Severe bladder contracture leading to cystectomy after intravesical mitoxantrone chemotherapy

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Since the early 1990s, mitoxantrone has been used as a chemotherapeutic agent for adjuvant intravesical treatment following transurethral resection of superficial transitional cell carcinomas of the bladder. Although its efficacy as adjuvant intravesical therapy remains questionable and its use has not gained wide acceptance, the safety profile of the drug has been reported as favorable. We report the first case of mitoxantrone-induced severe bladder contracture leading to a completely nonfunctional bladder after intravesical administration of the drug. Cystectomy and urinary diversion were the final consequences for the patient. *Anti-Cancer Drugs* 19:325–328 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Transurethral resection of moderate- to high-risk bladder tumors is usually followed by adjuvant intravesical chemotherapy or immunotherapy in an effort to lower the recurrence and progression rate and prolong the disease-free interval. Intravesical chemotherapy is used as first-line treatment, whereas intravesical immunotherapy with Bacillus Calmette–Guerin (BCG) is reserved for high-risk or recurrent tumors because of its higher toxicity [1,2].

Mitoxantrone, a DNA topoisomerase II poison, is one of the relatively newer agents that have been used for adjuvant intravesical chemotherapy, having demonstrated in some reports efficacy comparable with other popular intravesically administered chemotherapeutic agents like epirubicin and mitomycin [3,4]. Additionally, the drug has shown a very good safety profile as the side effects reported in most publications are mild to moderate [3–5]. We report here the first case, to our knowledge, of mitoxantrone-induced severe bladder contracture leading to a completely nonfunctional bladder, after intravesical administration of the drug. Cystectomy and urinary diversion were the final consequences.

Case report

In August 2005, a 67-year-old woman was referred to our department with severe irritative symptoms including frequency, urgency, dysuria and incontinence over the last 10 months. The patient was voiding almost every 30–40 min day and night. She was wearing pads. The patient had elevated serum creatinine (2.1 mg/dl) and anemia. Bilateral hydronephrosis was detected on renal ultrasound.

Her medical history included transurethral resection of stage Ta, grade II transitional cell carcinoma, 1 year before (August 2004) at another hospital. The tumor was completely resected and no intraoperative or postoperative complications were reported. Two weeks after operation she was started on adjuvant intravesical chemotherapy with mitoxantrone. According to the referring physician, the patient had no previous history of adjuvant intravesical therapy. The treatment schedule included 8 weekly intravesical instillations of 20 mg mitoxantrone (Novantrone; Wyeth-Ayerst Lederle Inc., Puerto Rico) diluted in 50 ml normal saline. The patient was instructed to retain the drug in the bladder for a period of 1 h after which the bladder was emptied by spontaneous voiding. Additionally, fluid restriction had been recommended 2 h before and immediately after the instillation to avoid reduction in drug concentration within the bladder. After the second of the eight scheduled intravesical doses, she developed frequency and macroscopic hematuria. One more instillation (the third), however, was given 1 week later. The condition continued to deteriorate leading finally to the full spectrum of symptoms reported before. No other intravesical instillation was performed thereafter.

On admission to our hospital a nephrostomy tube was inserted on the left side to improve renal function. Computerized tomography demonstrated a markedly thickened bladder wall with perivesical stranding

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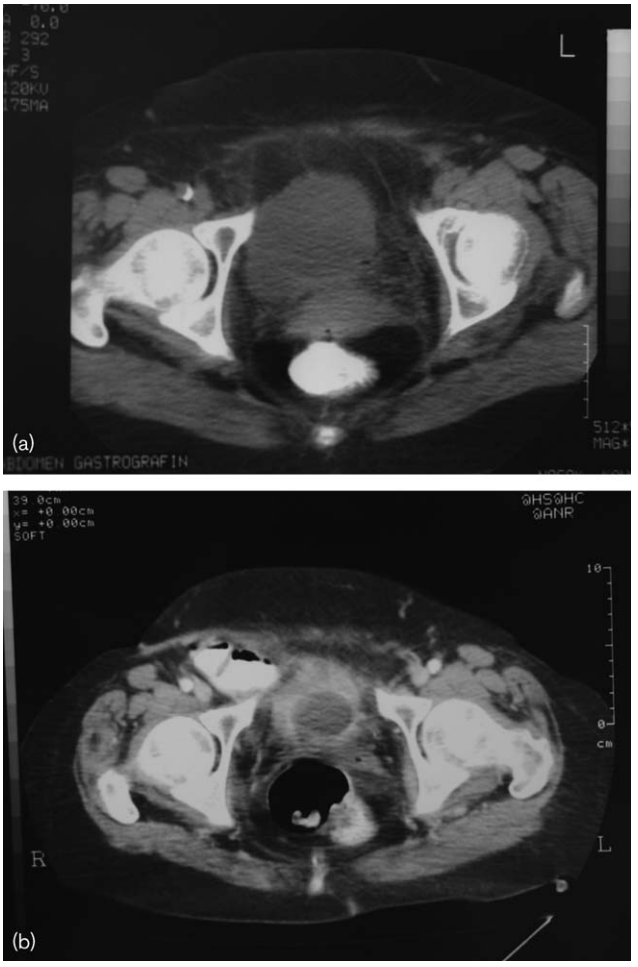
Fig. 1



(a) Normal-appearing urinary bladder before intravesical mitoxantrone chemotherapy. (b) Markedly thickened bladder wall 10 months after treatment.

(Fig. 1a and b). Cystography showed a small-capacity bladder (less than 50 ml) with bilateral ureteral reflux. Cystoscopy demonstrated diffuse edema of the bladder mucosa with patchy areas of hemorrhage. Bladder biopsies and urinary cytology were negative for malignancy. After renal function had been improved a few weeks later, the patient underwent radical cystectomy and ileal loop diversion. The operative findings included a small bladder with markedly thickened wall and extensive perivesical fibrosis. Pathology revealed extensive ulcerations of the epithelium, fibrosis and granulomatosis inflammation of the bladder wall. Inflammatory cellular infiltrations consisted mainly of granulocytes, lymphocytes and histiocytes, but eosinophils could be recognized as well. No evidence of malignancy was found. Eighteen months after surgery the patient is in good condition, tumor-free, with stabilized renal function (creatinine 1.3 mg/dl) and normal serum hemoglobin.

Discussion

Intravesical chemotherapy for reduction of tumor recurrences in superficial bladder cancer was initiated in the mid-1950s with the drug thiotepa. The principal side effect of thiotepa was myelosuppression related to its systematic absorption because of its low molecular weight [6]. To avoid the systematic toxicity of thiotepa many different agents have been tested and many have been abandoned due to low efficacy or severe toxicity. The chemotherapeutic agents that have been used most widely are thiotepa, ethoglucid, mitomycin, doxorubicin, epirubicin and mitoxantrone [2].

Mitoxantrone is an anthraquinone antineoplastic agent with structural similarities to doxorubicin and a mechanism of action similar to the anthracyclines. An extensive binding to tissues, with a steep dose–response curve and better local tolerance compared with anthracyclines has been reported [7,8]. Additionally, in in-vitro studies on transitional cell carcinoma of bladder cell lines, mitoxantrone was classified as one of the most cytotoxic agents tested [9]. Contrary to thiotepa, mitoxantrone has a high molecular weight. Therefore, systemic absorption and toxicity are negligible after intravesical application in patients with bladder tumors, as was demonstrated in a phase I study [10]. Mitoxantrone lacks the amino sugar moiety of anthracyclines that has been implicated as the causative mechanism for cardiac toxicity. This theoretical advantage is translated clinically into less severe cardiotoxicity than after anthracycline therapy, yet cardiac toxicity can occur especially when the drug is administered systematically [7].

Mitoxantrone has been tested in clinical trials as a chemotherapeutic agent for intravesical instillation since the early 1990s. Flamm *et al.* [5] compared two groups of patients with superficial bladder tumors, one treated only with transurethral resection (TUR) and the other with TUR plus mitoxantrone (20 mg) instillations. They found no statistically significant differences regarding recurrence rate, progression rate and overall disease-free interval. The only side effect was chemical cystitis in 11% of the patients. Contrary to the earlier study, Papatsoris *et al.* [11] reported superior results with the use of 10- or 20-mg of mitoxantrone compared with TUR alone in terms of tumor recurrence, but no difference in tumor progression. Toxicity was recorded in 23 and 31% for the 10- and 20-mg dose, respectively. Yaman *et al.* [4] reported a 63% overall response rate for a group of patients treated with 20 mg of mitoxantrone weekly for 6 weeks and then monthly for 10 months, after a mean period of 12 months follow-up. Chemical cystitis was observed in 14 out of 35 patients (40%). Good results have also been reported in other studies demonstrating efficacy comparable with that of other chemotherapeutic agents [3,10,12]. Nevertheless, a clear superiority of mitoxantrone over the other chemotherapeutic agents or

vice versa cannot be concluded from the data currently available. The lack of systemic side effects after intravesical instillation is definitely an advantage of mitoxantrone, especially over thiotepa. Doxorubicin, epirubicin and ethoglucid, however, only rarely have been implicated in systemic reactions [2,6]. Allergic reactions like palmar and genital skin rashes seen with mitomycin [6] have never been reported for mitoxantrone or other chemotherapeutic agents [2,6]. In contrast, the most prominent adverse effect of intravesical administration of mitoxantrone is genitourinary symptoms in the form of chemical cystitis [2,4,5,11,12]. The rate of chemical cystitis seems more or less comparable with that of other chemotherapeutic agents [6]. Treatment interruption owing to this side effect ranges in most studies between 0 and 9.5% [3–5,10–13]. A noticeable exception is a Spanish study comparing mitoxantrone and mitomycin, in which a 63.5% discontinuation rate owing to side effects for mitoxantrone, compared with only 15% for mitomycin, had been reported [14]. Additionally, Sharifi *et al.* [13], in a phase I–II study of intravesical mitoxantrone, reported on a case of severe chemical cystitis with significant reduction in bladder capacity and urge incontinence that took 6 months to recover.

Bladder contracture is a well-known and fortunately rare complication of intravesical therapy for superficial bladder tumors. It has been reported in the use of some popular chemotherapeutic agents like mitomycin C [15] and doxorubicin [16], but it is slightly more common after BCG immunotherapy [17,18]. Lamm *et al.* [18] reviewed the complications of intravesical BCG therapy in 2602 patients and reported the incidence of bladder contracture to be 0.2%. The underlying mechanism of this serious complication is unclear both for chemotherapeutic and immunotherapeutic agents. Dmochowski and Rudy [16] postulated that a benign recurrent bladder ulceration during doxorubicin therapy may have potentiated a fibrotic response in the bladder to doxorubicin. Nieder *et al.* [17], suggested that possible BCG extravasation at a nonhealed site of the bladder wall might have initiated an extensive perivesical inflammation with resultant bladder contracture.

A literature search was performed for cases of bladder contracture associated with intravesical chemotherapy, using the *PubMed* and *Scopus* databases from 1985 to June 2007. The search terms used included 'bladder contracture', 'bladder cancer', 'mitoxantrone', 'chemotherapy' and 'immunotherapy'. We considered papers in English, French, German, Italian and Spanish languages. We were able to locate only one similar case of bladder contracture after intravesical mitoxantrone chemotherapy reported by Stewart *et al.* [10]. This was a patient treated with a weekly dose of 7.5 mg. The patient developed urinary frequency and dysuria. Cystoscopy revealed a necrotic-appearing urothelium. After cessation of treatment, however, the urothelium eventually healed. No further treatment is reported for this patient and definitely cystectomy is not mentioned as the final treatment. Contrary to the case of Stewart *et al.* [10], our patient had the worst possible outcome regarding her bladder as the urothelium never healed. Rather, the process of bladder fibrosis continued, leading eventually to a contracted nonfunctional bladder. This was suggested by the severe lower urinary tract symptoms and confirmed both radiologically and cystoscopically. Cystectomy and urinary diversion was the only realistic treatment option. A noticeable difference between the two cases is the dose of mitoxantrone used, as our patient received 20 mg per instillation versus 7.5 mg per instillation for the patient reported by Stewart *et al.* [10]. Perhaps this could explain the different outcome in terms of bladder preservation, although most authors recommend the 20 mg dose as more appropriate for an anthracycline cytostatic drug [3,5,12]. In the studies using a dose of 20 mg, chemical cystitis was the only side effect reported, with the majority of patients experiencing no side effects [3,5,11,12]. No differences in the dilution of the drug or the exposure period were reported between patients with and without chemical cystitis. Although treatment interruption was required in very few cases [3,12], the final result of bladder contracture with complete loss of bladder function was not seen in any of these studies. Discontinuation of treatment is probably the key point here, as the drug dilution (20 mg mitoxantrone in 50 ml normal saline) and exposure time (1 h) for our patient were the same with those used in most studies. Indeed, both in our case and the case reported by Stewart *et al.* [10] additional intravesical treatment was given to the patients despite the fact that their clinical course indicated the onset of chemical cystitis. From a clinical point of view this is an important observation that suggests immediate discontinuation of intravesical mitoxantrone chemotherapy should severe irritative symptoms appear in the course of treatment. This is also true for all other chemotherapeutic and immunotherapeutic agents used for intravesical instillations [6]. We are, however, unable to explain the initiating factor of this serious event unless the explanation suggested for doxorubicin by Dmochowski and Rudy [16] is also adopted for mitoxantrone given the structural similarities of these two drugs.

In conclusion, we report the first case of mitoxantrone-induced severe bladder contracture after intravesical chemotherapy leading to cystectomy and urinary diversion. This severe, albeit extremely rare, complication of intravesical mitoxantrone chemotherapy should be added to the list of potential side effects of the drug. Irritative symptoms during treatment with mitoxantrone should prompt the physician to delay further instillations until symptoms have settled or, even better, to abandon treatment.

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