CASE REPORT
Pathology

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Male Urethral Clear Cell Adenocarcinoma: Case Presentation and Literature Review of a Rare Cancer

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Abstract

Primary urethral carcinomas account for less than one percent of all genitourinary cancers. Primary clear cell adenocarcinoma of the urethra (CCAU) is an extremely rare and aggressive tumor which predominantly presents in adult women but has rarely been documented in males. Diagnosis of CCAU is difficult as its clinical presentation shows significant overlap with various other conditions and carcinomas. Controversies remain regarding the histogenesis of CCAU. The histological diagnosis can be challenging and there are no definitive treatment guidelines. English literature to date only describes 17 previous cases of CCAU in males. Here we present an 18th case in a 29-year-old man.

Keywords: Clear cell adenocarcinoma, urethral cancer, nephrogenic metaplasia

Introduction

Urethral malignancies are rare, compromising less than one percent of all genitourinary cancers (1). Clear cell adenocarcinoma of the urethra (CCAU) is the least common subtype, which is an aggressive tumor with a poor five-year survival rate and a strong female predominance (2). Diagnosis of CCAU is difficult as it often clinically presents similar to various other conditions and carcinomas (2). One previous case series of CCAU raised the possibility of association with diverticula, documenting their presence in 12 of 18 cases (3). The histopathological origin of CCAU is poorly understood and many possible theories have been postulated, including origins from mesonephric (4), Müllerian duct (5) or pre-existing areas of nephrogenic metaplasia (6). As the pathophysiology of CCAU is not fully understood there has been no definitive treatment guideline. The literature to date only describes 17 previous cases of CCAU in males. Here we present an 18th case in a 29-year-old man.

Case Report

A 29-year-old male presented with several weeks of macroscopic hematuria and perineal pain. Urine microscopy showed sterile pyuria and the cytology was atypical flexible cystoscopy revealed multiple papillary lesions in his urethra and a normal bladder. Subsequently, rigid cystoscopy, biopsy and diathermy of the urethral tumors were performed. Histopathological assessment demonstrated a clear cell adenocarcinoma, with superficial invasion of the lamina propria. The tumor had a tubulopapillary architecture and comprised large pleomorphic cells with hobnail cytology, eosinophilic cytoplasm, and areas of cytoplasmic clearing (Figure 1). A panel of immunohistochemical (IHC) stains was performed, with the tumour cells showing diffuse strong positive staining for PAX8, CK7, and p53, with MIB1 (Ki-67) staining 75% of tumour nuclei. There was no significant staining within the tumour cells for CK20 or GATA3. The morphology and IHC staining pattern were in keeping with a diagnosis of CCAU.

Magnetic resonance imaging (MRI) showed no significant invasive lesions in the urethra and staging computed tomography (CT) demonstrated no metastatic disease. The patient declined a cystoprostourethectomy and after a multi-disciplinary discussion, underwent a urethrectomy, apical prostatectomy and suprapubic catheter insertion. Despite the MRI findings, histopathology of the excision specimen did show the CCAU invaded the lamina propria of the urethra. No muscularis propria invasion was identified.

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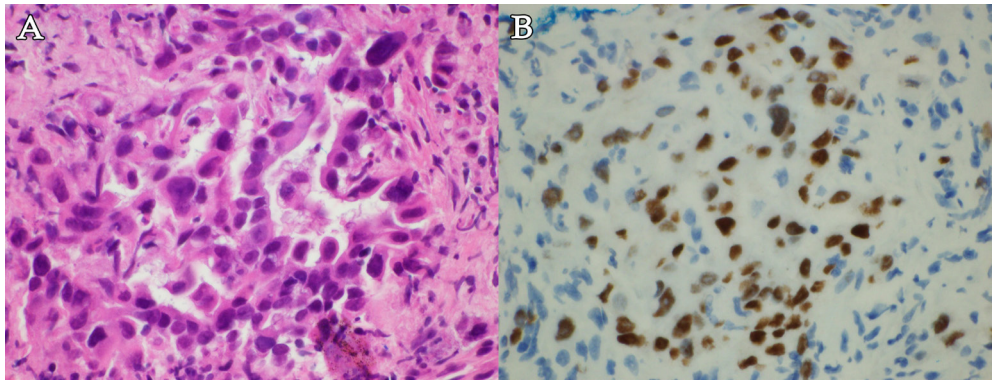

Figure 1. Clear cell adenocarcinoma of the urethra showing hobnailed cells in a tubulopapillary arrangement (A, Haematoxylin and eosin, 600x magnification), showing positivity for PAX8 (B, 600x magnification)

The patient was subsequently placed on a surveillance program, which comprised six-monthly cystoscopy and CT scans. Two and half years later, he was diagnosed with dyspnea. A CT at that time demonstrated mediastinal lymphadenopathy, pericardial and pleural effusions, and abnormal interstitial markings suggestive of diffuse lymphangitic disease within the lungs. Cytology and IHC of the pericardial fluid demonstrated metastatic clear cell adenocarcinoma.

He received four cycles of gemcitabine and cisplatin chemotherapy with complete radiological remission. Twenty months after chemotherapy, he developed metastatic disease to his left adrenal gland and pembrolizumab was started. There was no response and disease progression was shown on positron emission tomography-CT in the adrenal with new metastases in the para-aortic lymph nodes and liver. He was enrolled in a clinical trial and completed 6 cycles of enfortumab vedotin with further progression. Further gemcitabine and cisplatin treatment was associated with a significant radiological response, but isolated relapse occurred in the paraaortic nodes eight months later, treated with radiotherapy. Fifteen months further recurrence occurred in the kidney and liver that again responded platinum-based chemotherapy. Next-generation sequencing of the primary urethral tumour DNA revealed a mutation in SMARCB1 (p.T9Dfs*61NM_001007468.1 c.23dup, reflected by lack of staining for INI-1/SMARCB1 IHC). After further progression, he was started on tazemetostat, an inhibitor of enhancer of zeste-homolog-2 (EZH2), without response. He is currently relatively well and active, and on platinum-based chemotherapy awaiting a suitable phase 1 trial. Written and informed consent was obtained from the patient for the publication.

Discussion

CCAU is a rare and aggressive carcinoma that predominantly affects females in 60-70 s (2). As with our case, CCAU typically present like a urothelial carcinoma with non-specific irritative or obstructive urinary symptoms including hematuria, frequency and dysuria. Histopathological features characteristic of CCAU include hobnail cells, clear cytoplasm and pleomorphic nuclei and mitotic figures (2,3,7). CCAU tumour cells exhibit a classic triad of tubulocystic, papillary and diffuse growth patterns, in variable proportions (2). The mainstay treatment for CCAU is surgical resection and in cases with pelvic lymph node involvement, radiotherapy may be of benefit, however there is a paucity of the literature surrounding the effectiveness of chemotherapy.

The histogenesis of CCAU is unclear, it was first described in 1973 by Konnak (4), who used the term "mesonephric carcinoma" postulating a mesonephric origin. However, most authors have suggested that CCAU most likely arises from a Müllerian (paramesonephric) origin (5,8,9) or areas of nephrogenic metaplasia, due to the morphologic and IHC overlap with the latter (6,10). Nephrogenic metaplasia/adenoma is a benign condition which is believed to arise in areas of chronic irritation or infection, and is most commonly seen in adult males (2,3,11). Interestingly, in renal transplant patients, nephrogenic adenomas have been shown to originate from the tubular epithelium of the donor kidney (12). In contrast, Kawano et al. (13), hypothesized that CCAU in females is an entirely separate entity, arising from the para-urethral ducts. Additionally, there appears to be an association between CCAU and urethral diverticulum, with possibly up to 56% of cases in females presenting in such a manner (3).

The relationship between nephrogenic metaplasia and clear cell adenocarcinoma remains controversial. Generally, nephrogenic metaplasia is usually thought of as benign though some evidence exists for its malignant potential (11). For example, Hartmann et al. (10), presented molecular evidence of the progression of nephrogenic metaplasia to clear cell adenocarcinoma in the urinary bladder. To date, in English literature, there have only been 17 reported cases of urethral clear cell adenocarcinoma in males (Table 1) with no clear demonstrable relationship

Table 1. Summary of Urethral clear cell adenocarcinoma in male patients

Reference	Age	Symptoms	Immunohistochemistry/ Special stains	Postulated origin	Therapy	Relapse	Metastases	Survival
Cantrell et al. (8)	68	Painless haematuria	Positive: PAS	Mesonephric or Mullerian	Pelvis lymphadenectomy + Radiation	20 months	Thoracic vertebrae, pulmonary hilar adenopathy	2.6 years
Ingram and DePauw (19)	38	Recurrent urethral stricture	NR	Nephrogenic metaplasia	Surgery	Nil	Nil	Alive, 5 years post-surgery
Oliva and Young (3)	46	Urinary retention	NR	NR	Biopsy + radiation	NR	NR	NR
Seseke et al. (6)	57	Urinary retention	Positive: PAS	Nephrogenic metaplasia	Total urethrectomy	10 months	Pulmonary	2.5 years
Gögus et al. (15)	44	Urinary retention	Negative: PSA	NR	Radical cystoprostatectomy and urethrectomy + chemotherapy	5 months	Para-aortic lymphadenopathy	10 months
Varachhia et al. (20)	68	Periurethral abscess	NR	NR	Drainage/debridement of abscess only	NR	Nil	2 months
Liu et al. (18)	37	Urinary hesitancy	Positive: CK7, CAM 5.2 Negative: CK20, AFP, CDX-2, PSA	NR	Surgery + palliative chemotherapy	15 months	Iliac, inguinal, supraclavicular, mediastinal, and hilar lymphadenopathy, pulmonary	2.4 years
Gandhi et al. (16)	55	Recurrent urinary tract infections	Positive: PSA, PSAP, CA125 Negative: p63, CK20	Paraurethral	Radical cysto-prostatourethrectomy + chemotherapy	NR	NR	NR
Sugimura et al. (21)	56	Haematuria	Positive: CK7, PAX-8, CK20, CK-HMW Negative: p63, PSA	NR	Radical cystectomy	NR	NR	Alive, 5 months post-surgery
Lin et al. (22)	31		Positive: PAX-8 Negative: TTF-1	Oncogenic (PI3K/ AKT/mTOR)	Radical cystectomy and urethrectomy	28 months	Lung	NR
Grosser et al. (17)	29	NR	Positive: PAX-8	NR	Urethrectomy + chemotherapy	NR	Mediastinal lymphadenopathy, lung and adrenal	Alive, 3 years post-surgery
Grosser et al. (17)	45	NR	Positive: PAX-8	NR	Transurethral resection + radiotherapy (for recurrence)	NR	NR	NR
Grosser et al. (17)	47	NR	Positive: PAX-8	NR	Cystoprostatectomy and lymph node dissection, sigmoid colon and rectum resection	NR	Extension to bladder and rectum	10 months
Grosser et al. (17)	36	NR	Positive: PAX-8	NR	Planned surgery	NR	Nil	Lost to follow-up
Our case	29	Haematuria	Positive: PAX8, CK7, and p53, with MIB1 75% Negative: CK20, GATA3, INI1/SMARCB1	Nephrogenic metaplasia	Urethrectomy, apical prostatectomy, SPC + chemotherapy + immunotherapy	18 months	Mediastinal, para-aortic and coeliac lymphadenopathy, adrenal, liver	Alive, 7 years post-surgery

NR: Not reported [3 further male cases were not included as no details were provided (23)]

to nephrogenic metaplasia. Here we present an interesting case of a male patient with evidence of both CCAU and nephrogenic metaplasia, which unfortunately progressed to distant metastasis. Furthermore, our case is the only one in the literature in which demonstrates a mutation in SMARCB1 and loss of INI1. Mehra et al. (14), demonstrated a dysregulation in different genetic/molecular pathways (ATM, ARID2). Whether nephrogenic metaplasia exists concurrently with CCAU or serves as a precursor to CCAU requires further study.

Despite the limited number of reported cases of CCAU in males, the prognosis is poor. Of the 17 previously reported cases, only three reported long-term survival past three years. Most of these cases presented with either irritative or obstructive symptoms and were treated with surgery and radiotherapy or chemotherapy. Seven patients progressed to distant metastases despite therapy. Only four patients received cisplatin-based chemotherapy; however three patients succumbed to progressive disease (15-18). In this study, the patient's tumor seemed extremely sensitive to platinum-based chemotherapy but resistant to anti-PD-1 immunotherapy and a novel EZH2 inhibitor. This case report demonstrates to our knowledge the 18th case of CCAU in a male patient who appears responsive to cisplatin-gemcitabine chemotherapy, partially responsive to immunotherapy, and is also the longest surviving CCAU patient in the literature.

Conclusion

Our case contributes to the current limited literature that shows that CCAU is an aggressive cancer and often presents with lower urinary tract symptoms. These patients should be closely monitored with regular surveillance for the development of local and distant metastases and managed with a multi-disciplinary input. Further studies are required to identify its relationship to nephrogenic metaplasia, which may reveal more robust treatment options.

Ethics

Informed Consent: Written and informed consent was obtained from the patient for the publication.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: J.K., F.M., H.G., M.A., Concept: B.R., J.K., F.M., H.G., M.A., Design: B.R., J.K., F.M., H.G., M.A., Data Collection or Processing: B.R., J.K., F.M., H.G., M.A., Analysis or Interpretation: B.R., J.K., F.M., H.G., M.A., Literature Search: B.R., J.K., F.M., Writing: B.R., J.K., F.M., H.G., M.A.

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