

Intravesical BCG Therapy and Side Effects-Case Reports and a Review of Literature

Vasudeva S^{1,2*} and Baffoe-Bonnie A³

¹Department of Internal Medicine, Veteran Affairs Medical Center, Salem, Virginia, USA

²Department of Internal Medicine, Virginia Tech Carilion-School of Medicine and Research Institute, Roanoke, VA, USA

³Department of Internal Medicine, Section of Infectious Diseases, Virginia Tech Carilion-School of Medicine and Research Institute, Roanoke, VA, USA

*Corresponding author: Vasudeva S, Department of Internal Medicine, Veteran Affairs Medical Center, Salem, Virginia, USA, Tel: 7572845342; E-mail: sharmavasudeva@yahoo.com

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Abstract

BCG installation in bladder for stage 1 bladder carcinoma is becoming more common with increasingly aging population. BCG can be absorbed systemically and cause granuloma formation in almost any organ of the body with symptom onset from a few hours after installation of BCG to several years later. The treatment can vary from close observation in some cases, to use of isoniazid and rifampin with and without steroids for 3-9 months. The overall prognosis is very good. There is need for greater awareness among physicians for considering BCG related disease processes in patients with past history of BCG installation so appropriate cultures can be sent and treatment instituted.

Keywords: Intravesical BCG; BCG granuloma; Mycobacteria granuloma; BCG therapy; BCG

Background

In USA, in 2014, about 75,000 new cases and 15,000 deaths are estimated to result from bladder cancer. Intravesical Bacille Calmette Guerin (BCG) therapy is a recommended treatment for stage 0 and stage 1 bladder cancer. Stage 0 bladder cancer is where cancer has not invaded bladder wall beyond the inner layer and stage 1 cancers have grown into the connective tissue layer but have not reached the muscular layer.

Transurethral resection (TURBT) is the initial treatment for these stages followed by intravesical therapy with mitocin or BCG or both. Although BCG may not prolong overall survival for T1 disease, it appears to afford complete response rates of about 70%, thereby decreasing the need for salvage cystectomy.

Studies show that intravesical BCG delays tumour recurrence and tumour progression. Intravesical BCG therapy is considered a relatively benign treatment for most patients, but both local and systemic reactions to this therapy are well documented in literature. In one study, serious adverse effects were seen in <5% of patients treated with intravesical BCG therapy.

We describe two patients who developed serious adverse reactions after receiving intravesical BCG therapy. These cases, besides illustrating the serious adverse events related to intravesical therapy also demonstrate the varied time range of presentation of symptoms after BCG installation.

Case Reports

Case 1

A 77-year-old male presented to an outside hospital emergency room with the complaint of fever, shaking chills, nausea, vomiting and diarrhoea that started a few hours after his fifth BCG instillation.

Bladder cancer, stage T1, had been diagnosed 4 months prior to this presentation. He had undergone TURBT followed by instillation of intravesical mitocin. He received his first dose of intravesical BCG 6 weeks after the surgery and his subsequent bladder instillations were without complications until his fifth session. A few hours after the procedure he became febrile, hypotensive and tachycardic, A complete blood count (CBC) revealed a peripheral leucocyte count of 4.5 K/uL, platelet 227 K/uL, creatinine 3.27 mg/dL, AST 151 IU/L, ALT 83 IU/L and alkaline phosphatase of 254 IU/L and elevated lactic acid. He was initiated empirically on intravenous piperacillin-tazobactam, vancomycin and vasopressor support for presumed sepsis. A CT abdomen and pelvis was unremarkable. Patient was transferred to our facility the same day for further care.

His clinical condition improved within 24 hours with a downtrend noticed in his serum creatinine, transaminases and resolution of hypotension. Blood cultures stayed negative and empiric antibiotics were discontinued. A diagnosis of hypersensitivity reaction to intravesical BCG was made and patient was discharged. Five weeks later AFB blood cultures obtained on admission showed growth. This was confirmed as MTB complex by direct probe. The culture was further spectated as *Mycobacterium bovis* BCG strain (CDC). In the intervening period and during a follow up clinic visit, he denied any recurrent fever, night sweats, weight loss, cough or sputum production or spine or joint pain. Patient had repeated AFB cultures which were negative. In absence of clinical findings and negative cultures the provider decided to do close follow up.

Case 2

A 74-year-old male with bilateral knee osteoarthritis presented with pain, swelling and purulent drainage of his left knee.

He had been treated for carcinoma *in situ* and high grade papillary transitional bladder cancer with weekly intravesical BCG that ended eight months prior to onset of knee symptoms. Episodes of cystitis and hematuria were noted during treatment but remission of cancer had been confirmed by biopsy. Five months prior to admission, he underwent an uncomplicated right total knee arthroplasty. Two months prior to admission, patient described worsening pain in his left knee which had moderate osteoarthritis. A decision was made to have an elective left total knee arthroplasty. Preoperative studies showed no peripheral leukocytosis, but elevated CRP 8.36 mg/dL and sedimentation rate of 60 mm/hr. A left knee arthrocentesis was done to rule out infection and showed 22,000 white cells/mm³. With 80% neutrophils, bacterial staining and culture were negative.

A week after the arthrocentesis, despite the negative synovial fluid routine cultures, patient presented to orthopedic office with continued left knee pain, low grade fever and was noted to be hypotensive. He was admitted emergently for arthroscopic debridement, where a large phlegmon with purulent fluid was described to be present in left knee. Despite negative cultures, he was discharged on a planned 6 week course of intravenous cefazolin. Two weeks into this empiric regimen, recurrence of left knee swelling was noted. A repeat arthroscopy and debridement noted an inflamed synovium, IV cefazolin was changed to IV vancomycin. Two weeks into this second antibiotic, swelling recurred with purulent wound drainage leading to readmission. At the same time, AFB cultures sent on initial arthrocentesis, 8 weeks prior returned as positive. This was confirmed as MTB complex by DNA probe. He did endorse a 2 month history of night sweats and weight loss but had no risk factors for exposure to mycobacterium tuberculosis. Quantiferon gold and HIV screen were negative. The MTB complex was further identified as *M. bovis* BCG strain by CDC. It was pyrazinamide resistant. He was on a three-drug anti tuberculosis regimen but unfortunately was unable to tolerate it and elective for palliative care.

Discussion

We presented two cases with rare complications of Intravesical BCG therapy. In first case, the patient developed symptoms while receiving intravesical BCG therapy and hence it was easier to correlate the symptoms to BCG therapy. However, in the second case, the time difference between BCG therapy completion and occurrence of a rare complication of the therapy, made the diagnosis more challenging.

This review of the complications of intravesical BCG immunotherapy hopes to shed more light on this subject.

BCG immunotherapy

The mechanism of action of BCG bladder cancer is not clearly understood. However it has been postulated that an intact immune system is required for BCG to work [1]. The antitumor activity of BCG is a local phenomenon [2]. After intravesical BCG installation, phagocytes present mycobacterial antigen to T helper cells leading to an inflammatory reaction with polymorphonuclear cell presence, and a significant increase in T cells, particularly of the CD4 phenotypes, and macrophages in the lamina propria for 3-6 months after therapy has been completed [3]. CD4 T cells secrete various cytokines which are

chemotactic for cellular infiltrate and activate the lymphocytes. The inflammatory response is associated with change in the phenotype of the bladder tumor cells with increased expression of ICAM-1 and MHC 2 which causes the activated leukocytes to conjugate with target cells for a lethal hit [4]. CD4 T cells causes further secretion of cytokines which cause maturation of cytotoxic T cells or possibly BCG activated killer cells (BAK) that are capable of differentiating between normal and tumor cells. IFN- γ released in the local immune response to BCG by CD4 cells can render bladder tumor cells capable of acting as both lymphokine- activated killer cell sensitive targets and antigen presenting cells for BCG.

Pathophysiology of adverse effects

Local adverse effects: After serial BCG installation, in approximately 50% of the 29 animals investigated, the inflammatory reaction was accompanied by non-caseating granulomatous lesions in bladder and in first retroperitoneal (iliac) lymph nodes draining the bladder [5]. Pathological evidence of granulomatous prostatitis with AFB is a common occurrence after intravesical BCG therapy in humans. Since the antitumor effect of BCG is a local phenomenon in bladder so local side effects such as cystitis, hematuria seen in vast majority of patients are common and expected.

Systemic side effects: There is more controversy regarding the cause of systemic side effects in patients undergoing intravesical BCG therapy. Hepatitis, pneumonitis, septic arthritis, chorioretinitis, arthritis all have been documented [6]. In most cases lack of AFB on stains on affected tissues, negativity of mycobacterial PCR, lack of recovery of viable organisms and response to steroids alone without combination with antimycobacterial therapy and lack of recurrence have led many to believe that the systemic side effects are primarily a hypersensitivity reaction to BCG leading to hypersensitivity granuloma formation. In one case of hypersensitivity pneumonitis, that improved with steroids only, an immunoblot assays with serum and BCG, had more than 10 IgG fractions binding to BCG providing support to their diagnosis of hypersensitivity pneumonitis [7].

However, as in our patients and some previously mentioned case reports, viable organisms have been found in various organs and with improvement in symptoms following anti tubercular treatment, leading one to believe that there is likely a hematogenous spread of the organism and subsequent seeding of organ. Also given the latency of symptoms as seen in our second patient, it seems dissemination leads to seeding of organ with a latency phase as with MTB followed by a later recrudescence.

Another hypothesis regarding arthritis following BCG therapy is the phenomenon of molecular mimicry suggested by shared homology between mycobacterium heat shock protein HSP65 and cartilage proteoglycan link protein, thus the bacteria or bacterial antigen spreading from bladder to the circulation may induce a systemic immune mediated response targeting joints especially in genetically predisposed patients as those with positive HLAB27 antigen [8].

The massive dose of BCG given intravesically is potentially lethal if given intravenously. The presence of intact uroepithelium that prevents systemic absorption of drug, can be breached with fresh wound or bleeding of bladder or urethral endothelium or severe inflammation of endothelium. Hence BCG is not recommended for at least a week after tumor resection. Traumatic catheterization [9], gross hematuria, active UTI and larger and repeated BCG doses have all been implicated in systemic reaction to intravesical therapy [10].

Local complications

Cystitis with or without hematuria: In a case series by Lamm et al. [10] drug induced cystitis was observed in 91% of patients receiving BCG therapy, 2-4 hours after instillation of BCG. Hematuria was seen in 43% of patients. Bladder wall biopsy was consistent with signs of acute and chronic inflammation with or without granuloma formation. In one study of 10 patients, BCG DNA was detected in urine of all patients 24 hours after instillation, in 24% of urine collected 7 days after the last instillation and in 1 specimen taken 6 weeks after last instillation [11]. All patients reported dysuria and frequency and three patients reported hematuria. However cases of clinical cystitis and recovery of *Mycobacterium bovis* from urine up to 8 months after completion of therapy has been documented [12].

Cystitis usually manifests as dysuria, frequency, suprapubic pain and sometimes hematuria. It is expected adverse effect and resolves spontaneously with minimal supportive therapy within 48 hours. The severity of cystitis worsens with repeated BCG instillations.

Bladder contracture: It was seen in 0.2% of the patients and it is unclear if it is the result of traumatic catheterization, multiple bladder surgeries, BCG therapy or a combination of all. In this case urology needs to be consulted. No treatment with anti-tubercular medicine is recommended.

Granulomatous prostatitis: In the case series by Lamm et al. [10] the incidence of granulomatous prostatitis was 1.3%. However asymptomatic granulomatous prostatitis is present in large number of patients [13]. In another study, incidence of this finding on prostate biopsy was 41% [14] and AFB was demonstrated in 3 of the 13 patients who underwent prostate biopsy. The mean interval between initiation and diagnosis was 11.5 months. Prostatic induration and nodularity is present on exam. PSA might be elevated. Ultrasound may show diffuse hypoechoic areas and certain MRI patterns have also been associated with granuloma findings [15]. Biopsy may be needed to distinguish the nodularity of a granuloma from prostate cancer. In asymptomatic patients, no treatment is required. Symptomatic patients may be treated with isoniazid and rifampin for 3 to 6 months.

Renal complications

The incidence of renal complications has not been well defined. Renal complications can occur in isolation or with other associated symptoms like hepatitis [6], pneumonitis [16] and in one case chorioretinitis suggesting a hematogenous route of a spread at least in some patients. Presence of vesiculoureteral reflux has been associated with local renal complications after intravesical therapy within 3 months of initiation. Most patients present with fever, malaise and hematuria although presentation as renal mass [17], and acute renal failure [18] have been documented. Proteinuria and elevated creatinine can be seen. On renal biopsy epithelioid granulomas, diffuse mesangial proliferation and interstitial nephritis all were commonly reported [6]. Stains for AFB and cultures are usually negative. Treatment regimen have varied in different case series but isoniazid with a second anti-tubercular agent mostly rifampin, with or without short course of steroids for 6-9 months was the most common regimen used.

Other rare local complications

Granuloma of penis/granulomatous balanoposthitis is a well-defined but rare complication that can present as painless erythematous nodules, papules, ulcers, abscesses and inguinal

lymphadenopathy. Histologically tubercular granulomas are observed with giant cells. Cultures were positive in only two case reports. The resolution of lesion with anti-tubercular therapy is the norm. Isoniazid and rifampin were the most commonly used regimen but duration varied from 3-12 months in different reports [19]. A few cases of granulomatous epididymo-orchitis with pain and unilateral swelling of scrotal content have been described [20].

Systemic complications

Constitutional symptoms: In a case series by Lamm et al. [10] low grade fever, malaise and nausea was reported in 28%, 24% and 8% of patients respectively and are very common after each BCG instillation. Low grade fever is common but fever above 39.5°F was seen in only 2.9% of patients and if associated with hypotension should raise suspicion of mycobacterial sepsis as seen in our patient. These symptoms are thought to be in response to the inflammatory response seen in bladder and usually resolve within 48 hours. He had suggested that if high grade fever persists despite antipyretics after 12 hours isoniazid for 3 months should be considered but there are no studies to prove the utility of this approach.

Hepatitis: The combined incidence of pneumonitis and hepatitis is 0.7% in patients undergoing intravesical BCG therapy. Liver can be the sole organ involved but more often it is part of a more systemic involvement. Hepatitis has been seen in association with pneumonitis [21], bone marrow involvement [22], gastric involvement and with sepsis. Clinical presentation of hepatitis can be acute presenting within 8 days of instillation [23] or indolent presenting months after completion of therapy [24] with median of about 3 months after initiation of therapy. Clinical presentation includes fever, chills, malaise, icterus and weight loss and hepatosplenomegaly. A cholestatic picture with elevated alkaline phosphatase and elevated bilirubin and milder elevation in transaminases is usually seen, Pancytopenia are usually noted with concomitant bone marrow involvement.

Diagnostic liver biopsy usually reveals non caseating granuloma with epithelioid cells. Usually AFB stains, PCRs and cultures of Liver tissue are negative giving rise to the notion of hypersensitivity hepatitis. However, in few cases the PCR in liver tissue was positive [25]. Anti-tubercular drugs were commonly used for treatment. Isoniazid and rifampin for 6 months was the regimen used in most reports but ethambutol had occasionally been used.

In some cases improvement in liver functions was not noted till after addition of steroids [22] and so it might be prudent to use tapering course of steroids at the initiation of therapy. Most cases resolve after initiation of therapy.

Pneumonitis: Pneumonitis seems to be early complication of BCG immunotherapy usually appearing within first 3 months after the start of therapy, as an isolated phenomenon as well as concurrently with hepatitis and sepsis [21]. The symptoms are nonspecific with fever malaise and cough with scanty phlegm production and dyspnea [7].

Hypoxemia is often noted. As opposed to primary tuberculosis, bilateral diffuse, reticulonodular or alveolar infiltrates with or without ground glass opacities [7,21,26] seem to be the most common radiological finding. A few cases of right sided lower lobe infiltrate with pleural effusion have been described but possibility of contiguous spread from a perforation was thought to be the etiology in that case [27]. PFTs can show restrictive defect with reduced DLCO. BAL fluid is almost always lymphocytic predominant with low CD4/CD8 ratios when checked. Biopsies once again show necrotizing granulomas.

There are very few case reports where *M. bovis* was recovered from lung and tissues but the AFB stain is rarely positive [28]. Bronchial fluid and tissue are usually negative for AFB stains, PCR and cultures.

The treatment for pneumonitis seems to be different from other entities. In granulomatous hepatitis anti-tubercular therapy was very consistently used. However post BCG installation pneumonitis seems to be a hypersensitivity reaction and has been successfully treated with steroids alone in a number of cases with improvement in clinical and radiological findings [28,29] and in a few cases there has been spontaneous resolution without any therapy [30]. However other physicians have chosen to treat with anti-tubercular therapy with or without steroids. If cultures or stains are positive anti tubercular therapy should be started however in certain patients a trial of steroids alone can be considered.

Cytopenia: Rate of cytopenias in Lamm et al. [10] series was only 0.1% and cytopenia has usually been seen in association with other systemic complications seen early within 3 months [22,28] WBC and platelets are usually low. Splenomegaly may be seen in some patients and a bone marrow biopsy showing multiple granulomas usually clinches the diagnosis. AFB stains have usually been negative in these patients. It has been treated with anti-tubercular therapy for 6-9 months.

Arthritis and arthralgias: These two complications occurred in 0.5% of patients in a 2062 patient series. Arthritis is thought to be a reactive and may be accompanied by extraarticular symptoms like conjunctivitis and dysuria [31] the most common time for presentation was following 4th-6th instillation [32,33]. The most common symptoms were joint pain, swelling, fever (70.4%). In one series polyarthritis was present in 55.1%, oligoarthritis in 37% and monoarthritis in 7.9% of patients. Polyarthritis could be symmetrical (51%) or asymmetrical (49%) in equal proportions but oligoarthritis was mainly asymmetrical (66.7%) of cases. The most common joints involved were knees and ankles followed by wrists and metacarpophalangeal joints. Conjunctivitis, urinary symptoms, dactylitis, sacroillitis, tenosynovitis are commonly seen in association with arthritis. Joint fluids were almost uniformly aseptic with presence of PMNs but negative stains, PCR and cultures for *mycobacterium*. Synovial biopsy was rarely obtained and obtained were negative for AFB stain and culture. HLA B27 was present in 42.6% of patient who presented with arthritis after intravesical BCG therapy [33].

Most patients were treated with NSAIDs for up to 2-3 months. In some patients' steroids were the mainstay of treatment however they were used more commonly after NSAIDs had failed to completely resolve the symptoms. In one case series anti-tubercular drugs were used in 12% of patients and in conjunction with NSAIDs or steroids. In patients with aseptic arthritis following BCG intravesical therapy anti-inflammatory seem to be the mainstay of treatment.

Septic arthritis: Reactive arthritis is oft reported in literature however there are very few cases of septic arthritis. In contrast to reactive arthritis which is an early complication of BCG therapy, septic arthritis is more indolent and may present years after the completion of therapy. Most of the case reports of septic arthritis have been reported in prosthetic joints. Ours is the first case, to best of our knowledge, of a report of *M. bovis* infection in a native joint. Most patients seem to present with sub-acute pain in the affected joint with

low grade fever. The initial stains in these patients are negative leading to treatment for culture negative arthritis. In patients with features of septic arthritis, culture negativity and a prior history of BCG therapy should alert surgeons to the possibility of *M. bovis*, arthritis and appropriate AFB cultures should be obtained and consideration of MTB PCR for early detection and prompt treatment. In the case reports 2-3 anti-tubercular drugs were used, usually for a year and in one case for 2 years. The anti-tubercular therapy is used in conjunction with a two stage procedure for arthroplasty for best results [32].

Sepsis: The incidence was 0.4% in case series by Lamm et al. [10]. Even though *M. bovis* has been recovered in liver, lungs, testes, prostate and vessels a true mycobacteremia is a very rare presentation [23].

In two reported cases it was associated with granulomatous hepatitis and patient were sick and deteriorating and ultimately anti-tubercular therapy was empirically started with improvements. Ours is the first case where patient improved without any treatment. Even though he had elevated LFTs his clinical course was not consistent with persistent hepatitis and repeat blood cultures were negative without treatment. Our case lends support to the theory that immunocompetent patients can mount a robust immune response and clear infection although long term follow up for late complications is still needed.

Vascular complications

Mycotic aneurysms, particularly infrarenal aortic involvement associated with aortoenteric fistula [34] or an iliopsoas abscess [35] has been observed and carries a very high mortality. It is usually a late complication occurring years after completion of therapy. Other arteries including carotid, femoral and popliteal have been documented.

The clinical presentation is usually associated with local features from the aneurysm. The diagnosis is usually made after surgical resection secondary to presence of granulomas on pathology or AFB stain, PCR positivity or culture of pus or tissue obtained during operation. All cases were treated with anti-tubercular therapy mostly for a year along with a surgical procedure [36].

Bone and soft tissue infections: Vertebral osteomyelitis with adjoining psoas [37] and epidural abscesses [38], a case of iliac muscle abscess [39] are other rare processes that have been described in literature. Osteomyelitis is a late complication, occurring more than 3 months to even up to 12 years 38 after completion of BCG therapy. Most patients presented with lower back pain with radicular pain and constitutional symptoms. The diagnosis was made after *M. bovis* was demonstrated from samples obtained during surgery or percutaneous aspiration [37]. Most of them responded well to anti-tubercular treatment with 2-3 drugs for 9-12 months. Some patients required surgical drainage (Table 1).

Rare complications

M. bovis abscess of pancreatic head, and infection of a defibrillator have been described [40,41]. Chorioretinitis [42], BCG endophthalmitis [43,44] and panuveitis [16] are some of the ocular complications of BCG therapy.

Local complications	Timing	Symptoms	Treatment
Cystitis	Early	Dysuria, Frequency, Hematuria, suprapubic pain	Resolves spontaneously with minimal supportive therapy
Granulomatous prostatitis	Early although diagnosis can be delayed	Mostly asymptomatic Perineal heaviness, prostatic tenderness	Asymptomatic-no treatment Symptomatic Isoniazid and Rifampin for 3-6 months
Renal complications	Early	Fever, malaise, hematuria Acute renal failure and renal mass	Isoniazid and Rifampin with or without steroids for 6-9 months
Granuloma of penis and granulomatous balanoposthitis	Early to up to a year after therapy completion	Painless erythematous nodules, papules or ulcers.	Isoniazid and Rifampin for 3-12 months
Systemic complications	Timing	Symptoms	Treatment
Constitutional symptoms	Early	Fever malaise, nausea	Usually no treatment required
Hepatitis	Early	Fever, chills malaise, icterus and weight loss	Isoniazid and Rifampin For 6 months with or without steroids
Pneumonitis	Early	Fever malaise dyspnea	Trial of steroids alone can be considered and Isoniazid and rifampin for 6 months if no improvement on steroids alone
Cytopenia	Early	Usually seen on lab work	Isoniazid and Rifampin for 6-9 months
Arthritis and arthralgias	Early	Joint pain, swelling, fever	NSAIDs for upto 2-3 months. Steroids if NSAIDs do not provide relief
Septic arthritis	Late	Subacute joint pain and fever	Isoniazid and Rifampin for 12 months
Sepsis	Early	Fever hypotension	Isoniazid and Rifampin for 3-6 months
Vascular complications	Late	Local features of aneurysm	Surgery with isoniazid, rifampin with or without ethambutol for 12 months
Bone and soft tissue infections- Vertebral osteomyelitis with psoas or epidural abscess	Late	Lower back pain, radicular pain and fever	Surgical drainage and Isoniazid and rifampin with or without ethambutol for 9 – 12 months

Table 1: Summary table of complications reported with intravesical BCG therapy and treatment regimen reported in literature.

Conclusions

Intravesical BCG therapy is a common and well tolerated therapy for early stage bladder cancer. It can present with complications both during therapy as well as many years after completion of therapy. Physicians need to have a high index of suspicion for these complications in patients with history of BCG therapy. The lack of PCR positivity, or culture growth should not be a deterrent in considering a diagnosis of BCG induced complications in patients with appropriate history and no other clear diagnosis. Early initiation of appropriate therapy can be potentially lifesaving in these patients.

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