Cutaneous BCG of the penis after intravesical therapy for bladder cancer: a case report in a 66-year-old male

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Objective: *Transitional cell carcinoma of the bladder is commonly treated with intravesical BCG. We report a cutaneous complication of BCG after therapy in 66-year-old male 4 years after initiating treatment.*
Materials and methods: *A case review including pathological slides, laboratory data, and radiographic findings.*
Results: *Biopsy findings showed an ill defined granulomatous process with chronic inflammation and necrosis.*
Conclusion: *The patient was managed on antituberculous therapy for a period of 6 months with resolution of symptoms.*

Key Words: BCG therapy, superficial bladder cancer, penile lesion

Introduction

The prevalence of bladder cancer has steadily risen by 50% between 1985 and 2005 in the United States.[1] Bladder cancer is nearly three times more common in men than women representing the fourth most common tumor in men. The median age of presentation in men is 69.[1] White males are affected more than African American males and also have a more favorable survival.[2] Approximately 70% of bladder tumors are non-muscle invasive at presentation. Of these, 70% present as stage Ta, 20% as T1, and 10% as CIS.[2] Transurethral resection of bladder tumor is the initial treatment for visible lesions to remove tumor and stage the lesion. For superficial disease, intravesical therapies with either immune modulating agents or chemotherapy are the standard treatment regiment used to treat bladder cancer. BCG, an immunotherapeutic agent, is an attenuated mycobacterium developed as a vaccine for tuberculosis.[2,5] It is used as first line therapy for superficial bladder TCC and has been approved by the FDA.[2]

We describe local cutaneous complication on the penis after intervesical BCG therapy for bladder cancer.

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Case history

A 66-year-old man initially presented secondary to gross hematuria for 3 weeks associated with urgency, frequency, and significant nocturia. Patient also had a known history of BPH and underwent a TRUS biopsy in 1999 with findings consistent with BPH. His initial PSA was 11.3. Patient is a social drinker, denies any tobacco use and currently takes ASA daily. Upon initial office visit on January 17th, 2003 patient had a flexible cystoscopy performed showing a 2 cm mass on the right lateral wall of the bladder. On January 31, 2003, a transurethral resection of bladder tumor (TURBT) was performed pathological findings were consistent with grade I papillary TCC with lamina propria invasion and no evidence of muscle or vascular invasion. In February of 2003 patient had biopsy performed in same location and of diverticulum showing no evidence of tumor. In May of 2003 patient underwent a cystoscopy showing tumor reoccurrence on left lateral wall. A second TURBT was performed with pathology consistent with grade I papillary TCC.

In June of 2003 patient had a preoperative chest x-ray performed prior to anesthesia with findings showing a nodule in the left lung. A CT scan was then obtained demonstrating a 5 mm calcified nodule in the apical posterior segment of the left upper lobe consistent with a calcified granuloma. There was a right hilar lymph node with punctuated calcifications in the spleen consistent with granulomatous disease.

On June 12, 2003, patient had a bladder biopsy done showing grade I papillary TCC. Patient was started on BCG therapy in August of 2003 for a full 6 week induction course until October 2003. During this time patient had a rising PSA level now at 15.73 in November of 2003. He underwent a transrectal ultrasound guided biopsy of the prostate demonstrating benign prostatic tissue. Patient subsequently had his first maintenance BCG treatment January 7, 2004 until January 22, 2004 with three total instillations. Cystoscopy performed at this time showed no evidence of reoccurrence. Again patient had a prostate biopsy secondary to elevated PSA on February 24, 2004. Maintenance 2 was started on the patient on April 28, 2004 with three instillations, however, after the third instillation patient developed significant hematuria and urgency. BCG urine cultures were sent at that time with negative results. Patient did not have any systemic symptoms of BCG sepsis and a cystoscopy done at that time showed no tumor reoccurrence.

The patient had the third and fourth maintenance regiment was given with three instillations from October 6, 2004 until April 20, 2005. A cystoscopy was done on January 25, 2005 showing no evidence of tumor reoccurrence.

In August of 2005 patient underwent a green light vaporization of the prostate for LUTS, elevated postvoid residuals, and BPH. Patient had an uneventful postoperative course. Patient had maintenance 5 through 7 given from November of 2005 until April of 2006 with three instillations per maintenance dose. Cystoscopies during this time were negative for reoccurrence, Table 1.

In April of 2007 patient presented to office complaining about erythema to glans of penis for 3 days. Patient had three spots over the dorsum of his glans, Figure 1. Patient had an associated cough and flu like symptoms. Patient was started on Floxin for 14 days and had a chest x-ray performed showing increased infiltrates in lung. Patient presented in 14

TABLE 1. **Summary of BCG instillations with cystoscopic findings**

BCG	Cystoscopic findings
Induction BCG (Aug 2005-Oct 2003)	June 2003-Grade I papillary TCC
Maintenance BCG 1 (Jan 2004)	Feb 2004-No reoccurrence
Maintenance BCG 2 (April 2004)	May 2004-No reoccurrence
Maintenance BCG 3 (Oct 2004)	-
Maintenance BCG 4 (April 2005)	Jan 2005-No reoccurrence
Maintenance BCG 5 (Nov 2005)	-
Maintenance BCG 6 (Jan 2006)	Jan 2006-No reoccurrence
Maintenance BCG 7 (April 2006)	April 2006-No reoccurrence

Induction BCG-6 cycles, 1 week apart
Maintenance BCG-3 cycles, 1 week apart

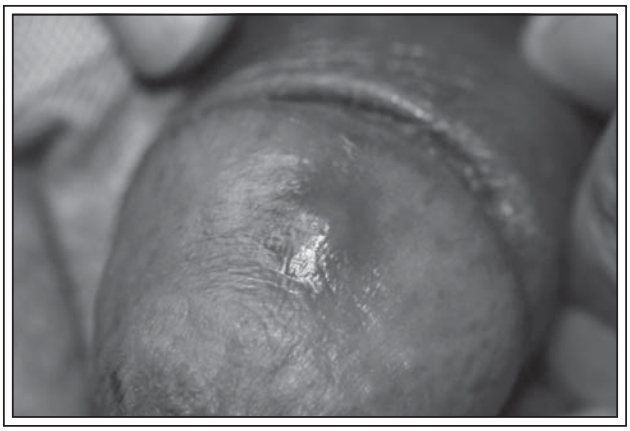

Figure 1. A erythmatous raised papule with central ulceration.

days later with two of the lesions disappearing and a third that was smaller in size now with a necrotic center and serous draining when lesion was squeezed. AFB cultures were sent from wound and sputum which where both negative. Patient continued to have cough with flu like symptoms. Patient agreed to undergo biopsy of lesion done in operating room in May of 2007. Pathology demonstrated an ill defined granulomatous process with chronic inflammation, Figure 2. AFB, fungal and wound cultures were all negative. Patient was started on INH 300 mg daily, rifampin 100 mg daily, ethambutol 200 mg daily and pyridoxine 200 mg daily. Patient's symptoms improved and repeat chest x-ray showed no evidence of infiltrates. Patient was treated as cutaneous tuberculosis of the glans penis secondary to BCG therapy.

Figure 2a. Low power H&E stain demonstrating an ill-defined granulomatous process with chronic inflammation.

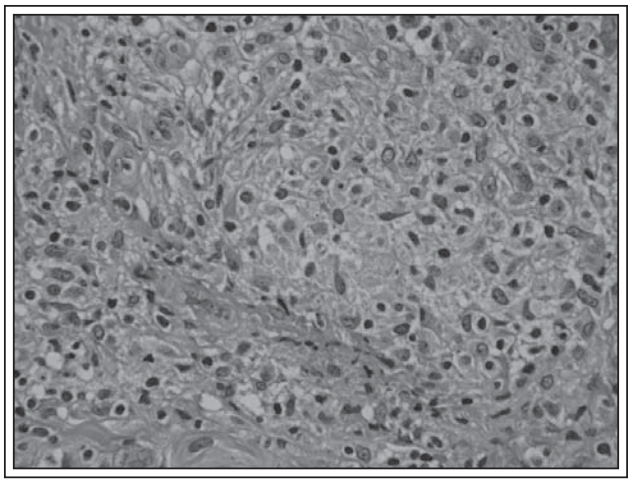

Figure 2b. High Power H&E stain demonstrating chronic inflammation.

Discussion

Intervesical BCG therapy for superficial bladder cancer was first introduced in 1976 by Morales and associates.[4] The mechanism of action is thought to arise from an induced cellular immune reaction.[2] Treatment with BCG is usually started 2 to 4 weeks after initial resection on a weekly basis for 6 weeks. No uniform consensus has developed for the best maintenance therapy, however, cancer reoccurrence is delayed with continuous therapy.[2] BCG has a number of side effects associated with it's administration including cystitis in up to 60% to 80% of patients and major infections in approximately 5% of patients.[2] Major infections such as sepsis must be recognized and treated with antituberculous medication immediately. On the other hand delayed infections result in more localized disease and are thought to result from reactivation of BCG.[2] In our patient, approximately 4 years after initiating BCG therapy, the patient presented with three erythematous spots over the glans of the penis, one of which had a necrotic center. Patient also had systemic symptoms with cough and flu like signs. Cultures for acid fast bacilli were negative along with an inability to demonstrate any organisms on tissue examination. Fungal and wound cultures also failed to show any causative organisms. Pathological examination of the slides demonstrated an ill defined granulomatous process with chronic inflammation and necrosis. There was no spillage of BCG or traumatic instillation. Our patient represents one of the few cases of cutaneous manifestations of immunotherapy complications. Previously a number of case reports indicated similar outcomes and one specified a BCG spillage after a traumatic foley insertion.[7] Previous

case reports managed the cutaneous lesions similarly by starting antituberculous therapy usually with INH, all of which responded to therapy.[3,5,6.7] In our case, due to the systemic symptoms and chest x-ray changes, full antituberculous therapy with four drugs was initiated for 6 months with resolution of the cutaneous lesions and pulmonary symptoms. Although cutaneous manifestations of BCG therapy are rare, they do exist and should be treated with antituberculin therapy even if there is no identifiable organism.[3,5,6] M Bovis is a difficult organism to identify but with advances in PCR, a new region known as RD-1 deletion has been discovered allowing rapid and specific identification of BCG.[8] Perhaps PCR will be an option for future cutaneous complications or systemic infections after BCG therapy.[8] □

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