Urology Case Reports 58 (2025) 102882

Contents lists available at ScienceDirect

Urology Case Reports

journal homepage: www.elsevier.com/locate/eucr

Oncology

Urethral clear cell adenocarcinoma in an adult female: A rare case report

Yacob Sheiferawe Seman [a,*], Michael Teklehaimanot Abera [b], Fadil Nuredin Abrar [c], Tesfaye Kebede Legesse [b], Mesfin Asefa Tola [d], Tsiyon Nigusie Alemu [a]

[a] Addis Ababa University, College of Health Sciences, Department of Urology, Addis Ababa, Ethiopia
[b] Addis Ababa University, College of Health Sciences, Department of Radiology, Addis Ababa, Ethiopia
[c] Addis Ababa University, College of Health Sciences, Department of Pathology, Addis Ababa, Ethiopia
[d] St Paul's Hospital Millennium Medical College, Department of Pathology, Addis Ababa, Ethiopia

A B S T R A C T

Clear cell adenocarcinoma of the urethra is an extremely rare malignancy with a poor outcome, mainly affecting females in old age. We present the case of a 42-year-old female patient who presented with progressively worsening lower urinary tract symptoms, leading to a cystoscopy-guided core needle biopsy diagnosis of clear cell adenocarcinoma of the urethra. We will mainly discuss the cross-sectional imaging and pathological aspects of the case.

1. Introduction

Clear cell adenocarcinoma of the urethra (CCAU) is a rare primary malignancy of the urethra, overwhelmingly affecting females.[1] The mean age at disease onset is 58 years.[2] Lower urinary tract symptoms, hematuria, and a recurrent urinary tract infection are present. CCAU is present in the bladder base and urethra. When it occurs in the urethra, around half of the cases arise from an underlying urethral diverticulum.[3]

The histological origin of CCAU has been debated, but new research suggests that it has a urological origin. This is supported by genetic and immunohistochemical study results that are similar to those of urothelial carcinoma. These include changes in chromosomes 3, 7, and 17, as well as positivity for CD10 and CK7.[4] Histologically, there are 3 main forms, namely the papillary, tubulocystic, and diffuse forms. We also see nuclear pleomorphism, cytoplasmic clearing, and cellular structural variations consisting of hobnailing, cuboidal, and flat structures.[2,3,5]

Cystoscopy investigation enables direct tumor visualization and sample acquisition. Imaging modalities consist of pelvic ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI). They help to outline the full extent of the lesion in relation to adjacent organs.[5–7]

1.1. Case presentation

A 42-year-old female presented with hesitancy and poor urinary flow, as well as abnormally increased urinary frequency and urge incontinence for a 1-year duration. Before coming to our hospital, she had received multiple antibiotic treatments for a suspected urinary tract infection. Other than her urination problems, she reported no previous history of chronic illnesses. On presentation, the patient had stable vital signs, and the physical examination was unremarkable. The baseline blood workup includes the complete blood count, renal function tests, and serum electrolytes within the reference range. Urinalysis revealed a turbid appearance, blood +2, and many RBCs per HPF.

The post-contrast abdominopelvic CT (Fig. 1) revealed a 3.7 cm × 3 cm x 2.7 cm (TRxCCxAP) enhancing mass of the entire urethra with superior extension to the bladder base. The MRI (Figs. 2 and 3) revealed T1W intermediate, T2W bright, and enhancing masses that completely filled the urethral lumen and completely obliterated the normal urethral signal stratum.

Both CT and MRI revealed no signs of abdominopelvic lymphadenopathy or solid organ secondaries. Upon cystoscopic evaluation, papillary growth filled the entire urethra, extending to the bladder neck. The bladder showed significant post-obstructive changes, including severe trabeculation and multiple diverticula. The bladder showed no growth, and both ureteric orifices were visible and appeared normal. We took multiple biopsy samples with transurethral resection and subjected them to pathological analysis. It was possible to see under a microscope that a lot of the tumor had mixed tubulopapillary and cribriform growth of highly pleomorphic cells, hobnailing, and cytoplasmic clear cell changes(Fig. 4). Immunohistochemical analysis (Fig. 5) showed strong and diffuse CK7 and PAX8 positivity. The tumor was negative for CK20, CDX2, PSA, and P63.

A multidisciplinary team comprising urologists, oncologists,

* Corresponding author.
E-mail addresses: emjactha@gmail.com (Y.S. Seman), michael.thaimanot@aau.edu.et, th.miki8441@gmail.com (M.T. Abera), fadil.nuredin@aau.edu.et (F.N. Abrar), tesfaye.kebede@aau.edu.et (T.K. Legesse), Mesfin.asefa@sphmmc.edu.et (M.A. Tola), tsiyonalemu2011@gmail.com (T.N. Alemu).

https://doi.org/10.1016/j.eucr.2024.102882
Received 27 July 2024; Received in revised form 28 October 2024; Accepted 5 November 2024
Available online 13 November 2024

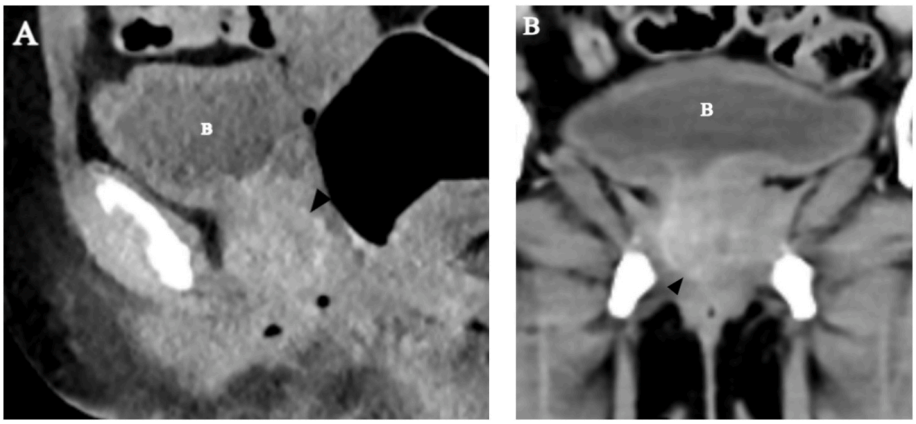

Fig. 1. Axial (A) and coronal (B) post-contrast pelvic CT show bulky and predominantly homogeneously enhancing urethral lesion with bladder base extension (arrowhead in A and B).Bladder is labelled B in both images.

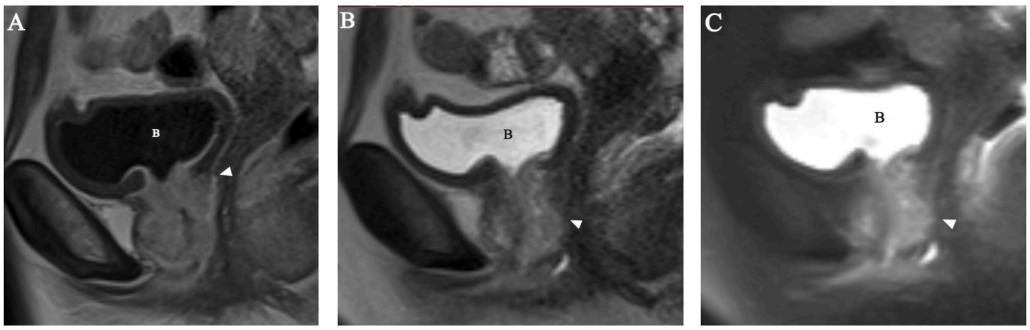

Fig. 2. Sagittal MRI in T1W (A), T2W (B), and T2W fat-suppressed (C) sequences: The entire urethra shows a T1 intermediate as well as T2 and T2 FS hyperintense bulky tumoral infiltration with luminal obliteration. The normal zonal anatomy of the urethra is lost. The lesion has anterior vaginal (white arrowheads) and bladder (B) base extensions.

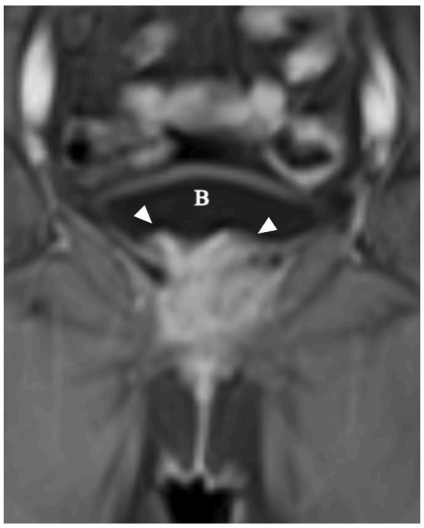

Fig. 3. Post-contrast T1W Volumetric MRI: The tumor shows marked enhancement along its entire height and width. The bladder extension is better appreciated.

radiologists, and pathologists discussed the patient's case and offered her a radical cystourethrectomy with an ileal conduit after a thorough workup. We thoroughly counseled her on the procedure's details and potential complications. Unfortunately, the patient refused to consent to the procedure, citing her concern about the impact it would have on her quality of life given her low socioeconomic status. Despite repeated attempts to persuade her, the patient did not consent to the procedure until this report was written. She is currently voiding via a transurethrally placed catheter.

2. Discussion

Urethral malignancies in general are extremely rare, accounting for less than 0.02 % of all malignancies in women.[8] Since its initial description in 1973, a few case reports and case series have documented the even rarer CCAU, which represents only 10 % of these tumors.[9] It is a distinct entity when compared to the commoner subtypes of squamous cell carcinoma (SCC) and transitional cell carcinoma (TCC) of the urethra. Previous case collections[2,5] have noted a higher prevalence of urethral diverticulum. The largest case series is Olivia and Young,[2] from 1996. According to their findings, 12/19 of CCAU occurred in the urethral diverticula.

Currently clear cell adenocarcinoma of the urethra is listed under Mullerian-derived tumors in the 2022 WHO (world health organization) classification of tumors of the urinary system.[10] Morphologically, the tubulocystic or papillary organization with hobnailing and clear or eosinophilic cytoplasm appeared similar to mullerian derived tumors of the female genital tract.[10]

In addition, pathologic analysis in CCAU showed strong positivity for PAX8, a specific mesonephric or Mullerian tumor marker. GATA3 reactivity was negative, suggesting a non-urothelial origin [11]. Genetic study of CCAU also revealed a significant lack of the TERT promoter mutation, the most prevalent urothelial carcinoma mutation.[11]

Imaging is important for assessing the urethra, as a clinical examination can be difficult or non-revealing. MRI is the modality of choice for

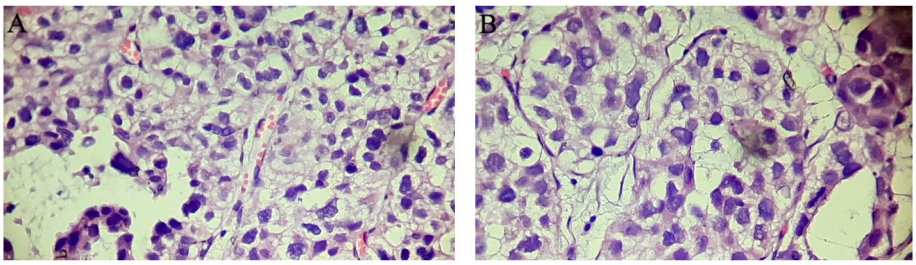

Fig. 4. A and B- Hematoxylin and Eosin stain (400x) - Cuboidal cells have hyperchromatic nuclei, abundant clear to pale eosinophilic cytoplasm and hobnailing.

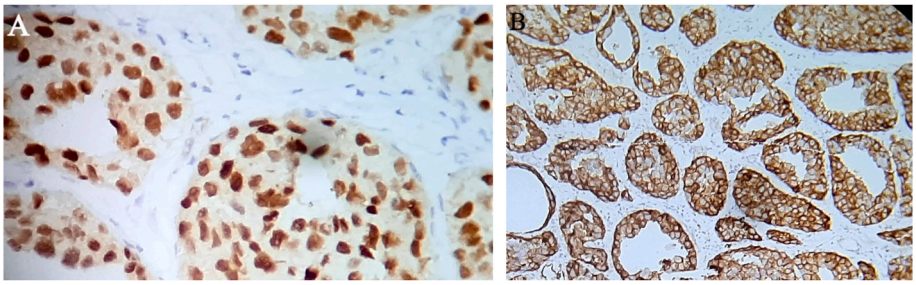

Fig. 5. Immunohistochemical staining for PAX8, 400x (A) and CK7, 100x
(B) - The tumor shows diffuse nuclear positivity for PAX8 and diffuse membranous positivity for CK7.

assessing the female urethra given its non-invasiveness, superior spatial and inherent tissue contrast, and high signal-to-noise ratio. The normal urethra measures 4 cm and spans from the bladder base to the external urethral meatus. Normally, the urethra on T2W and post-contrast T1W sequences has a layered or target-like appearance. From periphery to center, the signal intensity consists of a hypointense layer (muscular layer), a hyperintense layer (submucosa), a hypointense layer (epithelium of the mucosa), and a bright urine-filled lumen. Disruption of the normal appearance by a tumor signifies local invasiveness to adjacent structures such as the vagina and bladder.[5–7]

Pretreatment planning uses MRI, which accurately assesses local tumor extension in 90 % of cases.[6] MRI evaluates the size, location, and extent of tumors. These are critical because the prognosis heavily depends on the stage rather than the grade of the tumor.[12] Tumors that involve the entire urethra (also called posterior tumors) drain to the external iliac, obturator, hypogastric, and paraaortic nodes and have a poorer outcome. Anterior tumors are limited to the distal one-third of the urethra and drain to inguinal nodes. They have a better outcome.[7,12]

MRI cannot adequately forecast specific tumor histology and requires histologic examination.[6,12] However, inherent urethral histology dictates tumor location, allowing for certain predictions to be made. SCC, which is the commonest type of urethral cancer, is usually located in the anterior or distal urethra. It is hypointense on T2W imaging. TCC has heterogeneous T1W and T2W signal intensities and commonly resides in the bladder neck. Adenocarcinomas tend to involve the entire urethral segment.[12] On MRI, CCAU appears to be a heterogeneously enhanced exophytic mass with a high signal intensity on the T2W sequence. In a case as advanced as ours, with a lot of concentric growth and periurethral extension, it might be difficult to see the diverticular origin, and a cytopathologic confirmation is required.

According to the European Association of Urology Guidelines on Primary Urethral Carcinoma[13], our case represents T3N0M0 disease because it clearly invades the bladder neck and anterior vagina. We recommend a multimodal treatment approach in such cases, which combines definitive surgery with chemotherapy, either with or without radiotherapy. Such an approach is superior to surgery alone in prolonging survival. The prognosis for advanced cases is guarded by the overall 5-year survival for $\geq$ cT3 estimated at only 29 % versus $\leq$ cT1 disease, which carries a much more favorable rate of 63 %.[14]

In conclusion, clear cell carcinoma of the female urethra is an extremely rare disease with a poor prognosis. Histologic and immunohistochemical analysis are important to make a definitive diagnosis. Early surgical treatment confers a better survival chance.

CRediT authorship contribution statement

Yacob Sheiferawe Seman: Writing – review & editing, Writing – original draft, Software, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Michael Teklehaimanot Abera:** Writing – review & editing, Methodology, Data curation. **Fadil Nuredin Abrar:** Writing – review & editing, Formal analysis, Data curation. **Tesfaye Kebede Legesse:** Writing – review & editing, Conceptualization. **Mesfin Asefa Tola:** Writing – review & editing, Formal analysis, Data curation. **Tsiyon Nigusie Alemu:** Writing – review & editing, Methodology, Data curation, Conceptualization.

Informed patient consent

Written informed consent was obtained from the patient for anonymized patient information to be published in this article.

Funding source

None.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Abbreviations:

CCAU	Clear cell adenocarcinoma of the urethra
CT	Computed tomography
MRI	Magnetic resonance imaging
SCC	Squamous cell carcinoma
TCC	Transitional cell carcinoma

WHO World Health Organization

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