Bladder Pathology

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List of Frequently Asked Questions

What Are the Most Common Presenting Symptoms of Bladder Cancer?

The most common presentation is painless gross hematuria, followed by urgency, nocturia, and dysuria. If a tumor is present at the bladder neck, irritative urinary symptoms may be prominent. Obstructive symptoms or palpable mass can be found in advanced and severe disease. Rarely, in patients who present with metastatic disease, weight loss, and bone pain can be the initial symptoms [1].

What Are the Two Pathogenetic Pathways and Molecular Aberrations in Urothelial Carcinoma?

Hyperplasia and dysplasia are the two essentially mutually exclusive pathogenetic pathways in neoplastic transformation of urothelium. The hyperplasia pathway is characterized by molecular abnormalities in fibroblast growth factor receptor 3 (FGFR3) gene, whereas the dysplasia pathway is characterized by abnormalities in *TP53* gene. Approximately 80% of urothelial carcinoma cases originate from abnormalities in the hyperplasia pathway, which start with urothelial hyperplasia and progress to low-grade papillary urothelial carcinoma. The abnormalities in the dysplasia pathway, however, account for about 20% of urothelial carcinoma cases, starting with dysplasia and progressing to high-grade papillary urothelial carcinoma, urothelial carcinoma in situ, and invasive urothelial carcinoma [2].

What Are the Roles of Cytology in the Diagnosis of Bladder Cancer?

Urine cytology has been used for many years as a tool to screen, diagnose, and monitor bladder cancer. Urine cytology findings allow cytopathologists to identify patients with increased risks of malignancy, and clinicians to choose management options accordingly.

Ancillary studies can be performed on urinary cytology specimens. These studies can be either cell or liquid based. The two commonly used, and FDA-approved cell-based studies are UroVysion (Abbott Laboratories, Abbott Park, IL, USA) and ImmunoCyt/UCyt+ (Diagnocure Inc., Quebec, Canada). UroVysion is a fluorescence in situ hybridization (FISH)-based test that detects numerical and structural abnormalities of chromosomes preferentially seen in urothelial carcinoma, whereas ImmunoCyt/UCyt+, as indicated by the name, is an immunofluorescence-based test at protein expression level. Examples of liquid-based studies are bladder tumor antigen and nuclear matrix protein 22 (NMP22), both of which are dipstick-based tests that can be performed in urologist clinics [3, 4].

What Are the Diagnostic Categories of Urine Cytology?

Diagnostic categories of urine cytology are standard terminologies that label cytology cases based on predefined morphologic criteria. These diagnostic categories distinguish from each other by the likelihood of malignancy and enable clinicians to choose the optimal management options based

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on risk and benefit assessment for individual patients. Prior to the Paris System for Reporting Urinary Cytology, several urine cytology classifications have been proposed and used. These classifications differ in diagnostic categories, diagnostic criteria, and terminology, which have caused inconsistency in reporting and confusion during communication among cytopathologists and clinicians.

The Paris System for Reporting Urinary Cytology is currently recommended by the International Academy of Cytology and the American Society of Cytopathology to report urine cytology. It is evidence and consensus based, incorporates the current understanding on the two pathogenetic pathways in neoplastic transformation of urothelium, acknowledges the suboptimal diagnostic sensitivity of urinary cytology on low-grade urothelial lesions, standardizes the terminology for reporting urinary cytology, and provides "Bethesda" type reference images illustrating definitions and diagnostic criteria for categories [4, 5].

What Are the Categories of Urine Cytology Recommended by the Paris System?

The categories of urine cytology defined in the Paris System are as follows:

- Adequacy.
- Negative for high-grade urothelial carcinoma.
- Atypical urothelial cells.
- Suspicious for high-grade urothelial carcinoma.
- High-grade urothelial carcinoma.
- Low-grade urothelial neoplasm.
- Other malignancies, both primary and secondary [5].

How Can We Distinguish Polypoid/Papillary Cystitis and Papillary Urothelial Carcinoma?

Polypoid/papillary cystitis is an inflammatory/reactive process that may have a similar cystoscopic finding as a papillary urothelial neoplasm. Histologically, it shows a broad frond and is lined by urothelial cells of normal thickness (Fig. 3.1a). Reactive epithelial changes associated with mixed inflammation are normally found (Fig. 3.1b). There may be mild cytologic atypia with uniform nuclear enlargement or small nucleoli. In contrast, papillary urothelial neoplasms have well formed, delicate to complex papillary architecture (Fig. 3.1c), and the cell linings are often markedly thickened and show mild to severe cytologic atypia (Fig. 3.1d). Although inflammatory background can be found in both lesions, it is much more frequently seen and more prominent in polypoid/papillary cystitis. In addition, patients with polypoid/papillary cystitis will often have clinical history of instrumentation, prior therapy, or stone.

What Are the Diagnostic Criteria of Low-Grade Dysplasia?

The diagnosis of low-grade urothelial dysplasia is often difficult. It is unlikely that it will be detected cystoscopically and presented as isolated finding. Generally, there are definitive dysplastic changes characterized by increased epithelial thickness and mild loss of cell polarity, mild nuclear enlargement and pleomorphism, and infrequent mitosis (Fig. 3.2a). Overall, the cytologic atypia is short of urothelial carcinoma in situ (Fig. 3.2b). There may be occasional mitoses, but atypical mitotic figures are not present. It is frequently seen in patients who have prior history or concurrent noninvasive low-grade papillary urothelial carcinoma or urothelial carcinoma in situ.

What Is the Definition of Urothelial Proliferation of Uncertain Malignant Potential?

Urothelial proliferation of uncertain malignant potential is a descriptive term for those lesions that show markedly thickened urothelial lining with no true papillary formation and have no or mild cytologic atypia (Fig. 3.3). This may be found in patients who had a history of papillary urothelial neoplasms or less commonly during work-up for patients presented with microhematuria or urinary obstructive symptoms. Based on the published studies on this not well-defined lesion, it has chromosomal changes similar to that of papillary urothelial neoplasm and occurs frequently in patients with a history of prior, concurrent, and subsequent urothelial neoplasia. Therefore, this lesion most likely represents an early urothelial neoplasia [6].

What Are the Diagnostic Criteria of Urothelial Carcinoma In Situ?

The main diagnostic criteria for urothelial carcinoma in situ (CIS) are severe cytologic atypia characterized by marked nuclear atypia, increased nuclear to cytoplasmic ratio, nuclear enlargement, and pleomorphism as well as hyperchromasia (Fig. 3.4a). Abnormal large nuclei, especially at the base and frequent mitotic figures are helpful features. Cellular discohesion is a frequent finding. The lesion may exhibit loss of cellular polarity and disorganized distribution of cells. Unlike cervical squamous cell carcinoma in situ, the cytologic atypia may not involve the entire thickness

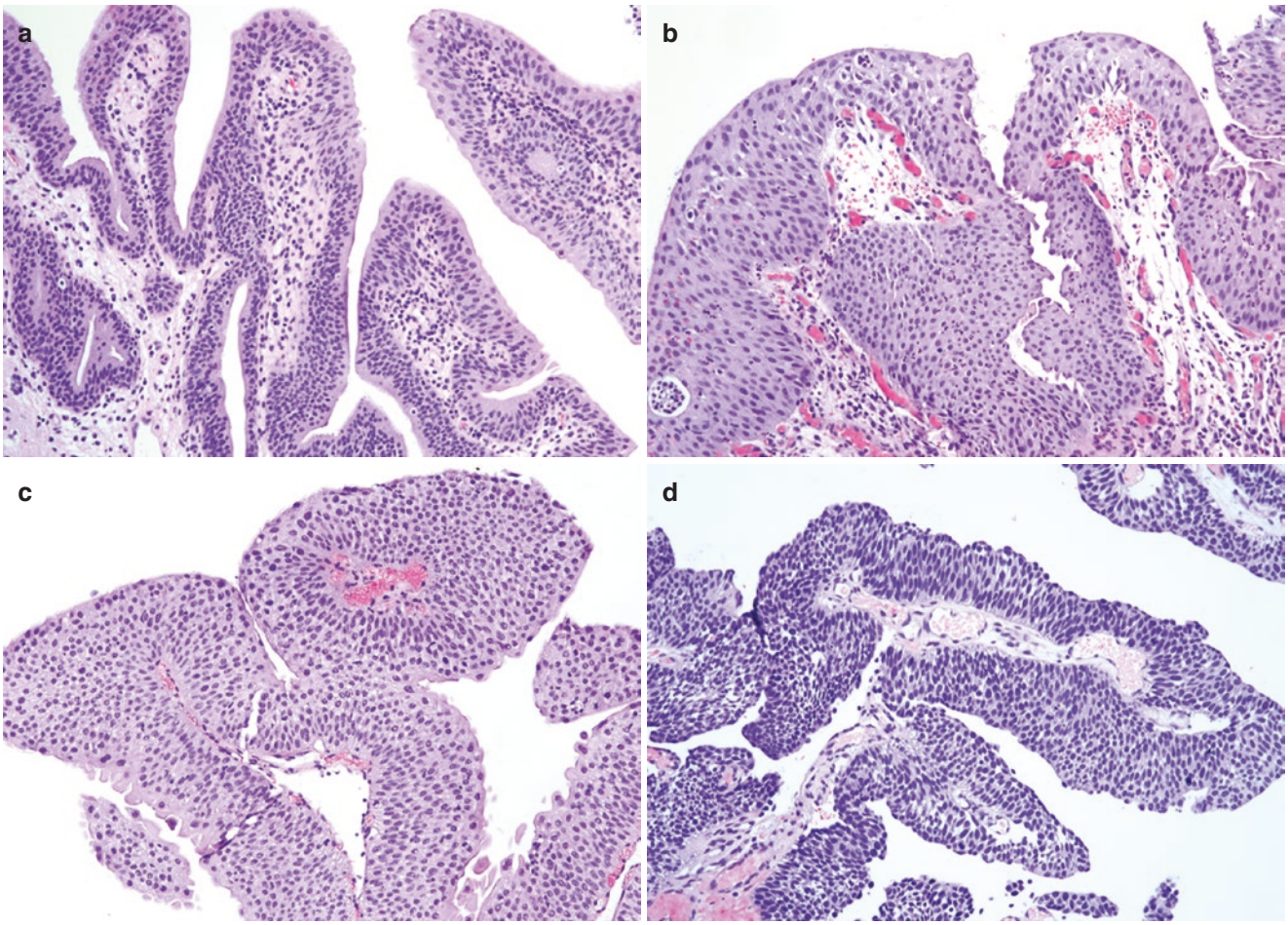

Fig. 3.1 Polypoid/papillary cystitis with broad papillary frond (**a**), edematous stroma, inflammatory infiltrate, and reactive epithelial changes (**b**). In contrast, papillary urothelial neoplasm exhibits well-formed delicate papillae (**c**) and lining cells with variable cytologic atypia (**d**)

of urothelium. In addition, CIS is frequently associated with neovascularization in the subepithelial tissue. It can be seen associated with high-grade papillary urothelial carcinoma. Occasionally, CIS may involve von Brunn nests (Fig. 3.4b), cystitis cystica, and cystitis glandularis, which can be pitfalls in routine practice [7].

What Are the Common Variants of Urothelial Carcinoma In Situ?

The common type of urothelial carcinoma in situ (CIS) is large cell CIS (most common) as described in the above question with large tumor cells (typically 5× size of small stromal lymphocyte). However, a type of small cell CIS has been described. It is composed of smaller neoplastic cells with high N/C ratio, hyperchromasia, and frequent mitoses or apoptosis. A "clinging" or "denuding" CIS is described as flat or isolated large tumor cells attached to the basement membrane (Fig. 3.5a). Pagetoid and undermining (lepidic) CIS is single or clusters of atypical large tumor cells present in otherwise normal urothelial cells (Fig. 3.5b). These atypical cells are usually present at the base of the urothelium, but can be present in any levels of urothelium. Urothelial CIS with glandular differentiation (Fig. 3.5c, d) has also been described [8].

What Are the Most Common Diagnostic Features of Reactive Atypia?

The common features of reactive atypia are uniformly enlarged nuclei with vesicular chromatin and prominent nucleoli in almost all cells. The lining cells are of normal thickness and have normal or mildly increased N:C ratio. There is often prominent background of mixed inflammation within the epithelium and/or subepithelial tissue (Fig. 3.6). Other associated changes such as vascular congestion and atypical stromal cells may be seen in patients with clinical history of infection, prior procedure, prior treatments such as intravesical therapy, radiation or chemotherapy, instrumentation, or stone.

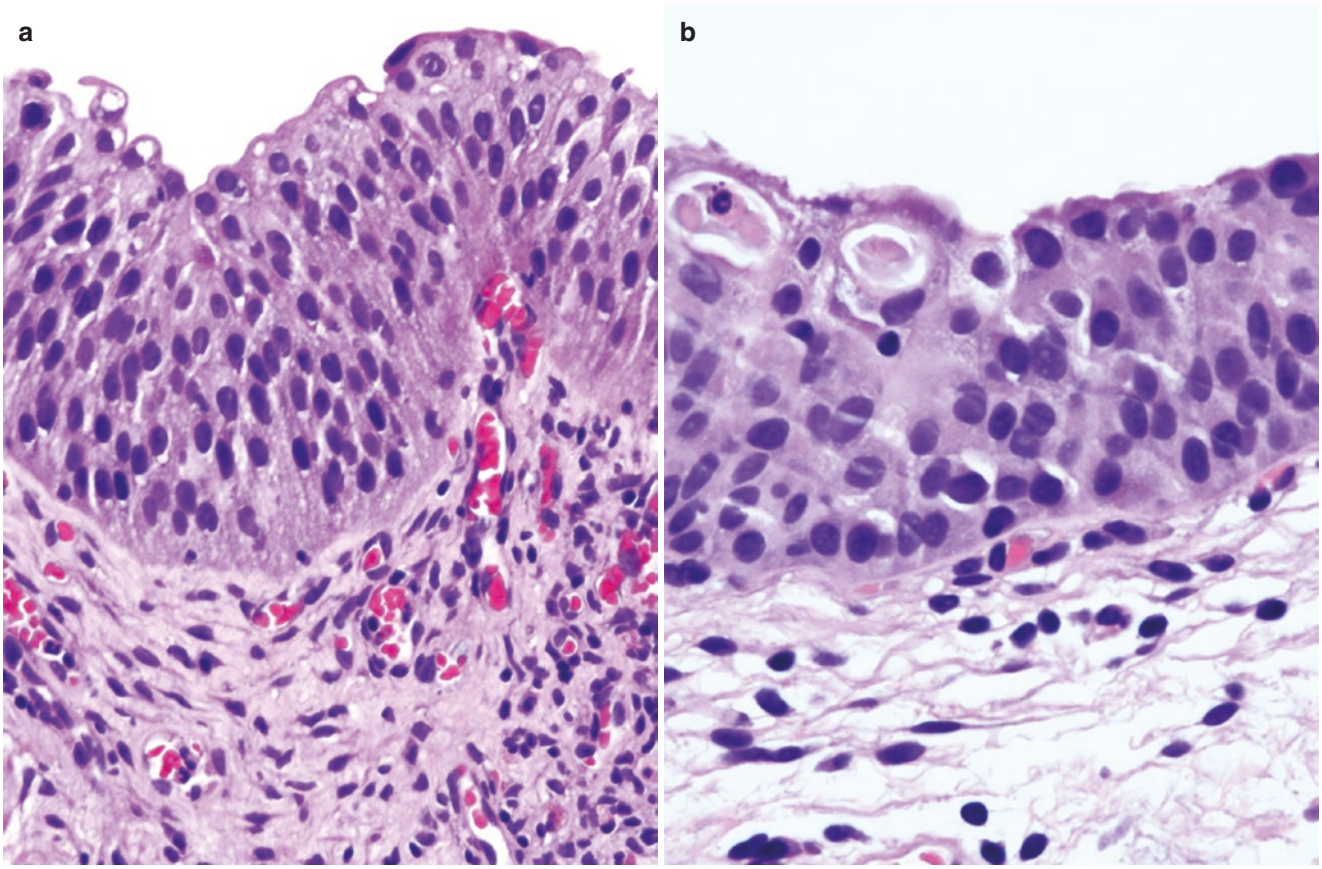

Fig. 3.2 Low-grade urothelial dysplasia showing thickened (**a**) or normal thickness urothelium (**b**) with mild loss of nuclear polarity, increasing of nuclear/cytoplasmic ratio, nuclear enlargement and hyperchromasia

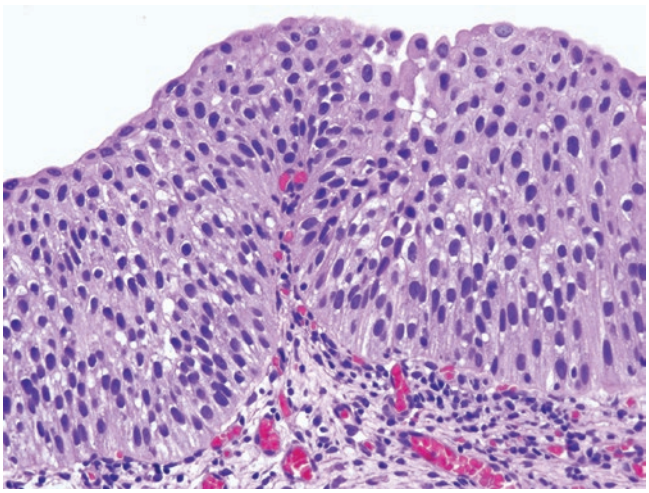

Fig. 3.3 Urothelial proliferation of uncertain malignant potential exhibits marked thickening and focal undulation of urothelium with minimal and mild cytologic atypia

Are There Any Reliable Immunohistochemical Markers that Can Help Diagnose Urothelial Carcinoma In Situ?

There have been some studies exploring the use of immunohistochemistry with markers such as p53, MIB-1 (Ki-67), CK20, CD44 as an adjunct for the diagnosis of urothelial carcinoma in situ (Fig. 3.7a) and distinction from reactive atypia. Urothelial CIS typically shows diffuse and strong stain for CK20 (Fig. 3.7b), and diffuse nuclear stain for p53 (Fig. 3.7c), but negative stain for CD44 (Fig. 3.7d). In contract, reactive atypia is typically negative for CK20 and p53, but often positive for CD44. However, these results are not uniformly reliable in routine practice, so the diagnosis should still be made primarily based on cytomorphology. Therefore, immunohistochemistry is not recommended by the International Society of Urological Pathology (ISUP) for the diagnosis of urothelial carcinoma in situ.

What Are the Diagnostic Criteria of Urothelial Papilloma?

Diagnostic criteria of urothelial papilloma include delicate, simple papillary architecture, and benign urothelial lining of normal thickness. There is no cytological atypia, architectural atypia, or mitosis. Reactive change, particularly in the umbrella cells, may be seen (Fig. 3.8). Sometimes, the papillary cores may contain dilated lymphatics or foamy histiocytes. The lesion is endoscopically similar to other papillary urothelial neoplasms, but it is usually solitary and small

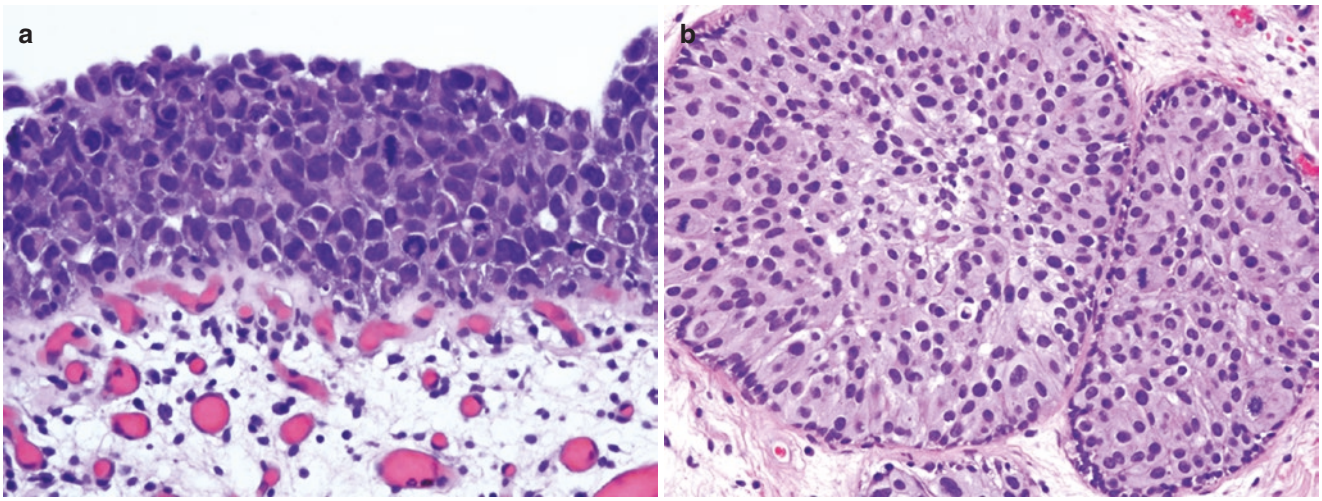

Fig. 3.4 Urothelial carcinoma in situ shows severe cytologic atypia with marked nuclear enlargement and irregularity, hyperchromasia and brisk mitotic figure (**a**). CIS involves von Brunn nests with large rounded nests composed of pleomorphic tumor cells with frequent mitoses (**b**)

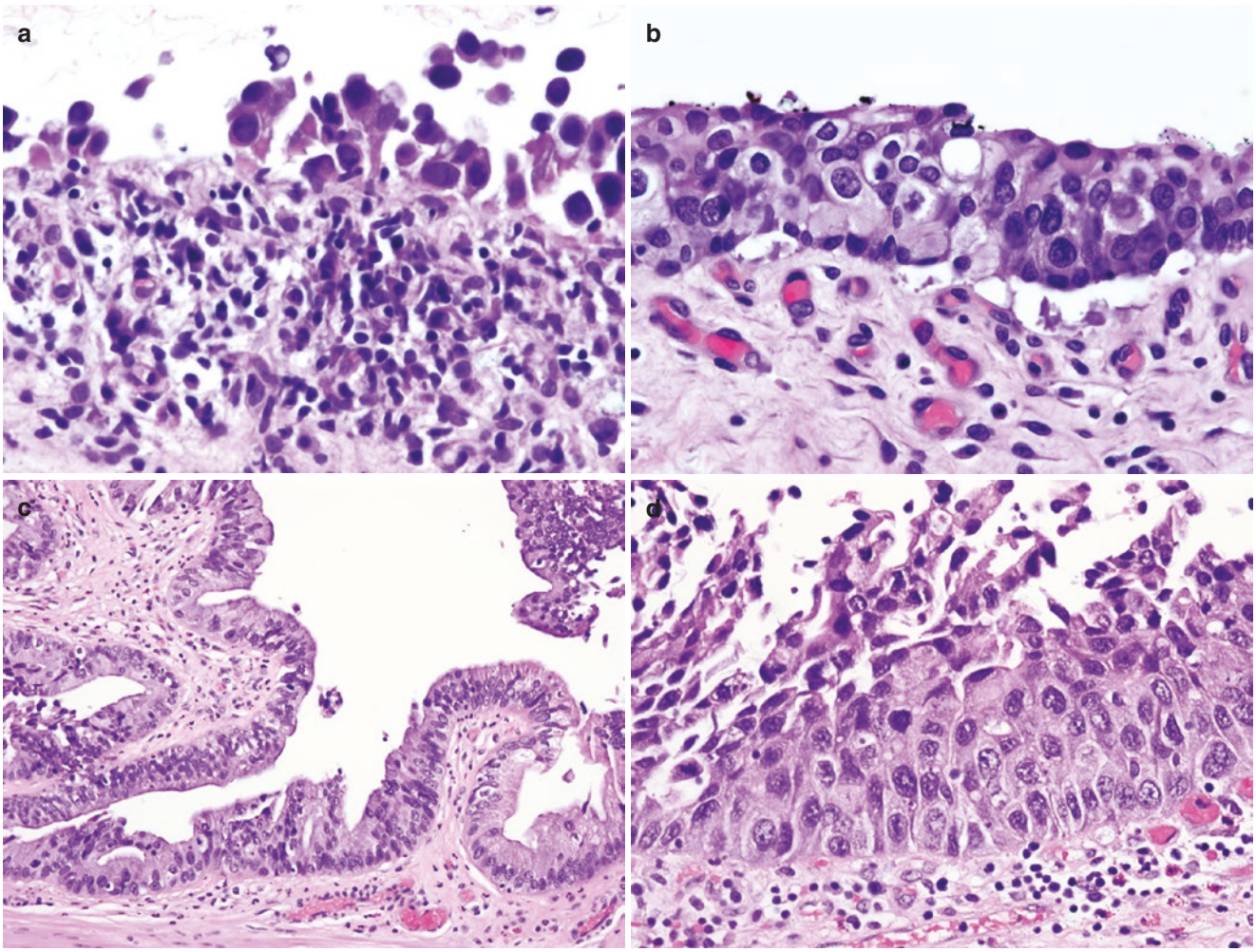

Fig. 3.5 Clinging or denuding urothelial carcinoma in situ (**a**) shows a few clusters of large atypical tumor cells attached to subepithelial basement membrane. An example of urothelial carcinoma in situ with pagetoid spread of tumor cells (**b**). Urothelial carcinoma in situ with glandular differentiation shows intratumoral tubular or enteric gland-like lumens (**c**, **d**)

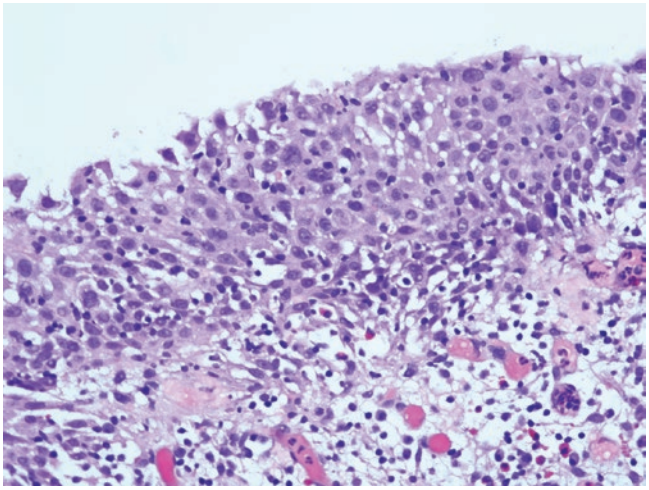

Fig. 3.6 Urothelial reactive atypia with uniform enlargement of nuclei and prominent nucleoli associated with prominent intraepithelial inflammation

lesion. Patients with urothelial papilloma are also typically younger than those with papillary urothelial carcinoma. It is usually an incidental finding and patient does not have prior history or concurrent urothelial carcinoma [6].

What Are the Molecular Subtypes of Urothelial Carcinoma?

Molecular characterization of bladder urothelial tumors shows that they can be subtyped into two major categories—luminal and basal type tumors, similar to those seen in breast carcinomas. Majority molecular subtyping studies focused on muscle-invasive bladder urothelial carcinomas (MIBC). In the protein expression-based, The Cancer Genome Atlas (TCGA) Research Network study, MIBCs were identified as four clusters. Clusters I and II MIBCs express high HER2, elevated estrogen receptor-β signatures, and positive for

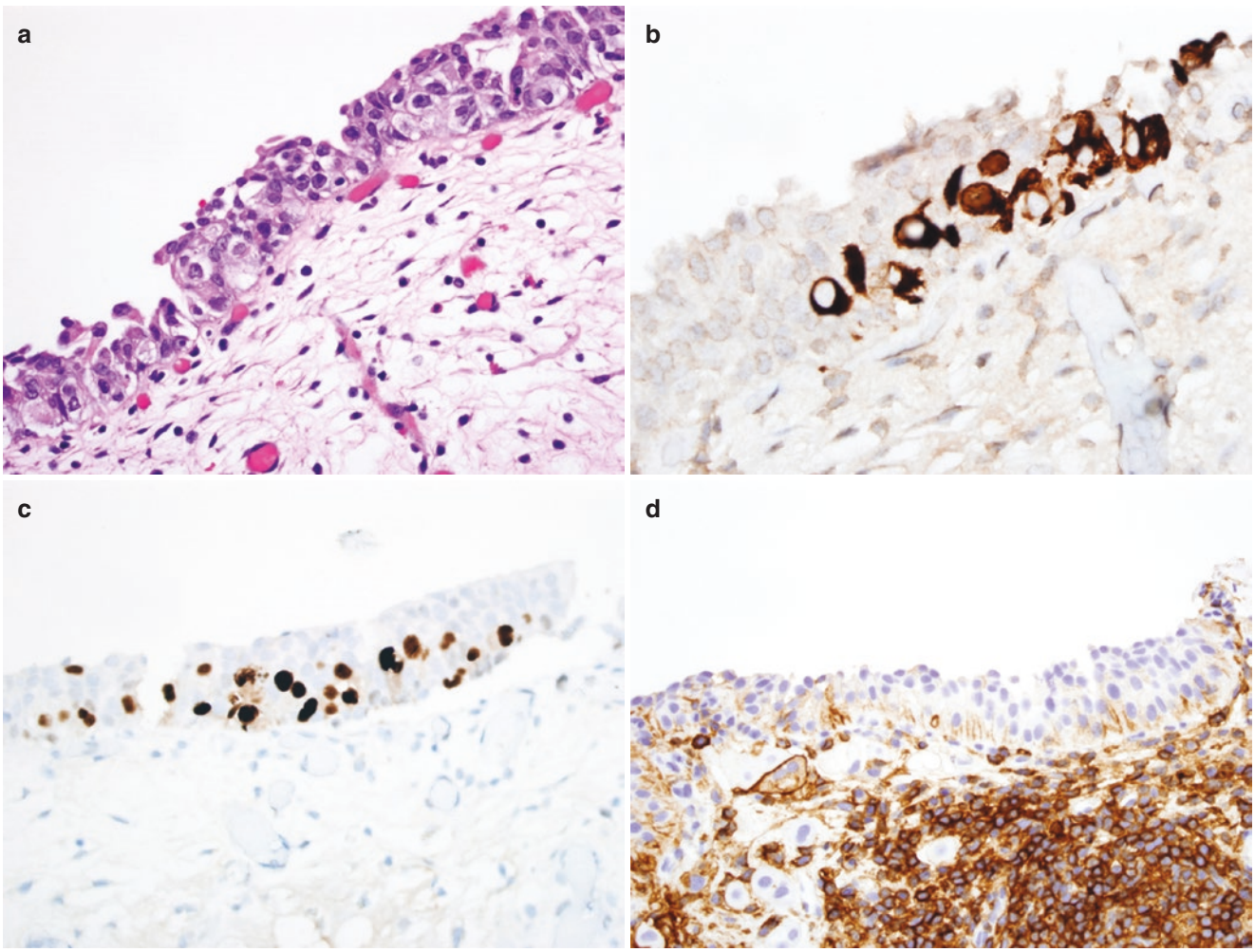

Fig. 3.7 Urothelial carcinoma in situ with pagetoid spread (**a**) showing strong CK20 (**b**) and p53 (**c**) staining patterns and loss of CD44 staining (**d**)

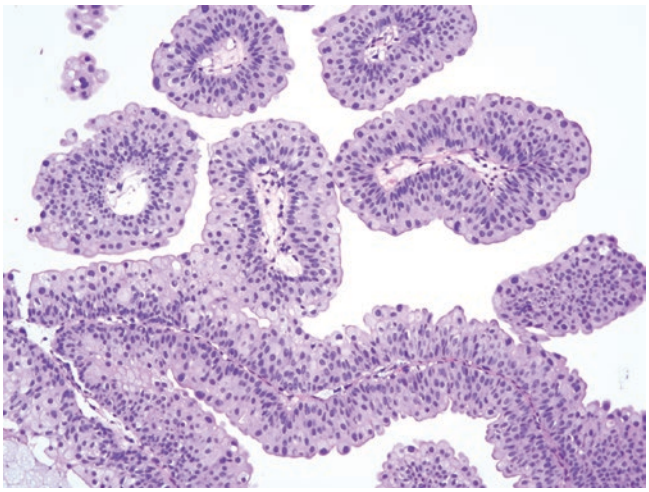

Fig. 3.8 Urothelial papilloma shows delicate papillae lined by normal thickness urothelium lined by normal urothelial cells

GATA3 and FOXA1, consistent with a luminal subtype. Markers for/consistent with urothelial differentiation, such as uroplakins and CK20, are also expressed in luminal tumors. A single study demonstrates that vast majority of micropapillary invasive carcinomas are luminal type tumors. Compared with Cluster II MIBCs, Cluster I MIBCs more commonly present with papillary morphology and harbor *FGFR3* gene alterations. Clusters III and IV MIBCs in the TCGA study, however, do not express high HER2, GATA3, or FOXA1. Cluster III tumors are more likely to present with basal/squamous features and express epithelial lineage-characteristic genes such as *KRT5*, *KRT6A*, *KRT14*, and *EGFR*. They are consistent with a basal subtype. Cluster IV tumors, in contrast, are less likely to present with squamous features or increased *KRT5*, *KRT6A*, *KRT14*, and *EGFR* expression. They could occasionally be papillary in architecture and typically show increased microRNA miR-99a-5p and miR-100-5p expressions.

In addition to TCGA classification for molecular subtypes of urothelial carcinoma, University of North Carolina (UNC), MD Anderson Cancer Center (MDACC), and Lund University (LU) classifications have also been proposed. The UNC classification subtypes urothelial carcinomas into luminal, basal, and claudin-low tumors. The MDACC classification includes luminal, basal, and p53-like subtypes. The LU classification, on the other hand, divides urothelial carcinomas into genomically unstable, urobasal A, infiltrated, urobasal B, and squamous cell carcinoma-like tumors. These classifications overlap more or less with each other.

Molecular subtypes of MIBCs may guide the selection of appropriate targeted therapies. For instance, luminal type (which corresponds to TCGA Cluster I, UNC and MDACC luminal, and Lund genomically unstable) tumors are more likely to respond to FGFR3 and PPARγ inhibitor-based therapies. Molecular subtypes of MIBCs are also of prognostic values. Luminal type carcinomas in general carry a more favorable prognosis compared with nonluminal counterparts [9–14].

What Are the Distinguishing Features of Papillary Urothelial Neoplasm of Low Malignant Potential and Low-Grade Papillary Urothelial Carcinoma?

They are both papillary neoplasms lined by thickened urothelial lining. Most of them show exophytic growth but inverted growth pattern can be present. Papillary urothelial neoplasm of low malignant potential (PUNLMP) typically has delicate papillae without fusion and complexity. Cytologically, and the tumor cells are monotonous and may show very minimal cytologic atypia and preservation of cellular polarity. The nuclei are slightly enlarged and more crowded than benign urothelial lining. Nuclear groove may be seen. Nucleoli are either absent or inconspicuous. The chromatin is uniformly even. Mitoses are very rare and mostly limited to the basal layer (Fig. 3.9a). In contract, low-grade papillary urothelial carcinomas have more complex papillae with branching and fusion. There is mild loss of cellular polarity, mild nuclear irregularity, and pleomorphism (Fig. 3.9b). Mitosis may be present away from the basal layer [6].

What Are the Most Helpful Features that can Distinguish Low-Grade from High-Grade Papillary Urothelial Carcinoma?

Low-grade papillary urothelial carcinoma shows preserved vertical orientation and more monotonous cell population in low power. However, in higher power it can show minimal loss of polarity, mild nuclear crowding, and mild nuclear atypia. Compared to low-grade papillary urothelial carcinoma, high-grade papillary urothelial carcinoma tends to have more fused and more complex papillae. However, the key difference between them is more cytologic atypia in high-grade urothelial carcinoma, including nuclear enlargement and pleomorphism, increased N/C ratio or hypercellularity, hyperchromasia, irregular prominent nucleoli, frequent mitoses including atypical mitoses, and rarely tumor necrosis (Fig. 3.10a). There are situations that a distinction between low and high grade is difficult. One scenario is that the combina-

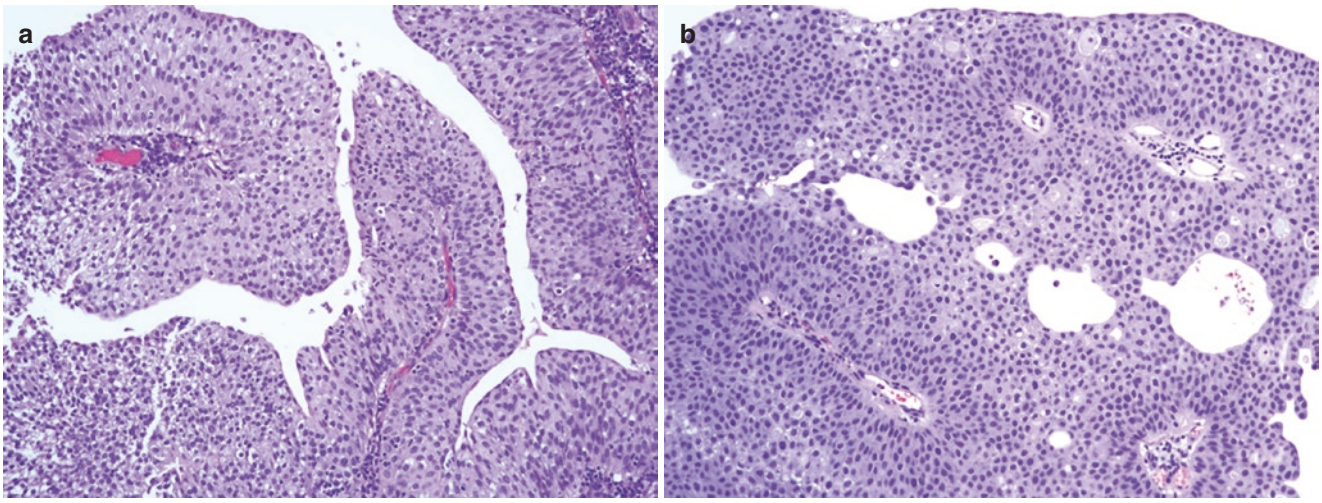

Fig. 3.9 Papillary urothelial neoplasm of low malignant potential (**a**) shows well-formed papillae lined by markedly thickened urothelial cells with minimal cytologic atypia. In contrast, low-grade papillary urothelial carcinoma (**b**) shows papillary complexity and mild cytologic atypia, loss of polarity, and occasional mitoses

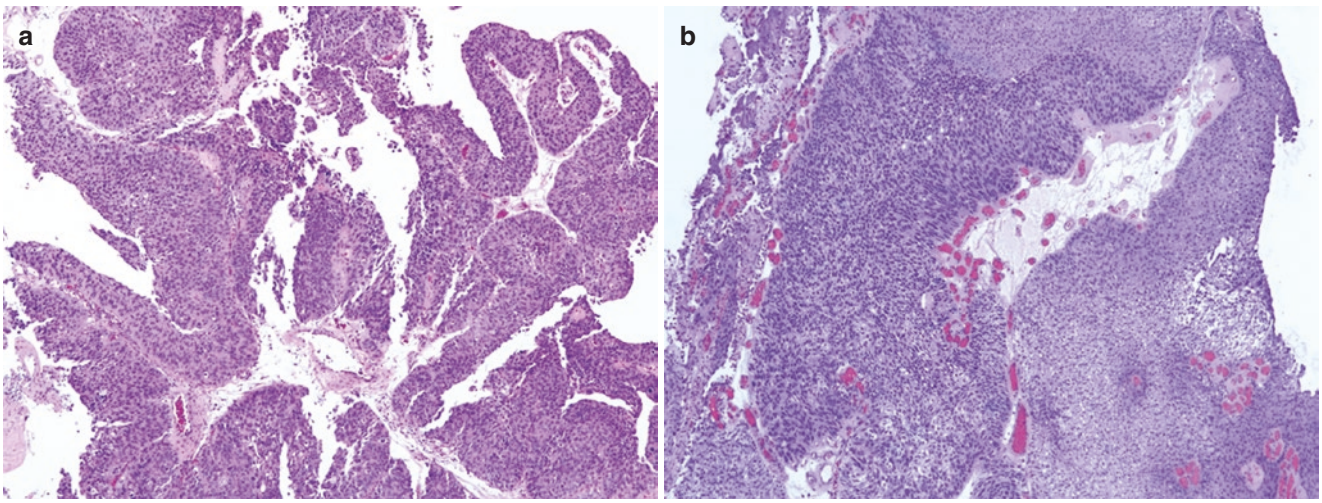

Fig. 3.10 High-grade papillary urothelial carcinoma with marked cytologic atypia which can be easily appreciated at low power magnification (**a**). One example of urothelial carcinoma exhibits low-grade papillary urothelial carcinoma with high-grade area (**b**)

tion of cytologic features in a papillary tumor is truly borderline between a low and high grade. The assignment becomes somewhat subjective depending on the assignment of relative weight of each cytologic and architectural features. The other scenario is that a mixture of distinct low-grade and high areas exist in the same tumor (Fig. 3.10b). It is unlikely that a clear cutoff point exists. A papillary tumor is diagnosed as high-grade urothelial carcinoma if there is more than 5–10% high-grade component. In this situation, a diagnosis of a low-grade papillary urothelial carcinoma with small component of high-grade carcinoma is very reasonable and conveys useful information for the management of patients [15].

What Are the Diagnostic Features and Clinical Significance of Squamous Metaplasia?

There are two types of squamous metaplasia; keratinizing (Fig. 3.11a) and nonkeratinizing (Fig. 3.11b). The diagnostic features of squamous metaplasia are polyhedral-shaped cells and presence of intercellular bridge. Keratinous material can be seen in keratinizing type. Most cases have no significant cytologic atypia. Keratinizing squamous metaplasia is usually a consequence of chronic inflammation result from infection, irritation, or radiation. It is associated with increased risk for squamous cell carcinoma, as well as urothelial carcinoma in urinary mucosa [16].

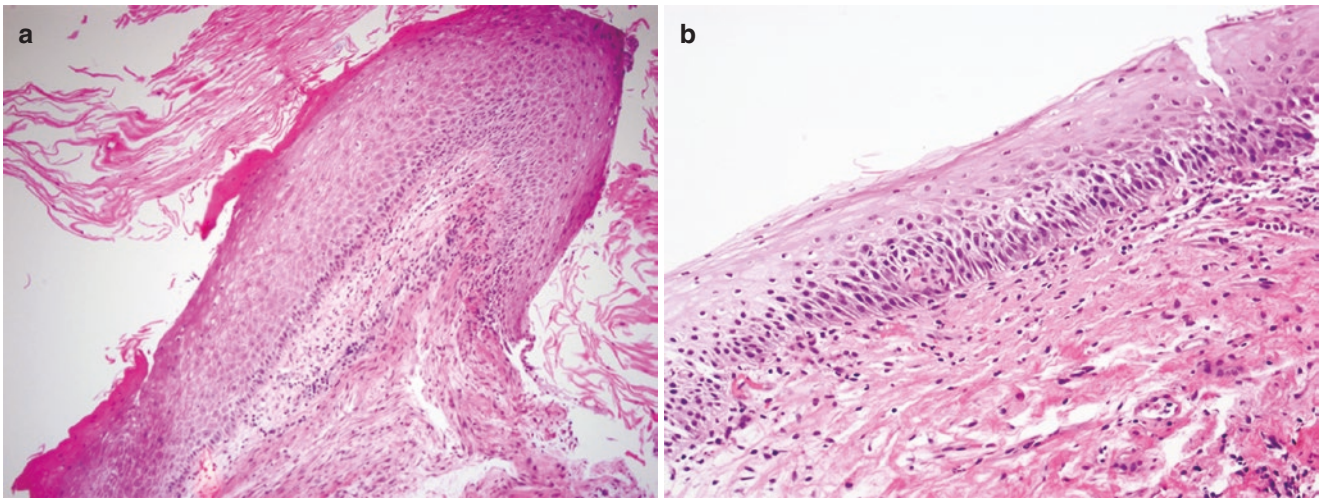

Fig. 3.11 Squamous metaplasia can be categorized into keratinizing (**a**) and nonkeratinizing (**b**) types

What Are the Diagnostic Features of Nephrogenic Adenoma?

Nephrogenic adenoma is typically composed of small compact tubules with or without mucin-like materials. The tubules are lined by monotonous cuboidal cells. The nuclei are centrally located, round, and hyperchromatic. The cells may show marked reactive atypia. The stroma is often very typical and shows granulation tissue with edema, mixed acute and chronic inflammation (Fig. 3.12a). The overlying or adjacent urothelium can range from normal, reactive to rarely urothelial CIS. Nephrogenic adenoma can have variable patterns such as tubular, cystic, polypoid, papillary, fibromyxoid, and diffuse. A mixture of patterns is very commonly seen. When predominantly papillary or polypoid, it may mimic papillary urothelial neoplasm cystoscopically and histologically (Fig. 3.12b). But unlike papillary urothelial neoplasm, papillary nephrogenic adenoma has a single-layer lining. The lining cells can have flat, elongated, or hobnail appearance. Cystic dilatation can be found in 72% of the cases (Fig. 3.12c). Eosinophilic or basophilic secretions can be found in the tubular lumen.

The main differential diagnoses of nephrogenic adenoma include urothelial carcinoma with glandular differentiation, cystitis cystica, or secondary involvement by prostate cancer. Nephrogenic adenoma is positive for Pax 8 (Fig. 3.12d), CK7, and AMACR, whereas urothelial lesion is positive for CK7, negative for Pax8 and AMACR. Prostate cancer would be positive for PSA and AMACR, negative for Pax 8 and CK7 [16].

What Are the Distinguishing Features of Nephrogenic Adenoma and Clear Cell Adenocarcinoma?

The architectural features, including tubular, cystic, and papillary structures and cells with hobnail appearance of nephrogenic adenoma may resemble clear cell carcinoma. However, there are some helpful features to help distinguish between the two lesions. Nephrogenic adenoma is usually small but clear cell adenocarcinoma is often large. Nephrogenic adenoma seldomly has solid growth pattern, clear cell change, glycogen in cytoplasm, nuclear atypia, and mitosis, but these features are common in clear cell adenocarcinoma (Fig. 3.13) [8].

What Are the Diagnostic Criteria of Urachal Carcinoma?

The diagnostic criteria of urachal carcinoma include location of tumor at the dome and/or anterior wall of urinary bladder, absence of cystitis cystica *et* glandularis near the area of tumor, epicenter of the mass in the muscularis propria of bladder with sharp demarcation between urachal tumor and overlying bladder mucosa, and no known primary elsewhere that has spread secondarily to the bladder. Most of the urachal carcinomas are adenocarcinoma which can be enteric, mucinous (colloid) (Fig. 3.14), signet ring, mixed, or not otherwise specified. However, urothelial and squamous cell carcinomas can also arise as urachal carcinoma [8, 17, 18].

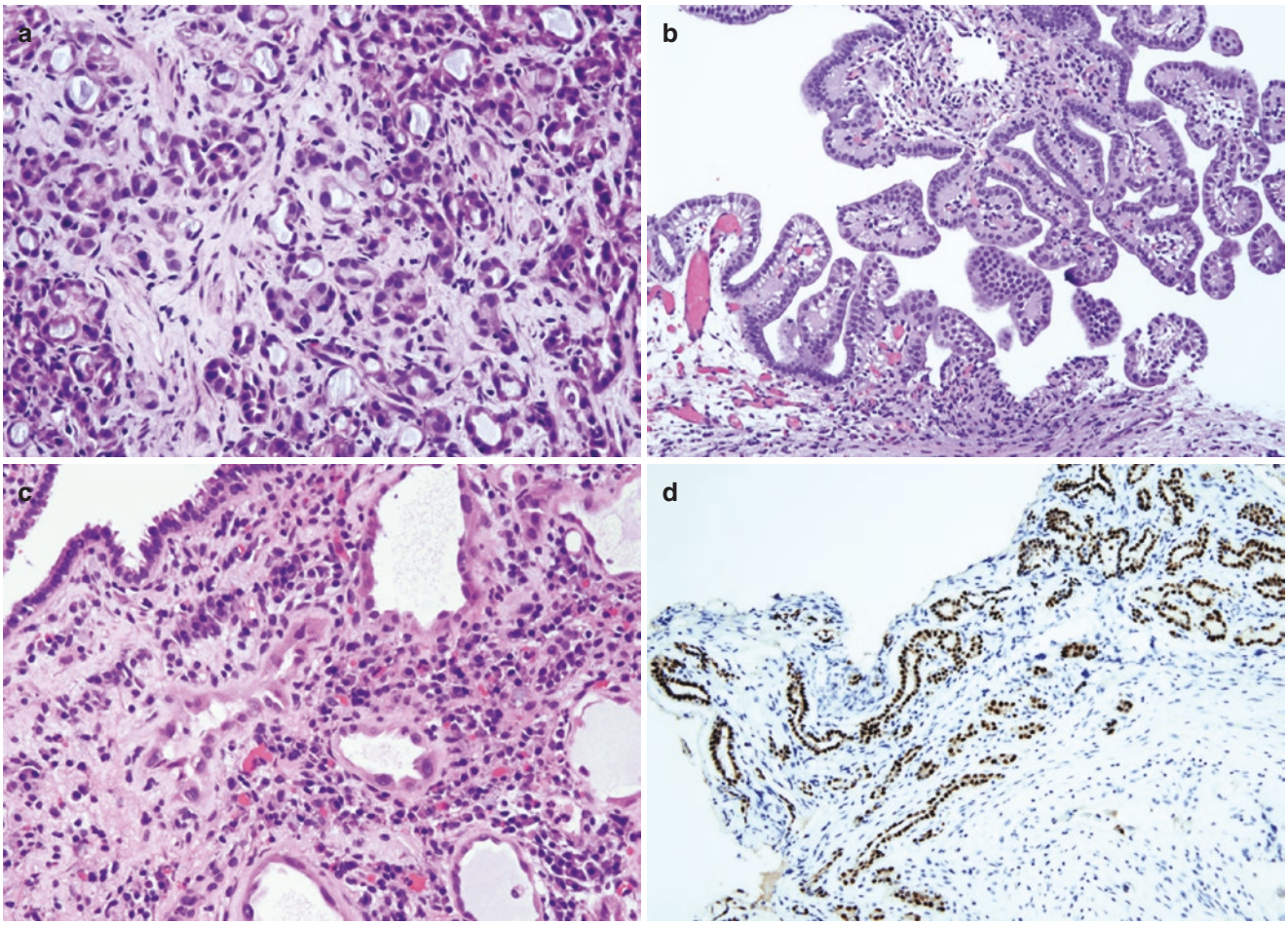

Fig. 3.12 Nephrogenic adenoma shows proliferation of small tubules with single layer of cells with hob nailing and luminal basophilic secretion (**a**), prominent papillary (**b**) or cystic component (**c**), and positivity for Pax8 (**d**)

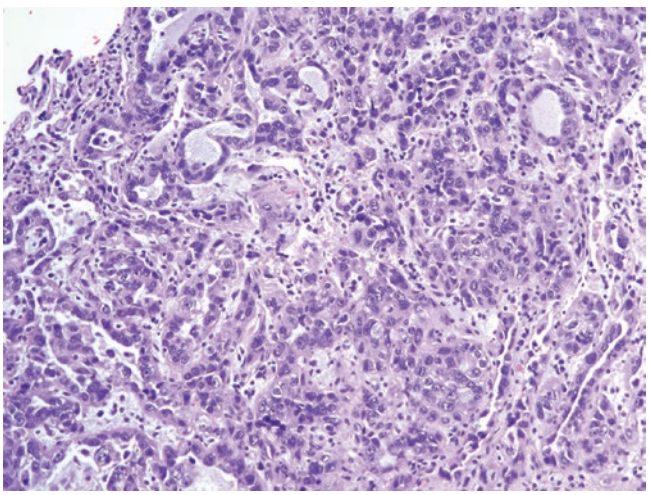

Fig. 3.13 Clear cell adenocarcinoma shows similar morphologic feature as that of nephrogenic adenoma, but more solid growth pattern and marked cytologic atypia and stromal reaction

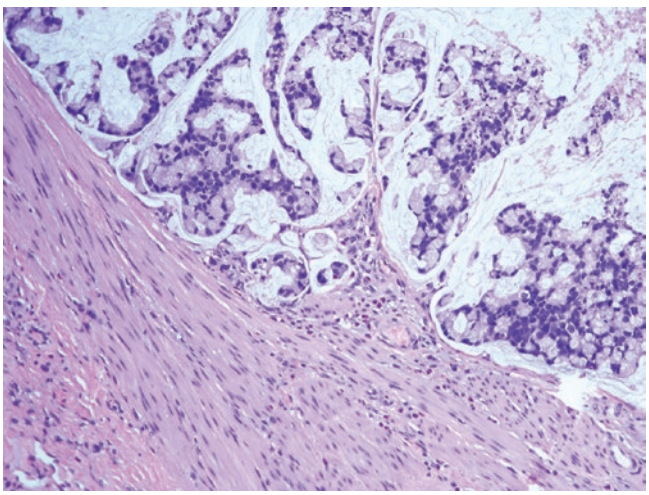

Fig. 3.14 Urachal mucinous adenocarcinoma of bladder shows bladder muscularis propria with infiltrating clusters of poorly formed and cribriform glands and abundant extracellular mucin

What Are the Diagnostic Features of von Brunn Nests, Cystitis Cystica, and Cystitis Glandularis?

von Brunn nests is described as well-circumscribed nests of urothelial cells in the lamina propria which may or may not connect to the surface epithelium. Usually, it presents as a few nests in superficial lamina propria but sometimes the nests can be found in deep lamina propria (Fig. 3.15a). They can be florid and may mimic nested variant urothelial carcinoma. Comparing with nested variant urothelial carcinoma, von Brunn nests have more regular spacing and never involves muscularis propria. Cystitis cystica is characterized by cystic change of von Brunn nests; therefore, the lining cysts are composed of normal urothelial cells. However, the cells can be flattened. Cystitis glandularis has a morphology of cystitis cystica with lining cells undergoing glandular metaplasia (Fig. 3.15b). The luminal cells become columnar with a smooth luminal cytoplasmic border. There are two types of cystitis glandularis: typical type and intestinal type. The typical type is much more common. It has cuboidal or columnar lining cells with minimal mucinous secretion in the lumen. The intestinal type consists of goblet cells and colonic type tall columnar epithelial cells with abundant mucin secretion (Fig. 3.15c). Paneth cells can rarely be present.

von Brunn nests, cystitis cystica, and glandularis are related reactive/proliferative changes and the same lesions occur in entire urinary tracts and are believed to be a local reaction to inflammation or insult [16].

Does Cystitis Glandularis Have Risk for Urothelial Adenocarcinoma?

Focal cystitis glandularis does not increase risk of adenocarcinoma but persistent diffuse cystitis glandularis of intestinal type, so-called "intestinal metaplasia" has association with increased risk of adenocarcinoma [16].

What Are the Most Common Invasive Urothelial Carcinomas with Divergent Differentiation?

Urothelial carcinoma with squamous differentiation (Fig. 3.16a, b) is the most common type, accounting about 40% of invasive urothelial carcinomas. Urothelial carcinoma with glandular differentiation is the second most common type, accounting about 18% of invasive urothelial carcinomas. Uncommonly or rarely, other divergent differentiation includes small cell, trophoblastic and Müllerian differentiation [1].

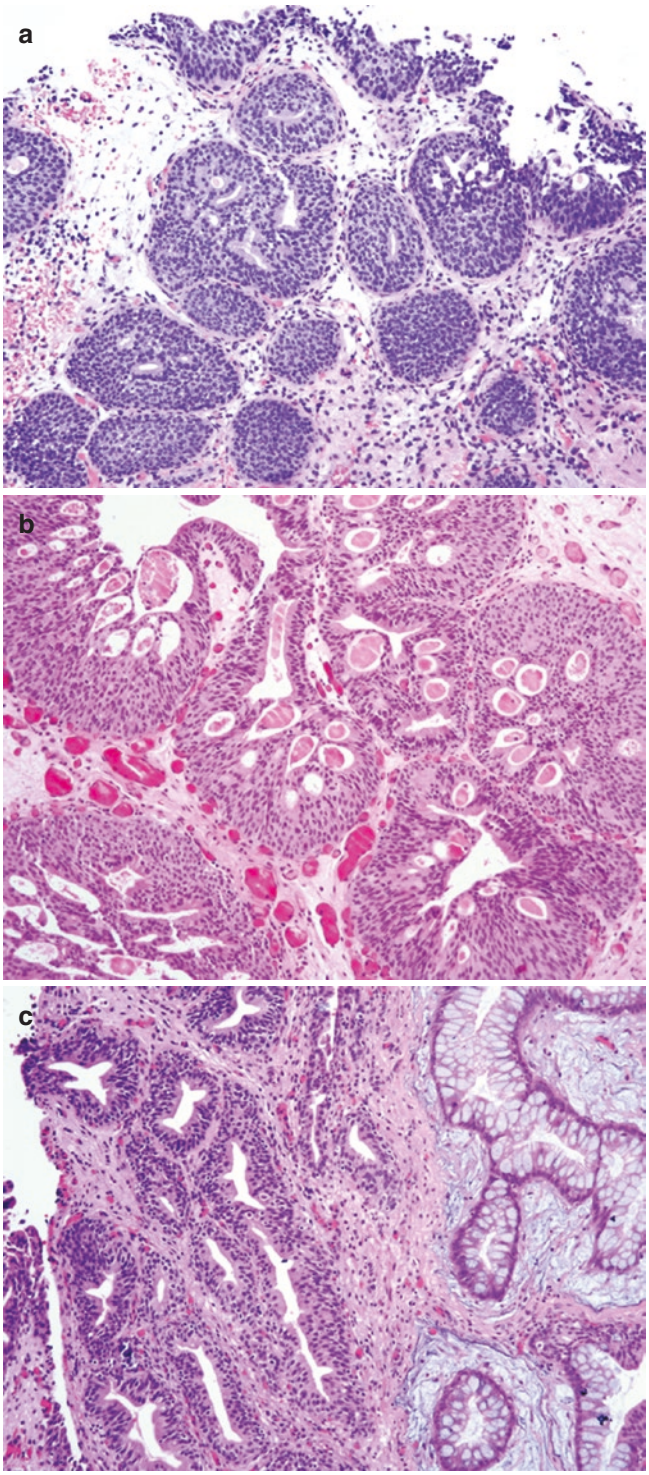

Fig. 3.15 Urothelium with prominent von Brunn nests within subepithelial tissue (**a**), florid cystitis cystica and cystitis glandularis with eosinophilic secretion (**b**), and cystitis glandularis of usual and intestinal type (**c**)

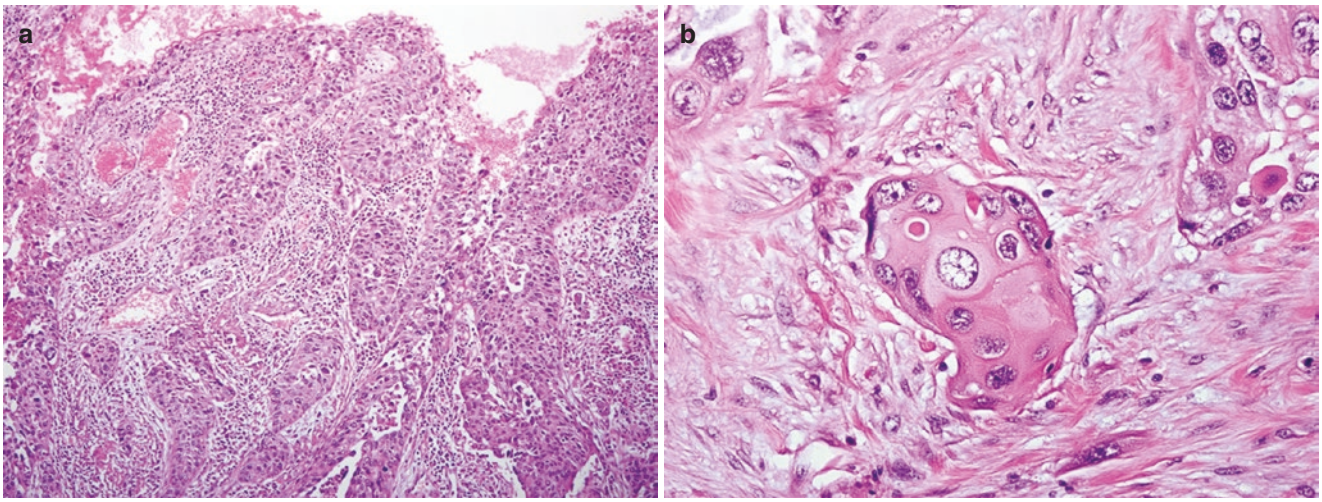

Fig. 3.16 Urothelial carcinoma with squamous differentiation showing intercellular bridges (**a**) and intracellular keratin (**b**)

What Are the Histologic Variants of Invasive Urothelial Carcinoma in 2016 World Health Organization Tumor Classification?

Invasive urothelial carcinoma has been recognized to have diverse morphologic appearances in terms of growth patterns and cytological features. Some of these variations are distinctive enough in terms of their morphologic diagnosis, prognosis, and treatment implication. The following morphologic variants are recognized by 2016 WHO classification.

- Urothelial carcinoma with divergent differentiation [squamous, glandular, trophoblastic (Fig. 3.17a, b), Mullerian differentiation (Fig. 3.17c–f)].
- Nested urothelial carcinoma.
- Microcystic urothelial carcinoma.
- Micropapillary urothelial carcinoma.
- Lymphoepithelioma-like urothelial carcinoma (Fig. 3.17g).
- Plasmacytoid urothelial carcinoma including signet ring cell and diffuse variants.
- Sarcomatoid urothelial carcinoma.
- Giant cell urothelial carcinoma (Fig. 3.17h).
- Poorly differentiated urothelial carcinoma (including those with osteoclast-like giant cells, Fig. 3.17i).
- Clear cell (glycogen-rich) urothelial carcinoma (Fig. 3.17j).
- Lipid-rich urothelial carcinoma (Fig. 3.17k, l) [1].

What Are the Diagnostic Features of Micropapillary Urothelial Carcinoma?

The diagnostic features of micropapillary urothelial carcinoma are small nests or aggregates of cells without vascular core in lacunar spaces resembling lymphovascular invasion by tumor. The most reproducible criteria for the diagnosis are confluent, back-to-back small lacunae, and multiple small nests within lacunar spaces (Fig. 3.18a). Other features include nests with reverse nuclear polarity or peripheral orientation of the nuclei and presence of cytoplasmic vacuoles. This unique variant is frequently mixed together with conventional high grade or urothelial carcinoma with other variant morphologies. Rarely noninvasive papillary urothelial carcinoma may have surface micropapillary component with delicate filiform configuration and lack of fibrovascular core (Fig. 3.18b). It is advisable that the term micropapillary is not used for noninvasive urothelial carcinoma to avoid confusion [1].

What Are the Diagnostic Features of Plasmacytoid Urothelial Carcinoma?

The diagnostic features of plasmacytoid urothelial carcinoma are invasive carcinoma with isolated, discohesive tumor cells with eccentrically placed nuclei and abundant cytoplasm, resembling plasma cells (Fig. 3.19a). The cytoplasm can be eosinophilic, clear, and vacuolated. The stroma is often

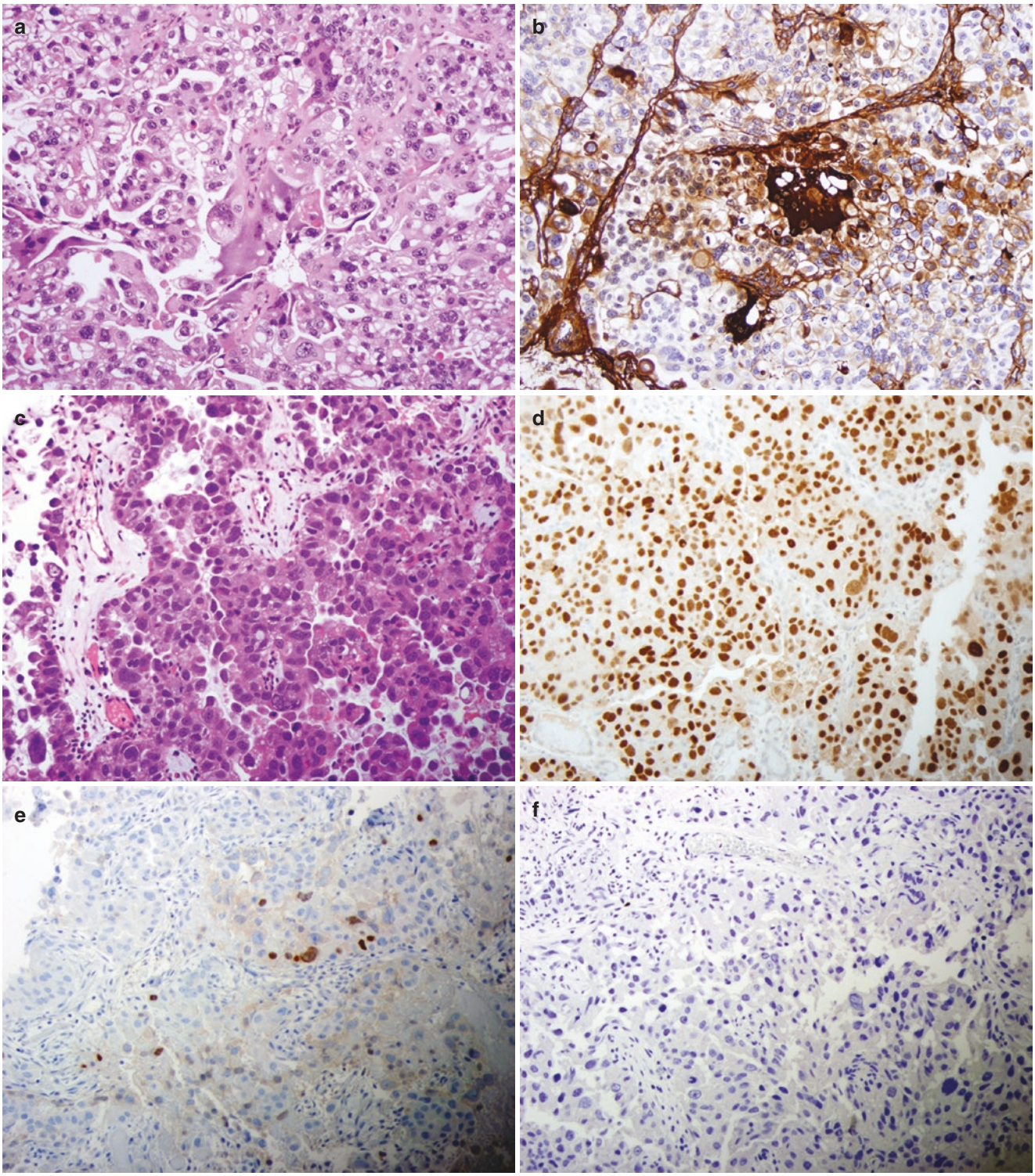

Fig. 3.17 Urothelial carcinoma with trophoblastic differentiation (**a**) is positive for β-HCG (**b**). Urothelial carcinoma with Mullerian differentiation (**c**) is positive for PAX8 (**d**) and p63 (**e**), and negative for GATA3 (**f**). Lymphoepithelioma-like urothelial carcinoma is composed of nests or sheets of pleomorphic cells with large nuclei and prominent nucleoli in a background of abundant mixed lymphoid infiltrate (**g**). Giant cells can be seen in giant cell urothelial carcinoma (**h**) and poorly differentiated urothelial carcinoma with osteoclast-like giant cells (**i**). Clear cell (glycogen-rich) urothelial carcinoma is composed of abundant tumor cells with clear cytoplasm secondary to glycogen accumulation (**j**) which are negative for Pax8, excluding the possibility of clear cell renal cell carcinoma. Lipid-rich urothelial carcinoma is characterized by clear cytoplasmic vacuoles (**k**) and lipoblast-like cells (**l**)

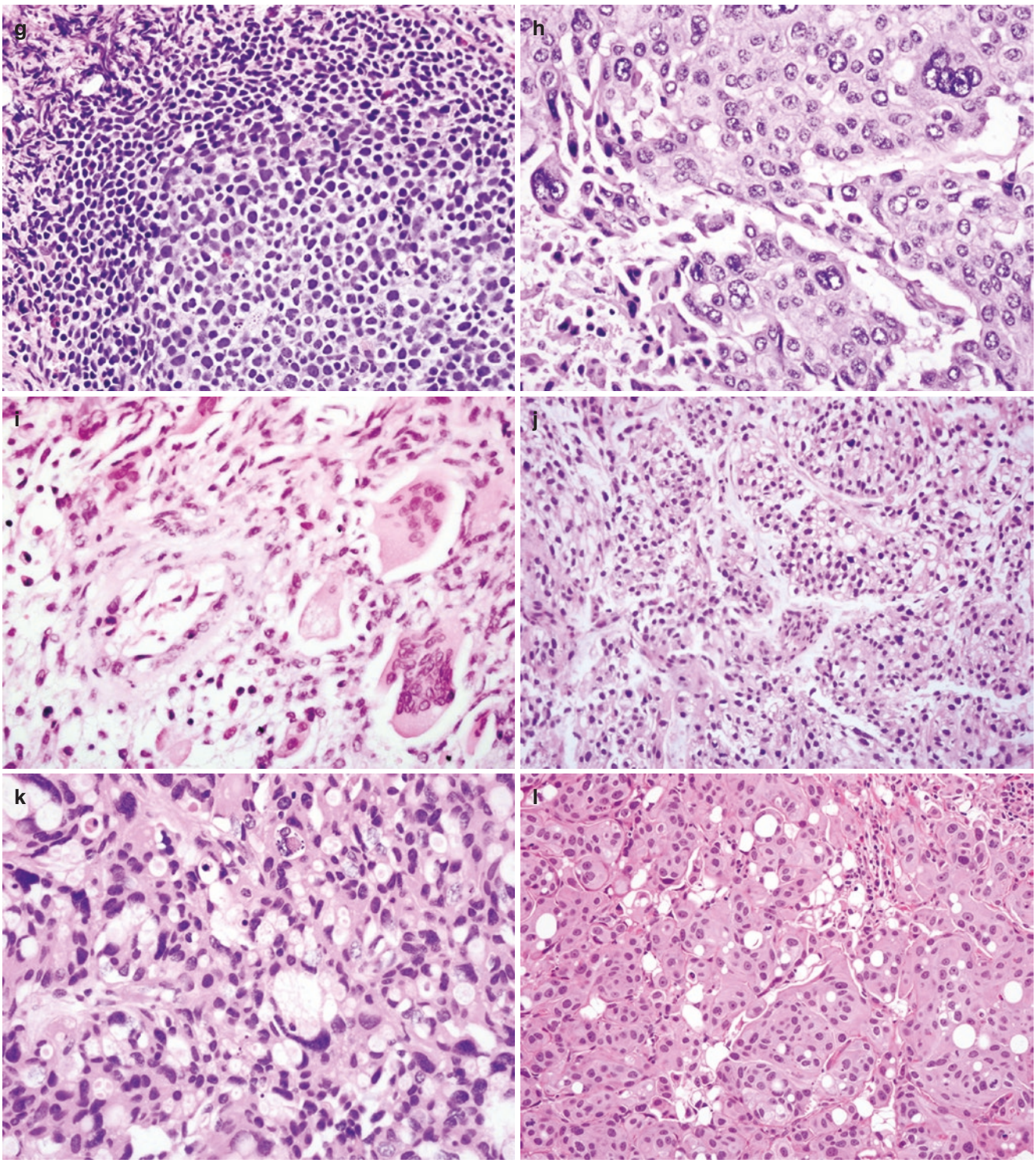

Fig. 3.17 (continued)

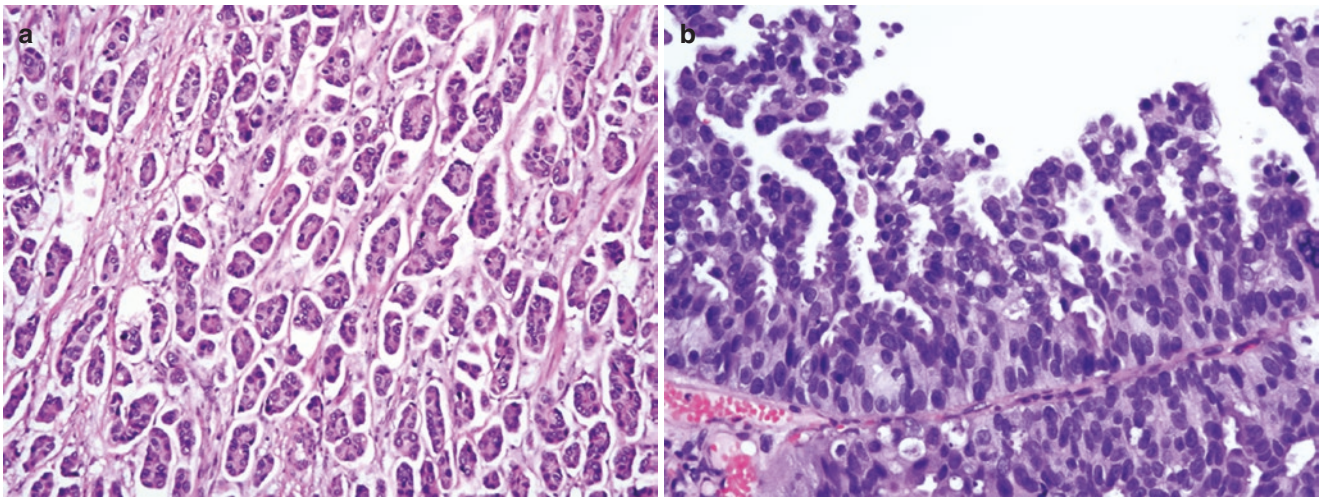

Fig. 3.18 Invasive micropapillary urothelial carcinoma shows exuberant small nests and clusters of tumor cells in lacunar spaces resembling lymphovascular invasion (**a**). Noninvasive papillary urothelial carcinoma exhibits surface micropapillary component composed of delicate filiform papillae with crowded nuclei without fibrovascular cores (**b**)

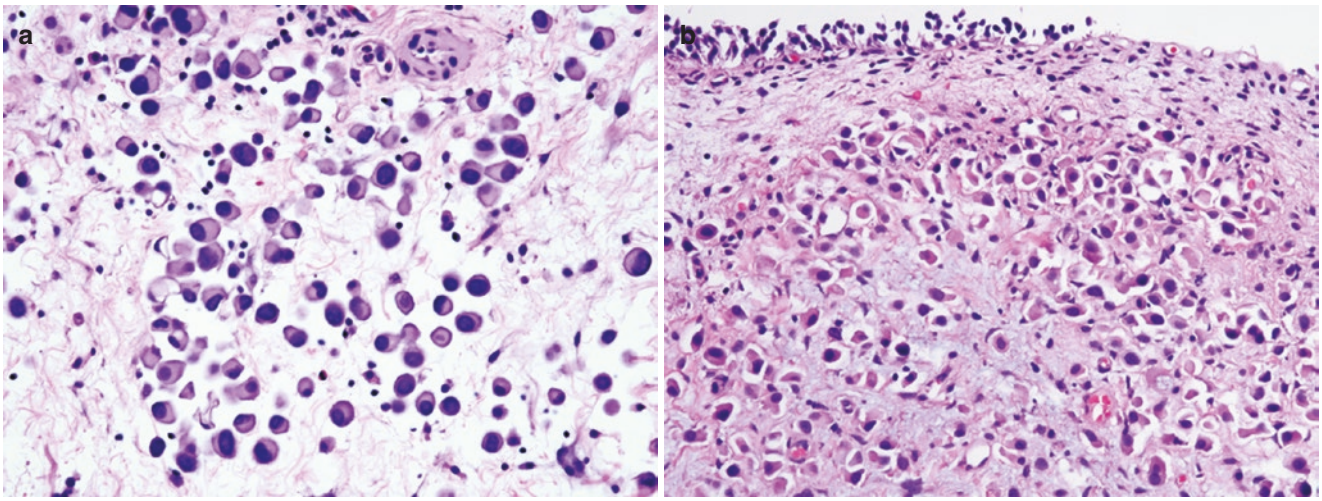

Fig. 3.19 Invasive plasmacytoid urothelial carcinoma shows infiltrating discohesive small cluster and single tumor cells with abundant dense cytoplasm resembling plasma cells (**a**) and rare signet ring cells (**b**)

loosely myxoid. The nuclei range from monotonous to highly pleomorphic. Sometimes, the tumor cells have intracytoplasmic vacuoles with or without intracytoplasmic mucin, giving the appearance of signet-ring cells (Fig. 3.19b). But unlike signet-ring adenocarcinoma, there is no extracellular mucin. Approximately half of the cases are associated with conventional high-grade urothelial carcinoma [1].

What Are the Diagnostic Criteria of Primary Adenocarcinoma of Bladder?

Primary urothelial adenocarcinoma is a malignant neoplasm derived from the urothelium with pure glandular phenotype. To make a diagnosis of primary adenocarcinoma, there should not be a component of urothelial carcinoma or squamous cell carcinoma. Using these strict criteria, primary adenocarcinoma is very rare and accounts for less than 2% of bladder carcinomas. The morphologic can be enteric (intestinal, Fig. 3.20a), mucinous (colloid), or mixed type. The presence of associated intestinal metaplasia or dysplasia or glandular-type carcinoma in situ might increase the possibility of this diagnosis. It is very important to exclude the possibility of direct invasion of prostate adenocarcinoma from prostate, direct extension or metastasis from colorectal adenocarcinoma (Fig. 3.20b–d), or metastatic adenocarcinomas of other primaries, urachal adenocarcinoma, and extensive cystitis glandularis [19].

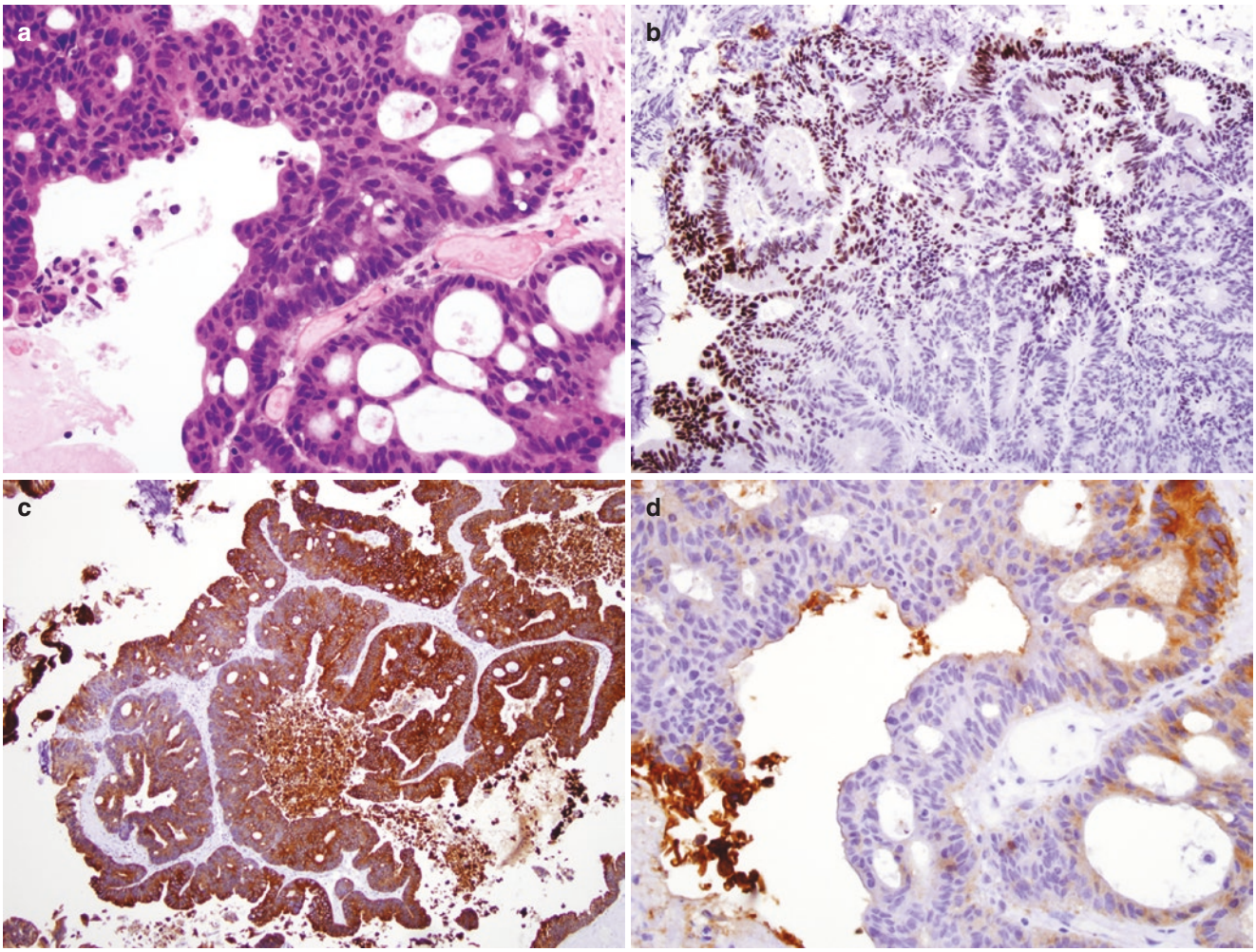

Fig. 3.20 Primary adenocarcinoma of bladder with enteric differentiation (**a**) is positive for CDX2 (**b**) and CK20 (**c**), but negative for β-catenin (**d**)

What Are the Useful Immunohistochemical Markers to Distinguish Bladder Primary Adenocarcinoma from Metastatic Adenocarcinoma?

For enteric-type primary bladder adenocarcinoma, it has overlapping features with colorectal adenocarcinoma. It can also show similar staining patterns with CK7, CK20, and CDX2. Beta-catenin might be helpful as it does not stain with primary bladder adenocarcinoma but frequently shows positive nuclear staining in colorectal adenocarcinoma. NKX3.1 and PSA are helpful when needed to exclude prostatic adenocarcinoma [19].

What Are the Differential Diagnoses of High-Grade Sarcomatoid Neoplasm of the Urinary Bladder?

Major differential diagnoses of spindle cell lesion of urinary bladder encompass malignant epithelial and mesenchymal neoplasms as well as benign tumors. The differential diagnoses of high-grade sarcomatoid neoplasm include mainly sarcomatoid urothelial carcinoma (Fig. 3.21a) and sarcomas including leiomyosarcoma, and rhabdomyosarcoma. The features that favor sarcomatoid carcinoma include history or presence of urothelial CIS or concurrent conventional urothelial carcinoma. Sarcomatoid carcinoma is usually positive for p63, CK5/6, and high-molecular weight cytokeratin and may contain heterologous mesenchymal elements, such as chondrosarcoma or osteosarcoma (Fig. 3.21b). Primary bladder leiomyosarcoma and angiomyosarcoma have the same features as the soft tissue counterparts. Immunohistochemical stains with tissue-specific markers will be helpful for the final diagnosis.

Primary bladder rhabdomyosarcomas occur predominantly in children with an average age of 4 years. Most of them are embryonal and exophytic with or without "botryoid" components. Other histologic subtypes such as small cell, alveolar, and unclassified have also been reported. The diagnosis can be confirmed by immunohistochemical stain

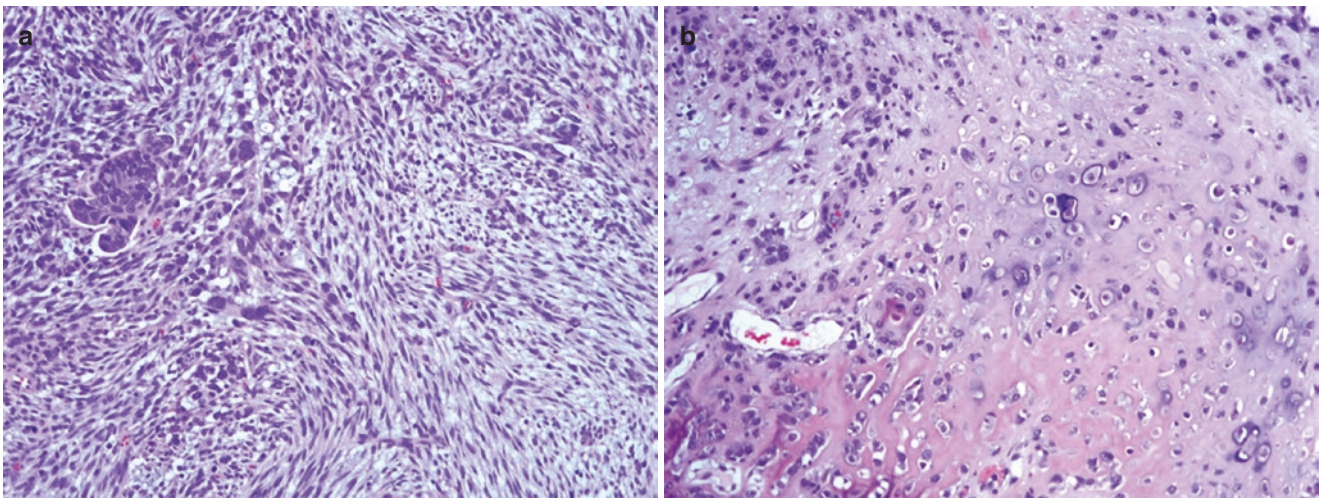

Fig. 3.21 Sarcomatoid urothelial carcinoma shows diffuse spindle cell proliferation with moderately pleomorphic tumor cells and small foci of carcinoma (**a**). Other example of sarcomatoid carcinoma with chondrosarcomatous and osteosarcomatous differentiation is shown (**b**)

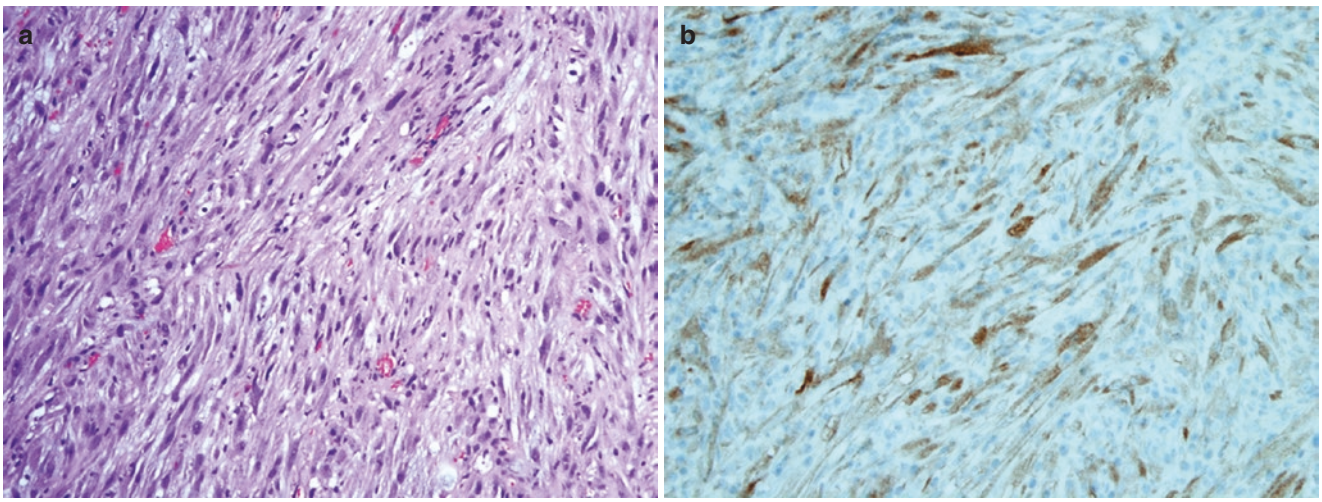

Fig. 3.22 Inflammatory myofibroblastic tumor shows cellular spindle cell proliferation with fascicular growth pattern and inflammatory infiltrate and myxoid stroma (**a**) and is positive for ALK-1 (**b**)

with markers of skeletal muscle differentiation (desmin, myogenin, and MyoD1).

What Are the Differential Diagnoses of Low-Grade Spindle Cell Lesion of Urinary Bladder?

There are a few benign spindle cell tumors that can occur in the urinary bladder. Two morphologically similar tumors are postoperative spindle cell nodule and inflammatory myofibroblastic tumor (IMT). Both tumors show cellular spindle cell proliferation with fascicular growth of plump or elongated cells (Fig. 3.22a). The stroma is edematous or myxoid with delicate vessels. There is viable mitotic activity. No significant pleomorphism or atypical mitotic figure is present. The tumor cells frequently have prominent nucleoli. Patients with postoperative spindle cell nodule has a history of prior bladder surgery or procedure and there may be more prominent extravasation of red blood cells within the stroma. In contract, inflammatory myofibroblastic tumor usually has more prominent inflammatory infiltrate and half of the cases are positive for ALK-1 (Fig. 3.22b).

Other benign mesenchymal tumors (i.e., solitary fibrous tumor (SFT), leiomyoma, and neurofibroma) also occur in urinary bladder and each shows similar features as its counterparts in soft tissue or other visceral organs [20–23].

What Are the Useful Panels of Markers for Diagnosis of Spindle Cell Tumor of Urinary Bladder?

Based on the differential diagnoses of spindle cell lesion of urinary bladder listed in the previous question, a useful panel should include at least following markers: Pan-cytokeratin, CD34, S100, desmin, caldesmon, MyoD1, myogenin, and ALK-1. Additional staining can be ordered based on the results of this basic panel.

What Are the Diagnostic Features of Bladder Paraganglioma? How to Distinguish It from Invasive Urothelial Carcinoma?

For paraganglioma, the tumor nests are typically present as distinctive nests which resemble nested variant urothelial carcinoma. However, paraganglioma cell nests are separated by delicate fibrovascular septa (so-called Zellballen pattern) (Fig. 3.23) while urothelial carcinomatous nests are surrounded by desmoplastic stroma. Unlike urothelial carcinoma, mitosis, hemorrhage, and necrosis are rare in paraganglioma. There is usually no history of bladder cancer and it is not associated with in situ or invasive urothelial carcinoma. In difficult cases, immunostains should be performed to confirm the diagnosis. Paragangliomas are negative for epithelial markers and positive for neuroendocrine markers. Sustentacular cells are highlighted by S100 [24].

What Are the Features that Are Helpful to Diagnose Subepithelial Invasion of Urothelial Carcinoma?

The most helpful feature is small clusters or isolated tumor cells extending beyond the outline of basement membrane with irregular edge and peritumoral retraction spaces (Fig. 3.24a). Look for cytologic differences between the suspicious area and noninvasive carcinoma area, such as greater nuclear atypia or pleomorphism and cytoplasmic eosinophilia or vacuolar changes will support the diagnosis of inva-

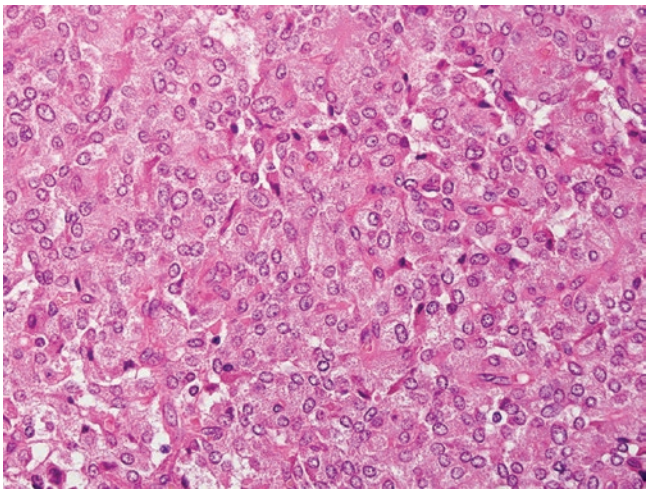

Fig. 3.23 Paraganglioma is composed of nests of polygonal neoplastic cells with abundant eosinophilic granular to clear cytoplasm, central nuclei, and vesicular chromatin

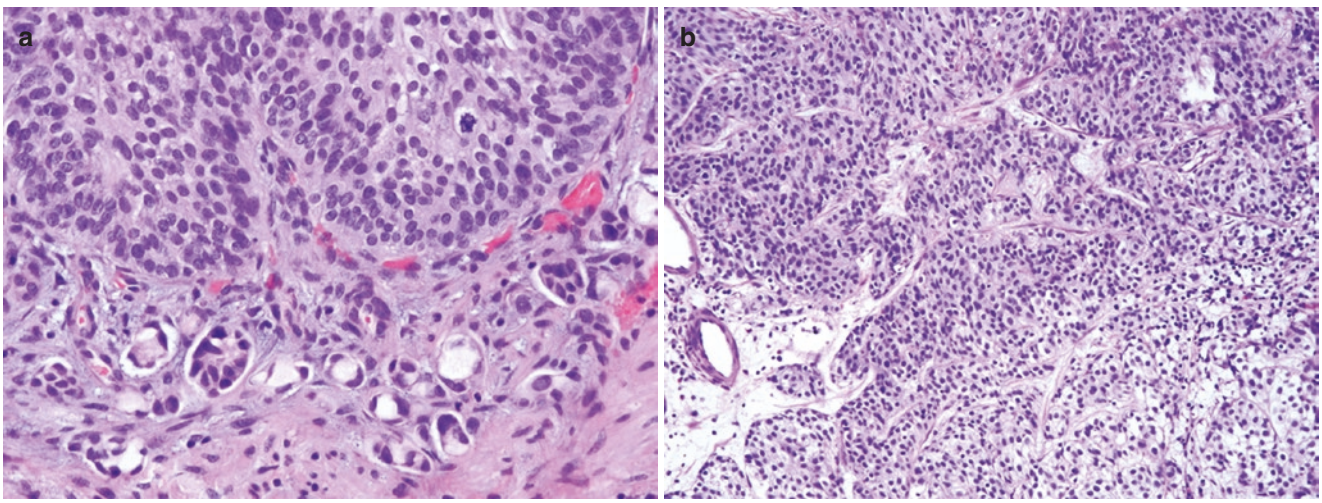

Fig. 3.24 Urothelial carcinoma shows sheets of noninvasive component and subepithelial small clusters tumor cells with pleomorphic nuclei, intracytoplasmic eosinophilia and vacuolization (**a**). Another invasive urothelial carcinoma with confluent growth pattern is shown (**b**)

sion. In addition, confluent tumor growth (Fig. 3.24b) associated with dense stromal desmoplastic reaction is consistent with invasion. Inflammatory infiltrate by itself is not very helpful for diagnosis of invasion.

How to Make a Diagnosis of Muscularis Propria Invasion and What Are the Common Pitfalls?

Muscularis mucosae fibers are usually wispy and discontinuous, whereas muscularis propria usually forms thick muscle bundles (>100 μm in thickness). Tumor cells invading into, surrounded by, and/or immediately adjacent to muscularis propria should be regarded as muscularis propria invasion (Fig. 3.25a). Sometimes, it is difficult to identify muscularis propria invasion when infiltrating tumor cells push apart bundles of muscularis propria widely from each other or destruct muscularis propria extensively which results in a fragmented appearance that may mimic that of muscularis mucosae invasion (Fig. 3.25b). Furthermore, sometimes muscularis mucosae can become hyperplastic so it may be very difficult to distinguish muscularis propria from muscularis mucosa. When associated with undetermined muscle fibers, the following features favor muscularis mucosa: location of muscle fibers near urothelial surface; disorganized, myxoid, and reactive stroma; presence of clusters of large caliber vessels (so called vascular plexuses) and inflammation [25, 26].

What Are the Differential Diagnoses of Urothelial Neoplasm with Endophytic Growth Pattern and What Are Features That Can Be Helpful in Resolving the Diagnosis?

Differential diagnoses of urothelial neoplasm with endophytic growth pattern range from benign inverted papilloma to invasive high-grade urothelial carcinoma. The prototype inverted urothelial neoplasm is benign inverted papilloma. Cystoscopically, it has a raised, pedunculated or rarely polypoid lesion with a smooth surface. Microscopically, it has a normal smooth surface urothelium and is composed of endophytically growing trabeculae or cords of urothelial cell with a smooth pushing border and a peripheral palisading. The tumor cells are bland with no or rare mitoses and there is no stromal reaction (Fig. 3.26a). Rarely, nests of inverted papilloma may show glandular differentiation or nonkeratinizing squamous metaplasia. It is important to differentiate benign inverted papilloma from malignant urothelial neoplasm with inverted growth. Papillary urothelial neoplasm of low-malignant potential (PUNLMP), low-grade and high-grade urothelial carcinoma can have focal or extensive component of inverted growth. The histologic features that can be used to distinguish urothelial neoplasms with inverted growth from benign inverted papilloma are: (1) presence of exophytic component (Fig. 3.26b), (2) thicker endophytically growing cords and more complex architecture, and (3) higher degree of cytologic atypia corresponding to PUNLMP, low- and high-grade urothelial carcinoma.

Occasionally, florid von Brunn nests, cystitis cystica/glandularis may mimic inverted papilloma. However, unlike inverted papilloma, it has more of a lobular architecture with round contour and lacks anastomosing cords or trabeculae [27].

Are There Any Immunohistochemical Markers that Can Help Diagnose Muscularis Propria Invasion?

In cystectomy specimen, distinction between muscularis mucosa and muscularis propria is usually not a problem. The muscularis mucosa is composed of delicate muscle bands often associated with large vessels, whereas muscularis propria consists of compact, thick muscle bundles (Fig. 3.27a).

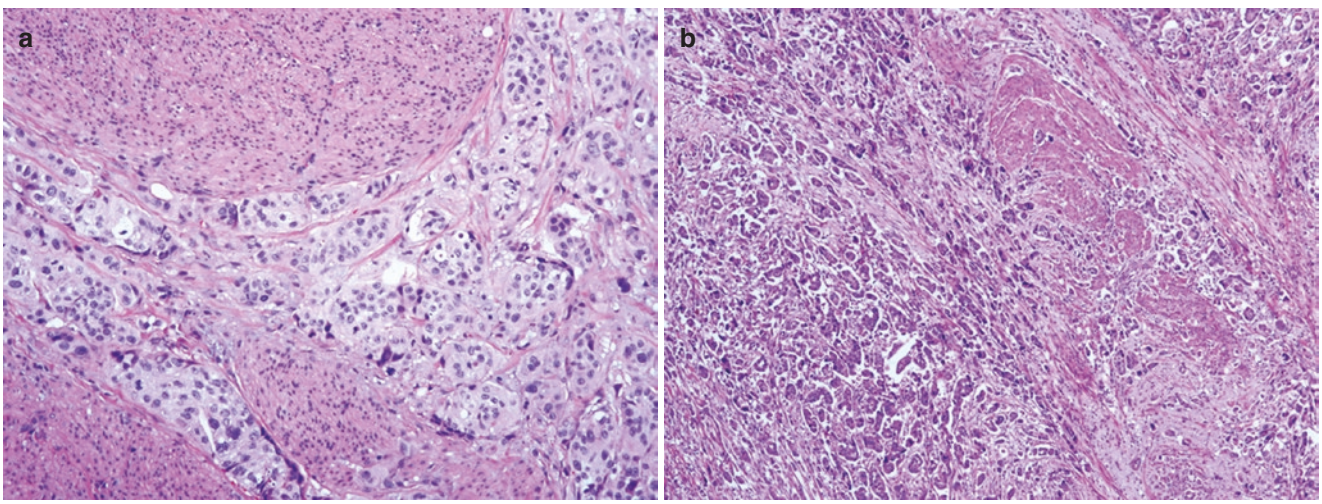

Fig. 3.25 Invasive urothelial carcinoma shows involvement of muscularis propria with nests of tumor cells surrounding large bundles of muscle (**a**). Another example shows invasive urothelial carcinoma destroying bundle of muscle into small fascicles obscuring the outline of muscularis propria bundles (**b**)

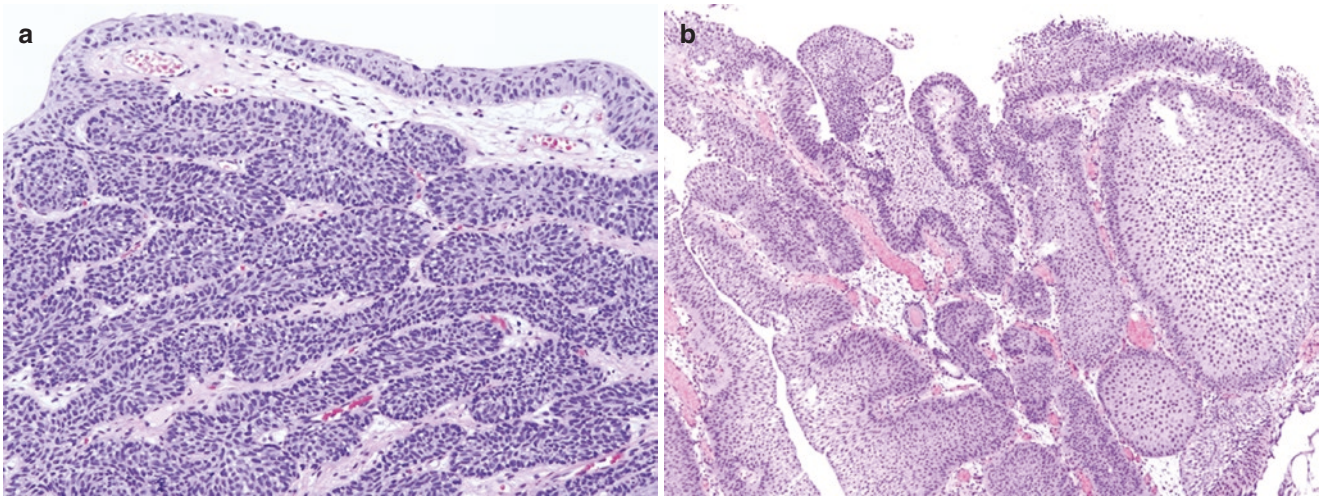

Fig. 3.26 Urothelial inverted papilloma shows a smooth surface with nests, cords and trabeculae of urothelial cells and focal peripheral palisading (**a**). Low-grade urothelial carcinoma with inverted growth pattern and exophytic component (**b**)

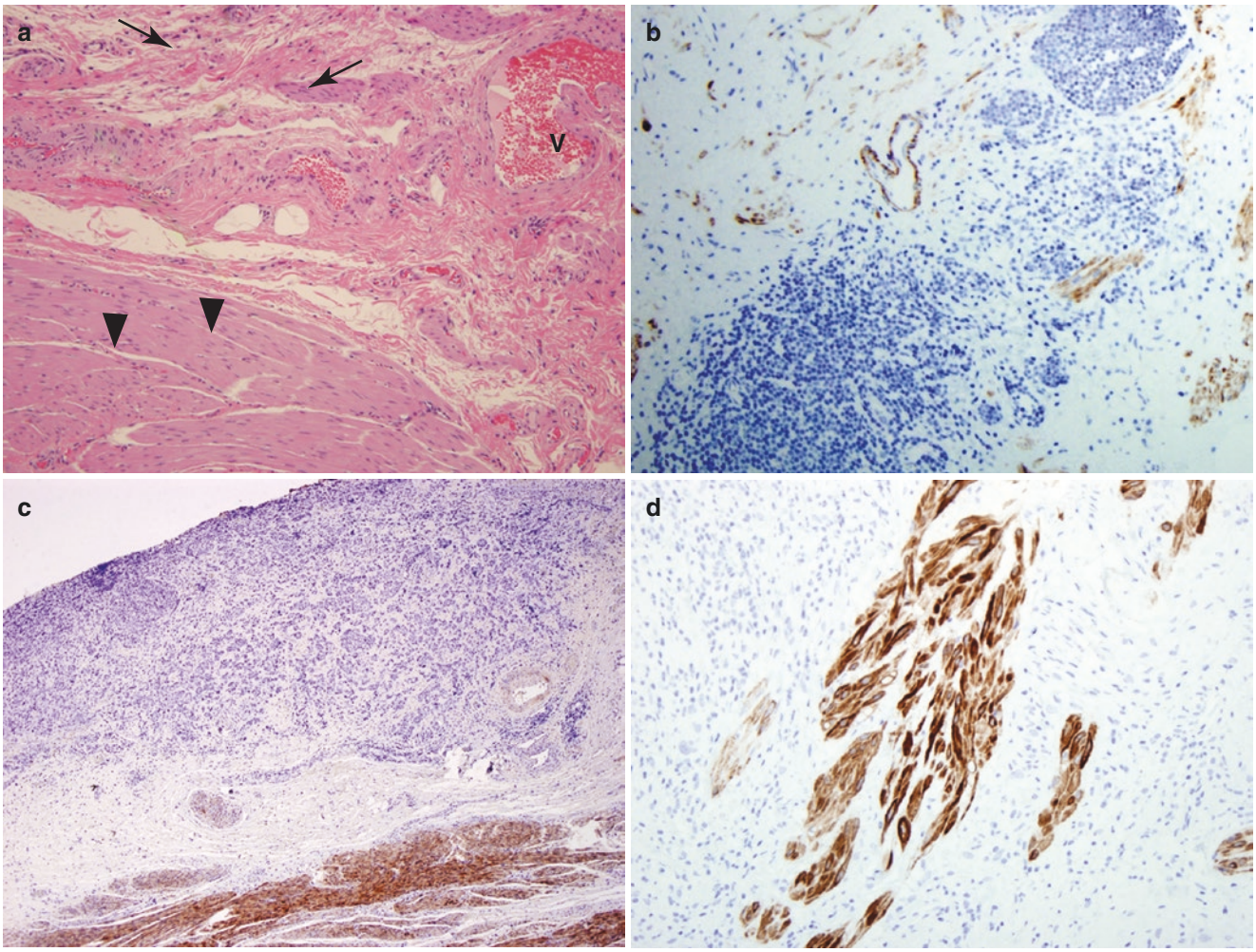

Fig. 3.27 Muscularis mucosae (arrow) consists of delicate muscle bands in close proximity to a large vessel (V), whereas muscularis propria (arrowheads) consists of thick muscle bundles deeper than muscularis mucosae (**a**). Muscularis mucosae is weakly positive for smoothelin (**b**, **c**), whereas muscularis propria is strongly and diffusely positive for smoothelin (**c**, **d**)

However, this distinction can be problematic in transurethral resection specimen. Both smoothelin and vimentin have been studied to aid the diagnosis of muscularis propria invasion, based on the difference in staining pattern of these two markers between muscularis propria and muscularis mucosae. Muscularis mucosae is either negative or stains weakly (occasionally moderately) and focally for smoothelin (Fig. 3.27b, c), and is rarely positive for vimentin. Muscularis propria, however, usually stains strongly and diffusely with smoothelin (Fig. 3.27c, d) and is positive for vimentin. However, one should bear in mind that staining pattern and intensity of smoothelin and vimentin may overlap between muscularis propria and muscularis mucosae [28].

What Are the Most Common Tumors that Secondarily involving the Bladder by Direct Extension or Distant Metastasis?

The most common primary tumor sites for secondary bladder involvement (mostly via direct extension, occasionally via metastasis) are colon (Fig. 3.28) and rectum (40% combined), prostate in men (19%), and cervix in women (11%). The most common primary sites for metastasis to the bladder are stomach, skin, lung, and breast with percentage rates of 4.3%, 3.9%, 2.8%, and 2.5%, respectively [29].

For a Poorly Differentiated Carcinoma, What Are the Best Markers to Establish that Urothelial (Bladder) as a Primary?

There is no great marker that is specific for urothelial carcinoma. However, for poorly differentiated carcinoma, starting with CK7 and CK20 immunostains can be a good option as 65–89% of urothelial carcinoma shows double positive stains for CK7 and CK20, and about 35% of urothelial carcinomas are positive only for CK7, but not for CK20. The other useful markers for urothelial differentiation are GATA-3, 34βE12, p63, CD141, uroplakin II, and uroplakin III.

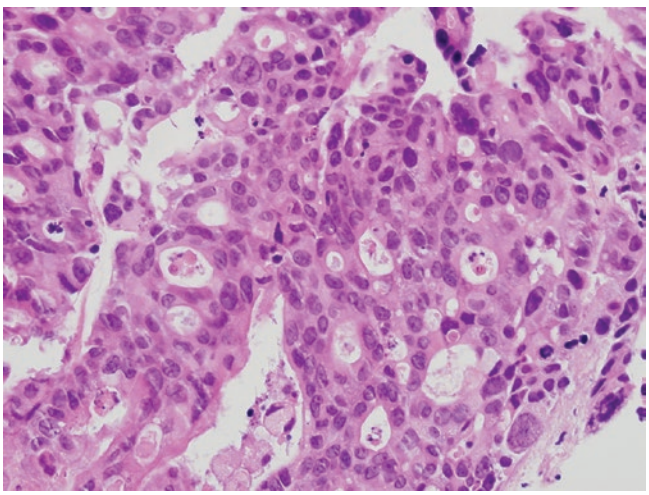

Fig. 3.28 Metastatic colonic adenocarcinoma involves the bladder

What Are the Most Useful Morphologic Features to Distinguish Urothelial Carcinoma from High-Grade Prostate Carcinoma?

In general, morphologic features that favor urothelial carcinoma include marked nuclear atypia and pleomorphism, frequent mitoses and tumor cell necrosis, squamous differentiation, and presence of conventional urothelial carcinoma or urothelial carcinoma in situ. In contrast, high-grade prostate carcinoma shows relatively uniform monotonous ovoid to round tumor cells, prominent nucleoli, grows in solid nests (Fig. 3.29a), and shows focal cribriform or glandular differentiation (Fig. 3.29b). In small or poorly preserved specimen, immunohistochemistry with a small panel of markers (GATA3, p63, PSA, PSAP or NKX3.1) will be helpful to confirm the diagnosis.

How to Distinguish Urothelial Carcinoma with Squamous Differentiation from Cervical Squamous Cell Carcinoma?

Squamous differentiation is a very common finding in urothelial carcinoma. In female patients, cervical squamous cell carcinoma may enter the differential diagnosis for urothelial carcinoma with squamous differentiation. In addition to the history of cervical primary or positive cytology, testing of high-risk HPV or p16 immunohistochemistry will indicate cervical squamous cell carcinoma. On the other hand, presence of urothelial carcinoma in situ and conventional papillary urothelial carcinoma strongly support a diagnosis of a urothelial carcinoma with squamous differentiation. Clinical and radiological correlations are necessary for a definitive diagnosis.

What Are the Most Common Patterns of Prostatic Urothelial Carcinoma in Patients with Bladder Cancer?

The most common pattern of prostatic urothelial carcinoma in patients with concomitant bladder cancer is urothelial carcinoma in situ involving prostatic urethra and prostatic ducts (Fig. 3.30a). Other patterns include subepithelial invasion of prostatic urethra (Fig. 3.30b), prostatic stromal invasion (Fig. 3.30c) resulting from either pros-

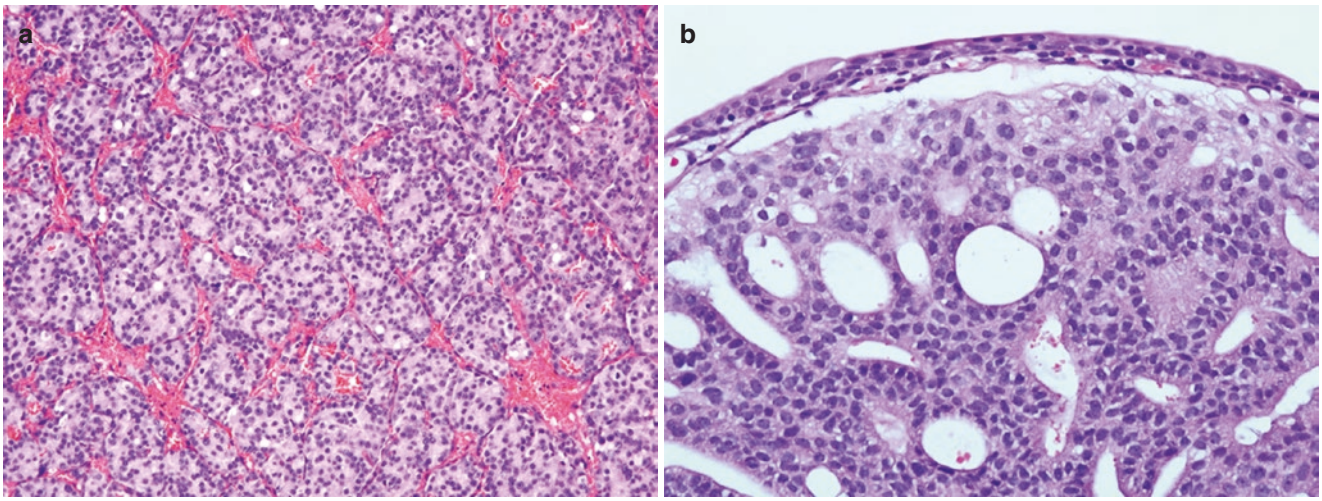

Fig. 3.29 Prostate adenocarcinoma with crowded back to back glandular proliferation of monotonous tumor cells (**a**). Cribriform prostate adenocarcinoma involves in the subepithelial tissue of bladder wall and overlying benign urothelium (**b**)

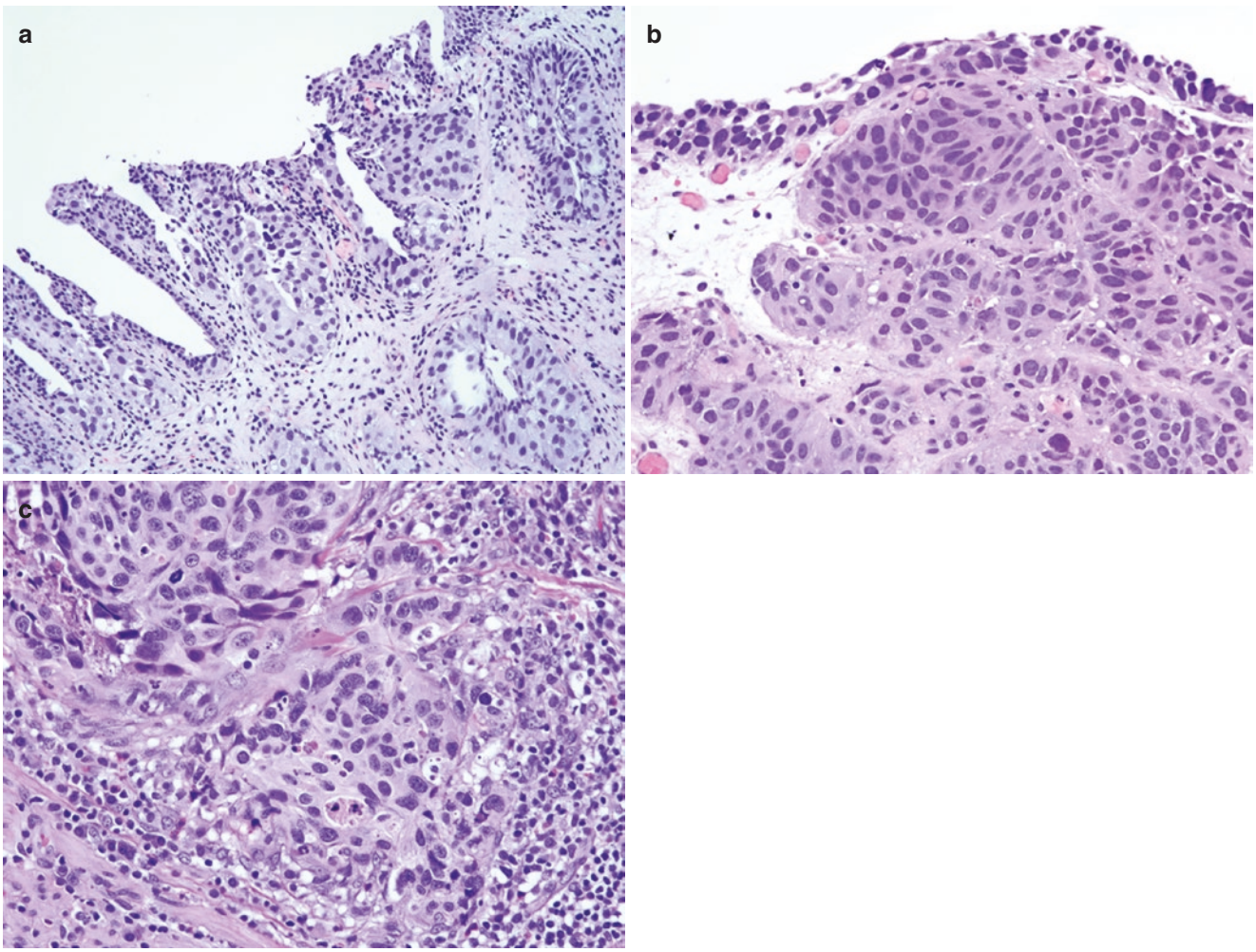

Fig. 3.30 This image shows prostatic urethra with urothelial carcinoma in situ involving prostatic urethra and duct (**a**). Prostatic urethra shows surface urothelial carcinoma in situ and invasive urothelial carcinoma within submucosal tissue (**b**). Urothelial carcinoma next to benign prostatic glands indicates prostatic stromal invasion (**c**)

tatic urethra or duct/acini, or direct transmural invasion of prostate by bladder cancer through bladder neck or extraprostatic tissue [30].

What Are the Diagnostic Features of Carcinoma of Müllerian Type?

Bladder carcinomas of Müllerian type are newly recognized variants of bladder adenocarcinoma. The two common histologic subtypes are clear cell carcinoma and endometrioid carcinoma. While endometrioid carcinoma occurs only in female, clear cell carcinoma is more commonly seen in females, but also in males. It appears that endometrial carcinoma and a small subset of clear cell carcinoma are associated with Müllerian precursors in the bladder such as endometriosis (common) and Müllerianosis (rare). Clear cell carcinoma often represents a specific form of glandular differentiation in urothelial carcinoma.

Morphologically, both clear cell carcinoma and endometrioid carcinoma are similar to their counterparts in endometrium or ovary. Clear cell carcinoma usually has a diverse growth pattern with tubulocystic, papillary, and diffuse solid growth patterns (Fig. 3.31a). The tumor cells are flat, cuboidal, or columnar with clear cytoplasm, hobnail appearance, marked cytologic atypia, and frequent mitotic features (Fig. 3.31b). The tumor usually involves bladder lamina propria and most tumors harbor genetic alterations similar to those reported in urothelial carcinoma, although clear cell carcinomas are associated with endometriosis. Immunohistochemically, clear cell carcinoma is positive for CK7, EMA, Pax8, HNF1β, AMACR, and CA-125. In contrast, endometrioid carcinoma (Fig. 3.17c–f) usually has an epicenter toward the bladder serosa and is frequently associated with adjacent endometriosis. The tumor has a variable histologic appearance ranging from well-formed endometrioid glands that may show squamous or mucinous differentiation to poorly different solid carcinoma and is usually positive for estrogen and progesterone receptors [31].

What Are the most Common Nonurothelial Carcinomas in Urinary Bladder?

Squamous cell carcinoma is the most common nonurothelial carcinoma in urinary bladder, accounting for 1.3% of bladder tumor in males and 3.4% of bladder tumor in females. However, in some African countries and Middle East, squamous cell carcinoma is much more common, and the prevalence can be higher than that of urothelial carcinoma, primarily due to *Schistosoma haematobium* infection. Primary adenocarcinoma in bladder is the second most common nonurothelial carcinoma, accounting for 0.5–2% of bladder carcinomas [32].

What Are the Diagnostic Features of Bladder Squamous Cell Carcinoma?

The diagnosis of bladder squamous cell carcinoma is reserved for tumors with purely squamous component and is characterized by the presence of tumor cells with keratin pearls and intercellular bridges (Fig. 3.32a, b). If urothelial CIS or conventional urothelial carcinoma is present, the tumor should be classified as urothelial carcinoma with squamous differentiation. Most bladder squamous cell carcinomas are moderately and poorly differentiated. Keratinizing squamous metaplasia and dysplasia are present in about half

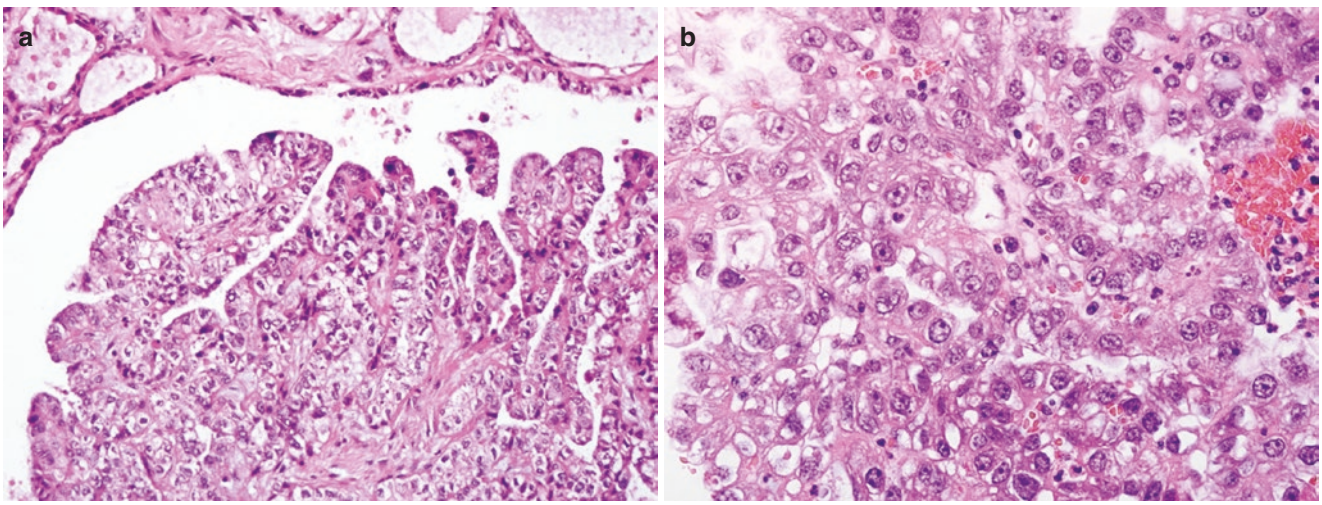

Fig. 3.31 A case of clear cell carcinoma shows papillary architecture (**a**), cells with clear cytoplasm and cytologic atypia (**b**)

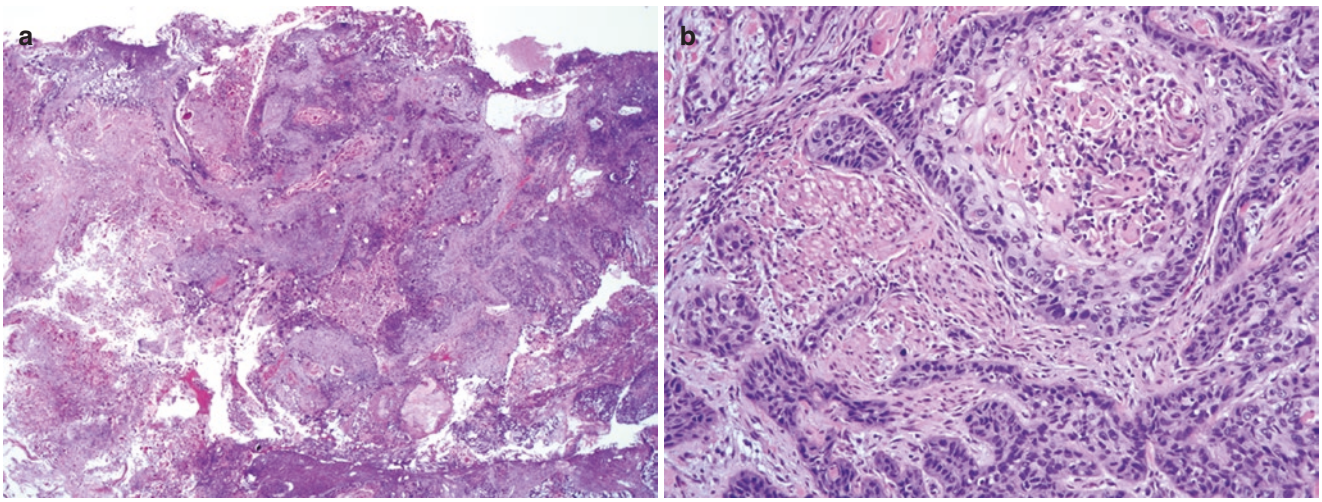

Fig. 3.32 This low power image shows well and moderately differentiated squamous cell carcinoma with prominent keratinization (**a**). An example of invasive moderately differentiated squamous cell carcinoma involving muscularis propria is shown (**b**)

of the cases. Infection of *S. haematobium* is a significant risk factor in some African countries [32].

What Are the Features of Tumors in Bladder Diverticulum?

About one-third of the tumors arising in bladder diverticulum are noninvasive papillary urothelial carcinoma (low or high grade). About half of the invasive carcinomas are conventional invasive urothelial carcinomas. The other histologic subtypes arising in diverticulum include small-cell carcinoma, squamous cell carcinoma, and adenocarcinoma [33].

Case Presentation

Case 1

A 65-year-old man with complicated medical history was found to have a bladder tumor and underwent transurethral resection. Microscopically, at low magnification, the tumor has complex papillary architecture (Fig. 3.33a). The surface noninvasive component shows micropapillary configuration (Fig. 3.33b). Within subepithelial tissue, the tumor shows irregular nests of tumor cells with prominent nuclear atypia and characteristic peritumoral retraction artifact (Fig. 3.33c). In addition, the tumor cells show paradoxical maturation with more abundant cytoplasm with eosinophilia and vacuolization (Fig. 3.33d).

Case 2

A 75-year-old man with biopsy diagnosis of invasive high-grade urothelial carcinoma underwent radical cystoprostatectomy and bilateral pelvic lymph node dissections. The biopsy shows both noninvasive high-grade papillary urothelial carcinoma (Fig. 3.34a) and invasive carcinoma with solid confluent growth (Fig. 3.34b) and focal micropapillary component (Fig. 3.34c). Final diagnose of cystectomy was invasive urothelial carcinoma with perivesical invasion and lymph node metastasis (Fig. 3.34d).

Case 3

An 82-year-old woman with hematuria and a CT scan showed exophytic bladder tumor at the left lateral wall. Transurethral resection of tumor was performed. Microscopically, the tumor is composed of both solid conventional urothelial carcinoma and small-cell carcinoma component (Fig. 3.35a). High power shows small-cell carcinoma with high N/C ratio, scant cytoplasm, nuclear crowding and molding, frequent mitotic figures and apoptosis (Fig. 3.35b). The tumor cells are diffused and strongly positive for CD56 (Fig. 3.35c) and positive for chromogranin (Fig. 3.35d).

Case 4

A 74-year-old man with history of prostate cancer status postradiation therapy and now presented with hematuria.

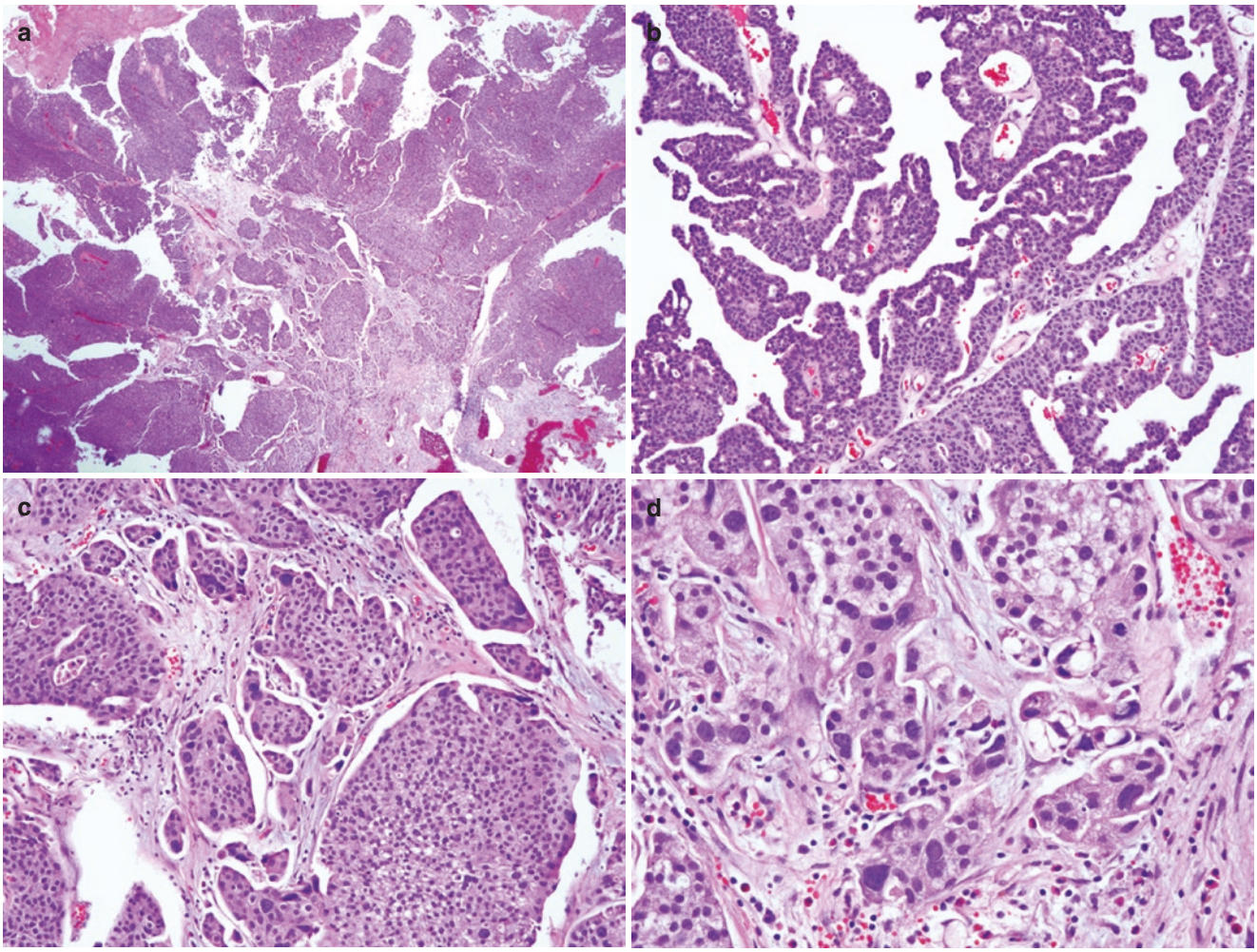

Fig. 3.33 Low power view of a high-grade papillary urothelial carcinoma with prominent exophytic component and subepithelial invasion (**a**). This area shows focal surface micropapillary component with secondary delicate papillae and lack of fibrovascular core (**b**), which is often associated with high-grade invasive urothelial carcinoma. At the interface of noninvasive papillary carcinoma and subepithelial tissue, multiple small irregular nests of tumor cells and retraction artifact are present, indicating invasive carcinoma (**c**). High-power view of small invasive foci with greater nuclear atypia and cytoplasmic vacuolization

He was diagnosed with high-grade papillary urothelial carcinoma and underwent multiple cycles of intravesical BCG therapy. Follow-up cystoscopy and biopsy show focal area of urothelial carcinoma in situ (Fig. 3.36a), and nephrogenic adenoma with denuded urothelium lined by single layer of cuboidal epithelial cells and subepitheliual proliferation of tubules and cysts lined by uniform cuboidal cells, luminal secretion, and a granulation tissue background (Fig. 3.36b). The tubules are positive for cytokeratin 7 (Fig. 3.36c) Pax 8 (Fig. 3.36d) by immunohistochemistry.

Case 5

A 47-year-old man with history of sigmoid colon cancer status post rectosigmoidectomy now presented with bladder cancer 3 years later underwent transurethral resection. Microscopically, the tumor shows a tubulopapillary growth pattern and invasive component within subepithelial tissue (Fig. 3.37a). On high power, the tumor glands are lined by pseudostratified columnar cells and desmoplastic stroma (Fig. 3.37b). By immunohistochemistry, the tumor cells are positive for Cytokeratin 20 (Fig. 3.37c) and CDX-2 (Fig. 3.37d).

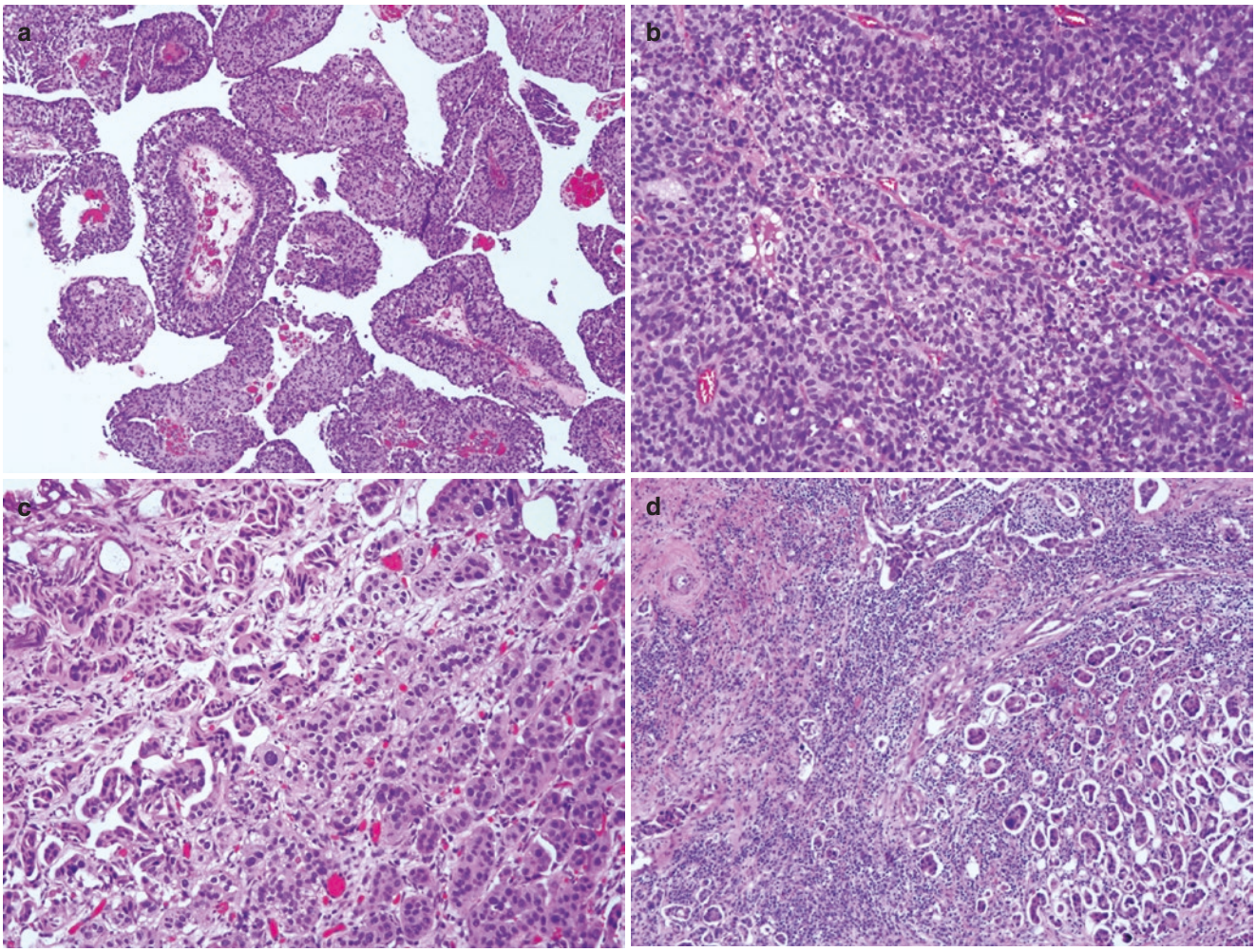

Fig. 3.34 This image shows exophytic noninvasive papillary urothelial carcinoma component (**a**). This area exhibits confluent invasive growth of urothelial carcinoma. Other areas show conventional invasive urothelial carcinoma with focal micropapillary carcinoma component (**c**). Nodal metastasis with micropapillary carcinoma is shown (**d**)

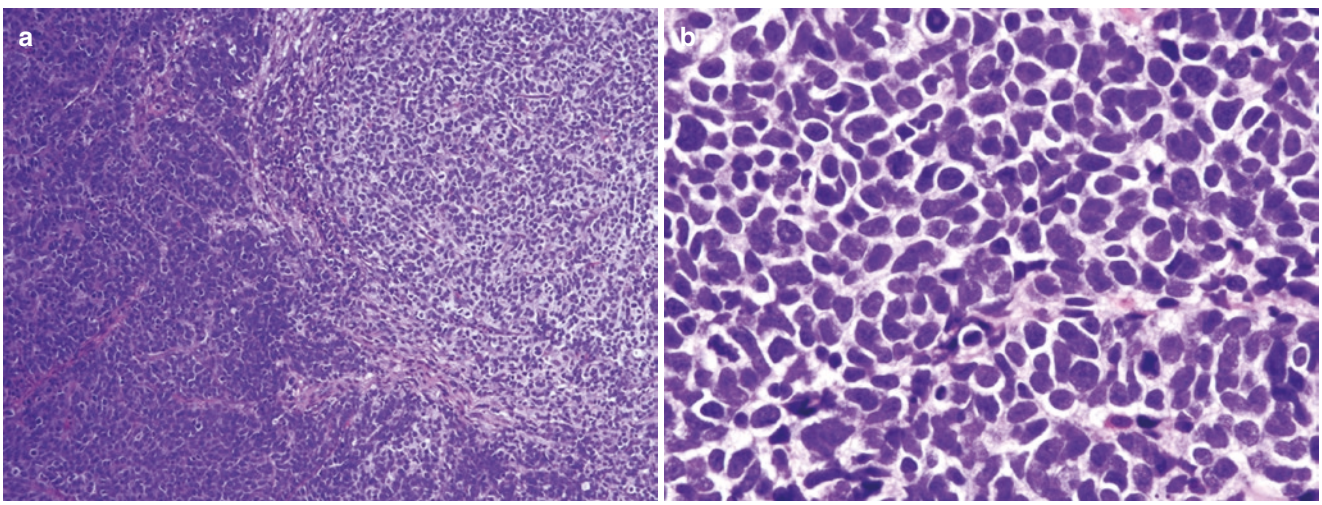

Fig. 3.35 This is an example of conventional high-grade urothelial carcinoma associated with small cell carcinoma (**a**). High power view of small-cell carcinoma exhibits nuclear crowding and molding, high N/C ratio, hyperchromatic nuclei and salt–pepper chromatin (**b**). The tumor cells are diffuse and strongly positive for CD56 (**c**) and chromogranin (**d**)

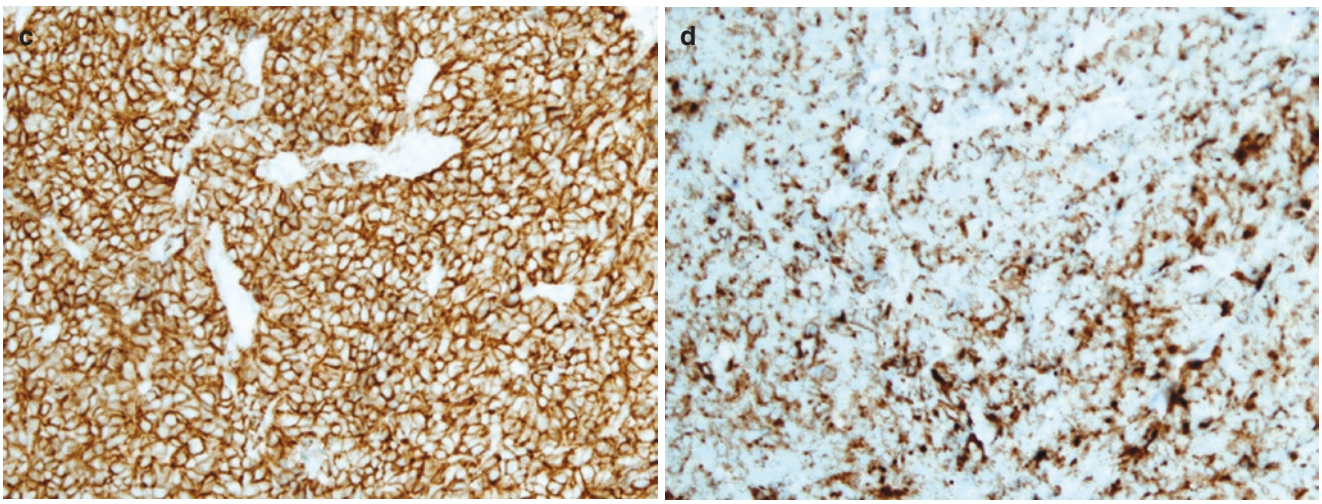

Fig. 3.35 (continued)

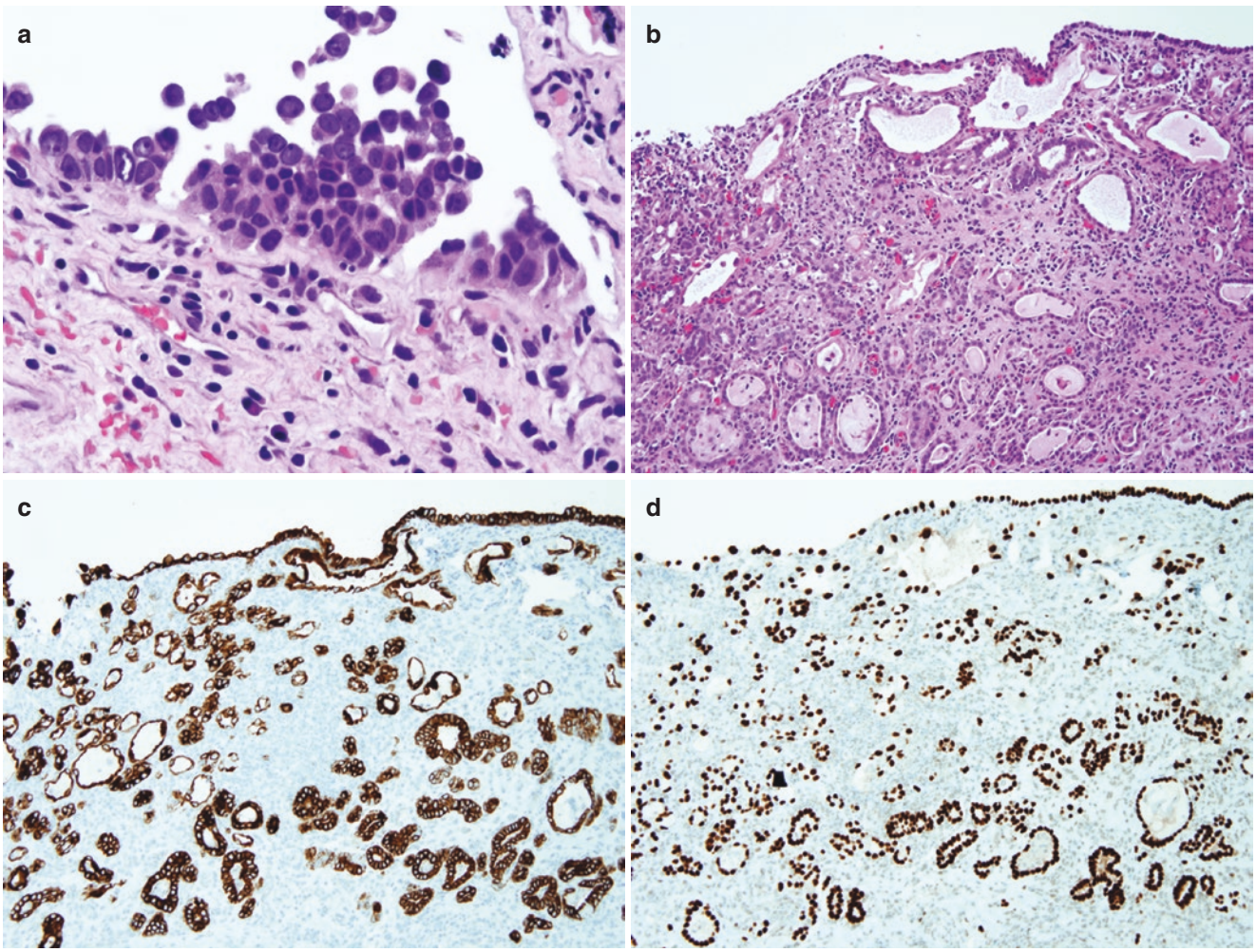

Fig. 3.36 Bladder biopsy shows urothelial carcinoma in situ characterized by nuclear pleomorphism and enlargement, high N/C ratio and hyperchromasia (**a**). This area shows features of nephrogenic adenoma with single layer surface lining, subepithelial proliferation of tubules and cysts lined by uniform cuboidal cells in a granulation tissue background (**b**). The diagnosis of nephrogenic adenoma is confirmed by positive immunoreactivity with CK7 (**c**) and PAX 8 (**d**)

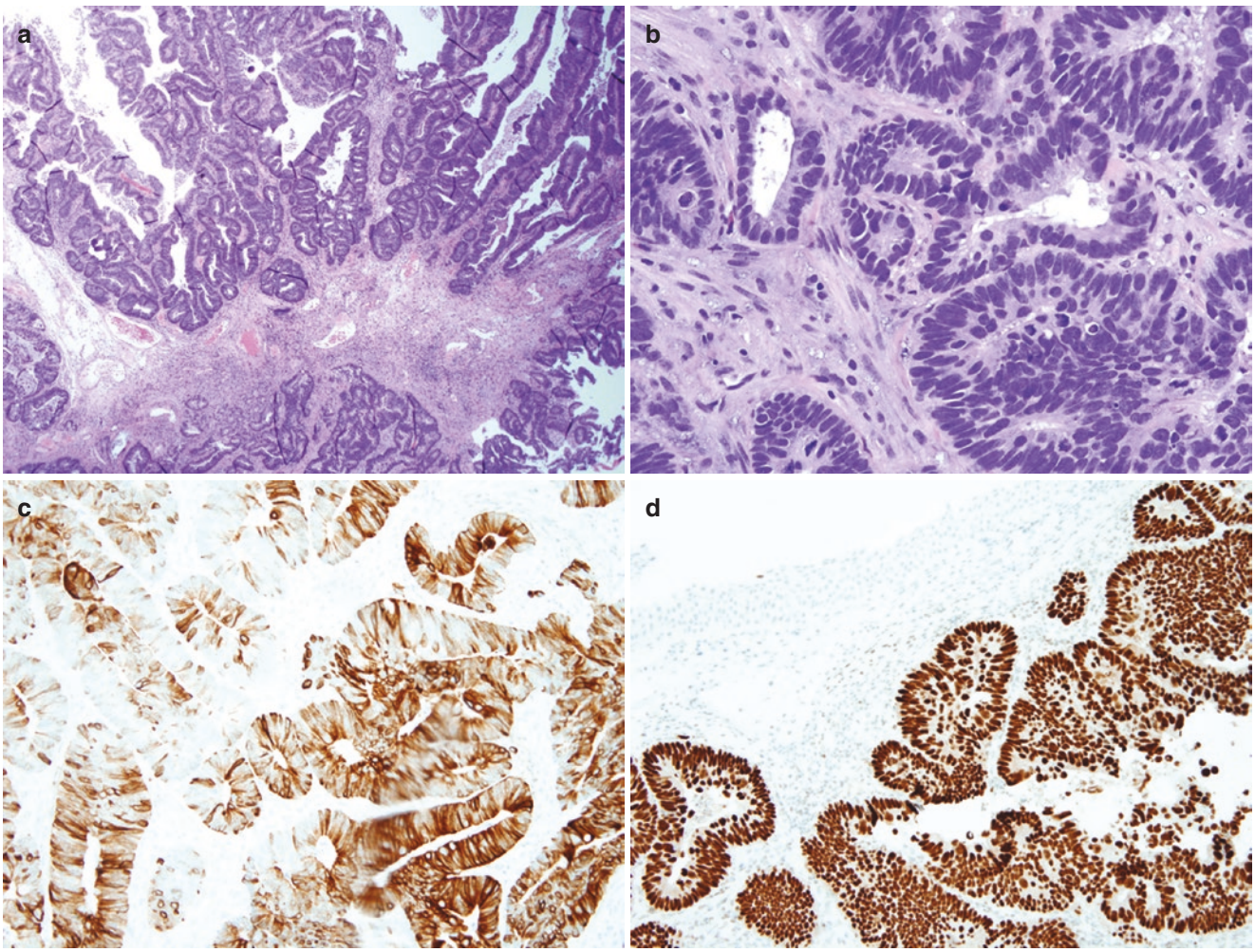

Fig. 3.37 This low power image shows invasive adenocarcinoma with tubulovillous pattern and subepithelial invasion (**a**). High power shows irregular glands lined by pseudostratified columnar cells and desmoplastic stromal reaction (**b**). The tumor cells are positive for CK20 (**c**) and strongly positive for CDX-2 (**d**)

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