This is an Open Access article licensed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs 3.0 License (www.karger.com/OA-license), applicable to the online version of the article only. Distribution for non-commercial purposes only.

Bacillary Prostatitis after Intravesical Immunotherapy: A Rare Adverse Effect

Ana Joaquim^a Sandra Custódio^a
Francisco Luís Pimentel^{c, d} José Fidalgo Matos^b
Vânia Peixoto^a Ana Luísa Faria^a Joana Espiga Macedo^a
Emílio Macias^a Sónia Rego^a António Araújo^a

^aMedical Oncology Department and ^bUrology Department, Centro Hospitalar de Entre o Douro e Vouga, and ^cLenitudes, SA, Santa Maria da Feira, and ^dHealth Sciences, University of Aveiro, Aveiro, Portugal

Key Words

Bacillary prostatitis · Intravesical bacillus Calmette-Guérin immunotherapy · Bladder carcinoma

Abstract

Nowadays, the most efficient form of intravesical immunotherapy for superficial transitional cell carcinoma of the urinary bladder is the instillation of bacillus Calmette-Guérin (BCG), proceeding from an attenuated strain of *Mycobacterium bovis*. In up to 40% of cases, its instillation is associated with significantly elevated prostate-specific antigen (PSA) levels. In these cases, prostate biopsy should be withheld for 3 months and PSA should be monitored. Bacillary prostatitis is a rare occurrence in patients treated with intravesical BCG immunotherapy. Although symptomatic bacillary prostatitis is even rarer, it is the worst type of this condition. The aims of this study are to report a case of bacillary prostatitis as a rare adverse effect of intravesical BCG immunotherapy and to make a theoretical review about how to manage this complication. A 58-year-old man, former smoker, underwent a transurethral resection of the bladder in February 2004 because of a papillary transitional cell carcinoma of the bladder (pT1G2N0M0). After surgery, BCG instillation therapy was given in a total of 15 instillations, the last one in March 2007. In the last 3 months of therapy, until May 2007, a progressive increase in his PSA level was registered, and he underwent a prostate biopsy revealing granulomatous prostatitis of bacillary etiology. The semen culture was positive for *M. bovis*. After 3 months of a two-drug (isoniazid and rifampin) antituberculous regimen, the semen culture became negative and the PSA level decreased. The early identification of intravesical BCG immunotherapy complications allows their effective treatment. However, when a histological diagnosis of asymptomatic granulomatous prostatitis is made, the execution and type of treatment are controversial.

Introduction

Superficial transitional cell cancer comprises carcinomas in situ (CIS), papillary tumours limited to the mucosa, papillary tumours involving the lamina propria but not the muscle layer of the bladder, or any combination of these. The primary treatment for CIS is transurethral resection (TUR), although it is often not curative.

Intravesical therapy is an integral part of treatment in patients with superficial urothelial carcinoma of the bladder. Bacillus Calmette-Guérin (BCG) has been in use as an intravesical immunotherapeutic agent since the 1980's and is the most effective proven form of this kind of therapy. BCG Immunotherapeutic is a freeze-fried preparation made from a culture of the Connaught strain of BCG, which is an attenuated strain of the living bovine tubercle bacillus *Mycobacterium bovis*. BCG Immunotherapeutic promotes local inflammatory effects that are associated with the elimination or reduction of superficial cancerous lesions of the urinary bladder. Although the exact mechanism by which this is accomplished is unknown, the antitumour effect appears to be T lymphocyte dependent. Intravesical immunotherapy is generally safe. There is a high incidence of local, usually self-limited, relatively minor side effects, and infrequent, potentially severe local and systemic side effects [1].

Bacillary prostatitis is a local complication of BCG immunotherapy. It can be suspected when there are symptoms like or a suggestive history of irritative voiding, male factor infertility, sterile urethral discharge, terminal hematuria, perineal pain, swelling and drainage, or when an isolated increase in the prostate-specific antigen (PSA) level is detected, corresponding to the histological diagnosis. Symptomatic bacillary prostatitis must be treated with antituberculous agents for 3 months. In cases with asymptomatic elevated PSA levels, the prostate biopsy should be withheld and PSA monitored. Histology is indicated when there is persistent increased PSA for more than 3 months and, if positive for granulomatous prostatitis, the optimal management is not established [2]. Primary treatment includes definitive discontinuation of intravesical immunotherapy. All patients must be advised to use condoms during intercourse because sexual transmission via infected semen has been reported to result in a vaginal tuberculous ulcer [2].

Antituberculous treatment is an option that should be discussed in a multidisciplinary way as well as with the patient. BCG is a mycobacterium sensitive to all currently used antituberculous drugs, with the exception of pyrazinamide. The pharmacokinetics of the antituberculous drugs frequently prevents them of achieving the optimal intracellular bactericidal concentrations. There are indicated combinations such as the two-drug combination with isoniazid 300 mg/day and rifampicin 600 mg/day, the three-drug combination of the two above-mentioned drugs plus ethambutol 1,200 mg/day, or the combination rifampicin plus ofloxacin 200 mg b.i.d. This last combination uses the group of antibiotics (quinolones) also indicated in cases of unsuccessful antituberculous therapy. Further outpatient care includes periodical examination of the semen cultures to monitor treatment. If the results are positive after 3 months of therapy, bacterial resistance to the current drug regimen or patient noncompliance – which is not unusual – should be strongly suspected. Most patients can be cured when treated early with a multiple-drug regimen [2].

Case Report

In February 2004, a 58-year-old man, former smoker, presented to his doctor complaining of haematuria starting 2 months earlier. Since ultrasonographic examination revealed an intravesical neof ormation, the patient underwent a TUR of the bladder. The histology confirmed the neoplastic nature of the surgical specimen, whose histology was described as follows: ‘superficial papillary transitional cell carcinoma pT1G2N0M0 without vascular, lymphatic and perineural invasion’.

Two weeks after surgery, according to the decision made by a multidisciplinary group from the Department of Oncology, the patient was started on BCG instillation therapy consisting of an induction course followed by maintenance therapy with a total of 15 instillations, the last one in March 2007. BCG was administered intravesically weekly for 6 weeks and in weeks 13, 14 and 15, with an additional single instillation in months 6, 12, 18, 24, 30 and 36. This therapeutical scheme was not interrupted or postponed, since the patient tolerated it very well, showing no immediate complications. During the 2 years of intravesical therapy, he was asymptomatic.

In the last 3 months of therapy, until May 2007, a progressive PSA increase was registered, with the PSA level being at last 6.0 µg/l. In May 2007, the patient underwent a prostate biopsy revealing ‘granulomatous prostatitis of bacillary etiology’. After a multidisciplinary meeting with members from the Departments of Oncology and Urology, it was decided to administer antibacillary treatment. The patient received a two-drug regimen of antituberculous therapy with isoniazid 300 mg/day and rifampin 600 mg/day, with associated pyridoxine/vitamin B6 75 mg/day to prevent neuropathy associated with isoniazid use.

The semen culture was analyzed and stained positive for acid-fast bacilli, confirming *M. bovis* infection a posteriori as well as excluding other affected organs and systems with thoracic X-ray and a nephro-computerized tomography, both unaltered. The plan was (1) to additionally prescribe ethambutol if renal affection was verified (which was not the case); (2) to test the infection eradication by doing another semen culture after 3 months of therapy, and (3) if the culture was negative, to stop the antituberculous agents. The patient tolerated the therapeutic regimen very well, with no side effects reported. The semen culture at the third month was negative for any kind of infection, so the antituberculous treatment was stopped in September 2007. Nowadays, the patient is doing well and remains asymptomatic, with a PSA level of 1.2 µg/l in November 2007 that remained 1.1 µg/l at the last urology visit in December 2011.

The Portuguese Sanitary Authority (INFARMED) and the pharmaceutical company (Aventis Pasteur) were notified about the occurrence of this rare adverse event.

Discussion and Conclusion

Intravesical therapy has been established as both an alternative to radical surgical treatment for CIS and as a prophylaxis for its recurrence. In superficial papillary tumours, intravesical therapy has significantly increased the time to recurrence when administered for prophylactic purposes following TUR [1].

The early identification of intravesical BCG immunotherapy complications allows their effective treatment with complete symptom regression. The most common local reactions are transient dysuria and urinary frequency, which occur in 26 and 14%, respectively, during the induction course and in 46 and 34%, respectively, during maintenance therapy. Serious genitourinary adverse events like bacterial urinary tract infection, epididymo-orchitis, urethral obstruction and renal abscess have been reported to be present in <0.5% of cases. The most serious adverse effect is systemic BCG reaction, defined as the presence of fever, pneumonitis or hepatitis, which is even rarer [3].

Intravesical BCG therapy is associated with significantly elevated PSA levels in up to 40% of cases. In the majority of them, granulomatous prostatitis is asymptomatic and not diagnosed. It is transient and self-limited, and treatment is not required [4]. Pathologic evidence of granulomatous prostatitis with acid-fast bacilli is a common complication after this kind of therapy, and its incidence is far higher than the reported incidence of symptomatic granulomatous prostatitis. The duration of therapy is a determinant factor in the induction of the granuloma type [5]. The importance of asymptomatic granulomatous prostatitis, histologically diagnosed after a more than 3-month history of an increased PSA level, is unknown. It is known that identifying BCG complications early, preventing them when possible and managing them efficiently is critical, as most complications are preventable [6].

In the presented case report, the progressive PSA increase was a major concern for both the patient and the physician, leading to the prostatic biopsy. After the diagnosis of granulomatous prostatitis of bacillary etiology was made, treatment with antituberculous agents was started, resulting in a consequent decrease in PSA and negative semen cultures.

In cases where a histological diagnosis of asymptomatic granulomatous prostatitis has been established, the execution and type of treatment are controversial. There is no certainty about its self-limited character, and we cannot be sure about the safety and side effects of the antibacillary therapy [6]. On the other hand, we must take into account the psychological impact of having a disease that has an effective treatment (with antituberculous agents) and accepting the decision not to treat it. It is much more comforting for the patient and his physician to follow a therapy. Thus, these cases must be discussed in a multidisciplinary way as well as together with the patient in order to achieve a balanced decision.

Disclosure Statement

The authors declare that they have no conflicts of interest. They also declare that they have full control of all data and agree to allow the journal to review their data if requested.

References

- 1 Aventis Pasteur limited: Immucyst for treatment of superficial transitional cell carcinoma of the urinary bladder. Business Briefing-European Pharmacotherapy 2003, pp 1–7.
- 2 LaFontaine PD, Middleman BR, Graham SD Jr, Sanders WH: Incidence of granulomatous prostatitis and acid-fast bacilli after intravesical BCG therapy. *Urology* 1997;49:363–366.
- 3 Koya MP, Simon MA, Soloway MS: Complications of intravesical therapy for urothelial cancer of the bladder. *J Urol* 2006;175:2004–2010.
- 4 Leibovici D, Zisman A, Chen-Levy Z, Cypel H, Siegel YI, Faitelovich S, Lindner A: Elevated prostate specific antigen serum levels after intravesical instillation of bacillus Calmette-Guerin. *J Urol* 2000;164:1546–1549.
- 5 Mukamel E, Konichezky M, Engelstein D, Cytron S, Abramovici A, Servadio C: Clinical and pathological findings in prostates following intravesical bacillus Calmette-Guerin instillations. *J Urol* 1990;144:1399–1400.
- 6 Saint F: Prévention et traitement des effets indésirables associés aux instillations endo-vésicale de BCG. *Prog Urol* 2006;16:780–785.