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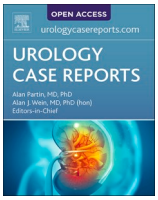

Oncology

Clear cell adenocarcinoma of the prostatic urethra with metachronous prostate adenocarcinoma

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A B S T R A C T

A 70-year-old male underwent a Transurethral Resection of Prostate for the management of obstructive voiding symptoms. On cystoscopy, papillary frond-like lesions up to 2cm in size were encountered, overlying the right side of the prostatic urethra. Histopathology from the resection revealed clear cell adenocarcinoma (CCA) of the prostatic urethra.

Primary clear cell adenocarcinoma of the prostatic urethra is exceedingly rare, with as few as 9 cases reported. We review the literature for its oncogenesis, discuss the histopathological features for diagnosis and report on our surgical management and outcome.

1. Introduction

Clear Cell Adenocarcinoma of the Urethra (CCAU) represents a rare uro-oncological entity. It occurs predominantly in females and has an association with urethral diverticuli.[1] It is exceedingly rare in the literature, with as few as 9 cases of CCAU reported to arise within the prostate or prostatic urethra.[2,3]

The histogenesis of this disease remains unclear. Current theories suggest the disease may derive from metaplastic urothelium or Mullerian rests.[4] Clinically, it is an aggressive cancer with a poor prognosis.[5] Optimal management is unclear due to its rarity.

2. Case presentation

A seventy-year-old underwent a re-do Transurethral Resection of Prostate (TURP) following recurrence of obstructive voiding symptoms. The patient was diagnosed with Grade Group 1 Acinar Adenocarcinoma of the Prostate 6 years earlier, managed with active surveillance. PSA was 5 ng/mL on diagnosis. Initial TURP was performed after this diagnosis, with benign prostatic hyperplasia histology. PSA was regularly monitored, with the most recent result being 1.7ng/mL.

On re-do TURP, multiple papillary frond-like lesions up to 2cm were seen overlying the right side of the prostatic urethra, causing obstruction. Histopathology demonstrated a mixture of exophytic papillary architecture and endophytic proliferation of small tubules within stroma [Fig. 1a]. The branching papillary processes and tubules were composed of clear and hobnail cells displaying mild to moderate nuclear pleomorphism and with scattered mitosis [Fig. 1b]. In some areas, the surface also showed squamous metaplasia. The stroma varied from sclerotic to oedematous with interspersed stromal smooth muscle amongst the tumour cells suggesting invasion.

Immunohistochemistry results included positive Keratin 7 (moderate to strong, extensive), PAX8 (strong, diffuse)[Fig. 2a], Napsin A (moderate to strong, patchy), AMACR (p504s, strong and diffuse), RCC Antigen (strong, extensive), CD10 (strong and patchy), Ki67 (10–20% overall; focal areas of 30%) [Fig. 2b]. Negative staining was noted with P63, GATA3, Keratin 20, NKX3.1 and P53 (wild type staining). ARID1A showed no loss of staining. Mismatch repair proteins for PSM2 and MSH6 were preserved.

Moderate cytologic atypia, significant clear cell population and areas of complex and solid growth with significant mitotic activity were consistent with primary Clear Cell Adenocarcinoma of the Prostatic Urethra.

Staging CT was performed with no metastases. The patient underwent an open radical cystoprostatectomy, urethrectomy, extended pelvic lymph node dissection and formation of ileal conduit [Fig. 3]. Histopathology demonstrated a 2mm focus of residual CCAU at the bladder neck and multifocal Grade Group 3 Acinar Adenocarcinoma with focal extraprostatic extension. Surgical margins were clear. All ten pelvic lymph nodes were negative.

At 6-months follow-up, the patient's PSA level was <0.01ng/mL and

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Abbreviations

CCA	Clear Cell Adenocarcinoma
CCAU	Clear Cell Adenocarcinoma of Urethra
TURP	Transurethral Resection of Prostate

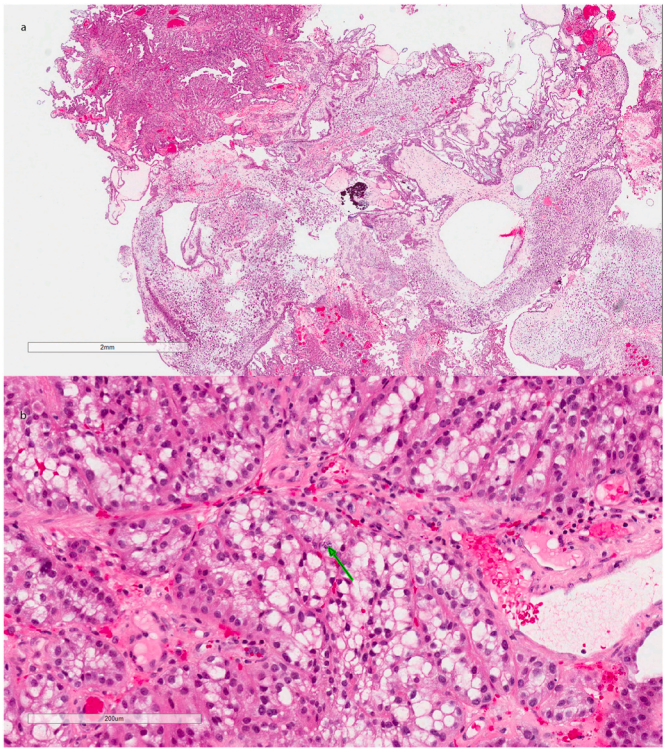

Fig. 1. (a) Polypoid exophytic tumour with complex papillary architecture and oedematous stroma
contains tubules (H&E 40X) and (b) clear cell carcinoma with moderate nuclear pleomorphism and mitotic figure (arrow; H&E 200X).

a progress CT Chest/Abdomen/Pelvis did not demonstrate recurrence or metastases.

3. Discussion

CCAU represents a rare and aggressive oncological disease. It occurs over 4-fold more commonly in females and is associated with urethral diverticuli.[1] As few as 9 cases have been reported in the prostate or prostatic urethra.[2,3]

Presenting symptoms for CCAU in males are most commonly gross haematuria (33%) and urinary retention (33%).[2] Mean age at diagnosis is 63 years (31–92 years).[5] It is an aggressive cancer with poor overall survival. A retrospective analysis of the National Cancer Institute's Surveillance, Epidemiology, and End Results database demonstrated a 2- and 5-year Overall Survival of 69.1% and 39.3%, and a 2- and 5-year Disease Specific Survival of 74.6%, and 46.7% respectively.[5] The largest CCAU series with long-term follow-up had a mortality of 4 out of 14 patients, at 35 months. Mean time to death was 16 months, and all 4 deceased patients had CCA of the prostate or prostatic urethra.[3]

The oncogenesis of CCAU remains unclear, with theories suggesting its origin as deriving from metaplastic urothelium or Mullerian rests. The cytopathological diagnosis of CCAU is challenging, requiring differentiation from other morphological entities including urothelial

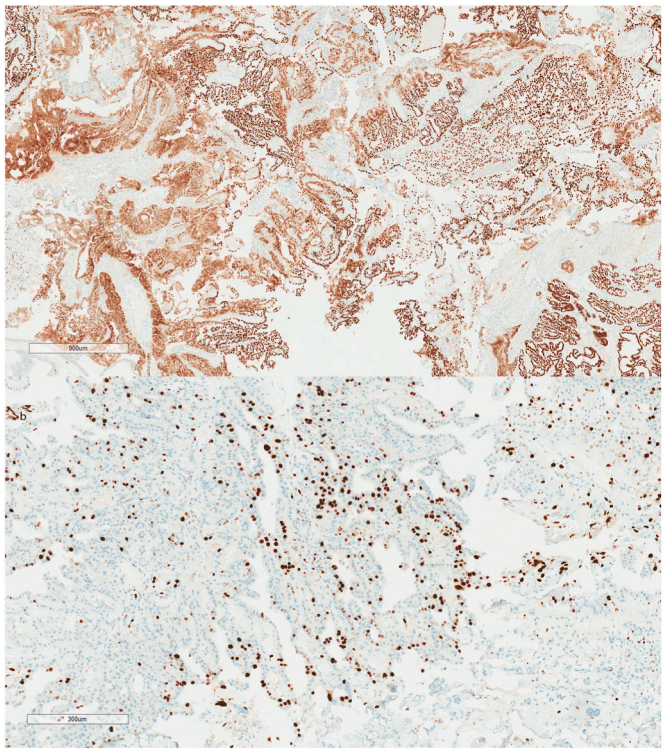

Fig. 2. (a) PAX8 positivity in the tumour and (b) increased Ki67 proliferation in the tumour (IHC).

carcinoma, metastatic clear cell RCC and nephrogenic adenomas.[4] Immunohistochemistry is an important tool in the diagnosis of CCAU. P53 positivity and high mitotic activity (Ki67 proliferation) favour CCA over Nephrogenic Adenoma. PAX8 favours CCA over Urothelial Carcinoma (associated with GATA3 and P63 positivity). Cytomorphological features include enlarged tumour cells with abundant clear cytoplasm, hobnail patterned cells and hyaline globules.[1] A triad of tubulocystic, papillary and diffuse pattern is also described. Next-generation sequencing has revealed insights into the molecular underpinnings of this disease, with findings including dysregulation of DNA damage response, chromatin remodelling and changes in signal pathways.[4]

In the only report describing endoscopic findings of CCA of the prostatic urethra, a diverticulum with multiple tumours was seen.[2] In our case, the tumours were exophytic in nature, covering the surface of the prostatic urethra. No cavity or diverticulum was uncovered during resection of the prostate.

CCAU has been managed with urethrectomy, radical cystectomy, transurethral resection, radiotherapy, chemotherapy or observation with mixed results.[1,2] Hormone, targeted and immunotherapy have been used in isolated cases.[3] The majority (80%) of CCAU cases underwent operative intervention, most commonly anterior exenteration and pelvic lymph node dissection.[1,3] Urethrectomy when performed, occurred in the setting of smaller tumours, and was suggested to be effective. Univariate and multivariate analysis demonstrated that surgical intervention was associated with a significant difference in overall and disease-specific survival.[5] Benefit was not seen with chemotherapy and radiotherapy, and the role of these interventions for CCAU remains unclear.

It is important to note that these cases are heterogeneous, and the small numbers involved are insufficient in drawing any definitive conclusions about ideal treatment. There may also be selection bias for operative intervention related to co-morbidity and age. Patients undergoing surgery were more likely to have regional disease.[5]

Increasing recognition and diagnosis of CCAU, and reports of patient outcomes will allow for more evidence-based decision making. More

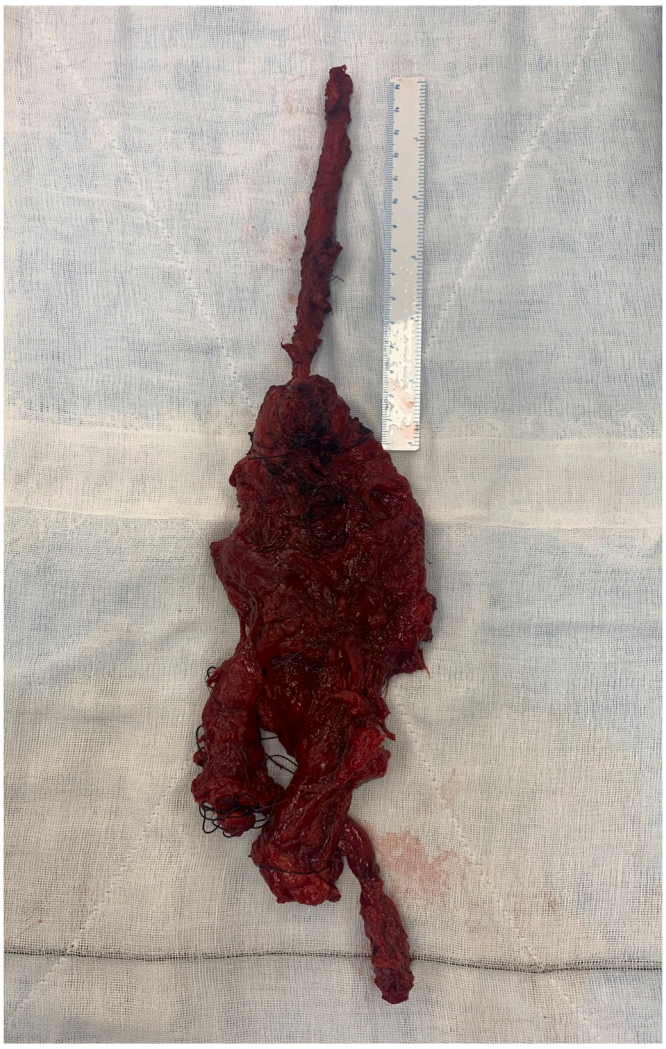

Fig. 3. Gross cystoprostatectomy and urethrectomy specimen.

research is required to determine the potential role of endoscopic interventions, chemotherapy, and radiotherapy. Finally, the significance of anatomical location and its impact on management and survival remains unclear.

4. Conclusion

We report a rare case of Clear Cell Adenocarcinoma of the Prostatic Urethra with metachronous Grade Group 3 prostatic acinar adenocarcinoma. Further data is required to enhance the available literature to help guide management in this exceedingly rare condition.

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Section headings

Oncology.

Consent

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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.

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