



Case report

An ambivalent prostate nodule after Bacillus Calmette-Guérin therapy

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ABSTRACT

A 65-year-old patient without specific associated pathology was treated for a high-grade non-invasive papillary urothelial carcinoma by surgery associated with repeated intravesical Bacillus Calmette-Guérin (BCG) instillations. During follow-up, magnetic resonance imaging (MRI) found a clinically indurated prostate nodule with suspected extensive capsular invasion. Prostatic biopsies showed epithelioid and giant-cell granuloma associated with a single focus of adenocarcinoma. Urinary culture test and specific PCR confirmed the involvement of *Mycobacterium bovis*. The patient was treated first by rifampin, isoniazid and ethambutol and then by rifampin and isoniazid for a total duration of 9 months, with MRI reassessment at various intervals. After BCG therapy, systemic infectious complications but also local complications such as granulomatous disease have been reported, but prostatic abscesses with *M. bovis* mimicking cancer on MRI are rare. Consequently, we advise specific local urinary and prostate samples to test for mycobacteria (staining, culture, PCR) in order to avoid aggressive high-risk prostatic surgery.

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1. Introduction

Bladder carcinoma is a common disease affecting 2.7 million people worldwide every year. The intermediate risk classification for cancers may indicate repeated intravesical BCG (Bacillus Calmette-Guérin (BCG)) instillations, which can be performed using an attenuated *Mycobacterium bovis* (*M. bovis*) strain similar to that used for the tuberculosis vaccine. The use of this therapy can lead to infectious complications that are known but nevertheless pose diagnostic difficulties. Clinical presentations differ with time of onset, probably due to localized infectious reaction [1] or more systemic inflammatory reaction (fever, malaise, multiple organ involvement [2]).

2. Case report

A 62-year-old male patient with no personal or family specific medical history, no foreign travel, and in 2015 a diagnosis of a high-grade non-invasive papillary urothelial carcinoma (pTa) by surgical resection on the right side of the bladder. This surgery was followed in January 2016 by 6 instillations of BCG (once a week for 6 weeks) that

were complicated by a urinary tract infection caused by secondary urethral stenosis due to a gram-negative bacilli in culture. In September 2016, the digital rectal examination performed as part of urological follow-up revealed induration at the right base of the prostate, without associated functional urinary or general signs. Prostate-specific antigen (PSA) increased to 8.5 ng/mL in September 2016 compared to 1.7 ng/mL in October 2015 (normal range 0–4.1 ng/mL).

In December 2016, one year after BCG therapy, prostate biopsies revealed two kind of lesions: inflammatory lesions with epithelioid and giant-cell granuloma on all samples associated with a localized focus of Gleason 6 (3 + 3) grade adenocarcinoma over 2 mm at the right base. Magnetic resonance imaging (MRI) of the prostate (Fig. 1) objectively revealed a tumor-like nodule over 2 cm at the basal peripheral and median right prostate, with signs of suspected capsular invasion.

In February 2017, further prostate biopsies confirmed prostatic adenocarcinoma lesions associated with nonspecific inflammatory and atrophic lesions. The nodule visualized on MRI was larger than the adenocarcinoma microfocus found on the prostate biopsies. We therefore had to envisage two discordant hypotheses with divergent therapeutic implications: excisional surgery for a 2-cm tumor nodule, or simple monitoring of the Gleason 6 nodule in case of concomitant infection.

Standard bacteriological culture was negative but PCR on the specific mycobacterial culture tested positive for *M. bovis*.

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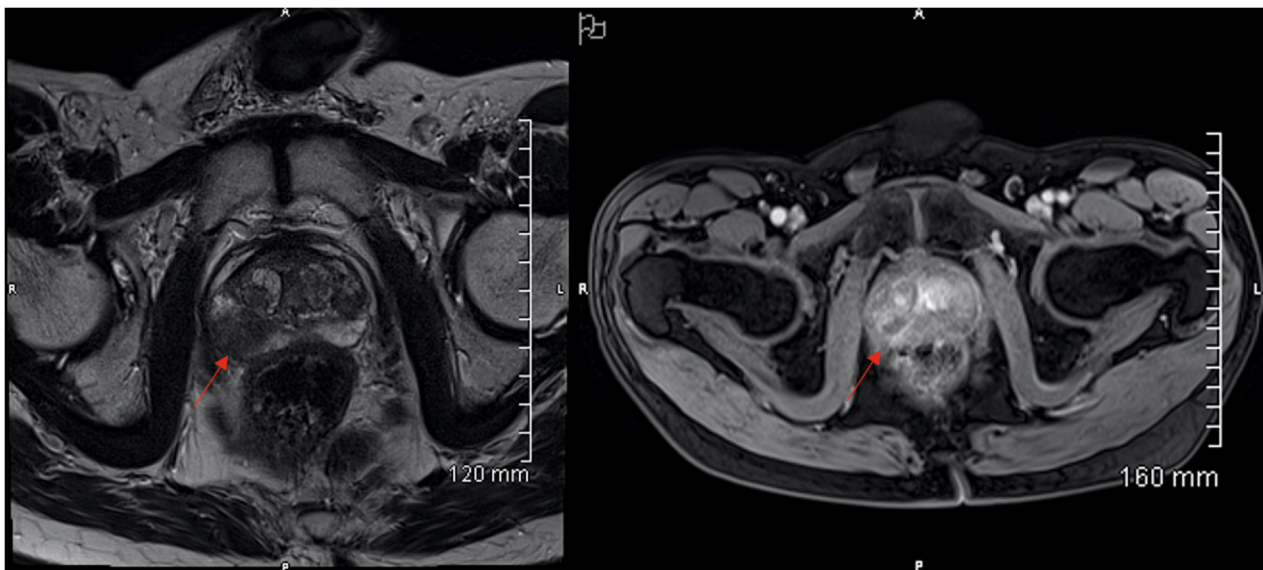


Fig. 1. Prostate MRI (12/2016), T2 Axial section and T1 Fat Sat after injection of gadolinium contrast material. Nodular lesion of the right base of the peripheral area invading the transitional zone with capsular invasion (red arrow). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

In March 2017, antimycobacterial treatment with rifampin (600 mg daily), isoniazid (300 mg daily) and ethambutol (1 g daily) was started for two months and then continued with only by rifampin and isoniazid. The challenge was therefore to rely on MRI to monitor the small adenocarcinoma lesion on prostate biopsies associated with an infectious granulomatous lesion that could give a nodule-like appearance that would hamper the MRI monitoring.

In June 2017, a re-assessment MRI objectively revealed a partial therapeutic response of the nodule. It was decided to continue antimycobacterial therapy for a further 3 months. After 9 months of antimycobacterial therapy (in December 2017), prostate MRI showed a clear regression of the nodular area initially described in the right basal peripheral localization associated with a triangular zone suggestive of sequelae lesion.

In February 2018, a monitoring prostate biopsy showed islets of subacute prostatitis without signs of malignancy associated with post-BCG necrotic epithelioid granulomas and fibromyxomatous hyperplasia with regressive glandular foci without adenocarcinoma. Urological management was therefore oriented towards clinical and biological monitoring with PSA assays and annual MRI imaging. In December 2017, PSA was 2.860 ng/mL (< 4.10 ng/mL) and 8 months after (in August 2018), PSA remained normal at 2.280 ng/mL. The last follow-up MRI in November 2020 showed only persistence of known lesions of granulomatous scarring and no suspicious intraprostatic nodule. The last cystoscopy in May 2020 was normal.

3. Discussion

Screening for prostate cancer uses PSA as an early biomarker. However, PSA is non-specific, and its level can also change with progressive prostate infection [3]. After BCG therapy, up to 40% of patients will have increased PSA levels in the months following instillation [4]. Histologic granulomatous prostatitis after BCG therapy for bladder cancer is known to occur, but its prevalence is low [5]. Moreover, it is difficult to systematically identify the etiology of this histological damage. In a cohort of 12 patients who received BCG therapy after total cystoprostatectomy surgery for invasive bladder cancer, 9 developed granulomatous prostatitis, and acid-fast bacilli (AFB) were identified in 7 of these 9 patients [6]. If patients were asymptomatic, non-treatment was the

systematic choice of care. Another study of 32 patients treated by BCG therapy also showed that the specific microbiological detection of AFB is difficult despite the presence of granulomatous prostatitis [7]. Out of 13 prostate nodules detected, only 3 cases of *Mycobacterium* were diagnosed.

Adenocarcinoma associated with granulomatous prostatic involvement is rarely described in the literature, even though it is often discovered incidentally after aggressive curative prostate surgery [8]. In addition to biopsies and mycobacterial examinations, imaging, mainly with 3-Tesla MRI, can differentiate a cancerous origin from a non-specific granulomatous lesion [9]. This technique can be faulted and overestimate non-specific granulomatous lesions with invasion suggesting infiltrated adenocarcinomas [10]. PET-CT can demonstrate benign non-specific-hypermetsabolic signals [11]. In this context, special systematic vigilance is warranted, as nodular prostate lesions can clinically and radiologically mimic cancers [12]. In the literature, and more specifically after BCG therapy, cases reported following clinical discovery of an image-confirmed prostatic lesion have been diagnosed as tuberculous abscesses directly due to the Ziehl-Neelsen stain [13], to specific culture, or to PCR [14]. The duration of the treatment of these cases reported by two-drug or four-drug therapy ranges from 3 to 12 months and may require a local surgical procedure with drainage [15].

In our case, the diagnosis of prostatitis with *M. bovis* was discussed at the first biopsy and confirmed by microbiology despite ambivalent anatomopathological results against the presence of adenocarcinoma. The decision to use antimycobacterial treatment avoided further prostate surgery, which could be highly risky given the initial size of the lesion and the suspicion of capsular invasion on imaging. The localized end-stage prostate cancer associated with a low progressive risk according to Amico's classification nevertheless required active surveillance. This course illustrates the need to combine both clinical, biological and radiological arguments to determine optimal management. Intravesical BCG instillations can be complicated by granulomatous prostatitis, which in our case presented as prostate cancer with induration, increased PSA levels, and the appearance of a cancerous nodule on MRI without local or general signs of infection. This triad of granulomatous prostatic disease, *M. bovis* infection and prostatic adenocarcinoma highlights the need for progressive therapeutic management.

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Author statement

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CRedit authorship contribution statement

Leo Sauvat: Conceptualization, Methodology, Validation, Investigation, Resources, Writing - Original Draft, Writing - Review & Editing, Visualization. **Quentin Lhermite:** Validation, Investigation, Resources, Writing - Review & Editing, Visualization. **Claude Desplechain:** Investigation, Resources. **Bertrand Long:** Validation, Investigation, Resources, Writing - Review & Editing. **Magali Vidal:** Conceptualization, Methodology, Investigation, Resources, Writing - Review & Editing, Visualization, Project administration, Supervision.

Conflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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