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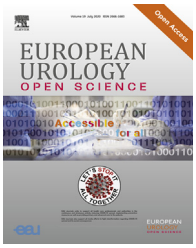

European Association of Urology

Case Report

Two Patients with Urachal Cancer with Multifocal Adenocarcinoma Recurrences in the Urothelium of the Prostatic and Penile Urethra

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Article info

Article history:
Accepted August 9, 2021

Associate Editor:
Guillaume Ploussard

Keywords:
Urachal cancer
Recurrence
Urethra
Urothelial
Adenocarcinoma

Abstract

We report two cases with recurrences of urachal adenocarcinoma (UrAC) in the urethra. Both patients had mucinous UrAC without metastasis, for which they were treated with en-bloc partial cystectomy and umbilectomy. The first patient developed recurrence of UrAC in the distal urethra after 1 yr. Distal urethrectomy revealed multiple additional recurrences in the penile and prostatic urethra. The patient underwent radical cystoprostatectomy with en-bloc urethrectomy. At 5 mo after surgery, liver metastases were found. A search in our institutional database revealed a second patient who developed a solitary recurrence of UrAC in the prostatic urethra 8 yr after partial cystectomy. Radical cystoprostatectomy was performed. The patient subsequently experienced recurring UrAC in the urethra, which were treated with multiple surgeries and radiation. Unfortunately, local tumor control could not be achieved and the patient developed distant metastases 7 yr after cystoprostatectomy. Our two cases and four comparable cases reported in the literature indicate that urothelial spread of UrAC is rare but possible. It remains to be determined if UrAC spreads along the urothelium similar to urothelial cancer or if these multifocal urethral recurrences were the first sign of local metastasis.

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http://dx.doi.org/10.1016/j.euros.2021.08.010

1. Case report

Urachal adenocarcinoma (UrAC) is a rare disease with an incidence of less than one in 1 000 000 [1]. It accounts for 0.2% of all bladder cancers and approximately 20–30% of bladder adenocarcinomas [2,3]. UrAC occurs in the persistent urachal remnant between the umbilicus and the bladder dome. In localized nonmetastatic urachal cancer, partial cystectomy with resection of the urachal remnant and umbilicus is the standard treatment [3,4]. Local bladder-dome recurrence after partial cystectomy occurs in approximately 10–15% of cases and metastatic progression as a sign of distant recurrence in 50–60% [3]. Other more or less local sites of recurrence include metastases to the pelvic lymph nodes and peritoneal spread and/or local metastases in the abdominal cavity and omentum [3]. So far, only four patients have been described, who had multifocal recurrent UrAC in the urothelium [5–7]. This phenomenon is very common in urothelial carcinoma of the bladder [8]. Here we describe two cases with multifocal recurrences of mucinous UrAC in the urothelium of the prostatic and penile urethra.

1.1. Case 1

A 50-yr-old male was referred to our hospital after transurethral resection (TUR) of the bladder dome for UrAC in 2017. Staging with fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT), CT of the chest, abdomen, and pelvis, and diagnostic laparoscopy with abdominal cytology revealed no signs of metastasis (cT3N0M0) or peritoneal spread [9,10]. The patient received neoadjuvant radiation followed by partial cystectomy with resection of the urachus and brachytherapy to the suture lines of the bladder. Pathological examination revealed an intestinal UrAC of 4 cm invading the detrusor muscle with a 7-mm margin to the detrusor resection site (ypT3NxMxR0 UrAC, Sheldon stage IIIa; Table 1). Figure 1 shows histological slides of the UrAC and the persistent urachal remnant. Following surgery, no signs of recurrence on urethrocystoscopy (UCS) and imaging were observed. At 11 mo after surgery, he presented with macroscopic hematuria and UCS showed a papillary lesion in the distal urethra. A biopsy was taken and pathological examination revealed recurrent adenocarcinoma. PET/CT and CT of the chest, abdomen, and pelvis were performed. PET/CT showed FDG uptake in the proximal and distal urethra without signs of lymph node or distant metastases. The FDG uptake in the proximal urethra was considered to be urine stasis because no lesions were seen there on UCS. A complete resection was planned, including a distal urethrectomy with frozen section. During this procedure the urethra was spatulated on the ventral side, which revealed a secondary tumor localization. Owing to this unexpected finding, UCS was performed and showed more than five papillary lesions covering the complete length of the urethra, including a lesion in the prostatic urethra (Fig. 2), which had emerged within 1 mo. No recurrent lesions were found in the bladder. Because of the multiple recurrences covering the complete length of the urethra, salvage cystoprostatectomy with en-bloc urethrectomy, an ileal conduit, and pelvic lymph-node dissection were performed. Pathological examination revealed multifocal localizations of intestinal adenocarcinoma of the urethra with invasion of the corpus spongiosum (foci varying between 3 and 10 mm in diameter; Figs. 3 and 4). The resection margins were free of tumor. In the prostate, bilateral adenocarcinoma of the prostate was found incidentally (pT2cN0, Gleason score 3 + 3, initial prostate-specific antigen 0.52 ng/ml). No residual malignancy was found in the bladder mucosa and none of the 27 lymph nodes were positive for any type of malignancy. A CT scan of the chest, abdomen, and pelvis at 5 mo after salvage surgery showed multiple liver metastases. The patient received six cycles of palliative chemotherapy with capecitabine and oxaliplatin. After initial stable disease, progression oc-

Table 1 – Overview of our two cases and four other patients [5–7] who had urachal adenocarcinoma and urothelial recurrences not at the original primary resection site. All six patients were males aged 50–68 yr with no signs of metastasis at first diagnosis (cN0M0)

Case	pT	R	MC	SCC	TTR (mo)	Treatment for recurrence	FU status
1 [a]	ypT3	R0	Yes	No	11	Salvage CyP with urethrectomy	DOD at 38 mo after initial Dx
2 [b]	pT2	R0–1	Yes	No	96	1. Salvage CyP	DOD at 198 mo after initial Dx
						2. RT to urethra	
						3. Urethrectomy	
						4. Local urethral resection	
						5. Total penectomy	
3 [5]	pT2	R0	Yes	No	12	1. Multiple TURs	DOD at 139 mo after initial Dx
						2. CyP	
4 [5]	pT3	R1	Yes	No	14	CyP and adjuvant RT	NED at 92 mo after initial Dx
5 [6]	pT3	R0	No	No	18	CyP with urethrectomy	No FU
6 [7]	pT2	R0	No	No	4	TUR	NED at 15 mo after initial Dx

R = radicality; R0 = radical resection; R1 = nonradical resection; MC = mucinous component; SCC = signet cell component; TTR = time to recurrence (from partial cystectomy to first urothelial recurrence); CyP = cystoprostatectomy; TUR = transurethral resection; RT = radiation therapy; FU = follow-up; DOD = death from disease; Dx = diagnosis; NED = no evidence of disease.

[a] Case 1 in this report.

[b] Case 2 in this report.

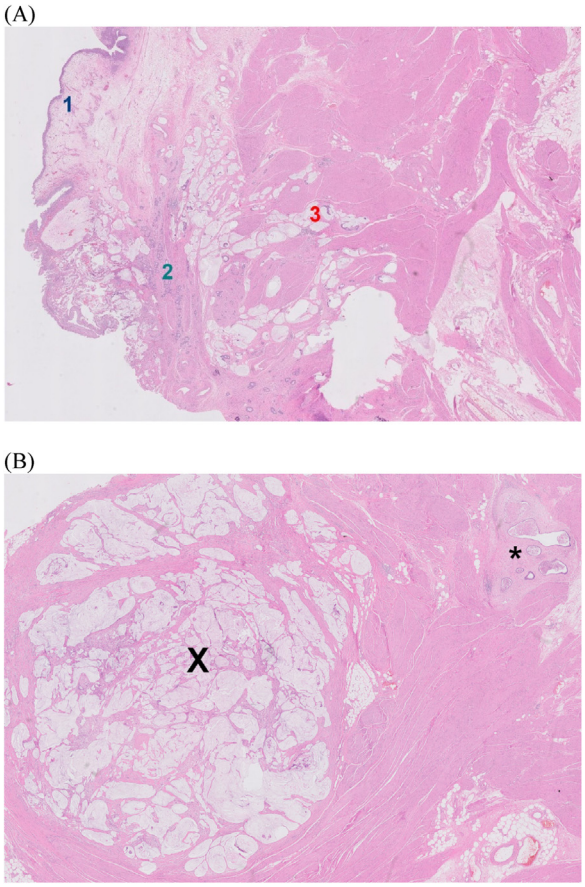

Fig. 1 – Histological slides for case 1 showing mucinous adenocarcinoma found at partial cystectomy and resection of the urachus. (A) 1, normal urothelial lining of the bladder; 2, intestinal-type epithelial cells with gland formation; and 3, mucin and tumor cells infiltrating the detrusor muscle of the urinary bladder. (B) X denotes a large mucinous nodule invading the bladder muscle. The asterisk denotes a persistent urachal duct.

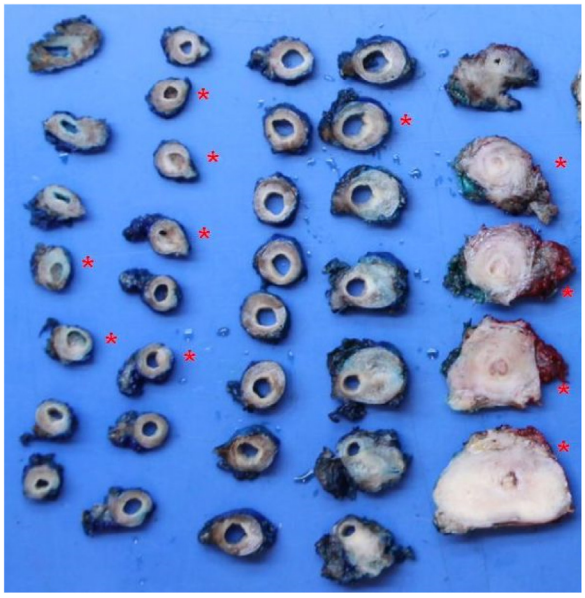

Fig. 3 – Overview of some of the slices from en-bloc salvage cystoprostatectomy and urethrectomy performed in case 1. Sagittal plane views of the penile and prostatic urethra are shown. Asterisks denote slices with recurrent urachal adenocarcinoma.

curred. After local radiation and second-line treatment with irinotecan, further progression was noted and the patient died 1 yr after the liver metastases were found.

1.2. Case 2

A search in our institutional database of 80 patients with UrAC diagnosed between October 1997 and August 2020 revealed 56 patients who were treated with TUR and partial cystectomy and had follow-up of >1 yr. Among these cases we identified a 55-yr-old male who was referred to our hospital in 2007 with signs of recurrent mucinous UrAC at the bladder neck/prostatic urethra. The patient was

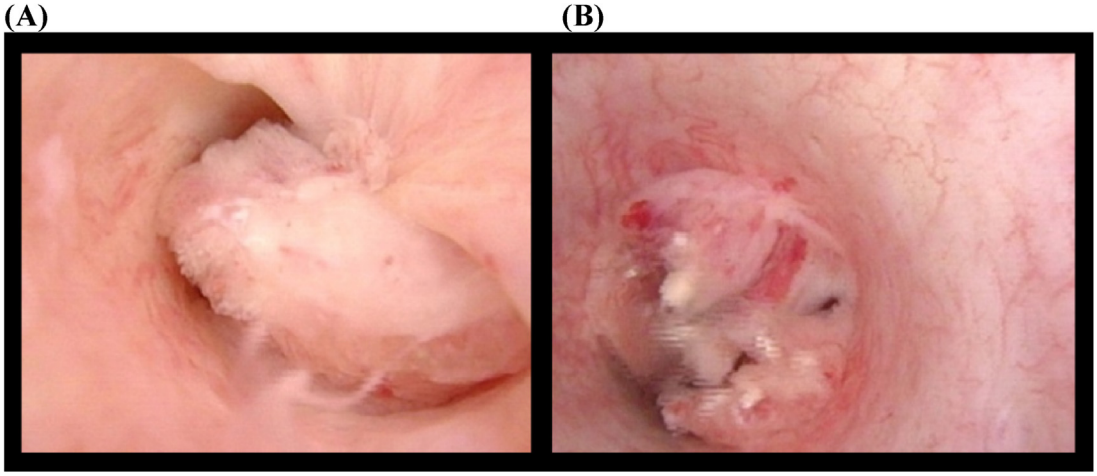

Fig. 2 – Urethrocystoscopy (UCS) performed in case 1 after the patient reported hematuria at 11 mo after the initial partial cystectomy. (A) Papillary lesion at the sphincter extending into the prostatic urethra and (B) an intraluminal mass observed in the distal penile urethra observed during UCS.

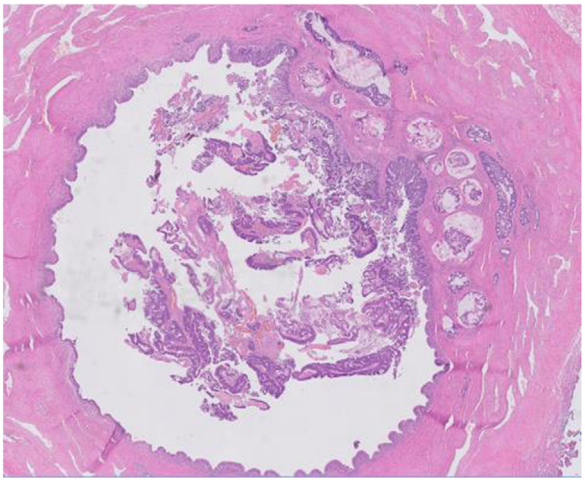

Fig. 4 – Histopathology demonstrating a transverse slice of the penile urethra with an intraluminal recurrent adenocarcinoma mass in case 1. An intestinal-type adenocarcinoma is evident in the lumen of the urethra, with infiltrative mucinous tumor cells in the corpus spongiosum.

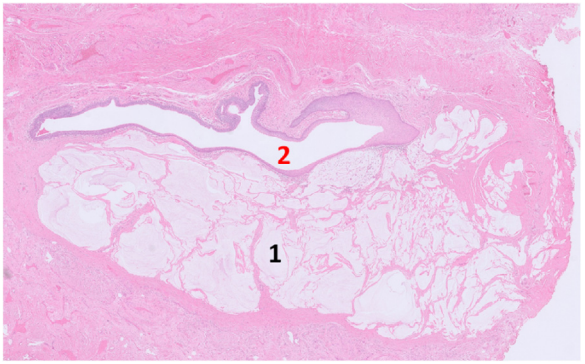

Fig. 5 – Histological slide showing mucinous adenocarcinoma at/near the remaining distal urethra in case 2. A large mucinous nodule (1) is seen close to the lumen of the urethra (2).

initially treated with partial cystectomy for localized UrAC at another hospital in 1999. Pathological examination revealed a mucinous UrAC (pT2NxMxR0–1, Sheldon stage IIIa) of 12 cm in diameter (Table 1). It remained unclear if the initial resection was radical. No adjuvant therapy was given. At 8 yr after his initial surgery, the patient experienced a decrease in urinary flow and a mucinous discharge. UCS was performed and revealed mucinous tissue in the prostatic urethra close to the bladder neck. TUR was carried out and pathological examination revealed recurrence of mucinous UrAC in the prostatic urethra. Imaging showed no signs of metastasis. At our hospital, the patient underwent salvage cystoprostatectomy with an ileal conduit; no residual carcinoma was found in the specimen (pT0N0R0 in the urethra). At 10 mo after surgery, he developed a mucinous urethral discharge and a recurrence was found in the proximal urethra. Biopsy confirmed the presence of (recurrent) adenocarcinoma, which was treated with radiation to the proximal urethra and prostatic fossa (47 Gy) and an additional boost to the proximal urethra (70 Gy in total). The patient presented again 1 yr later with a mucinous discharge from the urethra and salvage (proximal) urethrectomy was performed. Imaging showed no signs of metastasis. Pathological examination of the urethrectomy specimen revealed multiple foci of mucinous UrAC in the lumen of the urethra with infiltrative growth into the corpus cavernosum at multiple sites. At 1 yr after urethrectomy, the patient experienced recurrence in the distal urethra, for which another local resection was performed (Fig. 5). Some 3 yr later, a FDG-PET/CT showed multifocal uptake in the penis suspicious of recurrence (Fig. 6). In addition, a FDG-avid inguinal lymph-node (left-side) and a lesion in corpus L1 suggestive of bone-metastasis were seen. Total penectomy was performed to minimize local symptoms. Mucinous adenocarcinoma was present in the corpora cavernosa and glans penis. The resection margin at the base of the penis was not free of adenocarcinoma. The patient received palliative radiotherapy to the spine (L1 vertebra). He died 1 yr later due to progressive disease.

2. Discussion

In both of our cases, the first manifestation of recurrent UrAC was found in the urethra. The mechanism underlying these urothelial UrAC recurrences in the prostatic and penile urethra remain unclear. Because the primary UrAC invaded through the bladder wall in both patients, it is possible that UrAC in the urethra manifested as local spread, as seen in multifocal urothelial carcinoma. UrAC in the urethra may also be regarded as local seeding, comparable to UrAC causing peritoneal metastases by invading the peritoneum and spreading mucinous tumor cells in the intra-abdominal cavity [4,7]. Another plausible explanation could be that these urethral UrAC recurrences were the first sign of local metastasis that subsequently progressed to nodal and organ metastases. Although the third explanation

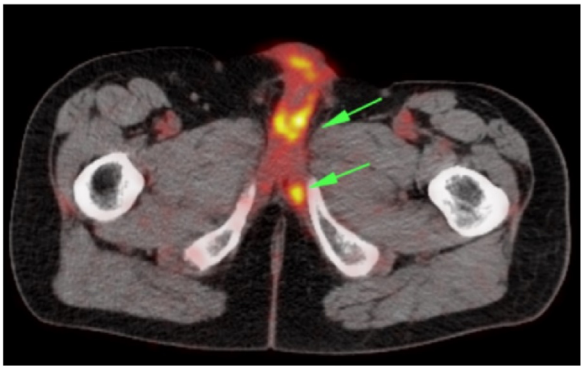

Fig. 6 – Positron emission tomography/computed tomography imaging with fluorodeoxyglucose (FDG)-avid lesions in case 2. Multiple FDG-avid foci are evident in the penis (green arrows). A total penectomy was performed to palliate local symptoms (pain).

seems the most appropriate one, we cannot exclude the other two.

Follow-up of UrAC with imaging (mostly CT and/or PET/CT) after local curative treatment is generally performed because of the frequent local bladder-dome recurrences and, in particular, distant metastases [4,9]. Whether routine UCS should be performed after local treatment, as in urothelial cancer, is unknown. Since the occurrence of urethral UrAC is at most anecdotal and recurrence at the bladder dome can also be detected by imaging, it remains debatable whether routine surveillance with UCS is beneficial. In the two cases reported here, routine UCS did not detect the urethral recurrences, as symptoms (hematuria and a urethral mucinous discharge) prompted further investigation(s).

The optimal treatment strategy for urethral recurrence of UrAC is not known. Of the four cases with UrAC recurrence in the urethra previously described in the literature (Table 1), two patients were treated with cystoprostatectomy with or without urethrectomy and two were treated with TUR [5–7]. Five of the six patients had adequate follow-up data and two of them showed no evidence of disease in follow-up after secondary treatment (Table 1). This indicates that recurrences of UrAC can be cured. It remains a question whether extensive surgery will lead to better oncological outcome. The treatments given to our two patients were empirical and based in an expert center. Both patients received salvage therapy but were not cured by urethrectomy and finally developed distant metastases. We believe that a better understanding of the pathogenesis of UrAC and international collaboration among experts are needed to treat these rare recurrent urethral lesions caused by UrAC.

UrAC is an extremely rare disease that can be treated via partial cystectomy with en-bloc resection of the urachal remnant and umbilicus in the case of local disease. Recurrence after surgery has been described at the initial resection site (bladder dome), in lymph nodes, as intra-abdominal spread (peritoneal metastases), and/or as organ metastases. Our two cases and the four comparable cases reported in the literature indicate that urothelial spread of UrAC is rare but possible. In the case of recurrent hematuria or mucinuria, UCS is recommended to detect any recurrence. Further research is needed to unravel the pathogenesis of these UrAC recurrences and to determine the best treatment strategy for recurrent urethral UrAC.

Conflicts of interest: The authors have nothing to disclose.

Ethics considerations: Appropriate ethical approval was obtained according to national regulations and the principles of the Declaration of Helsinki. The patients in this manuscript have given informed consent for publication of their case details. Institutional ethical guidelines were followed and approval was obtained (number: IRBd21-015).

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.euros.2021.08.010.

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