

Oncology

Clear cell adenocarcinoma of female urethra: A case report

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ABSTRACT

Primary malignancies of the female urethra are rare, accounting for less than 1% of genitourinary malignancies. Clear cell adenocarcinoma of the urethra (CCAU) occurs more infrequently, accounting for 0.003% of malignancies of the female urogenital tract. Definitive clinical diagnosis of CCAU is difficult and must be differentiated from tumors of the vagina. Currently, there is limited understanding of the causes of CCAU and there is no established standard of care for treatment. Immunohistochemistry and pathologic analysis can be used to identify the origin of the tumor.

Introduction

Primary malignancies of the female urethra are rare, accounting for less than 1% of genitourinary malignancies.¹ Clear cell adenocarcinoma of the urethra (CCAU) occurs more infrequently, accounting for 0.003% of malignancies of the female urogenital tract.² Definitive clinical diagnosis of CCAU is difficult and must be differentiated from tumors of the vagina. Currently, there is limited understanding of the causes of CCAU and there is no established standard treatment. Here, we report a case of a 74 year old female diagnosed with CCAU who underwent surgery and radiation therapy, with no evidence of disease recurrence at one year of follow-up. Immunohistochemistry and pathologic analysis was performed to identify the origin of the tumor.

Case presentation

A 74 year old female presented with urinary incontinence, hematuria, and a 40 pound weight loss over two months. She underwent a hematuria evaluation with CT urogram and cystoscopy. CT urogram demonstrated an enhancing soft tissue mass inferior to the bladder and anterior to the vagina, along the course of the urethra. Cystoscopy demonstrated a diverticulum versus necrotic tumor with connection to the posterior urethra at the 6 o'clock position near the bladder neck. On pelvic exam, a 4mm papillary lesion in the mid-anterior vagina was visualized. An MRI of the pelvis demonstrated a large urethral mass 3.0 × 2.9 × 3.8 cm with heterogeneous enhancement in the bladder neck and urethra concerning for a urethral neoplasm (Fig. 1). A biopsy was significant for adenocarcinoma with clear cell features. A PET scan

showed no clear evidence of metastatic disease.

The patient underwent radical cystectomy with urethrectomy, anterior vaginectomy, bilateral pelvic lymph node dissection, and ileal conduit urinary diversion. The postoperative period was uneventful. Gross examination of the resected specimen revealed a poorly defined exophytic fungating mass in the urethra, measuring 3.5 × 3.5 × 2.2 cm. The mass protruded into the anterior vaginal wall, creating a 0.4 cm defect. Bilateral ureteral margins and bilateral pelvic lymph nodes were free of tumor. The final pathological staging was pT3N0M0 with negative margins.

Microscopic assessment of the mass revealed a high grade carcinoma with markedly atypical cells in a glandular and acinar architecture, with focal clear cytoplasm (Fig. 2A). The tumor cells had a focal hobnail pattern, a common histologic feature of clear cell carcinoma (Fig. 2B). On immunohistochemical (IHC) analysis, the tumor cells were positive for PAX8, HNFb, and CK7 with patchy ER, and they were negative for CK20 and GATA3 (Fig. 3). The tumor morphology and immunophenotype supported the diagnosis of clear cell carcinoma. With no clinical evidence of gynecologic primary, the tumor was found to be consistent with a clear cell carcinoma of the urinary tract.

The patient completed pelvic radiation for a total dose of 5000cGy in 25 fractions to the tumor bed, pelvic lymph nodes, and inguinal lymph nodes. Follow up was conducted every 3 months with urine cytology and alternating MRI pelvis and PET scans. She was well at her one-year follow-up without recurrence or metastases.

Abbreviations: CCAU, Clear cell adenocarcinoma of the urethra; CT, Computed tomography; IHC, Immunohistochemical; MRI, Magnetic resonance imaging

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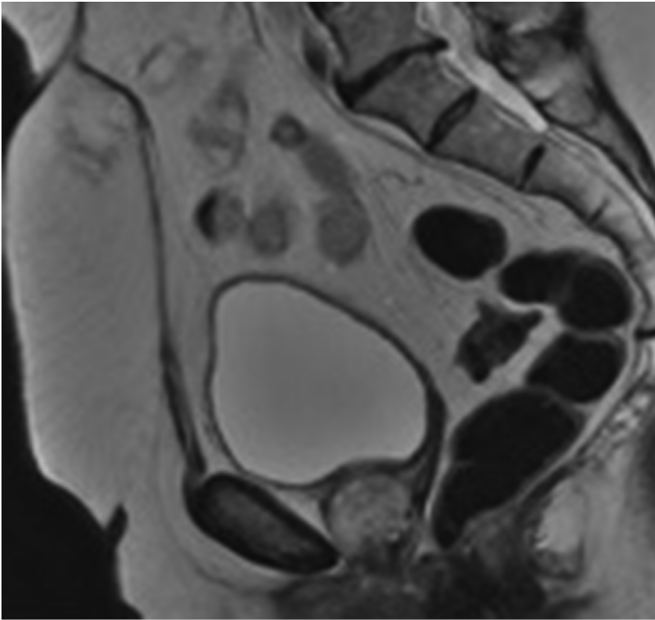


Fig. 1. MRI pelvis showing a large urethral mass $3.0 \times 2.9 \times 3.8$ cm with heterogeneous enhancement in bladder neck and urethra concerning for urethral neoplasm.

Discussion

Primary urethral cancer is rare and occurs more frequently in females with male to female ratio of 1:4³. Squamous cell carcinoma is the predominant histology in women, accounting for 70% of cases. Urothelial carcinoma is the second most common histologic type, accounting for 20% of cases. CCAU of the female urethra is extremely rare and represents 10% of all cases⁴ and is believed to originate from surface urothelial metaplasia or Mullerian rests.⁵ Alternative theories implicate periurethral (Skene's) glands or malignant transformation of nephrogenic adenoma.⁴

CCAU arises as a mass from urethral diverticulum and is thought to occur secondary to chronic inflammation and urinary stasis. Hematuria is the most frequent presenting symptom. Other symptoms may include urinary hesitancy, urinary incontinence, and recurrent urinary tract infection.⁵ A urethral diverticulum can be identified using ultrasound, CT, or MRI. CCAU is best evaluated with sagittal T2-weighted MRI images, where the tumor appears hyperintense. Tumors of the distal

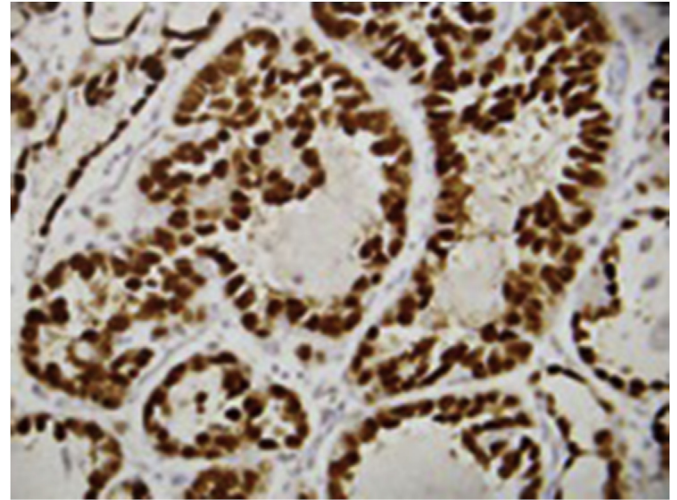


Fig. 3. The tumor cells show nuclear immunoreactivity for Pax-8: a marker usually expressed by clear cell carcinoma (40x).

urethra may extend into the adjacent perineum, distorting the target-like appearance of the normal urethra.³

A biopsy of the mass is the mainstay of diagnosis. CCAU has characteristic microscopic features including enlarged tumor cells containing abundant clear cytoplasm with conspicuous vacuoles, hobnail patterned cells, and hyaline globules. On immunohistochemistry, CCAU frequently stains positive for PAX2, PAX8, CK7, p16, p53, CA125 while exhibiting negative staining for PSA, PAP, CK20, p63, CD10⁵.

CCAU is generally diagnosed at advanced stages. The tumor spreads by local extension to affect the vagina or bladder neck. Lymphatic spread is infrequent. The most common sites of hematogenous spread include lung, liver, bone, and brain.³ Standard treatment consists of cystourethrectomy with pelvic lymph node dissection. Adjunct radiotherapy has been utilized in a few cases with pelvic lymph node involvement. Few reports support the use of chemotherapy in the treatment of CCAU.⁵

CCAU appears to be an aggressive tumor with low five-year survival rates and prognosis worsens with lymph node involvement. Few cases of CCAU have been reported and typically only include one-year patient follow up. There is no established surveillance and follow-up scheduled for CCAU. As there is no standard, this patient has received repeat imaging and cytology screening every 3 months in accordance with the National Comprehensive Cancer Network guidelines for follow-up of pT3 urothelial cancer.

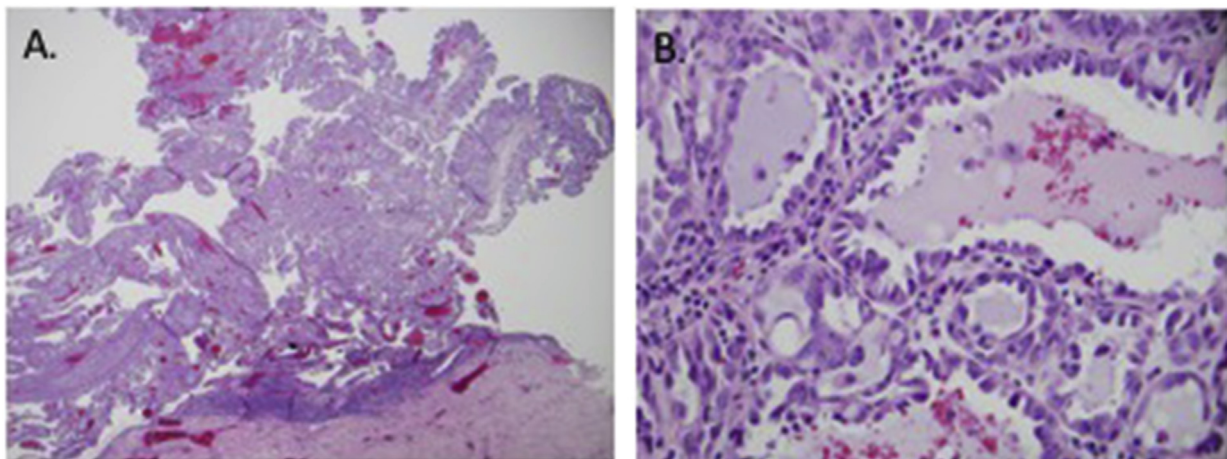


Fig. 2. A: Low power (4x) shows a carcinoma arising within urethra with an exophytic growth. B: High power (40x) shows the tumor with hobnail appearance: a morphological feature of clear cell carcinoma.

Conclusion

Clear cell adenocarcinoma of the female urethra is an extremely rare disease. Diagnosis is difficult to make clinically, therefore pathological and IHC staining are critical to ensuring an accurate diagnosis. Early radical surgery followed by radiation therapy achieved excellent oncologic outcomes at one year in this patient.

Conflicts of interest

None.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.eucr.2018.04.008>.

References

1. Satyanarayan A, Redd L, Dyer A, Wright A, Walker J. Adenocarcinoma of the urethra with mucinous features. *Rev Urol*. 2015;17(1):38–41.
2. Rane SR, Ghodke AN, Vishwasrao S. Clear cell adenocarcinoma of female urethra. *J Clin Diagn Res*. 2017 Jul;11(7):ED01–ED02.
3. Wang X, Bai P, Su H, Luo G, Zhong Z, Zhao X. Management of primary adenocarcinoma of the female urethra: report of two cases and review of the literature. *Oncol Lett*. 2012 Nov;4(5):951–954.
4. Mehra R, Vats P, Kalyana-Sundaram S, et al. Primary urethral clear-cell adenocarcinoma: comprehensive analysis by surgical pathology, cytopathology, and next-generation sequencing. *Am J Pathol*. 2014 Mar;184(3):584–591.
5. Venyo AK. Clear cell adenocarcinoma of the urethra: review of the literature. *Int J Surg Oncol*. 2015;2015:790235.