Granulomatous Prostatitis After Intravesical Bacillus Calmette-Guérin Instillation Therapy: A Potential Cause of Incidental F-18 FDG Uptake in the Prostate Gland on F-18 FDG PET/CT in Patients with Bladder Cancer

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Abstract

Purpose This study aimed to evaluate the possibility that Bacillus Calmette-Guérin (BCG)-induced granulomatous prostatitis can be a potential cause of benign F-18 FDG uptake.

Methods A total of 395 bladder cancer patients who underwent F-18 FDG PET/CT (PET/CT) were retrospectively evaluated. Patients were divided into two groups according to BCG therapy status. Elapsed time after BCG therapy, serum PSA level, results of prostate biopsy, and the SUVmax and uptake pattern in the prostate gland were reviewed. For patients who underwent follow-up PET/CT, the changes in SUVmax were calculated.

Results While 35 % of patients showed prostate uptake in the BCG therapy group, only 1 % showed prostate uptake in the non-BCG therapy group ($p < 0.001$). Among 49 patients with FDG-avid prostate lesions, none had suspected malignancy during the follow-up period (median: 16 months). Five patients revealed granulomatous prostatitis on biopsy. The incidence of FDG-avid prostate lesions was significantly higher if the elapsed time after BCG therapy was less than 1 year compared to more than 1 year ($p < 0.001$). Serum PSA was normal in 88 % of patients. All patients with incidental F-18 FDG

uptake in the prostate gland showed focal or multifocal prostate uptake, and median SUVmax was 4.7. In 16 patients who underwent follow-up PET/CT, SUVmax was decreased in 14 patients (88 %) without treatment, and no patients demonstrated further increased prostate uptake ($p < 0.001$).

Conclusions BCG-induced granulomatous prostatitis can be a potential cause of benign F-18 FDG uptake, especially in those with a history of bladder cancer treated with BCG. In BCG-induced granulomatous prostatitis, focal or multifocal prostate uptake is frequently seen within 1 year after BCG therapy, and the intensity of prostate uptake is decreased on the follow-up PET/CT without any treatment.

Keywords Bladder cancer · Intravesical BCG therapy · F-18 FDG PET/CT · Granulomatous prostatitis

Introduction

As 18-fluoro-2-deoxyglucose positron emission tomography/computed tomography (F-18 FDG PET/CT) scans become more widely used, the importance of incidental F-18 FDG uptake outside the region of primary interest is also increasing quickly. Since many of these incidental findings on F-18 FDG PET/CT represent physiologic properties or benign lesions such as inflammation, it is important to differentiate benign from malignant lesions related to the increased F-18 FDG uptake.

Incidental uptake in the prostate gland is discovered in approximately 1.2–1.5 % of patients on F-18 FDG PET/CT [1, 2]. This uptake can represent prostate malignancy, but many of these findings indicate benign lesions such as benign prostatic hyperplasia (BPH) or prostatitis [3]. In recent years, a few case reports regarding incidental detection of increased

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F-18 FDG uptake in the prostate gland in patients with granulomatous prostatitis after intravesical Bacillus Calmette-Guérin (BCG) instillation therapy (BCG therapy) for bladder cancer have been published [4–6].

BCG therapy has been applied as an additional treatment option for patients with superficial bladder cancer, usually following transurethral resection of a bladder tumor (TURB) [7]. BCG-induced granulomatous prostatitis is a common disease reported to occur in up to 75 % of patients who have received BCG therapy for bladder cancer [8], but a survey of FDG-avid BCG-induced granulomatous prostatitis in patients with bladder cancer has not yet been undertaken.

In this study, we evaluated the incidence of F-18 FDG uptake in the prostate gland on F-18 FDG PET/CT in patients with bladder cancer who received and did not receive BCG therapy, and we tried to find clinical and imaging clues to interpret this incidental F-18 FDG uptake in the prostate gland as BCG-induced granulomatous prostatitis.

Patients and Methods

Patients

We performed a retrospective review of 395 male patients with bladder cancer who underwent F-18 FDG PET/CT from November 2005 to January 2015. Clinical and pathological parameters were reviewed and retrieved, including age, pathological stage and grade of bladder cancer, history and protocol of BCG therapy, presence of BPH, serum PSA level, and pathologic results of prostate biopsy. Patients were divided into two groups, the BCG therapy group and non-BCG therapy group, to compare the incidence of F-18 FDG uptake in the prostate gland. For patients in the BCG therapy group, the elapsed time from the end of BCG therapy to the F-18 FDG PET/CT scan was reviewed. Data collection and analysis were approved by the Institutional Review Board of Kyungpook National University Medical Center and School of Medicine, and the requirement for written informed consent was waived.

F-18 FDG PET/CT Image Acquisition

All patients fasted for at least 6 h, and their blood glucose levels were checked before the administration of FDG. Patients with blood glucose levels higher than 150 mg/dl were rescheduled for examination, and treatment was administered to maintain a blood glucose concentration <150 mg/dl in all subjects. Patients received an intravenous injection of 3.7–5.5 MBq of F-18 FDG per kilogram of body weight and were advised to rest for 1 h before the acquisition of the F-18 FDG PET/CT image. The F-18 FDG PET/CT scans were performed using a 16-slice CT Discovery 600 apparatus[®] (General Electric Healthcare, Milwaukee, WI, USA) and a 16-slice CT

Discovery STE apparatus[®] (General Electric Healthcare). 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. In Discovery 600 PET/CT, PET scans with a maximum spatial resolution of 5.1 mm were obtained from the skull base to thigh at 1.5 min per bed position. PET images were reconstructed with a 192×192 matrix, an ordered-subset expectation maximum iterative reconstruction algorithm (4 iterations; 16 subsets), a Gaussian filter of 6.4 mm and a slice thickness of 3.27 mm. In Discovery STE PET/CT, PET scans with a maximum spatial resolution of 5.5 mm were obtained from the skull base to the thigh at 3 min per bed position. PET images were reconstructed with a 128×128 matrix, an ordered-subset expectation maximum iterative reconstruction algorithm (4 iterations; 8 subsets), a Gaussian filter of 5.0 mm, and a slice thickness of 3.27 mm.

Image Analysis

For patients who showed incidental F-18 FDG uptake in the prostate gland, the maximum standardized uptake value (SUVmax) and pattern of F-18 FDG uptake in the prostate gland were evaluated. Routinely, two specialized nuclear medicine physicians interpreted the F-18 FDG PET/CT results and reached a consensus. Image display and analysis were achieved using the volume viewer software on an Advantage Workstation 4.5 (GE Medical Systems, Milwaukee, WI, USA). All axial, coronal, and sagittal images were carefully analyzed. Incidental F-18 FDG uptake in the prostate gland was considered significant if the FDG activity was higher than the surrounding prostate gland on visual analysis. If the FDG activity was located in the center of the prostate gland and was highly suspected to be physiologic urine activity in the prostatic urethra, it was excluded from the analysis. Regions of interest were manually placed over the area of maximal activity on slices of the lesions of prostate gland with care to exclude physiologic urine activity in attenuation-corrected images, and the SUVmax within the region of interest was obtained. The SUVmax was calculated using the following formula: $\text{SUVmax} = \frac{\text{maximum activity in region of interest (MBq/g)}}{[\text{injected dose (MBq)} / \text{body weight (g)}]}$. If a patient underwent follow-up F-18 FDG PET/CT, we evaluated the change in SUVmax between two serial scans. The pattern of F-18 FDG uptake in the prostate gland was categorized as focal, multifocal, or diffuse. If the only one FDG-avid lesion was located in the prostate gland, this pattern was categorized as focal. If more than one FDG-avid lesion was located in one or both lobes of the prostate gland, this pattern was categorized as multifocal. If diffuse F-18 FDG uptake was shown in the whole prostate gland, this pattern was categorized as diffuse.

Diagnosis of Incidental F-18 FDG Uptake in the Prostate Gland

A total of 49 lesions in the BCG therapy group of incidental F-18 FDG uptake in the prostate gland discovered on F-18 FDG PET/CT were correlated with the results of urological examinations such as the digital rectal examination ($n=49/49$), serum PSA level ($n=33/49$), or pathologic result of prostate biopsy after F-18 FDG PET/CT if a patient agreed to undergo the procedure ($n=5/49$). The diagnostic flowchart of incidental F-18 FDG uptake in the prostate gland is shown in Fig. 1.

BPH was defined as lower urinary tract symptoms resulting from prostate enlargement, and the diagnosis of BPH was made at the discretion of the urologist. Since BPH is known as one of the benign causes of incidental F-18 FDG uptake in the prostate gland, we reviewed the presence of BPH and compared the incidence of F-18 FDG uptake in the prostate gland between patients who had clinically diagnosed BPH and those who had no BPH.

Statistical Analysis

Statistical analysis was performed using MedCalc for Windows, version 15.2.1 (MedCalc Software, Mariakerke, Belgium). Differences in clinical characteristics between patients in the BCG therapy group and those in the non-BCG therapy group were analyzed using the Pearson chi-square exact test for categorical variables and Mann-Whitney test for

continuous variables, respectively. Changes in SUVmax between initial and follow-up F-18 FDG PET/CT scans were assessed using a paired Wilcoxon signed-rank test. P values less than 0.05 were considered statistically significant.

Results

Among 395 male patients with bladder cancer, 150 (38 %) patients received BCG therapy and the remaining 245 (62 %) patients did not. In the BCG therapy group, 53 of 150 patients (35 %) showed increased F-18 FDG uptake in the prostate gland on the F-18 FDG PET/CT. However, only 2 out of 245 patients (1 %) showed increased F-18 FDG uptake in the prostate gland in the non-BCG therapy group. The incidence of F-18 FDG uptake in the prostate gland was significantly higher in patients in the BCG therapy group than those in the non-BCG therapy group ($p<0.001$).

The incidence of F-18 FDG uptake in the prostate gland was not significantly different between patients who had clinically diagnosed BPH (17 of 83 patients, 21 %) and those who had no BPH (38 of 312 patient, 12 %, $p=0.078$). Among 53 FDG-avid prostate lesions in the BCG therapy group, 3 were pathologically diagnosed as prostate adenocarcinoma and 1 lesion as BPH. Two FDG-avid prostate lesions in the non-BCG therapy group were regarded clinically as BPH. All six of these lesions were excluded from further analysis.

In the BCG therapy group, the median elapsed time from the end of BCG therapy to the F-18 FDG PET/CT scan was

Fig. 1 Diagnostic flowchart of incidental F-18 FDG uptake in the prostate gland in patients with bladder cancer

8 months (range, 1–59 months). Among 59 of the 146 patients who underwent F-18 FDG PET/CT scans within 1 year after completion of BCG therapy, 35 (59 %) showed increased F-18 FDG uptake in the prostate gland. Among the remaining 87 patients who underwent the scans 1 year after completion of BCG therapy, however, only 14 (16 %) showed increased F-18 FDG uptake in the prostate gland. The incidence of F-18 FDG uptake in the prostate gland was similar among the patient groups who underwent F-18 FDG PET/CT within 3 months, 6 months, and 1 year after completion of BCG therapy. However, the incidence was significantly higher in patients who underwent F-18 FDG PET/CT within 1 year of BCG therapy compared to those who underwent the scan after 1 year of BCG therapy ($p<0.001$, Fig. 2).

Median follow-up duration of 49 FDG-avid prostate lesions was 16 months (range 0–72 months). Serum PSA levels were within normal range (<4 ng/ml) in 29 patients (88 %). Four patients (12 %) had increased PSA levels (range 4.36–6.8 ng/ml), but the levels decreased to within normal range after 3–12 months without any treatment. Although PSA levels were not checked after F-18 FDG PET/CT in the remaining 16 patients, none of the patients had clinically or radiologically suspected malignancy. Eighteen of 49 patients underwent additional conventional imaging studies such as transrectal ultrasonography (TRUS) ($n=3$) and pelvis CT ($n=15$), but only 1 showed a focal hypoechoic lesion in the left peripheral portion of the prostate gland on TRUS, corresponding to the focal uptake on the F-18 FDG PET/CT.

The median value of the SUVmax in the prostate lesion was 4.7 (range, 2.8–21.5). The features of F-18 FDG uptake in the

prostate gland were focal ($n=36$, 73 %) or multifocal ($n=13$, 27 %) patterns, but no patients showed a diffuse pattern of F-18 FDG uptake in the prostate gland. Sixteen of 49 patients underwent follow-up F-18 FDG PET/CT, and the median time interval between two scans was 15 months (range, 9–46 months). Although none of the patients received any specific treatment for BCG-induced granulomatous prostatitis, the SUVmax in the prostate lesion decreased in 14 patients (88 %), and none of the patients had further increased F-18 FDG uptake on the follow-up scan compared with a prior scan ($p<0.001$; Fig. 3). Five of 49 patients had prostate biopsies and revealed granulomatous inflammation of the prostate gland without any evidence of malignancy. The patient characteristics are presented in Table 1, and a representative patient with BCG-induced granulomatous prostatitis is shown in Fig. 4.

Discussion

BCG is a live attenuated strain of *Mycobacterium bovis*, and it was first developed by Calmette and Guérin as a vaccine against tuberculosis. In the 1970s, the immunomodulatory effects of BCG were applied to the adjuvant treatment of patients with superficial bladder cancer, usually following TURB [7]. Although the mechanism of intravesical BCG action in preventing or suppressing bladder cancer growth is unknown, the efficacy of BCG is believed to be caused by antigen-mediated local production of cytokines and stimulated accumulation of inflammatory cells. The hypothesis that hypersensitivity reactions to BCG antigens can cause BCG-induced

Fig. 2 Comparison of the incidence of F-18 FDG uptake in the prostate gland according to the time elapsed from the end of BCG therapy to the F-18 FDG PET/CT scan

Fig. 3 Changes in the SUVmax of the prostate gland between the initial and follow-up F-18 FDG PET/CT scans

infectious complications including BCG-induced granulomatous prostatitis has been widely accepted [9, 10]. The reason for BCG-induced granulomatous prostatitis is a prostatic inflammatory reaction resulting from the intraprostatic reflux of BCG-contaminated urine in the bladder [11].

BCG-induced granulomatous prostatitis is indistinguishable from prostate malignancy, both clinically and radiologically, like some other infections. It is most often asymptomatic, and the granulomas cannot be distinguished from prostate malignancy by digital rectal examination. It raises the serum PSA level in almost half of the patients [12, 13], and the image features are similar to those of prostate malignancy as the lesion can appear as a hypoechoic region within the peripheral zone of the prostate on transrectal ultrasound [14] or as low signal intensity on T2-weighted imaging on magnetic resonance imaging (MRI) [15].

Because FDG accumulates in the inflammatory cells, increased F-18 FDG uptake can be shown in the prostate gland on F-18 FDG PET/CT in patients with BCG-induced

granulomatous prostatitis. The previously reported F-18 FDG PET/CT finding in nonspecific prostatitis was diffusely increased F-18 FDG uptake in the whole prostate gland [2]. On the other hand, none of the patients showed a diffuse pattern of F-18 FDG uptake in the prostate gland in this study. All five FDG-avid lesions in the prostate gland pathologically confirmed as BCG-induced granulomatous prostatitis also showed focal or multifocal patterns. The reason why BCG-induced granulomatous prostatitis looks like more than one foci of the focal F-18 FDG uptake pattern might be associated with the small granulomas in one or both lobes of the prostate gland. Recently, two reports have demonstrated similar F-18 FDG PET/CT findings of biopsy-proven BCG-induced granulomatous prostatitis in patients with bladder cancer [4, 5].

Since most patients with BCG-induced granulomatous prostatitis are asymptomatic, there are few reports on the actual time when BCG-induced granulomatous prostatitis starts. It was reported that the incidental diagnosis of BCG-induced granulomatous prostatitis was made 2 to 45 months after the

Table 1 Characteristics of patients with pathologically confirmed BCG-induced granulomatous prostatitis ($n=5$)

Characteristic	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age (years)	71	59	59	60	70
T Stage	T1	Ta	Ta	Ta	Ta
Histologic grade	High	High	High	High	Low
BCG therapy protocol	6+3	6+3	6+3	6	6
Serum PSA level	6.8	0.5	1.7	1.6	1.6
Follow-up serum PSA level	2.2	–	1.1	1.2	1.3
Elapsed time from the end of BCG therapy to F-18 FDG PET/CT scan (months)	10	11	8	1	8
Pattern of F-18 FDG uptake	Multifocal	Focal	Multifocal	Focal	Focal
SUVmax on initial F-18 FDG PET/CT	5.0	3.7	8.3	4.9	15.6
SUVmax on follow-up F-18 FDG PET/CT	2.1	–	2.8	–	2.8

Fig. 4 Representative patient with BCG-induced granulomatous prostatitis. **a** F-18 FDG PET/CT fusion image performed about 8 months after BCG therapy shows focal F-18 FDG uptake at the left lobe of the prostate gland with a maximum standardized uptake value of 15.6 (*arrow*). **b** The follow-up F-18 FDG PET/CT fusion image performed about 1.5 years later shows a decreased degree of focal F-18 FDG uptake in the prostate gland, and the SUVmax was 2.8 (*arrow*). **c**

Transrectal ultrasound shows an approximately 2.2-cm-sized hypoechoic lesion in the left peripheral portion of the prostate gland (*arrow*), corresponding to the focal F-18 FDG uptake. **d** In the transrectal ultrasound-guided biopsy of the prostate gland, minute noncaseating epithelioid granulomas (*arrows*) are observed in the prostatic stroma adjacent to the atrophic prostatic glands (H&E, $\times 100$)

completion of BCG therapy [14]. A recent report suggested that it takes more than 1 year after completion of BCG therapy to have abnormal signal changes in the prostate gland on the MRI [15]. In this study, however, increased F-18 FDG uptake in the prostate gland was detected on the F-18 FDG PET/CT earlier than 1 year after completion of BCG therapy. F-18 FDG PET/CT may be more helpful than MRI for early detection of BCG-induced granulomatous prostatitis. We also confirmed that the incidence of prostate uptake in early F-18 FDG PET/CT, which was performed within 1 year after completion of BCG therapy, was higher than in the late scan. In the same patient, the intensity of F-18 FDG uptake in the prostate gland was decreased on the follow-up F-18 FDG PET/CT performed about 1 year later without any treatment.

Mukamel et al. [16] reported that caseating granulomas were found during the early period after BCG therapy (1.5 to 3.0 months), whereas noncaseating granulomas were detected at a later time after BCG therapy (4 to 14.5 months). However, pathologic differences of FDG-avid lesions of the prostate according to the time of F-18 FDG PET/CT were not found in this study. Only five patients underwent prostate biopsy and were diagnosed with BCG-induced granulomatous prostatitis pathologically, and none of the patients who underwent biopsy in the early period after BCG therapy.

There are several limitations to our study. First, this was not a prospective study, and the results might not reflect the exact incidence of BCG-induced granulomatous prostatitis. Second, prostate biopsy was not performed in 44 of the 49 patients in the BCG therapy group who had increased F-18 FDG uptake in the prostate gland, and we could not confirm all of the FDG-avid lesions in the prostate gland pathologically. Also, measurement of the serum PSA level or follow-up F-18 FDG PET/CT scan was not performed in all patients. However, none of the patients were diagnosed with prostate malignancy during the follow-up period. Although BPH is also one of the benign causes of incidental F-18 FDG uptake in the prostate gland, there was no statistical difference in the incidence of F-18 FDG uptake in the prostate gland between patients who had BPH and those who did not.

In summary, although there were no specific F-18 FDG PET/CT findings that could reliably differentiate BCG-induced granulomatous prostatitis from prostate malignancy, BCG-induced granulomatous prostatitis is a potential benign cause of incidental F-18 FDG uptake in the prostate gland if the patient has a prior history of BCG therapy for bladder cancer, and a focal or multifocal pattern of F-18 FDG uptake in the prostate gland was observed on F-18 FDG PET/CT performed within 1 year after completion of BCG therapy.

Also, if the follow-up F-18 FDG PET/CT shows decreased or disappeared F-18 FDG uptake in the prostate gland without any treatment compared with the previous F-18 FDG PET/CT, this finding can also be indirect evidence of BCG-induced granulomatous prostatitis.

Conclusion

BCG-induced granulomatous prostatitis can be a potential benign cause of incidental F-18 FDG uptake in the prostate gland discovered on F-18 FDG PET/CT, especially in patients with a prior history of bladder cancer treated with BCG therapy. In BCG-induced granulomatous prostatitis, focal or multifocal F-18 FDG uptake is frequently seen in the prostate gland within 1 year after completion of BCG therapy, and the intensity of F-18 FDG uptake is decreased on the follow-up F-18 FDG PET/CT without any treatment.

Conflict of interest Choon-Young Kim, Sang-Woo Lee, Seock Hwan Choi, Seung Hyun Son, Ji-hoon Jung, Chang-Hee Lee, Shin Young Jeong, Byeong-Cheol Ahn, and Jaetae Lee declare that they have no conflicts of interest.

This manuscript has not been published before and is not under consideration for publication anywhere else. It has been approved by all co-authors.

Ethics Statement This study was approved by the Institutional Review Board of Kyungpook National University Medical Center and School of Medicine, and the requirement for written informed consent was waived. This study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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