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Case Report

Plasmacytoid urothelial carcinoma of the urinary bladder: a clinical pathological study and literature review

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Abstract: Purpose: Plasmacytoid carcinoma of the urinary bladder or plasmacytoid urothelial carcinoma (PUC) is a rare and only recently described histological variant of transitional cell carcinoma (TCC). We herein report the clinical and histopathological features for a new case of PUC. By combining with those reported cases, we intend to define the characteristics of PUC and to provide a therapeutic and prognostic guidance for this disease. Materials and Methods: The index case at our institution was a patient with complaint of lower abdominal pain but without any urological symptoms. The patient underwent radical cystectomy, and the representative sections of tumor were submitted for immunohistochemical analysis. The data for this patient were collected from clinical charts, histological review and follow-up studies. We also performed an extensive literature review of PUC including clinical presentation, pathological features, therapy and prognosis. Results: Clinically, patients with PUC are associated with nonspecific abdominal pain but absent of hematuria. Cystoscopy analysis revealed that PUC is manifested by the coarse and indurated mucosal fold. Macroscopic studies demonstrated an ulcerated firm mass which was present in the left lateral wall of the bladder. Histologically, PUC appeared to be dyscohesive, plasmacytoid cells with eccentric nuclei and abundant eosinophilic cytoplasm with characteristics of plasmacytoid morphology. The tumor cells are negative for E-cadherin, but positive for CD138 expression. This particular patient died 3 months after the radical cystectomy and one course of adjuvant chemotherapy. Literature review revealed that most PUC cases showed similar clinical and pathological features along with poor prognosis. Conclusions: PUC is a rare tumor associated with poor prognosis due to its advanced clinical stage upon its diagnosis. The delayed diagnosis is mainly due to the late occurrence of hematuria and absence of papulary mucosal surface at cystoscopy. Diagnosis can be achieved based on its typical histological features, clinical history and immunohistochemical results. Other than radical cystectomy, postoperative adjuvant treatment could be a good approach to prolong the survival time of PUC patients.

Keyword: Urinary bladder, plasmacytoid urothelial carcinoma, cystectomy

In China, bladder cancer ranks the 8th most common malignancy in males. It most commonly exists as an epithelial tumor in which around 90% of cases are transitional cell carcinoma (TCC) with a papillary appearance. As a rare variant of urothelial carcinoma with histological characteristics similar to plasma cells [1, 2], plasmacytoid urothelial carcinoma has been recognized in the current World Health Organization (WHO) classification of urothelial neoplasms.

Up to date, only 61 cases of primary PUC have been reported in the English literatures. We herein report another case of primary PUC and review the current literatures regarding to this tumor by a pooled analysis of all cases reported and the one presented in the current report.

Case presentation

A 58-year-old man was admitted with a complaint of diffuse lower abdominal pain for 3

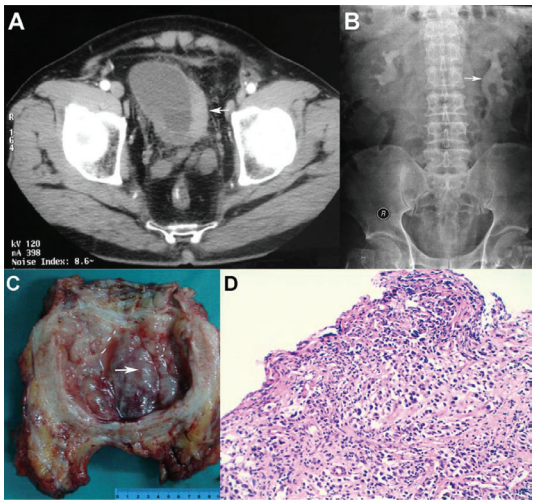

Figure 1. A. Computerized tomography showed a large intravesical mass associated with thickening of the left lateral wall and trigone of the bladder with possible extravesical local extension. B. IVP revealed dilation of the left pelvicaliceal system. C. In the cystectomy specimen, macroscopic morphology showed erosion in ulcerated firm mass in red color which is present in the left lateral wall of the bladder. D. Sections derived from tumor showed cords and sheets of infiltrating malignant epithelial cells with high nuclear to cytoplasmic ratio and enlarged nuclei with irregular contour, vesicular chromatin, and prominent nucleoli. (HE, ×200).

days, but absent of other symptoms such as macroscopic hematuria, urgency, or frequency. His past medical history was unremarkable, while physical examination and hematologic and biochemical laboratory tests failed to show significant alterations, and the patient was also noted absence of microhematuria. Urine cytology revealed a scant number of atypical cells, frequently without tumor diathesis. Ultrasound of the urinary tract demonstrated a solid mass with a dimension of 3.7cm×2.1cm protruding from the left wall and the trigone of the bladder. Computerized tomography showed a large enhancing intravesical mass associated with thickening of the left lateral wall and the trigone of the bladder with possible extravesical extension. (**Figure 1A**) IVP revealed dilation of the left renal collecting system. (**Figure 1B**) Cystoscopy displayed a sessile 2cm elevated area on the left lateral wall of the bladder which had coarse and indurated mucosal fold, and the remaining bladder mucosa has normal appearance. Cystoscopic biopsy suggested a high-grade PUC, and immunohistochemical staining of the tumor sections showed positive for pan cytokeratin (PCK) and epithelial membrane antigen (EMA). The patient was then diagnosed as highly invasive and poorly differentiated urothelial carcinoma with plasmacytoid features.

The patient was first scheduled for radical cystectomy with ileal conduit formation. The cystectomy specimen showed erosive and red firm mass located in the left lateral wall of the bladder (**Figure 1C**). Pathological examination revealed high grade urothelial carcinoma of the bladder with plasmacytoid features penetrating through the entire bladder wall into the serosa. The sections of the tumor showed cords and sheets of infiltrating malignant epithelial cells with high nuclear to cytoplasmic ratio and enlarged nuclei with irregular contour, vesicular chromatin, and prominent nucleoli. The neoplastic cells extended through the lamina propria into the muscularis propria, perivesical fat, with scattered atypical cells arranged in loose clusters on high power (**Figure 1D**). The pathological diagnosis was PUC (Grade 3) with diffuse muscle and vascular invasion. The obturator lymph nodes and left iliac artery lymph nodes were also found to be metastatic. The immunohistochemical profiles of the tumour cells were focal positive for E-cd, PCK, EMA, CAM5.2, CK7, CD138, AE1/AE3, and CK20, but negative for LCA, Vim, and S-100. The patient was next scheduled for one course of MVAC (methotrexate, vinblastine, etoposide and cisplatin) adjuvant chemotherapy after the radical cystectomy.

One month after the cystectomy, the patient developed small bowel obstruction, and thus underwent exploratory laparotomy and intestinal drainage. After which, the general condition for the patient became worse and worse, and the patient died three months after cystectomy due to extensive local recurrence, retroperitoneal metastasis, severe ascites and intestinal occlusion.

Discussion

The plasmacytoid urothelial carcinoma (PUC) is a rare type of UC. The histological feature for the tumor tissue is predominantly manifested by infiltrating tumor cells with characteristics of plasmacytoid morphology. The first PUC case was reported by Sahin et al, which was

Table 1. Clinical and pathological features of plasmacytoid bladder urothelial carcinoma

First author	Age/Sex	Presenting symptoms	TNM Stage	Follow-up status (mo)	**Treatment**
Sahin [3]	63/M		not determined	alive without the disease(24mo)	chemotherapy
	73/M		T2	not determined	palliative
Zukerberg [10]	68/M		T2	alive without the disease(17mo)	radiation therapy+ chemotherapy
J Y. Ro [11]	68/M	hematuria for 8mo	T4	dead of disease(12mo)	radical cystectomy+ chemotherapy
	65/M	hematuria for 2wk	T3	dead of disease(5mo)	radical cystectomy+ chemotherapy
	46/M	urgency,microhematuria for 1mo	T3	dead of disease(20mo)	chemotherapy
	81/M	hematuria for 5mo	T3	dead of disease(36mo)	radical cystectomy+ chemotherapy
	79/M	hematuria for 3mo	T1	alive with disease(47mo)	BCG
	59/M	hematuria for 1mo	T3	dead of disease(10mo)	radical cystectomy
	61/M	hematuria for 2mo	T3	alive with disease(30mo)	radical cystectomy+ chemotherapy
	54/M	hematuria for 2wk	T2	alive with disease(36mo)	radical cystectomy
	66/M	hematuria for 4mo	T2	lost of follow-up	no further treatment
Gaafar A [12]	75/M	hematuria	T3	dead of disease(24mo)	TURBt+ chemotherapy
	70/M	hematuria	T3	alive with metastases (24mo)	TURBt+ chemotherapy
	74/M	hematuria	T3	dead of disease(24mo)	TURBt+ chemotherapy
	73/M	hematuria	T3	alive with metastases (24mo)	TURBt+ chemotherapy
	65/M	hematuria	T3	dead of disease(24mo)	TURBt+ chemotherapy
	58/M	hematuria， hydronephrosis	T3	alive with disease (4mo)	radical cystectomy + chemotherapy
	69/M	hematuria， hydronephrosis	T3	alive with disease (8mo)	radical cystectomy + chemotherapy
Antonio [13]	63/M	gross hematuria	T4	dead of disease(2mo)	TURBt+ chemotherapy
	55/M	hematuria, dysuria	T3	alive with disease (8mo)	radical cystectomy + chemotherapy
	76/M	hematuria	T3	dead of disease(2mo)	TURBt+ chemotherapy
	87/M	hematuria, frequency, dysuria	T4	dead of disease(8mo)	TURBt+ chemotherapy
	62/M	gross hematuria, dysuria	T4	dead of disease(4mo)	TURBt+ chemotherapy
	80/F	gross hematuria, nocturia	T3	dead of disease(11mo)	TURBt+ chemotherapy
	56/M	hematuria, urgency	T3	dead of disease(2mo)	TURBt+ chemotherapy
	65/M	hematuria, frequency	T4	dead of disease(8mo)	radical cystectomy + chemotherapy
	87/M	gross hematuria	T3	dead of disease(10mo)	TURBt+ chemotherapy
	48/M	hematuria, frequency	T3	alive with disease (16mo)	radical cystectomy + chemotherapy
	62/F	gross hematuria	T3	dead of disease(9mo)	TURBt+ chemotherapy
Priya [14]	65/ M	hematuria	T1	dead of disease(43mo)	radical cysto-prostatectomy+ chemotherapy
	72/ F	hematuria	T4	dead of disease(1.5mo)	radical cystectomy
	85/ F	hematuria	T3	dead of disease(36mo)	radical cystectomy
	54/ M	hematuria	T2	dead of disease(10mo)	TURBt+ chemotherapy
	49/ M	N/A	T3	alive with disease at 9mo, LFU	TURBt+ chemotherapy
	60/ M	hematuria	T3	alive with disease(9mo)	radical cysto-prostatectomy

	79/ M	hematuria	T1	alive with disease(4mo)	biopsy only
	62/ M	N/A	T4	dead of disease(6mo)	radical cysto-prostatectomy
	64/ M	hematuria	T1	alive with disease(8mo)	TURBt+ chemotherapy
	69 /M	hematuria	T2	alive with disease(7mo)	TURBt+ chemotherapy
	56 /M	hematuria	T4	dead of disease(22mo)	TURBt+ chemotherapy
	77/ M	hematuria	T3	dead of disease(5mo)	TURBt+ chemotherapy
	74 /M	microscopic hematuria	T3	dead of disease(1mo)	radical cysto-prostatectomy
	82/ M	hematuria	N/A	N/A	TURBt+ chemotherapy
	89/ M	hematuria	T4	dead of disease(2w)	radical cysto-prostatectomy
	84 /M	hematuria	N/A	dead of disease(13d)	biopsy only
	86/ M	hematuria	T4	dead of disease(4w)	biopsy only
Kohno [9]	76/M	painful micturition	T4	alive without the disease(36mo)	radical cystectomy + chemotherapy
Mitsogiannis [7]	60/M	low back pain, gross hematuria	T3	dead of disease(7d)	biopsy only
Saad [15]	57/M	lower abdominal pain,gross hematuria	T3	dead of disease(6mo)	palliative cystectomy + chemotherapy
Katsuaki [16]	50/M	pollakiuria,urinary incontinence	T4	dead of disease(24mo)	radical cystectomy
Mai [5]	69/F	lower abdominal pain, urinary urgency	N/A	alive with disease (12mo)	anterior pelvic exenteration
Fritsche [17]	54/F	voiding irritation	T4	dead of disease(14mo)	radical cystectomy
	56/M	pollakiuria	T4	dead of disease(29mo)	radical cystectomy + chemotherapy
	63/M	nocturia pencil-like stool	T4	N/A	radical cystectomy + chemotherapy
	79/ N/A	lower urinary tract symptoms,microhematuria	N/A	N/A	transurethral resection of the prostate+BCg
	79/N/A	macrohematuria	T3	N/A	transurethral resection+ chemotherapy
Sakuma [18]	66/M	haematuria	T3	dead of disease(24mo)	radical cystoprostatectomy+ chemotherapy
	79/M	urinary urgency	T3	alive without the disease(16mo)	radical cystoprostatectomy+ chemotherapy
Shimada [8]	46/M	haematuria	N/A	dead of disease(8mo)	transurethral resection+ radiotherapy+ chemotherapy
Soylu [19]	67/M	hematuria	T2	dead of disease(18mo)	salvage cystectomy+ bilateral percutaneous nephrostomy
Present case	58/M	lower abdominal pain	T4	dead of disease(3mo)	radical cystectomy + chemotherapy

Table 2. Summary of immunohistochemical data

Case	E-cd	CD138	PCK	EMA	CAM5.2	AE1/AE3	CK7	CK20	CA199	β-HCG	S-100	LCA	Vim
Gaafar(1)				+	+	+	+	-	-		-		
Gaafar(2)				+	+	+	+	+/-	+/-		-		
Gaafar(3)				+	+	+/-	+	-	-		-		
Gaafar(4)				+	+	+	+	+/-	+		-		
Gaafar(5)				+	-	+	+	-	+/-		-		

Gaafar(6)				+	-	+	+	-	+			-			
Gaafar(7)				+	-	+	+	-	+			-			
Gaafar(8)				+	-	+	+	-	-			-			
Carlo(9)		+		+	-		+	+							
Shimada(10)		+							+	+					
Sakuma(11)	-				+	+		-							
Fritsche(12)	-						+	+							
Fritsche(13)	-						+	+							
Fritsche(14)	-						+	+							
Fritsche(15)	-						+	+							-
Fritsche(16)	-						+	+							
Mai(17)	-	+		+		+	+	+							
Mai(18)	-						+	+							
Mai(19)	-						+	+							
Mai(20)	-						+	+							
Mai(21)	-						+	+							
Mai(22)	+						+	+							
Mai(23)	+						+	+							
Sato(24)	-		+			+	+	-	+			-			-
Kohno(25)			+				+	+							
Antonio(26)	-		+			+	+	+				-	-	-	
Antonio(27)	+		+			+	+	+				-	-	-	
Antonio(28)	-		+			+	+	+				-	-	-	
Antonio(29)	-		+			+	+	+				-	-	-	
Antonio(30)	-		+			+	+	+				-	-	-	
Antonio(31)	+		+			+	+	+				-	-	-	
Antonio(32)	-		+			+	+	+				-	-	-	
Antonio(33)	-		+			+	+	+				-	-	-	
Antonio(34)	-		+			+	+	+				-	-	-	
Antonio(35)	+		+			+	+	+				-	-	-	
Antonio(36)	-		+			+	+	+				-	-	-	
Iraklis(37)	+		+												
Sahin(38)	-						+	+							
Our case	+	+	+	+	+	+	+	+				-	-	-	

mistakenly considered as multiple myeloma at first, because of multiple lytic tumors involving the bone of the ribs and skull [3]. The first report for the noninvasive PUC was provided by Coyne and Sim [4]. To the best of our knowledge, there are only 61 cases of PUC reported in the English literatures with detailed pathological information. The clinical features for all reported cases including the one in the current report are summarized in **Table 1**. According to these reports, the mean age of initial diagnosis is 69 years (range 46–89), and the constituent ratio shows a male predominance (M: F =3:1).

As indicated in **Table 1**, the most common presenting symptom for diagnosis is hematuria, generally accompanied by urgency, frequent micturition and/or lower abdominal pain. However, early diagnosis cannot be made due to the absence of hematuria until the late stage of the disease. For example, for the case we presented here, the initial complain from the patient was lower abdominal pain absent of hematuria. As a result, the major diagnostic pitfall is the deficiency of specific clinical features to differentiate 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 5cm 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 (age > 40) 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 [5]. Similarly, tumor sections from our case were also characterized by large, dyscohesive cells with enlarged nuclei and irregular contour, vesicular chromatin, and prominent nucleoli. Unlike Zhang and colleagues reported that cytological evidence can be obtained from PUC patients in voided urine samples procured before and after cystoscopy [6], we only detected a few atypical cells in the urinary samples. Therefore, additional studies would be necessary to evaluate the significance of urinary cytology in the diagnosis of PUC.

Immunohistochemical staining plays an important role in the diagnosis of PUC. The staining was performed on paraffin-embedded tissue sections by employing the avidin-biotin approach. The panel of antibodies for immunophenotyping of the atypical neoplastic cells comprises EMA and cytokeratins (CKs) including AE1/AE3, CAM5.2, CK7, CK8, CK10, CK18, CK19, and CK20. It has been noted that loss of E-cadherin expression might be associated with a plasmacytoid differentiation pattern in UC, while studies in our case suggest that loss of E-cadherin expression is probably associated with increased cellular invasiveness or correlated with muscularis mucosal involvement and tumor recurrence. Mitsogiannis et al. [7] recently reported that plasmacytoid tumor cells were immunoreactive for CD138 in the bladder. Furthermore, Shimada et al. [8] reported the first case of urothelial carcinoma with a plasmacytoid variant expressing both CA19-9 and β-HCG. Therefore, tumor cells positive for CD138 (a marker of plasma cell origin) provides the evidence to support the diagnosis of PUC. In line with this assumption, immunohistochemical staining of tumor sections from our case revealed positive results for CD138. We also detected positive staining for E-cd, PCK, EMA, CAM5.2, CK7 and AE1/AE3, as well as focal positive staining for CK20, while LCA, Vim and S-100 were negative. These results actually provided pivotal information for final diagnosis of PUC. Common immunohistochemical features for those reported cases in literature and our case are summarized in **Table 2**.

Although it might be a rare condition, there are still some diseases should be considered in the differential diagnosis with PUC. One of these diseases is chronic bladder inflammation with abundant plasma cells, but the more prominent cytological anaplasia feature distinguishes PUC from chronic bladder inflammation. Another disease is primary signet ring cell adenocarcinoma because of its occasional presence of intracytoplasmic vacuoles and the noncohesive nature of the tumor cells. The signet ring cells may permeate the wall of the urinary bladder in a manner similar to linitis plastica, but lack of mucin staining helps to distinguish PUC from signet ring-cell carcinoma. Likewise, carcinoma with rhabdoid phenotype is considered in the differential diagnosis, its

diagnosis is mostly based on cytoplasmic features and prominent nucleolus, and PUC in rhabdoid cells is mainly determined by positive immunostaining of vimentin. 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. From the clinical point of view, PUC have 3 salient features that may provide help to reach its diagnosis, high histological grade, high stage, and rapid progression to death.

Clinical management of PUC patients remains debate. Because it is a rare disease, there are no clear guidelines for the treatment of PUC. Primary treatments performed in the past include deep transurethral resection of the tumor (TURBt) and partial or radical cystectomy. While bladder sparing treatment is possible for primary PUC for stage T2 to locally control the tumor, the high metastatic potential of this variant of UC clearly needs more aggressive treatment. To date, the radical cystectomy is considered as the first choice for invasive or non-invasive PUC, we thus selected radical cystectomy to be the initial treatment for our case.

Both neoadjuvant and adjuvant treatments should be considered to reduce the risk of systemical progression of PUC. Patients with lymphovascular or nodal involvement and invasive tumors showed a moderate benefit from adjuvant combination chemotherapy, which includes 3 to 5 courses of MVAC chemotherapy. PUC is sensitive to both cisplatin-based chemotherapy and radiotherapy, which can be performed as adjuvant treatments after radical cystectomy. Kohno et al. recently reported a case of PUC, which showed a complete response to neoadjuvant chemotherapy with 2 courses of MVAC chemotherapy [9]. Although our patient survived for just 3 months after one course of chemotherapy, but the postoperative complications along with poor general condition should be considered as the main cause of death. Therefore, published data along with the results from our case support that postoperative adjuvant treatment after operation should be highly advised for patients with PUC.

Current published data indicate that the prognosis for PUC patients is poor. The prognosis for PUC is relatively favorable for the pure and predominant forms, which may be related to inflammatory infiltration that initiates a strong immune response against the atypical cells. Disease specific survival rate resulted 93% for both pure and predominant PUC (mean follow-up of 48.1 and 32 months) while it was 0% for focal PUC (mean follow-up 30.3 months). In some large series reports, the 5-year disease-free survival rate for stage T3+ tumors ranged from 8% to 40% [20-22]. Together, these cases including our case suggest that PUC predicts poor prognosis.

Conclusions

PUC is a rare variant of UC with distinctive pathological and clinical features. It deserves highly attention since it demands aggressive clinical multi-modality treatment. It is necessary to perform cystoscopy and biopsy for earlier diagnosis of PUC because of the delayed occurrence of hematuria. Histological features, clinical history and appropriate immunohistochemical studies are important to collect enough information for PUC diagnosis. Although it is still lack of guidelines for treatment of PUC, radical cystectomy and postoperative adjuvant therapy are highly advised. To date, limited available data suggest that PUC is an aggressive high grade tumor with poor prognosis, but larger cohorts are needed to prove this concept. Future studies with focus to dissect the mechanisms underlying different survival rates between patients with different subtypes of PUC would be important for the development of novel and effective strategies for treatment of this devastating disease.

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Abbreviations and acronyms

CK, cytokeratin; PUC, plasmacytoid urothelial carcinoma; UC, urothelial carcinoma

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