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Bladder Wall Calcification Following Transurethral Resection of Bladder Tumor and Intravesical Mitomycin C Instillation

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In rarely reported instances, the use of intravesical mitomycin C appears to have caused bladder wall calcification. We report two patients treated for non-invasive urothelial carcinoma of the bladder with transurethral resection and mitomycin c instillation. Both of these patients experienced new onset of severe irritative voiding symptoms shortly thereafter. Although one patient completed a six-cycle course of Bacillus Calmette-Guerin (BCG), the other only received one instillation due to symptom severity. On cystoscopy the resection beds appeared calcified and necrotic. Biopsies revealed dystrophic calcification and necrosis without evidence of tumor. Resection of this area led to complete resolution of symptoms and normal healing of the resection site. Our results are consistent with the current hypothesis that these calcifications are not related to recurrence or persistence of tumor. Although there have not been reported cases of these calcifications signifying recurrence of tumor, it is important for clinicians to rule out recurrence as a cause for these symptoms. Resection of the area has the added benefit of alleviation of irritative voiding symptoms encountered shortly after mitomycin c instillation.

bladder calcification | mitomycin, bladder cancer | intravesical chemotherapy

Bladder wall calcification is an uncommon finding, having only a few known etiologies including schistosomiasis, tuberculosis, amyloidosis, cyclophosphamide and neoplastic processes (1). In rarely reported instances, the use of intravesical mitomycin C appeared to cause bladder wall calcification (2-4). We report two cases of bladder wall calcification after intravesical mitomycin C therapy.

Case 1.

A 76-year-old Caucasian male presented to the urology clinic for a follow up of a ureteral calculus successfully treated with medical expulsive therapy and complained of new intermittent painless gross hematuria for the past 2 weeks. He had a history of benign prostatic hyperplasia (BPH) with lower urinary tract symptoms (LUTS), primarily nocturia, treated with finasteride and terazosin and low post void residuals. His medical history included recurrent urolithiasis, hyperlipidemia, hypertension, myocardial infarction, hypothyroidism, emphysema and a 52-pack year smoking history.

Computed tomography with and without contrast (CT Urogram) demonstrated a filling defect on the left wall of the bladder. Flexible cystoscopy confirmed a papillary bladder tumor in this location. The patient subsequently underwent transurethral resection (TUR) of bladder tumor of an approximately 2.5 cm, superficial-appearing tumor. There was very low suspicion for perforation during resection. Mitomycin C 40 mg was instilled post-operatively and retained for one hour. Pathology demonstrated a focally high grade papillary urothelial carcinoma, negative for lamina propria invasion. Muscularis propria was not present in the specimen. The patient then underwent a six-cycle course of intravesical Bacillus Calmette-Guerin (BCG). During his BCG treatment he had dark urine consistent with small amounts of old blood but reported no dysuria, gross hematuria or irritative voiding symptoms beyond baseline.

On post-BCG cystoscopy four months after the initial resection, a small recurrence was noted on the right lateral wall and the patient underwent TUR of this bladder tumor. At this time it was noted that at the initial resection site there was an extensive area of dystrophic calcification and necrotic appearing tissue. Biopsies were taken to rule out recurrence. Pathology from the new resection site also showed non-invasive, high-grade papillary urothelial carcinoma. Biopsy of the previous resection site demonstrated necrotic tissue with scant viable muscle and urothelium with no evidence of tumor. A CT with contrast depicted irregular bladder wall thickening with some calcifications at the initial resection site on the left wall but no evidence of extravesical extension of the tumor (Figure 1).

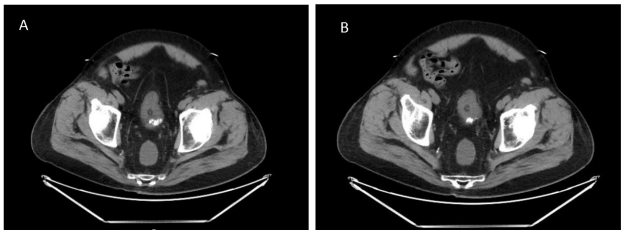

Figure 1. A: CT image of bladder wall calcification on the posterior bladder wall. B: Calcification of the posterior inferior bladder wall.

Four months later the patient had another small recurrence at a new site on the posterior bladder wall. Cystoscopy, bladder biopsy and fulguration were performed. It was noted that the patient had an extensive area of dystrophic calcification overlying a necrotic ulcer on the posterior wall. The area was biopsied twice and continued to

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show necrotic tissue with fragments of fibrous, calcified debris. The patient complained of worsening irritative voiding symptoms and had worsening intermittent gross hematuria. Another cystoscopy showed diffuse bleeding from the edges of the calcified areas of the initial resection site. The decision was made to resect the calcified in an attempt to alleviate his symptoms.

The patient was taken back to the operating room for a transurethral resection of the calcification. The area appeared severely inflamed and calcified (Figure 2). Pathology showed benign mucosa, fibromuscular tissue with ulceration, acute and chronic inflammation, foreign body type giant cell reaction, fibrosis and dystrophic calcification with no evidence of dysplasia or malignancy. He tolerated the procedure well and over the next several weeks his gross hematuria resolved. His irritative voiding symptoms improved. One month after the resection he underwent surveillance cystoscopy during which it was noted that the resection bed appeared to be healing well and there was no sign of recurrence of tumor or calcification.

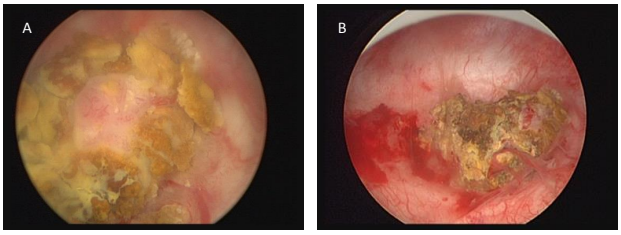

Figure 2. A: Cystoscopic image of bladder wall calcification. B: calcification with adjacent inflammation and bleeding.

Case 2.

An 83-year old man underwent local cystoscopy for surveillance of low grade Ta urothelial cell carcinoma of the bladder diagnosed 30 months prior and treated with TUR and intravesical instillation of mitomycin C. All follow-up surveillance cystoscopies and cytologies were negative. Three small papillary tumors were noted on the right lateral wall of the bladder and he was again treated with TUR and intravesical mitomycin C. Pathology showed high grade Ta urothelial cell carcinoma.

One week later the patient returned to clinic to discuss pathology and complained of worsening irritative voiding symptoms. He was chronically on alfuzosin for BPH with low post void residual (PVR). He was given oxybutynin. Three weeks later he returned for his first BCG instillation and complained of persistent and worsening irritative voiding symptoms. BCG was instilled and he was given solifenacin.

The patient continued to call the office on a weekly basis complaining of persistent and worsening irritative voiding symptoms including nocturia, voiding five times per night and frequency, voiding every thirty minutes which was preventing him from leaving his home.

His subsequent BCG instillations were cancelled and over the next two months he tried oxybutynin, solifenacin, mirabegron and behavioral modification all with no improvement. Three months after TUR he underwent cystoscopy. There were no tumors but there was an area of necrosis on the anterior bladder, which was resected. Pathology revealed chronic inflammation, and necrotic tissue with prominent dystrophic calcifications (Figure 3).

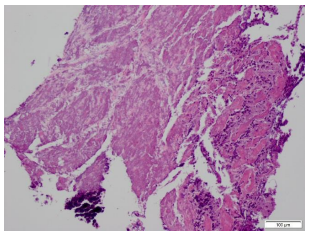

Figure 3. Necrotic tissue with prominent dystrophic calcifications.

Discussion

A single dose of intravesical chemotherapy with mitomycin C is frequently used within 24 hours of after TUR of non muscle-invasive bladder tumors to reduce the risk of recurrence by 13% (5). mitomycin C is an alkylating agent that inhibits DNA synthesis by acting as a potent DNA crosslinker. When used as a topical chemotheraputic agent it causes degenerative changes leading to ischemic necrosis of tumor cells (2). Although normal, intact urothelium is resistant mitomycin C, tumor cells are subject to these antitumor effects (2). Because intact urothelium is resistant and the high molecular weight of mitomycin C prevents systemic absorption, there is a very low risk of damage to healthy urothelium or systemic side effects. The most common side effect of intravesical mitomycin C is chemical cystitis. Less common side effects include contact dermatitis, allergic reaction, reduced bladder capacity, leukopenia and thrombocytopenia (6).

There have been rare reports of bladder wall calcification following instillation of intravesical mitomycin C. In previous reports these calcifications are always at the previous resection site and appear between six months and three years from the initial resection and instillation of mitomycin C (1,2). There is a classic curvilinear appearance to the calcified bladder wall on radiographic imaging, giving it an appearance distinct from other types of calcification in the bladder (1). In previous reports, only one patient had pathology that showed recurrence or progression of cancer within the calcified specimen (3) and that patient had more than ten transurethral resections for suspected bladder cancer with multiple recurrences. It is much more common for these calcified lesions to be composed of necrotic tissue, microscopic calcifications and scant urothelium than recurrent tumor cells (2).

The mechanism of bladder wall calcification after instillation of mitomycin C is theorized to be an exaggerated form of the normal response of the tissue at the resection site (2). Mitomycin C causes the plasma of the cell to undergo degenerative changes leading to fibrinoid degeneration of the interstitial tissue and necrotic degeneration of vessels. This eventually leads to ischemia and necrosis of cells and in rare cases, calcific degeneration (2). This would suggest that allowing the bladder time to heal before instillation of mitomycin C would decrease the likelihood of bladder wall calcification, but this is not realistic as instillation within 48 hours is necessary for maximal efficacy in reducing the rate of progression. Also, there is significant variability in the temporal relationship reported in the literature. In one case the appearance of calcification was not until three years after mitomycin C instillation (3). This suggests that the pathophysiology is variable and incompletely understood.

Other reported cases of calcification after mitomycin C have been criticized for failing to adequately investigate other causes of calcification such as alkaline encrusted cystitis, as mitomycin C itself is an alkylating agent (7). Since presentation Patient Ones urine pH ranged from 5.0-6.5. Only one of his five urine cultures was positive for *E. coli* which was promptly and successfully treated with oral antibiotics. Patient two did not have a urine pH measured and did not have any positive urine cultures. Both had histories of BPH but consistently low post void residuals. Although both patients had a history of upper tract urolithiasis, neither had any specific risk factors for bladder calculi.

Many of the previously reported cases involve the use of several other intravesical treatment such as thiotepa, doxorubicin and cisplatin (4). Both of our patients did receive intravesical BCG following mitomycin C. Patient Two only received one dose due to severe and worsening irritative voiding symptoms, suggesting an abnormal response prior to BCG instillation. There are two reported cases of dystrophic bladder wall calcification following BCG therapy for non-invasive bladder cancer (8). Both patients, however, had other risk factors such as history of pelvic radiation, parathyroid disease and use of intravesical mitomycin C. These two cases do not provide compelling evidence that the use of intravesical BCG is an independent risk factor for dystrophic bladder wall calcification. It is reasonable to conclude that the instillation of mitomycin C immediately following resection in our patient led to pathologic calcification of the bladder wall.

Currently, the literature on bladder wall calcification following mitomycin C instillation is incomplete. Although only one of the reported cases involved a recurrence one cannot assume that this is a benign process and adequate tumor surveillance is paramount. Biopsies or resection of abnormal appearing tissue can rule out recurrence or progression, and complete resection can palliate any symptoms the patient may have from the calcifications themselves.

Conclusion

Bladder wall calcification is a rare and incompletely understood complication of mitomycin C instillation. The benefit of mitomycin C far outweighs the risk of bladder calcification, but physicians should be aware of the morbidity that these calcifications can cause. A patient who complains of severe and persistent irritative voiding symptoms after instillation of mitomycin C may benefit from early cystoscopy and resection of dystrophic calcifications. There does not appear to be an increased risk of tumor recurrence with calcification although this should always be confirmed on pathology. After resection of these lesions and resolution of symptoms the patient can resume a regular surveillance schedule.

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