

Case report

Mycobacteria Bovis osteomyelitis following intravesical BCG for bladder cancer



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ABSTRACT

Mycobacteria Bovis osteomyelitis is a rare adverse effect after Bacillus Calmette-Guerin (BCG) intravesical therapy. A 62-year-old male presented with acute spinal cord compression three months after completing his second course of therapy for bladder cancer. The first course with intravesical BCG was complicated with an episode of hematuria. He reported intermittent subjective fever for 3 weeks thereafter which resolved with Tylenol. Interferon- α 2 B was added to the second cycle of intravesical BCG with the indication here being residual tumor, and was tolerated well. His complete blood count and liver function tests were unremarkable on admission. MRI showed features of osteomyelitis with cord compression at T4/T5. Biopsy of the affected bone showed caseating granuloma which was positive for acid fast bacilli, later confirmed to be Mycobacterium Bovis by PCR and pyrazinamide resistance. He was started on intravenous steroids and underwent spinal cord decompression. Rifampin, Isoniazid, and Ethambutol were then commenced. His weakness improved and after two months of therapy he was asymptomatic and back to his baseline function. Osteomyelitis is a rare but serious complication. Early diagnosis and treatment is important as the outcomes are good.

Background

Since 1976, BCG has been administered intravesically to treat transitional cell carcinoma of the bladder, and has proven to be a safe and effective therapy for various carcinomas in situ [1,2]. It comes with potential side effects [3], where serious reactions may occur in less than 5% of patients [2]. One of the most worrisome is a systemic granulomatous infection with the BCG strain [2]. Osteitis is rare following BCG immunization, occurring in less than 37 per 100,000 cases [2]. As of 2016 there were only 16 cases of vertebral osteomyelitis secondary to intravesical BCG reported in the English literature [1]. Venous translocation via the Batson plexus or hematogenous spread are postulated mechanisms for dissemination [1]. Strict preventative measures should be adhered to reduce complications [3], and prompt appropriate treatment of early side effects should significantly decrease the incidence of severe adverse outcomes [4]. Here we report a case presenting with vertebral osteomyelitis and cord compression following initial treatment with intravesical BCG.

Case

A 62-year-old male with a past medical history of in situ transitional cell bladder cancer had transurethral resection of the bladder tumor (TURBT) followed with, intravesical BCG. He had an episode of hematuria during this first cycle of treatment. He had no history of back trauma.

One week after completing the first cycle he had subjective fever for three weeks which resolved with Tylenol. Due to evidence of residual tumor during his follow up, he was treated with another six-weekly course of BCG together with interferon- α 2 B therapy eleven months after completing the first treatment. He had no further evidence of residual tumor in his subsequent follow up.

Three months after completing the second cycle, he experienced gradual onset back pain associated with numbness from the nipple line down and lower extremity weakness. There was no bowel or bladder dysfunction. On examination, he was not in any respiratory distress, and vital signs were within normal limits. He had reduced sensation to light touch below the nipple line, and reduced power of 4/5 in the right and left lower extremities. Proprioception and vibration were intact.

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Fig. 1. MRI T spine sagittal view showing edema within the T4 and T5 vertebral bodies and T4-T5 intervertebral disc with a collection extending posteriorly into the spinal canal in the anterior epidural space with mass effect on the spinal cord.

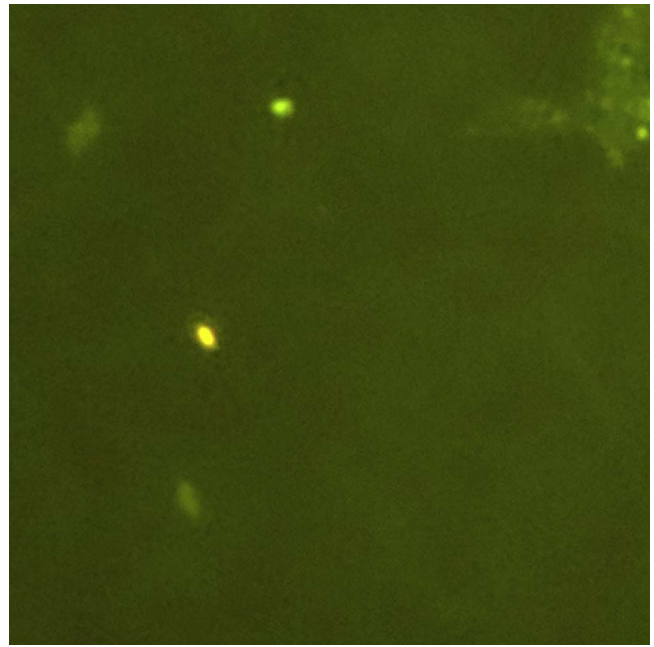


Fig. 2. Auramine-rhodamine stain showing acid fast bacilli.

His CBC, renal function, liver function, PSA, and serum protein electrophoresis were all unremarkable. Magnetic Resonance Imaging (MRI) of the thoracic spine (Fig. 1) showed edema within the T4 and T5 vertebral bodies and T4-T5 intervertebral disc with a collection extending posteriorly into the spinal canal in the anterior epidural space. This collection exerted a mass effect on the spinal cord and severely narrowed the spinal canal. There was proximally anterior 40% height loss of the T4 vertebral body. There was no intrathoracic, abdominal or pelvic lymphadenopathy on the CT chest abdomen and pelvis.

He was started on intravenous steroids and underwent posterior fusion of T3 to T6 and laminectomy of T4/5 with decompression of anterior epidural granulation tissue. The tissue sample showed chronic inflammation with caseating necrosis involving bone and adipose tissue. He was started on rifampin, isoniazid, ethambutol and vitamin B6 in the post operative period. The auramine-rhodamine stain (Fig. 2) and Kinyoun stain (Fig. 3) was positive for mycobacteria. The Lowenstein Jensen media (Fig. 4) grew mycobacteria. This was later confirmed to be *Mycobacterium bovis* by PCR and pyrazinamide resistance. Two months later, he was doing well without any weakness or numbness. Rifampicin and isoniazid was continued for seven more months.

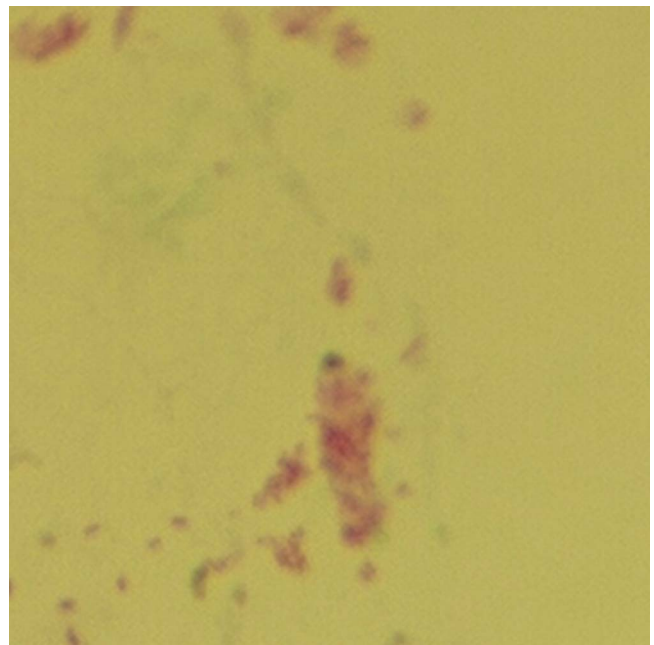


Fig. 3. Kinyoun stain showing acid fast bacilli.

Discussion

Bladder cancer is the ninth most common cancer worldwide and has a strong male predominance [5]. Smoking is the main risk factor [6]. Strikingly the incidence of bladder cancer is decreasing, and this is attributed both due to the downward trend in smoking prevalence [6], and improvement in treatment [6].

Since 1976, BCG has been administered intravesically to treat transitional cell carcinoma of the bladder, and has previously been proven to be a safe and effective therapy [1,2]. *Mycobacterium bovis* was first isolated by Nocard from the milk of a heifer with tuberculosis mastitis, this strain was called 'lait Nocard' [7]. During the making of the BCG vaccine different variants have emerged [7]. Today, the most widely used BCG vaccine sub strains include Connaught, Danish, Glaxo, Moreau, Pasteur, and Tokyo – all of which show morphological, biochemical and immunological differences [7]. We were not able to identify the strain of the *Mycobacterium bovis* in this case. Before

administering this, patients should be screened thoroughly for any contraindications to treatment [8]. These include recent bladder or prostate surgery, traumatic catheterization, gross hematuria on day of treatment, symptomatic urinary tract infection, immunocompromised state, active tuberculosis, pregnant patients, and prior adverse reactions to BCG [8]. Strict protocols exist and must be followed for the preparation and administration of this agent [8].

BCG comes with many potential side effects [3]. These include granulomatous prostatitis, epididymo-orchitis, systemic BCG reactions, allergic reactions, cystitis, hematuria, contracted bladder, ureteral obstruction, and vertebral disease [1,3]. Less than 1% have a systemic disease followed by dissemination of mycobacteria into other organs [9]. In one report of 2600 patients treated with intravesical BCG, 27%-95% had symptoms of irritative lower urinary tract symptoms (LUTS),



Fig. 4. Lowenstein Jensen media with culture showing the growth of mycobacteria.

2.9% with fever, 1.0% with hematuria and 0.4% with severe disseminated BCG sepsis [10]. In another study of 1316 patients, the reported BCG-induced cystitis was 35% and bacterial infection 23.3%, with frequency in 23.6%, and macroscopic hematuria in 22.6% [11]. The most frequent systemic side effects were general malaise in 15.5% and fever in 8.1% [11]. BCG sepsis was observed in four patients (0.3%) [11].

Two mechanisms proposed for the spread of infection include venous translocation via the Batson plexus or hematogenous spread [1]. Mycobacterium is internalized by both normal and malignant cells, resulting in urothelial activation and subsequent inflammatory responses in the bladder [12]. Before BCG therapy, bladder tumor cells express the class I MHC antigen (HLA-ABC), but the class II MHC molecule (HLA-DR) is expressed weakly or not at all [13]. ICAM-1 and ICAM-2 are not expressed [13]. After BCG therapy, the bladder cancer cells express HLA-ABC, HLA-DR, and ICAM-1 [13]. This results in immune production of cytokines and promotes local migration of polymorphonuclear leukocytes and macrophages, ultimately leading to the death of tumor cells [14]. Epithelial infection can spread to the lymphatics and then to the blood stream [14]. Disruption of bladder endothelium is one prerequisite for dissemination [15]. The urothelium comprises of three layers and acts as protective barrier [16]. Local factors such as tissue pH, mechanical or chemical trauma, and bacterial infection can disrupt this barrier [16]. Once the barrier is compromised, the patient can experience urgency, frequency and pain [16].

Clinical features of disseminated disease include malaise, persistent fever, myalgia, and nausea [3]. Our patient had subjective fever for several weeks after the initial intravesical BCG treatment which was complicated with an episode of hematuria, it is likely that he developed dissemination of the BCG during this period. It is possible that he went on to develop latent stage disease as he was asymptomatic thereafter. This asymptomatic infection or latent stage is a long-term hidden threat to the host [17].

The IFN- α family is well known to stimulate natural killer (NK) cells, induce MHC class I response, and increase antibody recognition [12]. They have antineoplastic properties by direct antiproliferative effects and complex immunomodulatory effects [12]. At present most research involves IFN- α 2b [12]. BCG efficacy depends on the induction of a robust Th1 cytokine profile, and IFN- α 2b has been shown to potentiate the Th1 immune response [12]. In one report combination

intravesical BCG plus IFN- α 2B was shown to be an effective and tolerable alternative for patients with superficial bladder cancer, including those patients in whom intravesical BCG therapy had previously failed [18]. Our patient had residual tumor after his initial treatment with BCG and was treated with the combination of intravesical BCG plus IFN- α 2B. Following this he has no further evidence of residual tumor. Little is known about the reactivation of Tuberculosis or opportunistic infections after treatment with interferon- α [19]. Though reactivation of tuberculosis is described after treatment of hepatitis C and other cancers with systemic interferon- α , we have not found any cases of this occurring with intravesical interferon α [20,21]. The role of intravesical interferon in the reactivation of mycobacteria bovis here is uncertain, further studies is needed to clarify if there is any association.

Conclusion

Physicians should enforce close monitoring and patient education in patients receiving intravesical BCG

Vertebral osteomyelitis is a rare and serious complication of intravesical BCG, where early diagnosis and treatment has good outcomes

Contributorship

The idea for reporting this case was that of KS. Further intellectual content and editing was done by all authors. All authors saw, edited and approved the final contents. KS assumes responsibility for the integrity of the contents.

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Patient consent

Informed consent was obtained for publication of this case and the attached images.

Conflict of interest

The authors have no potential areas of conflict to declare.

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