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Case report

Bacillus Calmette-Guérin (BCG) prostato-epididymitis in a patient treated for a non-invasive urothelial cancer: A case report

Ayemane Salif [a], Ferdinand Bigirimana [b], Sophie Willems [b], Gina Reichman [b], Johanna Noels [b], Sigi Van Den Wijngaert [c], Sophie Lecomte [d], Evelyne Maillart [b], Philippe Clevenbergh [b,*]

[a] Department of Surgery, Brugmann University Hospital, Free University of Brussels, Brussels, Belgium
[b] Department of Infectious Diseases, Brugmann University Hospital, Free University of Brussels, Brussels, Belgium
[c] Department of Microbiology, University Laboratory of Brussels, LHUB-ULB, Free University of Brussels, Brussels, Belgium
[d] Pathology department, Brugmann University Hospital, Free University of Brussels, Brussels, Belgium

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ABSTRACT

Introduction: The Bacillus Calmette-Guérin (BCG) used as anti-tuberculous vaccine is also a well-known therapy for superficial urothelial cancer. Local or general side effects can occur, although it is generally well tolerated.
Case: We present the case of a 65 year-old caucasian man consulting for gross hematuria and lower urinary tract symptoms. Magnetic resonance imaging (MRI) demonstrated a non-invasive urothelial carcinoma (NMIBC) and Prostate Imaging–Reporting and Data System (PIRADS) IV lesions. Transurethral resection of the bladder tumor revealed a non-invasive transitional cell carcinoma. Intravesical Bacillus Calmette Guerin (BCG) therapy was provided. After 6 intravesical instillations, the patient presented with prostato-epididymitis. Forthcoming BCG instillations were canceled, and cancer treatment was switched to epirubicine. Treatment with ethambutol, rifampicin and isoniazid was started with rapid resolution of the symptoms. Urinary and semen cultures grew *Mycobacterium tuberculosis* complex strain BCG. As prostate specific antigen (PSA) rose, prostate's biopsies were performed showing extensive necrosis boarded by granulomas without signs of malignancy.
Discussion: BCGitis is a rare complication in patients treated for non-invasive urothelial cancer. Several risk factors, local and systemic, should be considered prior to this immunotherapy. BCGitis (local or disseminated) or hypersensitivity reactions to BCG must be included in the differential diagnosis even if therapy was administered several years before the symptoms. Adequate treatment must be started as fast as possible to avoid serious complications.

Introduction

Bacillus Calmette-Guérin (BCG) is a live attenuated strain of *Mycobacterium bovis*. It is used as a vaccine against *Mycobacterium tuberculosis* (MTb). In addition, BCG intravesical instillation is approved by the FDA since 1990 for the treatment of non-invasive urothelial carcinoma [1]. Its mode of action mimics immunotherapy. It eliminates the residual tumor after transurethral resection, slows disease development, minimizes the need for cystectomy, and extends survival. It is usually well tolerated. Side effects may be due to a true mycobacterial infection or less likely to an hypersensitivity reaction [2,3]. Pure hypersensitivity reactions to BCG are matter of debate as granulomas are often found on histopathology even though cultures remain negative. Local side effects are the most common and involve the lower genitourinary tract. Ascending infection may affect the kidneys. Systemic infectious complications, after hematogenous dissemination, have also been reported. Lungs, bones, and the liver are among the most commonly affected organs [2]. Risk factors for systemic complications include primary, acquired or induced immunodeficiency [4]. Additionally, breaches in the bladder epithelium increase the risk of local and generalized infections [5]. Those complications may occur early after therapy or emerge years later as the result of BCG's reactivation after a period of latency. Symptoms are non-specific and may be confused with tumor progression [6]. Timely diagnosis and treatment require awareness of those complications by the doctor in charge [7]. Here we report a case of an immunosuppressed patient who developed a genitourinary infection due to BCG, diagnosed after several rounds of ineffective antibiotic treatment for a presumed bacterial infection.

* Corresponding author.
E-mail address: philippe.clevenbergh@chu-Brugmann.be (P. Clevenbergh).

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Clinical case

A 65-year-old male presented to the urology department for gross hematuria and lower urinary tract infection symptoms. Medical history included stented ischemic heart disease, gout, hyperlipidemia, polymyalgia rheumatica (February 2021), facial paralysis, appendectomy, high blood pressure, left total hip prosthesis, costal fracture and colon polyp resection. The patient had no history of active TB nor risk factor for TB acquisition. His treatment consisted of low dose aspirin 80 mg, telmisartan 80 mg, allopurinol 100 mg, tamsulosine 0,4 mg, atorvastatin 40 mg, methylprednisolone 20 mg and methotrexate 2,5 mg, a day. Immunosuppressive therapy for his polymyalgia rheumatica was started 3 months earlier. MRI showed bladder polyps and a Prostate Imaging–Reporting and Data System (PIRADS) IV lesions. Transurethral resection of the tumor (TURT) and prostate biopsies were performed in May 2021. The prostate biopsies were negative and the TURT showed a non-invasive high-grade urothelial carcinoma. BCG instillations were started in June 2021, weekly, for a total of 6 doses. Dosage and frequency of BCG, strain TICE, 0,4–1,6 $\times 10^7$ CFU/ml in 50 ml, instillations were done as per protocol (OncoTICE® (MSD, Belgium). OncoTICE® is a lyophilized preparation containing attenuated *Mycobacterium bovis* bacilli, prepared from a culture of Calmette-Guérin bacilli [8]. After 6 instillation of OncoTice®, the patient presented with fatigue, fever and gross hematuria. An ultrasound showed no bladder nor kidneys abnormalities. Urine analysis showed pyuria, hematuria but no bacteria. An empiric ten-day course of ciprofloxacine was prescribed with an improvement of the signs and symptoms (07/2021). Urine culture turned back negative. Gonorrhea/chlamydia NAAT testing was not performed as the patient was sexually inactive. Two weeks after treatment completion, his condition worsened with a swollen and painful right epididymis. He had persistent weakness and night sweats without fever. Laboratory exam showed c-reactive protein of 40 mg/l (Normal range < 10 mg/l) without elevated leukocytes. A diagnosis of right epididymitis was made on clinical basis. The patient was started on levofloxacin for 7 days without significant improvement. The patient was then referred to an Infectious Diseases specialist's consultation for further investigations (08/2021). An ultrasound (08/2021) confirmed the right-sided epididymitis without testicular involvement. Urine samples (100 ml on three consecutive days) and semen were sent for mycobacterial culture. Direct examination for Acid-fast Bacilli (AFB) was negative. Empiric anti-tuberculous treatment was initiated with INH 300 mg QD, rifampicin 600 mg QD and ethambutol 1200 mg QD. Four weeks later, urine and semen cultures came back positive for *Mycobacterium tuberculosis* complex. A Whole Genome Sequencing identified *Mycobacterium tuberculosis* complex, strain *Mycobacterium bovis* BCG, spoligotype 482 - Bovis1_Bcg. There was no mutation associated to resistance for isoniazid, rifampicin, ethambutol, fluoroquinolone, neither for other first line or second line anti TB drugs. The identified resistance mutations pncA His57Asp for pyrazinamide and cycA Gly122Ser for cycloserin are typical for the vaccinal strain of *M. bovis* BCG. General status and symptoms improved one week after anti-BCG treatment initiation. There was no clinical sign of hip prosthesis infection. As PSA rose, prostatic biopsies were performed showing a granulomatous prostatitis with extensive necrosis without signs of malignancy (12/2021) (Fig. 1). Those biopsies were not examined for AFB nor cultured for MTBc. Concomitant urine cultures (3 samples, 12/2021) remained negative for mycobacteria. A control cystoscopy came back negative. The total duration of tuberculosis treatment was

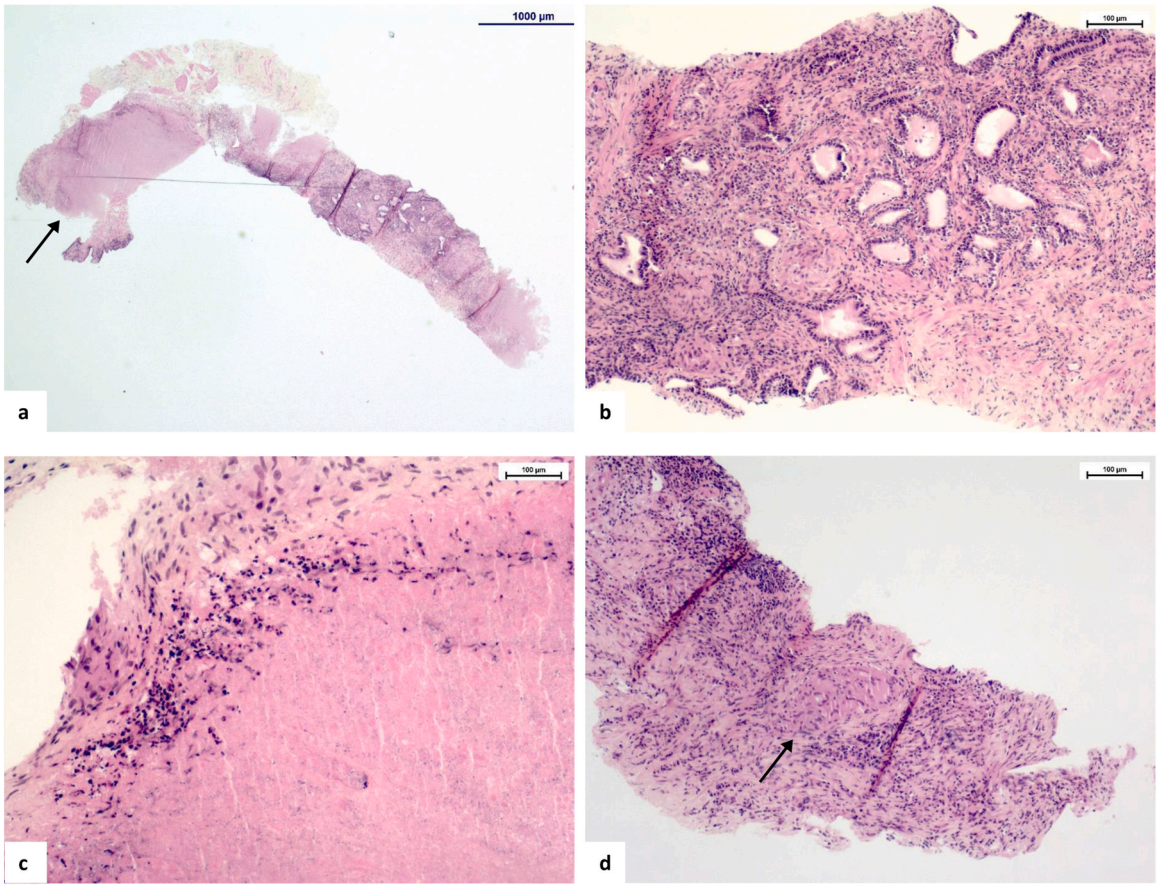

Fig. 1. Fig. 1 Prostate biopsy, Hematoxillin-Eosin-Safran stain. (a) x2 Extensive zone of necrosis, stained in pink. (b) (x10) Evident features of prostatis. Lymphocytic infiltrate, dilated glands. No evidence of malignancy. (c) (x10) Presence of polymorphonuclear neutrophiles at the border of the necrotic zone. (d) (x10) Presence of poorly formed granulomas, with giant cells.

nine months. Two years later (09/2023) the patient is doing well with a normal urine analysis and normal appearance of the bladder on cystoscopy.

Discussion

Bacillus Calmette Guérin is a live-attenuated strain of *Mycobacterium bovis* used as a vaccine against tuberculosis. BCG as *in loco* vesical instillations is also a registered therapy for non-invasive bladder cancer and acts as an immunomodulatory agent on the urothelial epithelium. Although generally safe, side effects do occur either as a true mycobacterial infection either as an immuno-allergic reaction. In a large EORTC study, two third of patients present local side effects (BCG cystitis, bacterial cystitis and gross hematuria), and about a third self-limited general manifestations (malaise, fever). About 10 % of the patients interrupt their therapy due to these side effects. Disseminated BCGitis occurs in about 0.5 % of patients [9]. Serious side effects may be due to local (urogenital, upper and lower urinary tract; …) or disseminated BCG infection/seeding. Disseminated BCGitis can occur in any organs (lungs, liver, bones and articulations, grafts on vascular or orthopedic prosthesis,). It arises within a few weeks to many years after vesical instillations [7]. Standards precautions should be applied before using BCG. Active TB, as a confusing factor, should be ruled out prior to BCG therapy. Systemic risk factors to be checked are acquired, congenital or iatrogenic immunosuppression. Instillation shouldn't be performed in case of breaches in the vesical mucosa like a recent (< 15 days) TURT, (symptomatic) bacterial cystitis, gross hematuria, traumatic urological procedures,… [5] To prevent infectious complications, instillation of a lower mycobacterial load, early short treatment with an anti-TB drug or a quinolone, symptomatic treatment of cystitis, use of inactivated BCG have been tried [7]. None of these interventions showed convincing evidence. The various strains of BCG: Tice and Connaught have the same efficacy and toxicity. It is advised to space the instillations in case of side effects. Our patient was immunosuppressed using corticoids and methotrexate which could explain his increased risk to mycobacterial infection. Delay between his TURT and his instillations complies with the safety precautions. While developing fever and epididymitis, he received a course of ciprofloxacin and later levofloxacine. This improved his condition but couldn't cure him. Quinolones indeed have anti-mycobacterial effects but shouldn't be used as monotherapy. Urines cultures remained sterile for classic uropathogens. In general, sterile pyuria should prompt a search for genito-urinary TB, or in our case BCG. A similar case treated with quinolones was described [10]. Centrifuged urines as well as a sperm samples were sent for AFB staining and cultures. AFB stainings were negative. However, empirical therapy was started while waiting for the culture result. Those cultures grew BCG only four weeks later. The mycobacteria was formally characterized using whole genome sequencing [11]. Cultures may come back negative in about 50 % of the cases [12]. Decision to pursue the anti-TB therapy will then be based on clinical, biological and imagery evolution. Our patient also presented a granulomatous prostatitis. Granulomatous prostatitis is quite frequent with up to 40 % of patients affected when systematically searched for [13]. These are not always symptomatic. In a collection of 307 case reports, it appears that infectious complications of BCG occur with different timings after instillation according to the organ involved [14]. Genitourinary infections are the first to occur with penile lesions as quick as one week after instillation and orchi-epididymitis after a median time of 8 weeks but up to 3 years. Disseminated BCGitis leading to granulomatous hepatitis or miliary pneumonitis also do appear soon after instillation (median time 1–6 weeks). However vascular, osteo-articular, and muscular complications take over 50 weeks to manifest and be diagnosed. Diagnosis of complications arising late or very late after the cure is very tricky. Physicians should be aware of these late-onset complications, even months or years after the last BCG instillation.

Another serious side effect is hypersensitivity reaction that can affect various organs like hypersensitivity pneumonia or hepatitis, reactive arthritis… [15] Those infectious or immune-allergic side effects usually have atypical presentations. Differentiating active mycobacterial infection from immune-allergic reaction is cumbersome. All available microbiologic techniques should be used to search for BCG like AFB staining, culture and PCR including GeneXpert^{TM}. Granulomas are often found in biopsies (lung, liver, kidney, vasculitis, orchitis, prostatitis, …) in case of BCG infection although AFB staining is usually negative. Granulomas are also found in case reports described as hypersensitivity reaction. Corticoids are the drugs of choice for hypersensitivity reactions, but are often combined with anti TB drugs due to the difficulty to differentiate between true mycobacterial infection or pure hypersensitivity [15].

True mycobacterial infections require an anti Tb treatment. Various schemes are proposed. OncoTICE® BCG strain is reported to be sensitive to most conventional anti-TB drugs such as streptomycin, para-aminosalicylic acid, isoniazid, rifampicin and ethambutol [8]. It is intrinsically resistant to pyrazinamide. In the larger context of *M. bovis*, first line drugs are usually effective except PZD. The different BCG strains have different susceptibility patterns with some presenting low level resistance to INH. Differences in susceptibility should be taken into account when providing anti TB drugs [16]. Susceptibility can be assessed using classic phenotypic culture assays. Whole genome sequencing can also reveal resistance associated mutations to anti-TB drugs and characterize the species. Therapy is not well standardized and should be proportionate to the severity of the disease with INH and RIF + EMB or moxifloxacin for a duration of minimum 2 months up to nine months. The recommended treatment for uncomplicated BCG epididymo-orchitis consists of 300 mg isoniazid and 600 mg rifampicin daily for 3 to 6 months. For symptomatic prostatitis, 300 mg isoniazid and 600 mg rifampicin are also prescribed daily for 3 to 6 months. In case of fever > 38,5 °C more than 48 h, 300 mg isoniazid, 600 mg rifampicin and 1200 mg ethambutol are given daily for at least 3 months [2]. We administered a triple INH/RIF/EMB therapy for the complete nine months treatment. The main risk of prolonged EMB therapy is optic neuritis.

Conclusion

We described a case of urogenital BCGitis occurring two months after intravesical instillations for a non-invasive urothelial cancer. Diagnosis was confirmed by urine and semen cultures. Immunosuppression was the risk factor in our patient. He received a nine months triple therapy with INH/RIF/EMB, BCG being intrinsically resistant to PZD. Complications of instillations may arise locally or affect a wide range of organs and consist either of a true mycobacterial infections or of an hypersensitivity reaction. Genito-urinary tract infection tend to occur early: within 2 months whilst distant pulmonary or liver dissemination arise later: 3–6 months and even MORE so for bone, vascular or muscles infections: exceeding 6 months. For late-onset manifestations, physicians should keep in mind that their patient was exposed to a live (attenuated) mycobacteria. Main risk factors are local breaches in the urinary tract and immune suppression. Diagnostic workup should include the full classic mycobacterial microbiology and pathology to differentiate between infection and hypersensitivity reaction. Corticoids are seldom used alone. Anti-mycobacterial empiric treatment should be initiate promptly as definite diagnosis may remain elusive.

Author's agreement

All the author have read and approved the submitted manuscript.

CRediT authorship contribution statement

Sophie Willems: Writing – review & editing, Supervision. **Ferdinand Bigirimana:** Writing – original draft. **Ayemane Salif:** Writing –

original draft. **Sophie Lecomte:** Supervision. **Sigi Van Den Wijngaert:** Supervision. **Philippe Clevenbergh:** Writing – review & editing, Supervision. **Evelyne Maillart:** Writing – review & editing. **Johanna Noels:** Writing – review & editing. **Gina Reichman:** Writing – review & editing.

Declaration of Competing Interest

There is no competing interest.

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