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UROTHELIAL CANCER (S DANESHMAND, SECTION EDITOR)

# Variant Histology in Bladder Cancer—Current Understanding of Pathologic Subtypes

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**Abstract**

**Purpose of Review** Urothelial carcinomas (UC) are characterized by variant morphologies. However, the diagnosis of these variants can be challenging, in part due to their evolving diagnostic criteria. This review discusses the diagnostic criteria, molecular features, and prognostic implications of the UC variants. Evolving subtypes of UC are also briefly discussed.

**Recent Findings** The WHO 2016 classification of tumors of the urinary system has refined the morphologic criteria for the diagnosis of UC variants. Many of these follow a more aggressive clinical course, but conclusive data on their effect on survival are lacking. The molecular alterations characteristic of some of these variants may be amenable to targeted therapies.

**Summary** Accurate identification of variant histology in UC has important implications for patient management. Despite identification of distinct molecular alterations in some of these variants, current molecular classifiers of invasive UC have not been significantly analyzed in these subtypes, opening up areas of future research.

**Keywords** Bladder carcinoma · Urothelial carcinoma variants · Variant histology · Divergent differentiation

## Introduction

Urothelial carcinoma (UC) accounts for about 90% of bladder cancers in industrialized countries with squamous cell carcinoma (1–7%) and adenocarcinomas (0.5–2%) forming a minor component of bladder cancers [1, 2]. UC is remarkable for showing marked diversity in its morphological appearance, which may in part be a reflection of its molecular heterogeneity, resulting in the recognition of various histologic variants. Variant histology is not uncommon and can be seen in as many as 33% of the cystectomy specimens [3]. Despite the high prevalence of variant histology its recognition remains challenging because of under-recognition, misclassification, lack of ancillary testing to confirm variant diagnosis, sampling limitations and the high interobserver variability in part due to evolving diagnostic criteria [4••, 5••, 6–10]. In some patients multiple variants may occur within a tumor, with many pathologists reporting the percentage of each variant within the lesion [11]. These variants are important to recognize because they may have important prognostic or therapeutic implications and misdiagnosis may result in inappropriate treatment [10]. The WHO 2016 classification of tumors of the urinary system and male genital organs addresses many of these issues by updating the diagnostic criteria and the molecular characteristics of the various subtypes (Table 1).

This review describes the diagnostic criteria of the histologic variants of UC with special emphasis on the morphologic features, molecular profiles and prognostic implications of the identification of the various subtypes. A brief description of the evolving UC subtypes not currently included in the WHO classification is included. Non-urothelial bladder cancer subtypes are not addressed in this review.

## Urothelial Carcinoma with Divergent Differentiation

The most common UC variant is UC with divergent differentiation, which includes squamous, glandular, trophoblastic and small cell differentiation (Fig. 1a–d). These tumors are characterized by varying components of urothelial carcinoma (invasive and or in situ) with the aforementioned

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**Table 1** Histologic variants of invasive urothelial carcinoma as per the WHO 2016 classification of tumors of the urinary

| |
|---|
| Urothelial carcinoma with divergent differentiation |
| - squamous differentiation |
| - glandular differentiation |
| - trophoblastic differentiation |
| - others including small cell carcinoma |
| Nested urothelial carcinoma (including large nested) |
| Microcystic urothelial carcinoma |
| Micropapillary urothelial carcinoma |
| Lymphoepithelioma-like urothelial carcinoma |
| Plasmacytoid urothelial carcinoma |
| Giant cell urothelial carcinoma |
| Lipid-rich urothelial carcinoma |
| Clear cell (glycogen-rich) urothelial carcinoma |
| Sarcomatoid urothelial carcinoma |
| Poorly differentiated urothelial carcinoma |

morphological subtypes [5••]. The general consensus among urologic pathologists is to report these cases with an estimated percentage of the divergent component.

## Urothelial Carcinoma with Squamous Differentiation

Squamous differentiation is defined by the presence of intercellular bridges or keratinization (Fig. 1a) and is seen in up to 40% of urothelial carcinomas of the bladder [7, 8]. They are frequently associated with high-grade and high-stage tumors [12•] and may show less favorable response to intravesical BCG and intravesical chemotherapy [13•, 14]; however, the response to neoadjuvant chemotherapy may be comparable with that of conventional urothelial carcinoma [15•, 16–19]. The presence of squamous differentiation, however, has been associated with higher rates of recurrences and poor prognosis [13•, 18, 20].

One of the challenges in the identification of this variant, especially in transurethral resection (TUR) and biopsy specimens, is its distinction from pure squamous cell carcinoma of the bladder and from secondary involvement of the bladder by squamous cell carcinoma of other pelvic organs. Both squamous cell carcinomas and UC with squamous differentiation share many basal markers including cytokeratin 5/6 and p63. In the absence of specific immunohistochemical markers to make this distinction, and as suggested by previous studies, I rely on the clinical history and the absence of a conventional urothelial carcinoma component to make this distinction [7, 10]. Unlike squamous carcinoma of the cervix, human papilloma virus is generally not considered to be causative in the development of squamous cell carcinoma of the bladder or UC with squamous differentiation [21].

## Urothelial Carcinoma with Glandular Differentiation

Glandular differentiation is not as frequent as squamous differentiation but has been documented in 6–18% of invasive bladder

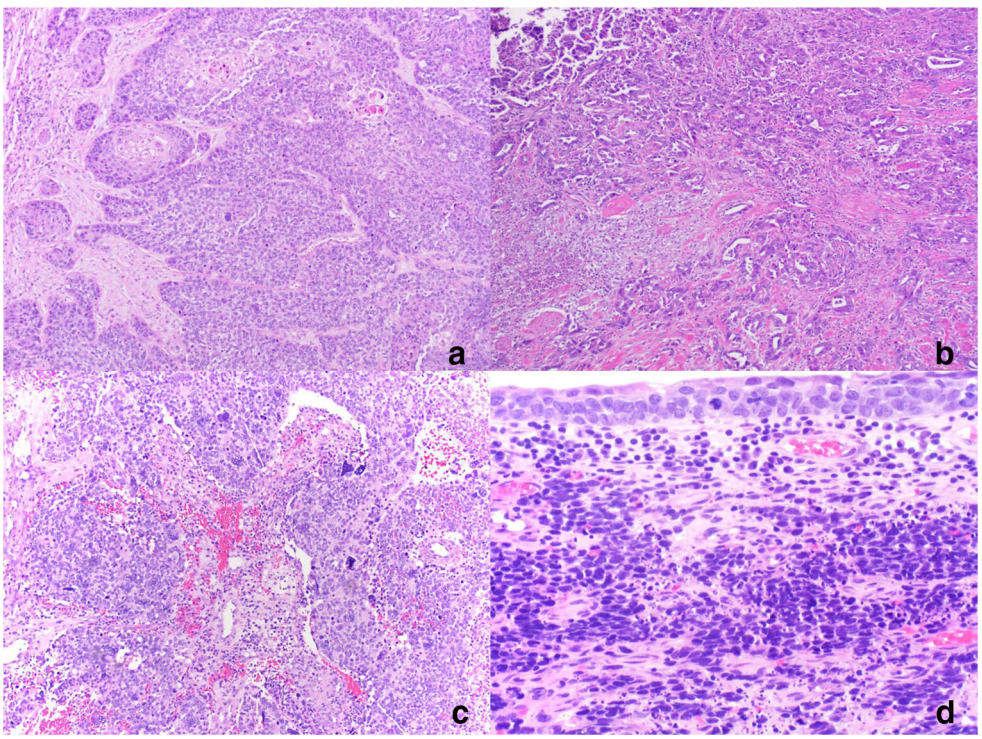


**Fig. 1** Urothelial carcinoma (UC) with divergent differentiation. Squamous differentiation with squamous pearls (**a**); glandular spaces lined by cuboidal appearing cells in UC with glandular differentiation (**b**); syncytiotrophoblastic giant cells scattered along with UC component (**c**); small cell carcinoma component with urothelial carcinoma in situ (**d**)

cancers [7, 22–24]. Glandular differentiation is characterized by true gland formation (Fig. 1b) resembling colonic adenocarcinoma, signet ring carcinoma or mucinous/colloid carcinoma (tumor cells floating in a pool of mucin). They may be associated with urothelial carcinoma in situ or rarely with in situ urothelial carcinoma with glandular differentiation [25]. Pseudo glandular spaces with intracellular mucin may be seen in conventional UC and should not be confused with either UC with glandular differentiation or bladder adenocarcinoma [26].

Robust immunohistochemical markers to distinguish UC with glandular differentiation, from primary bladder adenocarcinomas and secondary involvement /metastatic colonic adenocarcinoma are lacking, making this distinction challenging [27, 28•]. Often in limited samples a definite diagnosis may not be possible and pathologists may give a general descriptive diagnosis and favor one of the differentials over the other. TERT mutations are seen in up to 70% of urothelial carcinoma with glandular differentiation and not in bladder adenocarcinomas [23]; however, this is seldom used in routine clinical practice.

UC with glandular differentiation tends to present at a higher stage but it is not a negative prognostic indicator in stage-matched patients [29].

### Urothelial Carcinoma with Trophoblastic Differentiation

UC showing syncytiotrophoblastic giant cells are rare (Fig. 1c), although the use of immunohistochemical markers for the beta subunit of human chorionic gonadotropin (βhCG) can highlight trophoblastic differentiation in up to 35% of UC [30].

βhCG expression within urothelial carcinoma cells without morphological evidence of trophoblastic differentiation correlates with the grade and stage of tumor; however, it is not included in this subgroup. These variants need to be distinguished from pure choriocarcinoma of the bladder, which is extremely rare and requires the demonstration of isochromosome 12p, which is a hallmark of germ cell tumors [31]. Elevated serum βhCG has been reported in 20–76% of metastatic urothelial carcinomas, and response to chemotherapy in these patients can be correlated with the levels of this marker [32–35].

### Other Forms of Divergent Differentiation

UC can show neuroendocrine differentiation in the form of small cell carcinoma (Fig. 1d), and any small cell carcinoma component when present should be reported. TERT promoter mutations have been reported in 55–95% of these tumors, similar to the concomitant UC component suggesting a common clonality [36••, 37]. TERT promoter mutation status may also help identify the site of origin of these tumors, as they are not present in small cell carcinomas of other sites including the prostate [36••, 38]. Coalterations in P53 and RB1, with resultant loss in function, are commonly seen in small cell carcinoma [37, 39••]. The small cell component is usually negative for both luminal and basal markers with few cases showing focal expression of CK5/6, a marker for the basal molecular subtype. This suggests evolution from a basal phenotype and better response to cisplatin-based chemotherapy [39••]. These tumors are treated similar to their counterpart in the lungs. Rarely urothelial carcinomas may show germ cell differentiation, including yolk sac tumor [5••].

## Nested, Including Large Nested Urothelial Carcinoma

As per the 2016 WHO classification, large nested variant of UC and UC with small tubules and microcysts that were earlier considered as distinct entities are now included within the category of nested variant [5••, 40, 41••]. This variant is characterized by its deceptively benign cytology and its superficial resemblance to benign mimickers of UC including von Brunn nests, nephrogenic adenoma, and paraganglia [40, 41••, 42–45].

Nested variant is characterized by a disorderly proliferation of discrete to confluent nests of urothelial cells usually with minimal cytologic atypia (Fig. 2a). The absence of cytologic atypia can make the diagnosis of this variant extremely challenging in small biopsy specimens and transurethral resections. In many instances, the diagnosis may be delayed until the tumor declares itself with unequivocal evidence of invasion of the muscularis propria. Unlike the usual nested variant, which is composed of small- to intermediate-sized nests, the large nested variant is characterized by irregularly infiltrating large aggregates of bland tumor cells which may sometimes be difficult to differentiate from conventional UC with an inverted growth pattern [46].

Nested urothelial carcinomas may be admixed with a component of conventional UC or may occur in a pure form. They usually present as a high-stage disease, which may in part reflect the delay in diagnosis, associated with this tumor [47]. Pure large nested variant may have a better prognosis than cases with a mixed histology [41].

The immunohistochemical profile of this variant is similar to conventional UC. In particularly challenging cases the presence of TERT promoter mutation within the tumor cells can help distinguish it from its benign mimics [48]. Preliminary studies have shown that these tumors express immunohistochemical markers characterized by the luminal molecular subtype of urothelial carcinomas [49, 50••].

## Microcystic Urothelial Carcinoma

Microcystic urothelial carcinoma, like nested urothelial carcinoma, is an example of urothelial carcinoma characterized by

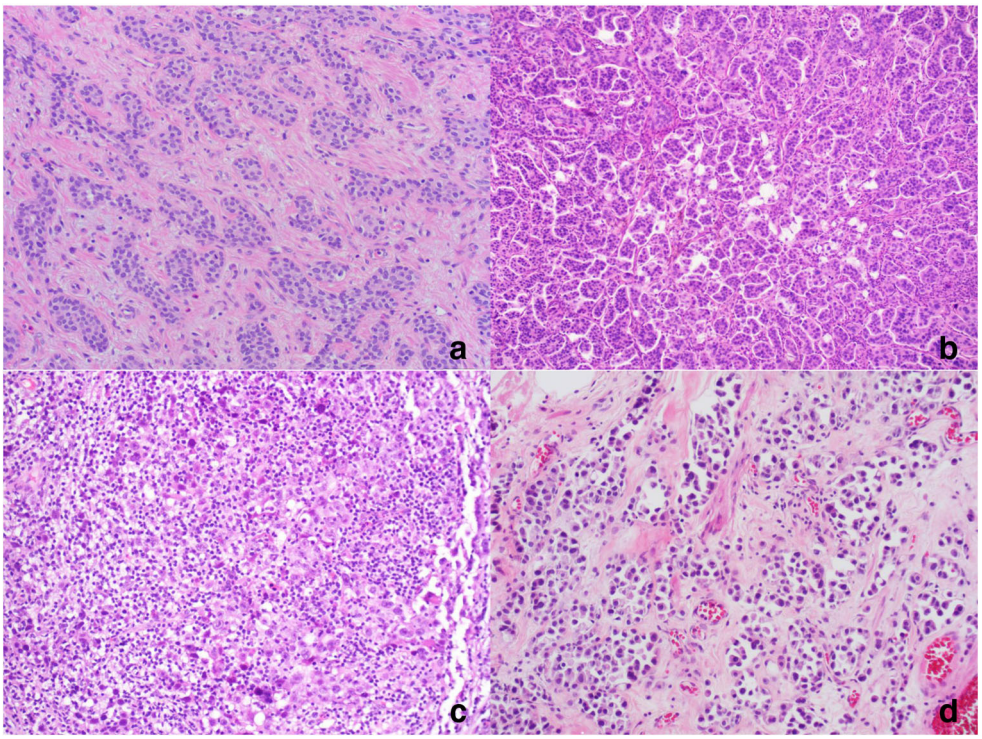


**Fig. 2** Cytologically bland nests of invasive carcinoma characteristic of nested variant (**a**); micropapillary UC with small nests within lacunar spaces (**b**); tumor cells obscured by brisk inflammatory infiltrate in lymphoepithelioma-like UC (**c**); singly discohesive bland plasma cell-like cells of plasmacytoid UC (**d**)

bland cytologic features. It is comprised of round-oval cysts up to 2 mm in diameter lined by urothelial, low columnar or flattened epithelium [51]. The cyst lining may be focally denuded and intraluminal secretions and calcifications may be present within some of the cysts. The cysts are infiltrating; however, a stromal response may be lacking. Focal high-grade conventional urothelial carcinoma may be present in up to 40% of the cases. Their immunohistochemical profile is similar to that of conventional UC [52].

These tumors should be differentiated from their benign mimics including cystitis cystica and cystitis glandularis [53]. TERT promoter mutation studies may help in difficult cases.

## Micropapillary Urothelial Carcinoma

This variant has been reported more commonly in men with a peak incidence in the 6th decade of life. It is associated with a poorer prognosis and usually presents at a higher stage with lymph node metastasis [54, 55]. The reported prevalence of this variant varies from 0.7 to 8% [56–58] and this may in part reflect the high interobserver variability and the cutoffs used in the diagnosis of this variant [58, 59]. The diagnosis of this tumor should be restricted to infiltrating tumors with slender filiform processes without fibrovascular cores and/or multiple small tumor nests within a single lacunar space (Fig. 2b). The tumor nests often show peripherally oriented nuclei with "reverse polarization" of the basal and luminal aspects of the cell, highlighted on electron microscopy and MUC1 staining [60]. Cytoplasmic vacuolization with indentation of the nuclei (ring forms) is also a characteristic of this tumor [59]. Lymphovascular invasion has also been commonly reported with this variant. Micropapillary carcinoma is frequently admixed with conventional UC and carcinoma in situ is present in more than 50% of the cases [61]. It is unclear if the prognosis of this variant depends on the proportion of the micropapillary component [61, 62]; however, most urologic pathologists report the percentage of this variant in the tumor. Although a surface micropapillary component may be identified in a non-invasive UC or rarely as a variant of urothelial carcinoma in situ, these should not be interpreted as micropapillary urothelial carcinoma. Micropapillary UC in addition to the usual urothelial markers also show immunoreactivity for MUC1 and CA-125 [28•]. They also usually express luminal markers including FOXA1 [37, 49] and have been reported to have a high prevalence of TERT promoter mutations [63••, 64]. HER2 amplifications have been documented in 15–42% of the cases [63, 65, 66].

Limited response to BCG therapy and adverse outcome despite chemotherapy has been reported in some studies, prompting early cystectomy in patients with T1 disease [67]. However, other studies have shown the utility of a bladder-sparing approach in select non-muscle-invasive patients [68, 69]. A recent prospective trial has also reported efficacy with aggressive neoadjuvant chemotherapy [70]. Neoadjuvant chemotherapy although decreased the frequency of non-organ confined disease it did not translate into a statistically significant overall survival benefit [71••]. HER2-amplified tumors have

been associated with a worse cancer-specific survival, opening up the potential role of ERBB2-targeted therapy [65, 63].

## Lymphoepithelioma-Like Urothelial Carcinoma

Lymphoepithelioma-like urothelial carcinoma is similar in morphology to the lymphoepitheliomas arising elsewhere in the body including the nasopharynx. However, unlike tumors of the nasopharynx this variant of UC is not associated with Epstein-Barr virus infection [72, 73]. It is more commonly seen in older men (mean age, 69 years) and usually presents as a stage 2 or 3 tumor [5••, 74].

It may occur either in the pure form or admixed with conventional urothelial carcinoma or other variants. The tumor is composed of sheets of undifferentiated cells with large pleomorphic nuclei and prominent nucleoli with indistinct cell borders forming a syncytium. The background comprises of an inflammatory infiltrate comprising predominantly of lymphocytes, which in some instances may be so dense so as to obscure the tumor cells (Fig. 2c). The tumor cells mark for urothelial markers including p63 and GATA-3.

Although it was suggested that pure/predominant forms of this carcinoma are associated with a relatively favorable outcome with good response to chemotherapy, a recent study of 30 cases has reported similar outcomes to conventional UC [75].

## Plasmacytoid Urothelial Carcinoma

This is a rare but aggressive variant of UC characterized by cells resembling plasma cells that present at a high stage with extravesical disease and intraperitoneal spread in 27–33% of the cases [76, 77, 78•]. They also have higher incidence of lymph node metastasis and are more likely to have positive margins after radical cystectomy [78•]. They generally have a poor outcome with higher rates of recurrence and death but in a recent study of 98 patients, plasmacytoid urothelial carcinoma was not associated with worse overall mortality compared with conventional UC [79••].

This variant is characterized by singly infiltrating, discohesive cells in an edematous or myxoid stroma. The tumor cells have eccentric enlarged hyperchromatic nuclei with eosinophilic to clear cytoplasm, without significant cytologic atypia (Fig. 2d). Signet ring cells with or without intracytoplasmic mucin may be identified, but unlike a signet ring adenocarcinoma extracellular mucin is absent [80, 81, 5••]. A high-grade urothelial carcinoma component is seen in about 50% of the cases. Perrino et al. [82•] recently classified plasmacytoid UC into three morphological subtypes (classic, desmoplastic, and pleomorphic) and reported that the desmoplastic variant had the worst clinical behavior. However, many of their cases of the desmoplastic and pleomorphic variants appear to have a morphologic overlap with UC with rhabdoid morphology. Further studies are required to validate the significance of these findings.

Up to 84% of these tumors show truncating mutations in the CDH1 gene, which encodes for E-cadherin, whereas these mutations have not been reported in conventional UC ( [83••, 84]. These mutations lead to the loss of E-cadherin (a cell adhesion molecule), which may be responsible for the marked discohesion of tumor cells seen in this variant [85]. Recently Fox et al. showed the lack of immunohistochemical staining for RB (retinoblastoma) protein in 62% of their cases, suggesting abnormal function of the *RB* gene [78•]. Plasmacytoid urothelial carcinoma must be differentiated from tumors arising from the breast and gastrointestinal tract among others because of overlapping morphological features. This is possible by the judicious use of immunohistochemical markers [85, 86•].

## Giant Cell Urothelial Carcinoma

Giant cell urothelial carcinoma is a rare aggressive variant characterized by highly atypical giant cells usually admixed with conventional UC component [87•]. Rarely the tumor may be composed entirely of large pleomorphic tumor giant cells, and in such instances immunohistochemical stains may be necessary to identify its urothelial origin. Atypical mitotic figures and areas of necrosis are often present. They are usually highly invasive with involvement of the muscularis propria. The prognosis is uniformly poor [88].

## Lipid-Rich Urothelial Carcinoma

This is another rare variant of urothelial carcinoma, with less than 40 cases reported in literature [5••]. The tumor cells resemble lipoblasts and have one or more vacuoles in the cytoplasm that indent the nucleus. The lipid-rich component usually comprises 10–50% of the tumor and is usually admixed with a component of conventional or other UC variants. These tumors usually present at a higher stage, with 60% of the patients dying of the disease within 58 months [89].

## Clear Cell (Glycogen-Rich) Urothelial Carcinoma

The clear cytoplasm seen in this variant is because of the presence of intracytoplasmic glycogen, which stains with periodic-acid-Schiff (PAS) stain and disappears after diastase

digestion [90].They resemble the cells seen in clear cell renal cell carcinoma, but can be differentiated from it because of its immunoreactivity with urothelial markers including GATA-3 and p63. This variant is also usually associated with in situ, papillary or conventional urothelial carcinoma [5••]. They are extremely rare with fewer than 25 cases reported in literature and therefore it is difficult to comment upon the effect of this variant morphology on prognosis.

## Sarcomatoid Urothelial Carcinoma

Sarcomatoid urothelial carcinoma usually presents as advanced disease with poor clinical outcomes [91]. Radiation exposure and chemotherapy with cyclophosphamide have been documented as known risk factors for this variant [5••]. On histology the sarcomatoid component is composed of high-grade spindle or pleomorphic cells indistinguishable from those of a sarcoma. Heterologous components including osteosarcoma, chondrosarcoma, and rhabdomyosarcoma may be identified in some of the tumors and may portend a worse prognosis [92]. Conventional urothelial, squamous, glandular, or small cell carcinoma may be identified admixed with the sarcomatoid component. The epithelial component expresses vimentin in up to 100% of the cases while the sarcomatoid component shows at least focal immunoreactivity for high molecular weight cytokeratins, p63 and GATA-3 [93]. Markers of epithelial-mesenchymal transition have been documented in this tumor both immunohistochemically and at a molecular level with nearly half of the tumors showing a heavily infiltrated immune phenotype [93, 94••]. These findings have important implications for prognostication and development of therapies for this aggressive variant of bladder cancer. Neoadjuvant chemotherapy may be beneficial in muscle-invasive cancers to downstage the tumor at the time of cystectomy, but the overall prognosis remains poor [71••].

## Poorly Differentiated Tumors (Including Those with Osteoclast-Like Giant Cells)

This entity has been introduced in the WHO 2016 classification and represents a wide range of tumors with mixed morphologies such as small cell carcinoma, giant cell carcinoma, and osteoclast-rich undifferentiated tumors. The latter tumors are characterized by osteoclast-like giant cells (CD68 positive) with undifferentiated UC cells (cytokeratin positive). Most of these cases are associated with in situ or invasive carcinoma, and the mononuclear cells mark for urothelial markers including GATA-3 [95••]. These are rare tumors and have been reported to be associated with a poor prognosis [95••].

## Evolving Entities of Urothelial Carcinoma

There are certain morphological variants of urothelial carcinoma that have not yet been included in the 2016 WHO classification of bladder cancers, because of their rarity and consequent paucity of literature regarding their biology and behavior. A brief description of these tumors is included below.

### Pseudoangiosarcomatous Variant of Urothelial Carcinoma

A total of 15 cases of this rare variant have been reported in literature and they have all been associated with poor prognosis [96, 97]. These tumors histologically resemble angiosarcomas with discohesive tumor cells forming pseudolumina (Fig. 3a). They are commonly accompanied with other UC types and show immunoreactivity for urothelial markers [96].

### Urothelial Carcinoma with Myxoid Stroma

This variant shows extensive mucinous-myxoid stroma with cords of cells suspended within the stroma, morphologically resembling patterns seen in chordoma, yolk sac tumor, and myxoid chondrosarcoma. These tumors present with high-stage disease, have an urothelial immunophenotype, and usually are associated with some component of conventional UC [98].

### Urothelial Carcinoma with Rhabdoid Features

UC with rhabdoid features are tumors comprised of undifferentiated tumor cells having eccentric nuclei, prominent nucleoli, and abundant inclusion like eosinophilic cytoplasm (Fig. 3b). These tumors are extremely rare and portend a poor prognosis [99]. Up to 70% of these tumors show loss of at least one SW1/SNF (chromatin remodeling complex) subunit. SMARCA2 is most frequently lost followed by ARID1A, SMARCB1/INI1, SMARCA4, and SMARCC1 [100•].

## Molecular Classification of UC with Reference to UC variants

The molecular landscape of UC is very large and complex and recently there have been many attempts to classify invasive UC using molecular classifiers based on RNA expression profiles. Many of these molecular classifiers have overlapping profiles, and the most comprehensive of these classifications were proposed by the Lund University group and the TCGA [101, 102••]. The TCGA classification identifies 5 subtypes of muscle-

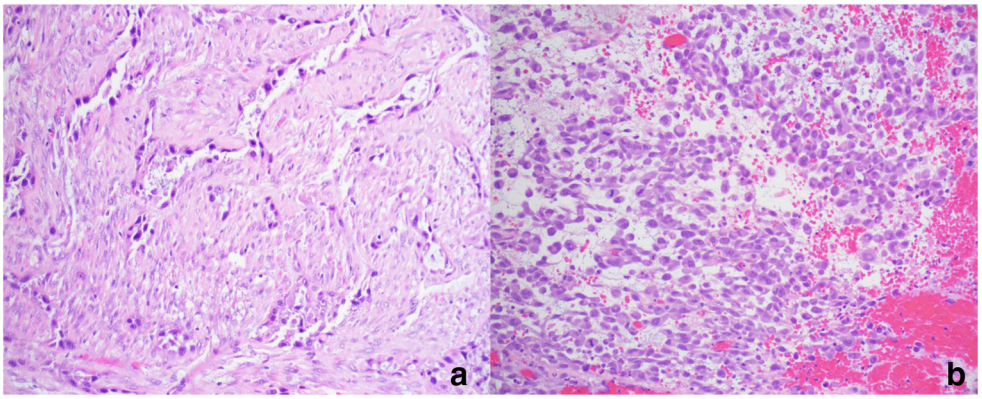


**Fig. 3** Vascular-like spaces lined by tumor cells in pseudoangiosarcomatous UC (**a**); rhabdoid UC with singly dispersed high-grade malignant cells in a myxoid stroma (**b**)

invasive UC, including luminal, luminal-papillary, luminal infiltrated, basal-squamous, and neuronal. These subtypes are characterized by specific RNA expression signatures and have different prognostic and therapeutic implications. Although some of the UC variants are characterized by certain characteristic molecular alterations as mentioned previously in this review, there is limited information regarding the classification of UC variants using the abovementioned molecular classifiers. Using RNA expression or immunohistochemical profiles, micropapillary, nested, and plasmacytoid urothelial carcinomas were found to have luminal features, whereas urothelial carcinoma with squamous differentiation was found to have basal characteristics [37, 49, 50••]. However, the available data in these variants is limited and further comprehensive studies are needed to test the validity of these molecular classifiers in UC variants.

## Conclusions

UC with variant histology is a heterogeneous group of tumors that are being increasingly identified because of their distinct morphological features and their reported association with variable clinical prognosis. Distinct molecular alterations have been described for some of these morphologic subtypes, which have implications for the use of targeted therapies. The use of molecular classifiers, currently used for invasive conventional UC, has yet to be fully explored in UC variants.

### Compliance with Ethical Standards

**Conflict of Interest** Manju Aron declares no potential conflicts of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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5.•• Moch H, Humphrey PA, Ulbright TM, Reuter V. WHO classification of tumours of the urinary system and male genital organs. Lyon: International Agency for Research on Cancer; 2016. **The WHO 2016 classification has updated the diagnostic criteria, prognostic features and molecular data on the histologic variants of UC. Some of the changes include recognition of the large nested variant of urothelial carcinoma and the signet ring morphology as histological subtypes of the nested variant and plasmacytoid urothelial carcinoma, respectively. A new category of poorly differentiated urothelial carcinoma has also been included.**
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12.• Liu Y, Bui MM, Xu B. Urothelial carcinoma with squamous differentiation is associated with high tumor stage and pelvic lymph-node metastasis. Cancer Control. 2017;24:78–82. https://doi.org/10.1177/107327481702400113 **This single institution retrospective study of 47 cases of UC with squamous differentiation, shows that these tumors present with higher stage when compared to pure UC (72.3% vs 43.1%; P< 0.01) and tumors with greater than 20% squamous differentiation had significantly higher nodal metastases compared to pure UC (46.2% vs 27%; P= 0.4), which may be contributing factors for the unfavorable outcomes seen in patents with UC with squamous differentiation**.
13.• Gofrit ON, Yutkin V, Shapiro A, Pizov G, Zorn KC, Hidas G, et al. The response of variant histology bladder cancer to intravesical immunotherapy compared to conventional cancer. Front Oncol. 2016;15:43. https://doi.org/10.3389/fonc.2016.00043 **This study involves 41 patients with Ta or T1 UC with variant histology who were treated with BCG. Patients with variant tumors had a significantly worse prognosis compared to patients with conventional high-grade UC, including 5-year recurrence-free survival (63.5 Vs. 71.5%, p = 0.05), 5-year progression (≥T2)-free survival (60 Vs. 82.5%, p = 0.002), 5-year disease-specific survival (73 Vs. 92.5%, p = 0.0004), and overall survival (66 Vs. 89.5%, 0.05). A patient with variant bladder cancer treated with intravesical immunotherapy has a 27% chance of dying from this disease within 5 years compared to 7.5% chance for a patient with conventional high-grade UC, indicating a poor response to BCG therapy**.
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benign mimickers by TERT promoter mutation. Am J Surg Pathol. 2015;39:127–31. https://doi.org/10.1097/PAS.0000000000000305.

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**were less likely to have non organ-confined disease after neoadjuvant chemotherapy, but only patients with neuroendocrine tumors had an overall survival benefit because of the NAC.**

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78.• Fox MD, Xiao L, Zhang M, Kamat AM, Siefker-Radtke A, Zhang L, et al. Plasmacytoid urothelial carcinoma of the urinary bladder. A clinicopathologic and immunohistochemical analysis of 49 cases. Am J Clin Pathol. 2017;147:500–6. https://doi.org/10.1093/ajcp/aqx029 **This study is a comprehensive clinicopathologic and immunohistochemical analysis of a large cohort of plasmacytoid urothelial carcinoma (PUC). All cases showed diffuse infiltration of the muscle wall, with 57% dying from the disease at a mean of 23 months. Majority of the cases showed lack of immunoreactivity for RB1 protein (12/32) and E-cadherin (8/30). The lack of E-cadherin in PUC may contribute to the discohesion of the tumor cells and to the aggressive nature of this variant.**
79.•• Li Q, Assel M, Benfante NE, Pietzak JE, Herr HW, Donat M, et al. The impact of plasmacytoid variant histology on the survival of patients with urothelial carcinoma of bladder after radical cystectomy. Eur Urol Focus. 2019;5(1):104–8. https://doi.org/10.1016/j.euf.2017.06.013 **One of the largest retrospective study of patients with plasmacytoid urothelial carcinoma (PCV) (98 patients) who underwent radical cystectomy compared to a large cohort (1312 patients ) with pure UC. The study found that patients with PCV UC were more likely to have advanced tumor stage (p=0.001), positive lymph nodes (p=0.038), and receive neoadjuvant chemotherapy than those with pure UC (46% vs 22%, p<0.0001). The rate of positive soft tissue surgical margins was over five times greater in the PCV UC group compared with the pure UC group, with median OS for pure UC being 8yr versus PCV patients of 3.8 yr. On multivariable analysis the association between PCV and OS was not significant. The authors conclude that patients with PCV features have a higher disease burden at RC compared with those with pure UC. However, PCV was not an independent predictor of survival after RC on multivariable analysis, suggesting that PCV histology should not be used as an independent prognostic factor.**
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86.• Borhan WM, Cimino-Mathews AM, Montgomery EA, Epstein JI. Immunohistochemical differentiation of plasmacytoid urothelial carcinoma from secondary carcinoma involvement of the bladder. Am J Surg Pathol. 2017;41:1570–5. https://doi.org/10.1097/PAS.0000000000000922 **Comparative immunohistochemistry study using a large cohort of plasmacytoid urothelial carcinoma (PUC), to distinguish from lobular breast carcinoma and signet ring adenocarcinomas of the stomach, which are close morphological differentials of PUC. The authors recommend a panel of mammaglobin, ER and uroplakin II to exclude lobular breast carcinoma, and the use of GATA-3 and uroplakin II to rule out gastric primary.**
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Histopathology. 2016;68:533–40. https://doi.org/10.1111/his.12785 **The largest study to date of this variant of UC, consisting of the clinical, morphological and immunohistochemical profile of 13 cases. 50% of patients with available follow up died within 1 year of diagnosis. The authors documented the presence of admixed conventional UC in 62% of their cases, with similar immunohistochemical profile as the conventional UC. They suggest that this variant represents an extreme form of de-differentiation of UC.**

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94.•• Guo CC, Majewski T, Zhang L, Yao H, Bondaruk J, Wang Y, et al. Dysregulation of EMT drives the progression to clinically aggressive sarcomatoid bladder cancer. Cell Rep. 2019;27(6):1781–93. https://doi.org/10.1016/j.celrep.2019.04.048 **The authors report a comprehensive genomic analysis of 28 cases of SARC and 84 cases of conventional urothelial carcinoma (UC), with the TCGA cohort of 408 muscle-invasive bladder cancers serving as the reference. SARCs showed a distinct mutational landscape, with enrichment of TP53, RB1, and PIK3CA mutations. They are related to the basal molecular subtype of conventional UCs and could be divided into epithelial-basal and more clinically aggressive mesenchymal subsets on the basis of TP63 and its target gene expression levels. Other analyses revealed that SARCs are driven by downregulation of homotypic adherence genes and dysregulation of the EMT network, and nearly half exhibit a heavily infiltrated immune phenotype. These findings have important implications for prognostication and the development of more effective therapies for this highly lethal variant of bladder cancer.**
95.•• Priore SF, Schwartz LE, Epstein JI. An expanded immunohistochemical profile of osteoclast-rich undifferentiated carcinomas of the urinary tract. Mod Pathol. 2018;31:984–8. https://doi.org/10.1038/s41379-018-0012-z **This is the largest study to date of osteoclast-rich undifferentiated carcinomas of the urinary tract (ORUCUT), which investigates the immunohistochemical profile of these tumors with respect to more specific urothelial markers. This study identified 21 cases of ORUCUT and performed immunohistochemistry for GATA3, uroplakin II, and thrombomodulin along with pancytokeratin (AE1/3) on all cases. Mononuclear cells stained positive in 20 cases (95%) for GATA3 and 19 cases (90%) for thrombomodulin. None of the mononuclear cells were positive for uroplakin II and only three cases showed focal positivity for AE1/3. The osteoclast-like giant cells were negative for GATA3, uroplakin II, thrombomodulin, and AE1/3, providing additional support to a reactive origin for these cells. Additionally, 15 cases (71%) were associated with either in situ or invasive urothelial carcinoma. The findings support a urothelial origin for this tumor.**
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100.• Agaimy A, Bertz S, Cheng L, Hes O, Junker K, Keck B, et al. Loss of expression of the SWI/SNF complex is a frequent event undifferentiated/dedif- ferentiated urothelial carcinoma of the urinary tract. Virchows Arch. 2016;469:321–30. https://doi.org/10.1007/s00428-016-1977-y **This is the first study exploring SWI/SNF expression in undifferentiated UC of the urinary tract. In this study, the authors analyzed by immunohistochemistry 14 undifferentiated UCs (11 from bladder and 3 from renal pelvis) with a nondescript anaplastic or rhabdoid morphology, using commercially available antibodies against the SWI/SNF components SMARCB1 (INI1), SMARCA2, SMARCA4, SMARCC1, SMARCC2, and ARID1A. All tumors were muscle-invasive (9 were T3-4). A conventional UC component was seen in 57% of the cases. The undifferentiated component expressed pan-cytokeratin AE1/AE3 (13/14), vimentin (8/14) and GATA3 (9/14). Complete loss of at least one SWI/SNF subunit was detected in 10/14 cases (71 %) in the undifferentiated component. SMARCA2 was most frequently lost followed by ARID1A. Their results are similar to studies in other epithelial tumors where the SWI/SNF complex has been implicated in the dedifferentiation process and association with aggressive clinical course.**
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102.•• Robertson AG, Kim J, Al-Ahmadie H, Bellmunt J, Guo G, Cherniack AD, et al. Comprehensive molecular characterization of muscle-invasive bladder cancer. Cell. 2017;171(3):540–56. https://doi.org/10.1016/j.cell.2018.07.036 **This study reports a comprehensive analysis of 412 muscle-invasive bladder cancers characterized by multiple TCGA analytical platforms. The study found fifty-eight genes to be significantly mutated, with the overall mutational load to be associated with APOBEC-signature mutagenesis. mRNA expression**

**clustering also identified a poor-survival "neuronal" subtype which is not characterized by small cell or neuroendocrine morphology. Clustering by mRNA, long non-coding RNA (lncRNA), and miRNA expression identified subsets with differential epithelial-mesenchymal transition status, histologic features, and survival. This study identified 5 expression subtypes that have a lot of promise to stratify response to different treatments**.