Plasmacytoid Urothelial Carcinoma
An Unusual Variant That Warrants Aggressive Management and Critical Distinction on Transurethral Resections

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Plasmacytoid urothelial carcinoma (PUC) is a variant of infiltrating urothelial carcinoma that is characterized by tumor cells that have striking morphologic resemblance to and immunohistochemical overlap with plasma cells, and that harbors CDH1 mutation. Plasmacytoid urothelial carcinoma can be widely infiltrative and may permeate the urinary bladder in a limitis plastica–like manner and spread along the fascial planes and into the peritoneum. Compared with conventional urothelial carcinoma, PUCs have a greater chance for higher-stage disease, surgical margin positivity, and metastasis at presentation that translate into its poorer outcome. Upstaging of lamina propria–invasive (pT1) tumors diagnosed at transurethral resections is common. Because of its unfavorable behavior, a more aggressive management approach is being recommended for PUC, including consideration for upfront cystectomy in pT1 tumors. Thus, accurate distinction should be made especially on the initial transurethral resection specimens because of the therapeutic and prognostic implications. Awareness of PUC’s unique clinical presentation, morphology, and immunohistochemical profile is important to avoid a potential misdiagnosis from its mimics.


It is estimated that there will be more than 81,000 cases of bladder cancer diagnosed in the United States in 2018, representing the fourth most common cancer in American men.1 Infiltrating urothelial carcinoma of the bladder exhibits a unique tendency for divergent differentiations and a wide range of morphologies, some of which can have a different behavior and response to therapy.2–4 Variant morphologies are estimated to be about 10% to 25% of invasive urothelial carcinomas, occurring purely or admixed with conventional urothelial carcinoma and other variant types.3 Many of these variants are now officially recognized in the 2016 World Health Organization (WHO) classification, and it is important for pathologists to be aware that some of these variants are factored into newer management recommendations for bladder cancer, necessitating their distinction.3–7

Plasmacytoid urothelial carcinoma (PUC) is a unique variant of invasive urothelial carcinoma characterized by tumor cells that exhibit a striking resemblance to plasma cells, and it is known to have an aggressive behavior.5–20 The 2016 WHO classification now recognizes signet ring cell and diffuse urothelial carcinoma as similar to PUC.5 Plasmacytoid urothelial carcinoma was first described by Sahin et al21 in 1991 in a 63-year-old man who presented with metastatic lesions in the ribs and skull that was misdiagnosed as multiple myeloma. At about the same time, Zukerberg et al22 reported a case of invasive bladder carcinoma that simulated lymphoma with tumor cells resembling plasma cells. Since then, several clinicopathologic case series have been reported that provided additional insights into and understanding of the pathobiology and behavior of this unusual tumor.16–19 More contemporary series from tertiary institutions reveal that PUC constitutes 1% to 4.9% of invasive urothelial carcinomas.8,12

CLINICAL FEATURES
The demographic and clinical features of PUC are not different from those of conventional urothelial carcinoma, including a preponderance of older men (mean, 62–66 years; median, 58–68 years) among the patients, and an association with smoking history.8–10 Most patients present with hematuria and other urinary symptoms, such as dysuria, frequency, urgency, and abdominal pain.

A higher proportion of PUCs are diagnosed at an advanced stage on presentation compared with conventional urothelial carcinoma.8,9,11,13,15 In the study by Li et al,8 53% of PUCs were locally aggressive (>pT2) and 30% had lymph node metastasis at the time of presentation. Upstaging of pT1 tumors on transurethral resection (TUR) to >pT2 at radical cystectomy is common (42%–80% of tumors, including those with lymph node involvement).8,13 In the series by Cockerill et al,9 85% of patients had >pT2 tumors, which included 37% with locally advanced pT4
disease. Reported lymph node metastasis at presentation ranged from 13% to 72%.\textsuperscript{8,9,11,12,15} The high tumor stage at diagnosis corresponded to higher positivity rates in the paravesical (21%–28%) and ureteral (32%) margins on radical cystectomy.\textsuperscript{8,12} Compared with conventional urothelial carcinoma, PUC has about 10-fold and 8.5-fold greater risks for involvement of the paravesical and ureteral margins, respectively. Plasmacytoid urothelial carcinoma also has a predilection to disseminate along the peritoneum and is encountered in 33% of cases at presentation, a spread that is not typical for conventional urothelial carcinoma.\textsuperscript{16} Pelvic peritoneal infiltration by PUC can be detected on radiology as thick sheets extending along the fascial planes and is suggested to be a characteristic imaging finding.\textsuperscript{20}

On follow-up, PUC has an aggressive course, with high recurrence rates.\textsuperscript{8,9,11,12,15} In the largest series of 98 PUCs from Memorial Sloan Kettering Cancer Center, the median overall survival was reported to be 3.8 years, 4.1 years shorter than in matched conventional urothelial carcinoma (8 years).\textsuperscript{8} The series from the Mayo Clinic of 46 PUCs reported a poorer 5-year cancer-specific survival of 36% (versus 57%) and poorer local recurrence-free survival of 63% (versus 81%) than conventional urothelial carcinoma.\textsuperscript{9} In both studies, however, when PUCs were matched with a cohort of conventional urothelial carcinomas, and with stage and other select clinicopathologic variables controlled, no significant differences in mortality exist, indicating that the higher mortality in PUC is likely due to the higher proportion of advanced-stage tumors at presentation. Plasmacytoid urothelial carcinoma may recur as peritoneal carcinomatosis encountered in 12% of cases.\textsuperscript{8}

**PATHOLOGY**

**Gross Pathology**

Plasmacytoid urothelial carcinomas may present as a single dominant tumor or multiple masses in the bladder (range, 2.5–6 cm).\textsuperscript{19} Diffuse and extensive infiltration of the bladder is common, producing a “linitis-plastica”–like permeation and thickening of the bladder wall (Figure 1). The tumor involvement may be more extensive than visualized at the luminal aspect, including during cystoscopic examination and TUR sampling.

**Histopathology**

Plasmacytoid urothelial carcinoma is characterized by the infiltration of discohesive oval to round neoplastic cells with moderate to abundant amphophilic to eosinophilic cytoplasm and eccentrically placed nuclei that resemble plasma cells (Figure 2).\textsuperscript{16,37,19} The neoplastic cells may also contain occasional vacuoles or form signet ring cells with focal intracytoplasmic mucin. The plasmacytoid cells are relatively monotonous and may form sheetlike growth; small, loose clusters; or cords, the last of these simulating lobular carcinoma of the breast. Patternless single-cell infiltration, however, is common. The tumor cell infiltrates, particularly when loose and dispersed, may not be readily visible on low-power magnification. The tumor cells are usually at least 3 times larger than a lymphocyte. Nucleolar prominence is inconsistent, but mitosis can be frequent. A surface urothelial carcinoma component can be present in the form of either papillary or in situ urothelial carcinoma, and their presence facilitates the diagnosis as urothelial lineage. Plasmacytoid urothelial carcinoma can also be admixed with invasive conventional or other variants of urothelial carcinoma. The amount of PUC component reported is in the range of 5% to 100%, although more often the plasmacytoid cells account for more than 50% of the tumor.\textsuperscript{16,17}

Because of the linitis plastica–like infiltration, PUC may spread within the bladder wall without involving an overlying benign surface urothelial mucosa (Figure 3). Thus, careful examination of the deeper aspects of the TUR chips should be made, particularly in the clinical context of a thickened bladder wall. Plasmacytoid urothelial carcinoma may also spread within the ureteral wall and adventitia and with tumor sparing the lumen or mucosa.\textsuperscript{12} Pathologists should be aware of this pattern of infiltration when examining the ureteral margins, particularly in frozen sections. The plasmacytoid morphology of PUC is maintained at metastatic sites and raises the differential diagnosis for a plasma cell neoplasm and other malignancy with discohesive cells.

**Immunohistochemistry**

The immunohistochemical profile of PUC is similar to that of conventional urothelial carcinoma. The plasmacytoid cells express the urothelial–associated markers GATA3, p63, S100P, high–molecular weight keratin, cytokeratin 7 (CK7), CK20, and uroplakin II (Figure 4). Aggregates studies show that GATA3 is expressed in 80% of PUC cases, and it is more sensitive than p63, which stains 45% of cases.\textsuperscript{10,24–26} Plasmacytoid urothelial carcinoma cells mostly coexpress CK7 (92%) and CK20 (72%). Uroplakin II, a highly specific marker for urothelial carcinoma and more sensitive than uroplakin III, is positive in only 33% of PUC (compared with 8% for uroplakin III).\textsuperscript{24,25} The lower expressions of uropakin II and p63 in PUC are in contrast to those observed in conventional urothelial carcinoma.

Interestingly, PUC cells express CD138, a marker commonly used to identify plasma cells that may lead to a misdiagnosis of a plasma cell tumor.\textsuperscript{17} In addition, PUC cells may also express gross cystic disease fluid protein-15 (GCPDFP-15), progesterone receptor (PR), caudal type homeobox 2 (CDX2), and polyclonal carcinoembryonic antigen (p-CEA) in 24%, 13%, 18%, and 49% of cases, respectively.\textsuperscript{20} Caution is advised when using these immunohistochemical stains in differentiating PUC from metastatic lobular carcinoma or gastrointestinal signet ring cell carcinoma. Plasmacytoid urothelial carcinoma does not express estrogen receptor (ER) and mammaglobin, which are helpful when distinguishing PUC from metastatic lobular carcinoma of the breast.\textsuperscript{25}

**Cytology**

The first urine cytology description for PUC was reported in 2002 where voided urine samples revealed discohesive atypical cells with abundant cytoplasm and eccentric hyperchromatic nuclei.\textsuperscript{15} The rare reports also described dysmorphic tumor cells about similar in appearance to high-grade urothelial carcinoma, but with less malignant–appearing nuclei (eg, less coarse and evenly distributed chromatin).\textsuperscript{28} There may be paucity of tumor cells in urine cytology specimens that can be a shortfall in the diagnosis, perhaps because of the minimal surface involvement by the tumor which mainly spread deep into the bladder wall and are thus, exfoliated in relatively lower numbers. Rare reports of PUC cell cytology at metastatic sites such as in cerebrospinal fluid and bone marrow described similar cytomorphology to that encountered in urine samples.\textsuperscript{29}
Figure 1. Diffuse bladder wall thickening due to the linitis plastica–like infiltration by plasmacytoid urothelial carcinoma.

Figure 2. A, Discohesive tumor cells infiltrating the bladder wall. B, Plasmacytoid cells with abundant cytoplasm and eccentric nuclei. C, Tumor cells arranged in cords and single cell filing (hematoxylin-eosin, original magnifications ×100 [A], ×400 [B], and ×200 [C]).

Figure 3. A, Transurethral resection chip with discreet tumor cell infiltrates deep in the lamina propria. B, Plasmacytoid cells adjacent to uninvolved benign urothelial surface (hematoxylin-eosin, original magnifications ×100 [A] and ×400 [B]).
Molecular Studies

It was noted that there is loss of E-cadherin in PUC as assessed by immunohistochemistry in several studies. E-cadherin is a protein that maintains adhesion between cells; loss of E-cadherin is associated with increased cellular invasiveness and lack of differentiation, and thus explains the diffuse permeation by the PUC cells. It was hypothesized that loss of E-cadherin is associated with the plasmacytoid features in urothelial carcinoma. However, E-cadherin–positive cases have also been reported, which led to the division of PUC into E-cadherin–negative and E-cadherin–positive types, with the former having a poorer prognosis. Furthermore, p53 accumulation was observed only in E-cadherin–negative cases.

The E-cadherin loss can be explained by cadherin-1 (CDH1) mutation or hypermethylation of the promotor region. A recent study by Al-Ahmadie et al showed frequent somatic CDH1 loss-of-function mutations in plasmacytoid bladder cancer, which is unique for this variant. Interestingly, in the same study E-cadherin expression was lost only in the invasive PUC cells and not in the concomitant urothelial carcinoma in situ component (Figure 5). Of all the genes mutated in PUC, CDH1 mutation that leads to E-cadherin loss may demarcate the evolution of plasmacytoid histology. CDH1 mutations are also known to be present in lobular carcinoma of the breast and diffuse gastric carcinoma, both of which have morphologic resemblance to PUC. However, unlike in a subset of diffuse hereditary gastric cancers and lobular breast cancers, no germ line CDH1 mutation is present in patients with PUC; further, the comutation patterns of diffuse gastric and lobular breast cancers are distinct from that of PUC except for the CDH1 alterations. Unlike in lobular breast carcinoma, where E-cadherin expression is lost in both the in situ and invasive components, E-cadherin in PUC is retained in the urothelial in situ component and is lost only in the invasive carcinoma component.

Differential Diagnosis

Maintenance of plasmacytoid morphology by PUC at metastatic sites, particularly in the bone, can lead to mistaken diagnosis as plasmacytoma or lymphoma, as was
the case when PUC was first described.\textsuperscript{21} The resemblance to plasma cells can be compounded by PUC’s positivity for CD138.\textsuperscript{17} Of note, neoplastic plasma cells may also express epithelial markers, such as keratin and EMA, and have diminished expression of CD45, a staining pattern similar to that of PUC cells, further complicating their distinction. Knowledge of clinical history of urinary tract tumors or plasma cell dyscrasia, including the presence of monoclonal gammopathy, may facilitate the distinction. Diagnosis of PUC can be confirmed by its expression of urothelial-associated markers, such as GATA3, p63, uroplakin II, CK7, and CK20, whereas plasma cells can express MUM1 and lymphoid cells express CD45.\textsuperscript{24,25} Plasmacytoma involving the bladder is exceedingly rare, and the presence of malignant-appearing “plasma cells” should prompt the consideration and workup first for PUC. Other systemic manifestations of multiple myeloma may also be present concomitant to a bladder plasmacytoma.

Carcinomas that mimic PUC include metastatic gastrointestinal signet ring cell carcinoma and lobular carcinoma of the breast. Both these tumors have infiltrative discohesive cells that may have intracytoplasmic mucus and loss of E-cadherin expression, similar to PUC. Distinction can be problematic in the bladder and at metastatic sites. Secondary involvement of the bladder by these tumors is more often part of a widespread dissemination rather than an isolated metastasis, and thus knowledge of the clinical history is vital. Searching for the presence of admixed conventional urothelial carcinoma, other variant morphologies, and concomitant surface papillary or in situ urothelial carcinoma is helpful in the diagnosis of PUC. It is important to know that a subset of PUCs may express CDX2 and p-CEA, complicating the problems in distinguishing PUCs from gastrointestinal signet ring cell carcinoma.\textsuperscript{25} GATA3 and uroplakin II, however, are not expressed by signet ring cell carcinomas, and expression can facilitate the diagnosis of PUC.\textsuperscript{25} A subset of PUCs may express GCPDF-15 and PR, and lobular carcinoma may also express GATA3, complicating the problems in distinguishing PUCs from these other carcinomas.\textsuperscript{25} Plasmacytoid urothelial carcinoma, however, is negative for the breast markers mammaglobin and ER, and lobular carcinoma is negative for uroplakin II, and thus inclusion of these immunostains in a panel may facilitate their diagnosis.\textsuperscript{25}

Rhabdoid urothelial carcinoma may resemble PUC because of the discohesive sheetlike growth pattern and close similarity in cytoplasmic features.\textsuperscript{2} Rhabdoid urothelial carcinoma can be discriminated from PUC by its greater degree of pleomorphism, prominent nucleoli, and distinctive cytoplasmic inclusion made of intermediate filaments that may indent the nucleus. Rhabdoid urothelial carcinoma is rare, and limited data suggests a poor prognosis. The clinical and therapeutic relevance of distinguishing rhabdoid urothelial carcinoma from PUC thus remains unclear.

Limited sampling of PUC may mimic chronic cystitis with ample plasma cells. Cystitis can be distinguished on the basis of its polymorphous inflammatory cell infiltrates and lack of cytologic atypia.

**MANAGEMENT**

Because of the unfavorable outcome of PUC, an aggressive approach to therapy has been recommended, including in the latest National Comprehensive Cancer Network bladder cancer guideline.\textsuperscript{3,4,7} Data showed that differentializing non–muscle-invasive (pT1) from muscle-invasive (pT2) tumors at TUR seems less critical because upstaging at radical cystectomy to locally advanced and metastatic disease is quite common.\textsuperscript{13} Thus, some experts advocate upfront cystectomy even for pT1 disease, in contrast to the conservative management approach of pT1 conventional urothelial carcinoma and other variants that considers restaging TUR and radical cystectomy only when there is recurrence or residual disease.\textsuperscript{4} For pathologists, it is therefore critical that PUC be identified and reported at the initial TUR sampling because of the need for a more aggressive treatment approach. Similar recommendations have been provided for other variants as well, such as micropapillary and sarcomatoid urothelial carcinomas.\textsuperscript{7} Newer management algorithms suggested for muscle-invasive PUC also differ from those for conventional urothelial carcinoma.\textsuperscript{3} So far, there are no strong data available that show a clear benefit of giving neoadjuvant chemotherapy in PUC.\textsuperscript{11} Further, despite the pathologic downstaging seen in PUC following neoadjuvant chemotherapy, relapses are common. Thus, chemotherapy before radical cystectomy in muscle-invasive PUC has not been strongly advocated, in contrast to conventional urothelial carcinoma.

**CONCLUSIONS**

Plasmacytoid urothelial carcinoma has a unique clinical presentation, tumor morphology, and molecular features, as well as immunohistochemical features that overlap with its main mimics. Knowledge of this uncommon variant is important to avoid a potential misdiagnosis in the bladder and metastatic sites. Because of the poorer outcome of PUC, aggressive management is recommended, including a consideration for cystectomy in pT1 disease. Thus, PUC must be distinguished from other urothelial carcinoma variants, particularly in TUR specimens because of the differing clinical management and aggressive behavior.

**References**


