Urethral carcinoma after skin substitution urethral reconstruction

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Urethral cancer after urethral reconstruction is an under-recognized, uncommon disease associated with significant morbidity and mortality. The survival rates of patients with carcinoma of the bulbar urethra are as low as 20%-30%. Stricture recurrence and unrecognized malignant changes present prior to reconstruction are major risk factors for urethral cancer. Skin substitution urethroplasty is subjected to higher rates of recurrence, which lends to the potential for carcinogenesis. We present a case of a 59-year-old male who underwent multi-stage skin substitution urethroplasty who developed urethral carcinoma 20 years later.

Key Words: urethral reconstruction, urethral cancer, skin graft, urethral stricture

Introduction

Urethral reconstruction is the gold-standard surgical treatment for urethral stricture disease which underwent significant evolutions in the last few decades with the development of new techniques and materials. It is recognized by the American Urological Association (AUA) as a highly effective surgical procedure with success rate of 80%-95%.[1] However, like with any surgical procedure, there are potential risks and complications associated with urethral reconstruction. One potential complication is the development of urethral cancer, which has been reported in rare cases following urethral reconstruction.

Urethral carcinoma is a rare and aggressive malignancy that makes up < 1% of all malignancies worldwide.[2] It has an estimated incidence rate of 4.3 per million men, which increases to 32 per million for men in the age group of 75 to 84. Squamous cell carcinoma of the urethra has been linked to urethral

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stricture, chronic catheterization, infection, radiation, urethral diverticula, and lichen sclerosis.[3] Urethral stricture disease is the most common risk factor, found in greater than 50% of patients with male urethral cancer.[4] High-pressure, turbulent urine flow caused by urethral stricture is thought to create a chronic inflammatory process that pre-disposes carcinogenesis.

Urethral carcinoma has been previously reported after different types of urethral reconstruction, including skin graft urethroplasty, penile skin flap urethroplasty, Turner-Warwick scrotal skin flaps, and buccal mucosal graft (BMG) urethroplasty. The proposed causes of urethral carcinoma after stricture recurrence include chronic inflammation, pre-malignant mucosal changes (i.e. human papillomavirus), malignant changes in the graft material, and unrecognized malignancy prior to reconstruction.[5,6]

A systematic review of the literature revealed 14 cases of urethral carcinoma after urethral reconstruction in addition to the case we are reporting on.[7] Ten cases occurred after urethroplasty using either skin grafts or penile skin flaps, suggesting a propensity for carcinogenesis in patients whose urethra compose of squamous cell epithelium. Patients who undergo urethral reconstruction using skin grafts/flaps may benefit from continued surveillance for evidence of urethral cancer.

Case report

A 59-year-old male with a history of long-segment anterior urethral stricture underwent Johanson-Leadbetter multistage urethral reconstruction using a split-thickness skin graft from his thigh in 1995. He presented to our clinic 20+ years after with obstructive urinary symptoms. He reported painful erections due to tethering of the penis. Physical exam showed significant ventral chordee and a sub-coronal neo-meatus. He did not have childhood hypospadias. Cystoscopy and retrograde urethrogram revealed near obliteration of the fossa navicularis and entire penile urethra. Since repeat urethral reconstruction would be complex in the setting of prior reconstruction and a near-obliterated urethra, he elected to undergo urethrectomy and creation of perineal urethrostomy.

The penile urethra was excised and pathology was benign. The distal bulbar urethra was widely patent. The left side of the proximal bulbar urethra had a cobblestone appearance and the tissue adjacent to it was very firm. The area appeared to be within a segment of previously reconstructed urethra. Tissue from this area was sent to pathology and the perineal urethrostomy was matured.

Patient's postoperative course was uneventful and his functional outcome was excellent. However, pathology from the proximal bulbar urethra showed invasive squamous cell carcinoma negative for HPV and p16. Postoperative MRI showed a 1.7 cm mass along the left side of the urethra at the perineal urethrostomy.

Consequently, complete local resection and redo perineal urethrostomy were warranted. Intraoperative cystoscopy during the second operation showed a 1.5 cm segment of the proximal bulbar urethra with cobblestone appearance. This portion of the urethra was excised en bloc with the surrounding corpus spongiosum and perineal skin. Surgical margins were sent for frozen section to verify a complete resection. Perineal urethrostomy was created by bringing perineal skin flaps onto the remaining proximal bulbar urethra.

The final pathology showed pT1 invasive, moderately differentiated squamous cell carcinoma with negative margins. He had an excellent functional outcome from his surgery. He continued to undergo cancer surveillance with an office visit with cystoscopy every 6 months and annual pelvic MRI. At 5-year follow up, he had no evidence of recurrence.

Discussion

Urethral carcinoma after urethral reconstruction is an uncommon occurrence that bears major clinical importance for patients. It is an aggressive disease with a 5-year survival of less than 50%.[8] Bulbar tumors like the one from our case portend worse survival of 20%-30%.[4] There is a well-established association between chronic inflammation and malignancies of all types throughout the body. Urethral stricture is not only an inherently inflammatory disease state due to the natural history of spongiofibrosis, but it also worsens inflammation by forcing urine through the area with high-pressure, turbulent flow. Patients who are offered reconstructive surgery tend to be those with long or complex strictures refractory to DVIU/urethral dilation. Perhaps, it is no surprise that urethral cancer is found in patients who had urethroplasties based on our understanding that severe stricture disease lends to metaplasia and carcinogenesis.

Even though urethral reconstruction seeks to alleviate chronic inflammation by excising the area of spongiofibrosis and restoring the original diameter of the urethral lumen, strictures do recur. The rate of stricture recurrence depends on the surgical technique and type of tissue substitution. Before the 1990s, genital skin flaps and extragenital skin grafts were

utilized by reconstructive urologists around the world. Thousands of patients underwent successful repairs during that time. BMG was first used for urethral surgery in the 1990s. Since then, it has become the first choice for tissue substitution due to its ease of harvest and handling, absence of hair, familiarity with a wet environment, resistance to infections, lower risk of diverticulum formation, and early inosculation. The use of skin flaps/grafts has fallen to the wayside due to an increased risk of graft contracture and stricture recurrence.

In the recent review by D'Amico et al, 10 of the 14 previously published cases of urethral carcinoma after urethroplasty utilized skin flap or graft as part of the repair.[7] Our patient underwent Johanson-Leadbetter staged urethroplasty using a split-thickness skin graft. The preponderance of urethral cancer cases after skin substitution urethroplasty may be explained by the increased risk of stricture recurrence after repair. There is currently no consensus surveillance algorithm after urethroplasty. However, many patients are monitored with routine office visits along with non-invasive uroflowmetry. Cystoscopy and retrograde urethrogram are performed when history or non-invasive testing are concerning for stricture recurrence. Although some cases of urethral cancer present dramatically with urinary fistulas and large groin masses, most urethral cancers present insidiously with irritative/obstructive voiding symptoms, hematuria, or discharge. Other signs/symptoms that may warrant evaluation include pelvic pain, induration, or nodularity along the course of the urethra. Given the risk of urethral cancer, clinicians should maintain a high-clinical suspicion and consider cystoscopy for patients who are more than 5 years out from skin substitution urethroplasty. Urologists should have a low threshold to obtain a biopsy if abnormal-appearing mucosa is encountered during cystoscopy.

The NCCN and EAU currently recommend surgical resection for localized (≤ T2) urethral tumors.[9] The guidelines and existing literature highlight the importance of obtaining clear surgical margins with initial resection since a positive margin is associated with poor outcomes even after clear margins are obtained with subsequent resection. To that end, we favor the liberal use of intraoperative frozen section and a minimum of 5-millimeter surgical margin as we had in our case. This is particularly important for our patient who needed a redo perineal urethrostomy after resection. We were also concerned about the possibility of unrecognized malignant changes on the skin graft. Therefore, we elected to completely excise the pendulous urethra and the portion of the bulbar urethra distal to the tumor even when there was no evidence of malignancy in the previously reconstructed portion of the urethra.

Conclusion

Urethral cancer after urethral reconstruction is an under-recognized, uncommon disease with the potential for significant morbidity and mortality. The preponderance of urethral cancer after urethroplasty using skin flaps/grafts is a testament to the fact that stricture recurrence and unrecognized malignant changes prior to urethroplasty are major risk factors. Although skin grafts and flaps are now rarely used, thousands of patients who underwent skin substitution urethroplasty in the past may benefit from cystoscopic surveillance to monitor for stricture recurrence and malignant changes. □

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