Management of hepatic granulomatous tuberculosis complicating intravesical BCG for superficial bladder cancer

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Abstract

Intravesical bacille Calmette-Guérin (BCG) therapy is the most effective treatment for high-risk superficial bladder cancer. Severe systemic complications are rare, but may occur in approximately 1% of cases. We report a severe complication of intravesical BCG: a disseminated *Mycobacterium bovis* infection with biopsy-proven granulomatous hepatitis in a patient with bladder cancer. We also elaborate on the different management alternatives.

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Introduction

Mycobacterium bovis was identified in 1904 by Nocard and it is the cause of bovine tuberculosis. Bacille Calmette-Guérin (BCG) vaccine, developed by Calmette and Guérin at Institut Pasteur (Lille, France), is a live-attenuated Mycobacterium bovis strain. Many therapeutic uses of the species have been described. Morales, in 1976, first described a technique of non-specific anti-cancer immunotherapy by bladder instillations of BCG for the treatment of superficial bladder cancer.[1] BCG is the first choice of adjuvant treatment for recurrent or high-grade superficial bladder cancer.[2,3] Complications related to its use have been well described,[4] but serious parenchymatous infectious complications are not widely reported. We report the case of a disseminated Mycobacterium bovis BCG infection with biopsy-proven granulomatous hepatitis. We also present a review of literature and the management options.

Case

A 75-year-old otherwise healthy patient was treated for recurrent superficial bladder cancer. He underwent multiple trans-urethral resections (TURs) of high-grade T1 bladder tumours. He also received 2 induction courses of intravesical BCG therapy once a week for 3 weeks, and then subsequently for an additional 6 weeks. Despite this intensive management, the patient presented with tumour progression at the subsequent TUR. The tumour was found to be muscle invasive (stage T2). The metastatic workup, including an abdominopelvic CT scan, an endovenous pyelogram, a chest radiograph, a complete blood count and biochemical laboratories, was negative with the exception of elevated liver enzymes (aspartate aminotransferase max 68 U/L, alanine aminotransferase max 59 U/L, alkaline phosphatase max 210 U/L). A preoperative hepatology consultation was ordered and a transjugular hepatic biopsy revealed a normal portocaval gradient. Histology demonstrated granulomas; however, auramine coloration for acid-fast bacteria, Grocott coloration for fungi and periodic acid-Schiff staining for other microorganisms were all negative. The purified protein derivate (PPD) subcutaneous test was negative. The patient underwent radical cystectomy, which was uneventful. The final pathology demonstrated muscle invasive transitional cell carcinoma (stage T2). At the time of surgery, a planned liver biopsy was done. Histology demonstrated granulomatous hepatitis and liver tissue culture, *Mycobacterium* infection.

The patient demonstrated persistent mild fever in the postoperative period as well as persistent intra-abdominal bleeding. Initial bacterial, viral and fungal cultures were all negative. Because the patient's infectious state was progressing, an empiric triple antituberculous therapy was started, with isoniazide 300 mg, rifampin 600 mg and ethambutol 1200 mg, and it was complemented with pyridoxine (B6 vitamin) 50 mg daily. A *Mycobacterium* was isolated in 2 out of 3 Midget broth (BD Bactec, Franklin Lakes, NJ) preoperatively taken urine cultures after 11 days of incubation, and the polymerase chain reaction (PCR) for group tuberculosis on the *Mycobacterium* strain was positive. The final identification, done by mycolic acid chromatography at the Quebec reference laboratory, Laboratoire de Santé Publique du Québec, reported a *Mycobacterium bovis* BCG susceptible to isoniazide, rifampin and ethambutol but, as expected, resistant to pyrazinamide. Two blood cultures using Myco F Lytic (BD Bactec, Franklin Lakes, NJ) that were taken before the start of empiric therapy were also positive for the same

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Mycobacterium after 27 days of incubation. The intra-operative hepatic biopsy was cultured. It initially demonstrated an absence of alcohol-resistant bacille and a negative PCR for mycobacteria, but after 25 days the culture became positive for the same *Mycobacterium bovis* BCG.

The patient unfortunately experienced numerous complications, including renal failure, and he eventually died of respiratory insufficiency.

Discussion

We report a disseminated *Mycobacterium bovis* BCG infection with granulomatous hepatitis after bladder BCG instillations for bladder cancer. In their series, Debois and colleagues,[5] and Lamm and colleagues[4,6] reported a 45%–90% rate of irritative symptoms and a 35%–43% rate of hematuria. Low-grade fever was reported in 16%–28% of cases, while high-grade fever was reported in 2%–4.2%. Serious complications related to intravesical BCG has an estimated rate of 0.35%–1.9%, the vast majority (70%–75%) of those being systemic. Debois and collegues analyzed the pharmacovigilance French data and described an infectious cause of serious BCG complications in 63% of cases, while the other causes were rheumatologic and unexpected. Lamm and colleagues[4] reviewed the existing data in 1986, in which 78% of serious complications were attributed to infectious causes (including fever above 103°F as infectious cause). In both series, diagnosis of infection, sometimes without any proof, was assumed. This implies that the true incidence of infectious complications related to intravesical BCG is probably less than what is estimated in the literature. Disseminated miliary disease,[7] vertebral osteomyelitis,[8] mycotic aneurysm[9] and skin abscess[10] have also been reported. The death rate related to intravesical BCG use has never been calculated, but it is estimated to be very low; there were 9 deaths (related or not) in Debois and collagues' pharmacovigilance study covering 3 years and an unknown number of treated patients. Acute BCG-related infectious complications were the cause of death in 4 patients on whom information was detailed. No deaths were reported in Lamm and colleagues' series.

Based on histological diagnoses from liver biopsies, the liver has been reported as a potential site of disseminated disease,[11] but tissue culture of *Mycobacterium bovis* BCG, which is the ultimate proof of the disease after intravesical BCG has not been described in the literature. Lamm and colleagues[4,6] reported a combined incidence of pneumonitis and hepatitis of 0.9%, but 7 out of 46 (15%) severe systemic complications had indirect proof of disseminated BCG with granulomatous lesions on biopsy and were considered diagnostic.[6] Granulomatous hepatitis is not a specific diagnosis. Differential diagnosis also includes sarcoidosis, foreign body granuloma (e.g., in intraveinous powder drug users) and mycotic infection such as histoplasmosis or toxoplasmosis. Histologically, mycobacterial granulomas are normally located around the centrolobular vein, have a more significant caseification reaction (but not in immunosuppressed patients) and have a predominantly lymphocytic inflammatory infiltrate in addition to well-formed epithelioid granulomas, caseous necrosis, and an absence of Langhans giant cells.[12] Clinically, fever and malaise are the predominant manifestations. The liver can be enlarged and painful upon palpation. Hepatocellular enzymes are usually elevated, but sometimes only hyperbilirubinemia and elevated alkaline phosphatase are noted in the laboratory workup. The syndrome of inappropriate anti-diuretic hormone secretion (SIADH) has also been described.

Suggested management

Prevention is the most important management strategy. Recent surgery (2–4 weeks after TUR), traumatic catheterization or cystoscopy, active hematuria, immunocompromised status (i.e., transplant, leukemia, Hodgkin's disease or AIDS), fever of unknown origin, pregnancy and active urinary tract infection are all contraindications to the administration of intravesical BCG and mandate postponing the treatment. Strict surveillance of patients before treating them with intravesical BCG is of the utmost importance, and the severity of symptoms at the beginning of treatment is predictive of the necessity to stop the maintenance BCG treatment.[13,14] In most of the reported cases with severe BCG-related infectious complications, a traumatic catheter or another contraindication is described. Prophylactic isoniazide has been evaluated during intravesical BCG therapy in a randomized study and is not considered efficacious owing to similar incidence of short-term complications and adverse effects related to isoniazide.[15]

If systemic complications from BCG are suspected, the following mycobacterial cultures are suggested: 3 urine cultures, 2 blood cultures and a liver biopsy for culture and histology, if hepatic granulomatous disease is suspected. Broth cultures are much more sensitive for *Mycobacterium* than are solid media. *M. bovis* BCG is much more fastidious to isolate in broth or on solid media than *Mycobacterium tuberculosis* or *Mycobacterium* other than the *tuberculosis* group. PCR, can also be performed on tissue or urine (but not on blood) to diagnose the *Mycobacterium tuberculosis* group, which encompasses *Mycobacterium bovis*. Having a definitive diagnosis, by liquid chromatography or by 16S rRNA gene sequencing, will help tailor the intensity of the therapy. Sensitivity testing to different antimicrobial agents also helps to rule out resistant strains.

Mycobacterium bovis BCG and *M. bovis* are intrinsically resistant to pyrazinamide. Resistance to β-lactams, macrolides (except clarithromycin) and some aminoglycosides has recently been reported.[16] The suggested first-line antimicrobial treatment for *M. bovis* BCG is isoniazide 300 mg daily and rifampin 600 mg daily with or without ethambutol 1200 mg daily by mouth for 6 months.[17] Ethambutol is recommended as complementary treatment for patients with significant systemic disease or to replace isoniazide in patients who do not tolerate the drug owing to adverse effects (i.e., liver dysfunction, fever, malaise or maculopapular eruption). Aluminum-containing antacids reduce oral absorption of isoniazide. Monotherapy is not recommended because of the development of resistance. Other alternatives include the addition of ofloxacin 400 mg daily, doxycyclin and gentamicin.[16,18] The usefulness of cycloserine is controversial. Because it inhibits BCG growth rapidly (24 h compared with isoniazide, which may take as long as 1 week), some consider cycloserine potentially life-saving in patients with fulminant systemic infectious complications from BCG. However, cycloserine has severe central nervous system side effects and *M. Bovis* BCG resistance has been frequently reported.[16,19] Cycloserine should not be used routinely. The actual recommended length of treatment is 6 months for those patients manifesting extravesical symptoms, but some authors prefer treating up to 12 months for culture-proven extravesical tissue disease.[8]

Prednisolone 40 mg daily may be considered for patients with systemic disease as hypersensitivity reaction is initially difficult to differentiate from infectious reaction.[20] If prescribed, corticosteroids should be maintained as long as systemic symptoms are present. They should be gradually tapered off because exacerbation of this hypersensitivity response has been seen in patients who have stopped corticosteroids abruptly.[3] Pyridoxine 10–50 mg daily should be added to prevent some side effects of isoniazid, like peripheral neuropathy, especially in high-risk patients such as the elderly, diabetics, people with chronic liver dysfunction and HIV patients.

Although the immunological mechanism of intravesical BCG against bladder cancer is becoming better understood,[21] many unanswered questions remain. Long-term mycobacterial persistence after intravesical BCG has been proven and represents an infectious risk but also a possible explanation of immune anticancer effect.[22] What should the waiting time between suspected mycobacterial infection after BCG and radical treatment of a muscle invasive bladder cancer be? Should all patients have empirical treatment before undergoing radical surgery?

In conclusion, granulomatous parenchymatous disease is a rare but potentially life-threatening complication of intravesical BCG and it is often associated with systemic febrile disease. Specific mycobacterial cultures and diagnostic biopsy should be part of the standard management. Appropriate treatment should be initiated rapidly because death from septic complications can happen. Collaboration between urologist, infectious disease specialist, pathologist and hepatologist is essential for these complicated cases.

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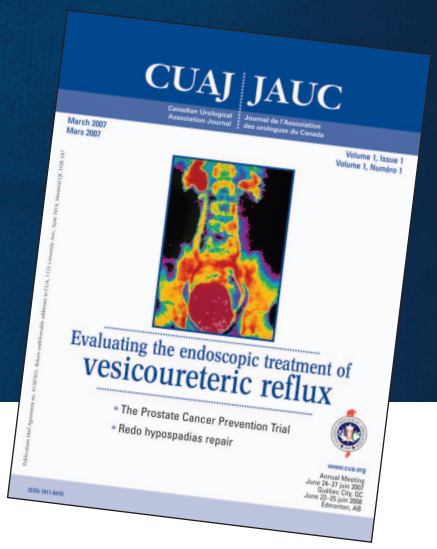

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