desmoplastic stromal reaction, and no free floating epithelium within stromal mucin. Identification of other müllerian components can be very helpful in the diagnosis. Treatment is transurethral resection of the lesion and/or hormonal ablation. Rare cases of carcinoma of endometrioid or clear cell type have been reported in association with bladder endometriosis.54

**Fig. 6** Prostatic-type urethral polyp. (A–B) Polyp has a rounded surface with stromal glandular structures. (C,D). Polyp showing delicate papillae with fibrovascular stromal cores. The glands and papillae are lined by two layers of benign prostatic-type epithelium with bland nuclei. Significant atypia is not seen.

**LESIONS WITH MORE THAN ONE PATTERN**

**Prostatic-type urethral polyps**

Prostatic-type urethral polyps are benign lesions which occur most commonly in the prostatic urethra but can also occur in the bladder, including the ureteric orifices and the bulbar urethra. These polyps occur in males in a reported age range of 13–84 years. Presentation can be with gross or microscopic haematuria, or obstructive voiding symptoms. Most are found incidentally on radiological investigation or on cystoscopy as a papillary or frond-like lesion and may resemble a neoplasm.58–61

Prostatic-type urethral polyps are often small, usually less than 1 cm in size, and are either single or multiple. They typically have a smooth surface with stromal glandular structures. Sometimes, the surface of these polyps shows delicate papillae with fibrovascular stromal cores. Both the glands and papillae are lined by two layers of benign prostatic-type epithelium with bland nuclei (Fig. 6A–D). Significant atypia is not a feature, although if ulceration or inflammation is present, there can be a reactive atypia with uniform nuclear enlargement and prominent nucleoli.62,63

Prostatic ductal adenocarcinoma arising from the prostatic urethra or the periurethral large ducts can mimic urethral or
bladder polyps clinically and cystoscopically. These lesions are often papillary. In ductal adenocarcinoma, there is typically severe atypia with prominent nuclear pleomorphism, hyperchromasia, pseudostratification and frequent mitotic figures. However, in some cases of ductal adenocarcinoma, nuclear atypia is not so pronounced and distinguishing this from a prostatic-type polyp can be difficult histologically. In one study three of eight cases of ductal adenocarcinoma had been initially reported as benign prostatic type urethral polyps. Ductal adenocarcinoma shows some nuclear enlargement and elongation, pseudostratification and at least mild to moderate atypia. Conversely prostatic urethral polyps have normal prostatic epithelium with round nuclei and no neoplastic-type atypia. Basal cell immunostaining may not be helpful as these may be retained in periurethral ductal cancers. Somewhat helpfully, a continuous layer of basal cells is more likely to be present in a benign urethral polyp. Race-mase immunostaining can also be useful as benign polyps are typically not positive. Assessment of the Ki-67 index may assist in differentiating between these two lesions as it is significantly higher in ductal adenocarcinoma (21–35% in ductal adenocarcinoma vs 2–5% in benign prostatic urethral polyps). Prostatic-type urethral polyps are reactive hyperplastic or metaplastic lesions and simple resection is curative.

Nephrogenic adenoma (metaplasia)

Nephrogenic adenoma or metaplasia is a commonly occurring reactive proliferative lesion associated with urothelial injury such as surgery, instrumentation, calculi, infection or trauma. Some cases are associated with renal transplantation. This lesion occurs in children and adults at any age and is more commonly seen in males. Nephrogenic adenoma may be seen in any part of urinary tract lined by urothelium, including bulbar and prostatic urethra and ureter, although most occur in the bladder. Cases occurring in diverticulae have also been reported. Most are found incidentally in biopsies or transurethral resections, although some present with haematuria, frequency or dysuria.

Grossly, nephrogenic adenoma can be papillary, polypoid or flat and velvety. Most measure less than 1 cm in size but can rarely be as large as 7 cm and can be multifocal. These can display a variety of histological patterns and mixed patterns are characteristic. Tubules and papillary structures lined by columnar or cuboidal cells, some with a hobnail

![Fig. 7 Nephrogenic adenoma (metaplasia).](image)
appearance, are the most common pattern. Cysts and dilated vascular-like tubules, lined by flattened, cuboidal or hobnail cells, are also seen. These cells have pale to dense eosinophilic cytoplasm and bland nuclei (Fig. 7A–C). Degenerative type nuclear atypia may be seen but mitoses are very rare. Unusual features include the presence of signet ring-like cells and clear cells arranged in a focally solid pattern. Collloid-like eosinophilic or basophilic secretions within the lumina and peritubular thickened hyalised basement membrane may be seen. Stroma is typically oedematous, highly vascular and inflamed. These lesions may appear invasive and can involve the superficial muscularis propria. 

Some cases of nephrogenic adenoma display a tubular or glandular pattern, sometimes with single cells and signet ring-like cells that can be mistaken for adenocarcinoma of the bladder or prostate. Prominent nuclear atypia in some of these cases can also be problematic. The glandular lining of a single cell layer with prominent nuclei and blue mucin also suggests prostatic adenocarcinoma (Fig. 7D). Although some can focally involve muscularis propria these are usually relatively superficial. The presence of other patterns of nephrogenic adenoma, the typical vascularised inflamed and oedematous stroma, degenerative type nuclear atypia and peritubular thickened hyalised basement membrane present in some cases help differentiate these lesions from adenocarcinoma. Mucin is positive for PAS with focal staining for mucicarmine. These tumours usually stain negatively for PSA and PSAP, but are rarely weakly immunoreactive for these markers and can be positive for 2-methylacyl-CoA-racemase (AMACR). Only some cases display immunoreactivity for p63 and 34BE12. Therefore, these lesions can mimic prostatic adenocarcinoma, not only histologically, but also immunophenotypically. These lesions can be positive for PAX2 and PAX8, similar to renal tubular epithelium, showing this to be a possible tissue of origin in some cases. S100A1 typically shows strong diffuse immunostaining.

Fibromyxoid nephrogenic adenoma is a recently described pattern. This is composed of spindle cells within a fibromyxoid background, with only rare tubules and cord-like structures. Mild nuclear atypia with small nuclei and clear pseudoinclusions are seen in some cases.

The presence of solid aggregates of clear cells and hobnailed cells in nephrogenic adenomas may suggest clear cell adenocarcinoma of the bladder. In contrast to clear cell adenocarcinoma, nephrogenic adenomas are smaller, not deeply invasive and lack a conspicuous solid growth pattern, prominent cytological atypia or frequent mitoses. Often there are other patterns of nephrogenic adenoma present. The characteristic mixed pattern and oedematous inflamed stroma also help identify nephrogenic adenoma. Both lesions are frequently positive for PAX2, PAX8, and CK7 and not infrequently positive for AMACR, so these do not help in differentiation. The Ki-67 index is markedly different, with the reported rate in clear cell adenocarcinomas ranging from 10% to 80% compared with 0%–5% in nephrogenic adenoma. Differentiation is even more difficult with the recently described nephrogenic adenoma-like clear cell adenocarcinoma which, in comparison with typical clear cell adenocarcinoma, has a less prominent solid pattern, pleomorphism, prominent nuclei, predominance of clear cytoplasm and necrosis. In these cases the features that differ from nephrogenic adenoma include more prominent pleomorphism with enlarged hyperchromatic nuclei, mitoses, extensive muscle invasion and a high rate of Ki-67 expression.

The nested variant of UC can have cysts and tubules and nephrogenic adenoma can be mistaken for this lesion in a superficial biopsy. The typical mixed pattern, including tubular, papillary and vascular-like dilated structures and the absence of deep muscle involvement, are useful in differentiating these lesions. A recent study found that the nested variant of urothelial carcinoma can be PAX8 positive. Therefore this immunostain is not useful in distinguishing this lesion from nephrogenic metaplasia. A mimic of the fibromyxoid variant of nephrogenic adenoma is UC with abundant myxoid stroma. The presence of other patterns typical of nephrogenic adenoma, peritubular hyaline basal lamina and the absence of prominent cellular atypia and mitotic activity are useful differentiating features.

Nephrogenic adenomas are benign. Recurrence is not uncommon, being seen in about one third of cases. Although some cases have been reported to be concurrent with bladder urothelial cancer, there is no evidence that this lesion predisposes to carcinoma. There is also no convincing evidence that these progress to clear cell adenocarcinoma, which occurs more commonly in the urethra and in women, in comparison to nephrogenic adenomas which occur more commonly in the bladder and in males. Also nephrogenic adenoma is a common lesion compared with the extremely rare clear cell adenocarcinoma of the urinary tract.

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**Address for correspondence:** Prof Hemamali Samaratunga, Aquesta Uropathology, 21 Lisnon Street, Toowong, Qld 4066, Australia. E-mail: hema@aquesta.com.au

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