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Case Report

Poor Outcome due to the Plasmacytoid Variant of Urothelial Carcinoma

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Keywords
Plasmacytoid variant of urothelial carcinoma · Urothelial carcinoma · Variant histology · Bladder cancer

Abstract
A 72-year-old man visited our hospital due to pollakiuria and lower abdominal pain. Urinary cytology was positive, and cystoscopy revealed diffuse edematous nonpapillary tumor. We performed transurethral biopsy, and clinical stage T3 plasmacytoid variant of urothelial carcinoma (PUC) was diagnosed. Although we planned for radical cystectomy, peritoneal dissemination and lung and pelvic lymph node metastases appeared 3 weeks after the initial visit. We also planned for chemotherapy; however, the metastases rapidly progressed, and he died 7 weeks after the biopsy. PUC is rare and shows an aggressive clinical course and poor prognosis.

Introduction

The plasmacytoid variant (PUC) is a rare subtype of urothelial carcinoma (UC) morphologically similar to plasma cells. Since Sahin et al. [1] identified PUC in 1991, only approximately 100 cases of PUC have been reported, and a treatment strategy of PUC has not yet been

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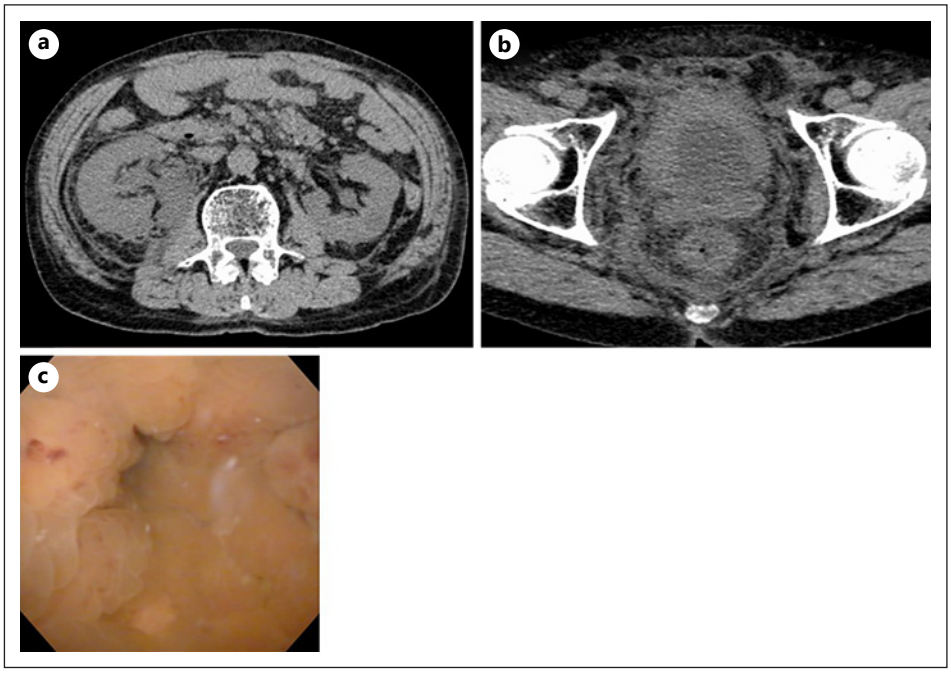

Fig. 1. Results of abdominal CT (**a**, **b**) and cystoscopy (**c**) at the initial diagnosis. CT shows bilateral hydronephrosis (a) and diffuse thickening of the bladder wall and suspicious to inflammation at retroperitoneal space (**b**). **c** Cystoscopy reveals the whole bladder mucosa is edematous change so that an atypical bladder tumor unlike conventional UC is suspected.

determined [1, 2]. However, PUC is an aggressive variant of UC associated with a poor prognosis [2]. Advanced stage upon at diagnosis is common, and the peritoneum is the most common site of early metastasis [3]. Although the treatment of metastatic UC has recently revolutionized chemotherapy and immune checkpoint inhibitors (ICIs) [4–6], sometimes patients could not administer systemic chemotherapy because of their aggressive clinical courses. Herein, a case of progressive PUC is presented.

Case Presentation

A 72-year-old man visited our hospital due to pollakiuria and lower abdominal pain. Computed tomography (CT) showed bilateral hydronephrosis and diffuse thickening of the bladder wall (Fig. 1a, b). Urine cytology was positive (class V), and cystoscopy revealed diffuse edematous nonpapillary tumor (Fig. 1c). Laboratory data showed acute renal failure (creatinine 9.38 mg/dL) because bladder tumor involved bilateral ureteral orifices. Transurethral resection of bladder tumor (TURBT) for diagnosis and left percutaneous nephrostomy were performed (Fig. 2a, c). Histological findings revealed discohesive tumor cells invading the muscularis propria. At higher magnification, the tumor cells showed plasmacytoid morphology: eccentrically located nuclei and relatively abundant amphophilic to eosinophilic cytoplasm. Therefore, the tumor was diagnosed with invasive PUC, high-grade, T2 (Fig. 2b, d, e). After renal failure improved, we planned for radical cystectomy. However, peritoneal dissemination and lung and pelvic lymph node metastases appeared on CT 3 weeks after the initial visit (Fig. 3a, b). Moreover, the metastases rapidly progressed, and he had ileus due to carcinomatous peritonitis. Thus, he could not receive systemic chemotherapy and died 7 weeks after TURBT.

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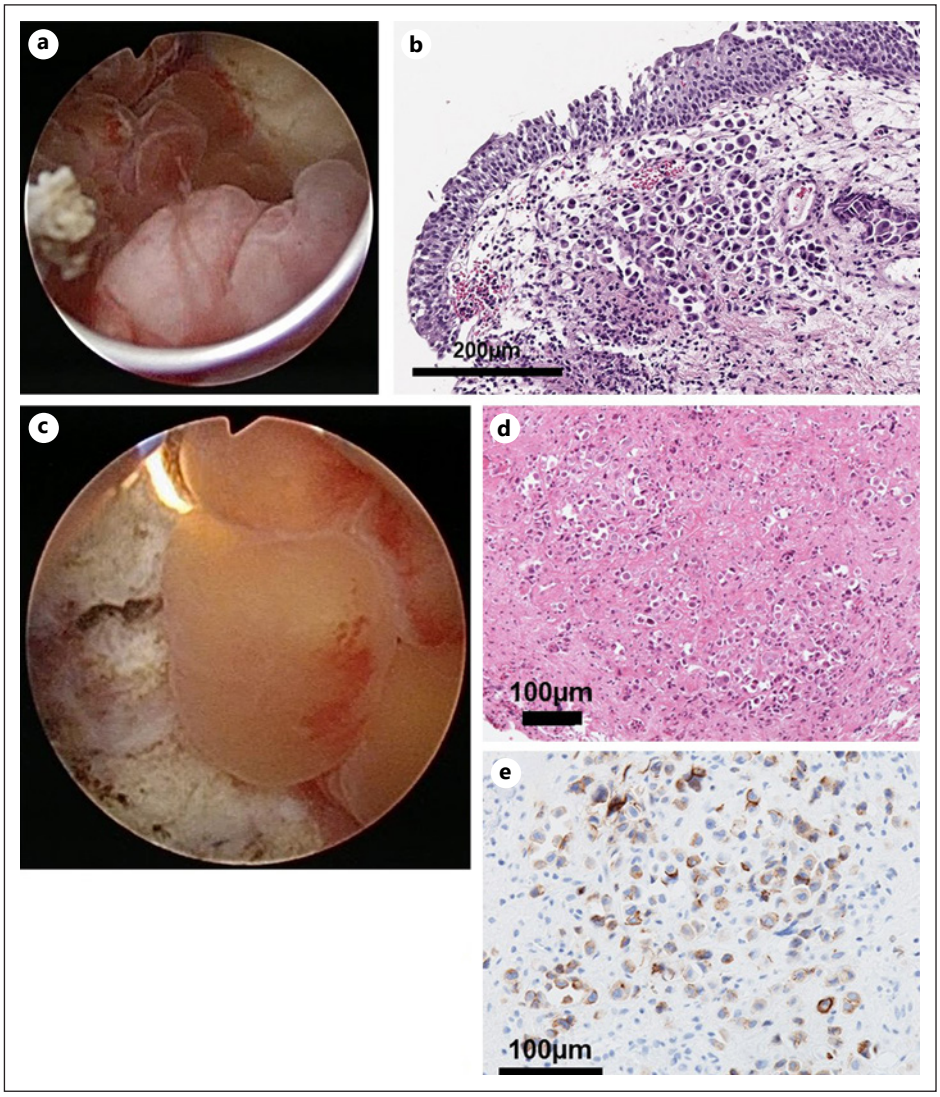

Fig. 2. Macroscopic and histopathological findings of the TURBT specimen. Since a nonpapillary tumor with edematous change appeared, we thought it is an atypical finding unlike UC. **a** Nonpapillary tumor in the bladder neck. **b** The tumor cells shows discohesive growth with typical plasmacytoid morphology. There are marked lymphovascular invasions. **c** Diffuse edematous nonpapillary tumor at the posterior wall. **d** Hematoxylin and eosin staining. It shows the malignant cells with plasmacytoid morphology and muscle-invasive, high-grade UC. There are also high expressions of lymphovascular invasion.

Discussion

PUC is a rare variant that accounts for 2.7% of muscle invasive UC cases [3]. PUC is also an aggressive variant histology because it is diagnosed at an advanced pathological stage (pT3: 64% and pT4: 23%; with metastases: 60%), and symptoms and signs might be related to metastatic disease [2, 3]. The reason why advanced stage at diagnosis remains common is that hematuria is typically a late manifestation, and some patients might not encounter any urinary symptoms in spite of conventional UC [3]. In our case, his chief complaints were pollakiuria and lower abdominal pain absent of hematuria. According to his symptoms, peritoneum metastasis might have been spread already although no metastasis appeared on CT

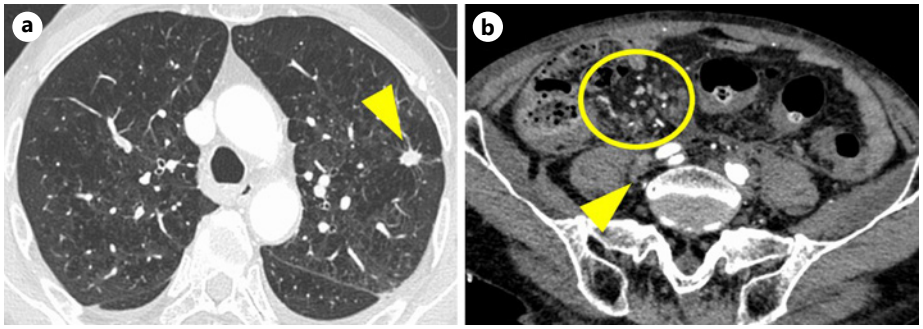

Fig. 3. CT findings 3 weeks after the initial diagnosis. A new metastases has appeared: (**a**) Lung, (**b**) pelvic lymph node (yellow allow), and peritoneal dissemination (yellow circle).

at the initial visit, and decreased bladder capacity due to diffuse thickening of the bladder wall might lead to pollakiuria. PUC has a specific feature in terms of spread of metastasis because peritoneum is the most common site of early metastasis [3]. The reason why PUC tends to spread to the peritoneum might be the existence of lymphatic obstruction due to high expression of lymphatic invasion and the loss of E-cadherin expression [7].

Despite PUC showing a poor prognosis, the optimal treatment remains controversial due to the infrequency of this variant disease. For locally advanced PUC, radical cystectomy is considered the primary treatment [3]. Ohtaka et al. [2] reported the case of a patient with PUC that was successfully controlled with adjuvant chemotherapy following radical cystectomy, and the treatment with radical cystectomy and adjuvant chemotherapy was relatively effective to improve the prognosis of PUC. Veskimäe's systematic review indicated neoadjuvant chemotherapy for PUC appeared to be beneficial, so that neoadjuvant cisplatin-based chemotherapy may be offered [8]. For metastatic PUC, systemic chemotherapy is recommended with overall response rate exceeding 50% [3]. Although the efficacy of ICIs for metastatic UC has been reported [4–6], the efficacy of ICIs for PUC remains unclear. In our case, we planned systemic therapy, but his poor overall performance status was getting worse due to carcinomatous peritonitis.

To detect PUC at an earlier stage is difficult. According to the previous reports, for macroscopic findings of PUC, cystoscopy revealed solitary, or multiple, solid tumors unlike conventional pure UC (Table 1). However, mucosal induration and a thickened bladder wall without masses unlike UC in situ lesions are also shown, which can lead to diagnostic pitfalls [3]. According to the report, cystoscopy revealed that bladder capacity was extremely decreased, and the whole bladder mucosa was irregular and thick at advanced PUC [9]. Otherwise, no masses were seen even after cystoscopic examination, and PUC was diagnosed after mucosal resection was performed [3]. Not detecting specific findings on cystoscopy even bladder cancer suspected by urine cytology, we consider narrow-band imaging or photodynamic diagnosis-TURBT to detect lesion. Our patient was showing an atypical cystoscopic finding that edematous change had affected the whole bladder mucosa. Although urine cytology was positive and suspected to high-grade UC, we should consider the existence of variant histologies including PUC based on the atypical cystoscopic finding. To the best of our knowledge, this may be the first report of macroscopic characteristics for PUC.

For microscopic findings, PUC is characterized by sheets of poorly differentiated discohesive round or oval cells with eccentric nuclei and abundant amphophilic to eosinophilic cytoplasm resembling plasma cells [3]. Our case had exactly this histology. Immunohistochemical staining is crucial for definitive diagnosis despite PUC cells being typically positive for CD138 that are plasma cell markers [3]. Recent studies have indicated that loss of E-cadherin expression is associated with malignant potential of PUC [10]. Our case also showed a loss of E-cadherin on

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Table 1. Tumor form of PUC patients

No.	Authors [Ref.]	Year	Age, years	Gender	Gender cystoscopic findings
1	Zhang et al. [11]	2002	79	F	Diffuse tumor solid tumor
2	Hayashi et al. [12]	2011	76	M	Solid tumor
3	Hayashi et al. [12]	2011	76	M	Solid tumor
4	Rahman et al. [13]	2011	54	M	Edematous and ulcerated mucosa
5	Philippou et al. [14]	2011	70	F	Diffuse deformity
6	Demellawy et al. [15]	2012	50	M	Extensive tumor
7	Wang et al. [16]	2012	58	M	Sessile lesion
8	Nomura et al. [17]	2013	75	F	Nonpapillary tumor
9	Ohtaka et al. [2]	2016	41	M	Nonpapillary tumor
10	Shao et al. [18]	2017	74	M	Diffuse edematous nonpapillary tumor
11	Kimura et al. [19]	2018	65	M	Nodular tumor
12	Carsel et al. [20]	2020	71	M	Sessile lesions
13	Telfah et al. [3]	2020	65	F	No masses
14	Kohada et al. [9]	2020	75	F	Irregular and thick bladder mucosa
15	Fukuta	2022	72	M	Diffuse edematous nonpapillary tumor

According to the previous reports, PUC had atypical macroscopic findings unlike conventional UC.

tumor cells (Fig. 2e). Moreover, immunohistochemical staining such as programmed cell death ligand 1 might be required for identification of biomarkers predictive of response to ICIs in the near future. Further studies are required to assess the role of programmed cell death ligand 1 expression for PUC. At the molecular level, *CDH-1* alterations seem to be characteristic for PUC. The *CDH-1* gene encodes the E-cadherin protein, which provides intraperitoneal spread. Kohada et al. [6] indicated HER2 might be a good target for PUC treatment because its positivity is higher than conventional UC. The limitation of this case report include macroscopic findings of PUC have been accumulated by several case reports due to the rareness of PUC. Further PUC cases are required, and exploring macro- and microscopic findings and the molecular landscape of PUC is essential to improve the treatment outcomes of this aggressive variant.

Conclusion

In conclusion, we reported a case of PUC that showed an aggressive clinical course and poor prognosis. The intensive treatment should be required to improve oncological outcomes for PUC.

Statement of Ethics

Ethical approval is not required for this study in accordance with local or national guidelines. Written informed consent for publication of this case report and any accompanying images was obtained from the next of kin of the patient.

Conflict of Interest Statement

The authors declare no conflict of interest.

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Author Contributions

Kyotaro Fukuta researched the literature and drafted the manuscript. Kyotaro Fukuta and Keito Shiozaki performed the surgery. Hirofumi Izaki, Saki Kobayashi, Ryoichi Nakanishi, Kazuya Kanda, Tohru Inai, Tomoya Fukawa, Kunihisa Yamaguchi, Yasuyo Yamamoto, Masayuki Takahashi, and Hiro-omi Kanayama critically revised the manuscript. Kyotaro Fukuta, Keito Shiozaki, Hirofumi Izaki, and Eiji Kudo performed the examinations before and after surgery, provided photographs, and drafted the first version of the manuscript. All the authors approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

References

1 Sahin AA, Myhre M, Ro JY, Sneige N, Dekmezian RH, Ayala AG. Plasmacytoid transitional cell carcinoma. Report of a case with initial presentation mimicking multiple myeloma. Acta Cytol. 1991;35:277–80.
2 Ohtaka M, Kawahara T, Kumano Y, Maeda Y, Kondo T, Mochizuki T, et al. Invasive urothelial carcinoma, plasmacytoid variant, successfully treated by radical cystectomy with adjuvant chemotherapy: a case report. J Med Case Rep. 2016;10:48.
3 Telfah M, Parikh RA, Zhang D, Kasi A. Metastatic plasmacytoid bladder cancer harboring a CDH-1 mutation and producing high levels of CA 19-9. A case report and literature review. Am J Case Rep. 2020;21:e923130.
4 Mollica V, Rizzo A, Montironi R, Cheng L, Giunchi F, Schiavina R, et al. Current strategies and novel therapeutic approaches for metastatic urothelial carcinoma. Cancers. 2020;12:1449.
5 Rizzo A, Mollica V, Massari F. Expression of programmed cell death ligand 1 as a predictive biomarker in metastatic urothelial carcinoma patients treated with first-line immune checkpoint inhibitors versus chemotherapy: a systematic review and meta-analysis. Eur Urol Focus. 2021;8(1):152–9.
6 Rizzo A, Mollica V, Santoni M, Ricci AD, Gadaleta-Caldarola G, Montironi R, et al. Impact of clinicopathological features on immune-based combinations for advanced urothelial carcinoma: a meta-analysis. Future Oncol. 2022;18(6):739–48.
7 Carranza M, Chahin M, Siddiqi A, House J. Malignant eosinophilic ascites due to metastatic urothelial carcinoma with peritoneal carcinomatosis. BMJ Case Rep. 2020;13(12):e238530.
8 Veskimäe E, Espinos EL, Bruins HM, Yuan Y, Sylvester R, Kamat AM, et al. What is the prognostic and clinical importance of urothelial and nonurothelial histological variants of bladder cancer in predicting oncological outcomes in patients with muscle-invasive and metastatic bladder cancer? A European association of urology muscle invasive and metastatic bladder cancer guidelines panel systematic review. Eur Urol Oncol. 2019;2:625–42.
9 Kohada Y, Kaiho Y, Ito J, Mikami J, Anan G, Asano K, et al. Progressive plasmacytoid variant bladder cancer with retroperitoneal dissemination: an autopsy case report. IJU Case Rep. 2020;3:166–9.
10 Frische HM, Burger M, Denzinger S, Legal W, Goebell PJ, Hartmann A. Plasmacytoid urothelial carcinoma of the bladder: histological and clinical features of 5 cases. J Urol. 2008;180:1923–7.
11 Zhang XM, Elhosseiny A, Melamed MR. Plasmacytoid urothelial carcinoma of the bladder. A case report and the first description of urinary cytology. Acta Cytol. 2002;46(2):412–6.

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DOI: 10.1159/000524038

12 Hayashi T, Tanigawa G, Fujita K, Imamura R, Nakazawa S, Yamamoto Y, et al. Two cases of plasmacytoid variant of urothelial carcinoma of urinary bladder: systemic chemotherapy might be of benefit. Int J Clin Oncol. 2011; 16:759–62.
13 Rahman K, Menon S, Patil A, Bakshi G, Desai S. A rare case of plasmacytoid urothelial carcinoma of bladder: diagnostic dilemmas and clinical implications. Indian J Urol. 2011;27:144–6.
14 Philippou P, Kariotis I, Volanis D, Ploumides A, Delakas D. Plasmacytoid urothelial carcinoma of the bladder: a rare malignancy. Urol Int. 2011;86(3):370–2.
15 Demellawy DE, Ahmed AD, Bora B, Bonin M. Plasmacytoid variant of urothelial carcinoma: a report of a rare case. Pathol Res Pract. 2012;208(9):561–4.
16 Wang Z, Lu T, Du L, Hu Z, Zhuang Q, Li Y, et al. Plasmacytoid urothelial carcinoma of the urinary bladder: a Clinical Pathological Study and literature review. Int J Clin Exp Pathol. 2012;5(6):601–8.
17 Nomura S, Suzuki Y, Saito Y, Tanabe K, Ogushi Y, Matsuzawa I, et al. Plasmacytoid variant of urothelial carcinoma of urinary bladder: a case report. Jpn J Urol. 2013;104(1):26–9.
18 Shao YH, Kaoa CC, Tanga SH, Chaa TL, Tsaoa CW, Meng E, et al. Unusual presentation of direct intraperitoneal metastases complicated with massive ascites from plasmacytoid variant of bladder cancer and adenocarcinoma of colon. Medicine. 2017;96(7):e5816.
19 Kimura H, Uemura Y, Megumi Y, Fukuzawa S. A case of PT1 plasmacytoid variant bladder cancer treated by bladder conserving therapy. Hinyokika Kiyo. 2018;64:369–72.
20 Carsel A, Levy C, Raghavan AM, Ortiz JA, Sindhwani P, Petros FG. Plasmacytoid variant of urothelial carcinoma of the bladder manifesting as bilateral ureteral and small bowel obstruction. Urol Case Rep. 2020;33:101415.