CASE REPORT

Mycobacterium bovis BCG spinal osteomyelitis in a patient with bladder cancer without a history of BCG instillation

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SUMMARY

BCG has been used as intravesical immunotherapy for the treatment of bladder carcinoma. However, this treatment is not harmless and may lead to complications, with a reported incidence of systemic BCG infection ranging from 3% to 7%. We report a case of culture-proven *Mycobacterium bovis* (BCG) vertebral osteomyelitis in a 72-year-old patient with bladder carcinoma who was treated with intravesical mitomycin C but did not receive BCG. Cultures from biopsy recovered isolate resembling *Mycobacterium tuberculosis* biochemically, but resistant to pyrazinamide (PZA). The patient was originally started on a four-drug antituberculous regimen of isoniazid, rifampin, ethambutol and PZA. After genotypic analysis identified the organism as *M. bovis* (BCG), the regimen was changed to isoniazid and rifampin for 12 months. The patient responded well to this treatment. This case is unique as the patient received only intravesical mitomycin and did not receive BCG, implying the possibility of transmission from contaminated equipment.

BACKGROUND

Intravesical administration of BCG, a live attenuated strain of *Mycobacterium bovis* is being increasingly used as immunotherapy for superficial bladder cancer.¹ While generally well tolerated, it can sometimes result in both local and systemic infectious complications.² The exact pathogenesis is unclear but it is believed that the organisms likely gain access to lymphatics and blood through disruption of uroepithelial cells and, as with other mycobacterial infections, disseminate to a variety of sites. In some patients, infection appears early (within 3 months after instillation) and is characterised by generalised symptoms, with pneumonitis and hepatitis. Late-presentation disease occurs >1 year after the first BCG treatment and usually involves focal infection of the genitourinary tract (the site at which bacteria were introduced) and/or other sites that are typical for reactivation of mycobacterial disease, such as the vertebral spine or the retroperitoneal tissues.^{3–4} Over the past years, many published case reports have described vertebral osteomyelitis (commonly called Pott's disease), after intravesical BCG instillation.^{5–17} In light of the numerous published reports of disseminated infection or vertebral osteomyelitis after BCG bladder

instillation, these infections are now recognised as a rare but certainly possible complication of this form of therapy for bladder cancer. The pathogenesis presumably is due to the spread of the *M. bovis* from the urinary tract through Batson's plexus or from seeding of spine from disseminated infection. Patients with vertebral involvement present with back pain initially; however, if diagnosis is delayed, progression of infection may lead to motor weakness. Other manifestations may include fever of unknown origin accompanied by night sweats, anorexia, fatigue and unexplained weight loss.^{18–19} For patients with disseminated mycobacterial infection, multidrug antibiotic therapy is recommended for several months, depending on the severity of symptoms and organ system involved. However, if left untreated it could lead to catastrophic consequences resulting in significant morbidity. In this case, patient did not receive BCG bladder instillations and hence the only explanation is likely contamination of the urologic equipment and/or medication (mitomycin C) with *M. bovis*.

To our knowledge, we report the first case of nosocomial BCG infection that was the result of either BCG contamination of cystoscope or contamination of the instilled chemotherapeutic medication.

CASE PRESENTATION

A 72-year-old man with history of bladder cancer presented to our institution with progressive worsening of chronic back pain of 10 months' duration. He also reported a 10–15-pound weight loss. He denied fevers, cough, night sweats or obvious exposure to tuberculosis (TB). The patient served in the US military and has had extensive travel history in the past. He was diagnosed with stage I uroepithelial cell bladder carcinoma and was treated with intravesical instillation of mitomycin C by a private urologist in the community 1 year prior to the onset of his back pain. Patient denied being treated with BCG and we also confirmed with the urologist treating the patient that he did not receive BCG. Although, there was no clear contraindication to BCG use, the urologist preferred treatment with mitomycin C.

The patient was originally referred to our institution with the diagnosis of chronic osteomyelitis of the spine at thoracic vertebrae T9 and T10.

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INVESTIGATIONS

Initial evaluation consisted of MRI of the spine which demonstrated compression fracture of the T9 vertebral body with a small amount of associated paraspinal soft tissue prominence. Percutaneous core biopsy of the lesion was performed. Pathology showed chronic inflammation and fragments of predominately necrotic bone without any overt features of malignancy. Gomori methenamine stain for fungal organisms and acid fast bacilli stain were negative on the direct smear. Cultures yielded the organism *Mycobacterium tuberculosis* complex on liquid media culture using the BACTEC 960 MGIT (Mycobacteria Growth Indicator Tube, System. Becton Dickinson, Franklin Lakes, New Jersey, United States). It was then that the Infectious Disease team was consulted. At that time, the history of treatment for bladder cancer with mitomycin was elicited. The patient was started on four drug therapy for TB on the basis of the culture results as TB was in differential diagnosis given his extensive travel history while in the military and based on the history that BCG was not used for the treatment of bladder cancer. Genotyping conducted in the Florida Department of Health TB laboratory, identified the organism as *M. bovis* and the presence of *pncA* mutation indicative of PZA resistance was established. Thus, tissue culture from the disk space confirmed the diagnosis of *M. bovis* (BCG) vertebral osteomyelitis and subsequently therapy was modified to isoniazid and rifampin. Since patient had not received BCG for his bladder cancer, an investigation was initiated for evaluation of contamination of equipment and/or mitomycin at the time of bladder instillation of mitomycin C.

An investigation was performed by the urologist's office and the local health department. The urologist did use BCG in that office and in the operating room. We did not have access to the precise dates or schedule of how BCG was used in the office and the operating room where the instillations were performed. It was felt that the contamination was likely the cystoscope. Remarkably, no other secondary cases were reported to the health department during the 3 years of follow-up after the initial mitomycin C instillation that our patient received. The health department tracks all of the cases of BCG infection related to bladder cancer therapy since all cases of documented infection are initially reported as tuberculosis cases. During the investigation, we determined that there were no obvious breaches in the protocol used for cleaning the cystoscopes; however, outside access to the cleaning logs was limited.

TREATMENT

The patient was originally started on a four-drug antituberculous regimen of isoniazid, rifampin, ethambutol and PZA based on initial identification of *M. tuberculosis* complex. TB was in the differential as patient had extensive travel history. Patient had not received BCG and hence the diagnosis of *M. bovis* was not expected. When identification confirmed *M. bovis* (BCG) and susceptibility studies were reported, the regimen was changed to isoniazid and rifampin for 12 months.

OUTCOME AND FOLLOW-UP

Patient responded well with medical therapy alone with near complete resolution of his symptoms.

DISCUSSION

To our knowledge, this is the first case report of nosocomial transmission of BCG infection from a cystoscope in which either the chemotherapeutic agent was contaminated with BCG or the scope itself was contaminated with BCG. Regarding the first possibility, at least two case reports have been published describing BCG infections due to contaminated medications. In 1995, Stone and colleagues described two children with leukaemia with BCG infection manifesting as meningitis that may have developed the infection by the accidental inoculation of BCG during the administration of intrathecal chemotherapy.²⁰ Vos and colleagues in the Netherlands described similar nosocomial infections due to *M. bovis* (BCG) Onco-TICE bacteria, transmitted via contamination of the medication prepared in BCG contaminated hoods in the pharmacy in five immunocompromised patients with either lymphoma or leukaemia.²¹ The patients received contaminated chemotherapy intravenously and/or intrathecally similar to the patients described in the report by Stone. The BCG strains cultured from the patients had the same DNA profile as the BCG Onco-TICE strain used for bladder instillation. In another case report, investigators in California reported a similar series of cases with evidence of transmission of *M. bovis* to healthcare personnel caring for one of the cases.²²

The second possibility is that the cystoscope itself was contaminated. There are many reports of contaminated medical scopes that were improperly cleaned that led to nosocomial transmission of tuberculosis or non-tuberculosis mycobacteria^{23–27} but no reports to date of transmission of BCG from a contaminated cystoscope. While it is certainly possible that the scope itself was contaminated after being used without being properly cleaned between procedures, the exact mechanism of transmission was not able to be determined. Our investigation after this case was identified did not make the mode of contamination clear, as there were no other cases identified.

Although uncommon, infectious complications of BCG therapy should always be considered in patients who received BCG for treatment of superficial bladder cancer.^{3 13 28 29} According to the package insert, 'TICE BCG' is an infectious agent³⁰ and contains live mycobacteria that should be prepared and handled using aseptic technique. BCG infections have been reported in healthcare workers preparing BCG for administration. Nosocomial infections have been reported in patients receiving parenteral drugs which were prepared in areas in which BCG was prepared.²¹ To avoid cross-contamination, parenteral drugs should not be prepared in areas where BCG has been prepared. A separate area for the preparation of the TICE BCG suspension is recommended. All equipment, supplies and receptacles in contact with TICE BCG should be handled and disposed of as biohazardous. If preparation cannot be performed in a biocontainment hood, then a mask and gown should be worn to avoid inhalation of BCG organisms and inadvertent exposure to broken skin.

In this case, the acquisition of patient's infection is most likely due to contamination of the cystoscopy equipment or contamination of the mitomycin prior to it being instilled. However, review by the urologist confirmed that BCG was not administered directly to the patient and there were apparently no breaches in protocol. Regardless, the risk of disseminated mycobacterial infection leading to significant patient morbidity and rarely mortality is very real and

should be considered in patients presenting with the above symptoms in the right clinical setting.

Learning points

- Clinicians should be cognizant of the risk of infectious complications of invasive procedures such as cystoscopy associated bladder washings and should consider disseminated mycobacterial infection in the differential diagnosis in patients presenting with symptoms suggestive of either systemic infection or bone infection in the setting of having a history of bladder cancer treatment using BCG immunotherapy.
- It is also important that clinicians and healthcare workers be aware that BCG contains live attenuated *Mycobacterium bovis* and poses infectious risks. The manifestations of these infectious complications could become apparent many years after receiving the BCG treatment.
- Because of the potential risk for transmission, care should be taken in the preparation and handling of BCG and it should be disposed of as a biohazard material.
- This report brings to light the possibility of transmission of *M. bovis* via contaminated equipment, or other chemotherapeutic agents, and underscores the importance of proper handling of BCG and proper decontamination of equipment such as cystoscopes in order to prevent cross contamination and iatrogenic transmission of *M. bovis*.

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