Incidental detection of increased ^{18}F-FDG uptake and its follow-up in patients with granulomatous prostatitis after BCG treatment for urinary bladder cancer

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Abstract
Incidental prostate uptake of fluorine-18-fluorodeoxyglucose in positron emission tomography/computed tomography (^{18}F-FDG PET/CT) may represent malignancies like prostate malignancy, inflammation or benign prostatic lesions. *We report two cases* of bacillus Calmette-Guérin (BCG)-induced granulomatous prostatitis that showed ^{18}F-FDG uptake of the prostate gland on ^{18}F-FDG PET/CT in patients who had previously received intravesical BCG treatment for bladder cancer. The degree of ^{18}F-FDG uptake was decreased on the follow-up PET/CT scan after one year, without any specific treatment.

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Introduction

With the widespread use of fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) scintigraphy, incidental ^{18}F-FDG uptake may be found outside the region of primary interest. Many of these incidental findings represent benign lesions, but nevertheless it is important to understand the potential and the cause of these findings.

Incidental ^{18}F-FDG uptake within the prostate gland is found in approximately 1.2%-1.5% of the patients examined [1, 2]. This uptake can represent prostate malignancy or most usually, benign lesions such as benign prostatic hyperplasia or prostatitis [1-3]. In case of bladder cancer patients who had undergone intravesical instillation treatment of bacillus Calmette-Guérin (BCG) may develop an increased ^{18}F-FDG uptake of the prostate, which can be due to granulomatous prostatitis.

We report two cases of BCG-induced granulomatous prostatitis that presented as incidentally found focal ^{18}F-FDG uptake within the prostate gland on the ^{18}F-FDG PET/CT scan.

Presentation of the cases

Case 1

A 59 years old man with non-invasive high grade papillary urothelial carcinoma of the bladder had undergone transurethral resection and additional intravesical instillations of BCG using 6-week induction and additional 3-week maintenance schedule. Eight months later, he was referred to us for a ^{18}F-FDG PET/CT examination for the evaluation of bladder cancer recurrence and/or distant metastases. He received an intravenous injection of approximately 3.7MBq of ^{18}F-FDG per kilogram of body weight. The ^{18}F-FDG PET/CT scan was performed using a 16-slice CT Discovery 600 apparatus® (General Electric Healthcare, Milwaukee, USA). Before the PET scan, for attenuation correction, a low-dose CT scan was obtained without contrast enhancement from the skull base to the thigh, with the patient supine and breathing quietly. A PET scan with a maximum spatial resolution of 5.1mm was also obtained from the skull base to the thigh, at 1.5min per bed position. Images obtained using the Discovery PET/CT scanner were reconstructed with a 192×192 matrix, an ordered-subset expectation maximum iterative reconstruction algorithm (4 iterations; 16 subsets), a Gaussian filter of 6.4mm, and a slice thickness of 3.27mm.

The scan showed focal ^{18}F-FDG uptake in the left lobe and mild ^{18}F-FDG uptake in the right lobe of the prostate gland. The maximum standardized uptake value (SUVmax) of ^{18}F-FDG uptake in the left lobe was 8.3 (Fig. 1). He did not show any significant symptoms, such as dysuria, fever, or irritative voiding. Serum prostate-specific antigen (PSA) was 1.68ng/mL, which is within the normal range. Transrectal ultrasound demonstrated a

1.7cm sized hypoechoic lesion in the left peripheral portion of the prostate gland, which was the corresponding location of the increased ^{18}F-FDG uptake (Fig. 2). The transrectal ultrasound-guided biopsy of the prostate gland revealed chronic granulomatous inflammation in both lobes of the prostate gland, without any evidence of malignancy (Fig. 3).

Decreased ^{18}F-FDG uptake was found on the follow-up PET/CT scan without any specific treatment (Fig. 4).

Case 2

A 54 years old man with non-invasive high grade papillary urothelial carcinoma of the bladder had undergone transurethral resection and additional several intravesical in-

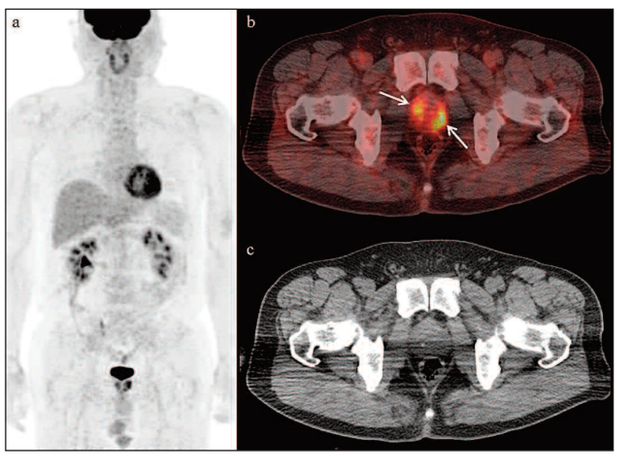

Figure 1. The ^{18}F-FDG PET/CT examination. a) Maximum intensity projection image, b) fusion image, c) CT image. The image shows focal ^{18}F-FDG uptake at the left lobe of the prostate gland with maximum standardized uptake value of 8.3 and mildly increased ^{18}F-FDG uptake at the right lobe of the prostate gland (arrows). There was no evidence of lymph node or distant metastases.

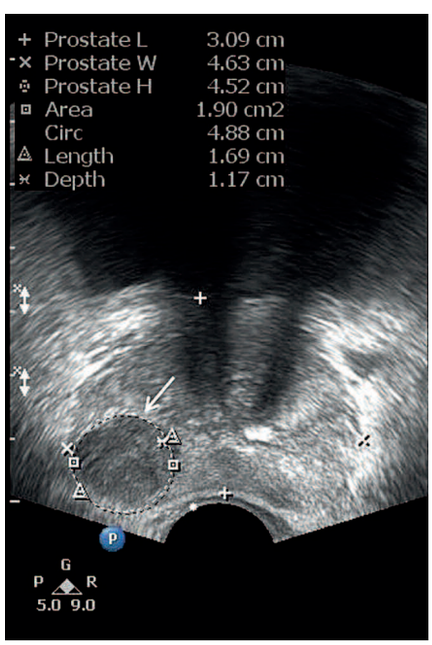

Figure 2. Transrectal ultrasound showed an about 1.7cm sized hypoechoic lesion in the left peripheral portion of the prostate gland (arrow), corresponding to the focal ^{18}F-FDG uptake.

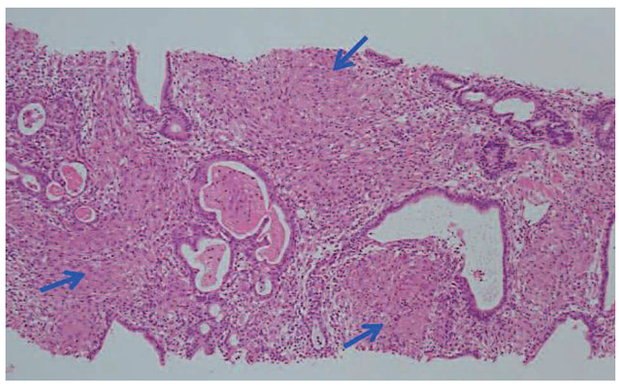

Figure 3. Small non-caseating granulomas (arrows) were found by histology in the periglandular stroma adjacent to the dilated prostatic glands (H&E, ×100).

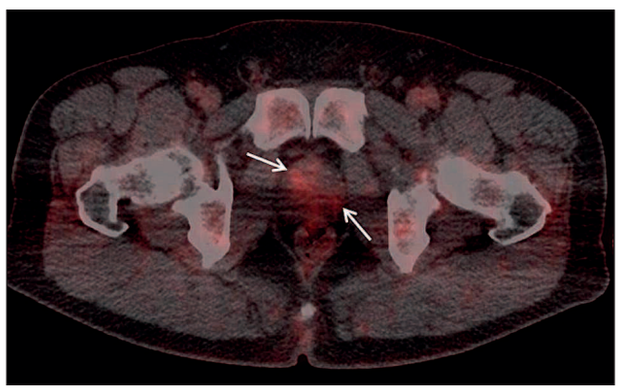

Figure 4. The follow-up ^{18}F-FDG PET/CT fusion image performed one year later showed decreased degree of focal ^{18}F-FDG uptake in the prostate gland, and SUVmax 3.0 (arrows).

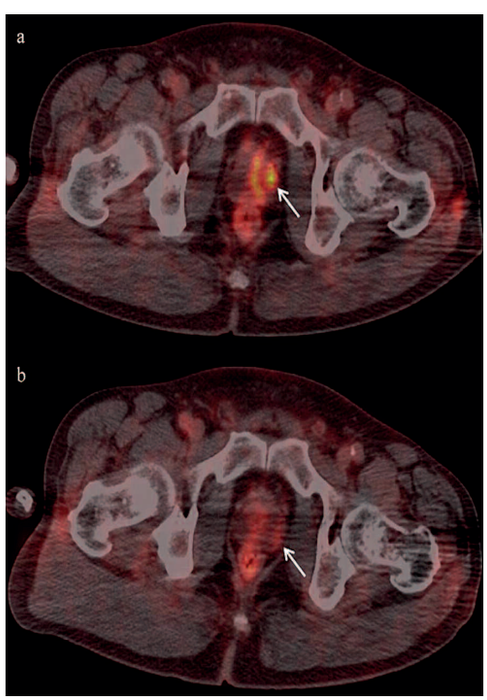

Figure 5. a) The ^{18}F-FDG PET/CT fusion image showed focal ^{18}F-FDG uptake in the left lobe of the prostate gland with SUVmax 6.5 (arrow). b) One year later, the degree of focal ^{18}F-FDG uptake in the prostate gland was decreased on the follow-up ^{18}F-FDG PET/CT fusion image, and the SUVmax was 3.4 (arrow).

stillations of BCG using 6-week induction and additional 3-week maintenance schedule. Five months later, a ^{18}F-FDG PET/CT scan was performed using the same instrument and acquisition as case 1. The ^{18}F-FDG PET/CT image showed focal ^{18}F-FDG uptake in the left lobe of the prostate gland, and SUVmax 6.5 (Fig. 5a). He was clinically silent, and the serum PSA level was 1.51ng/mL, which is within the normal range. The urologist assumed that this ^{18}F-FDG uptake was caused by the BCG-induced granulomatous prostatitis, and did not suggest any further examination. The ^{18}F-FDG uptake in the prostate gland was decreased to SUVmax of 3.4 on a follow-up ^{18}F-FDG PET/CT examination performed one year later (Fig. 5b). During this time the patient had received no treatment.

Discussion

Bacillus Calmette-Guérin is a live attenuated strain of *mycobacterium bovis* and this has extensively been employed as an immunization for tuberculosis. After it became known that BCG treatment shows a better antitumor effect than chemotherapy, BCG was applied as an additional adjuvant treatment option for patients with superficial bladder cancer, usually following transurethral resection of the tumor. The BCG treatment is being used since the 1970s in order to reduce the rate of tumor recurrence and progression [4]. The supposed mechanism of action of BCG in bladder tumor cell eradication may be summarized as follows: After BCG installation antigen-presenting cells, tumor cells and chemokines secreted partly by BCG-internalized tumor cells contribute to local activation of the immune system. Furthermore, activated leukocytes and mononuclear cells invade the bladder wall. Furthermore, Th1 cytokines promote delayed-type hypersensitivity response, cytotoxic cell response and macrophage activation or cellular immune inflammatory reaction. These inflammatory reactions can cause complications, like cystitis, epididymo-orchitis, granulomatous prostatitis, and rarely systemic manifestations [5].

Although a clinically evident case is quite rare, BCG-induced granulomatous prostatitis has been reported in up to 75% of patients who received the intravesical BCG instillation treatment for bladder cancer [6]. The reason of prostatitis is prostatic inflammatory reaction resulting from the intraprostatic reflux of BCG contaminated urine in the bladder [7].

This granulomatous prostatitis, like some other prostatic infections, is indistinguishable from prostate malignancy, both clinically and radiologically. It is most often asymptomatic and the granulomas cannot be distinguished by digital rectal examination from prostate malignancy. Serum PSA level in almost half of the patients can be elevated [8, 9]. The image features can be similar to those in the prostate malignancy, in that the lesion within the peripheral zone of the prostate on transrectal ultrasound can be hypoechoic or express a low signal intensity on the T2-weighted imaging on magnetic resonance imaging (MRI) [7].

Since ^{18}F-FDG accumulates in the inflammatory cells, increased ^{18}F-FDG uptake can be shown within the prostate gland on the ^{18}F-FDG PET/CT imaging examination in these patients. In a previous report (2008), in nonspecific acute prostatitis the ^{18}F-FDG uptake was diffusely increased [3]. In our case, the ^{18}F-FDG uptake pattern was rather focal, associated with small granulomas in one or in both lobes of the prostate gland, as others also have reported [10, 11].

Since most of patients with BCG-induced granulomatous prostatitis are asymptomatic, there are few reports on the actual time that granulomatous prostatitis starts. It was reported that the incidental diagnosis of BCG-induced granulomatous prostatitis was made 2 to 45 months after the completion of BCG treatment [12]. A recent report (2014) suggested that it takes more than 12 months after completion of BCG treatment to have abnormal signal changes within the prostate gland on the MRI [13]. In our cases, however, increased ^{18}F-FDG uptake within the prostate gland was detected on the ^{18}F-FDG PET/CT scan earlier than 12 months after completion of BCG treatment. Thus, ^{18}F-FDG PET/CT may be more helpful than MRI for an early detection of BCG-induced granulomatous prostatitis. In addition, we confirmed decreased intensity of the ^{18}F-FDG uptake of the prostate gland on the follow-up ^{18}F-FDG PET/CT scan performed one year later. This is to our knowledge, the first report of the change of imaging findings on the ^{18}F-FDG PET/CT scan after one year.

Although there are no specific ^{18}F-FDG PET/CT findings to differentiate BCG-induced granulomatous prostatitis from prostate malignancy, a normal serum PSA and a history of BCG treatment may support the diagnosis of BCG-induced granulomatous prostatitis. A decrease in the follow-up uptake of ^{18}F-FDG PET/CT after a year may also support the above diagnosis.

Transrectal ultrasound-guided biopsy is often recommended to differentiate BCG-induced granulomatous prostatitis from prostate malignancy. Histological evidence of non-caseous or caseous granulomatous inflammation and the acid-fast bacilli (AFB) identified by the Ziehl-Neelson stain can be seen in the majority of patients with BCG-induced granulomatous prostatitis [14, 15]. As for treatment, only patients with acute severe symptoms may be treated with 300mg isoniazid and 600mg rifampicin orally for 3-6 months. Asymptomatic patients require no treatment, even in the presence of AFB because the disease usually subsides by itself [7].

In conclusion, BCG-induced granulomatous prostatitis can be one of the benign causes of incidental ^{18}F-FDG uptake within the prostate gland on the ^{18}F-FDG PET/CT scan, in cases of a prior history of bladder cancer treated with intravesical BCG instillation.

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The authors declare that they have no conflicts of interest.

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