



Oncology

BCG Induced Necrosis of the Entire Bladder Urothelium



Malte Krönig^{a,*}, Cordula Jilg^a, Dieter Burger^b, Mathias Langer^b, Sylvia Timme-Bronsert^c, Martin Werner^c, Ulrich Wetterauer^a, Wolfgang-Schultze Seemann^a

^a Medical Centre, University of Freiburg, Department of Urology, Hugstetter Strasse 55, 79106 Freiburg im Breisgau, Germany

^b Medical Centre, University of Freiburg, Department of Radiology, Hugstetter Strasse 55, 79106 Freiburg im Breisgau, Germany

^c Medical Centre, University of Freiburg, Department of Pathology, Breisacher Strasse 155a, 79106 Freiburg im Breisgau, Germany

ARTICLE INFO

Article history:

Received 24 May 2015

Accepted 3 June 2015

Available online 21 June 2015

Keywords:

BCG

Urothelial necrosis

Bladder cancer

Cystectomy

ABSTRACT

Instillation therapy with attenuated tuberculosis bacteria (BCG) can significantly reduce rates of recurrence of non-muscle invasive bladder cancer. Local and systemic side effects such as dysuria, irritative voiding symptoms or partial bladder contracture and systemic inflammation were reported. A 75-year-old male patient with recurrent non muscle invasive bladder cancer developed necrosis of the entire bladder urothelium more than six years after BCG instillation immunotherapy. The resulting irritative voiding symptoms and low bladder capacity required radical cystectomy. BCG instillation can cause severe side effects, which develop gradually and eventually need radical surgical therapy such as cystectomy without tumor recurrence.

© 2015 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Urothelial cancer of the bladder is the sixth most common cancer with an estimated 74,000 newly diagnosed cases in 2014. It can be divided into non muscle invasive (NMIBC: pTa, pT1 and carcinoma in situ (CIS), 86% of the patients) and muscle invasive bladder cancer (MIBC: >pT2, 14% of the patients) with worse prognosis of the latter. MIBC requires open surgical therapy such as cystectomy with urinary diversion and often adjuvant chemotherapy. NMIBC is treated by an initial transurethral resection (TUR) and in case of intermediate or high risk tumors by adjuvant intravesical instillation chemotherapy or immunotherapy. Intermediate risk is defined as multifocal pTa high or solitary T1 tumors and high risk is defined as multifocal T1 tumors and carcinomas in situ (CIS). Standard of care for high risk tumors is intravesical instillation of attenuated tuberculosis bacteria (Bacille Calmette Guerin: BCG), which is proven to be most effective in reducing the risk of disease recurrence. BCG induces a cellular and a humoral based immune reaction with anti-tumoral effects.¹ Localized side effects have been reported such as abacterial cystitis, dysuria or partial bladder contracture and systemic side effects such as systemic inflammation (BCGitis) with fever, malaise and sepsis.² Local side effects can

be treated symptomatically and only require surgical therapy in case of bladder contracture and fibrosis with reduced bladder capacity.² Systemic side effects require tuberculostatic treatment.²

Case presentation

The patient (male; 75 years) presented with BCG induced urothelial necrosis of the entire bladder, which required cystectomy. Ten years earlier he was first diagnosed with multifocal non-muscle invasive bladder cancer (NMIBC, transurethral resection (TUR): pT1 G2). A standard second transurethral resection 4 weeks later did not show any remaining tumor. However, 18 and 30 months later he was diagnosed with recurrent NMIBC (pTa low grade and pTa high grade/carcinoma in situ (CIS) respectively). Due to the CIS component of the tumor the patient received induction therapy with Bacille Calmette Guerin (BCG) instillations at 31 months. No side effects were reported. Until 61 months regular cystoscopies did not show any sign of recurrence. However at 61 months, 30 months post BCG, the patient first reported irritative voiding symptoms and urine diagnostics showed cells typical for chronic recurrent inflammation but no bacterial infection. A cystoscopy at 62 months showed fibrin coated old scars and the patient continuously reported irritative voiding symptoms and decreasing bladder capacity. At 67 Magnetic Resonance Imaging (MRI) of the pelvis showed no sign of recurrent tumor or extra vesical disease. The following transurethral resection showed urothelial necrosis extending into the muscle layer but no recurrent tumor. In the following months

Abbreviations: NMIBC, non muscle invasive bladder cancer; MIBC, muscle invasive bladder cancer; BCG, Bacille Calmette Guerin.

* Corresponding author. Tel.: +49 761 270 28931.

E-mail address: malte.kroenig@uniklinik-freiburg.de (M. Krönig).

urine analysis showed persistent leukocyturia (>500 leukocytes/ μl) but no bacterial infection. At 75 months cystoscopy showed fibrin coated scars covering the entire bladder but no sign of recurrent tumors. A second MRI showed signal reduced urothelium of the entire bladder compatible with urothelial necrosis (Fig. 1A). No sign of tumor growth beneath the necrotic urothelium. Irritative voiding symptoms of the patient did not improve over the next 2 years. Follow up did not show any sign of recurrent tumors. At 106 months the cystoscopic finding has changed from fibrin coated urothelium to completely dissolving necrotic tissue covering the entire bladder sparing only the interureteric crest including the ostia (Fig. 1B) (for complete video see [Supporting Information Video S1](#)). This finding and the persistently low bladder capacity of the patient required cystectomy with urinary diversion and ileum neo bladder – nearly 6 years post BCG instillation therapy. Histopathologic analysis of the

cystectomy specimen did not show any sign intra- or extravesical tumor recurrence and confirmed the extensive urothelial necrosis (Fig. 1C). The patient fully recovered with good continence, normal bladder capacity and manually assisted voiding.

Discussion

Local or systemic side effects from BCG instillation are reported frequently and are the main reason for discontinuing therapy.^{3,4} BCG induced local and systemic side effects were analyzed in several trials: Brausi et al analyzed 1355 patients for BCG induced toxicity in different doses and duration of BCG therapy. 30.6% of the patients were reported with systemic side effects and 60.8% with local side effects. The most common effects were chemical or bacterial cystitis, increased voiding frequency and hematuria. No

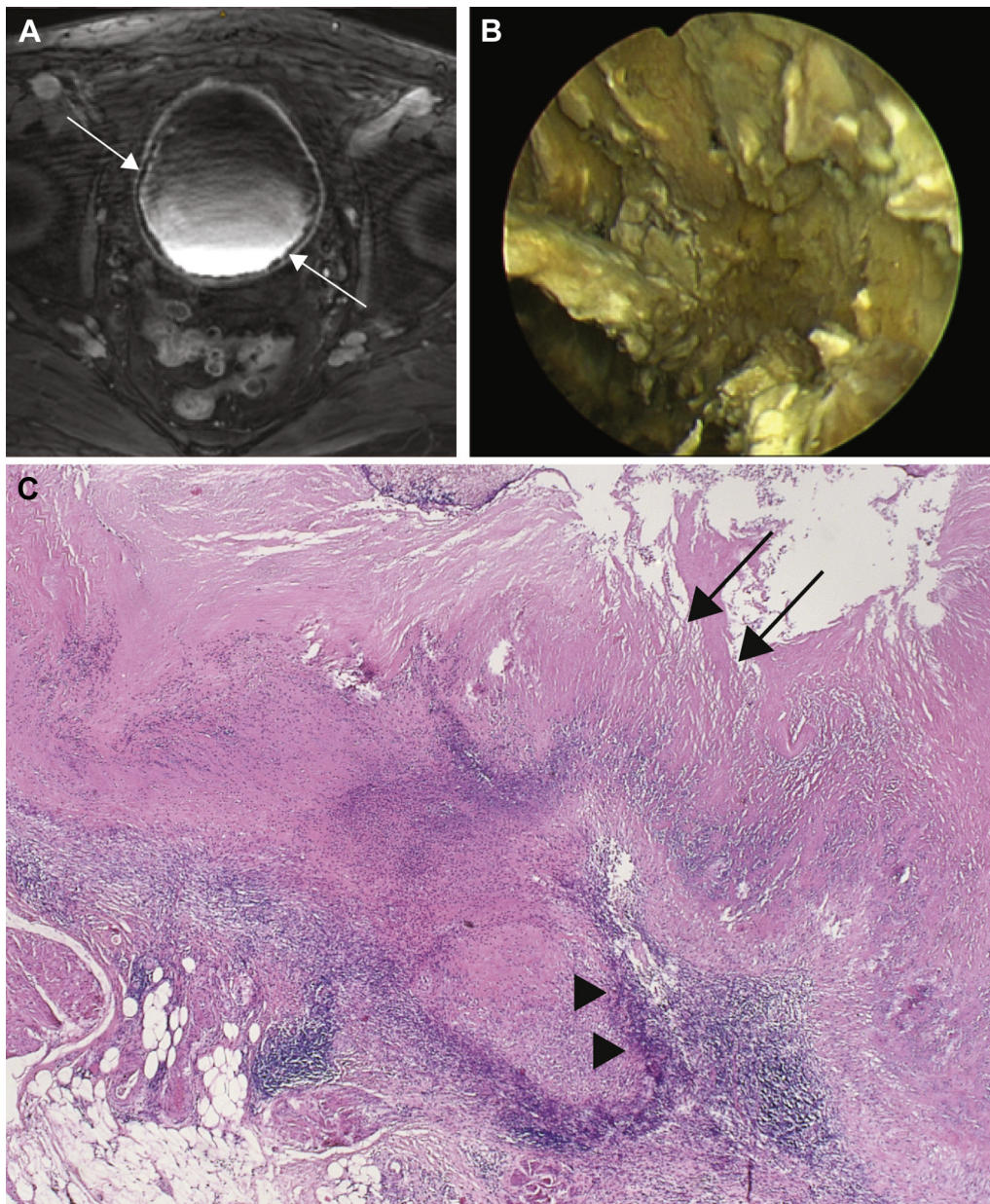


Figure 1. A) Magnetic Resonance Imaging of the pelvis (axial T1 fs post CM) at 75 months post BCG treatment shows entirely hypoperfused urothelium (arrows); B) Macroscopic validation of necrosis of the entire urothelium: Cystoscopy of the patient's bladder at 75 months post BCG treatment months showing a representative section with complete urothelial necrosis; C) Histological analysis (H&E staining; 20 fold magnification): extensive necrosis of the urothelium (arrows) and the granulomatous and lympho-follicular inflammation (arrowheads) as a sign of the former BCG therapy.

specification regarding the follow up period were made and no contracted bladder or necrosis of the urothelium have been reported. Van der Meijden et al.² analyzed 487 patients also for BCG induced toxicity for different treatment durations. Overall 75.2% of the patients showed local side effects. Contracted bladder was summarized among others under “other local side effects” and was reported in 35.7% of the patients. No specifications were made for contracted bladder or necrosis of the urothelium. Follow-up was at least 42 months. A third large trial by Lamm et al.⁵ analyzed 660 Patients for BCG induced toxicity for different treatment durations but did not specify side effects in detail. Follow-up was at least 120 months. Orihuela et al.⁴ analyzed 107 patients for BCG induced toxicity and specifically reported no bladder contracture or necrosis. The above trials show that local side effects are common in BCG instillation therapy but late onset necrosis of the entire urothelium as in our case has not been reported yet. Follow up of the above trials might have been too short to systematically detect such long term toxicity 6 years post BCG instillation. The history of our patient shows that severe long term BCG induced side effects exist and even require radical surgical therapy such as cystectomy without tumor recurrence.

Competing interests

All authors declare no competing interests.

Consent

Written informed consent was obtained from the patient for publication of this Case report and any accompanying images. A

copy of the written consent is available for review by the Editor of this journal.

Acknowledgment

We would like to thank the patient for providing his data and history.

Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.eucr.2015.06.002>.

References

1. Bohle A, Brandau S. Immune mechanisms in bacillus Calmette-Guerin immunotherapy for superficial bladder cancer. *J Urol.* 2003;170(3):964–969. Epub 2003/08/13.
2. van der Meijden AP, Sylvester RJ, Oosterlinck W, et al. Maintenance Bacillus Calmette-Guerin for Ta T1 bladder tumors is not associated with increased toxicity: Results from a European Organisation for Research and treatment of cancer Genito-urinary Group Phase III trial. *Eur Urol.* 2003;44(4):429–434. Epub 2003/09/23.
3. Braasch MR. Intravesical instillation treatment of non-muscle-invasive bladder cancer. *Eur Urol.* 2009;8:549–555.
4. Orihuela E, Herr HW, Pinsky CM, Whitmore Jr WF. Toxicity of intravesical BCG and its management in patients with superficial bladder tumors. *Cancer.* 1987;60(3):326–333. Epub 1987/08/01.
5. Lamm DL, Blumenstein BA, Crissman JD, et al. Maintenance bacillus Calmette-Guerin immunotherapy for recurrent TA, T1 and carcinoma in situ transitional cell carcinoma of the bladder: A randomized Southwest Oncology Group Study. *J Urol.* 2000;163(4):1124–1129. Epub 2000/03/29.