Other Types of Carcinoma

7

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Squamous Cell Carcinoma

Introduction

The 2016 World Health Organization (WHO) classification defines urinary bladder squamous cell carcinoma (SCC) as a carcinoma derived from the urothelium with a histologically pure squamous cell phenotype [1]. Therefore, if elements of an invasive or noninvasive urothelial carcinoma (UC) are present, the tumor should be classified as urothelial carcinoma with squamous differentiation. Although there are several potential etiologic factors, such as prolonged catheterization and smoking, which lead to the development of urinary bladder SCC, the most significant factor is chronic bilharzial infection. In Western countries where bilharzial infection is not endemic, pure SCC is an uncommon variant of urinary bladder cancer. In contrast, urinary bladder SCC is the most prevalent histological type of bladder cancer in the Middle Eastern and African countries, where its pathogenesis is linked to an endemic, chronic bilharzial infection. A comparison between non-bilharzial and bilharzial SCC is summarized in Table 7.1.

Epidemiology

Primary SCC in non-bilharzial urinary bladder is uncommon. In Western countries, pure SCC of the bladder represents 2.1–6.7% of all bladder malignancies [2–5]. The tumors are most often diagnosed in the seventh decade [2, 3, 5]. The male-to-female ratio for non-bilharzial SCC is slightly lower than that reported for UC and varies from 1.3:1 to 1.8:1 [2–4].

The incidence of bilharzial bladder SCC is highest in Egypt, yet other countries, including Iraq, parts of Saudi Arabia, Yemen, and Sudan, also share a high incidence of this cancer type. In an earlier case series reported by Ghoneim et al., SCC accounts for 608 (59%) of 1026 cystectomy specimens collected in Egypt over a 21-year span [6]. However, a more recent report from Egypt has indicated that UC is currently more common than SCC, which corresponds to a decrease in bilharziasis incidence [7]. The male-to-female ratio is 5:1, and patients with bilharzial SCC are on an average 10–20 years younger than those diagnosed with non-bilharzial SCC, which is

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H. Zhou et al. (eds.), *Urinary Bladder Pathology*, https://doi.org/10.1007/978-3-030-71509-0_7

Table 7.1 Comparison between non-bilharzial and bilharzial SCC of the urinary bladder [4]

Features	Non-bilharzial SCC	Bilharzial SCC
Epidemiology, causes, and clinical findings		
Geographical distribution	Western countries	Middle East, Africa, Southeast Asia, South America
% in all bladder malignancies	2.1–6.7%	59%
Age	Seventh decade	Fifth decade
Male/female	1.3–1.8:1	5:1
Principal predisposing factor	Prolonged catheterization in patients with spinal cord injury	Bacterial infections associated with bilharziasis
Principal symptom	Hematuria	Irritative bladder
Pathological findings		
Commonest gross feature	Ulcerative	Nodular
Predominant site	Lower part of the bladder	Upper part of the bladder
Differentiation	Most are moderately to poorly differentiated	Most are well to moderately differentiated
Stage	Most are advanced	Most are advanced
Nodal involvement	8–10%	15–20%
Treatment and prognosis		
Standard treatment	Radical cystectomy	Radical cystectomy
5-year survival	50–55%	43–57%

SCC, squamous cell carcinoma

most likely related to an increased occupational bilharzial exposure in men who work in the fields infested with these parasites [8, 9].

Etiology

In the United States, SCC of the bladder often occurs in patients with a spinal cord injury who are subjected to prolonged placement of indwelling catheters [10]. In these patients, diagnosis of non-bilharzial SCC is linked to bladder inflammation caused by chronic urinary tract irritation from bacterial infections, foreign bodies, bladder calculi, or chronic bladder outlet obstructions. These recent studies reveal that the declining bladder cancer incidence may be associated with a change in catheterization procedures from chronic indwelling catheters to clean intermittent catheterization [11]. In addition to catheterization-associated bladder SCC, there are several other potential causes that give rise to this cancer. There has been one case report of an SCC of the bladder diagnosed consequently to intravesical immunotherapy with bacillus Calmette-Guérin (BCG) in a patient with preexisting squamous dysplasia [12].

Bilharzial SCC carcinogenesis is most likely related to the secondary bacterial infections that accompany bilharzial infestation, rather than the parasite itself. This chronic bacterial infection has two distinct sequelae: (1) nitrates and secondary amines in the urine are reduced to carcinogenic nitrosamines through bacterial catalysis, and (2) bacterial infection is implicated in the secretion of the β-glucuronidase enzyme, which may split conjugated carcinogens to yield free carcinogenic products [13, 14]. These carcinogens then act upon the mucosal epithelial cells of the bladder, resulting in irreversible and potentially carcinogenic changes in the DNA. Additionally, mechanical irritation and inflammation of the bladder caused by the parasite's eggs also appears to be an important tumor-promoting factor [7]. Finally, other contributing factors include liver dysfunction, vitamin A and B deficiency, smoking, chronic irritation due to urinary calculi, and exposure to pesticides [7, 14].

Clinical Features

Principal clinical features of non-bilharzial urinary bladder SCC are similar to those of UC. Hematuria is the most common symptom, seen in 63–100% of patients, and irritative bladder symptoms are seen in two-thirds of these patients. Weight loss, back or pelvic pain, and obstructive symptoms are often suggestive of advanced disease, seen in one-third of patients [2, 3]. At diagnosis, most patients have no previous history of urologic tumors. Finally, the tumor may occupy a diverticulum, and its relationship with bladder calculi has been well described [2, 3].

The clinical presentations of bilharzial SCC are similar to those of chronic cystitis: frequent and painful micturition, hematuria, suprapubic pain, and pyuria [8, 15]. Consequently, symptoms of regular bilharzial cystitis and early SCC significantly overlap, leading to a delay in cancer diagnosis. Therefore, almost all patients with SCC have at least some degree of muscle-invasive disease, and 25–30% of the patients are clinically inoperable at the time of diagnosis [8, 15].

Pathological Features

In terms of gross findings, non-bilharzial SCCs of the bladder are not much different from UC and tend to be ulcerated, infiltrating, and unifocal at the time of diagnosis (Fig. 7.1a), while 60–80% of the bilharzial SCC cases appear as nodular fungating tumors [8, 16]. In a study of 114 patients with non-bilharzial SCC, a predilection for the trigone and lateral wall has been recorded, occurring in 56 and 99 patients (including those with multiple tumors), respectively [3]. The tumor usually arises from the upper part of the urinary bladder at the posterior/lateral wall or vault. In contrast to the non-bilharzial SCC, trigonal tumors are rare. The cut surface usually demonstrates a firm, white tumor that spans the entire wall of the bladder, lamina propria, muscularis propria, and perivesical fat, and sometimes extends to adjacent organs (Fig. 7.1b).

Regardless of the existence of bilharzia, the histological hallmarks of bladder SCCs are polygonal tumors cells with individual keratinization or group keratinization (keratin-pearl formation), intercellular bridges, and keratotic cellular debris. Well-differentiated SCCs show tumor nests with marked squamous differentiation (Fig. 7.2a). In moderately differentiated SCCs, nests are more irregular in outline, and keratotic foci are smaller (Fig. 7.2b). Poorly differentiated SCCs consist of even smaller infiltrative nests, cords, trabeculae, or isolated anaplastic cells (Fig. 7.2c). Tumor necrosis is frequently seen and appears to inversely correlate with tumor differentiation. Keratinization of cells at the stromal interface is a sign of invasion. Most non-bilharzial SCCs are moderately to poorly differentiated, and well-differentiated SCCs comprise less than 10% of all cases [17]. In contrast to non-bilharzial SCC, almost half of the bilharzial SCCs are well-differentiated and show abundant keratinization with keratin pearl formation. Of the remaining tumors, 30–40% and 10–20% are moderately and poorly differentiated, respectively [8, 15, 16]. As shown in Fig. 7.2d, almost all of the bilharzial SCC specimens show histological evidence of bilharzial infection [8]. Active bilharzial granulomas are observed in 10% of the cases, although mature worms of *Schistosoma* species are rarely seen inside veins.

Both bilharzial and non-bilharzial SCCs are usually diagnosed at a muscle-invasive stage

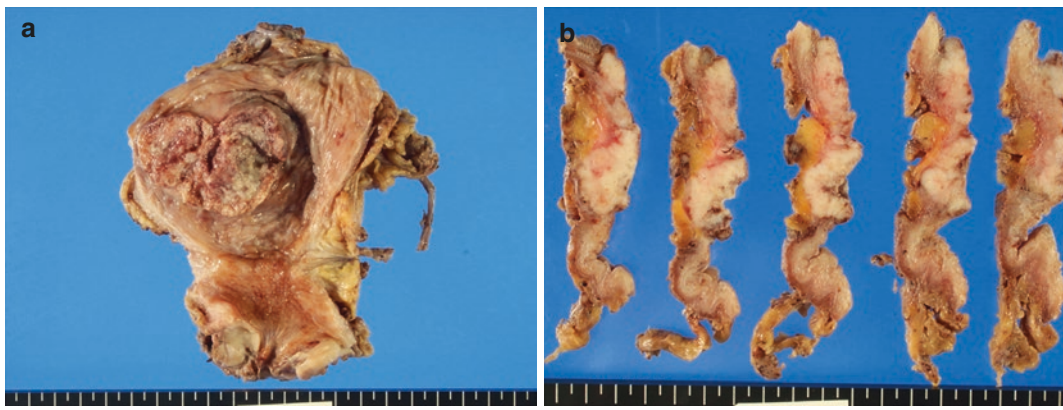

Fig. 7.1 Gross appearance (**a**) and cut surface (**b**) of squamous cell carcinoma of the urinary bladder

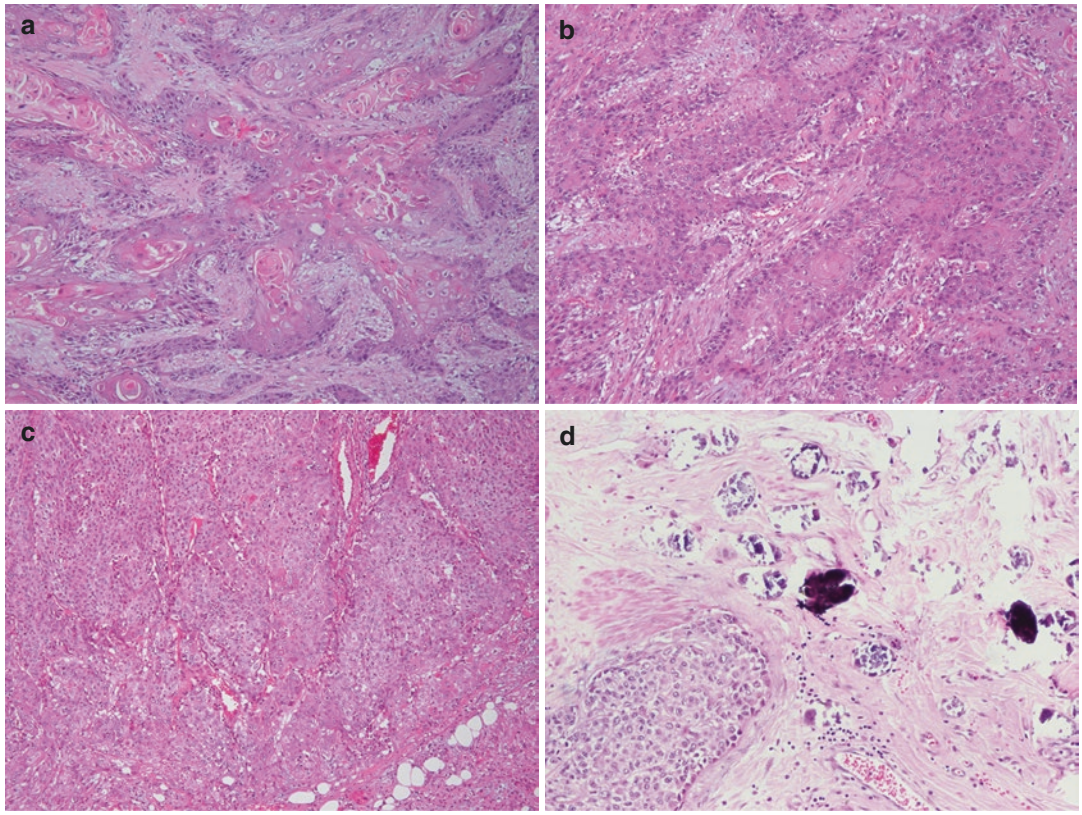

Fig. 7.2 Squamous cell carcinoma of the urinary bladder. Well-differentiated (**a**), moderately differentiated (**b**), and poorly differentiated (**c**) squamous cell carcinoma. (**d**) Bilharzial squamous cell carcinoma of the urinary bladder showing poorly differentiated features and ova of *Schistosoma* species. (Original magnification: **a**–**c**, x200; **d**, x100)

[18, 19]. Compared to pathological staging, clinical understaging has been reported in 30–60% of the cases [8, 19–21]. Importantly, in spite of the advanced T stages, the incidence of lymph node metastasis is relatively lower, in the order of 15–25% [8, 15–17, 19]. In addition, when compared to UC, SCC has a lower incidence of distant metastasis which is estimated to be present in 8–10% of all cases [1, 22].

Molecular and Genetic Aspects

The molecular data for SCC of the bladder has been compiled based mostly on the bilharziasis-associated cohort analysis. Several cytogenetic and classic molecular studies have showed gains of chromosomal material predominantly at 5p, 6p, 7p, 8q, 11q, 17q, and 20q, while losses are most frequent at 3p, 4q, 5q, 8p, 13q, 17p, and 18q [23–25]. Classic cytogenetics and comparative genomic hybridization (CGH) have been performed in only a few non-bilharzial SCC cases [26, 27]. Results of a single CGH study of 11 non-bilharzial SCCs show that the predominant chromosomal changes are gains at 1q, 8q, and 20q, as well as losses of 3p, 9p, and 13q [26]. With respect to the differences between SCC and UC, loss of 3p has been demonstrated as a relatively specific genetic aberration for SCC [26, 27].

In a recent mutational analysis for *TERT* gene, *TERT* promoter mutation, which is the most common genetic alteration in UC of the urinary tract, is detected in 12/15 (80%) of non-bilharzial SCCs [28]. As with UC, p53 immunopositivity and gene mutation have been observed in a wide range of bilharzial SCCs [29–31]. Specifically, *TP53* mutations in bilharzial SCC include more

base transitions at CpG dinucleotides than those seen in UCs [30]. Other molecular aberrations known to occur in UCs, including *HRAS* mutations, EGFR overexpression, and HER2 expression, have also been detected in bilharzial SCC at comparable frequencies [31–33].

Treatment and Prognosis

Irrespective of the bilharzial status, there are few treatment options available for patients diagnosed with bladder SCC. In most cases, radical cystoprostatectomy or radical cystectomy is recommended as the only viable therapeutic approach, as radiation and chemotherapy offer limited therapeutic benefits [34, 35]. Consequently, the 5-year disease-free survival rate following a radical cystectomy is 43–57%, with poor prognosis attributed to an advanced tumor stage and lymph node involvement at diagnosis [18, 19, 35]. Most bladder SCC patients die due to failure of locoregional tumor control: about 90% of the bladder SCC deaths are caused by a locoregional recurrence within 3 years of diagnosis. As shown by a recent study, the pathologic stage is the most important prognostic parameter for patients diagnosed with the bilharzial SCC of the bladder: in a series of 154 bilharzial SCC cases, the overall 5-year survival rate for patients with pT1 and pT2 tumors was 66.9%, compared to only 19% in those diagnosed with pT3 and pT4 tumors [36].

Histological Variants of Bladder SCC

Verrucous Carcinoma

Verrucous carcinoma is a rare, clinically indolent variant of invasive SCC, more commonly seen in the oral cavity, larynx, anus, and genital areas. Grossly, verrucous carcinoma appears as an exophytic, fungating, or filiform tumor. Microscopically, this tumor is characterized by a broad-pushing tongue-like stromal invasion by large-sized proliferations of very well-differentiated squamous epithelium, frequently associated with a dense infiltration of inflammatory cells at the interface between the atypical squamous proliferation and the underlying stroma [1]. Additionally, verrucous carcinoma tumor cells show lack of anaplastic features and frequent mitoses.

Pathologically, care should be taken to distinguish verrucous carcinomas from verrucous/pseudoepitheliomatous hyperplasia. Verrucous carcinomas exhibit a downgrowth of the well-differentiated squamous epithelium, which extends to a much wider and deeper extent than that encountered in verrucous/pseudoepitheliomatous hyperplasia. Therefore, in a superficial biopsy, the differentiation of these two conditions is almost impossible, mandating sampling of deeper tissue for a definitive distinction.

Basaloid SCC

Basaloid SCC is an aggressive and often deeply invasive neoplasm found mainly in the upper aerodigestive tract, penis, vulva, and cervix. The typical microscopic picture comprises of centrally necrotic, solid nests of small, poorly differentiated cells with scant cytoplasm resembling basal cell carcinoma, except that peripheral palisading is not conspicuous and numerous mitoses are often present. Only two cases of basaloid SCC of the bladder have been described [37, 38]. Specifically, Vakar-López et al. described a case of a 60-year-old woman with a bladder tumor that was morphologically characterized by small nests of basaloid cells with numerous mitoses [37]. However, the reported case also had microscopic foci of UC with squamous differentiation and SCC in situ. Neves et al. presented a case of the bladder basaloid SCC with a small amount (5%) of small cell carcinoma component [38]. The authors did not mention whether a concomitant UC component was detected. As seen in penile basaloid SCC, there is one case report suggesting the relationship between bladder basaloid SCC and human papilloma virus infection of the urinary tract [39].

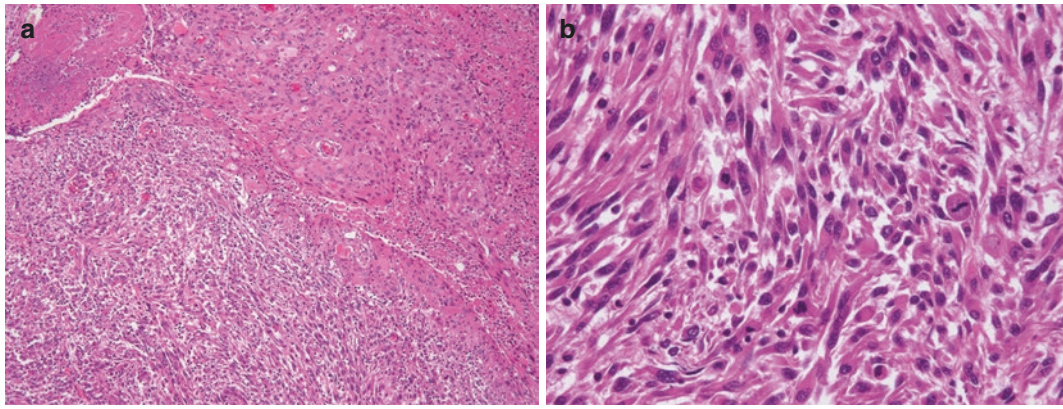

Fig. 7.3 (**a**) Sarcomatoid squamous cell carcinoma with a histological transition between typical squamous cell carcinoma (upper right) and sarcomatoid carcinoma (lower left). (**b**) Spindled tumor cells with marked cytological atypia and frequent mitoses. (Original magnification: **a**, x100; **b**, x400)

Sarcomatoid SCC

Sarcomatoid SCC is an aggressive variant of SCC predominantly composed of spindle and pleomorphic cells, with at least focal histological or immunohistochemical evidence of squamous differentiation (Fig. 7.3). In a case series of 45 bladder SCCs, 3 tumors showed a prominent focal spindled morphology [18]. However, the percentage of a sarcomatous component in comparison to the total tumor volume was not mentioned in the study. There has been a total of two reported cases of sarcomatoid carcinoma of the urinary bladder with SCC and small cell carcinoma components [40, 41].

Adenocarcinoma and Other Glandular Neoplasms

Introduction

Primary adenocarcinoma of the urinary bladder is derived from the urothelium but represents a pure glandular phenotype. Secondary adenocarcinomas involving the bladder either by direct invasion or by metastasis are more common than primary adenocarcinomas, and sometimes it may be challenging to distinguish each other, even with a comprehensive immunohistochemical study. Most urachal carcinomas are adenocarcinomas. Urachal adenocarcinoma is usually described together with bladder adenocarcinoma as they exhibit similar clinical and histological features. However, a classification system recently proposed delineates urachal glandular tumors into two broad categories: mucinous cystic tumors and non-cystic adenocarcinomas. The clinicopathological features and molecular aspects of these distinct glandular lesions are discussed in this chapter.

Primary Adenocarcinoma

Primary adenocarcinoma is an uncommon malignant neoplasm, accounting 0.5 to 2.0% of all bladder cancers. This neoplasm is usually seen in the patients' sixth decade of life with a male-to-female ratio of 2.7:1 [42]. Hematuria is the most common symptom, but some patients may present with irritative voiding symptoms and rarely mucusuria [43]. Although the pathogenesis is still unclear, several risk factors for primary bladder adenocarcinoma have been recognized, including bladder exstrophy, bilharziasis, cystocele, and bladder endometriosis [42].

There is no specific gross finding of primary bladder adenocarcinoma, except for a gelatinous appearance on cut surface in some cases. Primary adenocarcinoma can arise anywhere in the urinary bladder but most commonly involves the base

(i.e., trigone and posterior wall). Histologically, bladder adenocarcinoma exhibits several different patterns, including enteric, mucinous, not otherwise specified (NOS), and mixed. The enteric type is similar to its gastrointestinal counterpart and is composed of pseudostratified nuclei and tall columnar cytoplasm (Fig. 7.4a). The mucinous type shows nests of infiltrating tumor cells floating in abundant extracellular mucin (Fig. 7.4b). In some cases of mucinous adenocarcinoma, signet ring cells with a large intracellular mucin vacuole that displace the nucleus to the periphery (Fig. 7.4c). Importantly, as carcinomas predominantly composed of signet ring cells without stromal mucin deposition have been reported to have a worse prognosis than do other histological types of adenocarcinoma [44], these are currently classified as plasmacytoid urothelial carcinoma [42]. Tumors with a mixture of the enteric and mucinous components are the most common histology of adenocarcinoma [42]. Other cases have nonspecific glandular growth; these are classified as the adenocarcinoma NOS type (Fig. 7.4d). There is no consensus on the grading system for bladder adenocarcinoma. Because immunohistochemistry is usually performed for the differential diagnosis between primary and secondary bladder adenocarcinoma, immunophenotype of the primary adenocarcinoma is integrally discussed in a section of secondary adenocarcinoma.

The molecular and genetic data on primary bladder adenocarcinoma are still limited. In a recent study using targeted next-generation sequencing for 15 primary adenocarcinomas, 11 exhibit at least one genomic alteration in *TP53*, *KRAS*, *PIK3CA*, *CTNNB1*, *APC*, *TERT*, *FBXW7*, *IDH2*, and *RB1*; however, all 3 adenocarcinomas with mucinous features show the distinct lack of genomic alterations across 51 cancer-related

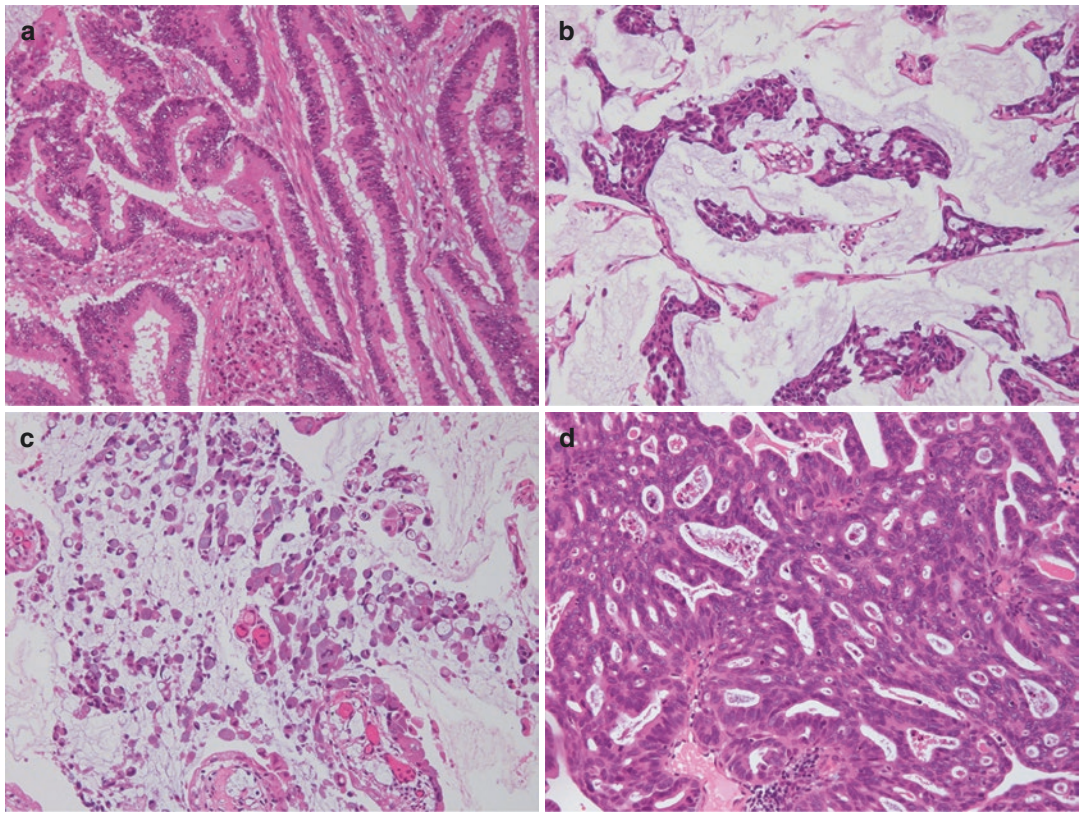

Fig. 7.4 Primary adenocarcinoma of the urinary bladder. Enteric type (**a**), mucinous type (**b**) with signet ring cells (**c**), and NOS type (**d**). (Original magnification, x200)

genes examined [45]. *TERT* mutation has also been reported in up to one-third of primary bladder adenocarcinoma [46].

Patients with bladder-invasive adenocarcinoma usually require radical cystectomy with pelvic lymph node dissection and urinary diversion. In some cases, partial cystectomy can be a treatment option, but a relatively high recurrence rate of the tumor after partial resection has been indicated [47]. Transurethral resection and intravesical BCG/mitomycin C therapy is generally ineffective for bladder adenocarcinoma. If the patient is not a candidate for surgery, radiation and chemotherapy may be considered. The prognosis for primary adenocarcinoma is generally poor, as most patients have advanced disease at diagnosis. The 5-year survival rate has been reported in the range of 40–50% [47, 48].

Secondary Adenocarcinoma

Secondary bladder involvement by adenocarcinoma of adjacent organs through direct extension or metastasis via a lymphovascular route is more common than primary bladder adenocarcinoma. The common primary organs to be considered include the colon, prostate, female genital tract, and breast.

Colorectal adenocarcinoma is the most frequent secondary tumor involving the bladder wall. It is generally difficult to differentiate primary bladder adenocarcinoma from secondary colorectal adenocarcinoma based on morphological features, especially on small biopsy specimens, as they share similar histological features. Immunohistochemistry has limited utility but is often used to help the differential diagnosis. Colorectal adenocarcinomas usually show nuclear and cytoplasmic/membranous staining for β-catenin, while primary bladder adenocarcinomas are negative or show only cytoplasmic/membranous staining [49]. Most bladder adenocarcinomas are immunoreactive for thrombomodulin and cytokeratin (CK) 7, whereas colorectal carcinomas are negative for thrombomodulin and CK7 [50]. CK20, CDX2, villin, and cadherin-17 are not useful, as they are commonly expressed in both colorectal and bladder adenocarcinomas [49]. Importantly, clinical history and colonoscopic findings are essential to identify the correct origin in most cases.

Prostatic adenocarcinoma also commonly invades the bladder, particularly the bladder neck and trigone regions. Because most prostatic adenocarcinomas are acinar type and demonstrate small atypical glands composed of relatively uniform malignant cuboidal cells, it is not difficult to distinguish them from bladder adenocarcinoma. However, a small subset of prostatic adenocarcinomas is ductal type with large tubulopapillary or cribriform gland with focal necrosis, resembling the enteric-type bladder adenocarcinoma. Although immunohistochemical study is extremely valuable in the differential diagnosis, a part of poorly differentiated or previously treated prostatic adenocarcinoma may not be immunoreactive for PSA and PSAP [51]. In this situation, the use of a panel together with additional prostate-specific markers including prostein and NKX3.1 is recommended [51].

Endometrial adenocarcinoma, especially endometrioid carcinoma, shows atypical glandular structures with occasional mucinous and squamous differentiations and may spread to the urinary bladder at advanced stages. Lobular-type breast carcinoma which seems to be more common involves the bladder than ductal type, although both types can involve the bladder. It may be challenging to distinguish these adenocarcinomas with bladder adenocarcinoma on a morphological analysis alone; however, immunohistochemical staining coupled with clinical history generally leads to the correct diagnosis [52]. Endometrioid carcinoma and breast adenocarcinoma are positive for estrogen receptor and progesterone receptor, whereas bladder adenocarcinomas are negative for these markers.

Urachal Adenocarcinoma

The urachus is a vestigial fibrous structure that connects the urinary bladder to the allantois during early embryogenesis. While the lumen of the urachus begins to be gradually obliterated during fetal

development, incomplete obliteration can cause a tubular or cystic structure in the dome and elsewhere along the midline of the bladder in approximately one-third of adults at autopsy [53]. The urachal remnant is usually lined by urothelium; however, a vast majority of the urachal tumors are adenocarcinomas (occasionally UC or SCC). Urachal adenocarcinoma is less common than primary bladder adenocarcinoma, accounting less than 1% of all bladder carcinomas but approximately 10% of primary adenocarcinomas involving the bladder [43]. Most cases occur in the fifth or sixth decade of life, with the mean patient age of 51 years, about 10 years younger than that for bladder adenocarcinoma [43]. A male-to-female ratio of patients is 2:1 to 3:1. Patients may present with hematuria, pain, irritative symptoms, mucusuria, and umbilical discharge.

The clinicopathological criteria for diagnosis of urachal adenocarcinoma includes (1) location of the tumor in the bladder dome and/or anterior wall, (2) epicenter of carcinoma in the bladder wall, (3) absence of mucosal surface changes such as cystitis cystica and/or cystitis glandularis beyond the dome or anterior wall, and (4) absence of a known primary elsewhere [54]. The presence of a related urachal remnant supports the diagnosis, but its absence does not exclude this possibility. The cut surfaces of tumors are typically firm, whitish gray masses but occasionally are discrete, cystic, or cavitary tumors (Fig. 7.5).

A classification system, proposed by Amin et al. [55] and adopted by the 2016 WHO classification, delineates urachal glandular tumors into two broad categories, mucinous cystic tumors and non-cystic adenocarcinomas (Table 7.2).

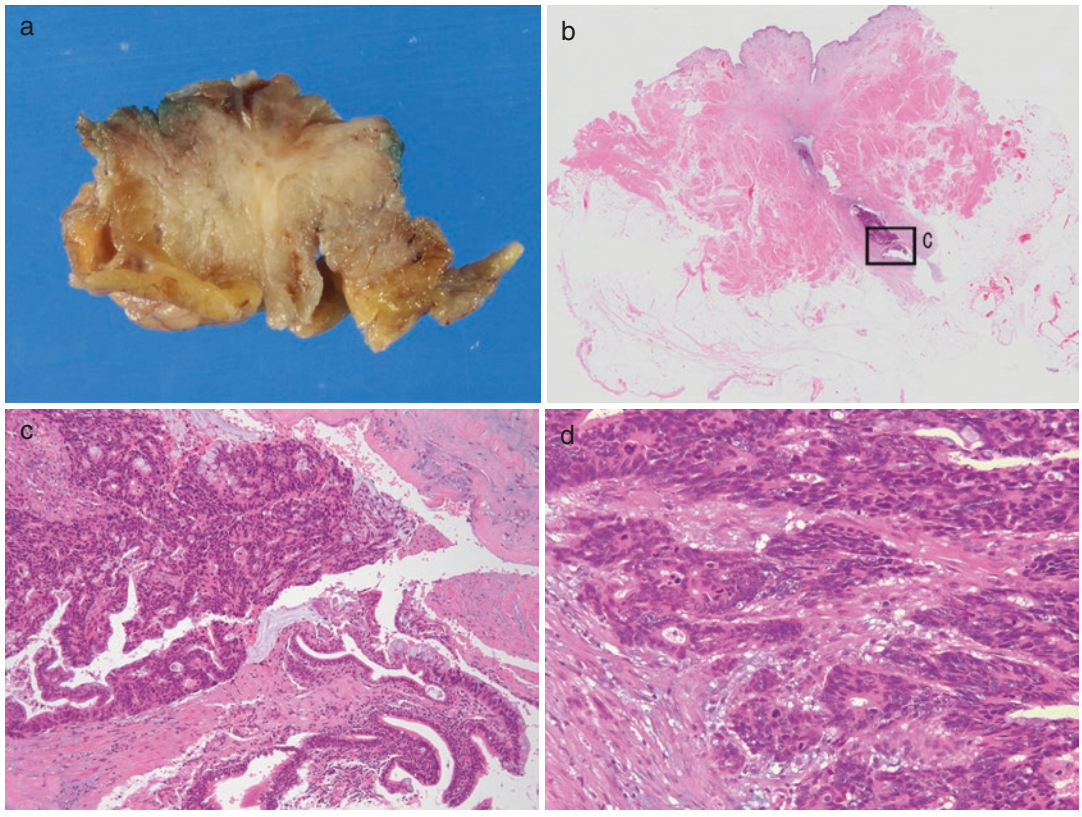

Fig. 7.5 Gross appearance (**a**) and a low-power view (**b**) of urachal non-cystic adenocarcinoma. Microscopically, enteric adenocarcinoma with focal urachal remnant (**c**) and stromal invasion (**d**) is noted. (Original magnification: **c**, x100; **d**, x200)

Non-cystic adenocarcinomas (accounting for 83% of cases) are more common than cystic tumors (17% of cases) [54, 55]. Non-cystic urachal adenocarcinomas exhibit a similar histology to primary bladder adenocarcinomas: enteric (Fig. 7.5), mucinous (with or without signet ring cells), and NOS types. On the other hand, mucinous cystic tumors demonstrate a morphological homology with mucinous tumors of the ovary: mucinous cystadenoma, mucinous cystadenoma of low malignant potential (MCTLMP) (with or without intraepithelial carcinoma), and mucinous cystadenocarcinoma with either microscopic or frank invasion [55]. Mucinous cystadenoma is a cystic tumor lined by a single layer of mucinous columnar cells with minimal cytological atypia and structural complexity. MCTLMP constitutes more than 50% of the mucinous cystic tumors and shows areas of epithelial proliferation, including formation of papillae and low-grade cytological atypia, resembling those of mucinous borderline tumor of the ovary (Fig. 7.6a, b and c). In a small subset of tumors, foci of intraepithelial

Table 7.2 Glandular tumors of the urachus [54]

Mucinous cystic tumors
Mucinous cystadenoma
Mucinous cystic tumor of low malignant potential with or without intraepithelial carcinoma
Mucinous cystadenocarcinoma with microscopic or frank invasion
Non-cystic adenocarcinoma
Enteric adenocarcinoma
Mucinous adenocarcinoma with or without signet ring cells
Adenocarcinoma, NOS
Mixed adenocarcinoma

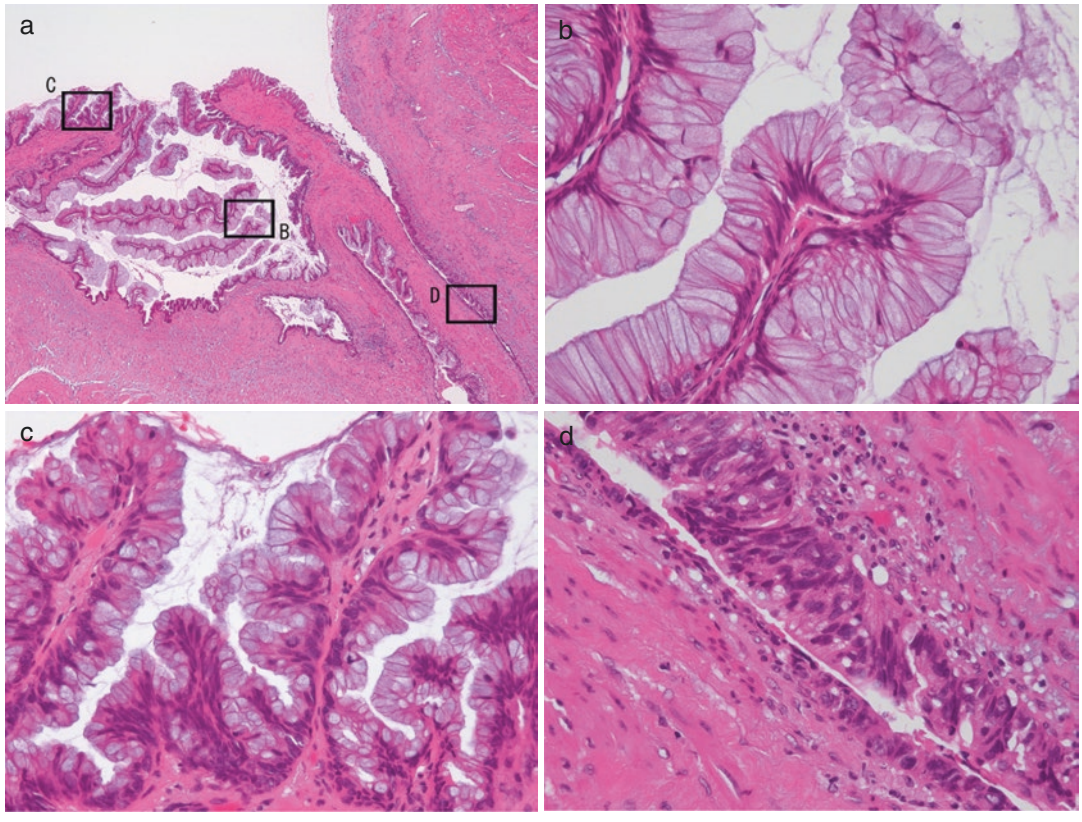

Fig. 7.6 Morphological spectrum of a single mucinous cystic tumor (**a**). Mucinous cystadenoma-like area (**b**), mucinous cystic tumor of low malignant potential (**c**), and a focal intraepithelial carcinoma component (**d**) are observed (original magnification: **a**, x40; **b**–**d**, x200)

carcinoma characterized by severe atypia, abundant mitoses, and complex architecture may be observed (Fig. 7.6d). For mucinous cystadenocarcinoma, Amin et al. defines lesions showing stromal invasion <2 mm and comprising <5% of the tumor as mucinous cystadenocarcinomas with microinvasion and lesions with more extensive invasion as those with frank invasion [55], although the interobserver reproducibility and clinical significance of this distinction have not been evaluated. Importantly, as the spectrum of atypia or only a small focus of invasive carcinoma may be present in individual cystic lesions (Fig. 7.6), rigorous sampling is necessary particularly when any degree of atypia is detected [56]. Immunohistochemical finding of non-cystic adenocarcinomas is essentially identical to that of mucinous cystic tumors; both types of tumors demonstrate variable (about 50%) CK7 and diffuse CK20 and CDX2 immunoreactivity [54, 55, 57]. There has been no helpful marker to distinguish between primary bladder adenocarcinoma and urachal adenocarcinoma. As with primary bladder adenocarcinoma, the lack of only focal positivity of nuclear β-catenin is potentially valuable in differentiating urachal adenocarcinoma from secondary bladder involvement of colorectal adenocarcinoma [57].

Recent studies using next-generation sequencing for urachal glandular tumors have revealed the molecular characteristics and genetic underpinnings of these rare neoplasms. Primary urachal adenocarcinomas harbor the spectrum of molecular alterations which are similar to those of primary bladder adenocarcinoma and colorectal adenocarcinoma, including *KRAS*, *NRAS*, *BRAF*, *APC*, *TP53*, *NF1*, and/or *SMAD4* mutations [58–60]. However, they generally lack *TERT* promoter and *PIK3CA* mutations, which are common in urothelial carcinoma [59, 61]. Of note, these sequencing studies to date have not subclassified urachal tumors according to the 2016 WHO classification; the molecular differences between urachal mucinous cystic tumors and non-cystic adenocarcinomas remain unclear.

The 5- and 10-year cancer-specific survival rates for patients with urachal adenocarcinoma are 40–64% and 31–49%, respectively [43, 62]. Importantly, progression-free survival of noninvasive mucinous cystic tumors is significantly better than that of non-cystic adenocarcinoma [55]. The Sheldon system is the most widely used staging system for urachal neoplasms and divides tumors as follows: confined to the urachal mucosa (pT1); extending into the urachal muscular layer (pT2); locally extending into the urinary bladder, abdominal wall, or other adjacent organs (pT3); and metastatic tumors (pT4) [63]. A variety of other similar staging systems, including Mayo and Ontario systems, have also suggested that clinically localized tumors have a good overall prognosis, whereas locally advanced and/or metastatic tumors have a poor overall prognosis [64, 65]. The current interest in staging for urachal carcinoma is a simplified dichotomous approach to divide tumors: (1) tumors confined to the urachus, bladder, and perivesical tissue and (2) tumors which spread to the peritoneum and other organs [66].

Clear Cell Carcinoma (Tumor of the Müllerian Type)

Clear cell carcinoma is a rare bladder carcinoma arising from preexisting Müllerian-type epithelium, typically endometriosis. Unlike other bladder glandular tumors, clear cell carcinoma occurs more frequently in females, and the mean age of patients is 57 years (ranging from 22 to 83 years) [67]. Patients usually present with hematuria, urinary frequency, or dysuria. Grossly, the tumor typically forms an exophytic and papillary mass. Histology of bladder clear cell carcinoma is similar to that of female genital tract, which is characterized by tubulocystic, papillary, and diffuse solid patterns of cuboidal or columnar tumor cells with clear and eosinophilic cytoplasm (Fig. 7.7). Hobnail cells are frequently observed. The nuclei are large with finely granular chromatin and prominent nucleoli (Fig. 7.7). Immunohistochemically, the tumor cells are usually positive for CK7, PAX8, AMACR, and CA-125, napsin A, and variably CK20, S100 protein, and PAX2 [67–70]. Nephrogenic adenoma,

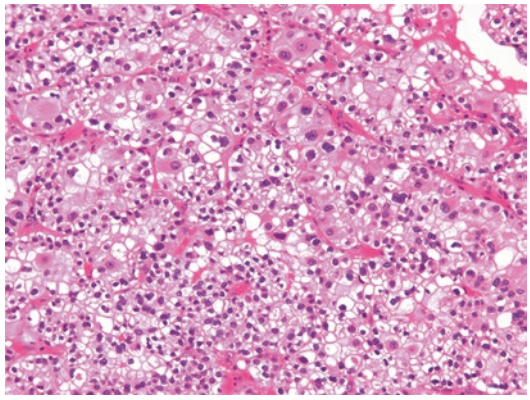

Fig. 7.7 Clear cell carcinoma of the urinary bladder. Densely packed tubulopapillary growth of tumor cells with clear and eosinophilic cytoplasm. (Original magnification, x200)

which also exhibits the proliferation of cuboidal or hobnail clear cells, should be differentiated from clear cell carcinoma [71]. Nephrogenic adenoma lacks prominent cytoarchitectural atypia and solid growth areas and more frequently affects males [71, 72]. Other differential diagnoses include metastatic clear cell carcinoma from the female genital tract and metastatic clear cell renal cell carcinoma. Overall, clinicoradiological correlations with careful immunohistochemical study are helpful for the correct diagnosis.

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