CASE REPORT

Tumor implantation: a rare but potentially preventable cause of death in cystectomy patients

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Early cystectomy has become an increasingly popular option for the treatment of high grade, stage T1 bladder cancer and has the advantage of removing sites that are often inaccessible to intravesical therapy. The following case report illustrates a possible lethal pitfall in cystectomy that leads us to suggest simple and inexpensive measures to prevent spillage of urine and the possible implantation of urothelial carcinoma during cystectomy.

Key Words: early cystectomy, preventable, bladder cancer, tumor implantation

Introduction

The treatment of high grade, T1 bladder cancer is highly controversial, but recent reports of reduced survival of patients who fail intravesical therapy and come to cystectomy[1] have prompted increased enthusiasm for early cystectomy.[2] Cystectomy has the advantage of removing the distal ureters and prostatic urethra, sites often inaccessible to intravesical therapy and at risk for progression.[3] Radical cystectomy is considered to be curative for disease pathologically confined to the bladder. The following unfortunate case illustrates the importance of early and effective treatment of high grade bladder cancer and an example of early cystectomy followed by early progression and death. This unfortunate result prompted a search for potential causes for failure. It subsequently led to a literature review and suggestion of additional measures to avoid leakage of bladder contents thereby reducing the risk of tumor implantation in the pelvis during cystectomy.

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Case report

A 62-year-old man who presented with gross hematuria underwent transurethral resection of a solitary 2 cm tumor near the right anterior bladder neck in November 2006. Biopsies revealed carcinoma in situ of the bladder and prostate and high grade Ta urothelial carcinoma of the bladder. Past medical history was significant for ulcerative colitis. He smoked one pack of cigarettes

daily. CT scan was negative and his PSA was 6.6. On physical examination he had 2+ enlargement of the prostate without nodularity or induration. He did not receive immediate postoperative chemotherapy or subsequent BCG immunotherapy.

Cystoscopy in February 2007 showed multiple tumors on the right dome. Resection revealed high grade (Grade 3/3) stage T1 papillary urothelial carcinoma and CIS. Muscle was present in the specimen and not involved. Needle biopsy was positive for Gleason 6 (3 + 3) adenocarcinoma of the prostate in 5 of 17 cores, all but one on the right side. He was referred to us and radical cystoprostatectomy was recommended.

In April 2007 he underwent radical cystoprostatectomy with extended pelvic lymphadenectomy and Studer orthotopic neobladder at a university near his family. He had 21 negative nodes, Gleason 6 adenocarcinoma confined to the prostate, and multifocal high grade T1 urothelial carcinoma with CIS. There was no muscle or lymphovascular invasion. All margins, including the urethra and ureter, were negative.

The patient did well for 6 months, but in November 2007 he began to experience severe rectal and abdominal pain. After repeated hospitalizations and emergency visits, exploratory surgery in January 2008 revealed extensive recurrent transitional cell carcinoma of the pelvis. Sigmoidectomy and colostomy were performed. Biopsy of the retroperitoneum showed transitional cell carcinoma. Extensive carcinoma was present in the sigmoid and 10 of 16 mesenteric nodes were positive for TCC. Shortly thereafter, he began cisplatin, gemcitabine and paclitaxel combination chemotherapy and responded well. PET CT scan in July 2008 showed only thickening of the rectal wall and in August 2008 he underwent pelvic exenteration with excision of his neobladder, ileal loop diversion and proctectomy. No tumor was found in the specimen, but in October 2008 he developed brain metastasis. He was treated with whole brain radiation therapy and intrathecal DepoCyt, but expired from progressive disease in January 2009. After the diagnosis of high gradeT1 TCC, he had seven operations, at least 10 ER visits, and 14 hospital admissions. He survived 1 year and 8 months after the cystectomy; 3 of these months were spent in the hospital.

Discussion

Risk factors for disease progression include high grade, lamina propria invasion, carcinoma in situ, tumor multiplicity, prostatic urethral involvement, tumor size over 3 cm, lymphovascular invasion and recurrence at 3 months.[4,5] At initial presentation he had only three of these eight risk factors. Immediate postoperative instillation of chemotherapy reduces risk of recurrence in meta-analysis by 39%[6] and is uniformly recommended by national guidelines.[7] Repeat resection of high grade lesions has also been recommended and is reported to reduce tumor recurrence in controlled trials even when immediate intravesical therapy is given,[8] but the importance of thorough, meticulous resection with adequate margins deserves further emphasis.[9] Wide resection and immediate intravesical chemotherapy, as important as they are, would not have been sufficient in this patient with CIS. BCG immunotherapy is generally recognized as the treatment of choice for CIS,[10] and maintenance BCG is demonstrated to be superior. In the SWOG maintenance study, 84% of patients on 3 week maintenance BCG had complete response compared with 69% without maintenance.[11] No intravesical therapy was used in this case, but intravesical therapy, even if effective, would have had no effect on his Gleason Grade 6 adenocarcinoma of the prostate.

The coexistence of prostate cancer and multifocal CIS and recurrent high grade, T1 TCC of the bladder at 3 months tipped the scale for radical cystoprostatectomy. The Studer orthotopic neobladder permits cystectomy patients to maintain both their body image and quality of life. The extended node dissection as performed in this case appears to significantly increase survival.[12] With state of the art treatment applied early for T1 TCC with CIS confined to the specimen, why did this patient do so poorly? The answer may be found in the operative report that reads: "After incising the urethra, the apex of the prostate was tied off with a 3-0 silk figure of 8 suture to avoid urine leakage." The history suggests that this technique may have failed to prevent urine leakage and seeding of the wound. No cytotoxic drug was given at the time of cystectomy. Before environmental concerns became paramount in operating rooms, formalin was instilled in the bladder to prevent seeding of viable tumor cells in the event of urine leakage. In one report 7 of 13 patients (54%) with high grade TCC undergoing partial cystectomy without formalin instillation developed wound seeding and all died within 10 months to 3 years postoperatively.[13] In a retrospective series, the incidence of local pelvic recurrence was reduced from 43.8% in patients undergoing radical cystectomy to 11.7% in those undergoing radical cystectomy and urethrectomy with formalin instillation.[14] The importance of preventing spillage of bladder tumor cells during cystectomy was recently emphasized in laparoscopic cystectomy

with the use of 10 mm endoscopic vascular clips and 2% formalin instillation,[15] but it is not emphasized in Campbell's and even ignored in Glenn's text book descriptions of open radical cystectomy. Even with careful dissection and the use of a large clamp or tie on the urethra, urine spillage cannot always be prevented. In our survey of 162 urologists doing cystectomy, only 11 (6.8%) instilled a cytotoxic at the time of cystectomy. Local recurrence in current cystectomy series is only in the range of 5%, but the possibility of seeding is well documented, as evidenced by international guidelines that uniformly recommend instillation of chemotherapy immediately following bladder tumor resection. Considering the lethal consequence of tumor seeding in the pelvis, we recommend consideration of the instillation of cytotoxic chemicals such as Thiotepa 60 mg in 30 cc, Mitomycin 40 mg in 20 cc water,[16] or 2% formalin at cystectomy and copious irrigation to reduce this risk.

Conclusion

Historical series and computer modeling report that 5 year survival in T1G3 bladder cancer treated with BCG immunotherapy is actually higher than the survival in patients who undergo cystectomy. This case illustrates one potential explanation for this paradox that might be corrected by carefully preventing spillage of bladder contents and instilling a cytotoxic drug into the bladder during cystectomy to reduce the potential for implantation if accidental spillage occurs.

The adequacy of training and performance of transurethral resection for bladder cancer has been questioned, but use of post resection chemotherapy to reduce intravesical seeding is widely accepted. This case raises the question: can radical cystectomy technique be improved? Wound seeding appears to be a rare occurrence, but considering the far worse prognosis than bladder seeding, should be prevented whenever possible. Careful avoidance of urine spillage, instillation of cytotoxic agent to kill cells that might be spilled, and copious irrigation to diminish their numbers are simple measures that could prevent recurrence and save lives. □

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