


Delayed Bladder Perforation Related to Immediate Single Dose Intravesical Doxorubicin Instillation After TURBT: A Case Report and Literature Review

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ABSTRACT

INTRODUCTION: Intravesical chemotherapy instillation immediately after tumor resection is a well-known practice in the management of non-muscle invasive bladder cancer. Despite being largely well tolerated in most cases, it is not devoid of severe and life-threatening complications.

CASE PRESENTATION: We present an unusual case of bladder perforation that happened 2 weeks after bladder tumor resection. The patient had received single dose intra-vesical instillation of doxorubicin after TUR-BT. Conservative managements failed to achieve bladder healing; as a result, open surgical repair was performed. To the best of our knowledge, this is the first reported case of bladder perforation after intra-vesical doxorubicin instillation.

CONCLUSION: The occurrence of such a rare serious complication in a mostly safe intervention must be taken into consideration. A high index of suspicion, timely management, and proceeding to more invasive surgical treatments when necessary are cornerstones in the management and preserving the bladder.

KEYWORDS: Intravesical chemotherapy, doxorubicin, bladder perforation, bladder cancer, fat necrosis, extravasation

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Introduction

Bladder cancer (BC) is the seventh most commonly diagnosed cancer in men worldwide. About 75% of the cases are Non-muscle invasive (NMIBC).¹ Transurethral resection of the bladder tumor (TURBT) remains the gold standard of therapy for diagnosing and treating NMIBC. To decrease the recurrence rate of low-risk tumors, a single, immediate, post-operative intravesical instillation of chemotherapy is recommended.¹

The most commonly used chemotherapeutic agent is Mitomycin C (MMC), which is an alkylating agent that inhibits DNA synthesis and causes single-strand breakage of DNA and chromosomal breaks.²

Immediate single instillation (SI) is largely well-tolerated. However, severe complications and even death have been reported in the literature. Here we present a case wherein the patient had an extraperitoneal bladder perforation that occurred 2 weeks after TUR-BT and immediate postoperative instillation of doxorubicin.

Case Presentation

A 63-Year-old male, a heavy smoker, with no other co-morbidities, was referred to urology clinic for evaluation and management of a lesion on the left bladder wall that was incidentally

detected on a CT scan. He did not have any urinary symptoms on initial presentation.

Cystourethroscopy revealed 2 papillary growths on the left lateral bladder wall, which were resected completely and smoothly by a resectoscope using a monopolar energy. Complete resection of the tumor was achieved without any intra-operative complication or perforation. Hemostasis was secured, and a urethral catheter was inserted.

In accordance of the EAU guidelines, the patient received an intravesical instillation of 50 ml of doxorubicin diluted in 100 cc of saline 6 hours after the TURBT. During the instillation, his vital signs were stable and he had neither hematuria nor abdominal pain. One hour after the instillation, the catheter was unclamped and was attached to continuous bladder irrigation.

Two days after the surgery and in the absence of hematuria, the indwelling catheter was removed, and the patient was discharged home the next day.

When seen in the clinic 1 week later the patient was fine with no alarming symptoms. The pathology report showed a low-grade Ta Papillary urothelial carcinoma. Based on the pathological diagnosis and according to the EAU guidelines, adjuvant chemotherapy instillations were planned.



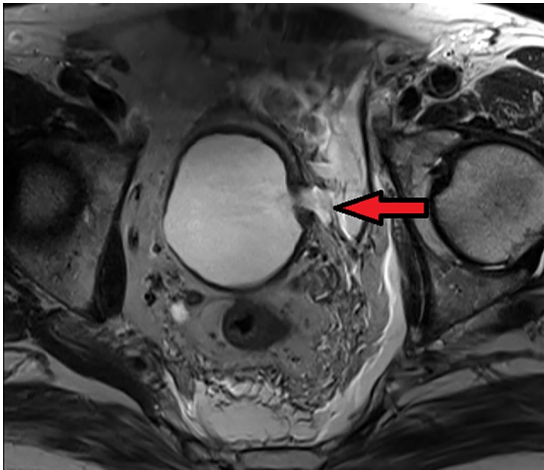


Figure 1. Pelvic MRI (axial view) showing extraperitoneal bladder perforation at the left lateral wall (arrow points to extravasated contrast).

Two weeks later, the patient presented with, dysuria, frequency, urgency, as well as pelvic and perineal pain. Physical examination was unremarkable. Urine analysis showed numerous WBC's, RBC's, and bacteria. An empirical antibiotics course was commenced.

In view of the worsening symptoms and the past history of anal fistula, a contrast enhanced pelvic MRI was performed. It showed a diffusely thickened urinary bladder wall, with evidence of a focal wall defect at its left aspect (the site of the resected tumor). The active urine leak into the perivesical space confirmed the diagnosis of retroperitoneal bladder perforation (Figure 1).

The patient was managed conservatively with antibiotics and an indwelling catheter for 3 weeks.

A follow-up retrograde CT cystogram showed no improvement and a gross contrast leak from the same site was identified. The catheter was kept for 6 more weeks and the CT cystogram was repeated showing the same results with no evidence of improvement. The patient refused to keep the catheter for a longer period so the option of open surgical repair was discussed with him.

Extraperitoneal laparotomy was performed, a perivesical small abscess was drained and cultured, necrotic tissues were debrided, and the bladder wall defect was rimmed and closed in 3 layers. Tissue biopsies from the pelvic wall and bladder wall were harvested. A urethral catheter and pelvic drain were kept in place. The postoperative course was uneventful, the drain was removed on the third-day postoperatively, and the patient was discharged home with the urethral catheter in.

Histopathological evaluation of the pelvic wall and the bladder biopsies verified acute and chronic inflammation as well as granulation tissue formation. However, both were negative for malignancy. The urinary bladder biopsy also showed extensive foci of dystrophic calcification while the pelvic wall biopsy revealed fat necrosis (Figures 2 and 3).

A follow up CT cystogram was done 3 weeks after the bladder repair. Although it showed a considerable regression in the

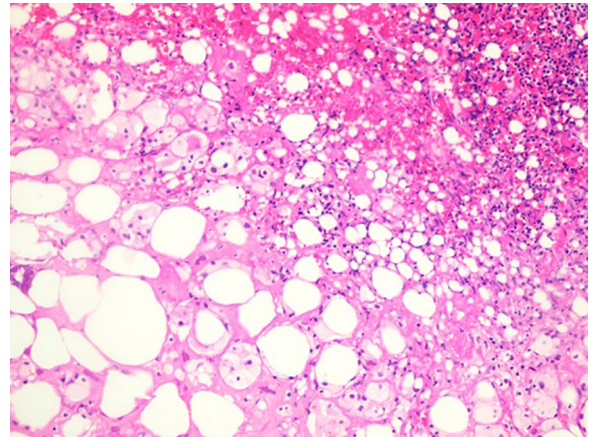


Figure 2. The histologic examination revealed fragments of soft tissue with fat necrosis in the lower left area, mixed acute and chronic inflammatory cell infiltrate and hemorrhage in the upper right area (Hematoxylin & Eosin, 200X).

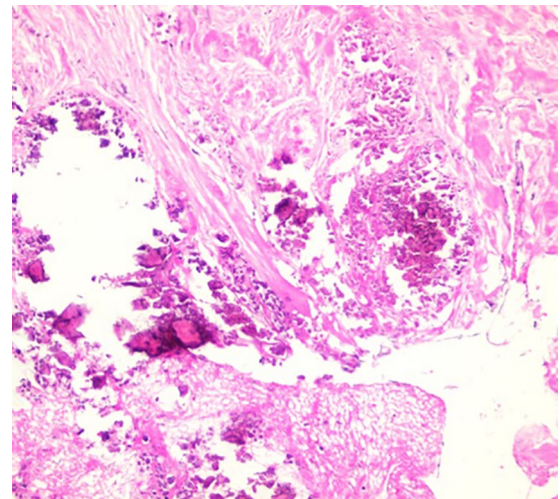


Figure 3. The histologic examination revealed multiple areas of calcifications embedded deep in the tissue with associated crystal-like material suggestive of calcium-oxalate or talc powder crystals (Hematoxylin & Eosin, 200X).

size of the bladder defect, interestingly it also showed persistent extra-peritoneal contrast leak from the bladder along its left lateral aspect (Figure 4).

Due to this slow healing, the catheter was kept in. Six weeks later, a follow up CT cystogram showed healing with no extra-peritoneal contrast leak (Figure 5). And hence the catheter was removed.

Two follow up cystoscopies and bladder biopsy (from an erythematous area on the left lateral wall) with 3 months intervals showed good healing of the bladder wall and no recurrence of the tumor.

Discussion

Single intravesical instillation with mitomycin C (MMC), epirubicin, or pirarubicin, have shown a beneficial effect in reducing recurrence rate compared to TURBT alone. However, randomized comparisons of individual drugs have not been conducted.³



Figure 4. Retrograde Ct cystogram showing persistent contrast leak from the left lateral aspect after surgical repair.

The high recurrence rate of NMIBC may be attributed to the seeding of floating tumor cells. Immediate chemotherapy instillation has been shown to act by destroying these circulating tumor cells after TURBT. Hence the EAU guidelines recommend initiating the instillation within the first few hours after TURBT.¹

Most of the complications of intravesical chemotherapy instillation are minor and can be managed medically. Dysuria and urinary frequency and urgency were the most common complications.⁴

On the other hand, reporting major complications such as bladder perforation, perirectal abscesses, eosinophilic cystitis, and ureteral stenosis is limited to case reports.⁵⁻¹⁴

In this case, we described our experience with bladder perforation after immediate intravesical instillation of doxorubicin.

One can argue that the perforation has occurred intraoperatively and gone unnoticed. However, in view of the absence of endoscopic evidence of perforation, late presentation of symptoms, and the absence of symptoms during and after the instillation we assume that the Single Dose Intravesical Doxorubicin Instillation caused the perforation rather than complicating an existing one.

To explain the mechanism of perforation, Lim et al⁷ and Cliff et al⁸ hypothesized that perforation is caused when attenuated muscularis propria gets necrosed after MMC instillation.

The presenting complaints of our patient were perineal and pelvic pain as well as urinary irritative symptoms. This is similar to Elmamoun et al⁹ cohort in which all the 6 patients presented with perineal and pelvic pain. Other symptoms such as fever, urine retention, and recurrent UTI were variably reported by others. Table 1 summarizes the clinical presentation and management of bladder perforation in the previously published case reports.

Concerning the management, almost all the reported cases were initially managed conservatively by urethral catheterization, anticholinergics, and antibiotics. However, this was insufficient

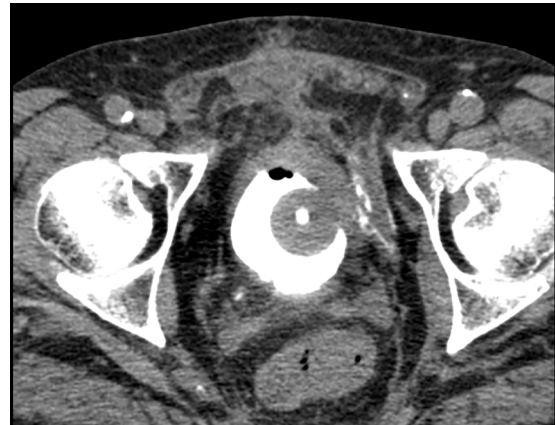


Figure 5. Retrograde Ct cystogram showing a healed bladder wall with no contrast leak.

to heal the bladder in some cases which needed open repair. Moreover, some ended with cystectomy.

In our case, the patient has an extraperitoneal extravasation that failed the conservative management and needed open surgical repair.

A striking feature of the healing process that was seen in many cases including ours is the poor and slow healing. In our case, the patient needed 9 weeks for complete healing after proper open 3 layers bladder wall repair.^{7-9,13,14}

While Lim et al attributed the slow healing in their case to the patient's pre-existing peripheral vascular disease and suboptimal tissue oxygenation, no risk factors were identified in the other cases including our patient who was free of any comorbidities. We suppose that the poor healing is linked to the chemotherapeutic agent inflammatory effect rather than to patient factor.

This assumption is backed by the reported characteristic of mitomycin induced skin ulcer in cases of extravasation after intravenous administration. These ulcers are well known for their chronicity and the low tendency of spontaneous healing. Moreover, debridement and soft-tissue reconstruction following extravasation of MMC are recommended for patients with persistent ulceration and pain.¹⁵

Another common finding in the cases that mandate open repair was the presence of perivesical soft tissue necrosis and extensive inflammation. Doherty et al observed that more extensive bladder wall and fat necrosis of extravasical tissue in cystectomy specimens occurred when either epirubicin or mitomycin instillation was administered than in that seen following TURBT alone.¹⁶

This cytotoxic effect was also reported by Tyrirtzis et al¹¹ after epirubicin instillation, and by Cliff et al,⁸ Nieuwenhuijzen et al,¹² and Hatem and Leifeld¹⁴ after MMC instillation. This cytotoxic effect was recognized herein for the doxorubicin instillation, which is the first time to be reported as a complication of doxorubicin.

It is worth to mention that the perforation had no adverse oncological effect on our patient as no tumor recurrence was detected during follow up.

Table 1. A summary of the presentation and management of bladder perforation after immediate chemotherapeutic agent intravesical instillation.

REF. NUMBER	THE INSTILLED DRUG	NUMBER OF PATIENTS	INITIAL PRESENTATION	MANAGEMENT OUTLINE
Lim et al ⁷	MMC	1	Pelvic and suprapubic pain	Exploratory laparotomy and bladder repair after failed conservative management
Elmamoun et al ⁹	MMC	6	3 patients presented with pelvic pain Pelvic pain Recurrent UTIs Left ureteric obstruction	Conservative management and urethral catheterization for 2, 26, and 52 weeks Partial cystectomy + left to right trans-ureteroureterostomy
			Pelvic pain, Persistent urinary leak Left ureteric obstruction	Augmentation cystoplasty + left Ureteric reimplantation The patient ended with persistent leak, so a long-term catheter was used
			Pelvic pain Severe LUTS Bilateral ureteric obstruction	Urinary diversion (ileal conduit)
Penna et al ¹⁰	MMC	1	Lower abdominal pain and inability to void	Analgesia, antibiotics and urethral catheter for 4 weeks
Tyritzis et al ¹¹	EPI	2	Fever and retroperic pain Fever, lower abdominal pain and cellulitis	Conservative: Antibiotics and urethral catheter Exploratory laparotomy and bladder repair after failed conservative management
Nieuwenhuijzen et al ¹²	MMC		Pelvic pain and fever	Exploratory laparotomy and bladder repair after failed conservative management for 1 month
Racioppi et al ¹³	MMC		Pelvic pain, fever and pancytopenia	Exploratory laparotomy and bladder repair after failed conservative management for 3 weeks
Hatem and Leifeld ¹⁴	MMC		Pelvic pain Fever and positive blood culture for ecoli as well as purulent discharge from the drain site after the first exploratory laparotomy	Conservative management for 10 days Exploratory laparotomy that revealed edematous anterior bladder wall without defect Renewed laparotomy, drainage of the abscess, debridement of the necrotic tissue, mono-J ureteral stents and nephrostomy Radical cystectomy with a urinary diversion through ureterocutaneousostomy
Shenaq et al ¹⁵	EPI	3	Strong urge and pain in the lower left abdomen Abdominal pain and intestinal obstruction	Conservative management with antibiotics and urethral catheterization Conservative management for 12 days Exploratory laparotomy that revealed infiltrative mass on the top of the bladder causing IO, so colostomy was done. The patient died due to multi organ failure
			Progressive pain in the lower abdomen	Conservative management with antibiotics and urethral catheterization

Abbreviations: Ep, epirubicin; MMC, mitomycin C.

Conclusion

Immediate intravesical instillations of chemotherapy are not devoid of risk and serious complications as bladder perforation can occur. Whether its value in decreasing the recurrence justify the risk of bladder perforation is not our argument in this case report. Nevertheless, this severe complication should be kept in mind, and high index of suspicion will aid in timely management. If perforation is suspected, urethral catheterization and contrasted imaging are mandatory. In the case of failed conservative management surgical repair is warranted even in extraperitoneal leak.

Author Contributions

Concept: AA, SAD. Design: MA, SA. Supervision: AA, SAD, MAA. Resources: MA, HM, NB. Materials: AA, MA, NB. Writing manuscript: AA, MA, HM. Critical review: AA, SAD, MAA.

Informed Consent

The patient has given his written informed consent to publish his case including publication of images. The study follows the guidelines for human studies and is conducted in accordance with the World Medical Association Declaration of Helsinki.

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REFERENCES

- EAU Guidelines. Edn. presented at the EAU Annual Congress Amsterdam 2020. ISBN 978-94-92671-07-3.
- Sylvester RJ, Oosterlinck W, van der Meijden AP. A single immediate postoperative instillation of chemotherapy decreases the risk of recurrence in patients with stage Ta T1 bladder cancer: a meta-analysis of published results of randomized clinical trials. *J Urol*. 2004;171:2186-2190.
- Sylvester RJ, Oosterlinck W, Holmang S, et al. Systematic review and individual patient data meta-analysis of randomized trials comparing a single immediate instillation of chemotherapy after transurethral resection with transurethral resection alone in patients with stage pTa-pT1 urothelial carcinoma of the bladder: which patients benefit from the instillation? *Eur Urol*. 2016;69:231-244.
- Filson CP, Montgomery JS, Dailey SM, et al. Complications associated with single-dose, perioperative mitomycin-C for patients undergoing bladder tumor resection. *Urol Oncol*. 2014;32(1):40.e1-40.e408. doi:10.1016/j.urolonc.2013.04.006
- Clark T, Chang SS, Cookson MS. Eosinophilic cystitis presenting as a recurrent symptomatic bladder mass following intravesical mitomycin C therapy. *J Urol*. 2002;167:1795.
- Oehlschlager S, Loessnitzer A, Froehner M, Hakenberg OW, Manseck A, Wirth MP. Distal ureteral stenosis after early adjuvant intravesical mitomycin C application for superficial bladder cancer. *Urol Int*. 2003;70:74-76.
- Lim D, Izawa JI, Middlebrook P, Chin JL. Bladder perforation after immediate postoperative intravesical instillation of mitomycin C. *Can Urol Assoc J*. 2010;4(1):E1-E3. doi:10.5489/cuaj.781
- Cliff AM, Romaniuk CS, Parr NJ. Perivesical inflammation after early mitomycin C instillation. *BJU Int*. 2000;85(4):556-557. doi:10.1046/j.1464-410x.2000.00539.x
- Elmamoun MH, Christmas TJ, Woodhouse CR. Destruction of the bladder by single dose Mitomycin C for low-stage transitional cell carcinoma (TCC)—avoidance, recognition, management and consent. *BJU Int*. 2014;113(5b):E34-E38. doi:10.1111/bju.12340
- Penna M, Mistry K, Pal P, Sudhanshu C. Intravesical instillation of mitomycin C: a cause of delayed bladder perforation? *Case Rep Urol*. 2012;2012:576519. doi:10.1155/2012/576519
- Tyritzis SI, Stravodimos KG, Mihalakis A, Constantinides CA. Complications associated with primary and secondary perforation of the bladder following immediate instillations of epirubicin after transurethral resection of superficial urothelial tumours. *Int Urol Nephrol*. 2009;41(4):865-868. doi:10.1007/s11255-009-9536-y
- Nieuwenhuijzen JA, Bex A, Horenblas S. Unusual complication after immediate postoperative intravesical mitomycin C instillation. *Eur Urol*. 2003;43(6):711-712. doi:10.1016/s0302-2838(03)00151-9
- Racioppi M, Porreca A, Foschi N, Delicato G, Destito A, D'Addressi A. Bladder perforation: a potential risk of early endovesical chemotherapy with mitomycin C. *Urol Int*. 2005;75:373-375.
- Hatem H, Leifeld J. A rare complication of intravesical early instillation of mitomycin C after TURBT. *Urol Case Rep*. 2019;26:100955. doi:10.1016/j.eucr.2019.100955
- Shenaq SM, Abbase EH, Friedman JD. Softtissue reconstruction following extravasation of chemotherapeutic agents. *Surg Oncol Clin N Am*. 1996;5:825-845.
- Doherty AP, Trendell-Smith N, Stirling R, Rogers H, Bellringer J. Perivesical fat necrosis after adjuvant intravesical chemotherapy. *BJU Int*. 1999;83(4):420-423. doi:10.1046/j.1464-410x.1999.00951.x