

Eosinophilic cystitis following immediate post-resection intravesical instillation of mitomycin-C

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We present a patient who developed severe lower urinary tract symptoms following resection of a Ta low grade bladder urothelial carcinoma with immediate post-

resection instillation of mitomycin-C. Urine cultures were negative. Radiographic imaging demonstrated a bladder mass. On biopsy she was found to have eosinophilic cystitis. We report the clinical scenario and discuss treatment options. A review of reported cases in the English literature is provided.

Key Words: eosinophilic cystitis, bladder, cancer

Introduction

Eosinophilic cystitis (EC) is a rare complication of intravesical therapy. It can present with severe urinary symptoms such as intense suprapubic pain, frequency, urgency and hematuria. These symptoms mimic a urinary tract infection; however, urine cultures can be negative leaving the condition unchanged after a course of antibiotics. Herein we describe a patient who developed a delayed-type hypersensitivity reaction following the immediate administration of mitomycin-C (MM-C) after transurethral resection of transitional cell carcinoma (TCCA) of the bladder.

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Patient presentation

A 59-year-old female presented to our care with a history of recurrent low grade non-invasive bladder tumors first diagnosed in 1995. Her remote bladder cancer history included bladder perforation from transurethral tumor resection managed conservatively with prolonged foley catheter drainage. She required no additional therapy and did not develop an extravesical recurrence. Three years prior to presentation she was treated with a single immediate post-resection dose of MM-C following another tumor resection. The patient remained cancer free on surveillance until she developed gross hematuria related to the initiation of anti-platelet therapy following angioplasty and coronary artery stenting. Office cystoscopy revealed a low volume, superficial appearing papillary tumor. Her other medical problems included a childhood history of asthma.

The patient consented for resection of the tumor followed by immediate post resection MM-C. The

tumor was removed with the cold cup biopsy forceps and the tumor base was subsequently fulgurated. After evacuation of urine, 40 mg of MM-C in 20 mL of sterile diluent was placed within the bladder and left indwelling for 45 minutes followed by evacuation of bladder contents and removal of the foley catheter. Pathology demonstrated a low grade non invasive tumor (clinical stage Ta, 1997 TNM staging).

Two months later the patient developed severe lower urinary tract symptoms including urethral burning, pelvic pain, and suprapubic pressure. She was prescribed ciprofloxacin by her primary care physician for a presumed urinary tract infection. Urine cultures were negative. The symptoms intensified, and the patient described discomfort similar to when her bladder was perforated. She was hospitalized for pain control and underwent evaluation with a CT scan of the abdomen and pelvis, Figure 1. A large portion of the bladder wall over the prior tumor site was noticeably thickened beyond what would be attributed to an uncomplicated transurethral resection procedure.

The patient was taken to the operating room approximately 1 week later. Cystoscopically, the bladder was noted to have pronounced erythema with an associated flat tumor-like appearance to the urothelium and underlying tissue. Given the brief time frame and non-aggressive pathologic features following the prior resection, a benign etiology was suspected. In order to establish a diagnosis, a portion of the pseudomass was resected. Pathology revealed reactive atypia of the urothelium, extensive necrosis, and significant eosinophilic infiltration of the tissue specimen, Figure 2. No malignant cells were identified.

The patient was treated with a combination of medications including antispasmodics, anticholinergics, nonsteroidal anti-inflammatory agents, antihistamines and oral narcotics. However, none of these medications provided any meaningful symptomatic relief. She next was given a month-long tapered course of prednisone supplemented with a proton-pump inhibitor for gastric ulcer prophylaxis. Her symptoms improved

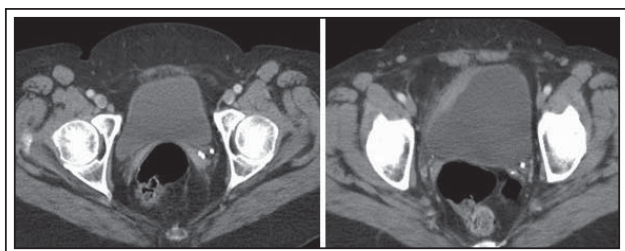


Figure 1. CT scan of bladder, pre-resection on the left, post-resection/post MM-C on the right.

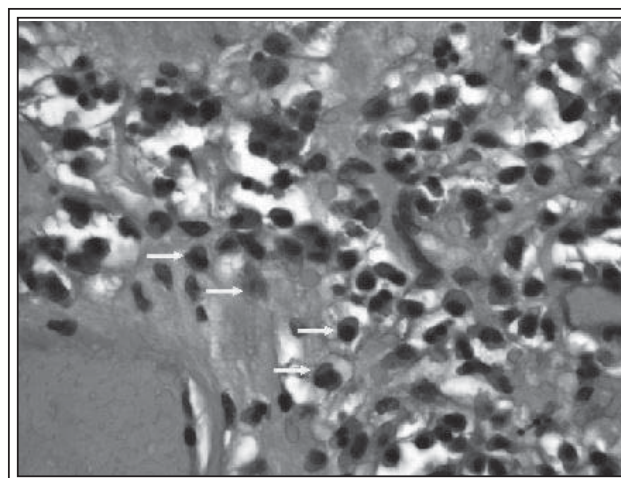


Figure 2. H&E stain of the bladder biopsy (x60 objective). Numerous eosinophils are identified at the lamina propria (arrows).

dramatically within 72 hours of the initiation of the prednisone. She has had minimal symptoms and no tumor recurrence for 18 months following the completion of her steroid taper.

Discussion

EC is a rare condition characterized histologically by eosinophilic infiltration of the lamina propria and muscularis propria.¹ It is usually associated with marked irritative lower urinary tract symptoms. EC has been reported following the administration of induction courses of intravesical chemotherapy for TCCA.²⁻⁴ Its presence may mimic an invasive bladder tumor, a confounding factor since about one quarter of reported cases have occurred in patients with a history of TCCA.⁵⁻⁷ There is also an association with respiratory disorders, such as asthma.¹

EC occurring following MM-C administration was first reported in 1987.⁴ The reaction typically follows multiple weekly administrations of the intravesical agent. In one postcystectomy patient an eosinophilic urethritis occurred after MM-C was placed in the urethral stump prior to a planned urethrectomy.⁴ EC is the final step in IgE mediated allergic cystitis and the cause is surmised to be from a hypersensitivity reaction occurring from a rechallenge with MM-C.^{1,6}

Another group has reported EC in a patient following a single dose of MM-C.⁵ In their case the CT scan findings suggested an invasive cancer, in similar fashion to our patient. The time of onset was also similar, occurring 2 months following MM-C instillation. The authors suggest performing cystoscopy and bladder biopsy

TABLE 1. Summary of cases of eosinophilic cystitis following MM-C.

| Study | Age | Sex | Stage/grade | Dose of MM-C | Time on therapy | Intervention |
|---------------------------|-----|--------|---------------|--------------------------------|-----------------|--------------|
| Inglis et al ⁴ | 70 | Female | pTa G2 | 30 mg in 30 mL | 2 mths + | MM-C stopped |
| | 70 | Male | pT1b G2 | 40 mg in 40 mL | 8 mths | Observation |
| | 57 | Male | pT1b G3 | 40 mg in 40 mL | 2 mths + | Urethrectomy |
| Ulker et al ¹³ | 50 | Male | pTa G1 | 40 mg in 40 mL, 10 mg in 10 mL | 10 mths | Observation |
| | 63 | Male | n/a | 40 mg in 40 mL | 5 mths | Observation |
| Clark et al ⁵ | 55 | Male | pTa G1 | 40 mg | 1 dose | n/a |
| Present | 59 | Female | pTa low grade | 40 mg in 20 mL | 2 doses | Medications |

n/a = not available

to confirm the diagnosis. Table 1 lists reported cases of eosinophilic cystitis following MM-C in the English literature.

As this is a rare disease entity, therapeutic guidance is based on the suspected etiology and from prior case reports and series. Management initially consists of observation and withdrawal of the offending agent. A course of antihistamines and non steroidal anti-inflammatory drugs could be considered, along with antibiotics if the urine cultures are positive. Steroids are used for non-responding patients.^{1,6-8} For symptomatic relief, bladder anti-spasmodics and narcotic pain medications may be useful. Refractory, severe cases may require surgery, including cystectomy.^{1,6,8} A pooled analysis of 135 cases in the literature from varying etiologies revealed that almost half the patients were treated with steroids, antihistamines, and antibiotics. The three drug combination in conjunction with transurethral resection appeared to offer the best therapeutic results.⁸

More commonly noted side effects from intravesical MM-C instillation include chemical cystitis and allergic skin reactions.⁹ Care should be taken to avoid extravasation of MM-C following a bladder perforation, as soft tissue necrosis, abscess formation,¹⁰ and peritonitis may develop. There has been a resurgence of immediate post-resection intravesical therapy used to diminish tumor recurrence in selected patients with non-invasive bladder cancer.^{11,12} In light of this paradigm, it is important for all urologists and treating physicians to understand the clinical scenario in which the rare condition of EC might develop. □

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