Case Report

A rare case of a clear cell carcinoma in a female urethral diverticulum

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Abbreviations & Acronyms
CK = cytokeratin
CT = computed tomography
LVI = lymphovascular invasion
MRI = magnetic resonance imaging
UCCC = urethral clear cell carcinoma
UD = urethral diverticulum

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Introduction: Urethral clear cell carcinoma is rare and often arises from a urethral diverticulum and rarely from the Müllerian duct. However, an explanation for this correlation remains unknown.
Case presentation: We report the case of a 46-year-old woman who presented with hypermenorrhea. Magnetic resonance imaging revealed a papillary tumor in a cystic lesion in the dorsal urethra. We performed a robot-assisted radical cystourethrectomy and created an ileal conduit. Since pathological findings revealed microvascular and lymphovascular invasions around the urethra, adjuvant radiation therapy was administered. The patient showed no signs of recurrence or metastasis after treatment.
Conclusion: We report a case of clear cell carcinoma in a female urethral diverticulum originating from a Müllerian duct cyst. While postoperative radiation therapy has been shown to produce a good outcome in carcinoma cases similar to this one, we recommend that a radical cystourethrectomy be performed.

Key words: clear cell carcinoma, cystourethrectomy, Müllerian duct cyst, transurethral biopsy, urethral diverticulum.

Keynote message

Here, we report a rare case of clear cell carcinoma in a female urethral diverticulum, which likely originated from a Müllerian duct cyst. Robot-assisted radical cystourethrectomy and postoperative radiation therapy provided a favorable outcome.

Introduction

UCCC is a rare type of tumor that commonly occurs in women with a mean age of 58 years (range 35–80 years), and 56% of UCCC cases appear to arise from the UD. However, the relationship between UCCCs and UD remains unclear. It seems that UCCCs originate from the Müllerian duct or due to urothelial dysplasia or glandular differentiation of urothelial carcinoma. Due to their low incidence, no standardized treatment exists for UCCCs in the UD.

Here, we describe a case of a patient with a UCCC in the UD that originated from a Müllerian duct cyst.

Case report

A 46-year-old woman with no remarkable medical history presented with hypermenorrhea and was referred to the gynecology department. MRI revealed a papillary tumor in a cystic lesion in the dorsal urethra (Fig. 1). The patient was, therefore, referred to our department for further evaluation and treatment.

Her only symptom was dysuria without other symptoms, such as hematuria and obstructive voiding. Laboratory evaluation demonstrated no elevation of tumor markers, such as CA19-19, CA125, CEA, and SCC. Cystoscopy revealed a papillary tumor in a UD at 6 o'clock direction. A transurethral biopsy was performed but it did not obtain enough to reveal the tumor details. Therefore, transperineal biopsies were performed using transvaginal ultrasound following transurethral biopsy. It confirmed the diagnosis of UCCC. A full-body CT revealed no metastases,

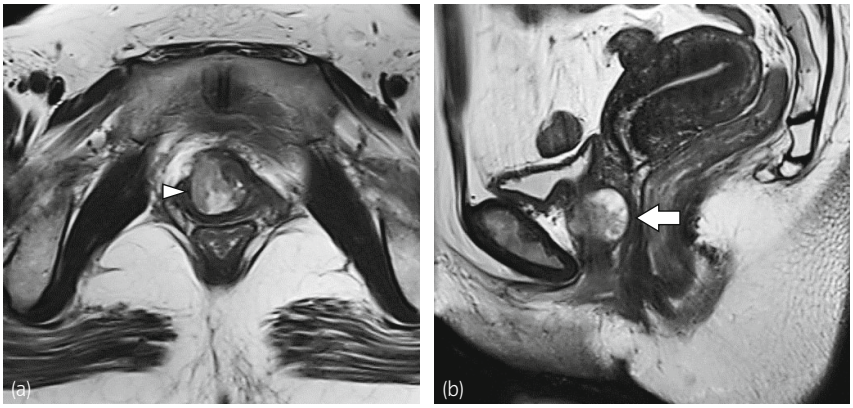

Fig. 1 T2-weighted MRI scans show the tumor in a cystic lesion in the dorsal urethra (*arrow* and *arrowhead*).

and the patient was diagnosed with UCCC cT2N0M0. Three months later, a robot-assisted radical cystourethrectomy was performed, and an ileal conduit was created. The operative time was 8 h 13 min, the robotic console operative time was 5 h 15 min, and the blood loss was 176 mL.

Pathological findings revealed microvascular and LVIs around the urethra. We conducted a tumor board review, including medical oncologists, radiation oncologists, and clinical pharmacists. Although there was no evidence for microvascular or LVI therapy in UCCC, we recommended chemotherapy with paclitaxel and carboplatin followed by whole-pelvic radiation therapy (50 Gy/25 Fr), including the inguinal regions. The patient opted not to undergo chemotherapy and only underwent radiation therapy. After radiation therapy, the patient was followed up every 3 months with a general blood test and a full-body CT. Since the patient became disease-free at 36 months, the duration of follow-up was extended to 6 months.

Discussion

UCCCs are very rare and account for 0.003% of female genitourinary cancers, and 56% of them occur in the urethral diverticula.[1] Patel *et al*. used the National Cancer Institute's Surveillance, Epidemiology, and End Results database and collected 61 UCCC cases. They suggested that UCCCs have a poor 5-year overall survival rate of 39.3%.[2] Although the origin of UCCCs has not been elucidated, they originate from urothelial metaplasia, Müllerian rests, and Müllerianosis.[3] In this case, the tumor cells expressed CK7 and PAX8 but not CK5/6 (Fig. 2). This result revealed that the tumor may have arisen from the Müllerian duct. Venyo *et al*. reported that UCCCs showed positive immunohistochemical staining for PAX2, PAX8, CK7, p16, p53, CA125, CAM5.2, and AE1/AE3, and negative staining for PSA, PAP, thrombomodulin, estrogen, progesterone, CK20, p63, CD10, CEAP, WTI, AFP, and s100.[3]

A UD can be classified as either congenital or acquired. Most UDs are classified as acquired and are found in adult women.[4] UDs generally arise from the periurethral gland (Skene gland). They arborize and are located on the primary dorsolateral urethra and in the distal 1/3 of the urethra.[4] UDs are mainly composed of the urothelium.[5]

In contrast, Mai *et al*. reported a case of a UCCC in a UD arising from a Müllerian duct cyst.[6] A UD from a Müllerian duct cyst seems to be lined by a single-layered columnar

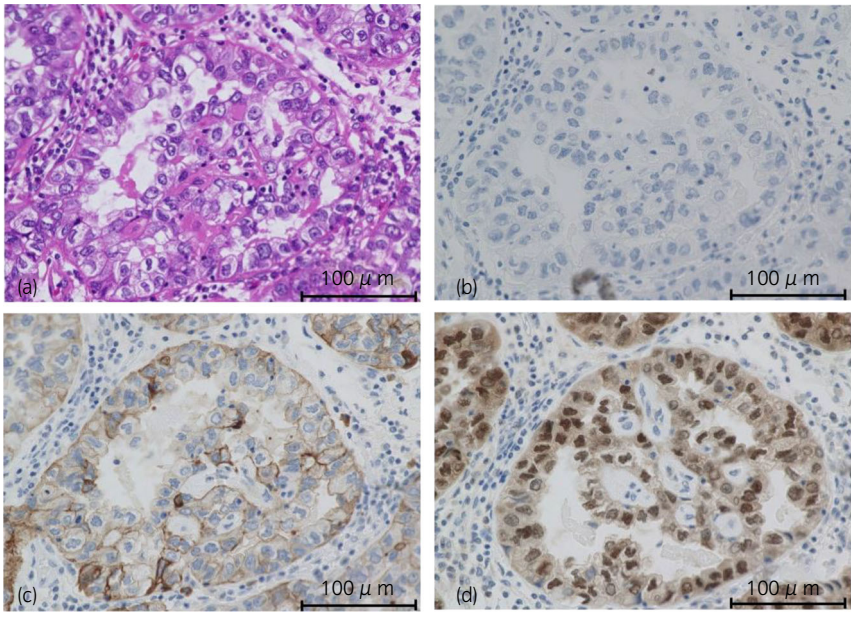

Fig. 2 (a) Hematoxylin and eosin staining and immunohistochemical staining of tumor cells for (b) CK5/6, (c) CK7, and (d) PAX8 to tumor cells.

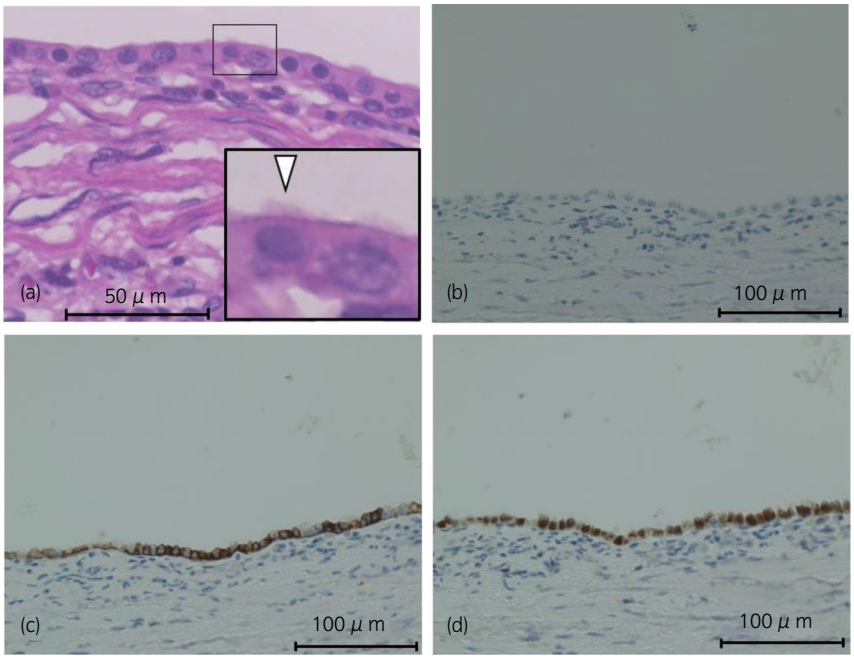

Fig. 3 (a) Ciliated cells seen on hematoxylin and eosin staining (*arrowhead*) and immunohistochemical staining of epithelial cells in the UD for (b) CK5/6, (c) CK7, and (d) PAX8.

epithelium; ciliated cells are also present.[6] In the patient in our report, the UD originated from a Müllerian duct cyst based immunohistochemical staining results and the presence of single-layered columnar epithelium and ciliated cells in the UD (Fig. 3).

Lin *et al*. reported that the pathological features of UCCCs are similar to ovarian clear cell carcinomas.[7] Furthermore, Matsuo *et al*. reported that the frequency of LVI is higher in the ovarian type than in others.[8] Therefore, UCCCs tend to have a higher frequency of LVI than other types of urethral cancers. In this case, the pathological findings revealed minute LVI around the urethra (Fig. 4). These invasions are uncommon in other types of urethral cancers. For successful UCCC removal, we recommend radical surgery with margins as much as possible to remove LVI.

Since there are few cases of urethral cancers arising from UDs, we reviewed 31 cases of UCCCs in a UD (Table S1).[9–15] Cystourethrectomy or anterior pelvic exenteration was performed in 28 patients. Urethrectomy was performed in two patients, and partial urethrectomy was performed in one patient. In the National Comprehensive Cancer Network-guideline, the primary treatment for under T2 urethral carcinoma is transurethral resection and cystourethrectomy or anterior pelvic exenteration. However, optimal treatment for urethral carcinoma in a UD is undecided because of its low prevalence. Awakura *et al*. reported that a local excision, such as diverticulectomy, increased local recurrence and metastasis than aggressive treatment, such as cystourethrectomy or anterior pelvic exenteration.[16] Therefore, Rajan *et al*. recommended anterior pelvic exenteration as the primary treatment.[17] Hence, we recommended a robot-assisted radical cystourethrectomy to reduce the possibility of recurrence or metastasis.

Pathological findings revealed minute LVIs, so whole-pelvic radiation therapy was performed after surgery. The patient has had no recurrence or metastasis 3 years after surgery. Thus, adjuvant radiation therapy may be a good choice for lymph node metastasis in patients with UCCC.

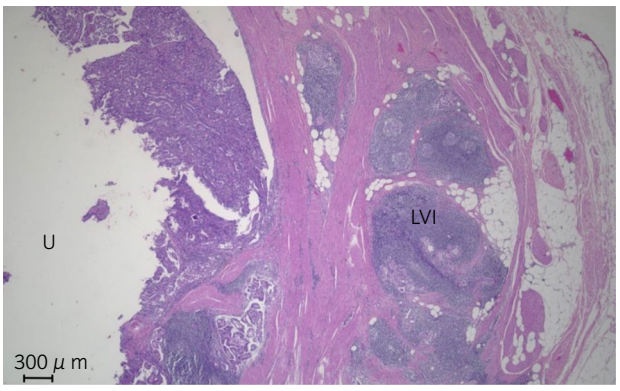

Fig. 4 Minute LVIs around the urethra (U, urethral lumen).

Conclusion

We report a case of clear cell carcinoma in a female UD originating from a Müllerian duct cyst. For successful UCCC removal, we recommend radical surgery with margins as much as possible to remove LVI.

Author contributions

Masakazu Gonda: Conceptualization; data curation; formal analysis; investigation; writing – original draft. Toshiki Etani: Investigation; writing – original draft; writing – review and editing. Masahiko Isogai: Writing – review and editing. Kengo Kawase: Writing – review and editing. Takashi Nagai: Writing – review and editing. Teruaki Sugino: Writing –

review and editing. Taku Naiki: Writing – review and editing. Shuzo Hamamoto: Writing – review and editing. Noriyasu Kawai: Project administration; writing – review and editing. Takahiro Yasui: Project administration; writing – review and editing.

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Conflict of interest

The authors declare no conflict of interest.

Approval of the research protocol by an Institutional Reviewer Board

The protocol for this research project has been approved by the Institutional Review Board of Nagoya City University Hospital, and it conforms to the provisions of the Declaration of Helsinki (Committee of Institutional Review Board, Approval No.60-22-0016).

Informed consent

Informed consent was obtained.

Registry and the Registration No. of the study/trial

Not applicable.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1.