Bladder perforation following intravesical mitomycin C instillation after the transurethral resection of bladder tumor: A case report and mini-review of the literature

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Abstract. Bladder perforation following mitomycin C (MMC) instillation post-transurethral resection of a bladder tumor (TURBT) represents a rare, yet clinically significant complication, with limited documented cases reported in the literature. The present case report describes a case of bladder perforation due to MMC instillation post-TURBT. A 61-year-old male patient underwent TURBT followed by MMC instillation for the treatment of low-grade papillary urothelial (transitional) cell carcinoma. Subsequently, he presented with severe suprapubic pain and dysuria. Computed tomography cystography demonstrated the presence of a bladder perforation, necessitating surgical intervention via laparotomy. A histopathological examination (HPE) of the perforation site revealed inflammatory changes. Following the initial laparotomy, the patient experienced persistent leak and collection, prompting a surgical procedure. A HPE, following the second laparotomy, demonstrated extensive fibrosis, chronic inflammation and necrotizing cystitis, consistent with drug-induced cystitis. Subsequent follow-up assessments demonstrated a gradual improvement in the clinical condition of the patient. In addition, herein, a literature review identified six reports on complications following MMC instillation post-TURBT; with equal gender distribution. Their ages ranged from 48 to 79 years. The clinical presentation included severe and excruciating lower abdominal pain and pelvic pain, irritative urinary symptoms, hydronephrosis and pudendal neuralgia. As regards management, 3 out of the 5 patients reported in the literature had undergone surgical interventions, such as exploratory laparotomy, bladder defect repair, TURBT, ureteric stenting and radical cystectomy. The other two cases were initially managed conservatively with antibiotics and indwelling catheters. On the whole, MMC instillation immediately after TURBT is a well-established method for reducing tumor recurrence. However, awareness of potential consequences, such as bladder perforation, is essential.

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Introduction

Bladder cancer (BC) is one of the most prevalent cancers of the urinary tract, with ~550,000 new cases identified each year (1). Transurethral resection of bladder tumors (TURBT) is a cornerstone in the treatment of non-muscle-invasive BC (NMIBC), and it is frequently combined with adjuvant intravesical therapies to minimize recurrence rates (2). Among these therapies, the instillation of mitomycin C (MMC) has demonstrated efficacy in preventing tumor recurrence post-TURBT (3,4). However, despite its benefits, MMC instillation is associated with inherent risks, including bladder perforation (5). Bladder perforation following MMC

instillation post-TURBT represents a rare, yet clinically significant complication, with a limited number of documented cases in the literature (6). The pathophysiology of this condition remains poorly understood; however, it is considered to result from the necrosis of the attenuated muscularis propria following MMC instillation (4). Delayed diagnosis could lead to increased morbidity, challenges in management and even mortality (7). The present case report describes a case of bladder perforation due to post-TURBT MMC instillation and also conducts a brief review of the literature.

Case report

Patient information. A 61-year-old male patient who was a smoker with diabetes presented to Smart Health Tower (Sulaymaniyah, Iraq) with an incidental finding of a bladder mass. He was on empagliflozin and gliclazide.

Clinical finding. A physical examination did not reveal any notable findings.

Diagnostic approach. A cystoscopy revealed a pedunculated mass at the posterior wall of the bladder (data not shown; images not available). A TURBT was performed; in addition, ahistopathological examination (HPE) was performed on 5-μm paraffin-embedded sections. The sections were fixed in 10% neutral buffered formalin at room temperature for 24 h and stained with hematoxylin and eosin (H&E; Bio Optica Co.) for 1-2 min at room temperature. The sections were then examined under a light microscope (Leica Microsystems GmbH). This revealed a low-grade, stage pTa papillary urothelial (transitional) cell carcinoma (Fig. 1). A single session of 40 mg intravesical MMC was administered. After 6 months, a follow-up cystoscopy revealed a small mass posteriorly near the bladder dome (Fig. 2). Another TURBT was performed. The surgery was uneventful, and no bladder perforation was noted. The mass was sent for HPE (Fig. 2) and this revealed a low-grade, non-invasive papillary urothelial carcinoma (stage pTa). At 6 h post-operatively, the patient received an MMC session. After 1 week, he complained of suprapubic pain, dysuria and insomnia. He was administered analgesics (paracetamol at 1,000 mg on need) for 1 week without symptom relief. An abdominal ultrasound (US) revealed mildly increased bladder wall thickness around the dome and a localized, irregular, loculated fluid collection (42 ml) with internal septa (data not shown; images not available). A Foley catheter was inserted, and he was discharged on analgesics (paracetamol at 1,000 mg on need) and antibiotics (meropenem at 1,000 mg, 1x2 for 4 days, followed by ciprofloxacin/ornidazole at 500/500 mg, 1x2 for 5 days). On the 22nd day after the surgery, he presented with severe suprapubic pain. A computed tomography (CT) cystography revealed diffuse vesical wall thickening up to 10 mm, with a focal wall defect in the urinary bladder dome (Fig. 3). The defect measured 5x5 mm. There was extravasation of contrast-enhanced urine into the perivesical space, forming a 7x5x5 cm fluid collection (almost 90 ml) containing gas bubbles. Under US guidance, a tube drain was placed. Despite maintaining the Foley catheter in place, he had ~200 cc of urine from the drain daily for 10 days.

Therapeutic intervention. An open repair of the perforation was performed via a lower midline laparotomy. A watertight three-layer suturing of the bladder was performed, and the edges were sent for HPE, which revealed only inflammatory changes with no evidence of malignant cells. A tube drain and a Foley catheter were inserted. At 1 week post-laparotomy, the drain was removed. A micturating cystourethrogram (MCUG) was performed 2 weeks later, and no leakage was observed. However, a US scan revealed an 8x3 cm collection behind the bladder. The collection was aspirated and sent for creatinine analysis, which returned 11.15 mg/dl. Culture on the same fluid yielded a growth of *Escherichia coli*. The patient was discharged on antibiotics (gentamicin at 80 mg, 1x2 for 4 days followed by nitrofurantoin at 100 mg, 1x3 for 10 days). At 6 weeks post-laparotomy, he presented again with suprapubic pain, and a US scan revealed a perivesical collection. Under US guidance, a drain was placed again. A CT scan revealed the features of an abscess by gas-forming microorganisms (Fig. 4). The patient was prepared for another operation. A lower midline laparotomy was done, and a thick adhesion (perivesical tissue) around the dome of the peritoneum was found. An erythematous part of the bladder was excised and sent for HPE. HPE was performed on 5-μm paraffin-embedded sections. The sections were fixed in 10% neutral buffered formalin at room temperature for 24 h and stained with hematoxylin and eosin (H&E; Bio Optica Co.) for 1-2 min at room temperature. The sections were then examined under a light microscope (Leica Microsystems GmbH). The bladder was sutured in three layers, and a flap of omentum was used to cover the sutures. A Foley catheter was inserted, and a drain was left in the pelvis. The HPE of the perivesical tissue revealed extensive fibrosis and chronic inflammation, while that of the bladder tissue revealed reactive urothelial change and necrotizing cystitis, consistent with drug-induced cystitis (Fig. 5).

Follow-up and outcome. At 10 days after the second laparotomy, the drain was removed and an abdominal US revealed no collection. The stitches were removed. A new Foley catheter was inserted, and the patient was discharged on antibiotics (meropenem at 500 mg, 1x2 for 3 days and then cefditoren pivoxil at 200 mg, 1x2 for 5 days). The general condition of the patient gradually improved. At 18 days after the last laparotomy, the MCUG was normal, revealing no leaks (Fig. 6). The Foley catheter was then removed. The patient is currently stable and on follow-up.

Discussion

Herein, a literature review was also conducted to identify relevant studies on complications following MMC instillation after TURBT. The process involved a Google Scholar and PubMed search without time restriction, employing key words, such as 'mitomycin C instillation', 'complications' and 'transurethral resection of bladder tumor'. A total of six studies on this topic were identified (Table I). Among the reviewed cases, three were female patients, and three were male patients. Their ages ranged from 48 to 79 years. The clinical presentation included severe and excruciating pelvic and lower abdominal pain, irritative urinary symptoms,

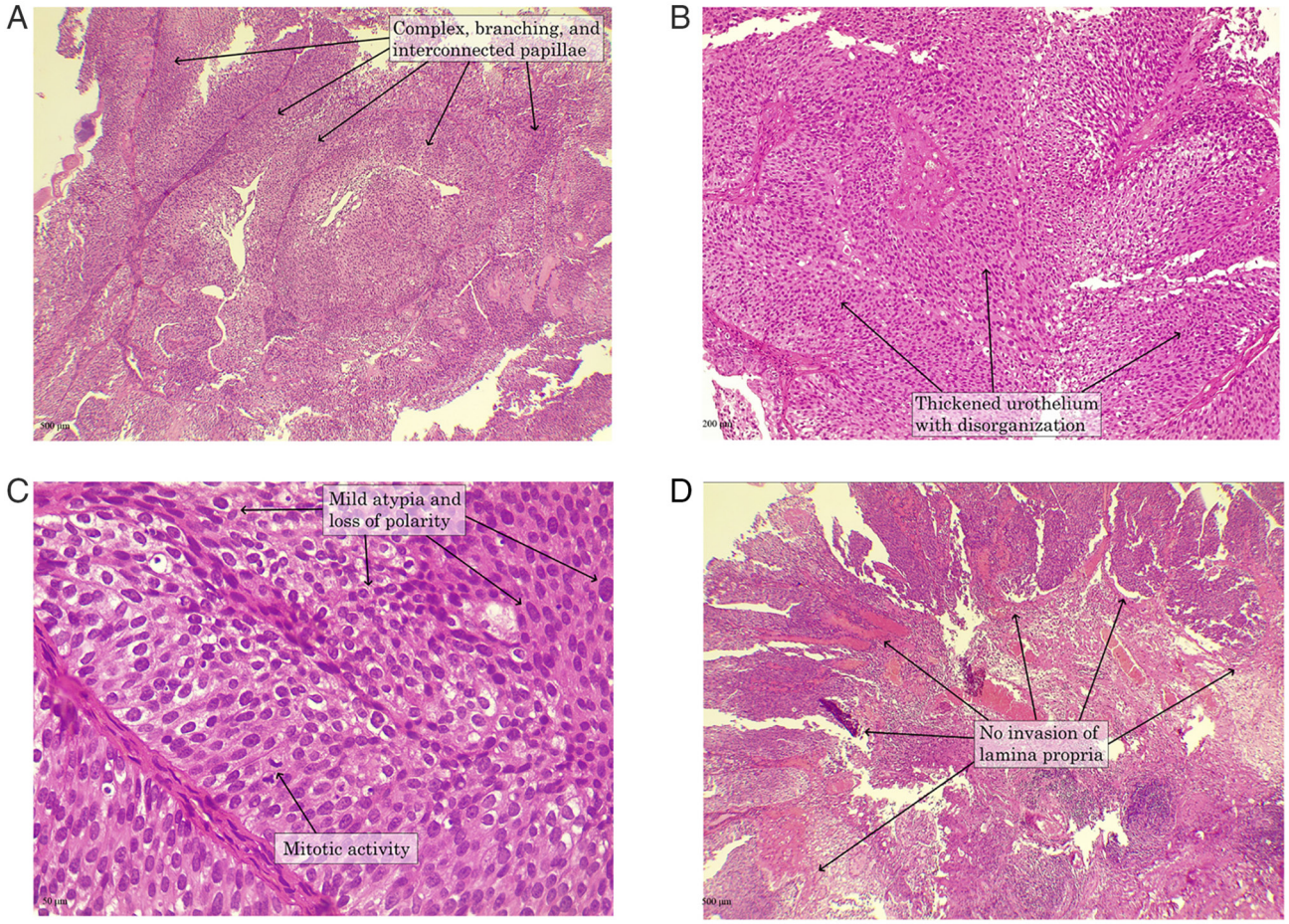

Figure 1. Low-grade papillary urothelial (transitional) cell carcinoma. (A) An exophytic tumor comprises complex, branching, and interconnected papillae. (B) A thickened urothelium with cellular disorganization lines the papillae. (C) The nuclei show mild atypia and pleomorphism with mild loss of polarity and occasional mitotic activity. (D) There is no invasion of the lamina propria. The figure depicts hematoxylin and eosin staining. Original magnification: (A and D) x40, (B) x100, (C) x400. Scale bars: (A and D) 500 μm, (B) 200 μm, and (C) 50 μm.

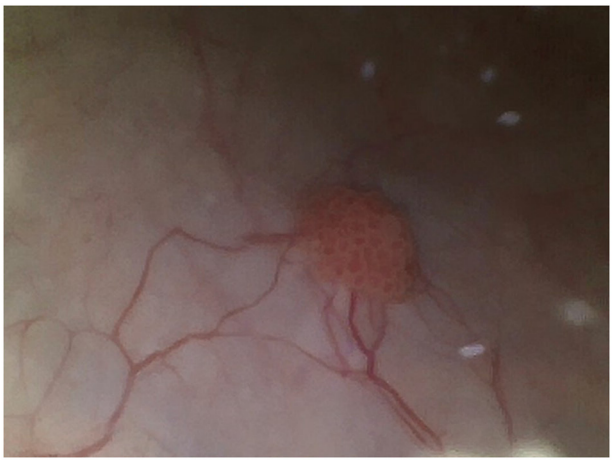

Figure 2. Cystoscopic view of a fungating mass on the posterior wall of the bladder.

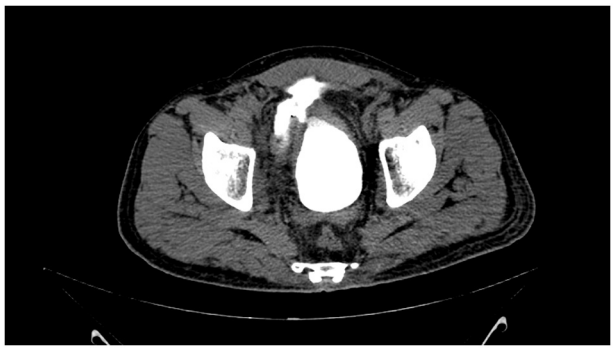

Figure 3. Selected transverse image of intravenous contrast-enhanced computed tomography scan in delay phase after 2 h, demonstrating almost 90 ml of extravesical contrast-opacified fluid collection anterior and superior to the urinary bladder, through a defect in the urinary bladder wall measuring 5x5 mm, with diffuse urinary bladder wall thickening.

hydronephrosis and pudendal neuralgia. Of note, 3 out of the 6 patients underwent surgical interventions, such as exploratory laparotomy, bladder defect repair, TURBT, ureteric stenting and radical cystectomy, while the remaining 3 cases were initially managed conservatively with antibiotics and indwelling catheters. On HPE, the complications in all cases revealed inflammatory and necrotizing changes consistent with complications resulting from MMC instillation. Notably, 5 of the patients were symptom-free on follow-up (4-6,8,9), while 1 patient still had persistent symptoms following a long stay in a rehabilitation unit (10).

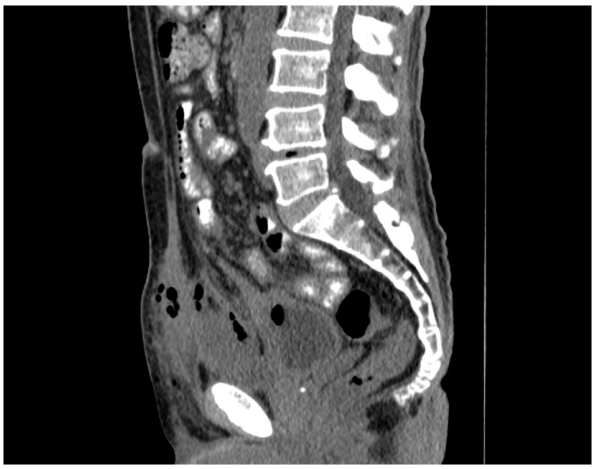

Figure 4. Selected sagittal image of abdomen computed tomography scan with oral positive contrast, illustrating bowel loops opacified with contrast, with a distinct, non-opacified collection anterior to the urinary bladder containing multiple foci of gas, suggestive of abscess formation by gas-forming micro-organisms.

BC is the seventh most commonly diagnosed type of cancer in men (11). The average age at diagnosis is 73 years of age, with Caucasian Americans having a higher incidence compared to African Americans. Of note, >90% of BC cases are urothelial carcinoma, while squamous cell carcinoma and adenocarcinoma are less frequent. This cancer is staged as either NMIBC or muscle-invasive (MIBC), with NMIBC being the more frequent diagnosis (70-85%). Smoking, occupational exposure, inflammation, radiation and chemotherapy all contribute to an increased risk of developing BC. Painless, gross hematuria is the most common symptom (80%), while 30% of patients may present with irritative urinary symptoms or clinical signs such as an abdominal mass or suprapubic distention (8). The case described herein was a 61-year-old male patient who was a smoker with diabetes; he was incidentally found to have a bladder mass despite a normal physical examination of the bladder.

The European Association of Urology (EAU) and American Urological Association (AUA) guidelines, based on the possibility of recurrence and progression, recommend the stratification of patients into risk groups, with low-risk tumors termed low-risk NMIBC (LR-NMIBC) and characterized by specific features such as being solitary, low-grade, stage pTa, primary, <3 cm in diameter and a lack of carcinoma *in situ* (12,13). The standard treatment approach for LR-NMIBC involves TURBT followed by a single dose of adjuvant intravesical chemotherapy, which has been demonstrated to significantly reduce disease recurrence rates compared to TURBT alone (14). In the case presented herein, TURBT was performed, and a low-grade pTa tumor was confirmed by HPE that was classified as LR-NMIBC. Subsequently, a single 40 mg intravesical MMC dose was administered in a single session. A follow-up cystoscopy 6 months later revealed a small posterior mass near the dome of the bladder. Another TURBT procedure was carried out, and the patient had another MMC session 6 h later. There was no evidence of bladder perforation following the uncomplicated surgery. The HPE again defined the mass as a low-grade, pTa NMIBC.

The rationale for adjuvant chemotherapy is its ability to target circulating tumor cells after TURBT and to exert an ablative effect on residual and overlooked tumors. MMC is the most commonly utilized adjuvant agent, functioning as an alkylating agent that inhibits DNA synthesis and causes DNA and chromosomal damage. Despite its efficacy, MMC administration may lead to mild, transient irritative bladder symptoms that can be managed medically. Dysuria, urinary frequency and urgency are the most common complications (8). However, the major complication is bladder perforation (6,9,15). Possible contributing factors to bladder perforation following MMC instillation include unrecognized bladder wall injury or microscopic perforation during TURBT, deep or extensive resection, immediate post-operative MMC instillation before adequate tissue healing and the direct cytotoxic effect of MMC, which can cause inflammation, necrosis, and impaired wound healing. The extravasation of MMC into perivesical tissues may lead to severe inflammation, fibrosis and delayed bladder rupture. Recurrent tumors and repeated prior TURBT procedures may further increase the risk (6,16,10).

Penna *et al* (6) described the case of a 77-year-old Caucasian male patient who received an early MMC instillation after TURBT. The patient reported urine retention after removing an indwelling catheter (6). Hatem and Leifeld (15) reported that a 74-year-old woman with a history of low-grade bladder cancer developed persistent abdominal pain and difficulty urinating just days after receiving MMC therapy for a recurrent tumor. The patient described herein developed suprapubic pain and irritative urinary symptoms 1 week after undergoing TURBT with subsequent MMC instillation. Intraoperatively, the operator had no concerns about bladder perforation. Furthermore, the early instillation of MMC was initially symptom-free.

The diagnosis of bladder perforation following intravesical MMC instillation involves clinical assessment, imaging studies and an endoscopic evaluation (7). Patients should be monitored for symptoms, such as severe abdominal pain, ileus and signs of peritonitis, which is of paramount importance (10). Imaging modalities, such as CT scans and cystoscopy aid in detection (7,14). A CT scan with retrograde cystography may demonstrate a localized extravasation (leakage) from the bladder wall into the extraperitoneal space (7). The CT cystography of the patient in the present case report revealed widespread vesical wall thickening with a 5x5 mm focal defect in the urinary bladder dome, resulting in contrast-enhanced urine extravasation into the perivesical space and a 7x5x5 cm fluid collection with gas bubbles.

In terms of management, some cases may initially be managed conservatively, including urethral catheterization, anticholinergic medications and antibiotic therapy (6,8). Nonetheless, these measures proved inadequate for bladder healing in certain instances, necessitating more invasive interventions, such as open repair procedures. Additionally, in some cases, the ultimate resolution involved cystectomy as a definitive treatment option (8,15). In the study by Penna *et al* (6), the patient was managed conservatively with analgesia, antibiotics and a 16-F indwelling catheter for 4 weeks. At the 2-week follow-up, non-tender suprapubic

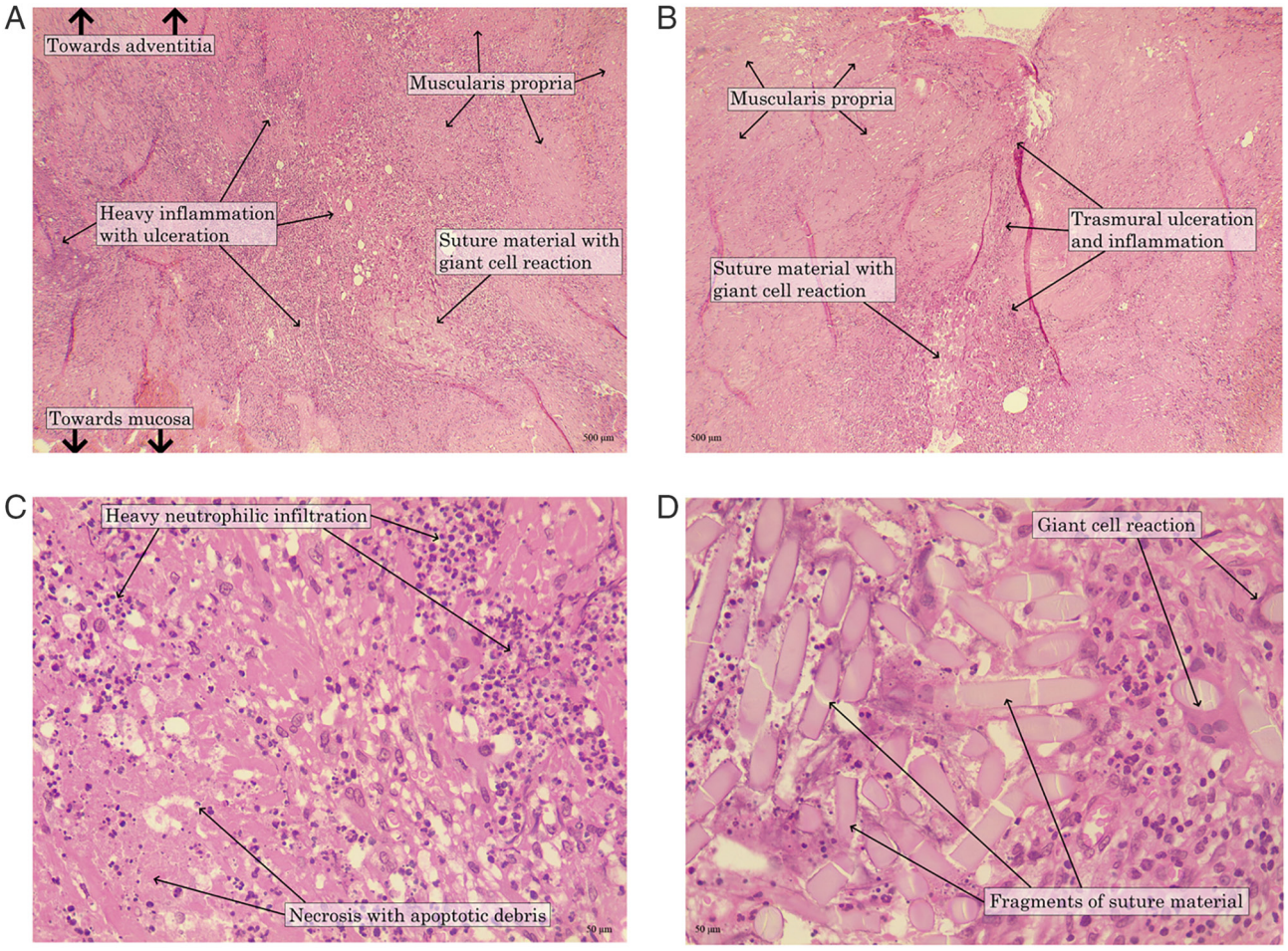

Figure 5. Necrotizing cystitis with perforation following mitomycin C therapy. (A) There is transmural ulceration with heavy mixed inflammation and giant cell reaction to suture material. (B) The ulceration and inflammation extend into the muscularis propria. There is entrapped suture material with a giant cell reaction. (C) There is heavy neutrophilic infiltration with necrosis and apoptotic debris. (D) Fragments of suture material are engulfed by multinucleated giant cells with neutrophilic activity. The figure depicts hematoxylin and eosin staining. Original magnification: (A and B) x40, (C and D) x400. Scale bars: (A and B) 500 μm, (C and D) 50 μm.

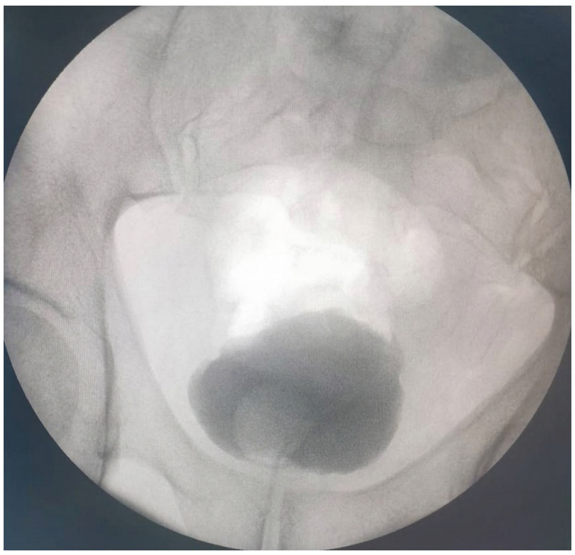

Figure 6. Cystography depicting a normal bladder; no leak was observed.

induration was palpable, which resolved within 6 weeks (6). In the study by Albradi *et al* (5), it was reported that the patient had an extraperitoneal extravasation that persisted with conservative management and necessitated an open surgical repair. Similarly, after multiple failed attempts at conservative treatment, the patient described herein underwent a lower midline laparotomy, which confirmed the presence of a bladder perforation. A watertight three-layer suturing of the bladder was performed. Subsequent imaging at 6 weeks post-laparotomy revealed a collection, leading to a secondary laparotomy. The bladder was sutured in three layers, and a flap of omentum was used to cover the sutures. The HPE of the perivesical tissue and bladder wall revealed extensive fibrosis, chronic inflammation, and necrotizing cystitis, consistent with a drug-induced cystitis. Follow-up revealed gradual improvement, and symptoms resolved, with normalization of findings on MCUG 18 days after the second laparotomy.

In conclusion, MMC instillation as an option to reduce tumor recurrence risk after TURBT may induce bladder perforation. Therefore, awareness of potential consequences is essential. The early detection of bladder perforation symptoms is critical, and urethral catheterization and imaging may be required, followed by surgical repair.

Table I. Summary of the reported literature on complications of mitomycin C instillation post-transurethral resection of bladder tumor.

First author, year of publication, country	Age (years)/sex	PMH	PSH	Presentation	HPE Finding	Management	Complication			Outcome	(Refs.)
							Sign and symptom	Diagnosis	Management		
Alrabadi, 2021, Jordan	63/male	No comorbidity	Negative	Incidental lesion in the left wall bladder on CT scan	Low-grade Ta Papillary urothelial carcinoma	Complete resection of the tumor was achieved without any intra-operative complication or perforation with instillation of 50 ml of doxorubicin diluted in 100 cc of saline 6 h after the TURBT	Dysuria, frequency, urgency, pelvic and perineal pain	CT cystogram showed Retroperitoneal bladder perforation	Conservative management initially with antibiotics and an indwelling catheter. Followed by open surgical repair due to persistent symptoms and failure of conservative measures	Follow-up CT cystograms showed healing with no extraperitoneal contrast leak. Two follow-up cystoscopies and bladder biopsies showed good healing and no tumor recurrence	(5)
Penna, 2012, UK	77/male	G1 pTa transitional cell carcinoma, ex-smoker	Open bilateral inguinal hernia repair	Not mentioned	A 30 mm Grade 1/2 (low grade) pTa papillary TCC	The lesion was completely resected hence mitomycin C, 40 mg in 40 cc of water for injection, was instilled into the bladder postoperatively	Excruciating pain in the lower abdomen, vasovagal syncopal attack	Localized extraperitoneal extravasation in continuity with the anterior bladder wall	Conservative management with analgesia, antibiotics, and a 16 F indwelling catheter for 4 weeks.	At 2 weeks follow-up, non-tender suprapubic induration was palpable which resolved at 6 weeks. Cystogram at 4 weeks showed no evidence of urinary leak. The urinary catheter was removed with no further complications	(6)
Chemi, 2020, Argentina	48/female	Non-Hodgkin's lymphoma, papillary thyroid tumor	TURBT	0.5 cm papillary lesion on the left bladder wall by US	Low-grade urothelial carcinoma stage pTa	En bloc resection of a left suprameatal tumor was performed followed by an immediate single instillation of 40 mg of MMC	Left pelvic pain, irritative urinary symptoms, pudendal neuralgia, ureterohydronephrosis	Left bladder wall thickening, periureteral edema, perivesical fat, left pudendal nerve inflammation, fistula.	Conservative management with methadone, gabapentin, corticosteroids; cystoscopy; Double-J stent placement	Complete resolution of pain and ureterohydronephrosis after 8 months. Follow-up cystoscopy showed full epithelialization of the scar. The patient remains asymptomatic.	(8)
Oehlschläger, 2003, Germany	76/female	None	None	Not mentioned	(pTaG2) of the left interureteric ridge	Transurethral resection of a recurrent superficial bladder 4 h following surgery, 50 mg of mitomycin C in 50 ml of physiologic saline were instilled into the bladder	Symptomatic hydronephrosis	Chronic ulcerative cystitis, scar tissue formation with histiocytic infiltration and necrosis	Transurethral resection of scar tissue, ureteric stenting	Symptom-free for 8 months after stent removal	(9)

Table I. Continued.

First author, year of publication, country	Age (years)/sex	PMH	PSH	Presentation	HPE Finding	Management	Complication			Outcome	(Refs.)
							Sign and symptom	Diagnosis	Management		
Hatem, 2019, Germany	74/female	bladder cancer (low-grade pTa diagnosed in 2005), HTN	Surgery for bladder tumor	In May 2018, the patient was admitted to our department to receive a TURBT due to tumor recurrence	Low-grade pTa	A multifocal papillary tumor on the bladder roof (each one smaller than 3 mm) was resected without endoscopic evidence of perforation. Postoperatively, an early instillation of MMC was performed without complaint.	Persistent abdominal pain and dysuria	US revealed free prevesical fluid, and a follow-up abdominal CT demonstrated an urgent suspicion of perforation with evidence of air bubbles in the bladder wall and in the pelvis	Radical cystectomy with a urinary diversion through ureterocutaneo-stomy	After 1 year of surveillance, no recurrence was found	(15)
Lim, 2010, UK	79/male	TaG2 bladder cancer, peripheral vascular disease with some intermittent claudication, chronic obstruc-tive pulmonary disease	TURBT	He presented again with a superficial bladder cancer	Two small recurrences of transitional cell carcinoma (stage TaG2). The biopsy site did not reveal perivesical fat.	Immediate post-operative instillation of 40 mg MMC in 40 cc of sterile water was performed in the recovery room 1.5 h postoperatively. There was no impression of intra-operative perforation	One day later, the patient complained of severe pelvic and suprapubic pain	Cystoscopy revealed a non-healed perforation	Recatheterization, exploratory laparotomy, repair of bladder defect, urinary diversion with bilateral 7 French ureteric catheters	The patient was discharged after a prolonged admission in the rehabilitation unit with ongoing irritative voiding symptoms	(10)

US, ultrasound; HPE, histopathological examination; CT, computed tomography, TURBT, trans-urethral resection of bladder tumor; PMH, past medical history; PSH, past surgical history.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

RB, KFHH and IA were involved in the conception and design of the study, and in the literature review. SSO, DHKR and BSS were involved in the design of the study, in the literature review, and in the critical revision of the manuscript. RMA was the pathologist who performed the histopathological examination and prepared the related images. CS and RJR were the radiologists who performed the radiological examination and prepared the related images. AAQ, HOA, NHH and FHK were involved in the design of the study, in the literature review, and in the drafting of the manuscript. All authors have read and approved the final version of the manuscript. RB and NHH confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Written informed consent was obtained from the patient for participation in the study.

Patient consent for publication

Written informed consent was obtained from the patient for the publication of the present case report and any accompanying images.

Competing interests

The authors declare that they have no competing interests.

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