Complete pathologic response of bulbar urethral squamous cell carcinoma in situ to topical 5-fluorouracil with urethral milking

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Primary urethral carcinoma is a rare oncologic condition with limited data to support organ-sparing therapies. Herein, we present a case of primary urethral squamous cell carcinoma in situ of the bulbar urethra treated with intraurethral 5-fluorouracil (5-FU) who exhibited a complete pathologic response observed at the time of dismembered urethroplasty. The clinical features, diagnosis, and treatment course of our case are reviewed. These data may support the use of intraurethral 5-FU for similar cases in the future.

Key Words: squamous cell carcinoma, urethra, urethroplasty, primary urethral carcinoma

Introduction

Primary urethral carcinoma accounts for < 1% of all malignancies with an annual incidence of only about 700 cases per year.[1-3] Management of lesions in the bulbar urethra has proven particularly challenging given the anatomic consequences of interventions in this location. Topical therapy has largely been limited to more distal urethral cancers.[1-3] Consequently, more proximal lesions are often managed with cystoprostatectomy with en bloc urethrectomy and urinary diversion. However, given the considerable morbidity of this approach, recent efforts have focused on appropriately selecting candidates for organ-preserving therapies.[1] We report a case of squamous cell carcinoma in situ of the bulbar urethra treated with 5-fluorouracil (5-FU) who was found to exhibit a complete pathologic response at the time of dismembered bulbar urethroplasty. These data may be useful to guide organ-sparing therapies to other similar patients in the future.

Case report

A 67-year-old man was referred for evaluation of long-standing and worsening urinary urgency, frequency, and incomplete emptying. He had tried tamsulosin which did not relieve any of his symptoms. At the time of evaluation, exam revealed no palpable inguinal adenopathy. The patient's penis was circumcised without plaques or nodule and he had a normal scrotal and testicular exam. The patient had no abdominal or urological surgeries prior to his lower urinary tract symptom evaluation.

Cystoscopy revealed a bulbar urethral stricture which was subsequently biopsied due to the frondular appearance of the stricture. Pathologic examination revealed squamous cell carcinoma in situ without definite evidence of invasion. Changes of squamous

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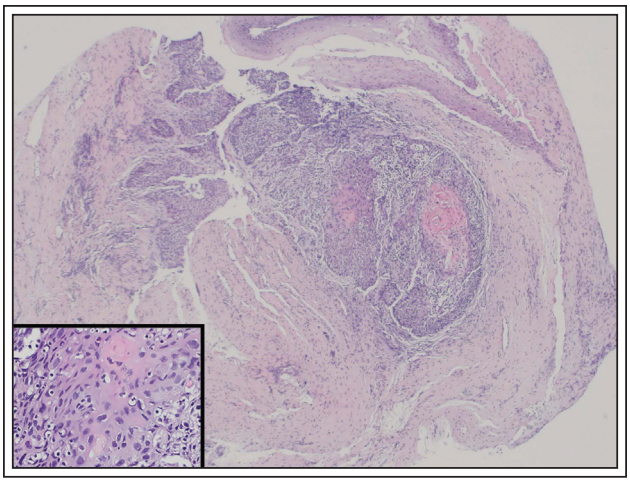

Figure 1. Squamous cell carcinoma in situ. Low and high power.

metaplasia associated with mild chronic inflammation and scattered mildly atypical squamous cells were also seen in adjacent urethral mucosa, Figure 1. Focal macrophage aggregates were present (not shown) in separate fragments compatible with prior biopsy site with cytokeratin immunohistochemistry negative for evidence of invasive tumor. A pelvic MRI with and without contrast revealed no pelvic lymphadenopathy or locally advanced disease around the time of initial surgery, Figure 2.

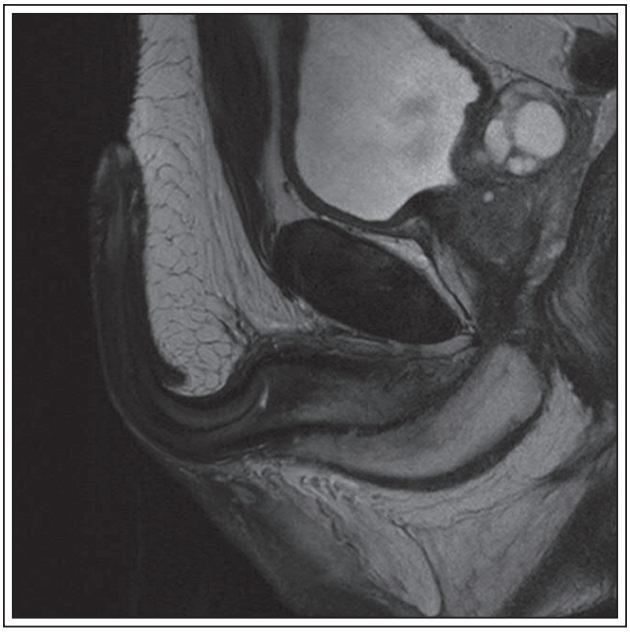

Figure 2. Pelvic MRI showing no lymphadenopathy or signs of locally advanced disease.

An in-depth discussion about treatment options was undertaken. The patient wanted to avoid any resection of penile tissue and wanted to avoid urethrectomy. We then discussed the option of 5-FU instillation to chemoablate the tumor as the least invasive potential option as has been previously described in urethral tumors.[4] The patient elected for this. We explained this would be an off-label treatment; however, the patient greatly desired urethral-sparing surgery. The patient started this therapy approximately 1 month after biopsy was performed.

Recognizing the potential difficulty of ensuring topical agents contacted the bulbar urethra, the patient was taught to self-administer this along with urethral milking. We began by inserting approximately 2 mL of lidocaine gel into the urethra and having the patient maintain the gel in the urethra for 5 minutes before milking out as much gel as possible. We then drew up 4 mL of 5% 5-FU cream into 10 cc syringe. The 10 cc syringe was attached to a urethral applicator which had already been placed into the distal urethra. The patient was then taught to milk the medication from the pendulous urethra back toward and into the bulbar and membranous urethral regions. We had the patient physically hold the 5-FU in the urethra with compression of the distal urethra between his fingers for at least 10 minutes before release. The patient wore gloves with each application and cleaned the genital area after each application. He performed this every other day for 10 days. After the first 10 days, the patient began application of the 5-FU daily for approximately 5 weeks. In all, the patient had approximately 45 days of treatment. We utilized an every-other day approach for the first 10 days to ensure the patient could tolerate the topical treatment from a toxicity standpoint. We decided on a 45-day 5-FU treatment course as 6-8 weeks of treatment for squamous cell carcinoma has been reported as sufficient in dermatology literature and in literature on non-invasive penile squamous cell carcinoma in situ.[5,6]

Repeat cystoscopy with biopsy 1 week after final 5-FU application revealed a stricture around the previously found cancer but multiple biopsies of the area were benign with no gross or pathologic evidence of cancer recurrence. About 3 months later (6 months after the original positive biopsy), another MRI and cystoscopy confirmed no evidence of cancer in the urethra or pelvis; however, there was stricture disease confirmed in the bulbar urethra. The patient had incomplete emptying and an acute episode of urinary retention. This reinforced the progression of the stricture disease. The patient had a suprapubic tube placed with plans to perform end primary anastomosis

urethroplasty to ensure no residual cancer was present and to address the stricture disease.

Prior to urethroplasty, a voiding cystourethrogram was performed via the suprapubic catheter. Another MRI of the pelvis did not reveal local or systemic recurrence.

Segmental urethrectomy with end-to-end primary anastomotic urethroplasty was performed. A 20-French Foley catheter was left in the bladder and exited via the native urethra. A frozen section of urethral margin was sent and noted to be negative for malignancy. The patient was discharged postoperative day 0. Final pathology of the urethral stricture revealed patchy mild chronic inflammation with no evidence of malignancy.

The patient's postoperative course was complicated by pseudomonas urinary tract infection managed with antibiotics. The patient returned for catheter removal approximately 3 weeks after urethroplasty for voiding cystourethrogram (VCUG) and catheter removal. The urethra was normal caliber with no contrast extravasation, Figure 3. The patient was able to void spontaneously and a bladder scan of 5 mL after voiding. Follow up at 6 months after catheter removal was arranged with a pelvic MRI which showed no evidence of local disease. In addition, patient had no voiding symptoms at that time and had a negligible post-void residual. A follow up plan of cystoscopy every 3-6 months with MRI once yearly was arranged for the patient.

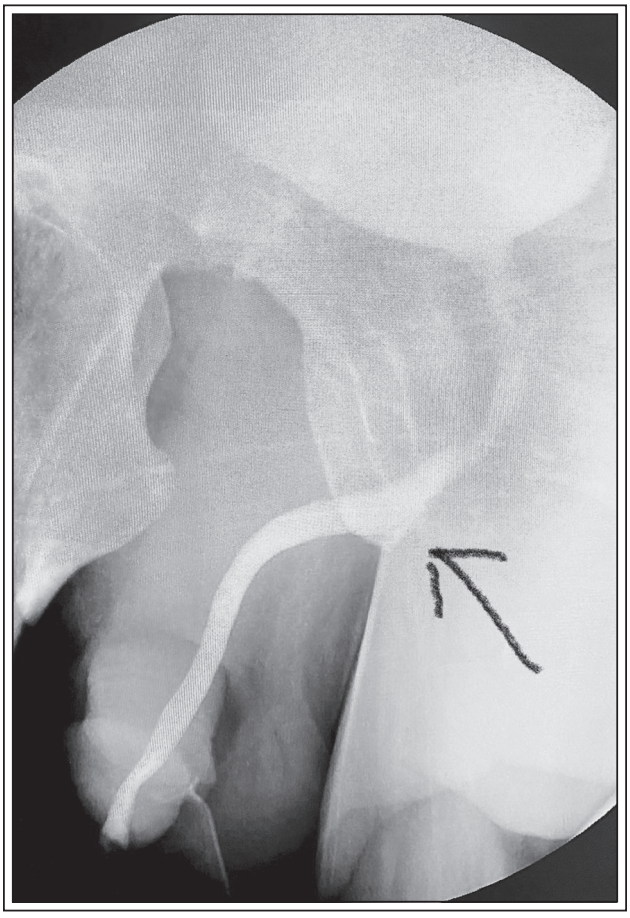

Figure 3. VCUG of normal caliber urethra with no contrast extravasation.

Discussion

Primary urethral squamous cell carcinoma is a rare malignancy which typically presents with voiding symptoms and microscopic or gross hematuria. Distal urethral tumors can be considered for partial urethrectomy or topical therapies to preserve penile tissues; however, there is a paucity of data on urethral-sparing techniques for proximal lesions. Herein, we report a case of squamous cell carcinoma in situ of the bulbar urethra with a complete pathologic response to 5-FU administered with urethral milking which demonstrates the potential viability of this treatment approach in appropriately selected patients.

Risk factors for urethral carcinoma include predisposing factors such as urethral strictures, chronic urethral irritation, radiation therapy exposure, inflammation, and infection such as that seen with human papilloma virus.[1,7,8] MRI can be utilized to evaluate local tumor extent as well as extent of any nodal or metastatic disease in the pelvis.[1,9] Indeed, the European Association of Urology recommends pelvic MRI to assess local disease as we utilized in our case.[1]

Localized primary urethral carcinoma found in the proximal male urethra often requires radical surgery including urethrectomy with or without concurrent cystoprostatectomy and urinary diversion.[1,2] Our patient strongly desired a urethral and penile-sparing approach. After reviewing urology literature, we noted the use of topical therapies in the distal urethra.[1-3] Additionally, dermatologic literature noted that 6-8 weeks of topical 5-FU was typically sufficient for non-invasive penile squamous cell carcinoma in situ.[5,6] Based on the patient's work up he was noted to have localized disease, so we chose to extrapolate other urologic and dermatologic data to this primary urethral carcinoma.

Our case certainly has its limitations. Approximately 12 months of follow up have been performed at this point so there is uncertainty about the durability of the response to 5-FU. Additionally, we only have one patient in our practice for whom we have utilized this method. Theoretically, the patient could have been treated completely with biopsy alone; however,

we do believe the 5-FU assisted in treating areas near the lesion. Unfortunately, our patient also required urethroplasty for symptomatic stricture disease. While this surgery did confirm a response to our treatment, it was an additionally surgery the patient needed, further enforcing the possible side effects to 5-FU.

Conclusion

We present a novel complete pathologic response to the use of intraurethral 5-FU, opening the door for this method and agent as a potential organ-sparing option in the treatment of urethral carcinoma. While primary urethral carcinoma is rare, urologists should be aware of appropriate diagnostic testing and treatment options. □

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