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CASE REPORT

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Prostatic urethra recurrence after transurethral resection of bladder tumor (TURBT) for non-muscle-invasive bladder cancer (NMIBC)

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Abstract

Urinary bladder cancer is frequently multifocal and has a high incidence of recurrence. Although the prostatic urethra is a frequent site of tumor relapse in patients with non-muscle-invasive bladder cancer treated with TURBT, such tumors are often underdiagnosed. Here we present two cases having urethral recurrence after TURBT.

KEYWORDS

bladder cancer, prostatic urethra, recurrence, transurethral resection of bladder tumor (TURBT), urethra, urothelial cancer

1 | INTRODUCTION

Urothelial cancer (UC) is the most common malignancy of the urinary bladder. It is frequently multifocal and has a high incidence of recurrence. Bladder carcinoma in situ (CIS) is especially prone to recurrence. Transurethral resection of a bladder tumor (TURBT) is a standard of care for newly diagnosed bladder tumors. Recurrence rate trend to be high even in cases of non-invasive tumors treated with TURBT with recurrence rates as high as 80%. Recurrences can occur in the bladder and throughout the urinary tract including the urethra. Urethral recurrence after radical cystectomy (RC) without urethrectomy is frequently reported in the literature[1] and is considered an indicator of poor survival.[2,3] Risk factors for urethral cancer recurrence after RC include tumors in the trigone of the urinary bladder, multiple or recurrent[4] tumors, non-papillary bladder tumors,[5] and bladder CIS.

Although the prostatic urethra (PU) is a frequent site of tumor relapse in patients with non-muscle-invasive bladder cancer (NMIBC), such tumors are often underdiagnosed. Risk factors for superficial UC of the PU include high-grade, multifocal bladder UC, and bladder CIS. Urethral involvement is diagnosed based on cystoscopy and urinary cytology findings. However, the diagnosis might often be challenging because of the microscopic involvement of the PU. The rate of lymph node (LN) metastasis is higher in patients with prostatic stromal invasion than in patients without stromal invasion.[6] Lymph drainage of the PU occurs into the pelvic LNs. Only a few reports have described urethral recurrence of bladder cancer after TURBT. We present two cases of urethral recurrence after TURBT.

2 | CASE PRESENTATION

2.1 | Case 1

An 86-year-old man was referred to our hospital with the chief complaint of asymptomatic microscopic hematuria.

He was taking warfarin for atrial fibrillation and had a history of cardiogenic cerebral infarction. Cystoscopy revealed a broad-based papillary tumor and an area of high index of suspicion for bladder CIS in the bladder. No urethral tumors were observed. Urinary cytology was class V. The tumor was resected transurethrally and no residual tumor was detected after TUR. We performed intravesical instillation of mitomycin C (40 mg) upon completion of the operation. Histopathological examination revealed a non-invasive (pTa) high-grade (G2) UC. Cystoscopy and computed tomography (CT) revealed no local recurrence or distant metastasis 3 months postoperatively. Follow-up cystoscopy performed 6 months after the initial TURBT showed a recurrent tumor involving the bladder neck extending to the PU to the level of the verumontanum and repeat TURBT was performed. Intraoperatively, the bladder neck tumor was resected without any residual lesion. However, resection of the PU (Figure 1A) revealed a deep-seated invasion of the prostate. Radical resection was impossible owing to spread of cancer to the prostate. The patient was histopathologically diagnosed with UC accompanied by prostate stromal invasion (Figure 1B). Salvage external beam radiotherapy was offered; however, the patient and family refused this treatment and opted for follow-up. A urethral tumor was detected on cystoscopy 1 month postoperatively (Figure 1C). Bladder recurrence was not observed at that time. CT revealed obturator (Figure 1D), and pararectal LN (Figure 1E) metastasis which showed gradual enlargement (Figure 1F) on subsequent CT. We observed several episodes of hemorrhage from the urethral tumor, which were successfully treated using placement of a urethral catheter and intravenous carbazochrome injections. Warfarin therapy was switched to apixaban. The patient died a natural death at the age of 89 years with stable disease 15 months after the last TUR.

2.2 | Case 2

An 80-year-old man was referred to our hospital with the chief complaint of asymptomatic microscopic hematuria. He was diagnosed with multiple papillary bladder tumors involving the bladder lateral walls, dome, trigone, and the bladder neck (Figure 2A) and underwent TURBT. Repeat TURBT was performed 2 weeks later for residual bladder tumors. Upon completion of the operation, we performed intravesical instillation of mitomycin C (40 mg). Histopathological evaluation confirmed diagnosis of invasive (pT1) high-grade UC. Second-look TUR revealed no residual tumor. Follow-up cystoscopy showed a solitary broad-based papillary tumor involving the left bladder wall and he underwent the fourth TURBT procedure 6 months after the initial TUR. Upon completion of the operation, we performed intravesical instillation of pirarubicin (30 mg). Histopathological evaluation confirmed diagnosis of non-invasive (pTa) low-grade (G1) papillary UC. Cystoscopy performed 10 months after the initial TUR revealed a papillary tumor near the verumontanum, and underwent wide TUR (Figure 2B–D). Histopathological examination revealed papillary high-grade UC without prostate tissue invasion (Figure 2E). The surgical margins were negative for malignancy. Follow-up urinary cytology results were negative and cystoscopy (Figure 2F) and CT revealed no local recurrence or metastases. The patient was disease-free 2 years after the initial diagnosis (15 months after the last TUR).

3 | DISCUSSION

The incidence of primary urethral UC is low. It does not exceed a few percent.[7,8] A study has reported UC of the male anterior urethra.[9] Several case reports have described primary UC of the prostate.[10,11] Primary UC of the PU is rare (1%−4% of patients).[12] In contrast, the estimated incidence of bladder UC with synchronous or metachronous involvement of the prostate is reportedly between 12% and 40%.[13–15] A study has shown that among patients diagnosed with superficial bladder cancer, 3.5% had macroscopic and 2.7% had microscopic involvement of the PU.[16]

The prostate is a frequent site of tumor relapse in patients with superficial bladder tumors.[17] PU tumors may remain undetected at the time of primary diagnosis of bladder cancer in a few patients. A study has reported a high incidence of recurrent extravesical UC after successful control of a primary bladder tumor. PU tumors were detected in 24% of men in the study. The median time to the detection of these recurrences was 11 months. Notably, PU recurrence is often diagnosed incidentally.[18] In these patients, we diagnosed recurrent UC in the PU 6 and 10 months after TURBT during scheduled cystoscopy.

Urothelial cancer in the PU may be non-invasive (involving the urethral mucosa and prostatic ducts) or invasive (extending to the acini and prostatic stroma). Depth of invasion is a predictor of survival. The incidence of stromal invasion of the prostate is reportedly between 7% and 17%.[19] Herr et al.[18] reported that 50% of patients with such relapse presented with prostatic stromal invasion. Stromal invasion is associated with significantly decreased survival.[15,17] Prostate ductal involvement after RC is associated with a high risk of metastasis.[20] Patients with PU involvement after RC also showed varied survival rates. Overall survival (OS) was 100% in patients with superficial tumors, and declined steeply to 50% and 40% in patients with ductal involvement and stromal involvement, respectively.[15] Invasive tumors can present with intraurethral or

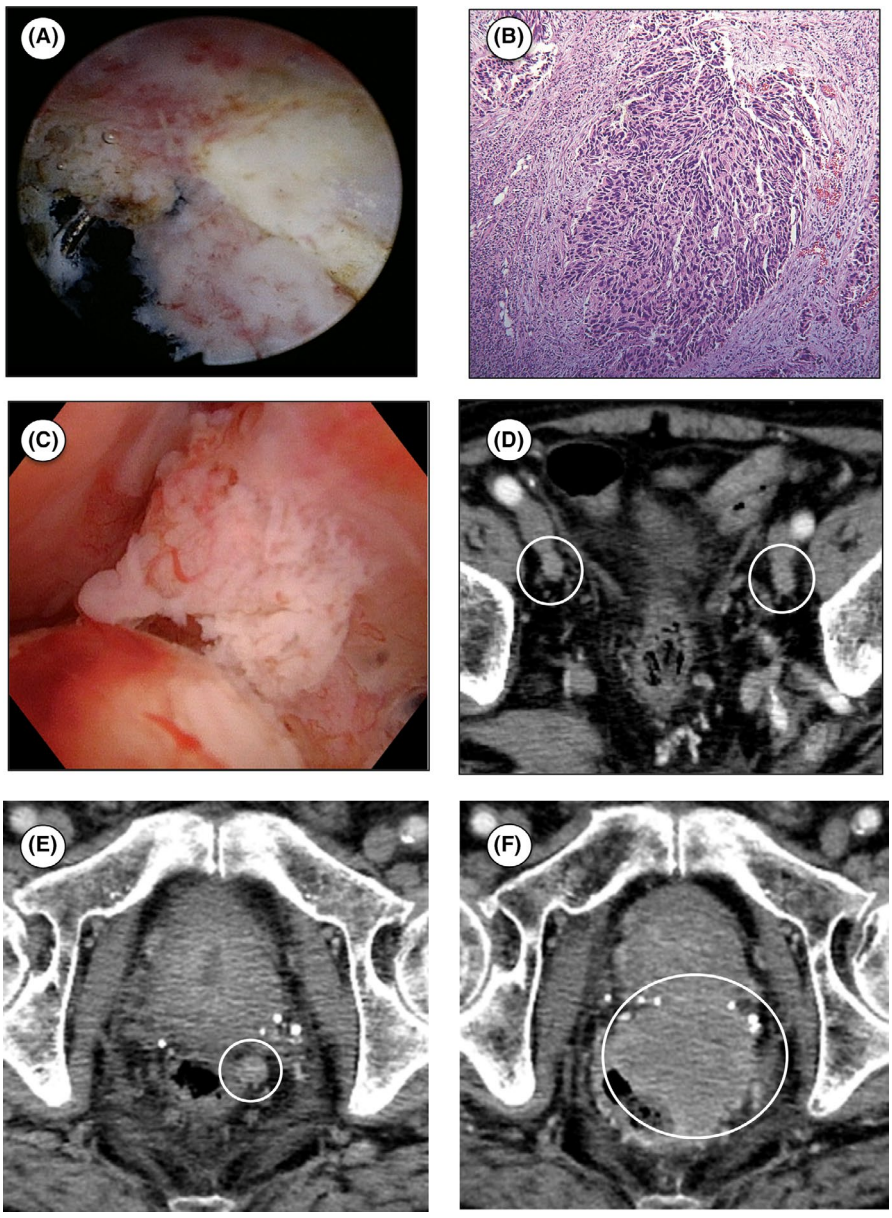

FIGURE 1 Urethral tumor was resected by TUR and a deep invasion into the prostate was revealed (A). Pathological diagnosis was UC with prostate stromal invasion (B, Hematoxylin-Eosin Stain, 200×). One month after the operation, recurrent urethral tumor was found during cystoscopy (C). CT revealed obturatory LN (D) and pararectal LN (E) metastasis which gradually enlarged (F)

direct prostatic invasion. Contiguous growth into the prostate is also associated with a poorer prognosis.[21] The patient described in Case 1 presented with stromal invasion secondary to intraurethral growth, based on the fact that no contiguous growth was detected. The patient developed LN metastasis and progressive disease. The patient described in Case 2 presented with a superficial tumor in the PU and is disease-free 15 months after the resection of the recurrent urethral cancer.

Higher grade and stage, multiple lesions and CIS in the bladder are shown to be risk factors for PU recurrence in patients with superficial bladder UC.[16,22] Furthermore, the risk of tumor recurrence in the PU is higher in patients with lesions involving the trigone.

Although regular cystoscopy is the gold standard for diagnosis of PU tumor recurrence in patients with bladder cancer, tumors may also involve the normal-appearing urethra. Evaluation of TUR biopsy specimens obtained from the 5 and 7 o'clock positions of the verumontanum is recommended in patients with persistent positive urinary cytology and negative cystoscopic findings. However, low-grade tumors may present with negative urinary cytology findings.

Superficial UC of the PU can be treated using TUR, BCG instillations, or combination therapy. The complete response to BCG without TUR is up to 75%, and the 5-year recurrence-free survival rate is 90% in patients with non-invasive tumors. The patient described in Case 2 was successfully treated using TUR. Conservative treatment options include intravesical instillation of mitomycin C, adriamycin, and epirubicin.[8] Urethral UC with prostatic stroma invasion and lesions that occur in BCG-unresponsive patients require radical cystectomy with lymphadenectomy.[19] Neoadjuvant platinum-based

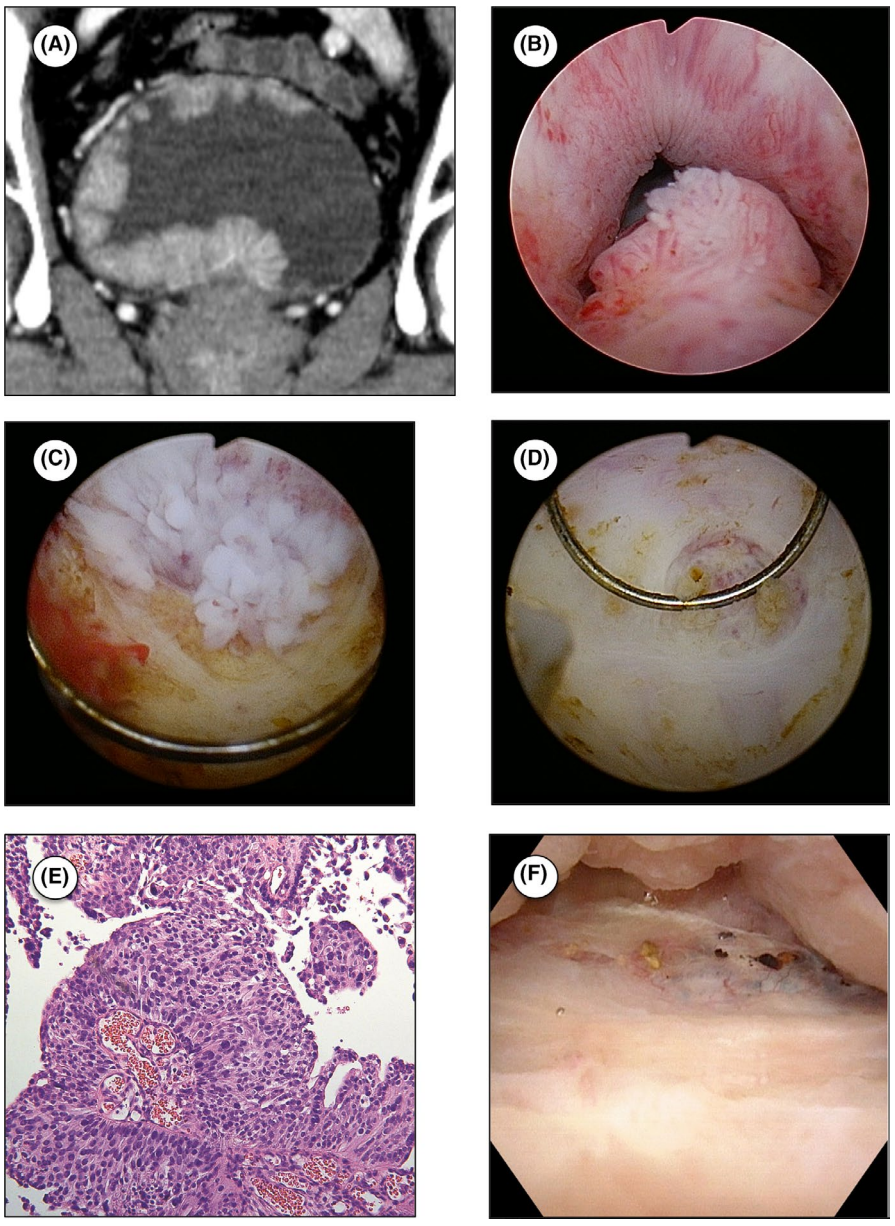

FIGURE 2 Initial CT revealed multiple papillary bladder tumors (A). Urethral tumor at the verumontanum (B) was resected (C) and no residual tumor was present (D). Papillary high-grade UC without prostate tissue invasion (E, Hematoxylin-Eosin Stain, 200×). No recurrence was detected during follow-up cystoscopy (F)

chemotherapy may be administered to patients with advanced disease. The LN metastasis rate was significantly higher in patients with prostatic stromal invasion than in patients without stromal invasion. Lymphatics of the PU drain into the internal and external iliac, the obturator, and the presacral regions. Pararectal, paravesical, and inguinal regions are considered aberrant sites of lymphatic drainage from the prostate. Reportedly, the incidence of LN metastases from prostatic cancer to pararectal LNs is 3%,[23] which is a rare case. The Gleason score is known to significantly correlate with positive metastatic pararectal LN in cases of prostate cancer,[24] which indicates that highly malignant tumors tend to metastasize to pararectal LNs. The patient described in Case 1 had prostatic stromal invasion and metastasis to the pelvic LNs (obturator and pararectal). Obturator LNs did not increase in size; however, the pararectal LNs showed gradual growth. The differential growth of metastatic LN may represent tumor heterogeneity. LN metastasis is an independent prognostic factor for poor OS in patients with recurrence of PU cancer. Radical cystoprostatectomy with pelvic lymphadenectomy with or without neoadjuvant platinum-based chemotherapy remains the only curative treatment in such cases.[7] The patient described in Case 1 had LN metastasis; however, he was deemed unfit for major surgery.

4 | CONCLUSION

The true incidence of recurrent PU cancer may be underestimated, and tumor recurrence is often diagnosed incidentally. Patients who are successfully treated for high-risk multiple bladder cancers show an increased risk of recurrent PU lesions and are deemed suitable for more

frequent and close follow-up with endoscopy, urinary cytology, and CT evaluation. These patients require aggressive treatment for recurrence to prevent prostatic invasion and lymphatic metastasis.

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CONFLICT OF INTEREST

The authors have no conflict of interest in the subject matter or materials discussed in this manuscript.

AUTHOR CONTRIBUTIONS

SH and VB made substantial contributions to the conception and acquisition of data; VB conceived the study, reviewed the literature, analyzed and interpreted the data, and drafted and revised the manuscript. All authors read and approved the final version of the manuscript.

ETHICAL APPROVAL

This manuscript was completed in accordance with the ethical standards of the institutional research committee.

CONSENT

Written informed consent was obtained from the patients and their relatives for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal upon request.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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