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Case Report

Micropapillary Variant of Urothelial Carcinoma in a Hemodialysis Patient

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Keywords
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Abstract
The micropapillary variant of urothelial carcinoma (MPUC) is an aggressive form of urothelial carcinoma with high metastatic potential and a poor prognosis. Although various therapies have been reported, there is still no established treatment strategy for MPUC due to its rarity. The incidence of urinary tract malignancies is higher in patients undergoing hemodialysis (HD) than in healthy individuals. Here, we report the case of an 82-year-old man on HD with end-stage kidney disease who visited our hospital for macrohematuria. Cystoscopy followed by computed tomography and urine cytology revealed a sessile papillary tumor around the left bladder wall. We performed transurethral resection of the bladder tumor. Based on histopathological and imaging findings indicative of clinical-stage T3N0M0 MPUC, we performed radical cystectomy. Histopathology revealed a pathological stage T4aN0M0 MPUC. Two months after the cystectomy, the patient complained of constipation and painful defecation due to local recurrence and rectal invasion. While colostomy was performed to improve defecation 3 months after cystectomy, he did not receive any chemotherapy due to his progressively worsening general condition. Six months after cystectomy, he died following rapid metastases. Our findings, in this case, confirm that bladder cancer in HD patients tends to be pathologically more advanced. Therefore, regular screening is recommended for its early detection in HD patients.

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Introduction

The micropapillary variant of urothelial carcinoma (MPUC) was first described by Amin et al [1]. A rare and aggressive variant of urothelial carcinoma (UC), MPUC, has high metastatic potential. Although various therapies have been reported, they are based mainly on small, single-center experiences due to the disease's rarity. Moreover, despite the treatment of metastatic UC have recently revolutionized chemotherapy and immune checkpoint inhibitors (ICIs) [2–4], sometimes, patients could not administer systemic chemotherapy because of their aggressive clinical courses. Hence, an optimal treatment strategy for MPUC remains to be established.

The incidence of urological malignancies is higher in hemodialysis (HD) patients than in healthy individuals [5]. In HD patients, the detection of bladder cancer is often delayed because of oliguria or anuria [5]. Here, we report a case of MPUC in an HD patient.

Case Presentation

An 82-year-old man who had been on maintenance HD for 10 months due to chronic renal failure with nephrosclerosis visited our hospital for macroscopic hematuria. Cystoscopy revealed a sessile papillary tumor and edematous changes around the left wall of the bladder (Fig. 1a). Computed tomography (CT) revealed left hydronephrosis and a bladder tumor involving the left ureteral orifice (Fig. 1b). Urine cytology was classified as class 3b, and UC was suspected. Transurethral resection of the bladder tumor was performed. Histopathological evaluation and CT findings revealed invasive MPUC (clinical-stage T3N0M0). Two months after the initial diagnosis, laparoscopic radical cystectomy and bilateral ureteral ligation were performed. However, due to adhesions involving the pelvic floor and significant extravesical invasion, these procedures could not be completed laparoscopically. Histopathology revealed pathological stage T4aN0M0 MPUC (UC, 5%; micropapillary variant, 95%)

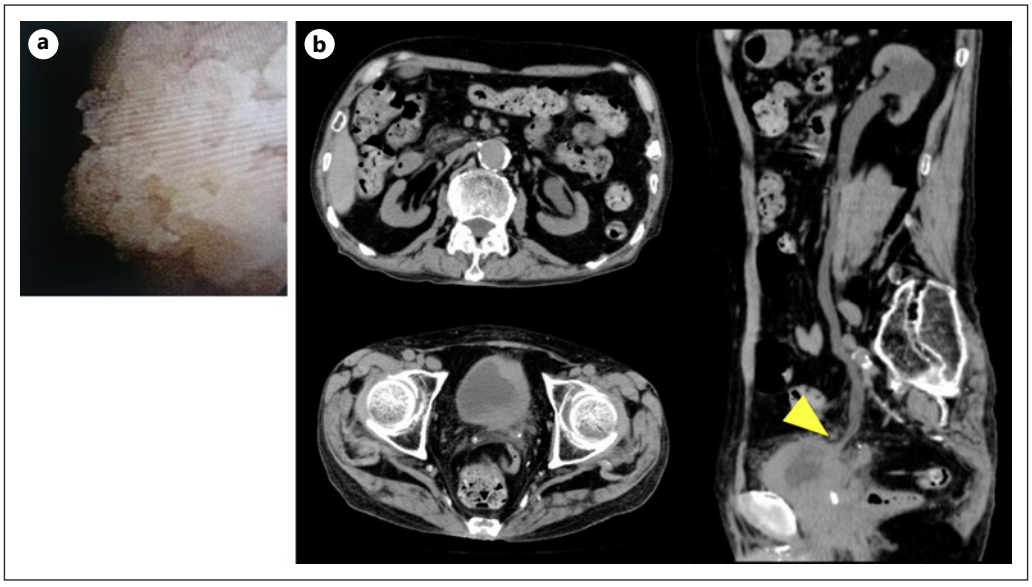

Fig. 1. Cystoscopy and abdominal CT findings at the initial diagnosis. **a** Cystoscopy shows a sessile papillary tumor and edematous changes around the left wall. **b** CT shows left hydronephrosis due to the bladder tumor invading the left ureteral orifice (yellow arrow).

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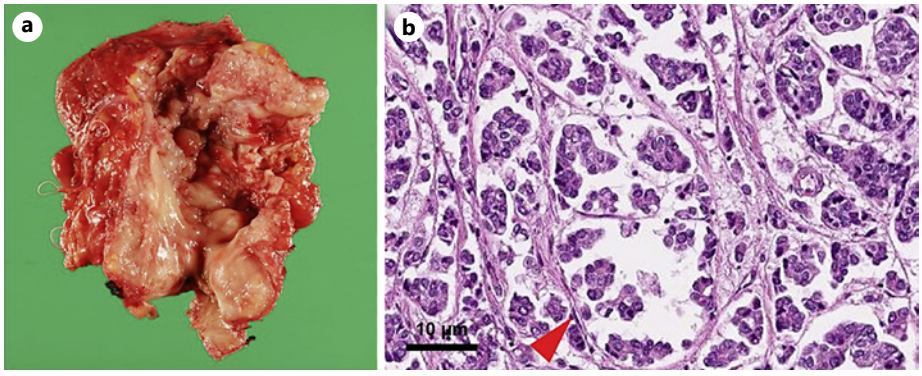

Fig. 2. Macroscopic and microscopic findings at cystectomy. **a** Macroscopically, tumors can be seen all around the bladder with significant extravesical invasion. **b** Hematoxylin and eosin staining show the malignant cells arranged in small papillary clusters in clear spaces with a high incidence of lymphovascular and vascular invasion (red arrow). The proportions were 95% micropapillary variant and 5% UC

(Fig. 2) and incidental prostate adenocarcinoma (Gleason score 4 + 4, pathological stage T2a). Although there were no perioperative complications, the patient complained of constipation and pain on defecation due to local recurrence and invasion of the rectum 2 months after cystectomy (Fig. 3a). As his general condition progressively worsened with the rapid progression of the disease, he could not undergo chemotherapy. Colostomy was performed to improve defecation 3 months after cystectomy. However, the patient died 6 months after cystectomy due to rapid metastases (Fig. 3b).

Discussion

MPUC is a rare variant that accounts for 0.7–2.2% of bladder cancers [6]. The histopathological features of MPUC are similar to those of papillary serous carcinoma of the ovary, with delicate filiform processes and infiltrating clusters of micropapillary aggregates without central vascular cores [7]. Although the optimal treatment for MPUC remains controversial, immediate radical cystectomy is considered the best option to improve prognosis, regardless of muscle invasion [7]. In addition, despite the efficacy of ICIs for metastatic UC has been reported [2–4], the efficacy of ICIs for MPUC remains unclear. However, the 5-year survival rate of patients with MPUC is ≤25%, even after cystectomy, chemotherapy, and radiotherapy [6]. Previous reports indicate that the proportion of MPUC determined histopathologically is a prognostic indicator, with >50% micropapillary variant associated with increased mortality [8, 9]. In the present case, the proportion of micropapillary variant was 95%, which might account for the aggressive clinical course. Further cases of MPUC need to be accumulated to establish more effective treatments.

The risk of all malignant tumors is 1.4–4.5 times higher in HD patients than in healthy subjects [10]. Gastrointestinal malignancies account for 44% of all malignant tumors in HD patients, followed by urological malignancies (15.4%) [5], and renal-cell carcinoma is a particular complication in these patients. Bladder cancer is the second most common urological malignancy worldwide. Why the incidence of urological malignancies is higher in HD patients remains unclear, although chronic urinary infections, weakened immune system, malnutrition, and DNA damage have been reported as possible etiologies [11]. Bladder cancer in HD patients is often diagnosed at an advanced stage [5]. Yonemura et al. [10] reported muscle invasion in 39 of 80 bladder cancer cases in HD patients. The histological type was

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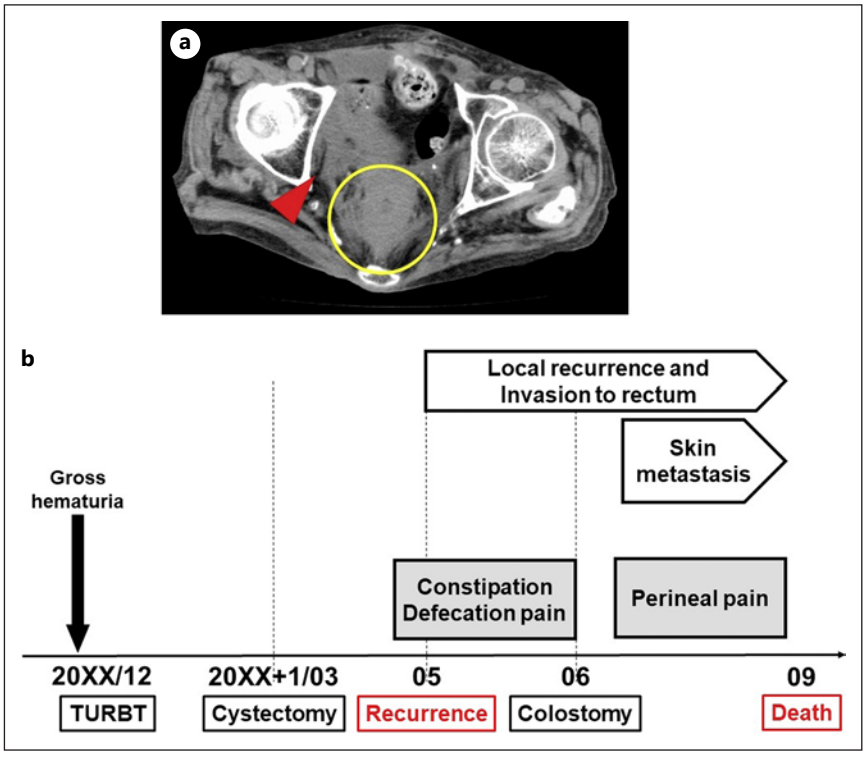

Fig. 3. CT findings at 2 months after cystectomy and clinical course. **a** Local recurrence was confirmed at the pelvic floor (red arrow), associated with annular thickening of the rectal wall (yellow circle). Constipation and defecation pain was believed to be caused by bladder cancer invading the rectum. **b** Clinical course. After local recurrence and invasion to the rectum appeared, colostomy was performed to improve defecation symptoms. However, local recurrence progressed rapidly, and he gradually felt perineal pain due to skin metastases at 3 months after cystectomy.

identifiable in 70 of the 80 cases, with UC accounting for 67 cases, including 4 cases of divergent differentiation and variant histologies [10]. Additionally, the proportion of divergent differentiation and variant histologies in HD patients was equivalent to that in healthy subjects [10]. Table 1 summarizes the reports of 13 bladder cancer cases with divergent and/or variant histologies in patients undergoing HD. In most of these cases, the disease was detected in the advanced stage, and 10 of the 13 cases had muscle-invasive bladder cancer. To the best of our knowledge, this is the first report of MPUC in a patient on HD.

The high incidence of muscle-invasive bladder cancer in HD patients is thought to be due to the poor awareness of oliguria or anuria symptoms. Although urinary cytology helps diagnose UC in patients on HD, adequate urine output is required [18]. Thus, additional imaging evaluations may be essential for diagnosing UC in HD patients with anuria. Yonemura et al. [10] recommended that screening for malignant tumors using CT and ultrasonography should be considered at least once a year in these patients. Cystoscopy is helpful in the early detection and diagnosis of bladder cancer. However, because it is invasive, urologists must judge whether it should be performed immediately as a screening procedure in cases without a history of bladder cancer. Satoh et al. [19] and Lin et al. [20] have reported the detection of bladder cancer in several cases within 1 year of starting HD. Therefore, screening for bladder cancer with urine cytology, ultrasonography, and CT should be considered shortly after starting HD and performed at least once a year. Further cases are required to determine the screening for bladder cancer in HD patients.

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Table 1. Clinical and pathological details of HD patients with divergent differentiation and variant histologies

No.	Author	Age, years	Gender	Duration of HD	Histology	Pathological T stage	Follow-up, months	Survival data
1	Ryoji et al. [12]	72	M	30	UC with glandular differentiation	3	Unknown	Unknown
2	Ryoji et al. [12]	44	F	125	UC with squamous/glandular differentiation	Unknown	4	DOD
3	Ryoji et al. [12]	61	M	6	UC with glandular differentiation	Unknown	Unknown	Unknown
4	Ryoji et al. [12]	61	M	6	Adenocarcinoma	4	0.6	DOD
5	Ryoji et al. [12]	41	M	15	Squamous-cell carcinoma	3b	15	DOD
6	Ryoji et al. [12]	53	F	12	UC with squamous differentiation	3b	Unknown	NED
7	Ryoji et al. [12]	72	M	32	UC with glandular differentiation	3b	1.5	DOC
8	Shirai et al. [13]	65	F	15	UC with sarcomatoid variant	4a	6	NED
9	Siqueira et al. [14]	58	M	Unknown	UC with sarcomatoid variant	4a	6	DOD
10	Yonemura et al. [10]	82	M	75	UC with small-cell carcinoma	2	1.5	DOC
11	Isono et al. [15]	69	F	21	UC with clear-cell variant	1	20	NED
12	Ishii et al. [16]	56	M	204	UC with small-cell carcinoma	4a	19	DOD
13	Jassim et al. [17]	59	F	Unknown	UC with clear-cell variant	3	36	NED
14	Fukuta (2022)	82	M	10	UC with micropapillary variant	4a	6	DOD

DOD, died of disease; NED, no evidence of disease; DOC, death due to complications.

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In this case, the patient developed gross hematuria 10 months after starting HD, and MPUC was first diagnosed using CT, cystoscopy, and urine cytology. Although no metastasis was detected at the time of diagnosis, MPUC being an aggressive variant of UC, the patient died of rapid disease progression 6 months after cystectomy. In addition, the limitation of this case report include bladder cancer with divergent and/or variant histologies in HD patients have been accumulated by several case reports due to its rarity. Since UC includes aggressive variants such as MPUC, careful screening is warranted for improved prognosis, especially in HD patients.

Conclusion

In conclusion, the detection of bladder cancer in HD patients is often delayed because of oliguria or anuria, resulting in disease progression. Bladder cancer often includes aggressive variant histologies such as MPUC. Therefore, regular screening for HD patients is recommended for the early detection of bladder cancer.

Statement of Ethics

Ethical approval was 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.

Conflict of Interest Statement

The authors declare no conflict of interest.

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Author Contributions

Kyotaro Fukuta reviewed the literature and drafted the manuscript. Kiyotaka Iihara, Takhahiro Moriyama, Ryoichi Nakanishi, Hirofumi Izaki, Kazuya Kanda, Tohru Inai, and Yasushi Sutou performed the surgery. Tomoya Fukawa, Kunihisa Yamaguchi, Yasuyo Yamamoto, Masayuki Takahashi, and Hiro-Omi Kanayama critically revised the manuscript. Kyotaro Fukuta, Kiyotaka Iihara, Hirofumi Izaki, and Eiji Kudo performed 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 in this study are included in this article. Further inquiries can be directed to the corresponding authors.

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