Case - Successful treatment of a SMARCA-4-deficient undifferentiated urethral cancer

Abrahim Chidiac[1], Lori A. Wood[1,2], Hannah Dahn[3], Kelly Dakin-Hache[4], Cheng Wang[1,4], Lana Saciragic[5], Ross Mason[1]

[1]Department of Urology, Dalhousie University, Halifax, NS, Canada; [2]Department of Medicine, Dalhousie University, Halifax, NS, Canada; [3]Department of Radiation Oncology, Dalhousie University, Halifax, NS, Canada; [4]Department of Pathology, Dalhousie University, Halifax, NS, Canada; [5]Department of Obstetrics and Gynecology, Dalhousie University, Halifax, NS, Canada

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Corresponding Author: Dr. Ross Mason, Department of Urology, Dalhousie University, Halifax, NS, Canada; ross.mason@dal.ca

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INTRODUCTION

Herein, we describe a case of a SMARCA4-deficient undifferentiated urethral tumour in a 64-year-old female who initially presented to her local emergency department in urinary retention. This case presents the first known report of a urethral origin SMARCA4-UT, which was successfully treated with neoadjuvant immunotherapy, radiation, then followed by consolidative surgery.

KEY MESSAGES

- SMARCA4-deficient undifferentiated tumors are newly characterized, highly aggressive tumours with poor prognosis that typically originate in the thoracic region.
- Treatment guidelines are not well established due to tumour rarity and discovery at late stages of disease.
- Immunotherapy appears to have the most impact on these tumour entities, with limited role of conventional cytotoxic drugs.
- Neoadjuvant immunotherapy, radiation therapy, and consolidative surgery are a promising treatment modality for consideration in future instances of SMARCA4-UT of at least urethral origin.

CASE REPORT

A 64-year-old female presented to her local emergency department in acute urinary retention requiring catheterization. She described several months' history of worsening urinary frequency and urgency prior to presentation. Physical exam revealed a firm fixed mass inseparable from the anterior vagina and urethra, although catheterization was uncomplicated. A computed tomography (CT) scan revealed a complex heterogenous lesion arising from the pelvis (Figure

1a). The lesion was inseparable from the uterus, vagina, bladder, and right ureter, resulting in mild right-sided hydroureter. Cystoscopy demonstrated a large mass arising from either the posterior urethra or anterior vagina. There was mass effect on the bladder, with intact overlying bladder mucosa.

Pelvic magnetic resonance imaging (MRI) was performed demonstrating a 7.4cm x 5.9cm x 5.7cm pelvic mass along the expected course of the urethra, with a 1.2cm nodule on the right external iliac artery, potentially consistent with metastatic nodal disease (Figure 1b).

A CT-guided 7-core biopsy was performed. The histological sections showed cores of cytologically malignant and mitotically active loosely cohesive histiocytoid cells arranged in sheets and vague nests with areas of necrosis (Figure 2). Extensive immunohistochemical evaluation showed expression of SALL4 (moderate to strong; 40%), vimentin (strong; 100%); CD34 (strong; 100%), cyclinD1 (strong; 100%), AE1/AE3 (rare dot), and synaptophysin (weak; 40-50%). The Ki-67 was ~100%. The LCA, CD30, ALK(5A4), OCT4, S100, SOX10, MDM2, ERG, BCOR, NUT-1, PAX8, and WT1, as well as a broad spectrum of other markers, were negative. There was retained nuclear expression of SMARCB1 (INI-1) and loss of SMARCA4 (BRG-1) nuclear expression (Figure 3). The unusual immunohistochemical profile combined with the loss of BRG1 nuclear expression suggested a tumor in the spectrum of SMARCA4 deficient undifferentiated tumor.

No metastases were noted on chest CT and positron emission tomography (PET). The mass itself demonstrated high avidity for fluorodeoxyglucose (FDG) on PET, while the enlarged pelvic lymph node did not.

After multidisciplinary consultations and discussion, she went on to complete 4-cycles of neoadjuvant immunotherapy, followed by radiation and consolidative surgical excision.

Neoadjuvant immunotherapy involved ipilimumab 1 mg/kg and nivolumab 3 mg/kg every 21 days for 4 cycles. Following cycle 2, in addition to clinical improvement, repeat pelvic MRI after demonstrated positive treatment response, with the tumour measuring 5.1cm in maximum diameter. Following the 4^{th} cycle, CT imaging showed continued positive response, with the mass measuring 4.4cm in maximum diameter.

Once neoadjuvant immunotherapy was completed, discussion ensued regarding proceeding with radiation alone or concurrently with chemotherapy. Chemoradiation began with cisplatin 40mg/m^2 weekly. Unfortunately, after the first dose of cisplatin, the patient presented to the emergency room with nausea, vomiting, and dizziness, requiring admission. She was subsequently diagnosed with immune mediated adrenal insufficiency and improved significantly with appropriate steroid replacement. Chemotherapy was halted, but radiation therapy was completed as planned with 25 fractions over 46 days, with a dosage of 50 Gray (Gy) being delivered to the urethral tumour region and 45Gy being delivered to the pelvic and inguinal lymph nodes using a two-level simultaneous integrated boost (SIB) volumetric modulated arc therapy (VMAT) plan with 6 Megavoltage (MV) photons. Radiation was tolerated well, with

minor mucositis within the urethra and diarrhea towards the end of treatment. Repeat pelvic CT scan was obtained showing no evidence of metastatic disease and the mass now measured 3.7cm in maximum diameter.

Five weeks post-radiotherapy, the patient underwent consolidative surgical excision involving an en-bloc radical cystectomy, urethrectomy, hysterectomy with bilateral salpingo-oophorectomy, and total vaginectomy with accompanying bilateral pelvic lymph node dissection and ileal conduit diversion. Final pathological examination revealed no residual active disease, ypT0N0, and negative surgical margins. The initial treatment plan included further single agent nivolumab post-operatively as well as a radiation boost to any positive margins; however, given the complete pathological response, close surveillance was chosen as the management strategy.

Delayed toxicity included bilateral hip fractures requiring arthroplasty, and bilateral ureterointestinal structuring managed with indwelling ureteral stents. At 20 months follow-up, the patient is free from recurrence or metastatic disease.

DISCUSSION

To our knowledge, this is the first case of a SMARCA4-UT of urethral origin. The treatment plan was developed through literature review, multidisciplinary discussion, and input from the patient and her family. There is no evidence of recurrence after 20-months of follow-up.

SMARCA4-UTs are a newly described, highly aggressive, tumour entity with poor prognosis and limited treatment evidence. The largest studies on treatment response of SMARCA4-UTs suggest immunotherapy may be superior to other modalities. A retrospective analysis by Shinno and Masuda (2022) of 18 patients with thoracic origin SMARCA4 deficient tumours showed promising results of immune checkpoint inhibitors (ICI) as first-line therapy.[7] Of these 18 patients, 12 received ICI, and 5 received it as first-line therapy; all 5 showed partial response, suggesting that PD-1/PD-L1 inhibitors impact SMARCA4-UTs.[7] A larger study by Zhou et al. (2024) examined 35 patients with thoracic origin SMARCA4-UTs and found similar results.[8] Despite overall unfavourable outcomes, immunotherapy recipients had better overall survival and progression-free survival compared to those who did not.[8] Our patient responded after 2 cycles with significant reduction in tumor size and clinical improvement. Tumour size decrease was even more marked after 4 cycles, supporting the efficacy of ICIs on at least some SMARCA4-UTs.

Most SMARCA4-UTs present in advanced stages and progress rapidly, rendering surgical resection alone rarely sufficient. Iguchi et al. reported a case of a 68-year-old male with pulmonary origin SMARCA4-UT treated with surgical resection alone without neoadjuvant or adjuvant therapy, and died 4-months post-operatively due to distant metastases.[9] Conversely, approaches involving neoadjuvant immunotherapies and radiation therapies followed by definitive surgical intervention have shown promise in the treatment of SMARCA4-UTs.[10] Similar to our case report, Kunimasa et al. (2022) described a case of thoracic origin SMARCA4-UT with vertebral invasion treated with neoadjuvant ICIs, paclitaxel, and

carboplatin before surgical excision.[10] We observed significant decrease in tumour size using neoadjuvant immunotherapy and radiotherapy, as did Kunimasa et al., who stated that neoadjuvant therapy enabled successful surgical excision.[10] Further, Kunimasa et al. did not employ adjuvant therapy, and did not see recurrence for 9 months.[10] Similarly, our patient did not demonstrate post-operative recurrence of their tumour.

Our patient received trimodal therapy, ending with surgical consolidation and complete pathological response. As such, the benefit of surgery in this case remains uncertain, as well as the benefit of radiation. However, in a rare disease entity with limited guiding evidence, and after a fully informed discussion with the patient, maximal neoadjuvant therapy with complete excision if feasible, seems like a reasonable inclusion into the treatment pathway.

CONCLUSIONS

This case is, to our knowledge, the first of a SMARCA-4 deficient tumour of urethral origin in a 64-year-old female. She was successfully treated with neoadjuvant ipilimumab-nivolumab immunotherapy, radiation therapy, and then consolidative surgery, demonstrating a viable treatment pathway for these rare tumours.

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FIGURES AND TABLES

Figure 1A, 1B. Computed tomography and magnetic resonance imaging, respectively, showing a large multi-located mass centered around the urethra.

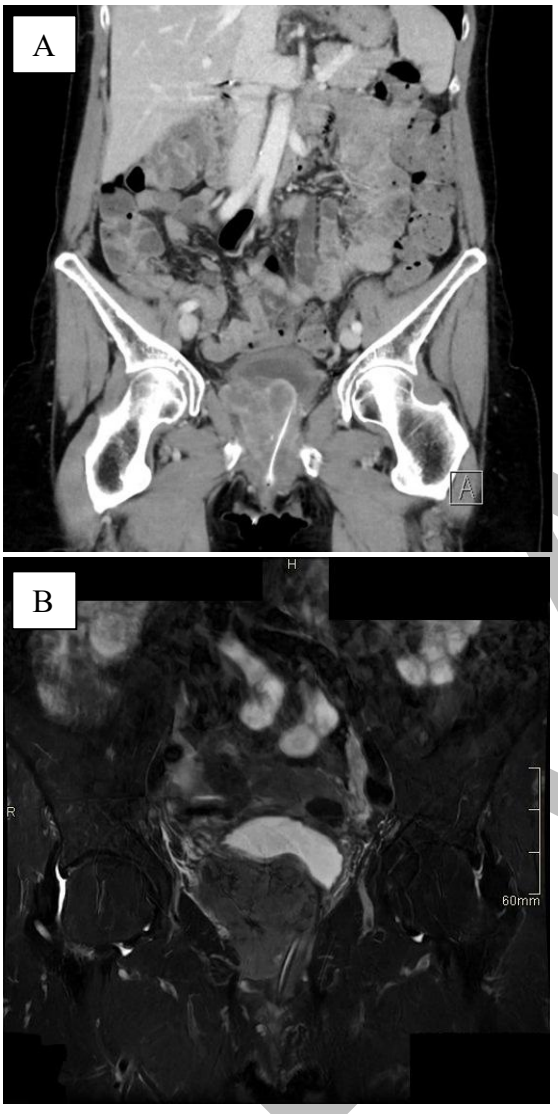

Figure 2. Neoplastic cells arranged within fibrous background with scattered inflammatory cells. The neoplastic cells have ill-defined cell borders, amphophilic cytoplasm, irregularly shaped nuclei, fine chromatin, and macronucleoli.

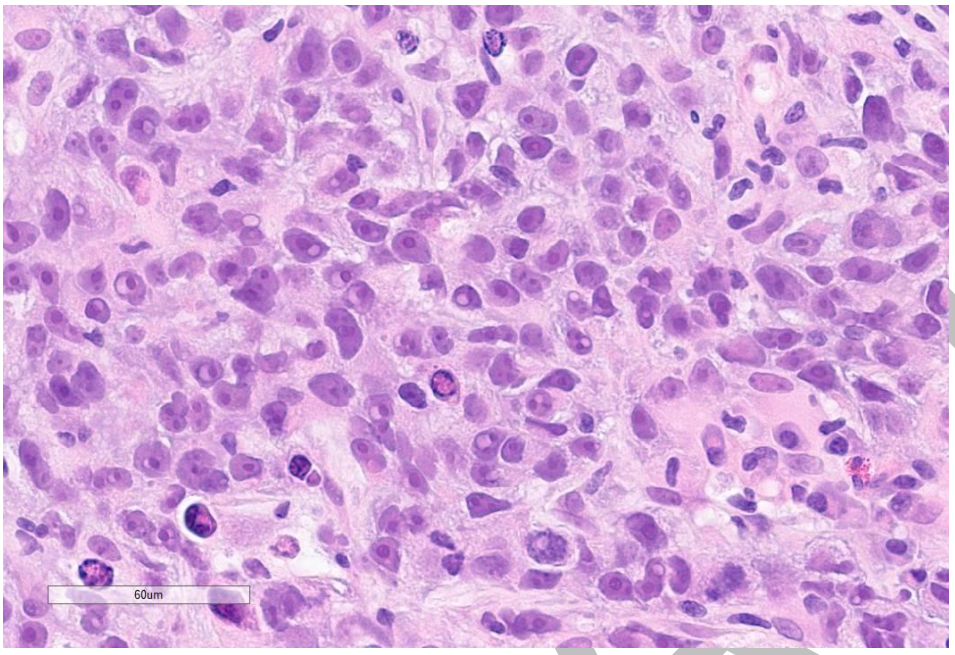

Figure 3. Immunohistochemistry shows loss of BRG-1 nuclear expression with appropriate internal control expression in non-neoplastic (stromal and inflammatory) cells.