Plasmacytoid Variant Urothelial Carcinoma of the Bladder with Different Proportion of Plasmacytoid Variant Urothelial Carcinoma Differentiation: Two Case Report and Literatures Review

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Abstract: Objective Plasmacytoid urothelial carcinoma (PUC) of the bladder is a recently identified rare variant of urothelial carcinoma (UC). The purpose of this study was to study the clinical, imaging and pathological characteristics of PUC. Methods We reviewed two cases of PUC with different aggressive behaviour related the proportion of Plasmacytoid variant UC differentiation. The clinical, imaging characteristics and pathological biological parameters including the express of several biomarkers of tumours detected by immunohistochemistry method and the levels of several serum tumour markers measured with Electrochemiluminescence method. Results A 74-year-old and 53-year-old Chinese male were diagnosed with high-grade PUC (pT4N2M0) by the microscopic plasmacytoid appearance of the tumor from the radical cystectomy specimen, but they had different proportion of plasmacytoid variant UC differentiation and different outcomes (8 months, 17 months, respectively). The elder had approximately ninety percent of PUC component and the younger had fifty percent of PUC component. Immunohistochemical staining in the two cases was positive for epithelial markers and weekly positive for CD138. They all lost the membranous expression of E-cadherin. The expression of Ki-67 of the elder was approximately 60%, and 30% of the younger. The microvascular density based on CD105 of the elder was about 42.23/HPL, and 13.12/ HPL of the younger. Conclusions PUC of the urinary bladder is an uncommon and aggressive variant of UC associated with late presentation and poor prognosis. The correct diagnosis of PUC of the bladder may be reached by combination of its typical histological features, clinic characteristics, and immunohistochemical results.

Keywords: Urinary bladder; Plasmacytoid urothelial carcinoma; Keratin; E-cadherin; CD138; Differential diagnosis; immunohistochemical.

1. Introduction

Plasmacytoid urothelial carcinoma (PUC) of the bladder is a recently identified rare variant of urothelial carcinoma with histological characteristics similar to plasma cells [1-4]. Currently, the largest series of PUCs so far is a series of 32 PUCs reported by Keck [5], and other large series of 19 cases reported by Gonzales-Roibon[6]. There were only 13 cases reported in China. It is an aggressive variant associated with poor prognosis that presents at an advanced clinical stage. Limited data is available about the pathological, immunohistochemical characteristic as well as clinical behavior of this rare variant. Almost all of the reported cases have had a component of high grade urothelial carcinoma in addition to the single malignant cells [7]. We herein report two cases of primary PUC with different proportion of PUC differentiation and review the current literature regarding to this tumor by a pooled analysis of all cases reported.

2. Materials and methods

2.1. Clinical materials

We reviewed two cases of PUC with different aggressive behaviour related the proportion of Plasmacytoid Variant Urothelial Carcinoma differentiation with a detailed description of the clinical and histopathological features from January 2010 to July 2013 in Affiliated Rizhao People's Hospital of Jining Medical Colleg. PUC
diagnosis was verified by histological methods, and pathological categorization was determined according to the current World Health Organization classification of the digestive system (WHO 2004)[7]. The two patients signed informed consents, and this study was approved by Local Ethical Committee. The two patients were male, age 74 and 53 years. They presented with the chief complaint of a 3-week (elder patient) to 2 months (younger patient) history of diffuse lower abdominal pain, associated with urological symptoms including macroscopic hematuria, urgency, and frequency, and whole stream hematuria and painful micturition. The patients were cigarette smokers with a history of smoking 20 cigarettes per day for 30 (younger patient) to 40 (elder patient) years. Their past medical history were unremarkable, and there were no significant findings on physical examination and hematological and biochemical laboratory tests, and the elder patient was also noted absence of microhematuria two years ago. The younger patient presented with hematuria and lower abdominal pain lasting 2 months. The clinical, imaging characteristics and pathological biological parameters including the express of several cytokeratin (including AE1/AE3, CK7, CK20, CAM5.2, CK18, and CK19), epithelial membrane antigen (EMA), E-cadherin, lymphoid markers (LCA, CD138, CD38, MUM-1, kappa, and lambda), embryonal rhabdomyosarcoma markers (desmin, SMA, myoglobin, MyoD1, and myogenin), malignant melanoma (HMB45, Melan A, S-100), neuroendocrine carcinoma (ChrA, Syn, NSE, CD56), PLAP, β-hCG, WT1, CD105 and microvascular density (CD105-MVD), and Ki-67 detected by immunohistochemistry S-P method and the levels of several serum tumour markers measured with Electrochemiluminescence method.

2. 2 Immunohistochemistry
Tissue samples were fixed in 10% neutral buffered formalin and embedded in paraffin. Tissue sections were deparaffinized and rehydrated using standard procedures. Immunoreactions were processed using the UltraSensitiveTM S-P Kit (Maixin-Bio, China) according to the manufacturer's instructions, and signals were visualized using the DAB substrate, which stains the target protein yellow. The pathological specimens were reviewed independently by two pathologists and the pathologists were blinded to the subject's clinical history, and the results of the immunohistochemistry staining assay. In brief, a proportion score was assigned that represents the estimated proportion of positive tumor cells on the entire slide. For each histological section, the percentage of positive cells was scored as 0 (<5%), 1 (6%-25%), 2 (26%-50%), 3 (51%-75%) and 4 (>75%), and the staining intensity was scored as 0 (negative), 1 (weak), 2 (moderate) and 3 (strong). The immunoreactive score (IRS) was obtained by multiplying IDPL the percentage of positive cells and the staining intensity. Immunohistochemical results with an IRS of 0 were considered negative(-), 1-4 weak positive(+), 5-8 moderate positive(++) and 9-12 strong positive(+++). The MVD recognized by CD105 was evaluated under light microscopy according to the procedure described by Weidner et al[8]. The number of vessels was counted in the hot spots at high magnifications (x200, HPL), and the average counts of the fields were recorded. In addition, for Ki-67 expression the percentage of cancer cells showing a nuclear reactivity was recorded after inspection of all optical fields at 200× and the mean value was used to score each case. Tumors with expression of >5% of tumor cells were considered to be positive.

2. 3 Measure of biomarkers in patient blood serum
We performed biomarkers of blood serum. For TSGF, OPN, TPS, CEA, CA153, TSGF, CA125 and CA199 analysis, 3ml heparinized blood was drawn from each individual. The biomarkers were detected with electrochemiluminescence method in the clinical laboratory in Rizhao People's Hospital.

3. Results

3. 1. Case 1
A 74-year-old Chinese male presented with the chief complaint of a 3-week history of diffuse lower abdominal pain, associated with 4 days of urological symptoms including macroscopic hematuria, urgency, and frequency, and 2 days of whole stream hematuria and painful micturition. The patient is a cigarette smoker with a history of smoking 20 cigarettes per day for 40 years. His past medical history was unremarkable, and there were no significant findings on physical examination and hematological and biochemical laboratory tests, and the patient was also noted absence of microhematuria two years ago. Tumor markers of TSGF, OPN, TPS, CEA, CA153, TSGF, CA125 and CA199 were negative within normal limits. Urine cytology revealed a scant number of atypical cells, with frequent presence of tumor diathesis. Urinary ultrasonography and Computerized tomography demonstrated a protruding solid mass measured 6.4cm×4.3cm×2.5cm located in the left wall and the trigone of the bladder (Fig. 1(①-④)). Cystoscopic examination revealed an ulcerated irregular thickened area at left wall and the trigone of the bladder, which was biopsied. Pathological examination identified a carcinoma in situ of the urothelial lining in the contiguous mucosa. On microscopy, the
tumor was shown to be an invasive carcinoma mimicking plasmacytoma, and was mainly composed of round cells with abundant eosinophilic cytoplasm and eccentric nuclei, suggesting a high-grade urothelial carcinoma (UC). Immunohistochemical staining of the tumor sections showed positive for CK7, weekly positive for CD138, but negative for several lymphoid markers including CD38, MUM-1, LCA. The patient was therefore diagnosed as a high-grade UC with plasmacytoid differentiation, and he was scheduled for radical cystectomy and reconstruction with an ileal conduit.

Figure 1 Computerized tomography of case 1
Pelvic computerized tomography scan showed a large intravesical mass measured 6.4cm×4.3cm×2.5cm associated with thickening of the left wall and the trigone of the bladder with possible extravesical extension

The cystectomy specimen showed an ulcerated irregular neoplasm which was present in left wall and the trigone of the bladder (Fig. 2①). Histologically, the tumor was found to penetrate throughout the entire bladder wall into the serosa, and the infiltrating malignant epithelial cells had mainly eccentric nuclei and abundant eosinophilic cytoplasm with characteristic plasmacytoid morphology with scattered atypical cells arranged in loose clusters on high power (Fig. 2②). The proportion of plasmacytoid variant urothelial carcinoma differentiation was about ninety percent. The obturator lymph nodes and right iliac artery lymph nodes were found to be metastatic. The pathological diagnosis was PUC (High-grade, pT4N2M0) with diffuse muscle, small tracts and vascular invasion. Immunohistochemical studies showed that the plasmacytoid tumor cells were positive for cytokeratin (including CK7, CK20 PCK, AE1/AE3) with different staining intensity ranging from slight to strong positivity (Fig. 2③). The tumor cells were also positive for epithelial membrane antigen (EMA), and the signet ring tumor cells were positive for carcinoembryonic antigen (CEA) (data not shown), while the tumor lost the membranous expression of E-cadherin as a molecular hall mark of PUC(Fig. 2④). The tumor was negative for several lymphoid markers (LCA, CD38, MUM-1, kappa, and lambda), and markers of embryonal rhabdomyosarcoma (desmin, SMA, myoglobin, MyoD1, and myogenin), malignant melanoma (HMB45, Melan A, S-100), and neuroendocrine carcinoma (ChrA, Syn, NSE, CD56). PLAP, β-hCG, and WT1 staining were also negative. The expression of Ki-67 was about 60%(Fig. 3①), and the CD105 marked microvascular density(CD105-MVD) of the tumor was approximately 42. 23/ HPL (Fig. 3②). The patient received routine perioperative care including close monitoring of patients’ general condition, prevention and control of postoperative complications, drainage tubes and stoma care, and psychological support. Unfortunately, the patient died 8 months after the surgery and two cycles of adjuvant chemotherapy with MVAC (methotrexate, etoposide, vinblastine, and cisplatin).
Figure 2 Histological and Immunohistochemical presentation of case 1

1. Gross examination of the cystectomy specimen showed an ulcerated irregular neoplasm. 2. The sections of the tumor showed infiltrating malignant epithelial cells mainly with eccentric nuclei and abundant eosinophilic cytoplasm with characteristic plasmacytoid morphology, penetrating through the entire bladder wall with scattered atypical cells arranged in loose clusters on low power (HE staining, scanning). 3. Immunohistochemical studies showed that the plasmacytoid tumor cells were positive for cytokeratin 7 on low power and high power (SP). 4. The tumor lost the membranous expression of E-cadherin (SP, high power).

3. 2 Case 2

A 53-year-old Chinese male presented with hematuria and lower abdominal pain lasting 2 months with a history of smoking 20 cigarettes per day for last 30 years. His past medical history was unremarkable too. Tumor markers of TSGF, OPN, TPS, CEA, CA153, TSGF, CA125 and CA199 were negative within normal limits. CT scan of abdomen and pelvis showed thickened urinary bladder wall with irregularity of the mucosa involving entire bladder. Cystoscopy revealed edema and ulceration of the entire bladder mucosa, which was biopsied. Pathological examination identified a malignant urothelial carcinoma with plasmacytoid appearance. Immunohistochemical staining of the tumor sections showed positive for CK7, while the tumor lost the membranous expression of E-cadherin, and negative for several lymphoid markers including CD38, MUM-1, LCA, but, weekly positive for CD138. The patient was therefore diagnosed as a high-grade UC with plasmacytoid differentiation, and he was scheduled for radical cystectomy and reconstruction with an ileal conduit. Microscopic examination showed a high-grade tumor composed of discohesive plasmacytoid cells replacing the lamina propria, and the tumor cells were seen extending from the mucosal aspect and invaded through the detrusor muscle to invade the perivesical fat and the serosa. The proportion of plasmacytoid variant urothelial carcinoma differentiation was about fifty percent. The expression of Ki-67 was about 30% (Fig. 3③), and the CD105-MVD of the tumor was about 13. 12/ HPL (Fig. 3④). The patient received routine perioperative care including close monitoring of patients’ general condition, prevention and control of postoperative complications, drainage tubes and stoma care, and psychological support. The patient died 16 months after the surgery.
Gross examination of the cystectomy specimen showed an ulcerated irregular neoplasm. The sections of the tumor showed infiltrating malignant epithelial cells mainly with eccentric nuclei and abundant eosinophilic cytoplasm with characteristic plasmacytoid morphology, penetrating through the entire bladder wall with scattered atypical cells arranged in loose clusters on low power (HE staining, scanning). Immunohistochemical studies showed that the plasmacytoid tumor cells were positive for cytokeratin 7 on low power and high power (SP). The tumor lost the membranous expression of E-cadherin (SP, high power).

4. Discussion

Bladder urothelial cancer has a propensity for divergent differentiation, which has increasingly been recognized in recent years due to heightened awareness and improved immunohistochemistry techniques. Furthermore, the recent World Health Organization classification of urothelial cancers improved clarity on this issue. PUC was reported mainly in western countries in White race. This rare variant of urothelial carcinoma has been described mostly in small case series [4, 9-10], with the largest series having 32 cases reported by Keck[5], and other large series of 19 cases reported by Gonzales-Roibon[6]. To the best of our knowledge, there are only 13 cases of PUC reported in the Chinese literature with detailed pathological information. In China, bladder cancer represents the 8th most common malignancy in males. It most commonly exists as an epithelial tumor in which around 90% of cases are urothelial carcinoma. The case in our report has the same clinical features as all other reported cases, with the mean age of initial diagnosis of 68 years (range 42–89). PUC is more common in males than in females (the constituent ratio shows a male predominance ratio of about 3:1). There are only one case(1/13) of PUC reported in the female in China. This variant has displayed aggressive behavior in the cases described thus far, usually diagnosed in advanced pathological stage (64% pT3, 23% pT4), showing metastases in 60% of the patients[5], although there is insufficient evidence to make any concrete recommendations from these small case series [3, 11]. Studies comparing PUC and conventional UC usually show a worse prognosis of PUC than UC, if treated with surgery and chemotherapy if treated with cystectomy and adjuvant cisplatin-based chemotherapy[5]. Overall survival of PUC patients was significantly worse than that of patients suffering from UC (27.4 months with 95% CI: 16.8-37.9 months, 62.6 months with 95% CI: 54.8-70.4 months, respectively) [5]. There is only a small number of case reports that report of a good response to chemotherapy, but the follow up of these patients is short and these conclusions can not be generalized in this way. Systemic cisplatin-based chemotherapy is regarded as the therapy of choice in metastatic UC. However, the role of adjuvant or neoadjuvant chemotherapy remains under
debate [12]. Most urological and oncological guidelines recommend neoadjuvant cisplatin-based chemotherapy as the therapy of choice in locally advanced bladder cancer [13].

There are several known and potential risk factors for bladder cancer. Cigarette smoking and occupational exposure to aromatic amines are the most important among them [14]. But it is unknown whether smoking is also the potential risk factors for PUC, and more studies are needed to evaluate the potential risk of smoking for PUC. The risk increases with increasing duration of smoking, and for those with the longest history of smoking (60 years or more) reaches approximately 6 in men and 5 in women [15]. The patients in our cases report is a tobacco smoker with the history of smoking 20 cigarettes per day for more than 30 years. PUC is included in the divergent differentiation patterns. As a rare variant of urothelial carcinoma with histological characteristics similar to plasma cells [2]. However, most of the reports failed to quantify the divergent differentiation present within the specimen. In our cases, the two patients were a 74-year-old and 53-year-old male both with a history of smoking more than 20 cigarettes per day for last over 30 years. A complaint of lower abdominal pain and urological symptoms were diagnosed with high-grade PUC (pT4N2M0) by the microscopic plasmacytoid appearance of the tumor from the radical cystectomy specimen, but they had different proportion of plasmacytoid variant urothelial carcinoma differentiation(approximately 90%, 50%, respectively) and different outcomes(8 months, 16 months, respectively). Immunohistochemical staining in the two cases was positive for epithelial markers. They all lost the membranous expression of E-cadherin, a molecular hallmark of PUC. The expression of Ki-67 of the elder was approximately 60%, and 30% of the younger. And the CD105 and microvascular density of the elder was about 42.23/HPL, and 13.12/HPL of the younger.

The most common presenting symptom for diagnosis is hematuria, generally accompanied by urgency, frequent micturition and/or nonspecific lower abdominal pain. However, early diagnosis cannot be made due to the absence of hematuria until the late stage of the disease. In our cases we presented here, the initial complaint from the patient was diffuse nonspecific lower abdominal pain without hematuria. The symptoms of whole hematuria and painful micturition are due to the late stage of the disease. As a result, the major diagnostic pitfalls is the lack of specific clinical features for differentiating PUC from other types of bladder tumors. Cystoscopy suggests that the tumor can be present as a single or as multiple lesions measuring from 0.9 to 6.4 cm in diameter, and can be located anywhere in the bladder. Therefore, earlier diagnosis of PUC depends on the cystoscopy and biopsy results for those patients with similar clinical presentation described above. Previous reports suggested some common features for PUC manifested by the medium sized and dyscohesive tumor cells with abundant eosinophilic cytoplasm, small hyperchromatic nuclei and frequent mitotic features [10]. Wang and colleagues reported that there were also features characterized by large, dyscohesive cells with enlarged nuclei and irregular contour, vesicular chromatin, and prominent nucleoli in tumor sections [3]. Most of the reports suggested that only a few atypical cells in the urinary samples were detected. Cytological evidence can be obtained from PUC patients in voided urine samples procured before and after cystoscopy probably because of the late stage of the disease. Additional studies would be necessary to evaluate the significance of urinary cytology in the diagnosis of PUC.

From the pathology point of view, caution should be taken in the evaluation of neoplasms with plasmacytoid morphology, and we suggest that ancillary tests such as immunohistochemical and electron microscopic studies are needed to document the cell of origin. Immunohistochemical staining plays an important role in the diagnosis of PUC. The panel of antibodies for immunophenotyping of the atypical neoplastic cells comprises EMA and cytokeratins (CKs) including AE1/AE3, CK7, CK20, CAM5.2, CK18, and CK19. And the cytokeratins with various molecular weights are expressed at different levels in PUC - diffuse positive for CK7, slightly focal positive for CK20, but negative for CK5/6. In the Keck’s report, Eighty-seven percent of the PUCs showed a negative or strongly reduced membranous staining of E-cadherin. b-Catenin staining was negative in 22.5%, and 16.7% of the remaining tumors showed nuclear accumulation. A aberrant CK20 expression (negative or >10% of cells stained) and negative CK7 staining was found in 100% and 22.6%, respectively. Ninety-seven percent revealed positive staining for PAN-CK[5]. CD138 is positive in 78%, whereas MUM-1 expression is negative in all cases. In our cases, CD138 are weekly positive. It has been noted that loss of E-cadherin expression might be associated with a plasmacytoid differentiation pattern in UC, and the studies suggest that loss of E-cadherin expression is probably associated with increased cellular invasiveness or correlated with muscularis mucosal involvement and tumor recurrence [3, 5, 15]. Mitsogiannis et al reported that plasmacytoid tumor cells were immunoreactive for CD138 in the bladder [16], while CD38 was negative [3, 15]. Shimada et al reported the first case of urothelial carcinoma with a plasmacytoid variant expressing both CA19-9 and β-HCG [15]. Therefore, tumor cells positive for CD138 provides an evidence to support the diagnosis of PUC. However, the immunohistochemical staining of tumor sections from our case revealed negative staining for E-cadherin, CD38, CA19-9 and β-HCG, but positive for CK7, CK20, PCK, and CAM5.2; the signet ring sample tumor cells were positive for carcinoembryonic antigen (CEA), as well as slight focal positive staining for epithelial membrane antigen (EMA), while several lymphoid markers were negative. The tumor was also negative for makers of
embryonal rhabdomyosarcoma (desmin, SMA, myoglobin, MyoD1, myogenin), malignant melanoma (HMB45, Melan A, S-100), and neuroendocrine carcinoma (ChrA, Syn, NSE, CD56). Multitarget fluorescence in situ hybridization showed all PUCs to be highly aneuploid and polysomic. Deletions on chromosome 9p21 seem to play an important role in this variant. FGFR3 and PIK3CA mutation analyses yielded no mutations in any of the PUCs analyzed. TP53 mutation analysis showed mutations in 29%[5]. This distinct pattern of immunoreactivity provided pivotal information for confirming the final diagnosis of PUC. The presence of urothelial carcinoma in situ in the contiguous mucosa and the pattern of invasion into the lamina propria confirmed the mucosal origin of the tumor, and excluded the possibility of bladder invasion by plasmacytoid carcinoma. The other differential diagnoses including small-cell carcinoma, malignant melanoma, and embryonal rhabdomyosarcoma were all ruled out because of the mucosal origin of the tumor. Chronic bladder inflammation with abundant plasma cells was also considered in the differential diagnosis, but the more prominent cytological anaplasia feature distinguishes PUC from chronic bladder inflammation. PUC is difficult to differentiate from signet ring cell adenocarcinoma of the urinary bladder due to overlap in clinical, morphological and immunohistochemical presentation[17,18]. From the pathology point of view, caution should always be taken in evaluation of neoplasms with plasmacytoid morphology, and immunohistochemical study is needed to document the cell of origin. The individual tumor cells of PUC had striking morphologic overlap with plasma cells with an eccentrically placed nucleus and abundant amphophilic to eosinophilic cytoplasm[17,18]. The nuclei of PUC were of low to intermediate nuclear grade with minimal nuclear pleomorphism[17,18]. The panel of antibodies for immunophenotyping of the atypical neoplastic cells comprises EMA and cytokeratins (CKs). In the Nigwekar’s report, CD138 was positive in 94% of cases. Therefore, tumor cells positive for CD138 provides an evidence to support the diagnosis of PUC. This often has been utilized as a surrogate marker for PUC along with cytokeratin reactivity, which would help to rule out PUC from signet ring cell adenocarcinoma to the bladder. The primary signet ring cell adenocarcinoma may have occasional presence of intracytoplasmic vacuoles and the noncohesive nature of the tumor cells and the signet ring cells may permeate the wall of the urinary bladder in a manner similar to linitis plastica, but the lack of mucin staining helps to distinguish PUC from signet ring-cell carcinoma. From the pathology point of view, caution should always be taken in evaluation of neoplasms with plasmacytoid morphology, and immunohistochemical study is needed to document the cell of origin.

Plasmacytoid urothelial carcinoma is an invasive urothelial carcinoma subtype and metastatic carcinoma. Frequent intraperitoneal spread is observed that is not typical of conventional urothelial carcinoma. The initial sites of metastatic spread include the prerectal space, ovary and vagina, fallopian tube, bowel serosa, and omentum. Ricardo-Gonzalez et al recently reported 40% of the patients presented with lymph node metastasis and 33% had intraperitoneal metastasis at cystectomy [4]. Another report showed that 33% of the patients with plasmacytoid variant of urothelial carcinoma presented with intraperitoneal disease and 20% had subsequent metastasis involving serosal surfaces [3]. Nabbout et al recently reported a case of PUC that metastasized to the stomach and the peritoneum after being initially misdiagnosed eight years earlier [19]. The possibility of noncontiguous intraperitoneal spread involving serosal surfaces should be recognized to ensure proper intraoperative staging and clinical follow-up for patients with plasmacytoid carcinoma [4].

5. Conclusions

Plasmacytoid urothelial carcinoma is a rare and aggressive subtype of UC with histological characteristics similar to plasma cells, and has distinctive pathological and clinical features of an aggressive high grade tumor with poor prognosis. Based on our cases and the literature review, this tumor can be misdiagnosed because of its rarity, leading to treatment delays. Both urologists and pathologists need to have a high index of suspicion for PUC whenever they encounter unusual clinical and/or pathological findings. It is necessary to perform cystoscopy and biopsy for earlier diagnosis of PUC because of the delayed occurrence of hematuria. Clinical history, histological features, and appropriate immunohistochemical studies are important to collect enough information for PUC diagnosis. Immunohistochemical staining positive for PAN-CK, whereas negative or strongly reduced membranous staining of E-cadherin, the presence of urothelial carcinoma in situ in the contiguous mucosa, and the pattern of invasion into the lamina propria constitute pivotal information for final diagnosis of PUC. Although there is insufficient evidence to make any concrete recommendations, this variant suggests poor prognosis if treated with cystectomy and adjuvant cisplatin-based chemotherapy. More studies are needed to quantify the divergent differentiation within the tumor specimen, which will be important for designing better treatment strategies for this distinct variant of urothelial carcinoma.
References