Case Reports in Oncology

Case Rep Oncol 2023;16:946–953
DOI: 10.1159/000532121
Received: May 3, 2023
Accepted: July 11, 2023
Published online: September 19, 2023

Case Report

Advanced Female Primary Urethral Carcinoma with Nodal Extension Managed with Exclusive Use of Chemoradiotherapy: Report of a Case and Review of the Relevant Current Literature

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Keywords
Chemoradiotherapy · Primary urethral carcinoma · Advanced primary urethral carcinoma · Oncology · Female

Abstract
Primary urethral carcinoma (PUC) is a rare disease with frequent nodal metastasis at the time of diagnosis. Few risk factors have been established and overall prognosis remains poor. As of now, no clear therapeutic guidelines are established and management of advanced PUC often involves surgery which can have negative functional and psychological outcomes for the patient. Few authors have already reported the use of chemoradiotherapy alone to avoid surgery with some good short-term results. We report the case of a 48-year-old woman with advanced high-grade urothelial carcinoma of distal urethra associated to bilateral inguinal nodal metastasis. She was similarly and successfully treated using chemoradiotherapy exclusively without significant adverse effects. This experience reinforces benefits of a surgery-sparing management, when possible, as recommended in current guidelines.

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Introduction

Primary urethral carcinoma (PUC) is a rare disease, accounting for <1% of urogenital cancers [1, 2]. The few established risk factors in females include human papilloma virus (HPV) 16/18 infection [3]. Clinical presentation is variable, but up to 30% of palpable lymph nodes are found at diagnosis and are metastatic in >90% of cases [4, 5]. The overall prognosis of PUC remains poor with no established therapeutic consensus due to the disease's rarity. Although surgery alone is considered effective in early-stage disease, multimodal therapy (surgery, radiotherapy, and/or chemotherapy) is currently recommended for advanced diseases [6–9]. Following recent data, chemoradiotherapy without use of surgery for selected patients with advanced disease may offer good short-term outcomes [9–17]. We report the case of a 48-year-old woman suffering from advanced high-grade urothelial carcinoma of distal urethra with bilateral inguinal node metastasis who benefited from chemoradiotherapy only with complete metabolic response. She remains recurrence-free at 2 years of follow-up. The CARE Checklist has been completed by authors for this case report, attached as supplementary material (for all online suppl. material, see https://doi.org/10.1159/000532121).

Case Report

A 48-year-old woman presented to her gastroenterologist with anal itching and non-painful left inguinal lump for 3 months. She had recent history of high-grade intra-epithelial anal neoplasy associated to HPV and managed via local excision and local adjuvant treatment (imiquimod cream). She continued imiquimod cream for 6 months after local excision and was followed-up via clinical evaluation (anal margin inspection and digital rectal evaluation) after multidisciplinary discussion. Follow-up occurred each month in the first trimester, at 6 months, and then bi-annually according to favorable results. At 18 months of follow-up, she returned with complaints of anal itching and non-painful left inguinal lump that had been present for 3 months. Physical examination revealed a hard, non-painful left inguinal adenopathy. The digital rectal examination and anal margin inspection were normal but anterior vaginal wall was indurated on vaginal palpation. She underwent anorectal echoendoscopy that showed no abnormal lesion arising from the anal and rectal walls. The results of laboratory blood tests and urine analysis were normal. Thoraco-abdominal computed tomography (CT) was performed and demonstrated two supra-centimetric left and right inguinal adenopathies. Pelvic magnetic resonance (MR) found a 3.6 cm height lesion of distal urethra with corresponding inguinal adenopathies (shown in Fig. 1a). A 18F-fluorodeoxyglucose positron-emission CT revealed hypermetabolism at the level of those adenopathies, with the left inguinal adenopathy measuring 21 mm of short axis (shown in Fig. 1b, c). There was no extension to bladder neck, corpus spongiosum, or clitoris. The left inguinal adenopathy was biopsied and the pathologic examination found moderately differentiated squamous cell carcinoma (SCC) histologic pattern on the material. The patient was referred to the urology team for an urethrocystoscopy which revealed an exophytic lesion of the distal urethra but with normal bladder wall. Forceps cold biopsies and urethral swab for HPV screening were obtained. The pathologic evaluation of the urethral biopsies revealed high-grade urothelial carcinoma of the distal urethra (shown in Fig. 2a). The previous lymph node biopsies were reviewed and showed urothelial carcinoma nodal metastasis with focal squamous cell differentiation (shown in Fig. 2b). Immunohistochemistry of urethral biopsy demonstrated a significant "cell-bloc" positivity for p16 protein and high-risk HPV was detected by in situ hybridization (shown in Fig. 2c, d). After multidisciplinary discussion, two therapeutic options

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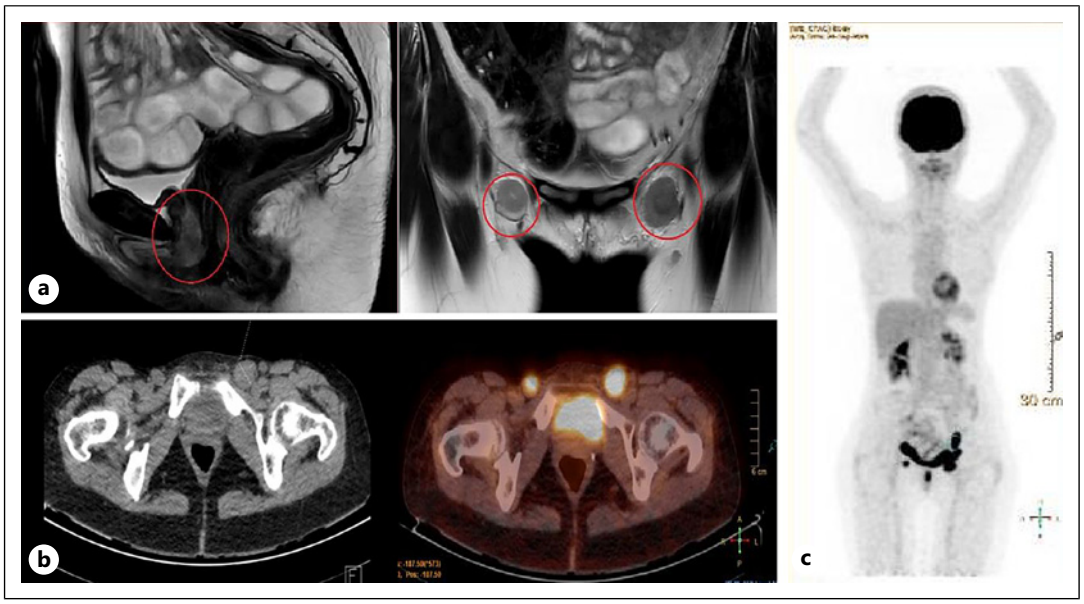

Fig. 1. a A 48-year-old woman presenting with advanced PUC (18 × 21 × 36 mm) and bilateral inguinal adenopathies on pelvic MR (sagittal and coronal; T2 sequence). **b**, **c** 18F-FDG PET/CT demonstrated significant hypermetabolism of those two inguinal adenopathies. The left adenopathy predominated in size with 21 mm of short axis.

were offered to the patient: neoadjuvant chemotherapy with radical urethrectomy or chemoradiotherapy alone. The patient refused surgery in favor of chemoradiotherapy involving seven cycles of cisplatin chemotherapy (40 mg/m^2 once a week concomitant to radiotherapy) and external radiotherapy (57.5 Grays to pelvic/inguinal lymph nodes and 59.4 Grays to urethral tumor over 33 sessions). Cisplatin was used in monotherapy with external radiotherapy to decrease toxicity, based on previous report of chemoradiotherapy for SCC PUC by Coop et al. [14]. The radiotherapy dosage relied on data for anal canal and gynecologic tumors at that time and a suprapubic catheter was placed pre-treatment to avoid acute urinary retention. The chemotherapy was well tolerated, and radiotherapy induced moderate vulvar dermatitis and vaginal atrophy. Pelvic MR and 18FDG-PET-CT performed 3 months after the treatment showed complete therapeutic response (shown in Fig. 3). Afterward, follow-up was performed each 3 months via clinical evaluation and imagery assessment (pelvic MR and chest CT). Currently, at 24 months of follow-up, clinical evaluation and imagery (pelvic MR and chest CT) show no disease recurrence at the anorectal or urethral levels and the patient remains recurrence-free.

Discussion

PUC is a rare disease, accounting for <1% of urogenital malignancies [1]. In the USA, annual incidence reaches 1,907 cases per year according to recent data with age-standardized incidence rates of 2.70 cases per million in men and 0.55 per million in women, contradicting previous reports of the female predominance of this disease [2]. PUC is rare in patients of <55 years but increases after 75 years [2]. In women, risk factors are sexually transmitted infections (of which HPV 16/18), urethral diverticula, chronic inflammation, and recurrent urinary tract infections [2, 3]. Histologically, the main subtypes are adenocarcinoma (AC), urothelial carcinoma, and SCC. The urothelial carcinoma is predominant in men (64.1%),

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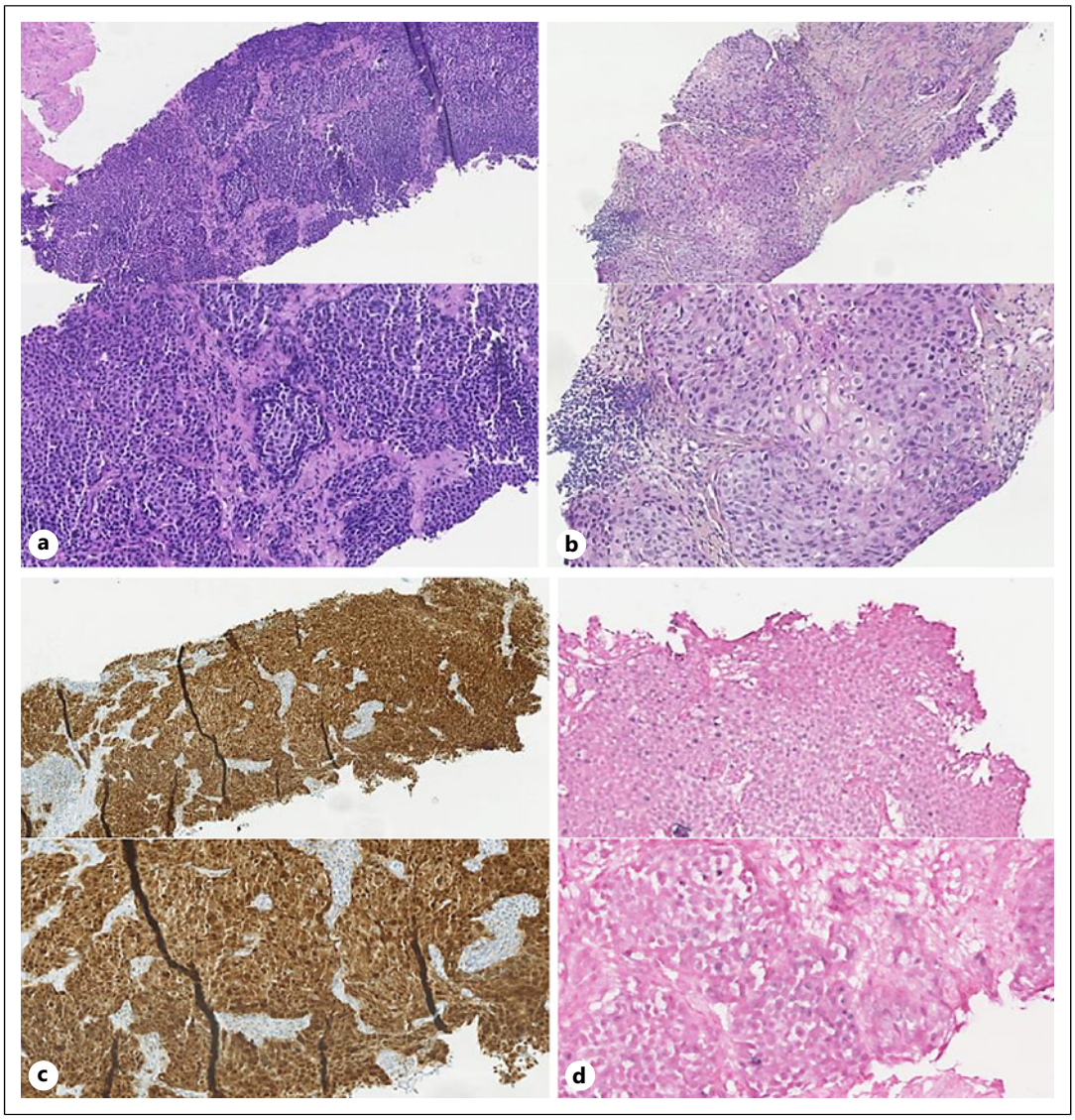

Fig. 2. a Urethral biopsy showed infiltrating urothelial carcinoma of distal urethra (hematoxylin and eosin; magnification: ×10) formed by urothelial cells displaying cellular and nuclear polymorphism with marked nucleomegaly (hematoxylin and eosin; ×20). **b** The inguinal node biopsy also showed confluents islets of large neoplastic urothelial cells with a focal squamous cell differentiation and desmoplastic stroma (hematoxylin and eosin, magnification: ×10). Abundant mitosis with eosinophilic cytoplasm and atypic irregular nucleus were also seen (hematoxylin and eosin, magnification: ×20). **c** Immunophenotypage of urethral biopsy showed diffuse nuclear and cytoplasmic ("cell-bloc") positivity for p16 protein, which is associated to high-risk HPV infection (magnification: ×10 and ×20). **d** The positivity of the urethral biopsy for high-risk HPV was confirmed by the in situ hybridization showing punctate nuclear staining within tumoral cells (HPV III Family 16 probe for high-risk HPV [HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 66] [Ventana, Tucson, AZ]; magnification: ×30 and ×40).

whereas it is only slightly more frequent than the two other main histologic subtypes of PUC in women [2]. It should be noted that urothelial PUC in females remains exceptional with few cases reported yet [1–3]. Most women (>70%) are symptomatic when diagnosed [4]. Symptoms include urinary complaints (dysuria, hematuria, urinary retention), pain (dyspareunia, perineal), or an urethral/meatal mass [5]. Half of symptomatic patients, especially

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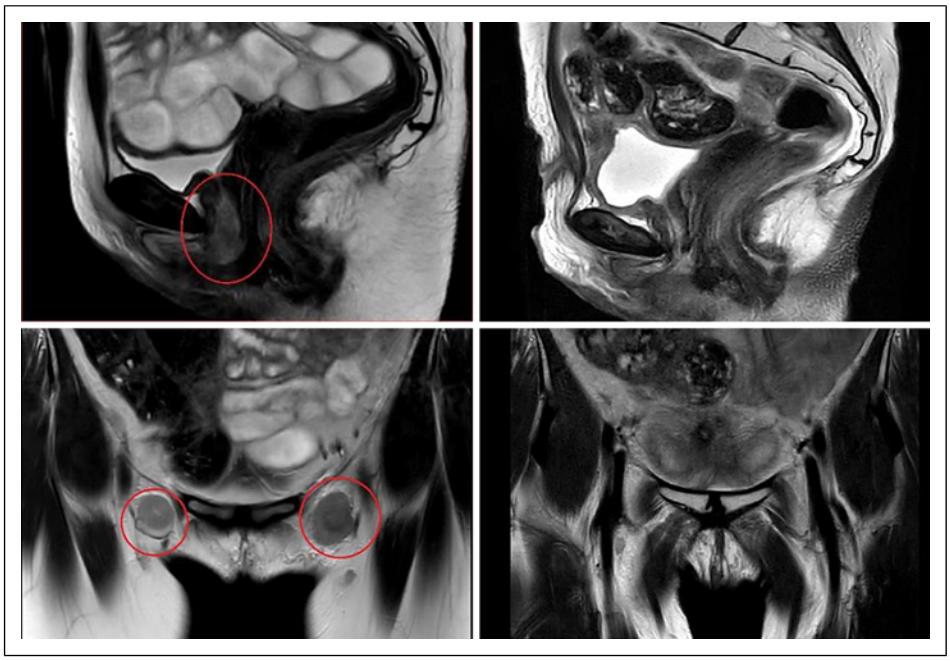

Fig. 3. Complete tumoral response on pelvic MR is seen 3 months after the treatment, with no residual tumoral mass or adenopathy.

females, present with locally advanced disease (≥cT2 or cN+) [3, 4]. Tumoral extension starts from periurethral tissues toward the regional lymph nodes which are common sites of regional metastasis and over 30% of patients have clinically palpable lymph nodes at the time of diagnosis, that are metastatic in >90% of cases [5]. The tumoral staging starts during physical examination with urethra palpation, speculum visualization in women, and inguinal lymph node palpation in both genders [1–3]. The definitive diagnosis relies on urethrocystoscopy to obtain cold biopsies and/or transurethral resection to evaluate tumor location, extension, and histology with exclusion of concomitant bladder tumor [5]. Sensitivity of the urinary cytology in biopsy-proven PUC only reaches 59% [4]. The imaging methods for tumoral staging include pelvic MR for local extension and chest and abdomen CT to exclude potential nodal and/or distant organ metastasis. Pelvic MR outperforms CT in local extension and regional lymph node assessment and evaluates response to chemoradiotherapy [4, 5]. Initial work-up requires biopsies of palpable lymph nodes [18]. Prognosis of PUC remains poor, even in early-stage diseases, and estimated 1-year and 5-year overall survival (OS) rates in European population are, respectively, 71% and 54% [6]. Most important prognostic factors are pathologic stage and lymph node positivity [1–4]. Lymph node positivity pejorates survival with 5-year and 10-year OS rates of 44% and 29%, respectively [1]. Other factors impairing survival include older age (>65 years), race, tumoral size, and non-squamous histology [1–4]. Management of PUC in current literature depends on initial tumor stage, although treatment consensus is lacking because of its low incidence [1, 3–6, 18]. In localized PUC, surgery (radical urethrectomy or urethra-sparing surgery) is the mainstay of treatment with 73% of 5-year OS [1]. In contrast, surgery alone in locally advanced tumors only results in 20–30% of 5-year disease-free survival [1]. Several authors previously reported worse survival and recurrence-free rates of monotherapies used for the high-stage PUC management, progressively favoring a multimodal approach (surgery, radiotherapy, and/or chemotherapy) [8, 9]. The European Association of Urology (EAU) currently recommends the use of multimodal therapy involving surgery, cisplatin-based neoadjuvant chemotherapy, and/or adjuvant radiotherapy

for locally advanced PUC (≥cT3 or cN+) [18]. This recommendation is based on several recent studies showing preoperative cisplatin-based chemotherapy/chemoradiotherapy in patients with locally advanced PUC (independently from lymph node status) to improve their long-term survival [10, 11]. In a series of 44 patients with locally advanced PUC (43% cN+) from Dayyani et al. [11], overall response rate to preoperative chemotherapy reached 72% with 50% of OS at 42 months. Particularly, the EAU proposes chemoradiotherapy alone as a therapeutic option for selected locally advanced PUC with squamous cell histology, independently from lymph node status [18]. This therapeutic approach is based on results from several studies, including a recently updated retrospective study from Kent et al. [12]. In this study, 25 patients with locally advanced urethral SCC (≥T3 or cN+) were treated with chemoradiotherapy and showed 80% clinical response rate with 52% 5-year OS and 68% disease-specific survival. Other authors also reported similar experiences for SCC subtype [13–17]. In our case, the tumor presented discrete squamous cell differentiation which was an argument supporting the use of chemoradiotherapy as curative treatment. Interestingly, Wiener et al. [19] found high association between oncogenic HPV and female urethra carcinomas. The presence of HPV inside the tumor was demonstrated by immunohistochemistry and ISH in our patient. In anal canal cancer, HPV positivity is associated to better prognosis [19]. Similar association could exist in PUC. Nowadays, children's preventive vaccination against most oncogenic HPV virus with Gardasil® vaccine is known to provide solid protection against some adult genital cancers. Unfortunately, the vaccine is not part of routine pediatric vaccination schedule. The potential benefits on the risk of developing urethral carcinoma in the adulthood could be an argument for HPV routine vaccination of children.

Conclusion

Locally advanced PUC in females is a rare disease with poor prognosis. Current therapeutic options are unestablished, and patients may be reluctant to undergo a major surgery in this sensitive area. Fortunately, conservative multimodal therapy avoiding surgery in selected high-stage diseases may offer good short-term outcomes. However, studies with longer follow-up periods and larger patient cohorts are needed to support the benefits of favoring this organ-sparing therapeutic approach.

Acknowledgments

The authors thank the oncologic and imagery departments of the Ambroise Paré Hospital for their support in data collection.

Statement of Ethics

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

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

No funding was received.

Author Contributions

All co-authors contributed to the redaction and critical revision of this manuscript. M. Al Barajraji performed the collection of clinical data, review of the relevant literature on the subject, and redaction of the core manuscript. S. Holz and M. Martinez contributed to critical revision of the content, especially the histopathological aspects for M. Martinez. S. Dingennen and A. Baize were, respectively, asked to review the oncologic and radiotherapeutic aspects of this case, especially for its therapeutic management. S. Taylor was asked to analyze the imagery as a radiologist. Finally, I. Moussa along with M. Coscarella and M. Naudin were asked to provide critical appreciation of the manuscript before submission. All authors have approved the final version to be published and thus agreed to be equally responsible for any question related to their part of this work.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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