CASE REPORT

Vesicoenteric, vesicovaginal, vesicocutaneous fistula –an unusual complication with intravesical mitomycin

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Intravesical instillation of mitomycin C is a routine practice for treatment of superficial transitional cell carcinoma of bladder. Despite usual precautions serious side effects like fistulation can occur with diverse presentation as illustrated by this report. The pathology demonstrates

Introduction

A single perioperative dose of intravesical mitomycin C (MMC) is a well-accepted treatment modality following resection of noninvasive transitional cell carcinoma (TCC) of bladder. Various local and systemic complications such as chemical cystitis, tissue necrosis, perforation, extravasation and systemic absorption leading to renal failure have been seldom reported.^{1,2}

We report an unusual complication of fistulation in two patients following intravesical instillation of mitomycin C.

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a dense necrotic and massive inflammatory reaction in the peri vesical tissue following the extravasation of an intravesically administered chemotherapeutic agent. The severe inflammatory tissue response and the necrotic effect associated with the extravasated chemotherapeutic agent could potentially lead to local sepsis with a subsequent fistula formation.

Key Words: fistulation, delayed presentation, intravesical instillation of chemotherapy

Case study

Case 1

A 43-year-old female with a history of cadaveric renal transplant was diagnosed with noninvasive multifocal high grade superficial papillary bladder cancer. Patient underwent complete resection of all the visible papillary disease with no signs of perforation. An immediate perioperative instillation of chemotherapy was deferred due to the extent of endoscopic resection. Due to multifocal, high grade and recurrent nature of the disease further intravesical therapy was considered to reduce the risk of recurrence. The option of intravesical therapy with BCG was excluded due to the preexisting immunosuppression for renal allograft. Mitomycin C was considered as an alternative and patient received weekly dose for 5 consecutive weeks without any local or systemic toxicity. Patient was complaint with the surveillance cystoscopy every 3 months and remained tumor free at 12 months follow-up. Shortly after her 12 month follow-up surveillance cystoscopy she presented with drainage of fluid from a longstanding midline surgical scar. On further studies of the fluid, it was consistent with urine. A CT cystogram revealed a cutaneous fistula between the anterior bladder wall and the skin. The fistula closed spontaneously following a placement of an indwelling foley catheter for a period of 6 weeks. Patient was asymptomatic from fistula for period of 8 weeks, only to present with total urinary incontinence and recurrent cutaneous fistula. The repeat CT cystogram revealed an active colovesical fistula between bladder dome and sigmoid colon, an



Figures 1a, 1b. CT cystogram showing vesicoenteric and vesicovaginal fistula and an incidental cystic lesion in left adnexa as shown.

active vesicovaginal fistula from left posterolateral aspect of bladder and a cutaneous fistula. Figure 1a and Figure 1b. The CT scan also ruled out any evidence of active colonic diverticular disease and cystoscopy demonstrated no evidence of tumor recurrence.

Case 2

A 72-year-old lady with an 8 year history of low grade papillary TCC was under surveillance, with a past history of left distal ureterectomy and a completion left nephroureterectomy for recurrent upper tract TCC in subsequent follow-up. Patient recovered well from the surgery and was under surveillance for a period of 6 months. A follow-up cystoscopy revealed multiple low grade TCC, treated by transurethral resection of bladder tumor (TURBT) and received a single dose of perioperative intravesical MMC instillation. The TUR of tumor was complete and uncomplicated without any intraoperative evidence of bladder perforation.

Patient recovered well after the procedure, to present at 6 weeks follow-up with signs of bowel obstruction. On admission to a general surgical service a CT scan of abdomen and pelvis with delayed images revealed a partial small bowel obstruction with a pelvic fluid collection but no signs of extravasation from the bladder. Patient was commenced on a conservative treatment with nasogastric decompression, intravenous fluid and bowel rest. In addition the pelvic collection was drained and the fluid was sent for microbiology and biochemistry. The fluid creatinine was normal (0.14mg/dl). Due to a limited clinical improvement a repeat CT scan of the abdomen and pelvis at 4 weeks of conservative treatment revealed a finding consistent with persistent high grade bowel obstruction with the delayed imaging suggestive of contrast extravasation from the bladder. At this stage the patient underwent exploratory laparotomy with findings of small bowel being adherent to the dome of the bladder with evidence of enterovesical fistula. On further examination liquefaction of a significant portion of the bladder wall suggested grossly areas of fat necrosis. Attempt of primary repair was unsuccessful due to lack of viability and integrity of tissue. The patient underwent radical cystectomy and urinary diversion with ileal conduit. The patient recovered uneventfully. The final pathology revealed extensive necrosis with inflammatory cell infiltration, peri vesical fat necrosis, and severe fibrinous serositis with no evidence of any neoplasm. The omentum and bowel revealed areas of focal fat necrosis and severe fibrinopurulent serositis with fibrinous adhesions. Figure 2a and Figure 2b.



Figures 2a, 2b. Hematoxylin and eosin stain with 40 X magnification. Figure 2a shows extensive necrosis with inflammatory cells in the necrotic background and adjacent non necrotic tissue with inflammatory cells with a clear boarder in between, Figure 2b area of fat necrosis appearing as vacuoles.

Discussion

A single perioperative dose of intravesical instillation of chemotherapeutic agent is well supported based on the meta-analysis of seven randomized trials showing a decrease in relative risk of recurrence by 39% in patients with low grade Ta, T1 disease.³

Local complications like cystitis, penile necrosis, injection site necrosis, calcification, perforation, inflammatory tissue reaction and extravasation has been described in the literature.

Nieuwenhuijzen et al reported a case of extraperitoneal extravasation following intravesical instillation of MMC in a post TUR resection of bladder tumor. The patient presented with persistent

which required a surgical repair. At surgery the intraoperative findings revealed perivesical and perirectal fat necrosis confirmed with postoperative histology. The proposed theory was necrosis due to mitomycin extravasating through a thin bladder wall following deep resection.² Doherty et al in their retrospective study of 12

pelvic pain and subsequent diagnosis of fistula

Doherty et al in their retrospective study of 12 patients who underwent radical cystectomy observed significant perivesical fat necrosis and tissue reaction with prior history of instillation of either epirubicin or MMC. Of these 12 patients, 6 patients received intravesical instillation with epirubicin in 5 and MMC in 1 patient. Of these six patients, five had extensive necrosis of the bladder wall and perivesical fat necrosis when compared to six who received no intravesical instillation. These inflammatory changes were confirmed by histopathology of tissue obtained following radical cystectomy and attributed to intravesical instillation.⁴

Similarly Shapiro et al⁵ in their retrospective review identified three patients treated with both perioperative single dose and 6 weeks course of MMC. Two patients developed a non-healing ulcer at the site of resection on successive follow-up cystoscopy. A third patient developed a more severe complication of lower abdominal pain and was discovered to have bladder perforation on subsequent investigation. The patient failed the initial conservative treatment for the perforation with eventual radical cystectomy as a definitive treatment. The author attributed the perforation to an impaired wound healing exacerbated by mitomycin C resulting in chronic ulceration and perforation.

In our experience at Ohio State University, the fistulous complications reported following MMC instillation were complex and pose a dilemma in the management of such a complication.

In case study 1, an immuno-compromised patient developed an insidious cutaneous fistulation at 12 month follow up after a 5 weeks induction course of MMC. On radiological investigations patient did not have active diverticular disease of bowel or any evidence of endoscopic tumor recurrence. There was no evidence of bladder perforation at the preinstillation TURBT and on subsequent surveillance cystoscopy. The only pertinent history associated with fistulation was previous MMC instillation. The multiple fistulas were assumed to be due to the perivesical drug extravasation leading to fat necrosis and necrotic lytic reaction involving the surrounding tissue. The underlying immunocompromised status may have aggravated the local reaction leading to sepsis and multiple complex fistulation.

Similarly a second case study was associated with significant perivesical fat necrosis with an enterocutaneous fistula that appeared to be induced by administration of MMC. In this patient the gross finding at surgical exploration revealed friability and nonviability of a portion of the bladder along with what appeared to be perivesical fat necrosis. This finding was associated with vesicoenteric fistula. The microscopic examination of the tissue showed a similar finding of extensive fat necrosis as that described by Nieuwenhuijzen et al.

Though the exact mechanism for the described fistula is unknown we propose that this may be due to seepage of MMC into perivesical tissue at the site of TUR resulted in subsequent fat necrosis and a delayed fistula formation. Our proposal is supported by the fact that asymptomatic extravasation can be seen in up to 58% of patients following TURBT. The extravasation observed does not impose a medical or surgical intervention and may or may not require catheter drainage.^{6,7} Though this complication is noted with MMC it is not restricted to MMC as similar reaction is noted with epirubicin.⁴

An animal model was developed by Shapiro et al⁸ to address the effect of intravesical MMC instillation on wound healing. Female Sprague Dawley rats were subjected to a surgical injury (anterior cystostomy and pinching of the mucosa) in an attempt to mimic the injury associated with bladder tumor resection. Histological inflammatory changes were quantitatively measured for odema, fibrosis, and chronic inflammation between the surgical injury group (control) and a group that not only sustained the injury but also received intravesical mitomycin C. The severity of inflammation was worse in the mitomycin treated animals when compared to controls. The authors thereby concluded the potential of MMC in impeding wound healing with chronic fibroinflammatory changes which hinders wound healing with increased susceptibility to complications.

Conclusion

With rising incidence of bladder cancer and routine use of intravesical chemotherapy one needs to be aware of such rare but serious complication of intravesical instillation of chemotherapeutic agents.

Any suspicion of perforation during transurethral resection should be excluded, especially in patients with wide and deeper resection. All patients following chemotherapy instillation should be closely observed for any new onset pelvic discomfort, pain in immediate postoperative period and/or after discharge as well as signs suggestive of fistulation either external or internal. All patients are informed to beware of such symptoms and return to the caring physician for immediate evaluation for possibility of such a complication. \Box

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