



Intravesical-BCG as an Unusual Cause of Elevated PSA Leading to an Elusive Diagnosis

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Abstract

Introduction: PSA elevation regularly demands additional investigation to rule out Prostate Cancer (PCa). PIRADS has been added to understand the myriad of prostate pathologies allowing conservative management in selected cases.

Case Report: A 71-year-old man who presented elevated PSA from 1.5 ng/ml to 13 ng/ml was investigated after mpMRI showed PIRADS-5 areas. Admittedly, rising PSA was due to urethral catheterization for BCG bladder instillation 3 weeks before. Persistent PSA elevation justified invasive investigation. Histology results of extended prostatic core-biopsies revealed diffuse granulomatous findings with no neoplastic lesions. Investigative tuberculosis exams were negative and PSA follow-up normalized to previous levels.

Introduction

Elevated PSA is a concern for any medical situation and clinical investigation is mandatory. Up to recent times PSA elevation was investigated with invasive biopsy. MRI and refinements through PIRADS system allowed better understanding of the progression of the disease and render conservative management as an alternative for some prostate cancers. However, minutia of particular prostatic diseases does not have treatments and workups well established and these cases merit report to add better understanding of them. Patterns and behavior of PSA elevation after BCG bladder instillation demands medical attention as concomitant diseases is possible.

Since the introduction of fined MRI protocols we were able to identify cases where more conservative investigation might be used as in cases where granulomatous prostatitis mimic cancer and is highly suspected.

Although histology is required to rule out prostate cancer it is becoming clear that some cases where BCG-therapy was past used might be offered close follow up management if mpMRI indicates suspicious findings.

Case Presentation

A 71 years-old patient was diagnosed with Transitional Cell Cancer (TCC) on US exam after 1-day self-limited macroscopic hematuria. Pathological exam revealed an isolated high-grade non-muscle invasive bladder cancer-pT1c. Six-cycles of weekly induction intravesical BCG instillation were done. Upon mild urinary discomfort at 14 weeks after instillation, urinary sediment, culture and PSA were requested revealing a jump of PSA from 1.5 ng/ml to 8.9 ng/ml. No fever, hematuria or systemic manifestation was observed. PSA repetition after additional 3 weeks and 20 weeks after the last urethral catheterization showed PSA stable at 13 ng/ml.

DRE was unremarkable with soft gland. Further mpMRI showed 42 cm, 3 gland and bilateral axial T2-weighted different lesions extending from both apices to middle zone in the left lobe and up to the base on the right lobe characterized as PIRADS 5 for both lesions.

Twenty core samples of MRI/US fusion targeted biopsy revealed granulomatous aggregates with infiltrating lymphocytes containing epithelioid histiocytes with no classification necrosis compatible with granulomatous prostatitis in all samples. Tb-PCR analyses and PPD test were negative for mycobacteria. PSA progressively returned and stabilized at 4.5 ng/ml at 38 and 42 and weeks.

Discussion

Granulomatous prostatitis is an elusive and seemingly frequent complication in patients who underwent intravesical BCG immunotherapy but as diagnosis can only be confirmed by histology

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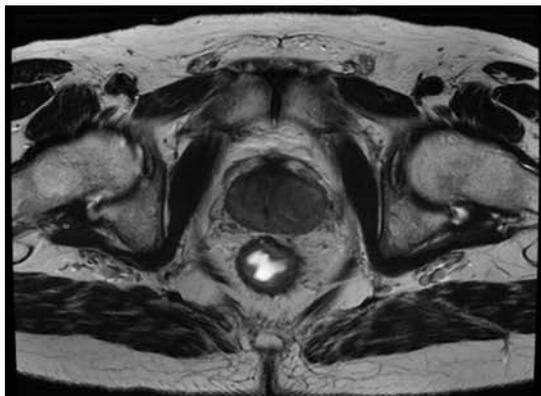


Figure 1: MpMRI T2 axial images showing low intensity signal bilaterally.

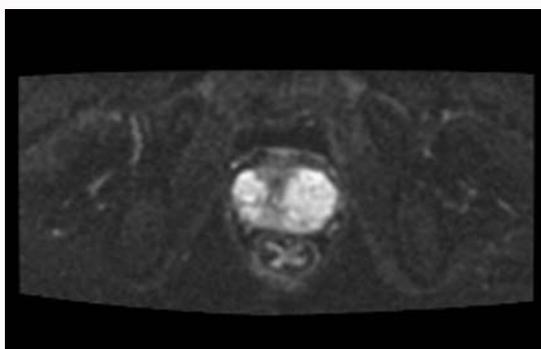


Figure 2: Diffusion Weighted Image (DWI) showing significant impairment of contrast diffusion in both lobes more importantly on the left.

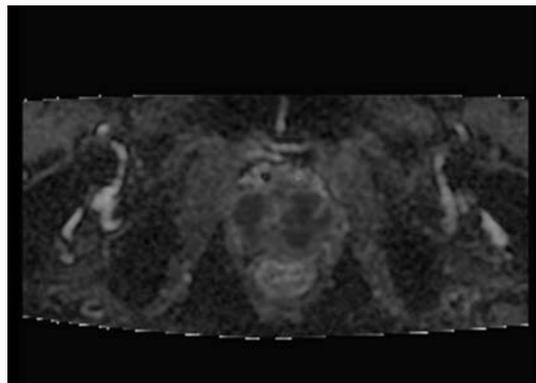


Figure 3: Diffusion Weighted Image (DWI) with a high-b value and focally hyperintense lesion on Apparent Diffusion Concentration (ADC) consistent with PIRADS 5.

it is grossly underestimated by the series of symptomatic cases [1,2]. Granulomatous prostatitis may be due to infectious or inflammatory causes. It is an infrequent urological diagnosis due to unspecific symptoms and seldom invasive histological confirmation. Periodic Acid Schiff, Gomori and Ziehl Neelsen's stain are the leading stains to diagnose the etiology. Histopathological exam shows aggregate of histiocytes, epithelioid cells and multinucleated giant cells nodes which are the types of cells mobilized in type IV (T-cell mediated reaction).

Histological granulomatous findings are observed in 1.4% of all prostatic resection specimens in different series resulting from large series of LUTS/TURP treatment [3]. Histological confirmation of granulomatous prostatitis comes from treatment for sheer LUTS treatment (58%) or LUTS/fever/hematuria (42%) investigation with 40% been associated with clinically incidental CaP [4]. DRE elevated PSA e MRIp findings mimicking CaP are all found on granulomatous prostatitis. Although, clinical suspicion for CaP is high association with it on histological examination is weak. The majority of granulomatous prostatitis cases started due investigation because of suspicious DRE or incidental PSA elevation that mimicked carcinoma in different aspects [5].

Knowledge from small series and illustrative case reports as ours made it reasonable to measure PSA before BCG therapy as it might be useful to compare had any gland alteration being observed. It seems that histological granulomatous prostatitis occurs frequently after BCG instillations as demonstrated on 75% of 119 cases who showed asymptomatic histological confirmation on later cystoprostatectomy

[2,6]. Another rare study in this matter with patients submitted to TURP after BCG therapy found an astounding incidence of 69% of chronic prostatitis 30% of whom were granulomatous in nature compared to none in 459 regular TURP cases [1].

PSA elevation in patients with intravesical BCG seems to be self-limited, and it typically returns to basal levels within 3 months in the absence of maintenance therapy. Beltrami et al. [7] showed that 42% of patients on intravesical therapy showed PSA elevation with return to previous levels after 12 months [8].

In recent times mpMRI (Figure 1) become an important tool to determine the need for prostate biopsy in cases of biochemical or clinical suspicion for CaP. mpMRI alterations in granulomatous prostatitis are yet poorly determined in the literature. Recognizing that mpMRI may have false-positive findings for CaP as for the cases of bacterial or granulomatous prostatitis acknowledgment of frequent MRI alteration on subjects submitted to BCG might allow conservative management in this clinical setting without invasive investigation. Scarcity of truly documented cases of granulomatous prostatitis limits diagnostic findings on mpMRI [6].

Cheng described a limited series of 6 cases of MRI findings in primary prostatic tuberculosis observing that nodular lesions showed very low intensity on T2-Weighted Imaging (T2WI) as well as in DWI and ADC map while diffuse granulomatous lesions were also low on T2WI but higher than in the muscle with high intensity on DWI and low signal on ADC [9].

Similarly, Lee et al. [6] identified 16 out of 819 cases with biopsied-proven granulomatous prostatitis studied with mpMRI reporting low signal on T2WI with high DWI (Figure 2 and 3). Surprisingly, as in our case, all of them were previously rendered PIRADS 5.

Although it is difficult to distinguish neoplastic from benign granulomatous lesion ring signal in DCE, firstly described by Kawada et al. [10] might suggest granulomatous origin of the lesion averting invasive measures. Although Leibovici et al. [11] showed an average rise of 6.9 ng/ml during BCG instillation with PSA normalization afterwards the exact MRI findings that characterize granulomatous prostatitis is largely dependent on the amount of water content and inflammatory process. ADC values <1000 with decreased or isointense signal on high-b-value ($b > 1200$) suggest inflammatory component in contrast to CaP pattern which presents lower b-value and faster clearance in Dynamic Contrast Enhancement (DCE) [12,13].

While MRI helps justify prostate biopsy rare case reports of suspicious laboratory or clinical findings describing mpMRI alterations after BCG instillations might legitimate conservative management [13,14].

PIRADS-5 is a strong finding to justify prostatic biopsy but the assistant doctor may vet the whole picture and admit that even for PIRADS-5 unexpected granulomatous findings might be observed in 38% of the 15.5% with non-cancer histological diagnosis [15]. However, if no exam comparisons are possible elevated PSA and suspicious PIRADS lesion will demand prostatic biopsy at the physician's discretion.

The reverse of this radiological conundrum is the more frequent usage of 18-Fluoro-2-Deoxyglucose Positron Emission Tomography/Computed Tomography (F-18 FDG PET/CT) with consequent prostate incidental lesions. It is acknowledged that 1.5% of the all F-18 FDG presents incidental prostate uptakes [16]. Although it can represent prostate malignancies many of them are related to inflammatory or benign lesions [17]. Albeit, not being specific to neoplastic lesion avid-lesions showed a high rate of clinically significant prostate cancer - 91%, when biopsies were done [16]. Surprisingly, 59% of F-18 FDG PET/CT was still positive in the prostate up to 1 year after BCG therapy revealing the lasting pattern of the granulomatous lesions [18].

In continuity to prostatic alterations observed in follow up images exams after BCG-therapy CT is no different. Prostate alterations are observed in 38% of asymptomatic cases with low attenuation areas or contrast enhancement in 21% of cases, the majority of them reversed along extended follow up [19]. Our case adds to the scarce information on PSA behavior and histological alterations observed after BCG-instillation.

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